RAMB

JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

AMB Associação Médica Brasileira

WMA

Volume **65** Number **5** **May 2019**
ISSN **0104-4230**
ISSN **1806-9282** (On-line)

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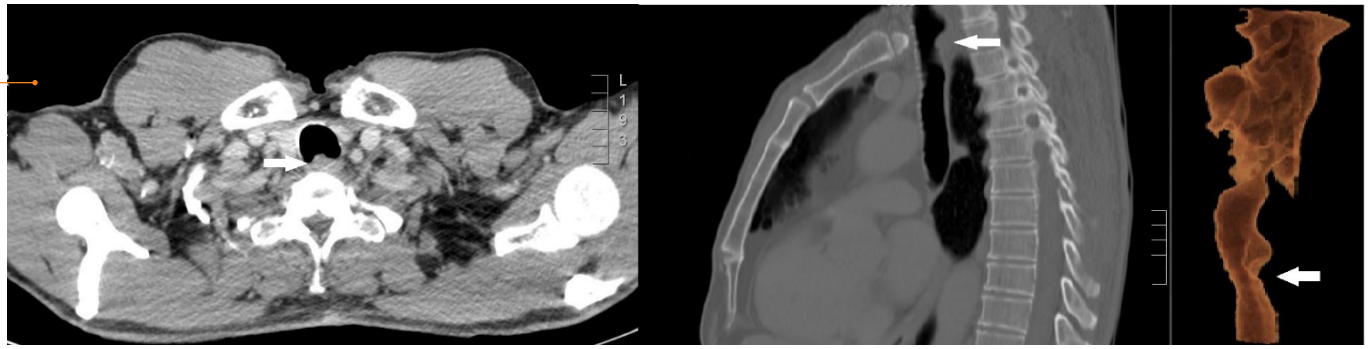

RAMB REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA
JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

RAMB - REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA (JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION)

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The RAMB, Journal of The Brazilian Medical Association, *is an official publication of the Associação Médica Brasileira (AMB – Brazilian Medical Association), indexed in Medline, Science Citation Index Expanded, Journal Citation Reports, Index Copernicus, Lilacs, and Qualis B2 Capes databases, and licensed by Creative Commons®. Registered in the 1st Office of Registration of Deeds and Documents of São Paulo under n. 1.083, Book B, n. 2.*

Publication norms are available on the website www.ramb.org.br

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Estrogens: possible protection against Amyotrophic Lateral Sclerosis?

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http://dx.doi.org/10.1590/1806-9282.65.5.576

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease characterized by progressive degeneration of upper and lower motor neurons in the motor cortex and spinal cord [1,2]. It can be sporadic, which corresponds to 90% of cases, or familial, mostly autosomal dominant, corresponding to 10% of cases. The disease's initial symptoms are local muscle weakness, progressing to rigidity and paralysis, also involving swallowing, diaphragm, which lead patients to death in 2 to 5 years due to respiratory failure [1,2].

In both etiology and physiopathogeny, there are reports of the influence of sex steroids. Epidemiologically, the disease's onset is later in women, around their 70 years, while in men approximately with 55 years [1-4].

In fact, gender and age exert a great influence on the risk of developing ALS, where the proportion between men and women would be between 4:1 in the period between 30 and 50 years of age. With the aging process and hypoestrogenism, this difference between the sexes decays to a ratio of 1:1 after age 65, leading to the idea that sex hormones can participate in onset, evolution, as well as intensity [1].

Due to aging-related changes, both estrogen synthesis and the expression of its receptors may differ based on cell and tissue types, an important aspect to understand the roles of cellular and tissue-specific hormonal synthesis to diseases that have being related to age [5,6].

The brain is a tissue responsive to the sexual hormone, and therefore affected by the drastic fall of estrogenic synthesis in menopause, a fact already associated with numerous affections, among these cognitive diseases such as Alzheimer's and other dementias, as well as recent studies pointing out to a possible

DATE OF SUBMISSION: 15-Apr-2019
DATE OF ACCEPTANCE: 16-Apr-2019
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relation of the sexual hormones with the ALS, where estrogens would possibly act as a neuroprotector [5,6].

There is evidence suggesting that the concentration of some specific hormones, such as estrogens and progesterone, or the expression of their receptors, may play an important role on the prevalence, progression, and survival of those patients [1,5].

This reality changes in terms of hormone replacement therapy, mainly estrogens, which do not have positive effects in postmenopausal women as in ALS. Also, the survival period will not change. It may be questioned that after neuronal damage, there is no therapy that can reverse the process [1].

There are other differences between the genres, among which, the clinical form: in men, the most frequent is in the upper limbs, whereas in women, the bulbar form is the predominant one. Another important factor is the possible increase in the risk of ALS for women who presented late menarche and early menopause [3].

There are some possible protective actions for estradiol (E2), such as the direct promotion of cell survival, preventing cell death by acting directly on the cascade of the apoptosis process. Estradiol is responsible for controlling the differentiation and plasticity of different neuronal populations in brain development, such as potentiating neurogenesis, modulating synaptogenesis and, finally, influencing axonal budding [5,6]. E2 also regulates neurotransmitter activity and their receptors among different populations of neurons. Therefore, it would have positive effects on neurological preservation, as long as the damage was not intense [5,6].

Other estrone protective actions would be the antioxidant action, removing reactive oxygen species, and anti-inflammatory, where it would act to diminish the production of TNF-α, IL-1β and IL-6 [1]. On the other hand, inflammatory processes in the central nervous system would stimulate the production of inflammatory mediators in response to estrogen: cytokines (produced mainly by glial cells), stimulate the immune system and can induce the death of neurons. This fact could explain why the hormone therapy did not improve ALS after its onset [1,6].

The mechanisms by which estrogen would exercise its protective action and benefit on the neurological system have not been fully known, but their action may be preventive, i.e, it would have no effect when the neurological disease, such as ALS, is already installed, and may even worsen it. In addition, progesterone in hormone therapy has negative action of motor plate, which would also be a negative influence on ALS [6].

Finally, postmenopausal hormone replacement therapy could improve connection and neurological protection when prescribed early, but belatedly, it would not have benefits over established degenerative diseases such as ALS [1,5,6].

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Total and partial laparoscopic adrenalectomy

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Final version: *January 7, 2018*

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http://dx.doi.org/10.1590/1806-9282.65.5.578

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

INTRODUCTION

The adrenal diseases of interest to urologists are those that require primarily surgical treatment. This group is composed mainly of solid tumors that can originate from various components of the gland, showing a great variety of clinical behaviors depending on their ability to secrete or not adrenal hormones. Macro and micronodular hyperplasias, adrenal gland cysts and pseudocysts, infectious processes such as abscesses and granulomas, and the presence of metastases from tumors of other origins are rarer.

Adrenal gland solid tumors are the primary indication for adrenalectomy and can be classified in various ways: according to the place of origin (cortical tumors, spinal cord tumors and other rarer tumors from the stroma, vessels and nerves), the hormonal profile (functioning tumors and non-functioning tumors), risk of malignancy, among others.

The indication for adrenalectomy is well established in two situations: in functioning tumors and suspicion of malignancy[1]. The hormonal profile of the tumor should always be investigated, regardless of the presence or absence of clinical manifestations and the size of the tumor. Recent studies have demonstrated that approximately 20% of patients with adrenal incidentaloma have some form of subclinical hormonal imbalance and may represent a population at greater risk of metabolic and cardiovascular disorders[1]. This assessment is particularly important in cases that will be submitted to surgical treatment since it brings clinical and anesthetic implications, especially related to systemic arterial pressure and hydroelectrolytic balance.

There is a consensus that all functioning cortical or medullary tumors must be surgically removed. With respect to non-functioning tumors, a biopsy does not bring any benefits, except in rare situations of bilateral tumors and suspected systemic or secondary disease.

The suspicion of malignancy is linked to tomo-

graphic findings. There is a direct correlation between the size of the tumor and the potential for malignancy. The adrenocortical carcinomas represent 2% of the tumors smaller than 4 cm, 6% of the tumors between 4.1 and 6 cm and 25% of the tumors larger than 6 cm[2]. Thus, lesions smaller than 3 cm are usually benign adenomas and are not necessarily removed but can be monitored. Tumors larger than 6 cm are normatively operated; those of intermediate size (3 to 6 cm) must be considered individually, and the presence of other signs of malignancy (heterogeneity, calcifications, rapid growth, low body fat percentage, among others) must be observed and can be further investigated radiologically (magnetic resonance imaging) and monitored serially[2]. Therefore, the adrenocortical carcinomas are generally large (>6 cm) and exhibit a heterogeneous radiological pattern and a great tendency of involvement of adjacent structures. Since these are potentially aggressive tumors, adrenocortical carcinomas should be treated radically, with en bloc resection of the tumor and adjacent structures affected associated with regional lymphadenectomy[3].

Laparoscopy has been considered, for some time, the preferential treatment for benign diseases of the adrenal glands. As the benefits of the laparoscopic access were demonstrated and the technical improvement was consolidated, indications for this route of access expanded and absolute contraindications reduced[3,4].

TECHNICAL ASPECTS

Preoperative preparation

Patient preparation for the surgical procedure is vital and must be multidisciplinary, involving, whenever possible, the urologist, endocrinologist, and anesthesiologist. Functioning tumors require additional care, relating, in particular, to the effect of hormonal overload-deprivation. Knowledge of the physiopathology of adrenal glands, as well as the effects of hormonal overload, is indispensable.

Basic principles for adrenal surgeries

- Appropriate and individualized preparation.
- Minimal manipulation of the gland to prevent rupture and tumor implant.
- Early ligation of the adrenal vein, when possible, which must precede the manipulation of the gland.

Operative technique

The technique of laparoscopic adrenalectomy has been widely described[5,6]. Briefly, the primary steps of the technique are listed below.

Immediate preoperative cares

- Antimicrobial chemoprophylaxis during anesthetic induction.
- Orogastric or nasogastric intubation, to be removed immediately upon completion of the procedure. Dispensable in procedures performed using retroperitoneoscopy.
- Urinary catheterization delay.

Patient positioning

- Transperitoneal procedure.
- Lateral decubitus at 45 to 60 degrees opposite to the gland that will be operated, ipsilateral upper limb elevated and attached to the arc of the operating table and the contralateral next to the body. The surgical team is positioned facing the patient's abdomen.

Retroperitoneal procedure

- Total lateral decubitus. The surgical team is positioned facing the patient's back.
- Pads should be placed to protect surfaces from friction, and the patient must be positioned on the table with adhesive tape.

ACCESS TO THE WORK AREA

Transperitoneal

The iliac crest, the costal margin, and umbilical scar are used as reference points for the introduction of the trocars.

Usually, four 10/11 mm trocars are used (umbilical scar, the middle line below the xiphoid appendix junction, costal margin, and point between the umbilical scar and the anterior superior iliac spine). In slim patients and children, two 10/11 mm and two 5 mm trocars are used.

A puncture is performed using a Veress needle in the median line, at the edge of the umbilical scar or the midclavicular line on the side that will be operated. The initial access must always be secure, so in special situations, the Veress needle should be replaced by a Hasson cannula or a balloon trocar inserted by minilaparotomy.

Retroperitoneal

The iliac crest, the 12th rib, and the paravertebral muscles are used as points of reference. The trocars can be introduced by direct vision or guided by the index finger, once you have created the surgical space.

Incision of approximately 2 cm below and immediately preceding the 12th rib (inferior lumbar Petit's triangle), followed by perforation of the lumbodorsal fascia, introduction of the index finger into the retroperitoneal region to create space by finger dissection. At this stage, the psoas muscle and the lower pole of the kidney must be digitally recognized. The use of a Gaur balloon is optional.

Insufflation

From the initial phase of the procedure until the trocars are completely introduced, the intracavitary pressure can be maintained between 15 and 18 mmHg. After the access is completely obtained, the pressure can be reduced to 12 mmHg.

STEP BY STEP PROCEDURE

Transperitoneal

Medial release of the colon - exposure of the anterior renal fascia and the large vessels. In proceedings on the right side, the colon usually does not need to be mobilized. Whereas on the left side, a broad mobilization of the colon from the splenic flexure up to the sigmoid is always necessary. For the medial mobilization of the spleen and the tail of the pancreas, which is not always indicated, it is necessary to make an incision on the parietal peritoneum cranially to the left subphrenic space, up to the diaphragm. This extensive mobilization allows gravity to move the left colon and the tail of the pancreas medially.

Dissection of the medial face of the gland — on the right side, the dissection should be performed next to the inferior vena cava, through the incision of the peritoneal reflection on the right edge of the vein. Then, the right adrenal vein, tributary of the inferior vena cava, is dissected with sections between metal or polymer clamps. This initial medial dissection favors the identification of the adrenal vein and its junction with the inferior vena cava when the gland receives lateral traction.

On the left side, the inferomedial portion of the gland is the starting point. The left renal vein is identified, more specifically its upper edge, where the left adrenal vein is identified and sectioned between clamps. The left adrenal gland is in close contact with the vessels of the renal pedicle, which requires greater attention during the inferomedial dissection.

Retroperitoneal

After the medial dissection and ligation of the adrenal vein, an incision is made on the renal fascia, and the gland is separated from the surface of contact with the upper pole of the kidney. Finally, the superior and lateral edges are separated from adjacent structures by means of delicate dissection, cauterization, and section of small arterial, venous and lymphatic vessels.

Removal of the specimen

Is done with the aid of an extraction sac. The entire piece is removed and should not be morcellated.

Partial adrenalectomy

Partial adrenalectomy requires the following technical steps, in addition to those already described:

Dissection of the gland, preferably without the ligation of the adrenal vein; section of the region compromised, with a margin of safety, by means of a 35 mm linear vascular stapler and incision with an ultrasonic scalpel or polymer clamps; review of hemostasis in recalcitrant part of the gland.

METHOD

We evaluated the therapeutic role of laparoscopic adrenalectomy based on a systematic review of the literature with no time restriction on the Medline database using the following descriptors: (Adrenalectomy OR adrenalectom*) AND (Laparoscopy OR laparoscop* OR endoscop* OR Robotic Surgical Procedures OR robotic*) AND (Random* OR Comparative study OR Comparative studies OR systematic[sb]). Were retrieved 473 papers, and of these, 16 were selected to answer the clinical question: Is laparoscopic adrenalectomy effective and safe in the treatment of surgical diseases of the adrenal gland?

The "Measurement Tool to Assess Reviews" (Amstar)27 was used to evaluate the quality of the systematic reviews. This tool provides a global quality rating on a scale from 0 to 11, in which 11 represents a review of the highest quality. Quality categories were determined as follows: low (0 to 3 score), medium (4 to 7 score) and high (8 to 11 score). SRs of low and medium quality were excluded.

The recommendations presented by the authors of the review had their strength estimated according to the Oxford/Grid.

RESULTS

Oncologic effectiveness of the laparoscopic access

To this moment, there have been no randomized controlled clinical trials (RCT) to guide or support the use of laparoscopic resection in adrenocortical carcinoma or malignant pheochromocytoma.

Adrenal carcinomas are rare tumors, with an incidence of 1-2 new cases per million people every year, representing 0.05% to 0.2% of malignant neoplasms. Most adrenal tumors are sporadic; however, some genetic syndromes increase the risk of adrenal tumorigenesis. The treatment of adrenal carcinoma includes resection of the primary tumor, resection of metastases and systemic chemotherapy. In the presence of disseminated disease, the answer to any form of treatment is very bad.

Walz et al. reported a prospective series of 560 retroperitoneal adrenalectomies, including tumors of up to 10 cm. Although technically challenging, it is possible to remove tumors of 6-7 cm via laparoscopic access; however, tumors larger than 6 cm are most often malignant[7,8](B).

A systematic review (SR) with meta-analysis, including nine historical cohort studies, compared laparoscopic and open adrenalectomy in 797 patients with adrenocortical carcinoma. Tumors treated with laparoscopy were smaller (p<0.001) and exhibited a greater proportion in the stadium (I or II) (p<0.001), in relation to tumors treated with open adrenalectomy. Laparoscopic adrenalectomy was associated with a shorter hospitalization time (mean difference (MD) -2.51 days, 95% CI -3.31 to -1.72, p<0.001) in the analysis of four studies with 266 patients; increased peritoneal carcinomatosis in recurrence (risk ratio [RR] 2.39, CI 95%: 1.41-4.04, p=0.001) in the analysis of five studies with 408 patients; non-significant decrease in mortality due to cancer (risk ratio [RR] 8%, 95% CI -17% to 1%) in the analysis of six studies with 499 patients. There was no difference between the two groups for postoperative complications in the analysis of four studies with 266 patients and the rate of recurrence in the analysis of nine studies with 797 patients; the results were limited by high heterogeneity[9](A).

Therefore, laparoscopic adrenalectomy is not the preferred approach for masses that are primary adrenal cancer[9](A).

Laparoscopic surgery in relation to perioperative parameters

A historical cohort study included 80 patients (mean age of 48 years) undergoing lateral transperitoneal laparoscopic adrenalectomy (n=40) or lateral transperitoneal open adrenalectomy(n=40) for removal of functional adenomas and adrenal masses <6 cm, with a mean follow-up time of 30 months. The patients in each group were compared regarding age, endocrine disorder, body surface area, side and size of the tumor. Aldosterone-producing adenomas were present in 41% of the cortisol-producing adenomas in 16%, pheochromocytomas in 19%, and non-functioning adenomas in 24%. Laparoscopic surgery, compared with the open approach: increased the average time of surgery (147 *vs.* 79 minutes; p<0.05) and reduced the use of analgesics in the postoperative period (average of doses = 2.9 *vs.* 5.2; p<0.05), the length of hospital stay (12 *vs.* 18 days; p<0.05), as well as the rate of late complications (pain, dysesthesia, muscle weakness = 0% *vs.* 47.5%, p < 0.05). There was no difference in time for oral ingestion, time for ambulation, and intraoperative or early complications. We conclude that the laparoscopic access presents superior results for peri- and postoperative parameters, such as a reduction in the use of analgesics, shorter time of hospital stay and late morbidity, when compared with the open access[10](A).

The choice between trans and retroperitoneal access for surgical procedures of the adrenal gland

A SR with meta-analysis of two small randomized clinical trials (RCTS) and 20 observational studies compared the retroperitoneoscopic and laparoscopic adrenalectomy in 1,966 adult patients with non-malignant adrenal tumors. A total of 709 patients underwent retroperitoneoscopic adrenalectomy (lateral or posterior), and 1,257 had laparoscopic adrenalectomy. Retroperitoneoscopic surgery was associated with a reduction in hospital stay time in the analysis of 14 studies and a total of 829 patients; however, this result is limited by high heterogeneity. There was no difference between the two procedures for the outcomes of mortality, hemorrhage, the overall risk of complications, conversion to open adrenalectomy, time for oral ingestion and time to ambulation[11](A).

Two studies, one RCT and a historical cohort, published retrospectively and not included in this SR, also compared access routes.

In the RCT, 65 adult patients with benign adrenal tumors ≤7 cm were randomized to posterior retroperitoneoscopic adrenalectomy or lateral transperitoneal adrenalectomy and followed-up for five years. The posterior retroperitoneoscopic adrenalectomy improved perioperative outcomes (intraoperative blood loss, pain during 48 postoperative hours, less time for oral ingestion, ambulation and hospital stay [p<0.001 for each], reduction of nausea [p=0.029]), in comparison with the lateral transperitoneal laparoscopic adrenalectomy. Posterior retroperitoneoscopic adrenalectomy reduced surgical time (50.8 minutes *vs.* 77.3 minutes; p<0.001) and the risk of incisional hernia (0% *vs.* 16.1%, p=0.022), NNH 6 for lateral approach, there were no surgical conversions[12](A).

In a retrospective cohort study, 251 patients (mean age 52 years) had 279 retroperitoneal laparoscopic adrenalectomies with the retrograde (n=107) or anterograde approach (n=172). A total of 38% had Cushing's syndrome, 27% Conn syndrome, 16% pheochromocytoma, and 11% non-functioning adenoma. The retrograde approach, in comparison with the anterograde, reduced: surgical time (101 minutes *vs.* 140 minutes; p<0.001), postoperative consumption of morphine (9.4 mg *vs.* 15.7 mg; p=0.026) and permanence in the intermediate unit (1.3 days *vs.* 1.8 days, p= 0.001). There was no difference in the rates of pre- or postoperative complications, as well as in mortality between the two groups[13](A).

Therefore, the choice between the trans and retroperitoneal approaches must be individualized and depends on specific situations related to the patient (obesity, previous surgery on the upper floor of the abdomen, among others), and the preference of the surgeon.

Indication for partial adrenalectomy

A "before and after" study included 93 patients (mean age of 38 years) with benign unilateral adenoma and hypercortisolism who had partial adrenalectomy and were followed-up for ≥1 year. The surgery was performed via retroperitoneal laparoscopic approach in 60 patients (65%), and the other 33 (35%) underwent open surgery. Six patients underwent conversion to total adrenalectomy due to recurrent disease or tumor size ≥5cm. All patients received therapy with postoperative cortisone for an average of 6.2 months. Surgery was associated with the resolution of hypercortisolism in 98% of patients (91 out of 93), hypertension in 53% (34 out of 64), diabetes in 26% (7 out of 27), obesity (body mass index ≥ 30 kg/m^2) in 58% (28 out of 48). Partial adrenalectomy via retroperitoneal laparoscopic approach, compared with the open adrenalectomy, demonstrated: (average) time of surgery (80 minutes *vs.* 125 minutes; p<0.01), intraoperative complications (1.7% *vs.* 9.1%; p=not reported) and length of hospital stay (7 days *vs.* 11 days - mean - p<0.01)[14](B).

One RCT compared partial adrenalectomy (n=104) *versus* total adrenalectomy (n=108), via retroperitoneal laparoscopic approach, in 212 patients with unilateral aldosterone-producing adenomas (2 cm on average); those with previous adrenal surgery on the same side were excluded. Both techniques were similar in the functional and perioperative parameters (surgical time, length of hospital stay, improvement of hypertension in up to eight years [NNT = not significant])[15](A).

It is concluded that the partial laparoscopic retroperitoneal adrenalectomy is effective and safe in patients with unilateral benign adenoma and hypercortisolism.

Adrenalectomy for patients with subclinical Cushing's syndrome

A significant portion of adrenal adenomas produce small amounts of cortisol autonomously, which are insufficient to cause the classical stigmata of Cushing's syndrome, but sufficient to determine subtle alterations in the hypothalamic-pituitary-adrenal axis. This clinical condition is known as subclinical Cushing's syndrome.

In a small RCT, without direct comparisons, 45 patients (mean age of 64 years) with subclinical Cushing's syndrome (SCS) and adrenal incidentaloma (3.5 cm on average) were randomized to receive lateral transperitoneal laparoscopic adrenalectomy or the conservative approach and were followed-up, on average, for 7.7 years. In the surgical group, diabetes mellitus normalized or improved in 62.5% of patients (5 out of 8), hypertension in 67% (12 out of 18), hyperlipidemia in 37.5% (3 out of 8), and obesity in 50% (3 out of 6). No change in bone parameters was observed after surgery in SCS patients with osteoporosis. On the other hand, some complications of DM, hypertension, and hyperlipidemia were ob-

served in patients who underwent the conservative treatment[16](B).

Laparoscopic adrenalectomy in pheochromocytoma

Most of the times, pheochromocytoma is a non-familial sporadic tumor. However, it can present itself as a genetic disease, with an autosomal dominant inheritance of high penetrance, occurring in isolation or associated with other pathologies.

In patients with pheochromocytoma, laparoscopic adrenalectomy can be as secure as open adrenalectomy, reducing the length of hospital stay, in an analysis including a small RCT and two retrospective cohort studies.

In the RCT, 22 patients with sporadic pheochromocytoma (non-familial) were randomized for laparoscopic *vs.* open adrenalectomy. The length of hospital stay, on average, was five days in the laparoscopic group *vs.* eight in the open approach group ($p<0.05$). There was no difference in the number of patients with hypertensive peaks during the intraoperative period or on the number of hypertensive peaks per patient[17](B).

In the first retrospective cohort, 44 patients underwent surgery for pheochromocytoma. The perioperative results of 30 laparoscopic surgeries (LA) were compared with 14 open surgeries (OA). The laparoscopic adrenalectomy group presented a smaller size of tumor (3.9 cm *vs.* 5 cm, $p<0.05$), the laparoscopic surgery reduced the length of hospital stay (median of 3 days for LA *vs.* 6 days for OA; $p<0.05$), there was no difference between the groups for the outcomes of surgery time, rate of postoperative complications, intraoperative hypertensive episodes, intraoperative complications related to hypertensive peaks, and risk of recurrence (duration of follow-up not reported)[18](B).

The second retrospective cohort compared to laparoscopic adrenalectomy for pheochromocytoma in seven patients *vs.* open resection in nine patients. Laparoscopic adrenalectomy compared with the open approach reduced: episodes of hypertension per procedure 1 *vs.* 2 ($p=0.008$), number of patients who needed vasoconstrictor drugs 2 *vs.* 8 ($p=0.035$), length of hospital stay (median of 3 days *vs.* 6 days; $p= 0.001$), and number of patients who needed postoperative opioid 1 *vs.* 9 ($p=0.001$). There was no difference in perioperative complications between both groups[19](B).

Laparoscopic adrenalectomy is an option in the treatment of pheochromocytoma in the sporadic form (non-familial).

Robotic adrenalectomy

A systematic review of nine studies (a small randomized study and eight observational studies) compared robotic and laparoscopic adrenalectomy in 600 patients with adrenal masses. Robotic adrenalectomy compared with laparoscopic reduced: length of hospital stay (mean difference in days [MD] = -0.43 95% CI -0.56 to -0.3, $I^2 = 88\%$), bleeding (MD = -18.21 ml, CI 95% -29.11 ml to -7.32 mL; $I^2 = 90\%$). There was no difference in the rate of complications (ARR = -0.04; 95% CI = -0.07 to 0.0; $p=0.05$; $I^2=0\%$), as well as the conversion rate (odds ratio [OR] = 0.82; 95% CI = 0.39 to 1.75; $I^2=0\%$) or time of surgery (MD = 5.88 min.; 95% CI = -6.02 to 17.79; $I^2=96\%$)[20](A).

A SR with recent meta-analysis included 13 studies that compared robotic and laparoscopic adrenalectomy. Robotic adrenalectomy was associated with a longer surgical time (OR = +15,60, IC95% +2.12 the +29.08; $I^2=77.4\%$), but a shorter length of hospital stay (OR = -0.40, 95% CI = -0.64 to -0.17; $I^2=78.3\%$). There was no difference in terms of intraoperative and postoperative complications, mortality and conversion rates[21](A).

The high heterogeneity (I^2) should be considered in the analysis of the results of both meta-analyses.

Robotic adrenalectomy is a therapeutic option; however, studies show results with minimal clinical significance.

Laparoendoscopic single site (Less)

A systematic review with meta-analysis including retrospective studies, with a total of 443 patients, compared to Less-AD and conventional laparoscopic adrenalectomy (171 patients in the Less group and 272 in the adrenalectomy group, in a total of nine studies). There was no significant difference in the estimated loss of blood, time for resuming oral intake and length of hospital stay between the two groups. Less-AD patients had a postoperative pain score based on the visual analogue scale significantly lower in comparison with the LC-AD group, but with a longer operative time. Both groups had comparable scores of cosmetic satisfaction. The two groups had a comparable rate of complication, conversion, and transfusion[22](C).

Less-AD can be considered an alternative to con-

ventional laparoscopic adrenalectomy but requires further studies[22](C).

Laparoscopic adrenalectomy in patients with previous abdominal surgery

A retrospective cohort study including 246 patients with laparoscopic adrenalectomy showed that there was no difference in the time of surgery, intraoperative blood loss, and the rate of perioperative complications in patients with previous abdominal surgery, compared with patients with no previous abdominal surgery[23](A).

RECOMMENDATION

- Laparoscopic adrenalectomy is not the preferred approach for masses that are primary adrenal cancer. (A)
- Laparoscopic access presents superior results for peri- and postoperative parameters, with a reduction in the use of analgesics, shorter time of hospital stay and late morbidity, when compared with open access. (A)
- The choice between the trans and retroperitoneal approaches must be individualized and depends on specific situations related to the patient (obesity, previous surgery on the upper floor of the abdomen, among others), and the preference of the surgeon. (A)
- Partial laparoscopic retroperitoneal adrenalectomy is effective and safe in patients with unilateral benign adenoma and hypercortisolism. (A)
- There are benefits in the surgical treatment (laparoscopic) for reducing the risk of metabolic syndrome (glucose intolerance), hypertension and dyslipidemia in patients with subclinical Cushing's syndrome. (B)
- Laparoscopic adrenalectomy is an option in the treatment of pheochromocytoma in the sporadic form (non-familial). (B)
- Robotic adrenalectomy is a therapeutic option; however, studies show results with minimal clinical significance. (A)
- Less-AD can be considered an alternative to conventional laparoscopic adrenalectomy but requires further studies. (C)
- Prior abdominal surgery is not a contraindication for laparoscopic adrenalectomy. (A)

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POINT OF VIEW

Effects of psychological problems on surgical outcomes

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http://dx.doi.org/10.1590/1806-9282.65.5.586

SUMMARY

Surgeons are becoming aware that surgical outcomes are not only based on technical skills. The impact of psychological problems on outcomes must be studied from both the patient's and the health care provider's viewpoint. Psychological problems may affect up to 20% of the population, with almost half of them non-treated. Surgeons have to deal with a significant number of patients with psychological problems, which affect surgical outcomes changing how symptoms, results and side effects are interpreted. Surgeons also face psychological problems at a significant rate. Although there are no studies on the effect of chronic psychological problems of the surgeon on outcomes, in simulated scenarios, acute stress usually leads to worse performance. Some initiatives can be implemented to improve outcomes based on the effect of psychological problems.

KEYWORDS: *surgery; treatment outcome; mental disorders; burnout, professional*

INTRODUCTION

Surgeons are becoming aware that surgical outcomes are not only based on technical skills. Thus, current surgical literature is open to multidisciplinarity, perioperative care, analysis of surgical team cognition and non-technical skills, among others. The impact of psychological problems on outcomes is also noteworthy from both the patient's and the health care provider's viewpoint.

Effects of psychological problems on surgical outcomes – Patients

The first question to be answered is how many of our patients have psychological problems. A survey in a large metropolitan area showed a prevalence of minor psychiatric disorders (anxiety/depression) in 20% of the population[1]. This figure varies according to geographic location, age, and socioeconomic status, but remains close to the 15 to 20% rate[2-4]. Moreover, a significant number of individuals have a non-diagnosed or non-treated status. In the US, the prevalence of mental disorder was 18% in 2016, but only 43% received some treatment, according to the National Institute of Mental Health. Thus, surgeons have to deal with a significant number of patients with psychological problems.

The second question is how the patient's psychological problems affect surgical outcomes. First, they change how symptoms are interpreted. Psy-

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DATE OF ACCEPTANCE: 07-Oct-2018
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chological problems may lead to hypersensitivity and hypervigilance. These two conditions may be part of the clinical presentation of the psychological problem, but there is also a molecular relationship between mental disorders and pain modulation[5]. Second, they affect the way results are interpreted. Patients may suffer from the *nocebo phenomenon*, defined as when a patient experiences adverse side-effects that are not a direct result of the proposed treatment[6]. Side effects, even irrelevant symptoms, of operation may be disastrous, and persistent unrelated symptoms may prevent expectations from being fulfilled.

The deterioration of surgical outcomes due to psychological problems has been studied in functional surgical diseases such as gastroesophageal reflux disease (GERD). Velanovich et al.[7] showed a decrease in satisfactory outcomes after a fundoplication from 95% to 11% in the presence of a psychiatric disorder. Outside the functional disorders in which a psychological problem could intuitively have more influence, psychological status also plays a role in the recovery from different types of operations in terms of pain perception, return to work, and quality of life[8]. Psychological problems seem to be detrimental even to oncological survival[9].

Effects of psychological problems on surgical outcomes – Surgeons

If we ask the same question as we did for patients, of how many surgeons have psychological problems, the first thing that comes to most of our minds is the estimate that surgeons are the 5th career with the highest proportion of psychopaths[10]. Is this caused by a peculiar "surgical personality" or surgeons do have psychological problems in a higher proportion? The surgical personality does seem to exist. Surgeons have higher levels of conscientiousness, agreeableness, openness, and neuroticism than non-surgeons[11]. Surgeons, however, are prone to psychological problems as well. Minor psychiatric disorders are diagnosed on 16-37% of surgeons[12]. Burnout is a serious problem that has been extensively studied. It is "a syndrome of emotional exhaustion and cynicism that occurs frequently among individuals who do people work of some kind"[13]. Burnout among surgeons is increasing in incidence, with a rate of 53% in 2014[13]. The scenario keeps getting worse. Alcoholism among surgeons reaches 15%[14], and suicidal ideation ranges from 6% in the US to 18% in Italy[15,16].

In regards to the second question, whether surgeons' psychological problems affect surgical outcomes is still debatable. Acute stress and stressors, such as sleep deprivation, certainly affect technical performance[17]. To the best of our knowledge, there are no dedicated studies on chronic psychological problems and surgical outcomes. Several studies, however, show that surgeons are profoundly affected by errors[18].

A third question arises when one inquiry if it is possible to select better psychologically prepared surgeons. We asked past and present surgical residents in regards to attitudes, experiences during training, and professional expectations to find less professional satisfaction among the present residents[19,20]. The decreased satisfaction with work, which is characteristic of the generation Y[21], may increase the level of burnout and probably of minor psychiatric disorders. Unfortunately, a good tool to select successful surgical residents is not yet available[22].

PREVENTION

Some initiatives could improve outcomes based on the effect of psychological problems (Figure 1).

In regards to the patient's psychological problems, the use of scores or questionnaires to diagnose psychological problems is restricted by limitations of the available tools and ethical aspects. Nevertheless, long conversations are necessary to understand the expectations of patients concerning outcomes and to express possible side effects. Patients must be carefully selected for adequate procedures. Finally, multidisciplinary care is essential since surgeons usually are not good for handling patients with psychological problems.

From the surgeons' perspective, they must take good care of their wellness, search for mentors[13], and learn how to deal with errors and adversities. In es-

FIGURE 1: IMPROVEMENT OF OUTCOMES BASED ON THE EFFECT OF PSYCHOLOGICAL PROBLEMS

Patients	Surgeons
Minor psychiatric disorders diagnosis (scores)	Care for personal wellness
Long conversations	Search for mentors
Careful selection for procedures	Learn how to deal with errors and adversities
Multidisciplinary care	

sence, they can do what they like but also need to like what they have to do and be resilient. Curiously, resilience was the theme of 3 presidential addresses from 3 different surgical societies[23-25]. In all 3, resilience was claimed as a desirable characteristic to excel in surgery.

Conflict-of-interest statement

There are no conflicts of interest to report.

Conference at the International Session "Non-technical skills for gastrointestinal surgeons" at the SSAT Annual Meeting, Washington, DC, June 2018.

RESUMO

Os cirurgiões atuais cada vez mais acreditam que o bom resultado das cirurgias não são frutos exclusivos de suas habilidades técnicas. O impacto dos fatores psicológicos nos resultados das cirurgias deve ser estudado do ponto de vista tanto dos pacientes quanto dos profissionais de saúde que os assistem. Os problemas psicológicos afetam mais de 20% da população em geral, sendo que metade destes não recebe qualquer tratamento específico. Assim, os cirurgiões tratam de números cada vez mais significativos de pacientes com problemas psicológicos. Esses problemas psicológicos afetam o resultado, na medida em que alteram a percepção e interpretação dos sintomas, resultados e efeitos colaterais dos procedimentos. Por outro lado, os próprios cirurgiões têm apresentado taxas crescentes de afecções psicológicas. Embora não existam estudos que demonstrem o impacto dos problemas psicológicos crônicos dos cirurgiões na evolução dos pacientes, em cenários simulados, observa-se que o estresse agudo desencadeia um desempenho pior desses profissionais. Concluímos, dessa maneira, que medidas direcionadas à detecção e tratamento dos problemas psicológicos, tanto dos pacientes quanto da equipe de saúde, devam ser implementadas visando melhores resultados cirúrgicos.

PALAVRAS-CHAVE: *Cirurgias. Prognóstico. Transtornos mentais. Esgotamento profissional.*

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The role of endoscopic ultrasound in the staging of tracheal neoplasm: a brief review

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http://dx.doi.org/10.1590/1806-9282.65.5.589

SUMMARY

Our case report shows the complexity of dealing with tracheal tumors, highlighting the importance of the method used for staging. In this report, endoscopic ultrasound (EUS) was crucial to identify the involvement of the esophageal muscular propria in a tracheal tumor and change the surgical planning of the case.

Staging this kind of tumor represents a challenge for physicians. There is no evidence in the literature on which methods represent the gold standard for T staging.

KEYWORDS: *Tracheal Neoplasms. Neoplasm Staging. Endosonography.*

CASE

A 66-year-old male patient, a former alcoholic and smoker, and with a hypopharyngeal neoplasia's history (T4aN2bM0) was treated in 2006 with radio and chemotherapy.

He remained asymptomatic since the treatment, only under surveillance. He presented an actinic lesion in the larynx indicated by laryngoscopy. One year ago, in a routine bronchoscopy examination, a tracheal lesion in the posterior wall appeared 3cm distally from the vocal folds and measuring 1cm. Endoscopy showed no evidence of infiltration in the esophagus wall and CT with no distant metastasis. The histopathological analysis revealed that it was a keratinizing, low differentiated and invasive squamous cell carcinoma, considered a second primary tumor. In PET CT there was anomalous concentration only at the interface of the posterior wall of the trachea with the cervical esophagus.

The patient missed follow-up and returned to re-staging in April 2018, still with no complaints. An-

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DATE OF ACCEPTANCE: 10-Oct-2018
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other bronchoscopy showed 1 cm of lesion growth. This recent CT scan, likewise, showed no signs of lymph node metastasis or distant metastasis.

Firstly, through bronchoscopy, it was possible to measure the distance from the tracheal lesion to the upper dental arch. The transbronchial ultrasound (EBUS) was inserted into the trachea, and the posterior wall of this organ was identified, distorting the architecture, but apparently preserving the esophagus muscularis propria (FIGURE 1).

Subsequently, the same device (EBUS) was inserted into the proximal esophagus up to the distance of the dental arch previously measured through bronchoscopy. Through this positioning, it was possible to identify the contact of the tracheal lesion on the anterior wall of the esophagus, with an invasion of the esophagic muscular propria (FIGURE 2).

This finding was crucial in surgical management, which included a more extensive procedure, with partial esophagectomy, in addition to segmental resection of the trachea. However, the patient refused the proposed treatment and opted for exclusive radiochemotherapy.

DISCUSSION

Primary tracheal tumors are a rare type of malignant neoplasm with an incidence of 0.1 per 10,000 people per year, and more than half of them are squamous cell carcinoma. This type of neoplasia may start as an intraluminal nodule and progress to a mediastinal invasion, lymph node metastasis, or even to stenosis or tracheoesophageal fistula [1-4].

While the most common clinical presentation of this type of tumor is the presence of a tracheal mass, these symptoms often do not appear until at least 50% of the lumen diameter grows. Symptoms vary according to the location of the tumor, as well as its histological type, and may vary from hemoptoic spasms, dysphagia and hoarseness, to wheezing [5-7].

In the staging of this type of tumor, multislice CT with reconstruction is now considered the best imaging method to detect tracheal lesions in the main bronchi. It is capable of revealing polypoid lesions, focal stenoses, or thickening of the organ wall. Positron emission tomography (PET / CT) may be useful in the staging of tracheal cancer, particularly in cases of squamous cell carcinoma, helping to access the entire extent of the disease and its resectability. [7,8]

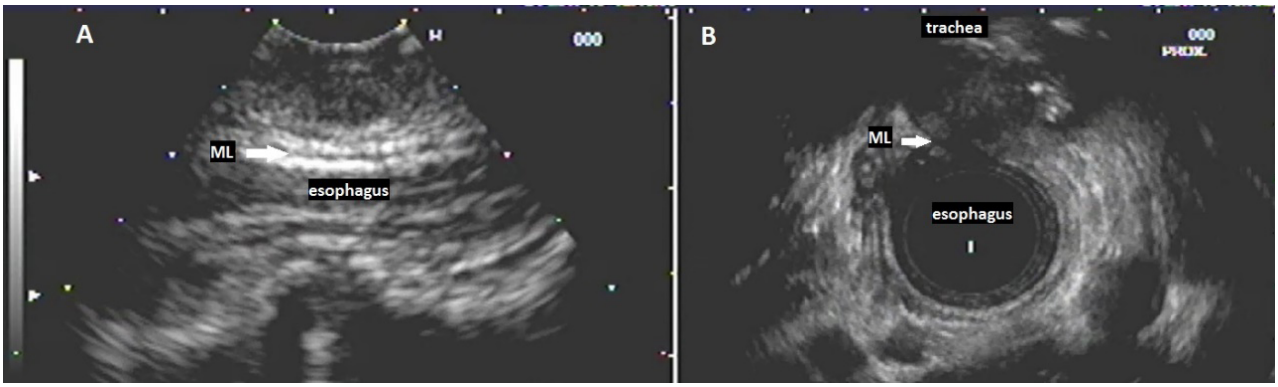

FIGURE 1: CT SCAN OF THE PATIENT WITH ARROWS INDICATING TUMOR LESION.

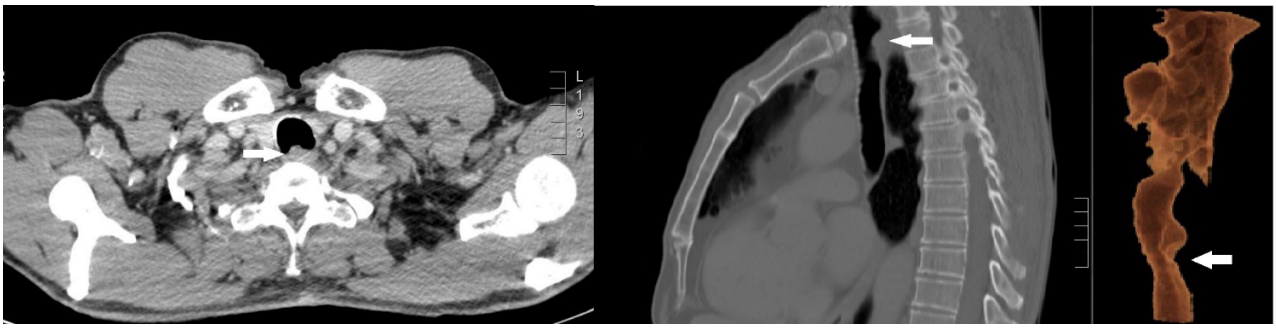

FIGURE 2: A: (EBUS IMAGE): TRACHEAL LESION AND MUSCULAR LAYER OF THE ESOPHAGUS (ML), WITHOUT INVASION CERTAINTY. B: (EUS IMAGE) TRACHEAL LESION SHOWING THE INVOLVEMENT OF THE MUSCULAR LAYER OF THE ESOPHAGUS (ML).

Some modalities are still considered minimally invasive in the diagnosis and staging of airway neoplasms. These include bronchoscopy, endobronchial ultrasound associated with a transbronchial puncture (EBUS-TBNA), transthoracic puncture (TTNA), and transesophageal echoendoscopy (EUS). In general, these procedures present a low risk of complications, but individual studies of sedation tolerance and potential clinical repercussions are still needed [9] .

According to literature, it is currently unclear what would be the best method for the loco-regional staging of primary tracheal neoplasia. It is not known whether EBUS or EUS would be the best method to define the T staging of the tracheal neoplasia of its membranous wall. According to some papers, EUS and EBUS would be complementary methods, improving accuracy in the diagnosis of mediastinal lesions[10]. No references were found in the literature that addressed the diagnosis of tracheal neoplasia by EBUS and EUS. Perhaps this is due to the rarity of this type of neoplasia and the consequent scanty studies in the area.

From our experience, EBUS may not be the best test for tracheal cancer staging when located in the membranous wall posterior), since, in this case, it was not able to show evidence of esophageal involvement. EUS, however, was able to point to the tracheal lesion clearly invading the anterior esophageal wall, with the involvement of the deepest organ (adventitious and muscular propria).

Perhaps the best form of staging for this type of tumor is through a radial device, which fills the esophageal lumen with the equipment itself. It improves acoustic coupling by reducing virtual space. However, more studies that establish the best diagnostic method to be used in this type of rare neoplasia are still needed in the area.

In this case, the finding of esophageal mucosal involvement was fundamental to modify the patient's behavior, opting for a broader surgical approach, with partial esophagectomy associated with segmental resection of the trachea.

RESUMO

Neste relato de caso mostramos a complexidade em lidar com tumores traqueais, destacando a importância do método usado para estadiamento. Neste relato, a ecoendoscopia (EUS) foi fundamental para identificar o envolvimento da camada muscular própria esofágica por um tumor traqueal e alterar o planejamento cirúrgico do caso. O estadiamento desse tipo de tumor representa um desafio para os médicos. Não há evidências na literatura sobre quais métodos representam o padrão ouro para o estadiamento T.

PALAVRAS-CHAVE: *Neoplasias da traqueia. Estadiamento de neoplasias. Endossonografia.*

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Is hepatojugular reflux a good predictor of heart failure with preserved ejection fraction?

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http://dx.doi.org/10.1590/1806-9282.65.5.592

SUMMARY

Hypertension may occur with left ventricular (LV) diastolic dysfunction, and the consequence may be symptoms and signs of heart failure (HF). Hepatojugular reflux (HJR), described as a sign of regurgitation of the tricuspid valve, may reflect structural and functional changes of the LV in the hypertensive patient. The signal may be present in the presence of HF. Case: male, 49 years old with uncontrolled blood pressure. Physical examination showed jugular turgescence, HJR, and elevated blood pressure. Complementary exams showed signs of atrial and left ventricular overload in the electrocardiogram and, the echocardiogram showed left atrium volume increase, concentric LV hypertrophy and signs of grade I diastolic dysfunction.

DISCUSSIO: *The HJR present correlates with pulmonary artery pressure and probably reflect the increase in central blood volume.*

KEYWORDS: *Hypertension. Jugular Veins/physiology. Heart failure.*

INTRODUCTION

Systemic arterial hypertension (SAH) is a multifactorial clinical condition characterized by elevated and sustained blood pressure (BP). It is often associated with functional and structural changes of the target organs, such as the left ventricular hypertrophy (LVH).[1] SAH is one of the most important factors related to congestive heart failure, and cardiac remodeling is a key mechanism of its progression.[2] LVH can lead to diastolic dysfunction of the left ventricle and is a risk factor for myocardial infarction, both important causes of ventricular systolic dysfunction. The asymptomatic dysfunction of the left ventricle (LV) may culminate with the clinical manifestation of heart failure (HF), when it exceeds a certain threshold or when other risk factors exist.[2]

The HF is classified using the ejection fraction in HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). It is known that cardiovascular morbidity and mortality in HFrEF patients improve with clinical treatment.[3] Mortality in HFpEF patients is high, and it is known that the prognosis is poor.[4] The early clinical diagnosis of HFpEF may involve the patient's prognosis. Clinical findings such as the hepatojugular reflux (HJR) may reflect structural and functional changes of the left ventricle in pa-

DATE OF SUBMISSION: 22-Jun-2018
DATE OF ACCEPTANCE: 10-Jul-2018
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tients with hypertension, and hypertension may precede HF.[5]

HJR was described by Pasteur[6] in 1885 as being a sign of tricuspid regurgitation. Subsequently, it was used in the diagnosis of congestive heart failure.[7] The signal comprises the compression of the hepatic region and the observation of the superficial veins of the neck[6], i.e., it involves the regurgitation of blood in the jugular vein while applying pressure on the abdomen.[8] During the HJR examination, one must apply pressure for 10 seconds and observe the jugular vein in the following 15 seconds[8]. When the regurgitation remains high for 10 seconds, the result is considered positive or present .[9]

HJR is present in several clinical conditions, for example, in constrictive pericarditis, in right ventricular infarction, and in restrictive cardiomyopathy. Later it was noted that it could also be present in the dysfunction of the left ventricle when the pulmonary capillary wedge pressure is greater than 15 mmHg, characterizing pulmonary hypertension caused by diseases of the left heart. Therefore, this finding may provide relevant clinical information in patients with LV dysfunction.

Echocardiography allows to evaluate the LV dysfunction and the E/e' ratio (ratio between the velocity of the initial transmitral flow and tissue Doppler recorded in the mitral valve ring) has a correlation with the left ventricular end-diastolic pressure (filling pressures) for both high pressures (E/E' >15) and normal pressures (E/E' <8)[10], providing an estimate of the filling pressures of the left ventricle in a non-invasive way. This case report aims to describe the importance of HJR in the evaluation of patients with HFpEF and discuss the possible use of this propaedeutics tool, with greater emphasis on clinical practice.

RESULTS

Clinical case report

A man, 49 years old, married, born in Paraíba and residing in São Paulo (capital) for 20 years. Blood pressure of 180x100 mmHg was observed. The patient was advised to seek medical evaluation and later return to service. He reported a diagnosis of hypertension since he was 39 years old and complained of recent onset of evening edema. He reported snoring, dyspnea on moderate exertion, fatigue, and weakness to conduct professional activities. He also reported an adequate intake of salt and denied consuming industrialized products. He also denied alcoholism and smoking.

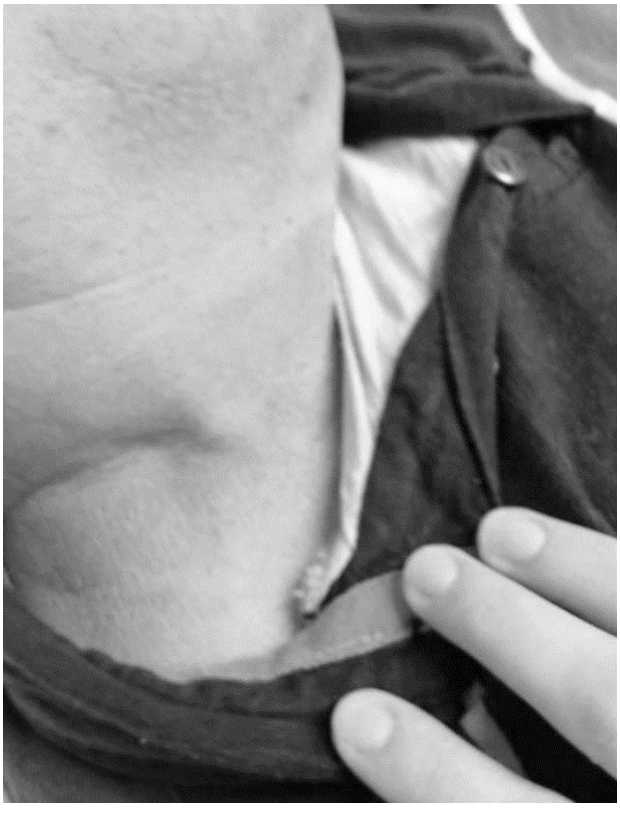
He takes hydrochlorothiazide 25 mg once a day, atenolol 50 mg once a day, amlodipine 5 mg twice a day, and losartan 50 mg twice a day.

The general physical examination showed: jugular venous distension and HJR (Figure 1) at 45º, BP 160x90 mmHg, a cervical circumference of 48 cm, an abdominal circumference of 103.5 cm, a hip circumference of 109 cm, and body mass index 34.5 kg/m^2. The special physical examination showed no changes in the respiratory and cardiovascular examination, except for the HJR. The abdominal, neurological, and muscular exams were also normal. The patient underwent laboratory exams (biochemical) that were within the normal range.

The 12-lead electrocardiogram showed sinus bradycardia, the normal axis (+60) and signs of left atrial and ventricular overload (Morris signal and Cornell index altered). The total abdominal ultrasound showed moderate hepatic steatosis (grade II) and a renal cyst on the left.

The endoscopic examination (esophagogastroduodenoscopy): intense enanthematous pangastritis (the study of *Helicobacter pylori* using urease test came back positive).

FIGURE 1. HEPATOJUGULAR REFLUX AT 45°



Polysomnography: fragmented sleep and mild obstructive sleep apnea.

The echocardiogram: an increase in left atrial volume, left ventricle with preserved dimensions, an increase in the myocardial thickness with LV mass estimated at 358 g and mass index of 186 g/m^2, characterizing concentric left ventricle hypertrophy. The left ventricular systolic function was preserved, with an ejection fraction of 70% and signs of diastolic dysfunction degree I (Figure 2).

DISCUSSION

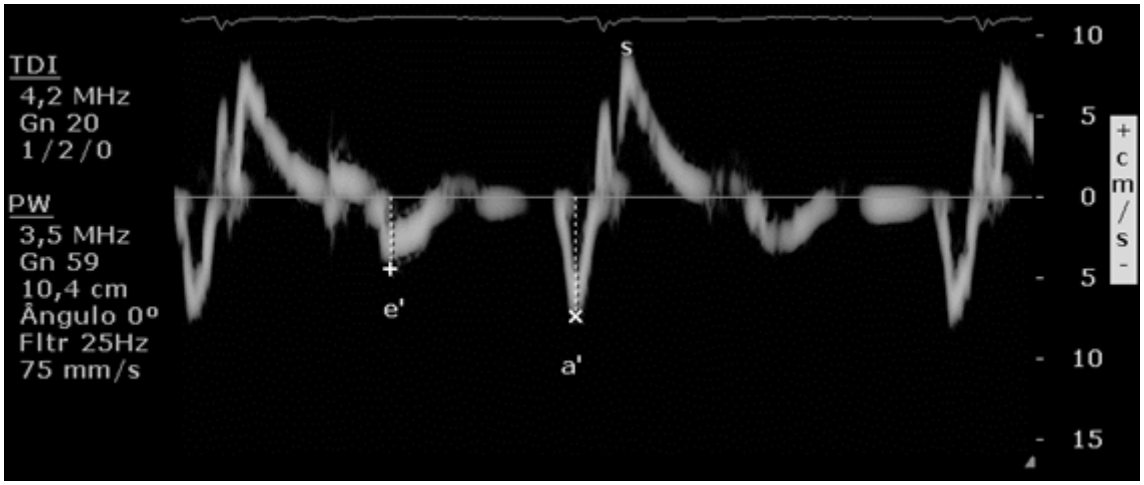
HJR may reflect structural and functional alterations of the left ventricle in hypertensive patients. According to Ewy[11], the positive HJR test correlates with the pressure of the pulmonary arterioles, being probably a reflex of the increased central blood volume. In the absence of right ventricular failure, it has been observed that in some patients with infarction of the right ventricle this test is positive and suggests a pulmonary artery pressure greater than or equal to 15 mmHg.[11]

The impairment of left ventricular function in hypertensive patients is not always of the systolic type. Quite the contrary, in most of the cases the dysfunction is diastolic. The patient presented in this study showed increased left atrial volume, left ventricle with preserved dimensions and increased thickness on the echocardiogram, characterizing concentric hypertrophy of the left ventricle. There are indirect signs of diastolic dysfunction degree I, characterized by the relationship of the E/A <0.8 waves; E<50 cm/s wave; e'<8cm/s wave (Figure 2) and the E/e'=14 ratio. These echocardiographic findings may justify the presence of HJR.

The HFpEF presumably called diastolic heart failure (DHF) is not fully defined, and there is doubt if it truly represents the clinical features of HF.[12] It is known that DHF has physiopathological characteristics similar to those of systolic heart failure (SHF), including: severely reduced exercise capacity, neuroendocrine activation and impaired quality of life.[13] In a study by Kitzman et al.[12], the pathophysiology of the DHF and SHF syndromes was evaluated. In this study, the relationship between the mass/volume of the left ventricle in DHF patients was 2.12 g/mL, and in SHF it was 1.22 g/mL. In patients with DHF, the septal wall was 13.1 mm and the posterior, 12.0 mm, while in patients with SHF they were 8.9 mm and 9.7 mm, respectively. The thickness of our patient's septum was 15 mm, and the wall thickness was 14 mm. The cut-off value for the e/a ratio to characterize diastolic dysfunction is < 0.8, and the patient presented an e/a ratio = 0.71. The patient's echocardiographic signs suggested diastolic dysfunction and positive HJR during the physical examination. On the other hand, the patient had no clinical sign or echocardiography finding suggestive of right ventricular dysfunction. This leads us to believe that the HJR present on the physical examination reflects the diastolic dysfunction of the left ventricle. This confirms the findings of the study by Kitzman et al.[12]

During the physical examination, the patient presented jugular venous distension at 45º and HJR, suggesting elevated cardiac pressures and reduction

FIGURE 2. DIASTOLIC DYSFUNCTION BY TISSUE DOPPLER



of cardiac performance. In the study by Butman et al.[13], 53 patients with HF functional class III (NYHA) with LV dysfunction were evaluated. The presence of jugular vein distension at rest or when performing the HJR maneuver resulted in the best combination of sensitivity (81%), specificity (80%), and predictive value (81%) for increased pulmonary capillary wedge pressure (≥ 8 mmHg). One limitation of this study was that the physical examination did not occur simultaneously with the hemodynamic study.

CONCLUSION

HJR was present in the physical examination of the systemic arterial hypertension stage III patient with heart failure class C according to the American Heart Association (AHA); HJR was associated with signs of LV diastolic dysfunction on the echocardiography. The findings reinforce the importance of research on HJR in clinical practice. There is a need for further studies to clarify the relationship between HJR and left HF.

RESUMO

A hipertensão pode cursar com disfunção diastólica de ventrículo esquerdo (VE) e a consequência disso pode ser sintomas e sinais de insuficiência cárdica (IC). O refluxo hepatojugular (RHJ), descrito como sinal de regurgitação da valva tricúspide, pode refletir alterações estruturais e funcionais do VE no paciente hipertenso. O sinal pode estar presente na vigência de IC. Caso: homem, 49 anos compressão arterial não controlada. Ao exame físico apresentou turgência jugular, RHJ e pressão arterial elevada. Os exames complementares mostraram sinais de sobrecarga atrial e de ventrículo esquerdo no eletrocardiograma, e no ecocardiograma foi evidenciado aumento do volume do átrio esquerdo, hipertrofia concêntrica do VE e sinais de disfunção diastólica grau I.

DISCUSSÃO: *RHJ presente correlaciona-se com a pressão da artéria pulmonar e provavelmente reflete o aumento do volume sanguíneo central.*

PALAVRAS-CHAVE: *Hipertensão. Veias jugulares/fisiologia. Insuficiência cardíaca.*

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Electrocardiographic changes in patients with acute brain injury

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http://dx.doi.org/10.1590/1806-9282.65.5.596

KEYWORDS: *Brain Injuries. Acute Disease. Electrocardiography.*

A 19-year-old man (patient 01) was admitted into the intensive care unit (ICU), in a coma, after surgical drainage of a traumatic subdural hematoma. Another patient (02), 40 years old, was admitted into the ICU for intraparenchymal cerebral hemorrhage (Fisher scale = 4; Glasgow coma scale = 4). Both patients had changes in continuous cardiac monitoring, which suggested ST-segment elevation. For diagnostic clarification, electrocardiograms (figure) were performed, which revealed Osborn waves (arrows), sinus bradycardia, longer intervals of QRS and corrected QT (QTc). Heated intravenous solution infusion and thermal blankets were used in an attempt to reverse hypothermia. However, both patients remained hypothermic and died in a few hours.

The Osborn wave, also called J-wave, was first described in 1953 as "a secondary wave that follows the S wave so closely that it seems to be part of the QRS complex"[1]. Hypothermia syndrome is predominantly described in Brazil in near-drowning cases; however, it is important to remember that acute brain injuries may evolve from it. In fact, the relationship between hypothermia and cerebral injury is controversial. The benefits of therapeutic hypothermia for neuronal protection after acute injury has been previously demonstrated in animal models, but have yet to be reproduced in humans[2]. More recently, the negative impact of spontaneous hypothermia in patients with acute brain injury began to be recognized. In these cases, the spontaneous fall in core temperature below 35°C increased mortality by 50%. Despite the absence of studies correlating Osborn waves and a worse prognosis for patients with hypothermia, QT interval prolongation is a known risk factor for cerebral vasospasm after subarachnoid hemorrhage[3]. Thus, professionals involved in the treatment of patients with acute brain injury should be able to recognize electrocardiographic changes that may indicate hypothermia and worse prognosis in these patients.

DATE OF SUBMISSION: 18-Apr-2018
DATE OF ACCEPTANCE: 27-May-2018
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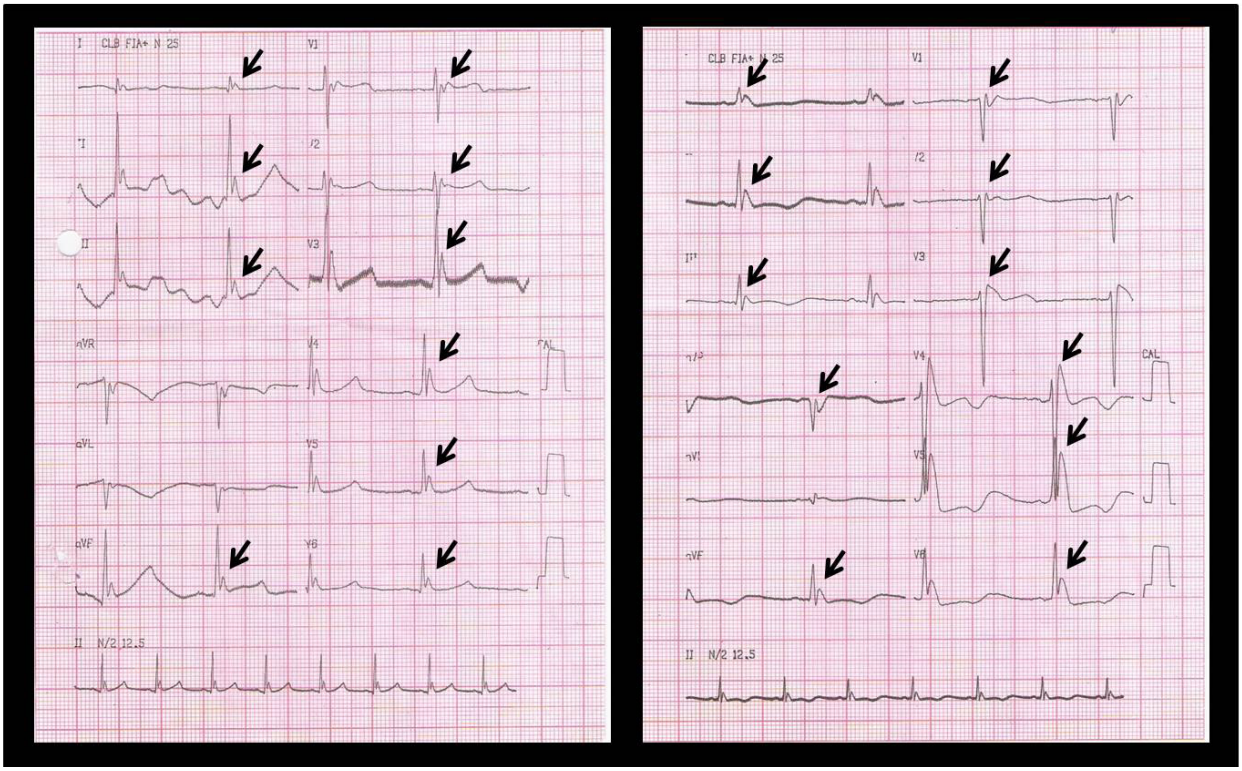

	Patient 1	Patient 2
Temperature (°C)	< 32	< 32
Heart rate (bpm)	56	46
QRS Interval (ms)	160	220
QTc Interval (ms)	502	600

PALAVRAS-CHAVE: *Lesões encefálicas. Doença aguda. Eletrocardiografia.*

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ORIGINAL ARTICLE

Emergency cerclage: gestational and neonatal outcomes

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http://dx.doi.org/10.1590/1806-9282.65.5.598

SUMMARY

BACKGROUND: *The gestational and neonatal outcomes of women with early cervical dilatation undergoing emergency cerclage were evaluated and compared with women treated with expectant management and bed rest.*

METHODS: *Retrospective analysis of pregnant women admitted between 2001 and 2017 with a diagnosis of early cervical dilatation and/or bulging membranes. Patients with a singleton pregnancy of a fetus without malformations, between 16 and 25 weeks and 6 days, with cervical dilatation of 1 to 3 cm were included; patients who delivered or miscarried within 2 days after admission were excluded.*

RESULTS: *The study enrolled 30 patients: 19 in the cerclage group and 11 in the rest group. There was a significant difference, with the cerclage group showing better results concerning gestational age at delivery (28.7 vs. 23.3 weeks; p=0.031) and latency between hospital admission and delivery (48.6 vs. 16 days; p=0.016). The fetal death rate was lower in the cerclage group (5.3% vs. 54.5%, p=0.004). Considering gestational age at delivery of live newborns, no difference was observed between the cerclage and rest groups (29.13 vs. 27.4 weeks; p=0.857).*

CONCLUSIONS: *Emergency cerclage was associated with longer latency, a significant impact on gestational age at delivery and reduction in the fetal death rate.*

KEYWORDS: *Cerclage, Cervical. Emergencies. Pregnancy, High-Risk. Premature birth. Uterine cervical incompetence.*

INTRODUCTION

Miscarriage during the second trimester occurs in less than 1% of diagnosed pregnancies[1,2] and is caused by many different etiological factors; however, approximately half of all gestational losses are due to idiopathic causes[3]. Among the etiological factors identified for these losses are antiphospholipid syndrome, genital infections, and cervical incompetence[3]. The latter is manifested as painless cervical dilatation and is a situation in which there is early uterine cervix opening and exposure of the membranes to the vaginal environment. Only 8% of patients who miscarry in the second trimester meet the criteria for cervical incompetence[3,4]. Cerclage indicated upon physical examination is recommended for pregnant women with early cervical dilatation in the absence of preterm labor[5]. Emer-

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DATE OF ACCEPTANCE: 03-Feb-2019
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gency cerclage is less effective in prolonging gestation when compared with elective cerclage and is associated with a higher rate of prematurity and complications[6,7].

Previous studies suggest that there is a benefit in performing cerclage, since these patients present a more extended period of latency until delivery, higher gestational age at birth and a lower rate of prematurity[8-11]. However, data in the literature on the outcome of pregnancies in patients undergoing emergency cerclage, as well as on the superiority of this treatment relative to expectant management are limited.

The objective of this study was to evaluate the effectiveness of cerclage in prolonging gestation and reducing the rate of extreme prematurity and neonatal complications in pregnant women diagnosed with early cervical dilatation.

METHODS

A clinical, historical cohort study was conducted at the Obstetric Clinic of the Clinical Hospital of the University of São Paulo Medical School. Data from medical records of patients hospitalized between 2001 and 2017 with a diagnosis of early cervical dilatation and/or bulging membranes were reviewed. The inclusion criteria were singleton pregnancies of a live fetus without malformations, gestational age between 16 and 25 weeks and 6 days, cervical dilatation between 1 and 3 cm and/or bulging membranes. The exclusion criteria were a latency period between admission and delivery or miscarriage less than or equal to 2 days.

Thirty patients were identified and divided into two groups: a cerclage group containing 19 patients undergoing emergency cerclage and a rest group with 11 patients receiving expectant management.

The choice of treatment was nonrandom, based on the indication of the attending physicians of the service according to a clinical, case-by-case assessment and patient agreement. In the cerclage group, surgery was performed using the McDonald technique[12] or the modified McDonald technique, in which a second stitch is performed in the cervix 1 cm below the first stitch using a no. 5 polyester suture. The stitches were removed approximately 37 weeks or earlier in the case of complications such as preterm labor, premature amniorrhexis or chorioamnionitis. In the cerclage group, 18 pregnant women were discharged over a variable period after undergoing cerclage and were readmitted due to obstetric complications or delivery. In the rest group, all patients remained hospitalized until miscarriage/delivery.

The groups were compared in regard to the following: maternal characteristics (age, obstetric history, gestational age, cervical dilatation, presence of bulging membranes at admission); gestational outcomes (gestational age at delivery/miscarriage, latency between hospital admission and delivery/miscarriage, birthweight, chorioamnionitis, placental infection, fetal death, prematurity below 24 weeks, survival to discharge); laboratory testing (leukogram and C-reactive protein (CRP) collected at admission and before delivery/miscarriage, screening for genital infections: urine culture, *Streptococcus agalactiae* culture in vaginal and anal secretions, trichomonas and yeast screening in vaginal secretion, hybrid capture for chlamydia and gonococcal culture in endocervical secretion); neonatal outcomes (birth weight, hospitalization time, 1- and 5-minute Apgar score, need for admission into the intensive care unit, need and duration of invasive mechanical ventilation, surfactant use, necrotizing enterocolitis, intracranial bleeding, neonatal death).

The quantitative variables were summarized using mean and standard deviation and compared using the nonparametric Mann-Whitney test. Qualitative variables were expressed through absolute and relative frequencies and compared using Fisher's exact test. For the variables that measure the time until an event, the Kaplan-Meier estimator and the Log-Rank test were used. A 5% significance level was adopted, and the IBM SPSS software version 20 was used.

Ethical approval: This study was approved by the Ethics Committee for Analysis of Research Projects of the Clinical Hospital of the University of São Paulo Medical School.

RESULTS

The final analysis included 19 pregnant women into the cerclage group and 11 into the rest group. Regarding the maternal characteristics, there was a significant difference between the cerclage and rest groups in mean cervical dilatation (1.8 ± 0.7 cm vs. 2.5 ± 0.7 cm, p=0.018) and rate of membranes extending beyond the external os (30.8% vs. 100%, p=0.005) (Table 1).

TABLE 1. MATERNAL CHARACTERISTICS AND GESTATIONAL OUTCOMES IN THE CERCLAGE AND REST GROUPS

	Cerclage (n=19)	Rest (n=11)	
	Mean ± SD		p-value
Maternal age (years)	28.4 ± 7.4	24.4 ± 6.1	0.145
GA at admission (weeks)	21.7 ± 2.3	21.1 ± 2.8	0.672
Dilatation (cm)	1.8 ± 0.7	2.5 ± 0.7	0.018
GA at delivery (weeks)	28.6 ± 6.9	23.3 ± 4.3	0.031
Latency (days)	48.6 ± 47.1	16 ± 19.2	0.016
Birthweight (grams)	1468.3 ± 1220.8	861.2 ± 448.8	0.418
	Absolut and relative frequencies		p-value
Nulliparity	12/19 - 63.2%	5/11 - 45.5%	0.454
Previous prematurity	5/19 - 26.3%	4/10 - 40.0%	0.675
Previous miscarriage	15/19 - 78.9%	5/11 - 45.5%	0.108
Bulging membranes	13/18 - 72.2%	10/11 - 90.9%	0.362
Membranes beyond external os	4/13 - 30.8%	7/7 - 100.0%	0.005
Chorioamnionitis	4/17 - 23.5%	4/9 - 44.4%	0.382
Placental infection	13/16 - 81.3%	7/11 - 63.6%	0.391
Delivery before 24 weeks	6/19 - 31.6%	6/11 - 54.5%	0.266
Fetal death	1/19 - 5.3%	6/11 - 54.5%	0.004
Survival to discharge	9/19 - 47.4%	4/11 - 36.3%	0.708
Cesarean section	8/19 - 42.1%	3/11 – 27.3%	0.466

GA: gestational age; SD: standard deviation

TABLE 2. NEONATAL OUTCOMES IN THE CERCLAGE AND REST GROUPS

	Cerclage (n=18)	Rest (n=5)	
	Mean ± SD		p-value
GA at birth (weeks)	29.1 ± 6.7	27.4 ± 2.3	0.857
Birth weight (grams)	1531.2 ± 1224.1	1129 ± 330.8	0.587
IMV duration (days)	17.9 ± 23.3	25.3 ± 32.7	0.6
Apgar 1´	5 ± 3.2	5.2 ± 2.3	0.94
Apgar 5´	7.1 ± 3.1	7.6 ± 0.9	0.649
	Absolut and relative frequencies		p-value
Neonatal death	9/18 - 50.0%	1/5 - 20.0%	0.339
ICU admission	14/18 - 77.8%	4/4 - 100.0%	0.554
IMV use	9/16 - 56.2%	3/4 - 75.0%	0.619
Surfactant use	8/15 - 53.3%	1/4 - 25.0%	0.582
Neonatal sepsis	8/16 - 50.0%	4/4 - 100.0%	0.117
Positive blood culture	5/10 - 50.0%	2/5 - 40.0%	0.999
Intracranial bleeding	2/17 - 11.8%	1/4 - 25.0%	0.489
Necrotizing entero-colitis	0/17 - 0.0%	1/4 - 25.0%	0.19

GA: gestational age; IMV: invasive mechanical ventilation; ICU: intensive care unit; SD: standard deviation;

The mean gestational age at delivery was 28.6 ± 6.9 weeks in the cerclage group and 23.3 ± 4.3 weeks in the rest group, p=0.031 (Figure 1). The mean latency period was 48.6 ± 47.1 days for the cerclage group and 16 ± 19.2 days for the rest group, p=0.016. Fetal death occurred in one case in the cerclage group (5.3%) compared to six cases in the rest group (54.5%, p=0.004). No differences were found for the other gestational outcomes analyzed (Table 1).

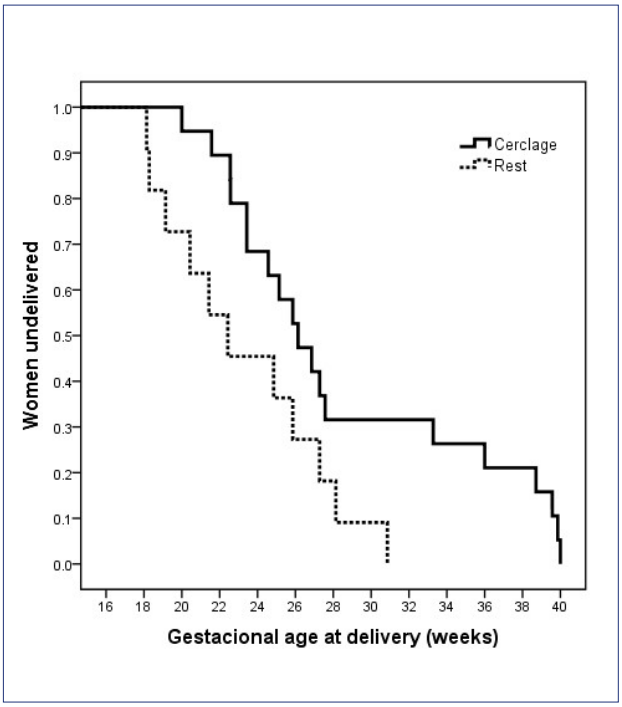
No significant differences were observed between the groups based on the results of the laboratory tests collected. There were no positive cases for chlamydia, gonococcus or trichomonas.

For the analysis of neonatal outcomes, after excluding the seven cases of fetal death, 23 live births (18 from the cerclage group and five from the rest group) were considered. The groups did not differ in gestational age at birth, birth weight, duration of invasive mechanical ventilation, or 1- or 5-minute Apgar scores. There were also no differences in neonatal death rates, need for admission into intensive care unit, invasive mechanical ventilation, surfactant use, neonatal sepsis, positive blood culture, intracranial bleeding or necrotizing enterocolitis (Table 2).

DISCUSSION

Early cervical dilatation is a rare condition, but it is associated with a high risk of extreme prematurity and, consequently, high neonatal morbidity and mortality. There are two therapeutic options for early cervical dilatation - cerclage or expectant management with rest. Among papers published since 2000 comparing the two treatments, there have only been two prospective studies[10,13]. Of these, only one was randomized[10], and it included a small number of cases (13 in the cerclage group and 10 in the control group) and twin pregnancies. The present study chose to exclude patients who delivered or miscarried within 2 days of hospital admission, considering that they would probably be cases already in a process of miscarriage or active phase of labor. The choice of treatment was nonrandom, based on the indication of the clinical specialists and agreement of the patient. Thus, the study is subject to possible selection biases. Given the difficulty of recruiting cases in the present study, a historical cohort design was chosen.

FIGURE 1



Although only patients with dilatation between 1 and 3 cm were included, there was a significant difference between the groups regarding cervical dilatation at admission and a higher frequency of bulging membranes extending beyond the external os in the rest group. Given these data, it is possible that the less severe cases were selected to receive the surgical treatment. However, the presence of bulging membranes beyond the external os was not related to a worse prognosis.

In this study, the emergency cerclage presented better gestational outcomes with a more extended latency period (48.6 vs. 16 days) and older gestational age at delivery (28.7 vs. 23.3 weeks). These results are in agreement with the literature on the subject that describes more favorable results in the cerclage group[11,14-16]. Based on these findings, the surgical approach with emergency cerclage seems to be superior to rest in prolonging gestation in patients with cervical dilatation in the second trimester. The cerclage group had a lower fetal death rate, but there was no difference in survival to discharge rates, meaning that the frequency of patients whose newborns were discharged home was equivalent between the groups (47.4% vs. 36.3%).

There were no differences between groups regarding variables related to infectious processes, including chorioamnionitis or placental infection. Additionally, no differences were identified between the groups for leukocyte count or CRP level in maternal blood. It is known that chorioamnionitis may occur subclinically, causing a delayed change in serum markers. Thus, it is difficult to identify any differences between groups for these variables. Screening for intra-amniotic infection may be a more accurate marker[17]. For this reason, some services perform amniocentesis prior to the emergency cerclage as a way to exclude subclinical chorioamnionitis, which is not part of the routine care of our service. There was no evidence of a higher frequency of genital infections in either of the groups studied. However, because of the retrospective design of the study, the analysis of the presence of genital infection was limited because not all patients were tested, especially in the rest group.

For the neonatal outcomes, data on the 23 live births during the study were evaluated. Fetal death occurred in one case among 19 in the cerclage group and six out of 11 in the rest group. Considering that delivery occurred before 24 weeks in 54.5% of the cases, the high fetal death rate in the rest group suggested that cerclage may reduce fetal risk, including late miscarriage and stillbirth, compared to resting management. However, after excluding the seven cases of fetal death, the gestational age at delivery was similar (29.1 ± 6.7 vs 27.7 ± 2.3 weeks, p=0.857), and neonatal death rate was higher in the cerclage group, but this difference was not statistically significant. Fifty percent of the newborns from the cerclage group died during the neonatal period, which may have contributed to the similar survival to discharge rates between the groups. Therefore, when fetal and neonatal deaths were considered, no differences were observed in the rate of newborns discharged to go home. The difference in the neonatal sepsis rate, 50% in the cerclage group and 100% in the control group, was noteworthy. This finding is important to consider when counseling pregnant women to undergo cerclage or bed rest because if the fetus remains alive, the gestational age at delivery will be similar despite the treatment applied.

Despite the limitations of a retrospective study with small sample size, emergency cerclage seems to be beneficial in prolonging gestation; however, no difference was found in the survival to discharge rate for newborns.

RESUMO

OBJETIVO: *Os resultados gestacionais e neonatais de mulheres com cervicodilatação precoce submetidas à cerclagem de emergência foram avaliados e comparados com mulheres tratadas com manejo expectante com repouso no leito.*

MÉTODOS: *Análise retrospectiva de gestantes admitidas entre 2001 e 2017 com diagnóstico de cervicodilatação precoce e/ou membranas protrusas. Foram incluídas pacientes com gestação única de feto sem malformações, entre 16 semanas e 25 semanas e 6 dias, com dilatação cervical de 1 a 3 cm; as pacientes que tiveram parto ou aborto dentro de 2 dias após admissão foram excluídas.*

RESULTADOS: *O estudo envolveu 30 pacientes: 19 no grupo cerclagem e 11 no grupo repouso. Houve diferença significativa, com o grupo cerclagem apresentando melhores resultados em relação à idade gestacional no parto (28,7 vs. 23,3 semanas; p=0,031) e à latência entre a admissão hospitalar e o parto (48,6 vs. 16 dias; p=0,016). A taxa de mortalidade fetal foi menor no grupo cerclagem (5,3% vs. 54,5%, p=0,004). Considerando a idade gestacional no nascimento dos recém-nascidos vivos, não houve diferença entre os grupos cerclagem e expectante (29,13 vs. 27,4 semanas; p=0,857).*

CONCLUSÕES: *A cerclagem de emergência foi associada a maior período de latência com impacto significativo na idade gestacional do parto e à redução da taxa de mortalidade fetal.*

PALAVRAS-CHAVE: *Cerclagem cervical. Emergências. Gravidez de alto risco. Nascimento prematuro. Incompetência do colo do útero.*

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ORIGINAL ARTICLE

Motivations for smoking in hospitalized patients

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http://dx.doi.org/10.1590/1806-9282.65.5.603

SUMMARY

OBJECTIVE: *To investigate the profile of motivations for smoking among inpatients at a hospital in southern Brazil.*

METHODS: *A survey study involving hospitalized smokers. The Modified Reasons for Smoking Scale (MRFSS) and its domains were analyzed according to gender and dependence degree.*

RESULTS: *The sample consisted of 85 adults (mean age 53 years), low schooling/family income, and well-adjusted in terms of gender (male= 52.9%) and clinical (48%) or surgical (47%) specialty. Most were in Action as the motivational stage (68%), with elevated smoking exposure (median = 39 years/packs) and dependence degree of nicotine (56.4%). The highest domains of the MRFSS were: Smoking Pleasure (4.34 ± 1.2), Relaxation/Tension Reduction (4.24 ± 1.2) and Dependence (3.8±1.4). Significantly, women presented higher scores, in domain Relaxation/Tension Reduction (4.7±0.9). In those with elevated nicotine dependence, higher scores were observed in the Automatism/Habit and Stimulation domains.*

CONCLUSIONS: *Smoking Pleasure and Relaxation/Tension Reduction, especially in women and Automatism, in those more dependents, are factors that should be more highlighted in future strategies for smoking cessation in inpatients.*

KEYWORDS: *Tobacco Use Disorder. Motivation. Inpatients.*

INTRODUCTION

Smoking, currently considered a pandemic by the World Health Organization (WHO), is the main risk factor for chronic non-communicable diseases such as cancer, cardiovascular and respiratory disorders.[1,2] According to a report published in 2017 by the WHO, over seven million people lost their lives annually due to the direct consumption of tobacco and secondary exposure to its pollutants.[1]

In the national population, in 2003, it is estimated that 178 thousand people aged 35 years or more died for reasons attributed to smoking.[3] Still at a national level, over the last 20 years, thanks to anti-smoking measures, there was a decline of approximately 50% in smoking prevalence in adults[4]. Pinto et al.[5] highlighted the high burden of diseases attributable to tobacco use, in Brazil, in addition to the potential bene-

DATE OF SUBMISSION: 23-Apr-2018
DATE OF ACCEPTANCE: 08-May-2018
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fits of the price increases through taxes. In 1989, the proportion of smokers in national territory reached 32%.[6] More recently, in 2016, the Surveillance System for Risk and Protective Factors for Chronic Diseases by Telephone Survey (VIGITEL) revealed that the prevalence of smoking had reached the total national average of 10.2% - 12.7% among men and 8% among women [7].

Why people smoke is an issue that has defied scholars for a long time. It is known that nicotine has psychoactive actions that result in dependence. However, the reasons that lead someone to smoke are multifaceted. Gately[8] pointed out smoking as a characteristic of different civilizations throughout history with a social, religious and, curiously, medicinal role in them. Whereas Tomkins[9], the pioneer in theories on the subject, stated that the four main reasons related to smoking are: habit, addiction, reduction of negative emotions, and reinforcement of positive emotions. Some studies have been directed toward identifying the reasons that lead an individual to cease smoking.[10,11] However, to know the profile of motivations that contribute to smoking has been shown to potentially assist in the creation of individual and collective anti-smoking strategies.[12-14]

Several instruments have been developed to evaluate the influence of psychosocial aspects on smoking.[12] Knowing these methods is the first step to draw qualified and comparative studies in this area. In 1966, the Scale of Reasons for Smoking emerged, divided into six categories: Handling, Pleasure, Automatism, Stimulation, Tension Reduction/Relaxation, and Addiction. However, it did not consider social smoking.[9] Since it was validated and considered to be adequate regarding its psychometric properties, it became the first useful tool for elucidation of the subject[15]. In the 1970s, Russel and collaborators[16] expanded the scale previously validated to add social issues related to smoking. Modified Scale of Reasons for Smoking (MRSS) was then born and originally used in France.[17] The scale was translated into Portuguese, culturally adapted and validated for use in Brazil, which made it possible to use it in national studies on smoking.[14,18] The scale has high internal consistency, stable factor structure, and temporal stability.

In recent years, specific groups of smokers have been well studied. Smoking in hospitalized patients is an example of a population often overlooked, as is withdrawal syndrome during the hospitalization period, which makes the need for a routine approach for this specific group of smokers relevant. Hospitalization allows for approaching and monitoring patients more intensely in order to transform this episode of "mandatory" tobacco interruption into a successful attempt of cessation.[19,20] Furthermore, currently, non-smoking environments have become a reality increasingly close, and they include health care units.

Until now, studies that examine the various motivations involved in smoking in hospitalized patients are unknown. In this context, considering hospitalization a window of opportunity to recognize the motivational profile is of utmost importance to understand and plan specific strategies of treatment.

With the use of a standardized and validated scale, this study aims to investigate the profile of psychosocial motivations for smoking among hospitalized patients in the University Hospital Polydoro Ernani de São Thiago of the Federal University of Santa Catarina (HU-UFSC). In addition, the reasons in the scale were analyzed according to gender and degree of dependence.

METHODS

This is a survey type of study, with a convenience sample, conducted between May 2013 and June 2014. The population studied was composed of smokers, hospitalized in the medical or surgical clinics of HU-UFSC.

Patients included were smokers, aged over 18 years, hospitalized in the HU-UFSC for more than 48 hours, who were approached to participate in the smoking cessation program. We excluded patients who were non-smokers, unable to respond to the questionnaire, pregnant or lactating women, with abuse of psychoactive substances, in treatment for severe psychiatric and neurological disorders, as well as those who refused to participate in the research.

The survey instrument was a semi-structured questionnaire with sessions broken into closed questions that included data on identification, demographics, socioeconomic scenario, hospitalization, characteristics of the current and previous smoking habit of each patient, and body mass index (BMI). We considered patients current smokers those who declared smoking at least one cigarette every day for the past six months.

We investigated the behavioral characteristics

related to smoking, including analysis of the motivational stage at the time of interview, classified using the scale by Prochaska and DiClemente[21] on Precontemplation (no intention to quit smoking for the next 6 months), Contemplation (there is awareness of the problem and intention to quit smoking, but at an undefined date - ambivalence), Preparation (there is a desire to quit smoking in the near future, within approximately 1 month, and there have been actions towards this goal), Action (the individual stopped smoking), Maintenance (there is abstinence to smoking and surveillance to prevent relapse), and Relapse (the habit or previous behavior of tobacco consumption was resumed due to failure in the maintenance of abstinence or reduction in the number of cigarettes). Depending on the degree of dependence, we considered the Fagerström Test as: Very Low (0-2); Low (3-4); Moderate (5); High (6-7), and Very High (8-10)[22].

We evaluated the patient's motivations for smoking using a previously validated instrument - the Modified Scale of Reasons for Smoking (MRSS). This scale has 21 questions, divided into seven motivational domains, namely: Dependency (questions E and S), Stimulation (questions A, H, and O), Pleasure from Smoking (questions C and J), Handling (questions B and I), Social Smoking (questions G and N), Reduction of Tension/Relaxation (questions D, K, and R) e Automatism/Habit (questions F, M, and T). To each alternative, increasing gradual weights were attributed between 1 (never) and 5 (always), with the use of a Likert scale. The mean scores of each question of the domains were considered in the analysis. The scale was applied with the aid of the interviewers.

The collection and tabulation of data were carried out by trained researchers and collaborators.

The research was approved by the Human Research Ethics Committee at the Federal University of Santa Catarina (CEPSH-UFSC), under number 245.656. The interview with data collection was performed after a detailed explanation of the study, including their objectives, risks, and benefits to the patient, who previously signed the Informed Consent Form (ICF). The behavioral and pharmacological treatment, when necessary, was made available for all patients in the study, according to current guidelines.[23]

The data were entered and analyzed using the Statistical Package for Social Sciences (SPSS) software version 22. A descriptive analysis was performed on the data of identification, demographic, socioeconomic, hospitalization, and the characteristics of the current smoking habit and progress of each patient. The mean scores per MRSS domains were calculated using the arithmetic averages of responses, first per question and after, per domains. The continuous variables with normal distribution were expressed as mean and standard deviation, while non-normal continuous variables were presented in the form of median and interquartile range 25-75% (IQR25-75). For purposes of comparison with the literature, the MRSS scores were expressed as mean and standard deviation regardless of the distribution. The categorical variables were expressed in terms of frequency and proportion. The differences between the reasons for smoking in relation to sex and degree of dependence were analyzed using the Mann-Whitney test. We considered $p < 0.05$ for statistical significance.

RESULTS

In the population studied of 85 smokers, we observed a median age of 53 years with a slight predominance of males (52.9%), mostly married or co-dwelling (52.9%), white (71.8%), with a BMI within the normal range, mostly from the city of Florianópolis (43.5%), natural of Santa Catarina (74.1%). More than half were illiterate or with incomplete primary education (54.1%) and with a median income of 1 minimum wage per capita (Table 1).

Among the patients included in the study, 41 were hospitalized in a surgical ward, 40 in a medical clinic, and 4 in the emergency. The median of hospital stay was 17 days (IQR25-75= 9 - 30). The main diagnoses of individuals were peripheral arterial occlusive disease (15.3%) and neoplasia (14.2%).

The participants in the sample began smoking early, with a median age of 15 years and a median of 37 years of exposure to tobacco. The median number of cigarettes smoked per day was 20, and the nicotine load was 39 packs/year. The nicotine dependence, according to Fargeström test, showed that over half of the individuals presented a high or very high degree of dependence (56.4%). In relation to the Prochaska and DiClemente motivational, the majority (68.2%) of the smokers were in a state of action (Table 1).

In relation to the MRSS, the average of scores of the smokers and their standard deviations in the domains are presented in Table 2. After analyzing the results of the MRSS per domain, the most relevant were: Pleasure from Smoking (4.34 + 1.2), Relax-

TABLE 1. DATA ON DEMOGRAPHICS, SOCIOECONOMIC FACTORS, AND FACTORS RELATED TO THE SMOKING HABITS OF THE POPULATION STUDIED. (GRAD, 2014)

Total	(n = 85)
Age (years)	
Mean (IQR 25 -75)	53 (45-61)
Sex n (%)	
Male	45 (52.9)
Marital status n (%)	
Married/co-dwelling	45 (52.9)
Separated/divorced	20 (23.5)
Single	11 (12.9)
Widow(er)	8 (9.4)
Others	1 (1.2)
Ethnicity n (%)	
White	61 (71.8)
Others	24 (28.2)
BMI (Kg/m^2)	
Mean (IQR $_{25-75}$)	24.4 (21.5-28.6)
Per capita income (SM)	
Mean (IQR $_{25-75}$)	1.0 (0.5-1.5)
Formal education n (%)	
Illiterate/IPE	46 (54.1)
CPE	14 (16.5)
CSE	19 (22.4)
Others	6 (7.1)
SMOKING	
Age that started	
Mean (IQR $_{25-75}$)	15 (13-17)
Exposure time	
Mean (IQR $_{25-75}$)	37 (28-46.5)
Smoking load	
Mean (IQR $_{25-75}$)	39 (24.2-74)
Degree of dependence n (%)	
Very low	6 (7.1)
Low	16 (18.8)
Moderate	15 (17.6)
High	28 (32.9)
Very high	20 (23.5)
Fagerström Test	
Mean (IQR $_{25-75}$)	6 (4-7)
Motivational stage	
Contemplation	17 (20)
Preparation	9 (10.6)
Action	58 (68.2)
Maintenance	1 (1.2)

BMI (body mass index), IPE (incomplete primary education), CPE (complete primary education), CSE (complete secondary education)

ation/Reduction of Tension (4.24 + 1.2), and Dependency (3.80 + 1.4), followed by Automatism/Habit (2.36 + 1.1), Handling(1.98 + 1.4), Social Smoking(1.81 + 1.2), and Stimulation (1.63 + 1.0). The individual responses with the highest scores were: "I light a cigarette when I am angry about something," "smoking gives me pleasure and is relaxing" and "I think cigarettes are pleasant", with, respectively, the following means 4.42 + 1.3, 4.38 + 1.2, and 4.29 + 1.4. "I smoke to keep me alert", mean 1.49 + 1.1 and "I smoke cigarettes to cheer myself up", mean 1.59 + 1.1, were less common reasons for smoking (Figure 1).

We found that the domain with the highest score among men was Pleasure from Smoking. Among women, with statistical relevance, it was Relaxation/Reduction of Tension (Table 2).

As for the degree of dependence, more than half (56.4%) of the patients presented a high to very high degree. These, when compared to those with less dependence, presented, with relevance, higher scores in the domains of Automatism/Habit (2.5 + 1.2) x (1.92 + 0.9), p=0.04 and Stimulation (1.77 + 1.1) x (1.3 + 0.4), p< 0.04. Those with high dependency cannot be differentiated from those with less dependence in the domains with higher scores: Pleasure from Smoking (4.45 + 1.1) x (4.02 + 1.5), p=0.28 and Relaxation (4.40 + 1.1) x (3.77 + 1.5), p=0.06.

No significant correlation (r > 0.5) was found between the domains and independent variables tested.

DISCUSSION

Through the use of a instrument validated for the Brazilian population, this study investigated the profile of psychosocial motivations for smoking in 85 patients hospitalized in a university hospital in southern Brazil. Additionally, we studied the MRSS domains in function of sex and degree of dependence and their possible correlations. The sample was composed of adults, white, with low formal education/family income and balanced regarding the distribution per sex and clinical and surgical specialty. The majority was in the motivational stage of Action, with high levels of nicotine load and degree of nicotine dependence. The results showed that the MRSS areas with higher scores were Pleasure from Smoking, Relaxation/Reduction of Tension, and Dependency. Significantly, the domain of Relaxation/Reduction of Tension had the highest score among women. In patients with a greater degree of dependence, we observed a significant difference in the fields Stimulation and Automatism/Habit. The main motivational domains identified, as well as the differences found in the subanalyses, can help in building a future approach for hospitalized smokers.

FIGURE 1. MEAN AND STANDARD DEVIATION OF THE SCORES OF THE MODIFIED SCALE OF REASONS FOR SMOKING PER GROUP OF QUESTIONS OF THE DOMAINS, IN DESCENDING ORDER. (GRAD, 2014)

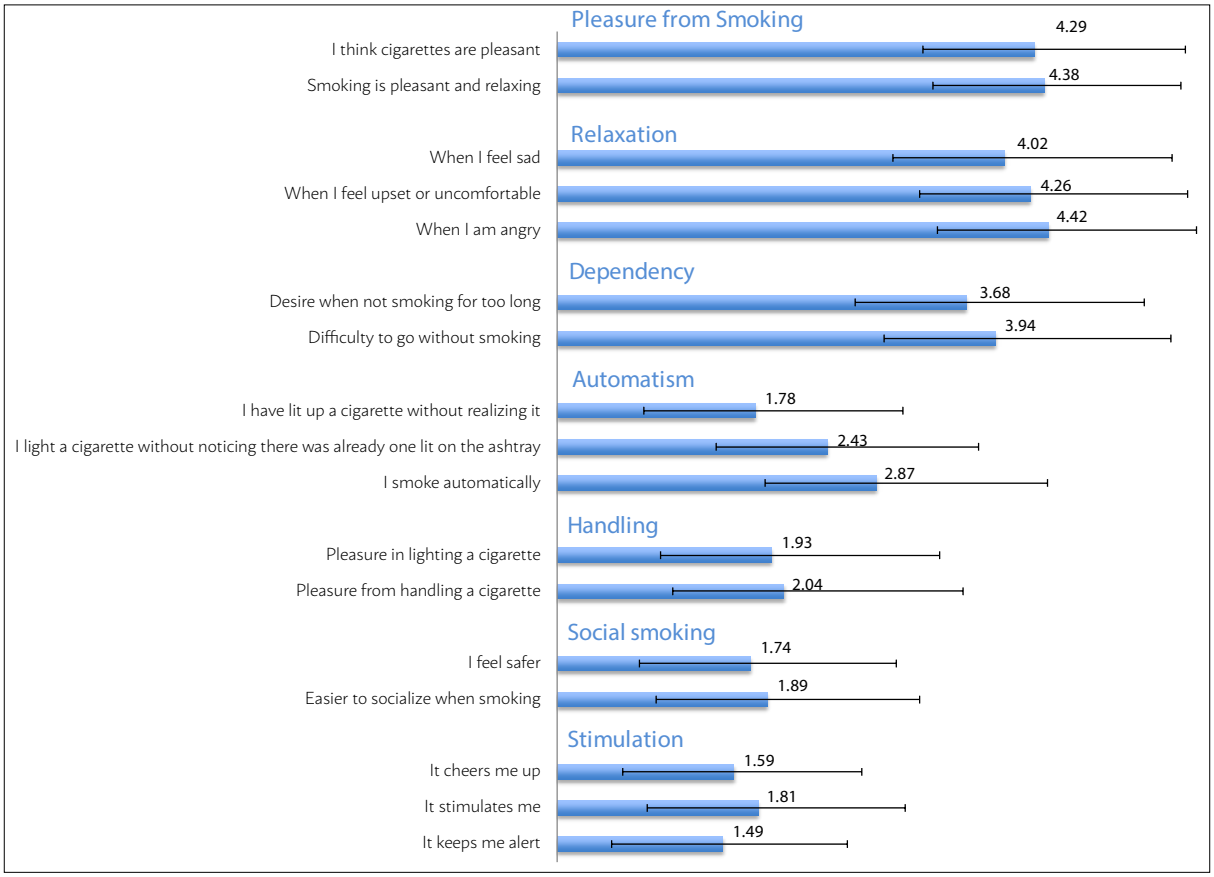

TABLE 2. MEAN SCORES FOR DOMAINS OF THE MODIFIED SCALE OF REASONS FOR SMOKING IN ALL PATIENTS HOSPITALIZED AND SEPARATED PER SEX. (GRAD, 2014)

	Total	Men	Women	P-value*
Domains	(n = 85)	(n = 45)	(n = 40)	
Pleasure from Smoking	4.34 (1.2)	4.20 (1.4)	4.51 (1.0)	0.49
Relaxation	4.24 (1.2)	3.85 (1.3)	4.67 (0.9)	<0.00
Dependency	3.80 (1.4)	3.63 (1.4)	4.01 (1.3)	0.24
Automatism	2.36 (1.1)	2.44 (1.2)	2.28 (1.0)	0.74
Handling	1.98 (1.4)	1.87 (1.4)	2.11 (1.3)	0.28
Social Smoking	1.81 (1.2)	1.70 (1.2)	1.95 (1.2)	0.24
Stimulation	1.63 (1.0)	1.49 (0.9)	1.79 (1.0)	0.10

Results were expressed as mean and standard deviation. * Mann-Whitney Test.

This is a study that involves a specific population, still little studied and often neglected, in a particular circumstance of hospitalization, in which the cessation of smoking is often imposed. In addition, this is an original study since there is a gap in the understanding of the main social and psychological reasons related to smoking in hospitalized patients. The standardization of instruments and the choice of validated questionnaires are fundamental points for data quality and reproducibility of studies on smoking. The ERPFM, already well-established in other countries, translated and with cultural identity, used by trained researchers to be applied in a homogeneous way, gives credibility to the results.

The findings of the current study are similar to those of Berlin et al.[17], in which a population of 330 adults with a high degree of dependency had the domains of Dependency, Pleasure from Smoking, and Reduction of Tension/Relaxation with the higher scores. A survey that applied the ERPFM in adult employees of the HU-UFSC with moderate dependence showed high scores in the same domains, with a predominance of Pleasure from Smoking, which also ranked high in this sample.[24]

A group of growing interest in the area of smoking is composed of adolescents and young adults since they constitute a preferential target of marketing strategies of the tobacco industry. Recently, the MRSS was applied in this age group among students

with low dependence from the Federal University of São Carlos[25] and the University of Ribeirão Preto[26], both in the interior of São Paulo, with results similar to those of this study: prevalence of Pleasure from Smoking and Relaxation/Reduction of tension. It is worth noting that the people quoted in these studies were not hospitalized, despite showing high scores in similar domains.

More recently, a new scale of motivation was drawn up, with the addition of some important issues arising from an extensive inventory with 68 items (Wisconsin of reasons for smoking addiction), the MRSS.[27] The so-called "Scale of Reasons for Smoking of the University of São Paulo" (ERF-USP)[28] was created with the potential to become an important instrument for assessing the motivations in several clinical contexts. The scale gained 2 new domains: Weight Control and Close Association (intense emotional connection with cigarettes). The motivational profile in 311 adult smokers with a low degree of dependence showed high scores for Dependence, Pleasure from Smoking, and the Reduction of Tension/Relaxation. In 2013, a study applied this new scale to 266 adolescents and identified that the most important domains were also Pleasure from Smoking and Relaxation/Reduction of Tension.[29] Pizzichini et al.[30] evaluated 183 smokers over 40 years in a population-based cross-sectional study who replied to the questionnaire of Scale of Reasons for Smoking of the University of São Paulo (ERF-USP). The main factors that lead the individual to smoke were Pleasure from Smoking and Physical Dependence. Further studies are still needed to evaluate the validity and usefulness of this scale.

It is known that men and women behave in different cultural, psychosocial and, socio-economical ways in relation to smoking.[1, 32] In this sample of hospitalized smokers, we observed that women presented significantly higher score on the domain of Relaxation/Reduction of Tension. The study of Berlin et al.[17] also points out that women generally smoke more in search of relaxation and also due to social smoking. More recently, in 2014, Pulvers et al.[31], applied the MRSS in 2376 adults smokers and found that the domain of Relaxation/Reduction of Tension had the highest score among women. These findings are relevant and in line with the results of the current study.

Comparing the MRSS domains in patients with different degrees of dependence, we found that all domains had higher scores in the group of greater dependence. However, there was a statistically significant difference in the fields Automatism/Habit and Stimulation. No strong correlation ($r > 0.5$) was found between the domains and independent variables tested. However, the study by Piper et al. found a correlation between the domain of dependence and the number of cigarettes smoked per day, as well as with the Fagerström Test.[27.]

One of the limitations of this study is the difficulty to generalize its findings since it involves a population with characteristics that are likely local-specific. Additionally, this study used convenience sampling, which only allows for exploratory analysis, but not probabilistic. Another criticism could be the fact that those who did not accept any approach to smoking cessation during hospitalization did not participate in the study. That group would likely be composed of a different motivational profile.

The domains mentioned are possible focus points for planning new strategies for smoking cessation involving hospitalized patients, even if they present a greater degree of dependence. Thus, during hospitalization, the Pleasure from Smoking is a factor that should be more intensely considered in order to seek new sources of satisfaction other than tobacco. In the process of cessation, stimuli to the practice of physical activity, reading, crafts, socialization, etc. must be sought individually and collectively. On the other hand, Relaxation/Reduction of Tension could involve a change in beliefs, that smoking is not relaxing, but that it reduces abstinence in dependency. In addition to the understanding of this concept, investing in teaching techniques of self-relaxation could also be a priority of the strategy directed to hospitalized smokers.

CONCLUSION

The more precise identification of factors that lead people to smoke can contribute to the development of strategies for the prevention, control, and cessation of smoking. The homogeneity of the findings in the application of motivational scales suggests that factors such as Pleasure from Smoking in general, Relaxation/Reduction of Tension especially in women, and Automatism in those more dependent should be more valued and approached on future strategies for smoking cessation of hospitalized patients.

RESUMO

OBJETIVO: *Investigar o perfil de motivações para o tabagismo entre pacientes internados em um hospital do sul do Brasil.*

MÉTODOS: *Estudo tipo* survey *que incluiu pacientes tabagistas hospitalizados. Utilizou-se a Escala de Razões para Fumar Modificada (ERPFM) e seus domínios, analisados em função do sexo e do grau de dependência.*

RESULTADOS: *A amostra foi composta por 85 adultos (média de 53 anos), com baixa escolaridade/renda familiar e equilibrada quanto ao sexo (masculino= 52,9%) e por especialidade clínica (48%) ou cirúrgica (47%). A maioria estava em estágio motivacional Ação (68%), com carga tabágica (mediana= 39 anos/maços) e grau de dependência à nicotina elevados (56,4%). Os domínios de maior escore da ERPFM foram: Prazer de Fumar (4,34 ± 1,2), Relaxamento/Redução da Tensão (4,24 ± 1,2) e Dependência (3,8 ± 1,4). De forma significativa, com maior pontuação, as mulheres apresentaram o domínio Relaxamento/Redução da Tensão (4,7 ± 0,9). Naqueles com maior grau de dependência, observou-se com significância, escores mais elevados nos domínios Automatismo/Hábito e Estimulação.*

CONCLUSÕES: *Prazer de Fumar e Relaxamento/Redução da Tensão, especialmente em mulheres e Automatismo, naqueles mais dependentes, são fatores que devem ser mais valorizados em futuras estratégias de cessação de tabagismo em hospitalizados.*

PALAVRAS-CHAVE: *Tabagismo. Motivação. Pacientes internados.*

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ORIGINAL ARTICLE

Evaluation of the systemic and therapeutic repercussions caused by drug interactions in oncology patients

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http://dx.doi.org/10.1590/1806-9282.65.5.611

SUMMARY

INTRODUCTION: *Drug interaction is an important cause of global morbidity. It is of particular importance in cancer patients since they are often in use of polypharmacy, related to interactions between the drugs and the chemotherapeutics used.*

OBJECTIVE: *To evaluate the drug interaction between chemotherapy and other drugs in cancer patients.*

METHODS: *a cross-sectional study carried out in the outpatient oncology department of a public tertiary hospital. Two hundred thirty-five patients were included, and the drugs they were using were identified. Using the MedScape and Epocrates database, we evaluated the interactions between medications and chemotherapy by defining their frequency and dividing their severity from interaction into mild, close monitoring necessity and severe.*

RESULTS: *161 patients had some drug interaction. We identified 9 types of mild interactions, 23 types of interactions with close monitoring necessity, and 2 types of serious interactions. The most frequent interactions were between fluorouracil and leucovorin (32 cases) and cyclophosphamide and doxorubicin (19 cases). Serious interactions were between aspirin and pemetrexed; and leucovorin and Bactrim.*

CONCLUSION: *In the present study, drug interactions were frequent, including serious interactions with a potential increase in morbidity and mortality. Thus, it is necessary for oncologists to draw up a therapeutic plan considering potential interactions between prescribed chemotherapy and current medications in use by patients.*

KEYWORDS: *Drug interactions. Antineoplastic agents/adverse effects. Medical oncology.*

INTRODUCTION

According to the World Health Organization (WHO), drug interaction is the main cause of morbidity and mortality in the world.[1] Data indicate that, in the United States, annually, over 2 million of patients

DATE OF SUBMISSION: 14-May-2018
DATE OF ACCEPTANCE: 26-May-2018
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who are hospitalized suffer from adverse reactions to drugs, and approximately 100,000 die from it. Drug interaction, defined as an increase or reduction of the clinical effect of a given drug due to the interference of another, it is responsible for about 3% to 5% of these cases.[2] This is because drug interactions can interfere in both pharmacokinetics and pharmacodynamics by inducing or inhibiting cytochrome P450, which can lead to a synergistic, additive or antagonistic effect of some drugs, thus compromising their effectiveness.[3]

In general, the patients who are mostly exposed to this scenario are those who make use of polypharmacy, such as oncology patients, who need to make use of drugs not only to treat the cancer itself, but also due to the toxicity induced by the treatment and syndromes related to neoplasia, in addition to the drugs used for possible comorbidities.[4]

In addition, several studies have investigated drugs with the potential to interfere with chemotherapy, showing remarkable rates of drug interaction.[5-9] As an example, it is known that drugs used to treat psychiatric disorders such as carbamazepine, phenytoin, phenobarbital, primidone, and valproic acid interact with chemotherapy treatments in general.[6] Other drugs such as fentanyl, midazolam, captopril, and potassium chloride have also shown a high prevalence of drug interaction.[10]

However, the main problem lies in the use of drugs whose effects on treatment are unknown and which are often bought without restrictions by the patients, who self-medicate, usually without informing the oncologist.[11,12]

Similarly, van Leeuwen et al.[7] predicted that over half of the patients in the use of chemotherapeutic agents present some kind of drug interaction, and a third of them suffer serious consequences.[13]

Due to this scenario, it is necessary to know the drugs that have the potential to interfere with the efficacy of chemotherapeutic agents, so that oncologists can draw a plan of action more accurate and individualized in order to improve the treatment offered to the patients.

OBJECTIVES

General objective

Assess drug interaction between chemotherapy and other drugs that are taken by cancer patients, with or without medical guidance.

Specific objectives

Assess the adverse effects resulting from drug interactions that might interfere with the prognosis and quality of life of patients under antineoplastic treatment.

List the drugs whose interaction is identified by this study.

Assess the effects of the drug interactions found.

METHODS

Study design

This is a cross-sectional study that analyzed patients treated by the Oncology Service linked to the FMABC (State Hospital Mário Covas, in Santo André and School Hospital Padre Anchieta, in São Bernardo do Campo). The patients were invited to participate in the study, with a previous explanation that their participation was voluntary and that their personal information would remain confidential.

We considered eligible for the study patients with age greater than or equal to 18 years, able to read and understand Portuguese and who were or were to be submitted to chemotherapy. We excluded from the study all patients younger than 18 years old, illiterate and who had not undergone chemotherapy or had no indication of a chemotherapy regimen.

After approval by the ethics committee, 235 patients were included in this study, which was based on data collection by means of an interview in which the patient answered open questions and in the evaluation of possible interactions between the drugs reported with the aid of Epocrates And MedScape applications. These free electronic applications for smartphones use, exclusively, the names of medications taken by each patient, indicating, when present, the possibility of interaction between them. The use of the applications was done by the researchers of this study, who reported the information to the participants. The information relating to the current chemotherapeutic treatment were obtained from the records of each individual patient.

After signing the Informed Consent Form - ICF, patients filled out an identification form with their clinical and demographic data, as well as a questionnaire in which they should indicate the drugs used by them: those who used without medical guidance as well as those prescribed, besides their chemotherapeutic agents.

The questionnaire contains general data of the

patient, as staging of neoplasia, previous surgery, beginning of chemotherapy; clinical data, in which the drugs taken were disclosed, as well as the doses administered and an assessment of signs and symptoms based on the information referring to the treatment during chemotherapy; and complementary data, obtained by means of a simpler questions, aiming to evaluate all drugs used, their dosage and symptoms.

The researcher, at the time of inclusion, was responsible for clarifying the purpose of the study and assisting the subjects in answering the questionnaires.

In relation to the risks and benefits, the present study had a minimal risk in relation to the emotional context of the patient, since it caused them to reflect on questions that involve the disease, but there were no risks related to the physical health of patients. In addition, there is an indirect benefit from the implementation of future projects which, based on the collected data, can contribute to the improvement of the quality of life of these patients.

TABLE 1. SOCIODEMOGRAPHIC DATA

		N = 161	
Gender	Female	62	38.5%
	Male	99	61.5%
Age	Mean	61 years	
	Interval	27 to 85 years	
Marital status	Single	45	27.9%
	Married	100	62.1%
	Widow(er)	16	9.9%
Formal education	Illiterate	6	3.7%
	Incomplete elementary school	66	40.9%
	Complete elementary school	18	11.1%
	Incomplete secondary school	10	6.2%
	Complete secondary school	40	24.8%
	Incomplete undergraduate program	11	6.8%
	Complete undergraduate program	10	6.2%
Ethnicity	White	92	57.1%
	Brown	37	22.9%
	Black	18	11.1%
	Indigenous	8	4.9%
	Others	6	3.7%
Occupation	Works	58	36.0%
	Does not work	103	63.9%
Origin	The ABC region	144	89.4%
	Others	17	10.5%
Site of the primary neoplasia	Head and neck	7	4.3%
	Lung	13	8.0%
	Gastrointestinal tract	58	36.0%
	Urinary tract	8	4.9%
	Gynecologic	50	31.0%
	Others	25	15.5%

RESULTS

The present study included 235 patients. Of these, 161 had some drug interaction in accordance with the criterion of Epocrates. Their sociodemographic characteristics are presented in Table 1.

We then excluded interactions that did not involve chemotherapy drugs, dividing them remaining between "chemotherapy and chemotherapy" or "chemotherapy and non-chemotherapy. The interactions found and their frequency are shown in Table 2.

The interactions were divided into "mild", "close monitoring" and "serious", as shown in the "*drug interaction Checker*" of MedScape. In the chemotherapy vs. non-chemotherapy group, we found eight types of mild interactions, 14 that required close monitoring and two considered serious. Whereas in the chemotherapy vs. chemotherapy group, we found a mild interaction, nine interactions with the need for close monitoring and no serious interaction. The results can be found in Table 3.

DISCUSSION

In oncological treatment, the concern with possible drug interactions should always be raised by the oncologist. It is worth noting that certain interactions are expected and may even be desired, especially in regard to interactions between chemotherapy drugs, between which there is a synergism of action, for example. In this context, we can cite as examples of known interactions 5-fluorouracil and leucovorin[14], or doxorubicin/cyclophosphamide followed by paclitaxel[15].

Also in the context of the expected associations, the most prevalent drug interaction was between fluorouracil and leucovorin (32 cases), and it occurs during the antineoplastic treatment, with increased toxicity of the medication due to the effect of pharmacodynamic synergism. The same goes for the second most frequent drug interaction, cyclophosphamide, and doxorubicin.[16]

TABLE 2. ANALYSIS OF DEGREES OF INTERACTIONS

Chemotherapy vs. Non-chemotherapy			Chemotherapy vs. Chemotherapy	
Chemotherapy	Non-chemotherapy	Frequency	Chemotherapy drugs	Frequency
Vincristine	Prednisone	4	Cisplatin + Paclitaxel	3
Docetaxel	Prednisone	2		
	Dexamethasone	2		
	Primidone	1		
Paclitaxel	Budesonide	1		
	Captopril	1		
Glimepiride	Prednisone	1		
	Aspirin	1		
Paclitaxel	Losartan	6	Fluorouracil + Leucovorin	32
	Dexamethasone	4	Cyclophosphamide + Doxorubicin	19
	Simvastatin	3	Paclitaxel + Doxorubicin	7
	Phenytoin	1	Paclitaxel + Trastuzumab	3
	Rosuvastatin	1	Irinotecan + Bevacizumab	2
	Cyclosporine	1	Paclitaxel + Lapatinib	1
Cyclophosphamide	Enoxaparin	1	Cisplatin + Cyclophosphamide	1
	Allopurinol	1	Cisplatin Decarbazine	1
Doxorubicin	Dexamethasone	2	Fluorouracil + Bevacizumab	1
Docetaxel	Simvastatin	2		
Irinotecan	Dexamethasone	2		
Bortezomib	Omeprazole	1		
Etoposide	Dexamethasone	1		
Eloxatin	Zidovudine	1		
Pemetrexed	Acetylsalicylic Acid	1		
Leucovorin	Bactrim	1		

TABLE 3. SEVERITY OF INTERACTIONS

Severity of interaction	Chemotherapy vs. Non-chemotherapy (Unexpected interactions)		Chemotherapy vs. Chemo-therapy (Expected interaction)
Mild	Vincristine	Prednisone	Cisplatin + Paclitaxel
	Docetaxel	Prednisone; Dexamethasone Primidone	
	Paclitaxel	Budesonide; Captopril	
Close monitoring	Glimepiride	Prednisone; Aspirin	Fluorouracil + Leucovorin
	Paclitaxel	Losartan; Dexamethasone Simvastatin; Phenytoin Rosuvastatin; Cyclosporine	Cyclophosphamide + Doxorubicin
	Cyclophosphamide	Enoxaparin; Allopurinol	Paclitaxel + Trastuzumab
	Doxorubicin	Dexamethasone	Irinotecan + Bevacizumab
	Docetaxel	Simvastatin	Paclitaxel + Lapatinib
	Irinotecan	Dexamethasone	
	Bortezomib	Omeprazole	
	Etoposide	Dexamethasone	
	Eloxatin	Zidovudine	
Severe	Pemetrexed	Acetylsalicylic acid	
	Leucovorin	Bactrim	

The third most frequent interaction, paclitaxel and doxorubicin, even though it was already expected to have increased toxicity related to their combined use bringing an improved oncologic prognosis[16], it should be mentioned that the interaction between them includes increased levels of doxorubicin, considering the decrease of renal clearance of creatinine generated by paclitaxel.[16] Thus, it is observed that associations of chemotherapeutic agents may present, concomitantly, intentional drug interactions associated to harmful interactions.

Among the serious interactions, the one between aspirin (acetylsalicylic acid; ASA) and pemetrexed is noteworthy. Pemetrexed is a chemotherapeutic agent indicated for the treatment of non-small cell lung cancer,[17] while acetylsalicylic acid is used as secondary prophylaxis of new cardiovascular events[18]. Considering the frequency of concomitance of these comorbidities, both in part secondary to smoking[19], there is the possibility of a same patient receiving the association of pemetrexed and ASA. Despite this, these medications should not be associated, since aspirin increases the levels of pemetrexed due to decreased renal excretion of the chemotherapeutic agent. It is worth mentioning that this association should be undertaken with caution in patients with normal renal function (creatinine clearance > 80 ml/min) and avoided in patients with preserved renal function, because, due to this factor, aspirin can raise the levels of pemetrexed and cause adverse events.[20]

To avoid such interaction, one possibility would be to replace acetylsalicylic acid by another antiplatelet agent that also causes reduction of cardiovascular risk during the period of oncological treatment, such as clopidogrel[21], which presents no drug interactions with the pemetrexed[16].

Another serious interaction was found between leucovorin and Bactrim (trimethoprim and sulfamethoxazole). Leucovorin corresponds to a drug used, among other reasons, in association with fluorouracil, for adjuvant chemotherapeutic treatment of colorectal cancer and for recovery in patients treated with high doses of methotrexate[22.23]. Bactrim, in turn, corresponds to an antibiotic often used for infectious prophylaxis in oncologic patients who are immunosuppressed during the chemotherapy treatment[24]. Thus, there is the possibility of the same patient using both drugs simultaneously, and leucovorin decreases the effect of trimethoprim due to a mechanism of pharmacodynamic antagonism.[16]

To avoid the interaction between leucovorin and Bactrim, the antibiotic can be replaced for another that is effective and does not interact with the leucovorin.[24.25]

As discussed, it is observed that drugs used for oncologic therapy are not an exception in the context of drug interactions. In addition, these drugs have important cytotoxic effects and feature many pharmacokinetic and pharmacodynamic variations among patients. As noted, the use of combinations and the number of drugs involved in the treatment increases the likelihood of such interactions.[26]

Thus, the presence of drug interactions among cancer patients is noteworthy. In this scenario, in addition to the associations made intentionally by oncologists with the purpose of increasing the effectiveness of the treatment, there are also those that occur without the supervision of these professionals, arising mainly from drugs taken without informing the medical team.

Furthermore, oncology patients are particularly prone to polypharmacy[27-29], making use of several drugs simultaneously. Thus, in addition to the greater risk of drug interactions, more than one interaction can be present in the same patient, increasing the possibility of unwanted effects and worsen prognosis[27-29].

An important example of multiple interactions in oncologic patients corresponds to that of chemotherapeutic agents, such as paclitaxel associated with simvastatin and losartan, drugs widely prescribed in older patients[30.31]. Although beneficial in isolation, paclitaxel presents drug interaction with both other drugs, with the need for close monitoring[16]. Simvastatin and losartan lead to unwanted increases in the levels of paclitaxel, increasing its toxicity; paclitaxel brings an increased risk of myopathy related to simvastatin.[16] Multiple interactions such as this should be carefully assessed by the oncologist, especially in patients in use of multiple drugs simultaneously.

The serious interactions found were between aspirin and pemetrexed, and leucovorin and Bactrim. Although the present study has found only individual cases of the concomitant use of drugs with serious drug interaction, this can probably be explained by the limitation of the small number of patients included, since the high prevalence of the use of these medications[18.24] indicates that the frequency of unwanted interactions is possibly even higher. Thus, it reinforces the idea that physicians should be alert

to the possible effects from such interactions and how they vary according to each patient, which can result in a worse prognosis for patients in neoplastic treatment.

CONCLUSION

Drug interactions were frequent in oncologic patients. Although the majority of interactions was related to the synergistic effect already expected between chemotherapy drugs, there were unexpected serious interactions and interactions with the need of close monitoring The main interactions found were the severe increase of chemotherapy toxicity due to the worsening of renal function, which may increase the mortality related to the treatment; and the reduction of the effect of antibiotic medication, related to an increased risk of bacterial infection and, consequently, an increase in mortality.

Thus, it is necessary that oncologists create a therapy plan considering possible drug interactions between the chemotherapy prescribed and other drugs used by the patients in order to ensure a better oncologic prognosis.

RESUMO

INTRODUÇÃO: *Interação medicamentosa é uma importante causa de morbidade mundial. Apresenta especial importância em pacientes oncológicos, pois esses frequentemente estão em uso de polifarmácia, podendo haver interações entre os medicamentos e os quimioterápicos utilizados.*

OBJETIVO: *Avaliar a interação medicamentosa entre a quimioterapia e outros medicamentos em pacientes oncológicos.*

MÉTODOS: *Estudo transversal realizado em serviço ambulatorial de oncologia de um hospital público terciário. Foram incluídos 235 pacientes, identificando-se quais medicamentos eram utilizados por eles. Por meio do auxílio do banco de dados do MedScape e Epocrates, avaliaram-se as interações entre as medicações e os quimioterápicos, definindo sua frequência e dividindo sua gravidade da interação em leve, monitorização próxima e grave.*

RESULTADOS: *Do total estudado, 161 pacientes apresentavam alguma interação medicamentosa, sendo nove tipos de interações leves, 23 tipos de interações com necessidade de monitorização próxima e dois tipos de interações graves. As interações mais frequentes foram entre fluoracil e leucovorin (32 casos) e ciclofosfamida e doxorrubicina (19 casos). As interações sérias foram entre aspirina e pemetrexed; e leucovorim e bactrim.*

CONCLUSÃO: *No presente trabalho, interações medicamentosas foram frequentes, incluindo interações graves com potencial aumento de morbimortalidade. Assim, faz-se necessário que oncologistas tracem um plano terapêutico levando em consideração as possíveis interações medicamentosas entre a quimioterapia prescrita e demais medicações em uso pelos pacientes.*

PALAVRAS-CHAVE: *Interações medicamentosas. Antineoplásicos/efeitos adversos. Oncologia.*

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ORIGINAL ARTICLE

Restless legs syndrome and quality of life in pregnant women

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http://dx.doi.org/10.1590/1806-9282.65.5.618

SUMMARY

OBJECTIVE: *In this study, we aimed to determine the extent of restless legs syndrome (RLS) in pregnant women and evaluate the relationship between the syndrome and quality of life.*

METHODS: *This is a cross-sectional descriptive study. A questionnaire developed by the researcher, the Short Form 36 (SF-36) Questionnaire to measure the quality of life, the International Restless Legs Syndrome Study Group (IRLSSG) Diagnostic Criteria for RLS and the Restless Legs Syndrome Rating Scale were applied to the women to collect the data. A total of 250 pregnant women were included in the study.*

RESULTS: *The mean age of the women was 28.11 ± 5.59 years and the mean gestational time was 26.26 ± 10.72 weeks. Symptoms of RLS were seen in 46.4 % of the women. The mean for the RLS Violence Rating Score was 20.82 ± 6.61 for the women with RLS. RLS was found to be mild in 5.2 % of the women, moderate in 45.7 %, severe in 40.5 % and very severe in 8.6 %. A statistically significant effect of RLS survival on quality of life was observed.*

CONCLUSION: *These results indicate that almost half of the pregnant women in this study experienced RLS, and about half of those with RLS experienced severe or very severe RLS. There is a significant relationship between RLS and six domains of SF-36 (physical, role limitations, pain, general health perception, energy/vitality, and mental health).*

KEYWORDS: *Restless legs syndrome. Quality of life. Pregnancy.*

INTRODUCTION

Restless legs syndrome (RLS) is a sensory and motor disorder characterized by uncomfortable and unpleasant sensations which lead to a strong and irresistible urge to move one's leg and occur during periods of inactivity, generally during sleep.[1] RLS prevalence has been reported to range from 2 to 15%.[2,3] A community-based study found a RLS prevalence of 3.19% in Turkey.[4]

The prevalence of RLS increases with age and is two times more common in women than in men.[3] The reason for this gender difference has not been explained accurately; however, it is considered that it may be due to hormonal changes during the periods of pregnancy, menstruation, and menopause.[5] Minar et al.[6] confirmed the relatively high prevalence of RLS in pregnant women compared with the general population. They found that more than 30% of positive cases had clinically significant symptoms, and 50% reported sleep disturbances.

Pregnancy is reported as a significant risk fac-

DATE OF SUBMISSION: 28-Nov-2018
DATE OF ACCEPTANCE: 31-Dec-2018
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tor which may precipitate and worsen RLS.[7] RLS affects up to one-third of pregnant women, peaks in the third trimester and usually subsides after delivery.[6,8-10] History of RLS before conception, RLS during a previous pregnancy, coffee consumption before pregnancy, peptic ulcer disease, hemoglobin < 11 g/dl, and inadequate supplementation of iron and folate during pregnancy, particularly when there is iron deficiency, were found to be risk factors for the development of RLS during pregnancy.[11,12] Hormonal factors are thought to play a role in the manifestation and development of RLS, especially during pregnancy.[13] It has been suggested that high estradiol, increased prolactin and increased progesterone during pregnancy may trigger RLS.[14] Thyroid hormone levels tend to rise during the third trimester. A negative relationship has been found between thyroid hormones and dopamine that indicates they can take part in the etiology of RLS.[15] Thus, dietary and hormonal factors have been found to be associated with RLS during pregnancy.

The World Health Organization's (WHO) broad and multidimensional definition of quality of life (QoL) incorporates physical, psychological, social, and environmental aspects of life and emphasizes the individual, subjective appraisals.[16] The construct of HRQoL enables the evaluation of how a health condition influences a person's perception of QoL. The concept assesses the impact of mental and physical health status on different areas in a person's life.[17] Pregnancy is a process that creates significant anatomical, physiological, and biochemical changes in a woman's life. These changes affect the physical and emotional behaviors of women and can lead to decreased health-related quality of life. Moreover, some complications such as RLS can lead to decreased health-related quality of life in pregnancy.[18] Individuals with RLS sometimes avoid participating in social activities and can experience chronic sleep disorders and psychiatric problems such as depression and anxiety disorders. Furthermore, Ramirez et al.[19] showed a high possibility of pregnant women who had symptoms of RLS developing pre-eclampsia. Meharaban et al.[13] reported that pregnancies complicated by RLS are at increased risk for preterm birth. It was found that compared to pregnant women without RLS, those with RLS were more likely to have poor sleep quality, poor daytime function, and excessive daytime sleepiness.[20] Therefore, RLS has significant impacts on daily life and quality of life. Although RLS is related to reduced quality of life and poor sleep in the general population, data on RLS-associated maternal sleep-wake disturbances are lacking.[21] Prior reports have linked sleep-wake disturbances to adverse pregnancy and delivery outcomes (e.g., preterm delivery, prolonged labor, cesarean section deliveries, and postpartum depression).[22] Terzi et al.[23] found a significant difference between RLS and obstructive sleep apnea symptoms (witnessed apnea and fatigue) in pregnant women. In order to suggest solutions to the problems experienced by pregnant women, it is important to determine these problems and their effects on pregnancy during follow-up, care, and counseling services for pregnant women. There are studies in the literature regarding the increase in the frequency of RLS in the past[8,10,24,25]; but there are limited studies evaluating the relationship between RLS and quality of life.[6,24,26,27] RLS is often underestimated and undiagnosed in pregnancy and can lead to a lower quality of life. Thus, it becomes significant to research RLS and its relationship with quality of life in pregnant women. The study findings will provide guidance for planning interventions to improve quality of life in pregnant women with RLS.

METHODS

Purpose and Design of the Study

This was a cross-sectional descriptive study that aimed to determine the extent of RLS in pregnant women and to evaluate its relationship with quality of life.

Population and Sample of the Study

The study population consisted of 2,900 pregnant women who applied to gynecology and obstetrics outpatient clinics in Karabük University Training and Research Hospital between 2015 and 2016. In order to determine the sample size, a power analysis was conducted (sample error: 0.01 and power: 95%), and the prevalence of RLS was accepted as 19-26 %.[8,10] The minimum number of people to be included in the study sample was calculated as 208. A total of 250 pregnant women were included in the study. In order to homogenize the sample group and remove as much as possible the factors that affect the quality of life outside the RLS, all women who were literate, had no chronic or psychiatric disease, did not have a high-risk pregnancy, and agreed to participate in the study were enrolled.

Data collection instruments

The data were collected using a questionnaire form that was developed by the researcher based on a literature review.[7,9,28] We evaluated the sociodemographic (9 questions) and pregnancy (5 questions) features of the participants. We administered the Short Form 36 (SF-36) Questionnaire to measure the quality of life, and the International Restless Legs Syndrome Study Group (IRLSSG) Diagnostic Criteria for RLS to evaluate the presence of RLS in all of the pregnant women. We then administered the Restless Legs Syndrome Rating Scale to the pregnant women who fulfilled diagnostic criteria for RLS.

IRLSSG Diagnostic Criteria for RLS: This questionnaire was developed in 1995 based on the experiences of patients and includes 5 questions. Patients who respond "yes" to all five questions are diagnosed with RLS.[9] The reliability and validity study of the Turkish version of the questionnaire was conducted by Sevim et al.[4], and Cronbach's alpha coefficient was above 0.81 for each item.

The Restless Legs Syndrome Rating Scale was developed by IRLSSG.[9] It includes 10 items which are scored from none (score 0) to very severe (score 4). The minimum and maximum scores obtained on the scale are 0 and 40, respectively. The severity is classified as mild (score 0-10), moderate (score 11-20), severe (score 21-30), and very severe (score 31-40). The Turkish version of the scale was found valid and reliable and has been used in many studies in Turkey.[2,28,29] In our study, Cronbach's alpha coefficient was 0.823 for the scale.

The Short Form-36 Health Survey Questionnaire (SF-36) is one of the most frequently used instruments to measure the quality of life. It was developed and presented by Rand Corporation in 1992.[28] The first version of the questionnaire used in the 1990s and was composed of 149 items. Then, the 20-item SF-20 health survey was developed based on the results from more than 22,000 patients in studies, which loaded factor analyses. However, in order to enhance its extent and psychometric features, the number of items was increased to 36, and the SF-36 was developed. This 36-item questionnaire measures quality of life across eight dimensions, which are physical functioning (10 items), role limitations due to physical problems (4 items), role limitations due to emotional problems (3 items), social functioning (2 items), mental health (5 items), energy/vitality (4 items), pain (2 items) and general health perception (5 items).[28] It is completed in response to how the patients have felt in the last 4 weeks and scored on a Likert-type scale (3-6 Likert type), except for the 4th and 5th items, which are responded to with "yes" or "no".[30] The questionnaire does not have a total score; however, each subscale has a total score, and the scores range from 0 to 100. A score of 100 indicates good health and a score of 0 indicates poor health.[28] The reliability and validity study of the Turkish version of SF-36 was conducted by Koçyiğit et al.[30] with a Cronbach's alpha coefficient between 0.73 and 0.76. The SF-36 is used to measure the quality of life in pregnant women both in Turkey and across the world.[31,32] In our study, Cronbach's alpha coefficient was found to range between 0.62 and 0.87 for the scale.

Procedure

The data collection instruments were administered to pregnant women in a face-to-face interview with the researcher. The data were collected in a calm environment in outpatient clinics, after or before the examination of the patient. It took approximately 20-25 minutes to complete the instruments per person. The questionnaire form, the SF-36, and the RLS criteria form were administered to all of the pregnant women. The RLS Rating Scale was administered only to the women fulfilling diagnostic criteria for RLS.

Data Analysis

The data were analyzed using SPSS 24.0 (Statistical Package for Social Sciences, version 24.0, for Windows) and values below 0.05 ($p < 0.05$) were accepted as statistically significant. Normality of the data was tested by performing the Shapiro-Wilk test. The comparison of variables with a normal distribution was tested by performing multiple comparison tests and Student t-test to compare the means of two independent groups. The Student t-test was used to determine the statistical relationship between RLS living conditions and SF-36 quality of life scale scores, and RLS severity and SF-36 quality-of-life scale scores.

Ethical Aspect of the Study

Before data collection began, we obtained ethics approval from the General Secretariat of the Association of Public Hospitals in Karabük (reference number 88919140/604.99) and Gazi University Ethics Committee (reference number issue:77082166-302.08.01-E.15258, date: 30.12.2016),

and written consent from the pregnant women participating in the study. The pregnant women who were identified as having RLS were referred to a neurologist.

RESULTS

The pregnant women's mean age was 28.11 ± 5.59 years; their mean gestation time was 26.26 ± 10.72 weeks. Among the women, 36.4 % were between 18-25 years, 50.8 % aged between 26-35 years, 12.8 % between 36-45 years, 30.8 % graduated from high school, 82.8 % were unemployed, 58.4 % perceived their economic level as moderate and poor, and 77.2 % were living in a city.

In total, 46.4 % of the pregnant women were found to meet diagnostic criteria for RLS, and among them, 5.2 % had mild RLS, 45.7 % had moderate RLS, 40.5 % had severe RLS, and 8.6 % had very severe RLS.

The mean scores of the participants for the SF-36 subscales were 58.04 ± 23.35 for physical functioning, 25.10 ± 33.86 for role limitations due to physical problems, 68.39 ± 24.93 for pain, 67.10 ± 22.30 for general health perception, 46.64 ± 24.57 for energy/vitality, 64.20 ± 27.93 for social functioning, 49.20 ± 39.20 for role limitations due to emotional problems and 77.52 ± 19.73 for mental health.

There were significant differences found in mean physical functioning, role limitations (physical), pain, general health perception, energy/vitality and mental health scores between the women with and without RLS ($p < 0.05$). The pregnant women with RLS had lower scores on physical functioning (50.09 ± 23.078), role limitations (physical) (17.89 ± 29.637), pain (63.09 ± 24.296), general health perception (63.97 ± 22.552), energy/vitality (38.75 ± 20.683) and mental health (74.55 ± 21.352) than those without RLS (Table 1).

There was a significant relationship between RLS severity and all SF-36 subscale scores, except the subscales "mental health" and "general health perception" ($p < 0.005$). The women with mild and moderate RLS had higher scores on the subscales physical functioning ($p = 0.001$), role limitations due to physical health ($p = 0.002$), pain ($p = 0.001$), energy/vitality ($p = 0.001$), social functioning ($p = 0.023$) and role limitations due to emotional problems ($p = 0.035$) than those with severe and very severe RLS (Table 2).

DISCUSSION

RLS, which is common in society, is a condition that causes an urge to move one's legs and leads to restlessness in extremities. Prevalence of RLS is re-

TABLE 1. RELATIONSHIP BETWEEN RLS AND SF-36 SUBSCALE SCORES (N=250)

	SF-36 Subscale Scores							
	Physical Functioning	Role Limitations (Physical)	Pain	General Health Perception	Vitality (Energy)	Social Functioning	Role Limitations (Emotional)	Mental Health
With RLS (n=116)	50.09±23.078	17.89±29.637	63.09±24.296	63.97±22.552	38.75±20.683	62.07±26.679	45.40±40.144	74.55±21.352
Without RLS (n=134)	64.93±21.390	31.34±36.103	72.97±24.654	69.81±21.808	53.47±25.680	66.04±28.947	52.49±38.209	80.09±17.905
Statistics	t: -5.273 p: 0.001*	t: -3.235 p: 0.001*	t: -3.180 p: 0.002*	t: -2.079 p: 0.039*	t: -5.107 p: 0.001*	t: -1.123 p: 0.263	t: -1.428 p: 0.154	t: -2.230 p: 0.027*

P<0.005, *Student t-Test

TABLE 2. CORRELATION BETWEEN RLS SEVERITY AND SF-36 SUBSCALE SCORES OF PREGNANT WOMEN WITH RLS (N=116)

	SF-36 Subscale Scores							
	Physical Functioning	Role Limitations (Physical)	Pain	General Health Perception	Vitality (Energy)	Social Functioning	Role Limitations (Emotional)	Mental Health
Mild and Moderate (n=59)	58.47± 21.36	26.27 ± 33.93	73.63 ± 21.17	67.46 ± 18.48	45.76 ± 19.23	67.58 ± 23.69	53.11 ± 36.68	77.49 ± 18.54
Severe and Very Severe (n=57)	41.4 ± 21.69	9.21 ± 21.46	52.19 ± 22.58	60.35 ± 25.78	31.49 ± 19.75	56.36 ± 28.56	37.43 ± 42.29	71.51 ± 23.70
Statistics	t: 4.271 p: 0.001*	t: 3.248 p: 0.002*	t: 5.275 p: 0.001*	t: 1.701 p:0.092	t: 3.943 p: 0.001*	t: 2.308 p: 0.023*	t: 2.135 p: 0.035*	t: 1.511 p: 0.134

P<0.005. *Student T-Test

ported at about 10% in the general population[33] and 11-26% in pregnant women.[8,10] Yüksel et al.[9] found a prevalence of RLS of 44.6% among pregnant women in their study. In our study, the RLS prevalence was found to be 46.4% for the pregnant women; thus, results in our study are higher than the RLS rates seen among pregnant women in the general population. Similarly, Telarovic et al.[24] reported that the frequency of RLS was found to be significantly higher in pregnant women when compared to non-pregnant women. The RLS prevalence in pregnancy has been reported between 10 and 34% worldwide in the literature.[6,25,34] It is reported that RLS affects up to one-third of pregnant women, peaks in the third trimester, and usually subsides after delivery.[6] However, in a study conducted with 231 pregnant women by Meharaban et al.[13], the prevalence was found to be 47.3 % for RLS. The results of our study are consistent with the literature. Our study has revealed that almost half of pregnant women experience RLS during pregnancy.

When assessing RLS severity, we found that the women's mean RLS severity score was 20.82 ± 6.61, and 49.1 % of these women experienced severe or very severe RLS. In a previous study, 53.5 % of pregnant women were reported to have severe and very severe RLS,[35] and in another, 74.7 % were reported to have moderate RLS.[25] Minar et al.[6] found that more than 30 % of positive cases had clinically significant symptoms. Our study findings are similar to the literature in Turkey and worldwide, revealing that about half of pregnant women experience RLS and that half of these cases are severe. When the negative effects created by RLS in pregnancy (poor sleep quality, poor daytime function, excessive daytime sleepiness, pre-eclampsia, preterm birth) and adverse effects of sleep problems created by the RLS (preterm delivery, prolonged labor, cesarean section deliveries, and postpartum depression) are considered, the necessity of screening pregnant women in Turkey for RLS becomes clear.[13,19,20,22]

RLS is often underestimated and undiagnosed in pregnancy and can lead to a lower quality of life. It is commonly associated with pregnancy, and its symptoms negatively impact the quality of life in pregnant women.[6] Sleep disturbance, tiredness during the day[34,36], leg cramps and anxiety due to RLS[13,37] may impair quality of life among individuals with RLS. Studies have shown that the use of estrogen for reducing sleep problems is effective in RLS[38,39]. However, the use of estrogen is not favorable in pregnancy. In our study, statistically significant differences were found between the women with and without RLS in the mean scores of the subscales (physical functioning, role limitations (physical), pain, general health perception, energy/vitality, and mental health) of the SF-36 scale ($p < 0.05$). Pregnant women with RLS were found to have a poorer quality of life compared to those without RLS with regard to these subscales. In addition, we found a significant relationship between RLS severity and all SF-36 subscale scores, except subacalesfor "mental health" and "general health perception" ($p < 0.005$). Pregnant women with mild and moderate RLS scored higher on the subscales of physical functioning, role limitations due to physical health, pain, energy/vitality, social functioning, and role limitations due to emotional problems than those with severe and very severe RLS. Similarly, Telarovic et al.[24] reported that analysis of different variables determining QoS and quality of life showed consistently significantly lower values for the group of RLS-positive pregnant women compared to pregnant women without neurological disorders. Allen et al.[21] stated in their population-based study that quality of life of among people with RLS was affected in all domains of the SF-36 scale. In another study with women of reproductive age, Güzel et al.[28] found that women with RLS scored lower on all SF-36 subscales than those without RLS, and these women with RLS had a poor quality of life. Similarly, Ghanei- Gheshlagh et al.[27] reported that quality of life in women with restless legs syndrome was lower than in healthy pregnant women. Our findings are consistent with the literature. All in all, it is considered that RLS and the severity of symptoms negatively affect the quality of life in pregnant women.

Strength and Limitations

This is the first study carried out to explore the relationship between RLS and quality of life in pregnant women in Turkey and is considered to be a guide for further studies. Nevertheless, it has some limitations which include the following: (1) The population is limited, so the results can only be generalized to this population; (2) The data were based on self-reporting of the pregnant women, and not observed by the researcher; and (3) Laboratory tests or imaging studies were not used to evaluate RLS in the pregnant women; and (4) Quality of life is a complex structure influenced by socioeconomic factors. Although there is a

statistically significant association between RLS and quality of life, quality of life may be affected by other factors associated with pregnancy. The fact that the changes in pregnancy cannot be excluded as a source of impaired quality of life is among the limitations of this study.

CONCLUSIONS

These results indicate that almost half of the pregnant women studied experience RLS and about half of those experience severe or very severe RLS. The women's quality of life is poor regarding role limitations due to physical health and is moderate regarding other subscales. There is a significant relationship between RLS and six domains of the SF-36 (physical functioning, role limitations [physical], pain, general health perception, energy/vitality, and mental health). Therefore, pregnant women with RLS have a poorer quality of life compared to those without RLS, regarding these domains. Additionally, there is a negative correlation between RLS severity and all SF-36 subscales, except for "mental health" and "general health perception," which indicates that an increase in RLS severity is accompanied by a decrease in quality of life.

Based on these findings, we recommend that regular monitoring of pregnancy should include an evaluation for RLS. Health professionals should plan interventions to improve quality of life in pregnant women with RLS (such as smoking cessation, nutrition education, sleep hygiene), and further studies should be carried out to investigate the relationship between RLS and quality of life with larger sample size and in different groups.

Acknowledgments

We gratefully thank Sultan Özkan Şat for her help in this study and the pregnant women who participated in this study.

RESUMO

OBJETIVO: *Neste estudo, objetivamos determinar a extensão da síndrome das pernas inquietas (SPI) em gestantes e avaliar a relação da síndrome com a qualidade de vida.*

MÉTODOS: *Este é um estudo descritivo transversal. Um questionário desenvolvido pelo pesquisador, o Questionário Short Form 36 (SF-36) para medir a qualidade de vida, o Grupo Internacional de Síndrome das Pernas Inquietas (IRLSSG) Critérios de Diagnóstico para SPI e a Escala de Avaliação da Síndrome das Pernas Inquietas foram administrados às mulheres para coletar os dados. Um total de 250 gestantes foi incluído no estudo.*

RESULTADOS: *A média de idade das mulheres foi de 28,11 ± 5,59 e a média das semanas gestacionais da gestação foi de 26,26 ± 10,72. Os sintomas da SPI foram observados em 46,4% das mulheres. A média para o Índice de Violência da RLS foi de 20,82 ± 6,61 para as mulheres com SPI. A SPI foi discreta em 5,2% das mulheres, moderada em 45,7%, grave em 40,5% e muito grave em 8,6%. Um efeito estatisticamente significativo da sobrevida da SPI na qualidade de vida foi observado (p<0,005).*

CONCLUSÃO: *Estes resultados indicam que quase metade das mulheres grávidas neste estudo experimentou a SPI, e cerca de metade das pessoas com SPI experimentou SPI grave ou muito grave. Existe uma relação significativa entre a SPI e seis domínios do SF-36 (físico, limitação de papéis, dor, percepção geral de saúde, energia/vitalidade e saúde mental).*

PALAVRAS-CHAVE: *Síndrome das pernas inquietas. Qualidade de vida. Gravidez.*

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ORIGINAL ARTICLE

Knowledge of human papillomavirus and Pap test among Brazilian university students

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http://dx.doi.org/10.1590/1806-9282.65.5.625

SUMMARY

OBJECTIVE: *Human papillomavirus (HPV) is the most prevalent sexually transmitted virus in the world and is associated with an increased risk of cervical cancer. The most effective approach to cervical cancer control continues to be screening through the preventive Papanicolaou test (Pap test). This study analyzes the knowledge of university students of health science programs as well as undergraduate courses in other areas of knowledge on important questions regarding HPV.*

METHOD: *Four hundred and seventy-three university students completed a questionnaire assessing their overall knowledge regarding HPV infection, cervical cancer, and the Pap test. A descriptive analysis is presented, and multivariate analysis using logistic regression identified factors associated with HPV/cervical cancer information.*

RESULTS: *Knowledge was higher for simple HPV-related and Pap test questions but was lower for HPV interrelations with genital warts and cervical cancer. Being from the health science fields and having high income were factors associated with greater knowledge. Only the minority of the participants recognized all the situations that increased the risk of virus infection presented in the questionnaire.*

CONCLUSIONS: *These findings highlight the need for educational campaigns regarding HPV infection, its potential as a cervical cancer agent and the forms of prevention available.*

KEYWORDS: *Papillomaviridae. Uterine cervical neoplasms. Papanicolaou test. Students. Knowledge.*

INTRODUCTION

Human papillomavirus (HPV) is the most prevalent sexually transmitted virus worldwide. According to two recent meta-analyses, prevalence rates of 11 and 12% are observed in the general population[1,2]. Although an initial peak of the disease is observed in women younger than 25 years, there is an increase in the prevalence of HPV in women of 45 years of age or older in the Americas and Africa[1,2]. The most common types of HPV worldwide in women with regular cytology are 16, 18, 58, 52, and 31, in this order. In Brazil, the prevalence of cervical infection by HPV ranges from 13.7% to 54%[3], while in wom-

DATE OF SUBMISSION: 14-Oct-2018
DATE OF ACCEPTANCE: 24-Nov-2018
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en presenting regular cytology it ranges from 10.4% to 24.5%, according to studies carried out between 1989 and 2008[4].

HPV cervical infections are mostly self-limited, regressing spontaneously between 12 and 30 months, even when caused by high-risk genotypes, such as HPV16 and HPV18[5]. Women with persistent HPV infection may progress to cervical intraepithelial neoplasia (CIN) in a rate of 8-28%[6].

In Brazil, cervical cancer is the third most prevalent type of cancer in women, excluding non-melanoma skin. By 2017-2018, the incidence rate of 15.4/100,000 women (16,370 new cases/per year) and mortality rate of 5 out of 100,000 women (5,400 deaths) were estimated[7].

The most effective approach to cervical cancer control is still screening through the Papanicolaou test (Pap test)[8]. Following the introduction of HPV vaccines, studies showed different levels of effectiveness in both strategies, either alone or combined[9-13]. The Pap test is quick, relatively inexpensive, and effective for the early detection of cervical cancer since it identifies cellular morphological changes resulting from HPV infection. However, awareness of the importance of HPV, the Pap test and the need for periodic screening are by no means widespread among sexually active women[8,14-16]. Factors that could explain the lack of knowledge concerning HPV infection and its relation to cervical cancer, as well as the lack of knowledge about the Pap smear test, include a low level of formal education, low income, and difficulty of access to the public health system[8,14-16]. Dissemination of information to women on this subject is of great relevance for disease prevention.

Several studies carried out in Brazil investigated the knowledge of the subject among university students[17-24]. All of them were descriptive studies using convenience samples, varying from 58 and 447 subjects interviewed, and none analyzed factors associated with awareness of HPV and its prevention[17-24]. It was expected that university students would know the subject in more depth since they have access to higher education. However, results showed varying levels of information. So far, only one study compared university students from different fields, and health science students performed better than those from non-health sciences[21].

Our hypothesis was that the awareness about HPV, the Pap smear test and its relation to cervical cancer is still low even among educated women, depending on factors such as age and income. The aim of this study is to verify this hypothesis, analyzing knowledge of the subject by university students from two public institutions of the southeast of Brazil.

METHODS

This was a cross-sectional study conducted with students from the Fluminense Federal University (UFF) and the Centre for Remote Education of the State of Rio de Janeiro (CEDERJ) between January and December 2015. Students attended health science undergraduate courses (medicine, nursing, veterinary medicine, pharmacy, dentistry, biomedicine, and biology) as well as undergraduate courses of other areas of knowledge (Chemistry, Administration, Accounting Sciences, Computer Sciences, and Mathematics). Participants were recruited during class breaks as well as in the classrooms on scheduled exams. Participation was voluntary, and inclusion occurred by spontaneous demand. Inclusion criteria were: females, and age equal to or greater than 18 years old.

Sample size calculations were based on a 90% estimated HPV knowledge prevalence for students from health sciences undergraduate courses (group 1) and 60% for students from other fields of study (group 2), with a 5% precision rate and a 95% confidence level, according to previous studies [17-24]. The formula for sample size determination (OpenEpi Epidemiologic Calculator 2006) indicated a total of 101 and 208 participants from groups 1 and 2, respectively. To compensate for possible losses, the number of participants was increased by 50% in both groups.

Students completed a questionnaire with questions about age (10-year intervals), family income (number of minimum wages per month, classified as high, > 7; medium, 3 to 7; and low, < 3), field of study (health sciences/other) and multiple choice questions on knowledge of the Pap test (frequency, interpretation of the result, and if the participant returns to receive the results), and HPV (main outcomes related to infection: genital warts and cervical cancer, and risk factors for virus infection: two related to sexual partnership, one on the use of condoms, and the other on first sexual intercourse). At the end of the interview, each participant received a folder with main issues asked on the questionnaire.

The study was approved by the Faculty of Medicine Ethics Committee from UFF (CAAE

14660613.2.0000.5243). All respondents were explained the goals of the study, and written consent was obtained. Confidentiality of data was kept throughout the study.

Data were entered and analyzed using IBM SPSS Statistics version 23. Descriptive analysis used means for continuous variables and proportions for categorical ones, testing differences on knowledge, according to the undergraduate field of study, by t-tests and chi-square, respectively. Multivariate analysis was performed by logistic regression to estimate OR and its 95% confidence interval for variables such as income, age, and undergraduate field of study.

In multivariate analysis, variables were dichotomized as follows: high income (greater than or equal to seven minimum wages) compared to low income (less than seven minimum wages); health sciences compared to other fields of study. For age, the cut-off point of 25 years of age was used, considering the age limit proposed by the Brazilian Ministry of Health to initiate the investigation of cervical cancer.

RESULTS

Four hundred and seventy-three university students were interviewed, 154 from health sciences and 319 from other fields of study. The mean age of participants was of 29.8 years old. Significant statistical difference between fields of study, with younger women composing the health sciences field (Table 1) was observed. As for family income, there was also a difference between fields of study, with a higher concentration of high income in the health sciences field (Table 1).

Results related to participants' knowledge on HPV and the Pap smear test are presented in Table 2. Most participants were aware of what the test is, as well as the periodicity in which it should be carried out. However, 30.4% were unaware of the meaning of an altered outcome, and 30% stated that they did not return to the doctor's office to receive the results. Regarding HPV, although most participants had already heard of the virus, 52.4% of the students did not associate the virus with genital warts, and 47.8% did not associate it with cervical cancer either. Knowledge related to HPV and the Pap smear test was significantly higher among students from the health science field compared to students from other areas, except for the interpretation of an abnormal result in the Pap test. Only 10.6% of participants recognized the four situations that increased the risk of virus infection presented in the questionnaire. Considering dichotomously (up to 2 risk factors/3 or more), 60% of the students from the health sciences recognized 3 or 4 factors while only 23% of those from other fields achieved this level of recognition.

A multivariate analysis of factors associated with knowledge on Pap smear test and HPV is shown in Table 3. Knowledge on the Pap smear test (OR = 4.32, 95% CI: 1.75-10.64), as well as its periodicity (OR = 2.53, 95% CI: 1.12-5.71), were higher in individuals with higher family income. Regarding knowledge about HPV, when questioned about the relationship of HPV with genital warts (OR = 1.70, 95% CI: 1.15-

TABLE 1: UNIVERSITY STUDENTS' SOCIODEMOGRAPHIC CHARACTERISTICS, ACCORDING TO THE FIELD OF STUDY

	Total n (%)	Health Science (n=154)	%	Other (n=319)	%	p
Age						
Average (SD)	29.8 (14.1)	24.4		32.5		P*=0.000
Age group (years)						P*=0.000
≤19	52 (11.0)	23	14.9	29	9.1	
20-29	248 (52.4)	107	69.5	141	44.2	
30-39	101 (21.3)	12	7.8	89	28.0	
≥40	61 (12.9)	12	7.8	49	5.1	
Not informed	11 (2.4)	0	0	11	3.6	
Family income***						P**=0.000
High (>7)	194 (41.0)	82	53.2	112	35.1	
Medium (3 to7)	143 (30.2)	30	19.5	113	35.4	
Low (< 3)	128 (27.1)	38	24.7	90	28.2	
Not informed	8 (1.7)	4	2.6	4	1.3	

*t-tests for mean difference ; **chi-square for proportions; ***number of Brazilian minimum wages (MW) per month (in 2015, 1MW= US$228); Baptista AD et al.

TABLE 2: UNIVERSITY STUDENTS' KNOWLEDGE ON THE PAPANICOLAOU TEST (PAP TEST) AND HPV ACCORDING TO THE FIELD OF STUDY

	Total (N=473) N (%)	Health Science (N=154)	%	Other (N=319)	%	p
Have you heard of the Pap test?						p=0.017
Yes	430 (90.9)	147	95.5	283	88.7	
No	43 (9.1)	7	4.5	36	11.3	
What is the periodicity of the Pap test?						p=0.001
Right answer	431 (91.1)	150	97.4	281	88.1	
Wrong answer	42 (8.9)	4	2.6	38	1.9	
What is the meaning of an abnormal result on a Pap?						p=0.688
Right answer	329 (69.6)	109	70.8	220	69.0	
Wrong answer	144 (30.4)	45	29.2	99	31.0	
Do you return to the doctor's office to collect the Pap results?						p=0.001
Yes	331 (70.0)	123	80.0	208	65.2	
No	142 (30.0)	31	20.0	111	34.8	
Have you heard of HPV?						p=0.001
Yes	447 (94.5)	153	99.4	294	92.2	
No	26 (5.5)	1	0.6	25	7.8	
Do you know that HPV may induce genital warts?						p=0.000
Yes	225 (47.6)	93	60.4	132	41.4	
No	248 (52.4)	61	39.6	187	58.6	
Do you know that HPV may induce cervical cancer?						p=0.000
Yes	247 (52.2)	117	76.0	130	40.8	
No	226 (47.8)	37	24.0	189	59.2	
Do you know the risk factors for HPV infection?						p=0.000
Yes*	50 (10.6)	33	21.4	17	5.3	
No	423 (89.4)	121	78.6	302	94.7	

* Participants who recognized the four HPV risk factors presented in the questionnaire were classified as "yes": having multiple sexual partners, having a sexual partner who has had several sexual partners, initiating sexual life before the age of 18 and not using a condom.

TABLE 3: FACTORS ASSOCIATED WITH KNOWLEDGE ON PAP TEST AND HPV (ADJUSTED OR/95% CONFIDENCE INTERVAL)

	PAP smear test				HPV			
	Knowledge on Pap test	Knowledge on Pap test periodicity	Knowledge on Pap test results meaning	Knowledge on the need to receive Pap results	Knowledge on HPV	Knowledge on relationship HPV/ genital warts	Knowledge on relationship HPV/cervical cancer	Knowledge on risk factors for HPV
Income								
High*	4.32 (1.75-10.64)	2.53 (1.12-5.71)	1.26 (0.82-1.93)	1.14 (0.74-1.74)	4.16 (1.21-14.28)	1.70 (1.15-2.52)	1.88 (1.25-2.83)	1.50 (0.78-2.88)
Low**	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Age								
≥ 25 years	1.40 (0.71-2.75)	1.15 (0.57-2.30)	1.53 (0.98-2.37)	1.17 (0.76-1.82)	0.43 (0.15-1.20)	1.50 (0.99-2.27)	0.83 (0.55-1.25)	1.01 (0.49-2.09)
< 25 years	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Field of study								
Health Science	2.25 (0,94-5.37)	4.24 (1.44-12.50)	1.07 (0.67-1.71)	2.24 (1.35-3.70)	8.14 (1.07-61.93)	2.37 (1.53-3.67)	3.66 (2.31-5.81)	4.58 (2.28-9.20)
Other	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

*High income: > 7 Brazilian minimum wages per month; **Low income: ≤ 7 Brazilian minimum wages per month; Baptista AD et al.

2.52) and cervical cancer (OR = 1.88, 95% CI: 1.25-2.83) (Table 3), we observed that higher knowledge occurred among students with high family income. Being a student of health sciences was associated with greater knowledge about the Pap smear test and HPV in most of the questions used in the investigation. Students from the health sciences field held more knowledge about how often the Pap smear test should be performed (OR = 4.24, 95% CI: 1.44-12.50), the need to get the results (OR = 2.24, 95% CI: 1.35-3.70), the association of HPV with genital warts (OR = 2.37, 95% CI: 1.53-3.67) and with cervical cancer (OR = 3.66, 95% CI: 2.31-5.81), as well as risk factors for infections (OR = 4.58, 95% CI: 2.28-9.20).

DISCUSSION

The study corroborated the greater knowledge (more than 90%) among university women when considering questions such as: a) do you know what the Pap smear test is? b) how often should it be carried out? and c) have you ever heard of HPV? In fact, studies carried out in Brazil[14,25-27] and in other countries[28,29] showed that educational level is strongly associated with knowledge of both themes.

However, as the questions became more complex, the level of knowledge on the subject decreased. Although most students know what a Pap smear test is and how often it needs to be performed, 30.4% of students are unaware of the meaning of an abnormal result. This is concerning since the Pap smear test screening is an important tool for cervical cancer prevention, allowing reduction up to 80% in mortality from this type of cancer among populations at-risk[30]. As for HPV, despite high knowledge on the virus by most university students, about half of them did not associate the virus with genital warts. This is a matter of concern since self-examination can be critical to recognize clinical active virus infection. Early detection of active infection is important since late diagnosis is associated with increased rates of complications, cancer among them[30]. The relationship between the virus and cervical cancer development was also unknown by about half of the students, and only a minority knew all the associated risk factors. Again, there is an agreement with Brazilian[20-25] and international studies[28,29]. Caetano et al.[24] had already described a poor knowledge concerning HPV transmission and its association with genital warts among undergraduate students in São Paulo, Brazil, which might favor their engagement in high-risk sexual behavior[25]. It is worrying to note that this lack of knowledge about HPV can be maintained even among graduated health professionals [31].

Starting in 2014, the Brazilian Government implemented the quadrivalent HPV vaccine in the National Immunization Program and made it available for girls aged from 9 to 14 years old. The vaccination process was initially carried out in elementary schools, allowing vaccination and educational programs to be carried out together with students. Currently, vaccination is only offered at primary care units. Thus, the opportunity for actions on health education about HPV and related diseases directed at the target public of the vaccine is often missed. Such modification may have resulted in a low adherence to the Program. Official data from the Information System of the National Immunization Program (SI-PNI) showed that in 2014, vaccination coverage rate was around 65%, considerably lower than the 80% expected[32], and less than half of the girls took the second dose of the vaccine.

When analyzed by field of study, we observed a higher knowledge of health science students in relation to students from other fields, with statistical significance in seven of the eight questions related to the Pap smear test and HPV, as expected. Multivariate analysis showed a strong association between the field of study and knowledge of frequency and need for returning to get the Pap test results and knowledge in all aspects of HPV. This association was also observed in a city in the south of Brazil[21], and in a city in Greece[29]. Health sciences students are privileged by greater access to specific themes and represent future health professionals playing an important role in health education with the population. However, there is still a shortage of knowledge of more complex relationships between HPV, its forms of infection, and related outcomes among these groups of students, with a standard of knowledge similar to that of students from non-health fields students. Only 21% of health students knew the four risk factors associated with HPV. As for non-health students, they generally do not receive formal education on HPV at an undergraduate level. Although lower than that of female health students, the level of general knowledge about the Pap smear test and HPV was greater than that reported in studies with populations of women of different levels of schooling[25-29]. However, for questions of

inter-relations concerning HPV, cancer, and warts, these university students have an equivalent level of knowledge. Considering the general population over 18 years, Abreu et al[14], reported that less than half of the respondents knew about HPV and its associated risk factors, a rate like those here described for students from non-health fields[14].

It is noteworthy that although the knowledge concerning the importance of the Pap smear test was high, 30% of the students do not return to the doctor's office to receive test results, invalidating its protective effect in the prevention of cervical cancer. Studies showed a relationship between greater knowledge, risk behavior, and adherence both to the Pap smear test and HPV vaccination[29,33-35]. Therefore, it seems relevant to extend the knowledge of these topics among women of different socioeconomic levels, in addition to university courses in the health sciences area, considering the relevance of HPV-related morbidity and mortality and cervical cancer.

The analysis of the socioeconomic data among university students evidenced that students from health sciences were younger and of higher income families, corroborating studies conducted by the National Student Performance Exam (ENADE – *Exame Nacional de Desempenho de Estudantes*) throughout the national territory[36]. On the other hand, age, unlike other studies, showed no association with any of the outcomes. Perhaps the form of analysis, with dichotomous variables and the 25-years-old cut-off point, contributed to this result. The result for the income variable was consistent with literature: higher income was associated with greater knowledge on issues related to the Pap smear test and HPV[26-28]. Higher income translates into greater access to information and quality education at the primary and secondary levels, as well as more significant contact with health services and adequate guidelines[26,27].

Although freely available in SUS (*Sistema* Único *de Saúde*), the vaccination program needs to be complemented with educational programs on HPV; otherwise, its effectiveness can be seriously undermined. It is important to note that even if the vaccination coverage rate reaches desirable values, the vaccine does not protect against all HPV genotypes [37,38]. Vaccinated individuals may have the false impression of being permanently protected from the virus as well as from other sexually transmitted infections (STIs).

Strategies to improve vaccination rates should include educational programs to be implemented in schools for the target population of the HPV vaccine, and other approaches designed for different populations, out of school, mainly in primary care[39-41]. At the time of the campaigns, media advertising should be reinforced[41].

Finally, it is essential that the Cervical Cancer Control Program receives ongoing investment from the Brazilian Ministry of Health, expanding its access to the screening program through Pap test preventive screening.

Acknowledgements

We thank Lilha Maria Barbosa dos Santos e a Raquel Alves Pinna for assistance with data from the Centre for remote Education of the State of Rio de Janeiro, São Gonçalo Unit (Cederj).

Conflict of interest

The authors declare no conflict of interest.

Financial support

This work was supported by grants from the Cecierj Foundation/Cederj Consortium/Remote Education, Rio de Janeiro. Aimée Denzeler Baptista, and Carolina Xavier Simão were supported by a scholarship from the National Council for Scientific and Technological Development (CNPq), Brazil.

RESUMO

OBJETIVO: *O papilomavírus humano (HPV) é o vírus sexualmente transmissível mais prevalente no mundo, estando a infecção por este agente associada a um aumento do risco do câncer de colo uterino. A abordagem mais eficaz para o controle desse tipo de câncer continua sendo a triagem por meio do exame preventivo (Papanicolaou). Este estudo analisa o conhecimento de estudantes universitárias de cursos da área da saúde, bem como cursos de graduação de outras áreas do conhecimento com relação a questões importantes sobre o HPV.*

MÉTODO: *Quatrocentas e setenta e três estudantes universitárias responderam a um questionário que avaliava os conhecimentos sobre a infecção pelo HPV, o câncer de colo do útero e o exame preventivo. Após análise descritiva, foi feita a análise multivariada por regressão logística para identificação dos fatores associados à informação sobre o HPV/câncer de colo do útero.*

RESULTADOS: *O conhecimento das universitárias foi maior para questões simples relacionadas ao HPV e ao exame preventivo, mas*

foi menor para as correlações do HPV com verrugas genitais e com o câncer de colo do útero. Ser aluna da área da saúde e ter alta renda foram fatores associados ao maior conhecimento. Somente uma minoria das participantes reconheceu todas as situações que aumentavam o risco de infecção pelo HPV apresentadas no questionário.

CONCLUSÃO: *Os resultados evidenciam a necessidade de realização de campanhas educativas sobre a infecção pelo HPV, do seu potencial como agente de câncer do colo uterino e as formas de prevenção disponíveis.*

PALAVRAS-CHAVE: *Papillomaviridae. Neoplasias do colo do útero. Teste de Papanicolaou. Estudantes. Conhecimento.*

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ORIGINAL ARTICLE

Platelet to lymphocyte and neutrophil to lymphocyte ratios as strong predictors of mortality in intensive care population

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http://dx.doi.org/10.1590/1806-9282.65.5.633

SUMMARY

OBJECTIVE: *Patients in intensive care units (ICU) have greater morbidity and mortality. We aimed to study neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in the ICU population.*

METHODS: *Medical and laboratory data of patients treated in ICU were retrospectively analyzed. Patients were divided into deceased and survived groups.*

RESULTS: *The NLR of survived and deceased groups were 3.6 (0.2-31) and 9.5 (1-40), respectively (p<0.001). The PLR of the survived group (111 [16-537]) was significantly lower than the PLR of the deceased (209 [52-1143]), (p<0.001). An NLR higher than 4.9 had 84% sensitivity and 67% specificity is selecting deceased patients (AUC:0.80, p<0.001). A PLR higher than 112 had 83% sensitivity and 52% specificity in predicting deadly cases (AUC:0.76, p<0.001). Both PLR and NLR were significantly and positively correlated with c reactive protein levels.*

CONCLUSION: *We suggest that physicians should pay particular attention to the treatment of patients in ICU with elevated NLR and PLR.*

KEYWORDS: *Critical care. Neutrophils. Lymphocytes. Blood platelets. Mortality.*

INTRODUCTION

Patients with organ dysfunction and failure, subjects that need to be followed-up closely, and patients who need urgent treatment usually require treatment in Intensive Care Units (ICU). Since mortality and morbidity rates are much higher in the ICU population compared to other patients who do not require treatment in ICU, surrogate markers for predicting mortality in ICU subjects have been established. C-reactive protein (CRP) is one of these markers and usually increases in conditions associated with inflammation or infection[1].

The utility of hemogram-derived inflammatory markers is on the rise recently. Several of hemogram markers have been suggested to be related to inflammatory situations and outcomes in the literature[2-5].

DATE OF SUBMISSION: 17-Apr-2018
DATE OF ACCEPTANCE: 27-May-2018
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Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are two novel markers reproduced from routine hemogram tests. The association between NLR and inflammatory conditions is reported in a recent study[6]. Moreover, Salciccioli et al.[7] proposed that NLR was related to the outcomes of critically ill subjects. Similarly, PLR was also regarded as a prognostic and inflammatory predictor in the ICU population[8]. However, further studies are needed to confirm the association between mortality and these markers and investigate the possible correlation between CRP and PLR and NLR.

In the present retrospective study, we aimed to compare the NLR and PLR values of deceased ICU subjects with those of patients who survived. We also aimed to find out whether PLR and NLR were correlated to the CRP.

METHODS

The medical records of patients treated in the intensive care unit of our institution between April 2017 and January 2018, were enrolled in the study. An approval of institutional directorate was obtained. The data of the subjects were recorded from an institutional computerized database and patient files. Pregnant patients, subjects with known hematologic disorders, on treatment that may interfere with platelet functions, and older than 18 years were excluded from the study. Patients were grouped into two groups according to the outcome, survived or deceased.

Age, gender, reason for ICU admission, duration of intensive care treatment, and laboratory parameters, including, white blood cell count (WBC), neutrophil count (neu), lymphocyte count (lym), hemoglobin (Hb), hematocrit (Htc), platelet count (plt), and c-reactive protein (cRP) were recorded. The NLR was calculated by merely dividing the neu by the lym, and PLR was calculated by dividing the plt by the lym.

Statistical analysis was done using SPSS software (SPSS 10.0 for Windows, IBM Inc., Chicago, Il, USA). Kolmogorov- Smirnov test was conducted to observe the distribution of parameters in the study groups. Homogenous variables were analyzed by independent samples t-test and expressed as mean +/- Standard Deviation, while non-homogenous variables were analyzed by Mann Whitney U test and expressed as median (min-max). Chi-square test was used to analyze categorical variables. The correlation between variables were conducted by Pearson's correlation analyze test. A ROC analysis was performed to define the cut off values of CRP, NLR, and PLR in predicting mortality. Statistical significance was set on a p-value lower than 0.05.

RESULTS

A total of 172 subjects were enrolled in the study; 95 in the survived group and 77 in the deceased. The mean age of the survived group was 63.3 ± 20.4 years and 71.5 ± 14.5 in the deceased group. Subjects in the deceased group were significantly older than those in the survived group (p=0.003). There were 41 women and 51 men in the survived group and 32 women and 45 men in the deceased. Gender was not significantly different between the survived and deceased groups (p=0.83).

Treatment durations in the intensive care unit for patients in the survived and deceased groups were 3 (1-118) and 6 (0-97) days, respectively. The difference was statistically significant (p=0.003).

Levels of WBC, plt, and plasma glucose were not significantly different between study groups (p>0.05 for all). Serum CRP (p<0.001) was significantly higher and Hb (p=0.02) and Htc (p=0.02), were significantly lower in the deceased group compared with the survived group.

The NLR of survived and deceased subjects were 3.6 (0.2-31) and 9.5 (1-40), respectively. NLR was significantly higher in the deceased group compared with the survived (p<0.001). The PLR of the survived group (111 [16-537]) was significantly lower than the PLR of the deceased group (209 [52-1143]), (p<0.001).

The ROC analysis revealed that a CRP higher than 51.5mg/dl had 84% sensitivity and 57% specificity in predicting mortality (AUC:0.76, p<0.001). An NLR higher than 4.9 had 84% sensitivity and 67% specificity in selecting deceased patients (AUC:0.80, p<0.001). A PLR higher than 112 had 83% sensitivity and 52% specificity in predicting mortal cases (AUC:0.76, p<0.001). Figure 1 shows the ROC curves of CRP, NLR, and PLR.

PLR was significantly and positively correlated with CRP levels (r=0.28, p<0.001). Similarly, NLR was also significantly and positively correlated with CRP levels (r=0.29, p<0.001).

DISCUSSION

The results of the present study showed that the elevation of both PLR and NLR was associated with mortality in intensive care patients. Moreover, PLR and NLR were better than CRP in predicting mortality. Finally, both PLR and NLR were significantly correlated with serum CRP levels.

The proportion of NLR to lymphocyte count, namely NLR, can be used as an inflammatory marker in intensive care practice since the physiologic response of circulating leukocytes to inflammatory stress cause an elevation in neutrophil count and decrement in lymphocyte count[9]. Activated neutrophils secrete enzymes such as acid phosphatase, myeloperoxidase, and elastase, which cause tissue destruction[10]. Thus, NLR is proposed as a marker that reflects the inflammatory burden by elevated neutrophil count and indicates physiological stress and poor health condition by decreased lymphocyte count[11]. Indeed, mortality due to coronary heart disease increased with higher NLR levels in studies in the literature[12,13].

The NLR has been introduced as a simple but effective marker of inflammatory condition, since it was found to be correlated with the severity and prognosis of the subjects with sepsis when compared and evaluated along with prognostic scores, such as APACHE 2 (Acute Physiology and Chronic Health Evaluation II) and SOFA (Sepsis-related Organ Failure Assessment)[14]. Similar to the knowledge found in the literature, the present study suggests that NLR could serve as a prognostic factor in the ICU population.

The association between PLR and inflammatory conditions is relatively a more recent finding then the association between inflammation and NLR. Besides NLR, PLR also predicted the prognosis of subjects with hepatic cancer[15]. In another study from 2014, authors reported that both NLR and PLR elevated with the increasing stage of ovarian carcinomas[16]. Moreover, it was found that NLR and PLR were higher in subjects with non-dipper hypertension compared with patients with dipper hypertension[17]. Shimoyama et al.[18] proposed that NLR and PLR were better than all other inflammation-related prognostic scores in predicting outcomes of subjects with gastrointestinal perforation. NLR and PLR were suggested as reliable prognostic indexes in renal cell carcinoma[19], in advanced pancreas carcinoma[20], in mesenteric arterial embolism and thrombosis[21], and in the severity of gallstone pancreatitis[22]. Qi et al.[23] reported that PLR was an independent prognostic marker for survival in melanoma patients in a recently published study. The results of the present study emphasize the significant association between mortality of ICU subjects and elevated PLR suggested by the data in the literature.

Even though CRP is the most important and commonly used inflammatory marker in clinical practice, our results show that both PLR and NLR predicted mortality better than CRP. This is an outstanding result which could add a lot to current literature knowledge.

The inevitable limitation of our study is its retrospective design, which could cause selection bias. Another limitation could be the relatively small study population. However, the results of the present study found a significant association between the prognosis of ICU subjects and PLR and NLR and a significant correlation between CRP and both NLR and PLR.

CONCLUSION

We suggest that automatic blood count devices should be arranged to calculate PLR and NLR levels since higher PLR and NLR levels predict increased mortality in the ICU population. We also suggest that physicians should pay particular attention in the treatment of patients in ICU with elevated NLR and PLR.

RESUMO

OBJETIVO: *Pacientes em unidades de terapia intensiva (UTI) apresentam maior morbimortalidade. Nosso objetivo foi estudar a razão de neutrófilos para linfócitos (NLR) e de plaquetas para linfócitos (PLR) na população de UTI.*

MÉTODOS: *Dados médicos e laboratoriais dos pacientes tratados em UTI foram analisados retrospectivamente. Os pacientes foram divididos em grupos de falecidos e de sobreviventes.*

RESULTADOS: *O NLR de indivíduos sobreviventes e falecidos foi de 3,6 (0,2-31) e 9,5 (1-40), respectivamente (p < 0,001). A PLR dos pacientes sobreviventes (111 [16-537]) foi significativamente menor do que a PLR do grupo dos falecidos (209 [52-1143]), (p < 0,001). Uma RNL maior que 4,9 teve 84% de sensibilidade e 67% de especificidade na previsão de casos mortais. (AUC: 0,80, p < 0,001). Uma PLR*

superior a 112 apresentou sensibilidade de 83% e especificidade de 52% na previsão de casos mortais (AUC: 0,76, p <0,001). Ambos, PLR e NLR, foram significativamente e positivamente correlacionados com os níveis de proteína reativa c.

CONCLUSÃO: *Sugerimos que os médicos prestem atenção especial ao tratamento de pacientes em UTI com valores elevados de RNL e RPL.*

PALAVRAS-CHAVE: *Cuidados críticos. Neutrófilos. Linfócitos. Plaquetas. Mortalidade.*

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ORIGINAL ARTICLE

Abnormal expression of b10 cell frequencies: possible relation to pathogenesis and disease severity of aplastic anemia

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http://dx.doi.org/10.1590/1806-9282.65.5.637

SUMMARY

OBJECTIVE: *Aplastic anemia (AA) is an immune-mediated disease that destroys hematopoietic cells through activated T lymphocytes. B lymphocyte-mediated humoral immunity also plays an important role in the pathogenesis of AA. Regulatory B cell (Breg) subpopulation, which is defined as "B10", secretes interleukin 10 (IL-10). The objective of our experiment was to investigate whether the scale-down proportion of B10 cells in AA patients may play a key role in the pathogenesis.*

METHODS: *A total of 38 AA patients (14 SAA patients and 24 NSAA patients) and 20 healthy control subjects were included. All subjects did not suffer from autoimmune diseases or any other diseases affecting the immune system, such as infectious diseases. Bone marrow mononuclear cells (PBMCs) were isolated and analyzed by Flow cytometry (FCM) and Immunofluorescence double-labeling assay. The relationship between the relative proportions of B10 and ProB10 and their associations to AA, as well as disease severity, were assessed by common clinical indicators and then examined.*

RESULTS: *Our analyses revealed AA patients had significantly lower proportions of peripheral B10 and B10pro compared to healthy controls. SAA patients had a substantially lower percentage of B10 cells and B10pro cells compared to NSAA patients. In addition, B10 cells and B10pro cells were negatively correlated with absolute neutrophil counts, hemoglobin levels and platelet, and absolute reticulocyte counts in AA patients.*

CONCLUSIONS: *The present study attempted to elucidate the potential role of the scale-down proportion of B10 cells in the pathogenesis of AA.*

KEYWORDS: *Anemia, Aplastic. B-Lymphocytes, Regulatory. Interleukin-10.*

INTRODUCTION

Aplastic anemia (AA) is an immune-mediated bone marrow failure disease. The clinical manifestations of AA include pancytopenia and bone marrow pimelosis[1]. The main pathogenesis of AA involves the reduced hematopoietic capacity of the bone marrow caused by the abnormal activation and proliferation of CD4+ T and CD8+ T cells and the abnormal secretion of cytokines [2,3].

B cells not only play a central role in humoral immunity but also regulate the responses of CD4+ T

DATE OF SUBMISSION: 01-Sep-2018
DATE OF ACCEPTANCE: 09-Jan-2019
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cells to foreign and autologous antigens. The study conducted by Hansen et al.[4] demonstrated that the rituximab monoclonal antibody can effectively treat AA once it binds to cluster of differentiation 20 (CD20) on B cells. In the pathogenesis of AA, the effect of abnormal immune function of B cells cannot be ignored[5]. Breg refers to the B cell subpopulation that has negative immunoregulatory effects and secretes negative regulatory factors, such as IL-10, TGF-β, FoxP3 and IL-35 [6]. Among all Bregs, the cells capable of secreting IL-10 are defined as "B10" cells [7]. B10 cells regulate the immune response mainly through secreting the negative regulatory factor IL-10. Human and mouse studies have shown that IL-10 exhibits a variety of multi-directional activities both in vivo and in vitro [6,8-11]. IL-10 inhibits the proliferation of CD4+ T cells and the production of the interferon gamma (IFNγ) cytokine by CD4+ T cells. IL-10 also suppresses the differentiation of Thl7h and type 1 T helper (Th1) cells while inducing the differentiation of naïve T-cells (Th0 cells) toward Th2, thereby affecting the Th1/Th2 balance. Furthermore, IL-10 inhibits the activation of antigen-presenting cells (APCs), macrophages and DCs and suppresses the secretion of proinflammatory cytokines from these cells. In addition, a variety of disease models have demonstrated that IL-10 plays important roles in Treg differentiation and maintenance[12]. The number of Foxp3 + Tregs increases with the amount of B cell-secreted IL-10. In addition to regulating immune responses through the secretion of negative regulatory cytokines, B10 cells act directly on CD4+ T cells via intercellular contacts. For example, B10 cells establish contact with effector T cells through CD40/CD40L, resulting in T cell death [13-15]. Many studies have shown that B10 cells deliver negative immunoregulatory effects in systemic lupus erythematosus (SLE), rheumatoid arthritis, psoriasis, multiple sclerosis, and other immune system disorders through IL-10 secretion[16-19]. However, the role of B10 cells in AA, an immune-mediated hematologic disease, remains unclear.

Since the cluster of differentiation 19 (CD19) is expressed throughout all stages of B cell development, CD19+ B cells were used as B cell markers in the present study. Due to the low proportions of B10 cells and progenitor B10 (B10pro) cells in the human body, the function of B10 cells was determined by analyzing IL-10 cytoplasmic expression levels after 5h of *in vitro* cell culture and stimulation, and the activity of B10pro cells was evaluated by analyzing IL-10 cytoplasmic expression levels after 48h of *in vitro* cell culture and stimulation[20]. For the first time, this study compared the percentages of bone marrow-derived B10 cells and B10 + B10pro cells in CD19+ B cells among patients with severe aplastic anemia (SAA), patients with non-severe aplastic anemia (NSAA) and healthy controls. Also, the present study analyzed the correlations between the proportions of the above cells in the bone marrows of SAA and NSAA patients and the indices reflecting the severity of bone marrow hyperplasia. The purpose of the present study was to explore the potential role and significance of B10 cells in the pathogenesis of AA and provide new clues for the future development of immunotherapy for AA.

METHODS

Research objects

A total of 38 AA patients who had been outpatients or inpatients in the Shandong Provincial Hospital Affiliated with Shandong University between February 2017 and July 2017 were included in the present study. Diagnoses were in accordance with the "Diagnostic criteria and therapeutic principles of hematologic diseases". Among the 38 AA patients, 14 patients suffered from SAA. The 14 patients included 7 males and 7 females, and the median age was 36 (14-65) years. The remaining 24 patients had NSAA; 14 of them were males and 10 were females. The median age of the NSAA patients was 36 (14-65) years. None of the 38 patients had a prior history of blood diseases. The patients did not suffer from autoimmune diseases or any other diseases affecting the immune system, such as infectious diseases. In addition, 20 healthy volunteers whose age and sex compositions were *well matched* with the above patients were selected as normal controls. All subjects and their family members signed informed consent documents. The study was approved by the Academic Ethics Committee of the hospital.

Bone marrow collection and in vitro cell culture

After 5 h of *in vitro* culture and stimulation, the IL-10 content in CD19+ cells reflected the changes in the levels of bone marrow-derived B10 cells. In the present study, bone marrow mononuclear cells (BMMNCs) were stimulated for 5h with a combination of phorbol ester, ionomycin, PIB, CpG and CD40L. Af-

ter 48h of *in vitro* culture and stimulation, the IL-10 content in CD19+ cells reflected the changes in the levels of bone marrow-derived B10 + B10pro cells. In the present study, BM-MNCs were stimulated with CpG and CD40L for 48 h. In addition, PIB stimulation was applied during the last 5h.

Bone marrow samples (20 mL) were harvested from the AA patients and the age- and sex-matched healthy controls and were placed in collection tubes with heparin anticoagulant (BD Biosciences). After the addition of an equal volume of lymphocyte separation medium (Tianjin HaoYang Biological Manufacture Co., Ltd.) to the tubes, Ficoll density gradient centrifugation was performed at room temperature to isolate the mononuclear cells. Subsequently, cell viability was examined using Trypan blue (Beijing Solarbio Science & Technology Co., Ltd.). The percentage of viable cells exceeded 96%, indicating that the cell preparation could be used in the subsequent experiments. The isolated mononuclear cells were resuspended in the Roswell Park Memorial Institute (RPMI) 1640 medium (Biological Industries) containing 10% calf serum (Biological Industries) at a concentration of 2×10^6 cells/L and were then seeded into 24-well tissue culture plates. The cells were divided into a 5-h culture group and a 48-h culture group. The controls were divided in the same manner. The 5-h culture group was treated as follows: First, phorbol ester (25 ng/mL, MultiSciences (Lianke) Biotech Co., Ltd.), ionomycin (0.5 μg/mL, MultiSciences (Lianke) Biotech Co., Ltd.) and Brefeldin A (PIB, 0.5 μL/mL, MultiSciences (Lianke) Biotech Co., Ltd.) were added to each well of the cells. Subsequently, the cells were stimulated with 5-μg/mL CpG (ODN 7909, InvivoGen) and 0.5-μg/mL CD40 ligand (CD40L, R&D Systems) for 5h. The 48-h culture group was stimulated with 5 μg/mL CpG and 0.5 μg/mL CD40L for 48h. PIB stimulation was applied during the last 5h. All cells were cultured in an incubator at 37°C and in an atmosphere of 5% CO2.

Flow cytometric (FCM) analysis

The stimulated cells were collected in fluorescence-activated cell sorter (FACS) tubes, washed once with 3 mL of phosphate-buffered saline (PBS) and centrifuged at 1,000 r/min for 5 min. The supernatants were discarded. Subsequently, 20 μL of the anti-human cluster of differentiation 19 (CD19) antibody (BD Biosciences) was added to each tube of cells. After incubation for 20 min at room temperature in the dark, the cells were washed once with 2 mL of PBS (centrifugation at 1,000 r/min for 5 min), and the supernatants were again discarded. The cells were then incubated with 500 μL of Fixation/Permeabilization Solution (BD Biosciences) for 20 min at room temperature in the dark. After centrifugation at 500xg for 5 min, the supernatants were discarded. The cells were fixed in 2 mL of 1xWash Buffer for 10 min at room temperature in the dark and then centrifuged at 500xg for 5 min. After removal of the supernatants, the cells were incubated with 5 μL of allophycocyanin-labeled anti-human IL-10 antibody (BD Biosciences) for 30 min at room temperature in the dark. The cells were then washed twice with 2 mL of PBS (centrifugation at 1,000 r/min for 5 min). The resulting supernatants were discarded, and the cells were resuspended in 400 μL of PBS. The experimental results were analyzed by flow cytometry (BD Biosciences, CellQuest software).

Immunofluorescence double-labeling assay

Bone marrow-derived mononuclear cells growing on glass coverslips were stimulated *in vitro* for 5h and 48h. Once the cells were dried slightly, they were incubated with 50-100 μL of fixation/permeabilization solution at room temperature for 20 min and then washed 3 times with PBS, each wash for 5 min. To block the non-specific binding of the antibody, the cells were evenly covered with 3% bovine serum albumin (BSA) solution and blocked at room temperature for 30 min. (When the primary antibody was derived from goat, 10% normal rabbit serum was used as the blocking reagent. When the primary antibody was raised in a species other than goats, 3% BSA was used as the blocking reagent.) After incubation, the blocking solution was gently shaken off. Rabbit anti-CD19 monoclonal antibody (purchased from Abcam, UK; diluted 1:100 in PBS) and mouse anti-IL-10 monoclonal antibody (purchased from Biolegend Company, USA; diluted 1:100 in PBS) were added dropwise to the cell culture plates. The plates were placed in a humidified container and incubated at 4°C overnight. Following incubation with the primary antibodies, the plates were washed 3 times (5 minutes each) on a *shaker and dried slightly by shaking off the wash buffer*. Subsequently, the cells were covered with the solution containing the corresponding secondary antibody (1:400 dilution, purchased from Servicebio, China) and incubated at room temperature for 50 min (the anti-CD19 antibody was directly conjugated

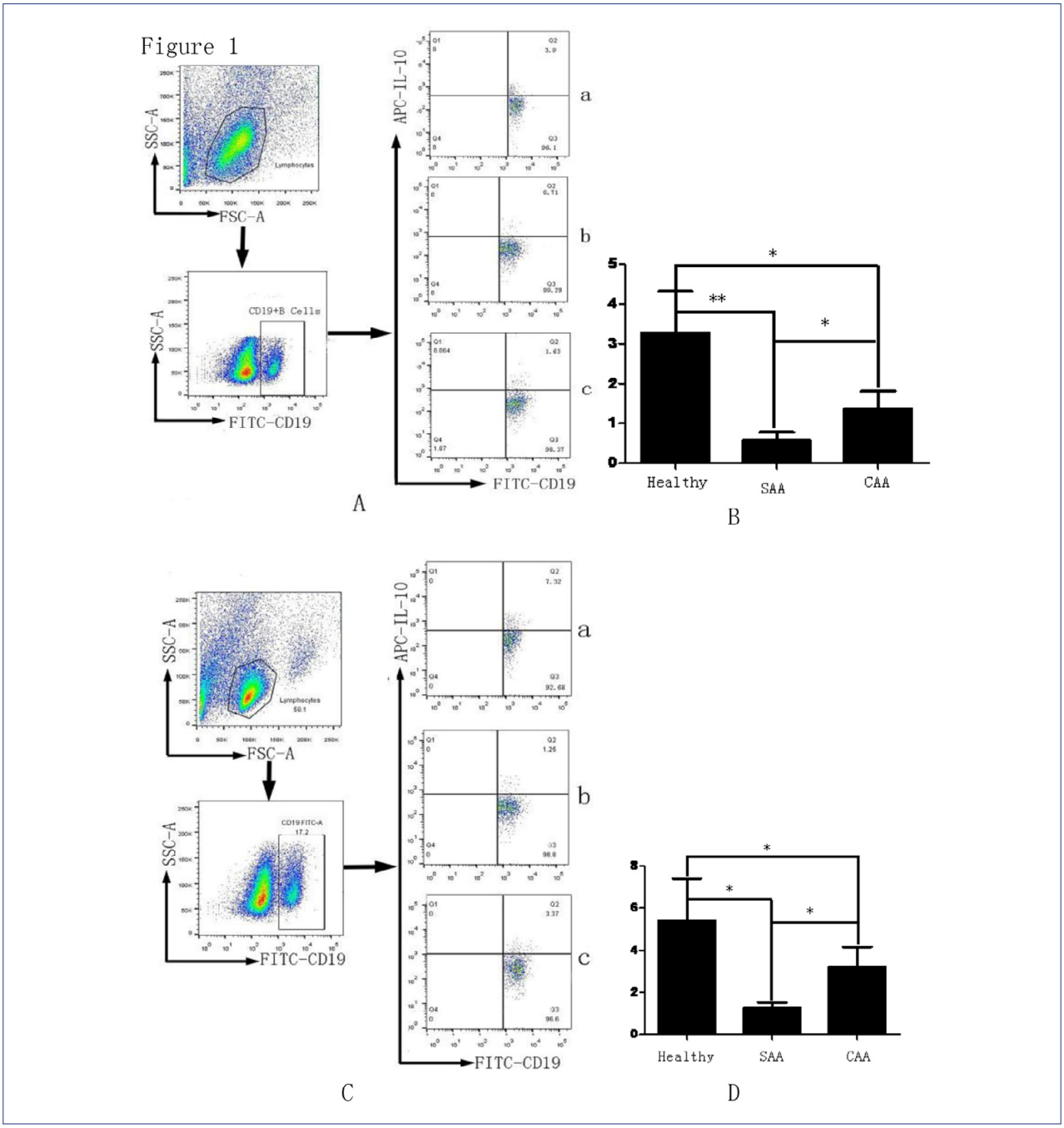


FIGURE 1 (A-B): Presence of B10 cells in the SAA, NSAA, and healthy control groups: Side scatter (SSC-A) measures intracytoplasmic granules, while forward scatter (FSC-A) measures cell size. To reflect the changes in the percentages of B10 cells, BM-MNCs were stimulated ***in vitro*** with a combination of phorbol ester, ionomycin, PIB, CpG and CD40L for 5h. A (a). The ratio of B10 cells to CD19+ B cells in the healthy control group. A (b). The ratio of B10 cells to CD19+ B cells in the SAA group. A (c). The ratio of B10 cells to CD19+ B cells in the NSAA group. B. The ratio of B10 cells to CD19+ B cells in SAA patients (0.57±0.21%) vs. the healthy control group (3.28±1.04%); the ratio of B10 cells to CD19+ B cells in NSAA patients (1.38±0.43%) vs. the healthy control group (3.28±1.04%); the ratio of B10 cells to CD19+ B cells in SAA patients (0.57±0.21%) vs. NSAA patients (1.38±0.43%). The results of statistical significance testing were as follows: * represents P<0.05; ** represents P<0.01.

FIGURE 1 (C-D): Percentages of B10 + B10pro cells in AA patients and the healthy control group: Side scatter (SSC-A) measures intracytoplasmic granules, while forward scatter (FSC-A) measures cell size. In the present study, BM-MNCs were stimulated with CpG and CD40L for 48h. In addition, PIB stimulation was applied during the last 5h. The percentages of B10 + B10pro cells in CD19+ B cells were determined in AA patients and the healthy control group. A (a). The ratio of B10 + B10pro cells to CD19+ B cells in the healthy control group. A (b). The ratio of B10 + B10pro cells to CD19+ B cells in the SAA group. A (c). The ratio of B10 + B10pro cells to CD19+ B cells in the NSAA group. (B). The ratio of B10 + B10pro cells to CD19+ B cells in SAA patients (1.28±0.25%) vs. the healthy control group (5.42±1.99%); the ratio of B10 + B10pro cells to CD19+ B cells in NSAA patients (3.2±0.96%) vs. the healthy control group (5.42±1.99%); the ratio of B10 + B10pro cells to CD19+ B cells in SAA patients (1.28±0.25%) vs. NSAA patients (3.2±0.96%). The results of statistical significance testing were as follows: * represents P<0.05; ** represents P<0.01.

to a label, and no secondary antibody was needed). The coverslips were placed on a *shaker and* washed 3 times in PBS (pH 7.4) for 5 min each with shaking. The coverslips were *dried slightly by shaking off the wash buffer.* To counterstain the nuclei, 4',6-diamidino-2-phenylindole (DAPI) was added dropwise to the coverslips and incubated for 10 min at room temperature in the dark. The coverslips were again placed on a *shaker and* washed 3 times in PBS (pH 7.4) for 5 min each with shaking. The coverslips were *dried slightly by shaking off the wash buffer and mounted using an anti-quenching mounting medium.* The slides were observed under a fluorescence microscope, and images were collected. Semi-quantitative analysis was performed using TissueQuest 4.0.1.0140 software. The relative counts of the $CD19^+$ $IL\text{-}10^+$ B cells in the bone marrow-derived mononuclear cells after 5 and 48 h of *in vitro* stimulation were determined by calculating the ratios of the numbers of CD19 and IL-10 dots to the number of DAPI dots.

Clinical evaluation

Complete medical histories were obtained from all patients, and physical examinations were performed. In addition, fasting peripheral blood was collected from the two groups of patients in the early morning shortly after the patients awoke. The absolute neutrophil counts, hemoglobin levels and platelet and absolute reticulocyte counts were determined by routine blood testing.

Statistical analysis

Statistical analysis was conducted using SPSS19.0 software. The measurement data are expressed as x±s. The t-test was employed to determine whether statistically significant differences existed between the means of two groups. Correlation analysis was performed using Linear correlation. A p-value lower than 0.05 indicated that the difference was statistically significant.

RESULTS

Regarding the percentage of B10 cells and B10+B10pro cells in AA patients versus healthy controls.

Flow cytometric analysis:

1) In bone marrow derived from SAA patients, B10 cells accounted for 0.57±0.21% of the CD19+ B cells, while in the normal control group, B10 cells accounted for 3.28±1.04% of the CD19+ B cells; the difference was statistically significant (t=6.26, P<0.01). Similarly, the percentage of B10 cells in the CD19+ B cells was statistically significantly lower in the bone marrow derived from NSAA patients (1.38±0.43%) in comparison to the normal control group (3.28±1.04%) (t=4.14, P<0.05). Moreover, the percentage of B10 cells in the CD19+ B cells was statistically significantly lower in the bone marrow derived from SAA patients (0.57±0.21%) in comparison to the bone marrow derived from NSAA patients (1.38±0.43%) (t=4.12, P<0.05). The results are shown in Figure 1 (A-B).

2)The percentage of B10 + B10pro cells in the CD19+ B cells was lower in the bone marrow derived from SAA patients (1.28±0.25%) in comparison to the normal control group (5.42±1.99%), and the difference was statistically significant (t=5.07, P<0.05). Similarly, the percentage of B10 + B10pro cells in CD19+ B cells was statistically significantly lower in the bone marrow derived from NSAA patients (3.2±0.96%) in comparison to the normal control group (5.42±1.99%) (t=2.47, P<0.05). Moreover, the percentage of B10 + B10pro cells in CD19+ B cells was statistically significantly lower in the bone marrow derived from SAA patients (1.28±0.25%) in comparison to the bone marrow derived from NSAA patients (3.2±0.96%) (t=4.76, P<0.05). The results are shown in Figure 1 (C-D).

Immunofluorescence assay

1) The results of the semi-quantitative immunofluorescence assay were as follows. Compared with the healthy controls(A), the percentages of CD19 + IL-10 + B10 cells in CD19+ B cells were decreased in SAA(C) and NSAA(B) patients after stimulating the BM-MNCs in vitro for 5h. Moreover, the percentage of CD19 + IL-10 + B10 cells was lower in SAA patients in comparison to NSAA patients. The results are shown in Figure 2 (a).

2). The results of the semi-quantitative immunofluorescence assay were as follows: after stimulating the BM-MNCs in vitro for 48 h, the percentages of B10 + B10pro cells in CD19+ B cells were lower in SAA(B) and NSAA(C) patients compared with the healthy controls(A). Moreover, the percentage of B10 + B10pro cells was lower in SAA patients in comparison to NSAA patients. The results are shown in Figure 2 (b).

The percentages of B10 cells and B10 + B10pro cells in the bone marrows of AA patients were negative with the neutrophil, reticulocyte and platelet counts.

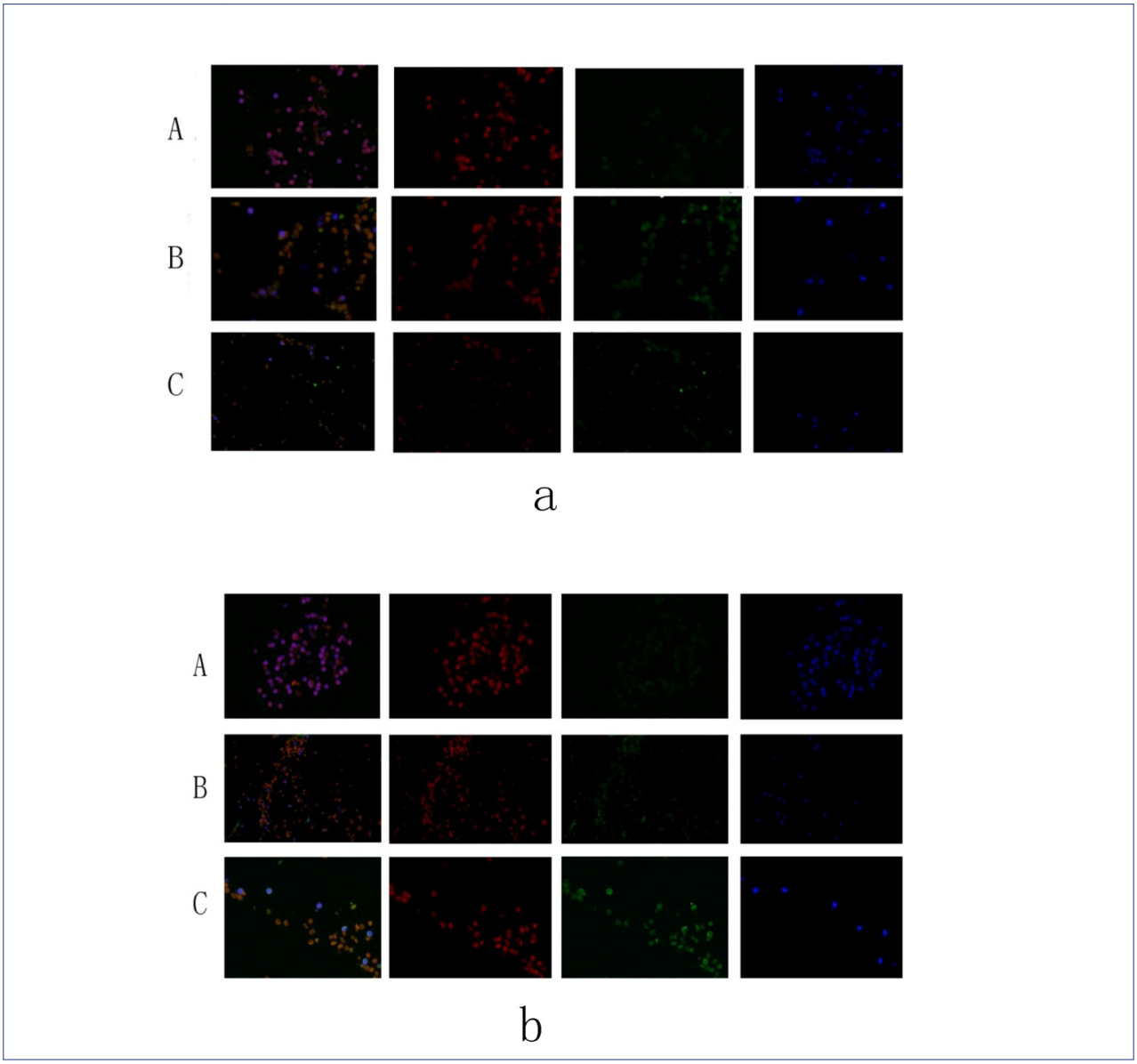
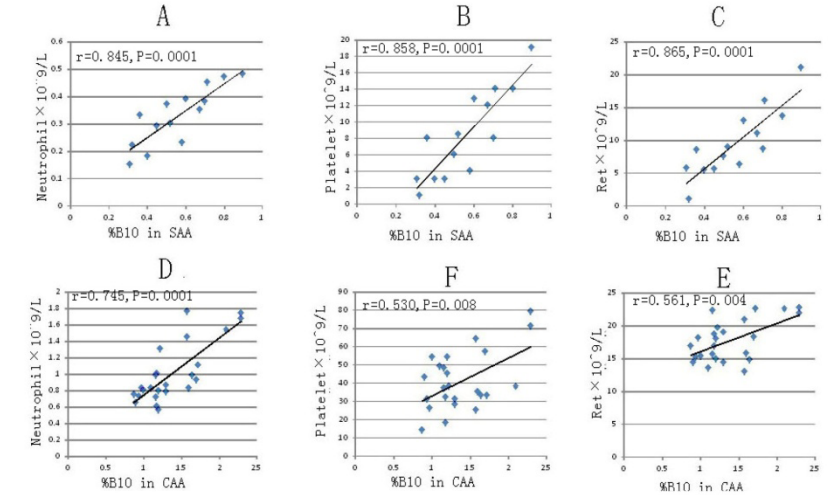


FIGURE 2(A-B)
Blue – nucleus; Green – CD19 (located in cell membranes); Red – IL-10 (located in the nucleus or the cytoplasm).
B10pro cells in the bone marrows of AA patients and the neutrophil, reticulocyte, and platelet counts
1) In patients with SAA, the ratio of B10 cells to CD19+ B cells was positively correlated with peripheral blood neutrophil, reticulocyte and platelet counts. In patients with NSAA, the percentage of B10 cells was positively correlated with peripheral blood neutrophil, reticulocyte and platelet counts. The results are shown in **FIGURE 3(A)**.
2) In patients with SAA, the ratio of B10 + B10pro cells to CD19+ B cells was positively correlated with peripheral blood neutrophil, reticulocyte and platelet counts. In patients with NSAA, the ratio of B10 + B10pro cells to CD19+ B cells was also positively correlated with peripheral blood neutrophil, reticulocyte and platelet counts. The results are shown in **FIGURE 3(B)**.
The peripheral blood neutrophil, reticulocyte and platelet counts were decreased in SAA patients compared with the healthy control group. Similarly, the peripheral blood neutrophil, reticulocyte and platelet counts were decreased in NSAA patients compared with the healthy control group. Moreover, the peripheral blood neutrophil, reticulocyte and platelet counts were reduced in SAA patients in comparison to NSAA patients. The results are summarized in **FIGURE 3(C)**.

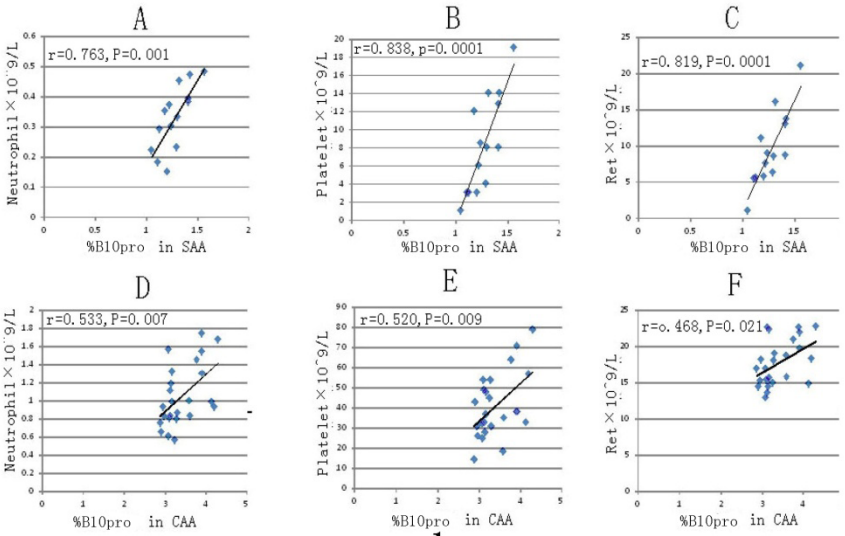
1) In patients with SAA, the ratio of B10 cells to CD19+ B cells was positively correlated with peripheral blood neutrophil, reticulocyte and platelet counts. In patients with NSAA, the percentage of B10 cells was positively correlated with peripheral blood neutrophil, reticulocyte and platelet counts. The results are shown in Figure 3 (a).

2) In patients with SAA, the ratio of B10 + B10pro cells to CD19+ B cells was positively correlated with peripheral blood neutrophil, reticulocyte and plate-

Figure 3



a



b

Group	Neut×10^9/L	Ret×10^9/L	PLT×10^9/L
SAA	0.33±0.11**	8.31±5.37** ▲▲	8.57±4.04** ▲▲
NSAA	1.05±0.34**	17.71±3.16**	40.96±16.13**
Healthy	4.7±1.0	65.0±6.1	229.5±41.8

*P<0. 05, **P<0. 01, compared with Healthy group; ▲P<0. 05, ▲▲P<0. 01, compared with NSAA group.. Neut: neutrophil ; Ret:ret; PLT: palette.

c

FIGURE 3

let counts. In patients with NSAA, the ratio of B10 + B10pro cells to CD19+ B cells was also positively correlated with peripheral blood neutrophil, reticulocyte and platelet counts. The results are shown in Figure 3 (b).

3) The peripheral blood neutrophil, reticulocyte and platelet counts were decreased in SAA patients compared with the healthy control group. Similarly, the peripheral blood neutrophil, reticulocyte and platelet counts were decreased in NSAA patients compared with the healthy control group. Moreover, the peripheral blood neutrophil, reticulocyte and platelet counts were reduced in SAA patients in comparison to NSAA patients. The results are summarized in Figure 3 (c).

DISCUSSION

For the first time, our present study showed that the percentages of bone-marrow-derived B10 cells in CD19+ B cells were lower in AA groups compared with the healthy control group using flow cytometric analysis and immunofluorescence assays. Moreover, the percentage of B10 cells was lower in the SAA group in comparison to the NSAA group. Also, the correlations between the percentages of B10 cells and the clinical parameters that reflected the severity of bone marrow hyperplasia were positive. Therefore, B10 cells are likely to play a pivotal role in the pathogenesis of AA.

AA is an autoimmune disease characterized by T cell hyperfunction-induced bone marrow hematopoietic tissue damage. The specific pathogenesis of AA is still not clear. Tregs maintain homeostasis, induce immune tolerance and prevent the occurrence of autoimmune diseases. However, the numbers of Tregs are decreased in the peripheral blood and bone marrows of AA patients, resulting in an inability to inhibit effector T cells normally [21]. However, the role of B10 cells in AA, an immune-mediated hematologic disease, remains unclear.

In the human body, T lymphocyte-mediated cellular immunity and B lymphocyte-mediated humoral immunity mutually influence and complement each other. Some scholars believe that the immune disorder in AA is also correlated with B cell-mediated humoral immunity [5] since kinectin, moesin and DRS-1 antibodies have been detected in the sera of AA patients [22-24]. B10 cells are a particular subpopulation of B cells with negative immunoregulatory capability. The immunoregulatory activity of B10 cells in immune responses has attracted special attention. Studies show that IL-10 regulates the Th1/Th2 balance, induces the apoptosis of effector T cells, reduces the production of tumor necrosis factor alpha (TNFα), IFNγ and other inflammatory factors and downregulates autoimmune and excessive immune responses [20,25]. In our study, B10 cells and B10 + B10pro cells levels were lower in AA patients than in healthy individuals; and we also found a correlation with severity. B10 cells promote Treg cell differentiation and simultaneously inhibit inflammatory cytokine production by T effector cells. Kessel et al.[26] found that B10 enhances the expression levels of Foxp3 and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) in Tregs through direct cell-cell contact. The decrease in the percentage of B10 cells limited the secretion of the negative regulatory factor IL-10. As the amount of B10 cell-secreted IL-10 decreases, the above immunosuppressive effects decline accordingly in AA patients. In summary, B10 cells may act on T cells and other related immune cells through IL-10 secretion and intercellular contact, thereby exerting a negative immunoregulatory effect.

The progenitor B (pro-B) cell stage is critical in B cell development and maturation. Pro-B cells have the potential to develop into mature B cells. Many studies have shown that the percentage of B10 + B10pro cells is increased in the peripheral blood of patients with various immune system disorders in comparison to the healthy control group [20]. The present study found that the percentages of B10 + B10pro cells in CD19+ B cells were decreased in the bone marrows of AA patients compared with the healthy control group, and correlation with severity. The above data suggest that B10pro cells may be damaged or experience differentiation disorder or obstacles exist in the process of B10pro cell development toward mature B10 cells in AA patients. While the specific factors that cause the injury and differentiation disorder have yet to be identified.

A previous study showed that in patients with AA, IL-10 promotes the growth of hematopoietic progenitor cells and enhances erythrocyte colony formation[22]. The decrease in absolute neutrophil, platelet and reticulocyte counts indicated the severity of AA. The statistical results of the present study showed that the absolute neutrophil, platelet, and reticulocyte counts in the peripheral blood of pa-

tients with SAA and NSAA were positively correlated with the ratio of B10 cells to CD19+ B cells in the bone marrow. The above results indicate that the decrease in the percentage of B10 cells contributes to the pathogenesis of AA and is related to the severity of AA. The lower the B10 cell level, the more severe the disease is.

The present study found that the percentages of B10 cells and B10 + B10pro cells in CD19+ B cells were decreased in the bone marrows of AA patients in comparison to the healthy control group. Such a finding suggests that B10 cells inhibit DCs, APCs, and macrophages and attenuate the activity of effector T cells, thereby affecting T cell-mediated immunity. This finding is conducive to the understanding of the potential role of B10 cell ratio changes in the pathogenesis of AA. It is not clear whether the function of B10 cells is normal in the bone marrow of AA patients and whether there are defects in B10 cell-activating signals in the bone marrow. The inhibition of B10 cells in abnormal T cell-mediated immunity and the targets of B10 cells in AA are also unclear. The potential immune functions of B10 cells in the pathogenesis of AA need to be further explored.

Conflict of interests

The authors declare no conflicts of interests.

Acknowledgments

This work was supported by grants from the National Science Foundation of Shandong (No.2016GSF201049), the key research and development project of Province (No. 2015GSF118058) and the Key Research and Development Project of Shandong Province (No. 2015GSF118025)

RESUMO

OBJETIVO: *A anemia aplástica (AA) é uma doença imunomediada que destrói células hematopoiéticas por meio dos linfócitos T ativados. A imunidade humoral mediada por linfócitos B também desempenha um papel importante na patogênese da AA. A subpopulação de células B reguladoras (Breg), que é definida como "B10", secreta interleucina 10 (IL-10). No experimento, investigou-se se a proporção reduzida de células B10 nos pacientes de AA pode desempenhar um papel-chave na patogênese.*

MÉTODOS: *Um total de 38 pacientes de AA (14 pacientes de anemia aplástica grave e 24 pacientes de anemia aplástica não grave) e 20 indivíduos de controle saudáveis foram incluídos. Todos os indivíduos não sofriam de doenças autoimunes ou de quaisquer outras doenças que afetam o sistema imunológico, tais como doenças contagiosas. As células mononucleares da medula óssea (PBMCs) eram isoladas e analisadas por citometria de fluxo (FCM) e ensaio de dupla marcação por imunofluorescência. A relação entre as proporções relativas de células B10 e as células ProB10 e as suas associações à AA, assim como a gravidade da doença avaliada por indicadores clínicos comuns, foram examinadas.*

RESULTADOS: *Nossas análises revelaram que os pacientes de AA têm proporções significativamente menores de células B10 e células ProB10 periféricas em comparação com indivíduos de controle saudáveis. Os pacientes de anemia aplástica grave tiveram uma percentagem substancialmente menor de células B10 e células B10pro em comparação com pacientes de anemia aplástica não grave. Além disso, as células B10 e B10pro foram negativamente correlacionadas com contagens absolutas de neutrófilos, níveis de hemoglobina e plaquetas e contagem de reticulócitos absolutos nos pacientes de AA.*

CONCLUSÕES: *Além disso, o estudo presente tentou elucidar o papel imunorregulatório potencial das células B10 na patogênese da AA e fornecer uma nova estratégia para a aplicação de imunoterapia baseada na célula B para tratar a AA no futuro.*

PALAVRAS-CHAVE: *Anemia aplástica. Linfócitos B reguladores. Interleucina-10.*

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ORIGINAL ARTICLE

Investigation of the relationship between umbilical cord pH and intraventricular hemorrhage of infants delivered preterm

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http://dx.doi.org/10.1590/1806-9282.65.5.647

SUMMARY

OBJECTIVE: *We measured the level of pH gases in premature infants at birth, and examined the relationship between brain ultrasonography on the third and seventh day after birth. A case-control study conducted at the Neonatal Intensive Care Unit (NICU) of Shahid Akbar Abadi Hospital, Iran, during the years 2016-2017.*

METHODS: *All premature infants who were admitted to NICU were enrolled in the current study. At birth, a blood gas sample was taken from the umbilical cord of the infants. On the third and seventh day after birth, an ultrasound of the brain of each neonate was performed by a radiologist. The umbilical cord was evaluated for blood gases in 72 neonates (mostly boys).*

RESULTS: *Sixty-six newborns had normal sonography, and 16.7% (12 cases) had anomalies. A total of 75% of the 8 infants with intravenous bleeding were girls, which were significantly different from those in the non-hemodynamic group (62.5% male) (P 0.049). However, the type of delivery, mean weight, height, head circumference, the circumference of the chest, and Apgar score did not differ between the two groups. Mean pH, HCO^{3-} and PCO2 in umbilical cord blood gas samples were not significantly different between the two groups with or without intraventricular hemorrhage (IVH). Although it was not related to gender and type of delivery in newborns*

CONCLUSION: *Blood gases do not help in determining the occurrence of IVH in infants. Nevertheless, it is associated with immaturity and fetal age.*

KEYWORDS: *Umbilical cord. Blood gas analysis. Cerebral hemorrhage. Infant, newborn.*

INTRODUCTION

According to the World Health Organization (WHO), preterm labor refers to the onset of uterine contractions after the 20th week and the 37th week of pregnancy, and the infants born of these births are called premature babies.[1] Among preterm infants, most have problems at the gestational age of 23-32 weeks. Although this group accounts for 1%-2% of all premature infants, it consists of 50% of long-term neurological morbidity and 60% of perinatal mortality.[2,3] The prevalence of prematurity in the United States and Europe has been estimated to be 10-8% and 7-5% respectively. Nonetheless, prematurity causes

DATE OF SUBMISSION: 22-Oct-2018
DATE OF ACCEPTANCE: 20-Dec-2018
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60 to 80 percent mortality in infants without anomalies.[4] It is noteworthy that infant mortality decreases by half starting from 25 to 37 weeks of gestation per week.[5] Some of the known risk factors involved in an early delivery include maternal age below 17, smoking, previous preterm delivery, multiple sexes, infection, and other issues such as black ethnicity and low socioeconomic status.[6-8] Preterm babies may present several problems, including intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), cerebral palsy (CP), frequent admissions, infection, apnea, among others. Prevention of early delivery is the best treatment.[9,10] Brain injury and functional disorders of the brain in preterm infants are associated with hypoxia hippocampus, hypoxia hypercapnia, and acidaemia.[11] Disorders of blood gases are more likely to cause brain damage than other factors.[12] For example, in preterm infants, inflammation of the placenta is accompanied by an increase in alveolar pressure of oxygen (PAO2) and the umbilical cord inflammation is linked to a reduction in partial carbon dioxide pressure (PCo2).[13] Intravascular endotoxins cause hypoxemia without acidosis, while chronic vascular disorders associated with pre-birth cause hypoxemia with acidosis in neonates.[14] Severe acidosis at birth is one of the most important predictors of death or neurodevelopmental impairment (NDI) in full-term infants who are suspected of hypoxic-ischemic encephalopathy (HIE), which is correlated with poor prognosis among these patients. However, in preterm newborns, several factors such as organ underdevelopment, IVH, infection, hypoxia due to an absence of lung function, and poor nutrition cause death or NDI. Regarding these combined problems, the role of acidosis and other metabolic disorders in preterm infants is not completely clear.[15] Overall, there are two main causes of neonatal white brain injury: ischemia and re-establishment of cerebral perfusion in preterm infants, which are often associated with cerebral vascular autoregulatory dysfunction and other maternal or fetal bacterial infections that trigger the secretion of various cytokines and lead to brain damage.[16] Bleeding inside the germinal matrix or intracerebral hemorrhages in neonates is associated with a risk of death and complications such as future cerebral palsy. The incidence of these complications is inversely related to gestational age. However, low-grade bleeding is not associated with the risk of developing cerebral palsy. Diagnosis of cerebral hemorrhages before birth and during the first few hours of birth is possible; most bleeding occurs within the first 48 hours, and only 10% occur after the first week of birth.[17]

IVH refers to bleeding into the ventricular system of the brain. Low gestational age and low birth weight, intrauterine infections, vaginal delivery, low Apgar score, acidosis, and sepsis. Additionally, prematurity is considered the main risk factor for this complication. Despite the decline of severe IVH (Grades 3 and 4) in recent decades, IVH has also been associated with high morbidity in preterm newborns, especially with a very low birth weight (ELBW). The disorder in cerebrovascular regulation is known as the most common etiology of these bleedings. On the other hand, hypercapnia during the first 3 days of birth causes cerebrovascular autoregulatory dysfunction and is accompanied by a high incidence of severe IVH. Some studies have shown that the effect of PaCo2 on cerebral circulation was related to the pH of arterial gases. However, most of these studies examined PaCo2 levels regardless of pH and base deficit (BD) levels, or the effect of hypercapnia at > 7.20 pH was evaluated. Therefore, PaCo2 may have its own effect independent of the pH of blood gases in the development of intense IVH.[18,19]

Oxygen is widely used in the regeneration and treatment of pulmonary diseases in premature infants. Additionally, preterm infants are at increased risk of developing hyperoxia due to the sudden increase in oxygen in the environment compared with intrauterine oxygen. This hyperoxia causes bronchopulmonary abnormalities, retinopathy, and apoptosis of the brain cells; therefore, its level of saturation in blood gases is very important.[20] The importance of brain hemorrhage and its complications are not overlooked either at or after admission.

The occurrence of risks such as hydrocephalus, CP, and other complications of cerebral hemorrhage are also very important. In this study, we show it is possible to reduce these risks by demonstrating the importance of analyzing blood gases and its relation as a sign of major risk of neonatal brain hemorrhage. The results will help reduce brain-related complications in neonates.

In this study, the pH of blood gases was evaluated at the birth of premature infants and its relationship with brain ultrasound at the third and seventh day after birth was also investigated.

METHODS

Ethics committee statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards and were approved by the Iran University of Medical Sciences Institutional Review Board (Protocol number 2016/2957, October 2016.10.19).

In a case-control study, all preterm infants who were admitted to the Neonatal Intensive Care Unit (NICU) of Shahid Akbar Abadi Hospital during the years 2016-2017 were evaluated. Data from data collection forms were extracted for all premature infants admitted by census method and all those who met the inclusion criteria without any exclusion criteria were included.

Inclusion criteria

Preterm infants (birth with gestational age 20 to 37 weeks) with survival for 3 days after birth.

Exclusion criteria

Term babies; death three days after birth; failure in collecting the sample of arterial gas at birth; incomplete ultrasound reports on the third day

Data collection

Demographic data of patients including gender, gestational age, the type of delivery, family history of anomalies and the presence or absence of other associated anomalies were recorded for each patient in the checklist. On the third and seventh day after birth, a brain ultrasound was performed by a radiologist and observations were finally recorded. A sample of blood gas was taken from the umbilical cord at birth; if sampling was not possible, samples were taken from the peripheral blood vessels and sent immediately to measure the blood gas indexes, HCo3, PCo2, and pH. Information was then recorded in the relevant checklist. On the third day after birth, cerebral ultrasound was performed by a radiologist using Sonosite Model P12163 with a linear probe (made in Malaysia); microcephaly, macrocephaly, ventriculomegaly, and echolucent lesions were subsequently evaluated. On the seventh day after birth, the ultrasound was repeated, and observations from both ultrasound investigations were recorded separately in the checklist for each neonate. A checklist containing patient information was completed. After collecting the data, the obtained results were evaluated statistically. The researchers were committed to the dispositions of the Helsinki Declaration, and all ethical issues were approved by the Ministry of Health of Iran. The names and characteristics of the patients were known only by the researchers.

Statistical analysis

The results of the quantitative variables were presented as mean and standard deviation (mean ± SD), while qualitative and stratified variables were shown as percentages. Quantitative variables were compared using the t-test or, if there was an abnormal distribution, the Mann-Whitney test. The comparison between qualitative variables was also performed using the chi-squared test or the Fisher exact test. Correlations between quantitative variables were investigated using the Pearson correlation coefficient test and Spearman rank correlation. For data analysis, Statistical Package for the Social Sciences (SPSS) software version 20 was used. The significance level was considered to be < 0.05.

RESULTS

The study consisted of 72 preterm infants, 42 boys (60.9%) and 27 girls (39.1%), born at a mean gestational age of 31.03 ± 2.87 weeks (Figures 1A and B). The frequency of infants based on the age groups is shown in Table 1. The age group of 32-36 weeks was determined to be the most frequent. (Table 1 and Figure 1C). Moreover, 74% (n = 52) of neonates were born via cesarean delivery, while 25.7% (n = 18) via normal delivery (Figure 1D). The weight of all neonates at birth was between 570 and 3450 grams (mean 1515 ± 1601.6 g) and the height varied from 33 to 54 cm (with a mean of 42.74 ± 4.83 cm), head circumference (29.02 ± 2.72cm) and circumference of the breast (26.63 ± 4.6), (Figures 5 to 8, 10, 11; Table 3). The mean of pH, HCo3, and PCo2 in umbilical cord blood samples were determined as 7.22 ± 0.8 mmHg, 20.78 ± 4.02 mEq/L, and 52.42 ± 11.22 mmHg, respectively (Figures 1D, 1E, 1F, 1G, 1H 1I and Figures 2A, 2B, 2C, 2D, 2E). Furthermore, pH, HCo3, and PCo2 were compared in terms of umbilical cord blood gases between two groups of infants with and without IVH, which was not significantly different (P = 0.5; P = 0.9; P = 0.7; Table 4; Figures 2F,

2H, 2G, 2I and Figures 3A, 3B). A correlation coefficient between fetal age and pH of cord blood gases from the umbilical artery was determined as +0.299, indicating a positive correlation between these two variables; indeed, the pH slightly increased with fetal age. Also, these two variables had a significant relationship between them (P = 0.01; Figure 3C). Based on the results of the pH of the cord blood gases from the umbilical artery presented here, preterm infants with IVH and/or without IVH have no significant difference regarding gender and type of delivery (Tables 5 and 4-6). Based on the finding presented here, pH levels in infants without IVH and cerebral anomalies were lower than other groups, to whom these values were statistically significant. (P = 0.03; 7.16 ± 0.07 versus 7. 23 ± 0.08; Table 7). The correlation between the pH and fetal age in the group of infants without intravenous hemorrhage was defined as 0.3, which indicates that there is a moderate positive correlation between these two variables (P = 0.01). However, no significant relationship was found between fetal age and cord blood pH in neonates with IVH (Pearson correlation coefficient: 0.29 and P = 0.4), (Figures 3D and 3E).

DISCUSSION

In this case-control study, the umbilical cord was evaluated for blood gases in 72 neonates (mostly boys) with an average fetal age of 31.03 ± 2.87 and with a mean weight of 1515.6011.66 grams. Of the 72, 74.3% (52 subjects) were born through cesarean section. Sixty-two neonates were diagnosed as normal using ultrasound, whereas 16.7% (12 subjects) had cerebral anomalies that included: IV in 5 subjects (6.9%), GMH in 6 neonates (8.3%), and hydrocephaly in 1 infant (1.4%). Unfortunately, 2 infants died. A total of 4.2% (3 individuals) had presented IVH grade (1 in the third-day ultrasound), while 1.4% (1 subject) presented Grade 3.

Furthermore, on the seventh day, 8.2% (2 subjects) presented IV (Grade 1), followed by 2.8% (2 subjects) IVH (Grade 2), 8.2% IVH (Grade 3), and 1.4% (1 subject) grade 2 to 3. On the other hand, 75% of 8 infants had IVH, which showed a significant difference compared with the group of infants without IVH (62.5% male), (P = 0.049). However, the type of delivery, mean weight, height, head and breast circumference, and Apgar score (first minute) did not differ between the two groups.

In this study, blood gases were compared between two groups and the mean pH, HCo3, and PCo2 in umbilical cord blood samples of neonates were determined as 7.2 ± 0.8 mmHg, 20.78 ± 4.02 mEq/L, and 52.42 ± 11.22 mmHg, respectively, which revealed no significant difference between the two groups with/or without IVH. The results did not show a significant relationship between gender and type of delivery in neonates. The pH increased slightly with gestational age, in which its relation to fetal age was significant (P = 0.01). Lower pH was observed in the umbilical cord of infants who did not have IVH but had cerebral anomalies (P = 0.03). In infants without intravesical hemorrhage, pH was associated with fetal age (P = 0.01), while this issue was not associated with the age of infants suffering from IVH (P = 0.4). A study by Sajjadian et al.[21], in Tehran, showed that 64% of preterm infants had Intraventricular-germinal matrix hemorrhage, of which 40% had grade I, 11% grade II, 25.7% grade III, 2.8% grade VI, which is about four times the value determined by the present study. The difference between the mean fetal age justifies this issue in two studies. The frequency of GMH has been reported to be 28% in a prospective study which, unlike the present study, did not differ between the two sexes but was related to the type of delivery, weight, and fetal age.[22]

Stewart et al.[23], have shown that the frequency of IVH (18.2%) was slightly higher than that of the current study (16.7%), which can be due to the very low birth weight (VLBW) of neonates investigated in our study. Another study in Nigeria indicated that 22% of infants presented mild IVH, followed by moderate to severe IVH (7.5%), and periventricular leukomalacia (PVL, 23%), with a 3.5-fold increase in IVH.[24] Our results are consistent with some studies.[15,19]

In the present study, there was no significant difference in blood gases (mean pH, HCo3 and PCo2) between the two groups with/without IVH. However, in the group without cerebral hemorrhage, acidosis decreased with fetal age (P = 0.01), and no relationship was found regarding gender and type of delivery. Furthermore, in infants with interventricular hemorrhage, acidosis was not found to be associated with fetal age. Leviton and colleagues observed that the disruption of each of the blood gas indexes, including pH, PCo2 and Pao2, alone could not increase the risk of brain damage. However, it may indicate an insufficiency or severity of brain disease when there is an interruption of more than one of these index-

es.[15] Randolph et al.[25] also found that perinatal acidosis is significantly associated with death or NDI in infants with very low birth weight. This study mentioned that although perinatal acidosis is uncommon in these infants, it was important in predicting mortality and/or NDI as well as other factors.[25] Locatelli et al.[15] demonstrated that severe acidosis at birth, the most important predictor of death or neurodegenerative disorders, in term neonates suspected of hypoxic/ischemic encephalopathy was a predictor of prognosis. Conversely, in preterm infants, acidosis has not played a role due to several pitfalls caused by premature status, such as acidosis and other metabolic disorders. The inverse effect of umbilical cord pH and BE on the outcome events for infants delivered preterm was demonstrated by Victory et al.[26]. Zayek et al.[27], who reported that the risk of severe IVH was elevated with higher Paco 2 and BD, but pH was the only predictor of severe IVH. A higher acidity level during the first 48 hours of life has been correlated with an increased occurrence of IVH.[27]

CONCLUSION

The measurement of umbilical cord blood gases as a non-invasive evaluation method can provide appropriate data for decision-making, treatment and prognosis; however, blood gases do not help determine the occurrence of IVH in infants. Nevertheless, it is associated with immaturity and fetal age. Checking the condition of the umbilical cord pH during the first hours after childbirth is very beneficial in the hospital, where it can provide important information about the respiratory, metabolic, and brain statuses, as well as specialized care setting.[28-31]

Sources of funding

None

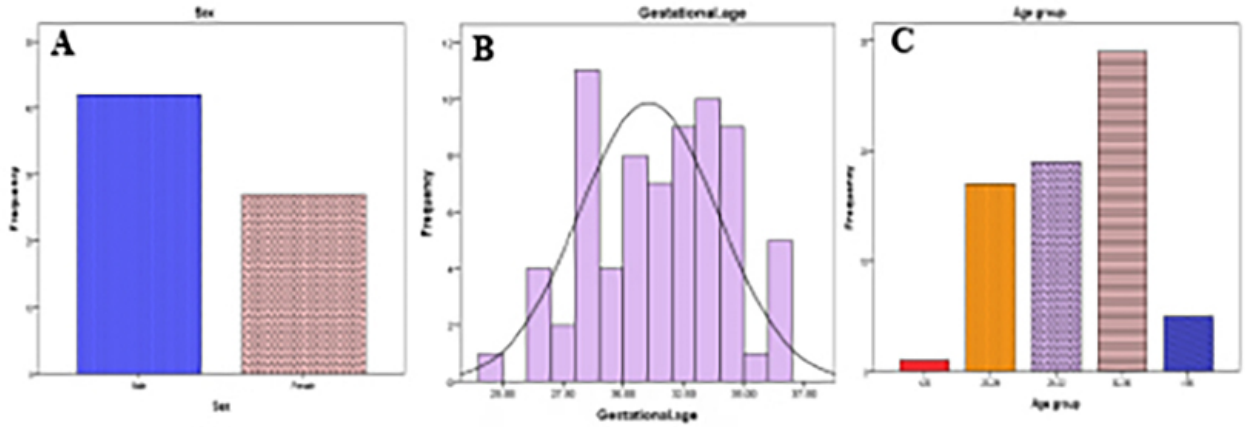
Conflict of interest

None

Authors' contributions

AM, MM, NKH, LYA, and MK carried out the statistical analysis, helped draft the manuscript, collected, analyzed and interpreted the clinical data, conceived, designed, and coordinated the study and wrote the manuscript. All authors read and approved the final manuscript.

FIGURE 1. A) THE FREQUENCY OF SEX IN INFANTS; B): HISTOGRAM OF FETAL AGE; C): FREQUENCY OF INFANTS IN TERMS OF AGE GROUPS; D): FREQUENCY OF PATIENTS PER TYPE OF DELIVERY; E): BIRTH WEIGHT HISTOGRAM; F): HISTOGRAM OF THE HEIGHT; G): HISTOGRAM OF THE HEAD CIRCUMFERENCE; H): HISTOGRAM OF THE BREAST CIRCUMFERENCE; I): NEONATAL ABNORMALITIES CHART BASED ON ANOMALY



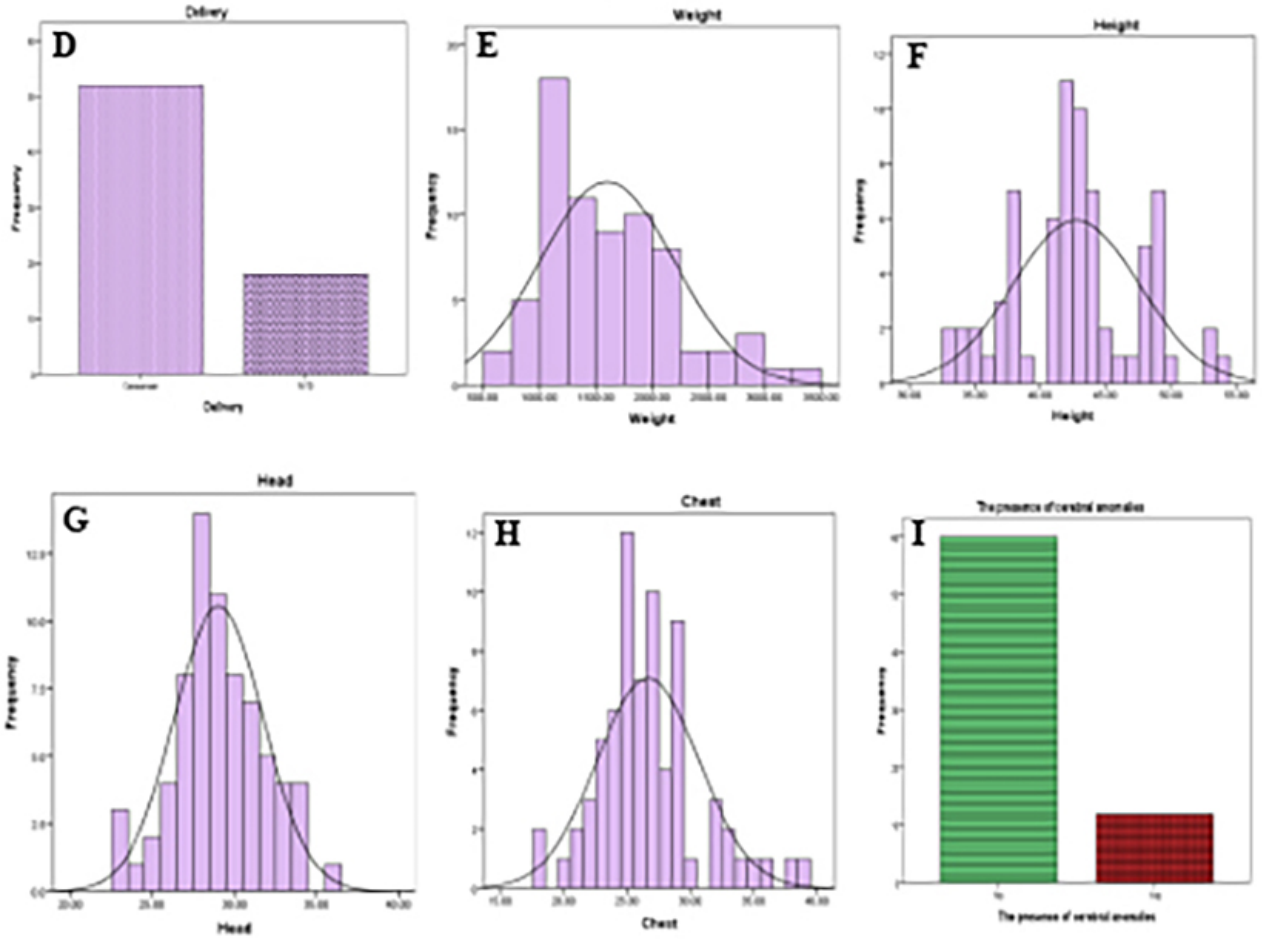
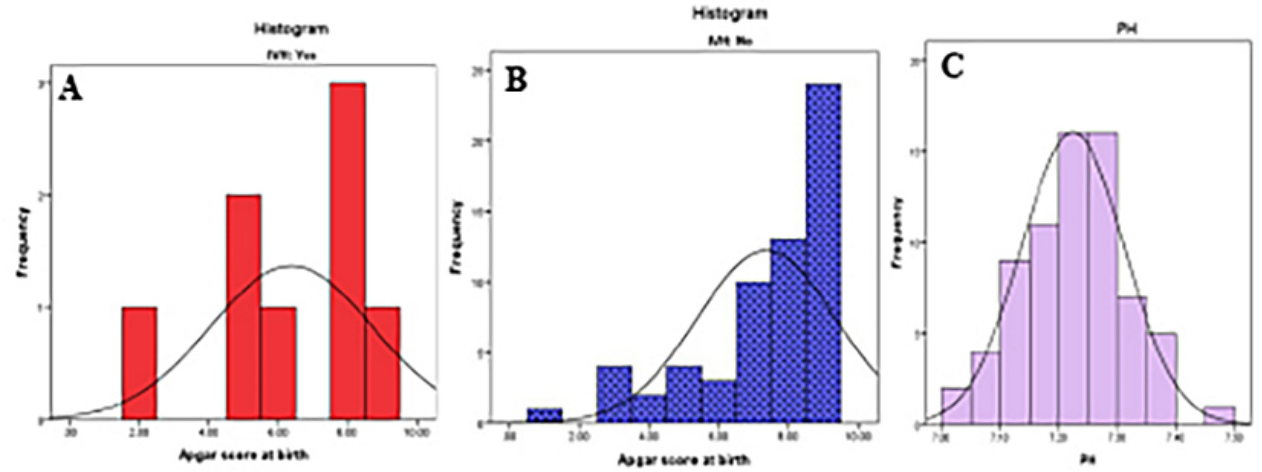


FIGURE 2. A) HISTOGRAM OF APGAR SCORE IN THE FIRST MINUTE IN THE GROUP OF INFANTS WITH INTRAVENTRICULAR HEMORRHAGE; B): HISTOGRAM OF APGAR SCORES IN THE FIRST MINUTE IN THE GROUP OF INFANTS WITHOUT INTRAVENTRICULAR HEMORRHAGE; C): pH LEVELS OF NEONATES' BLOOD; D): THE LEVEL OF HCo3 IN THE NEONATES' BLOOD; E): Pco2 LEVELS IN INFANTS' BLOOD; F): pH HISTOGRAM OF NEONATAL BLOOD AMONG INFANTS WITH INTRAVENTRICULAR HEMORRHAGE; G): BLOOD pH LEVEL IN INFANTS WITHOUT INTRAVESICAL HEMORRHAGE; H): HISTOGRAM OF BLOOD Pco2 LEVEL IN INFANTS WITH INTRAVENTRICULAR HEMORRHAGE; I): HISTOGRAM OF BLOOD Pco2 LEVEL IN INFANTS WITHOUT INTRAVENTRICULAR HEMORRHAGE.



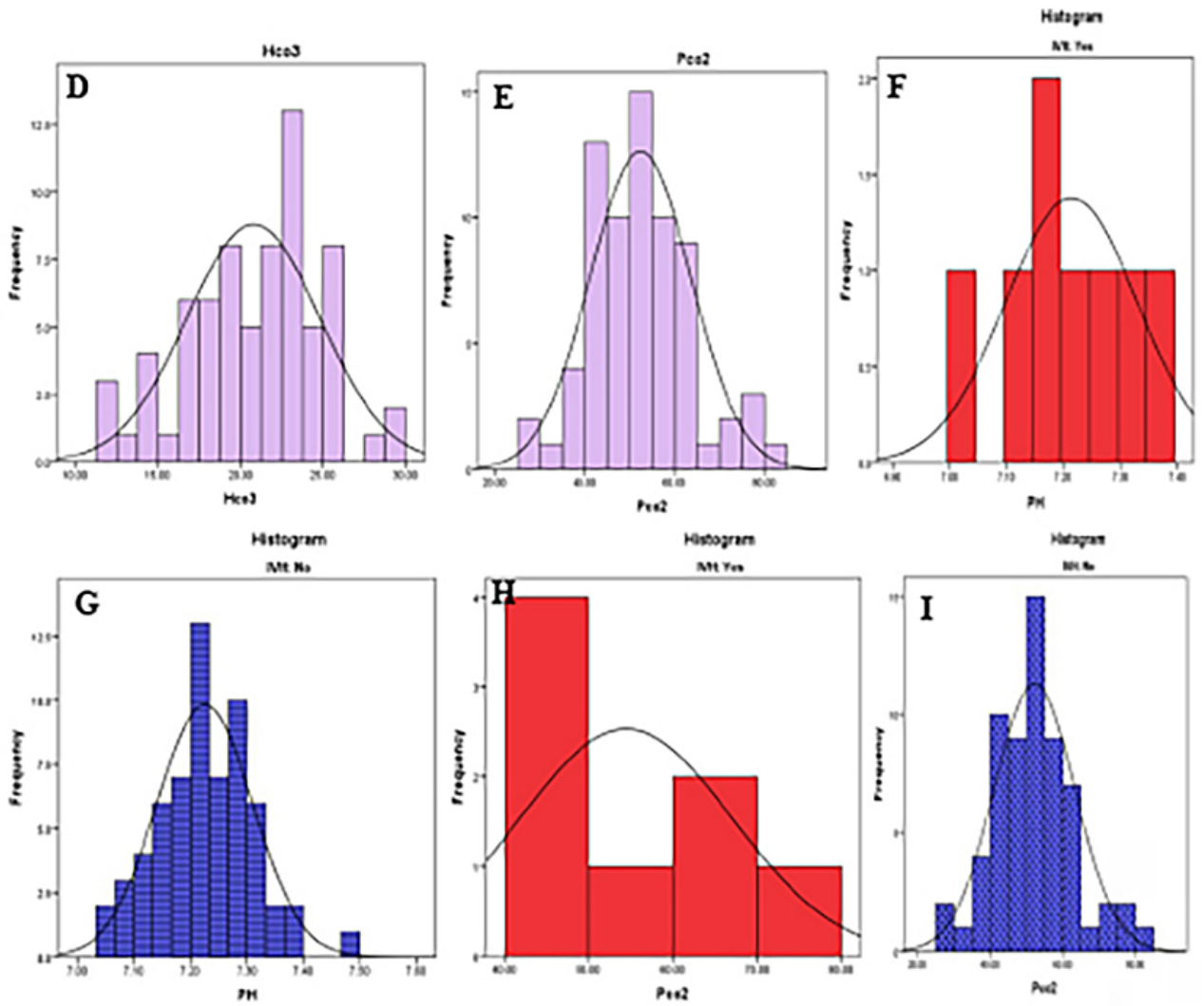
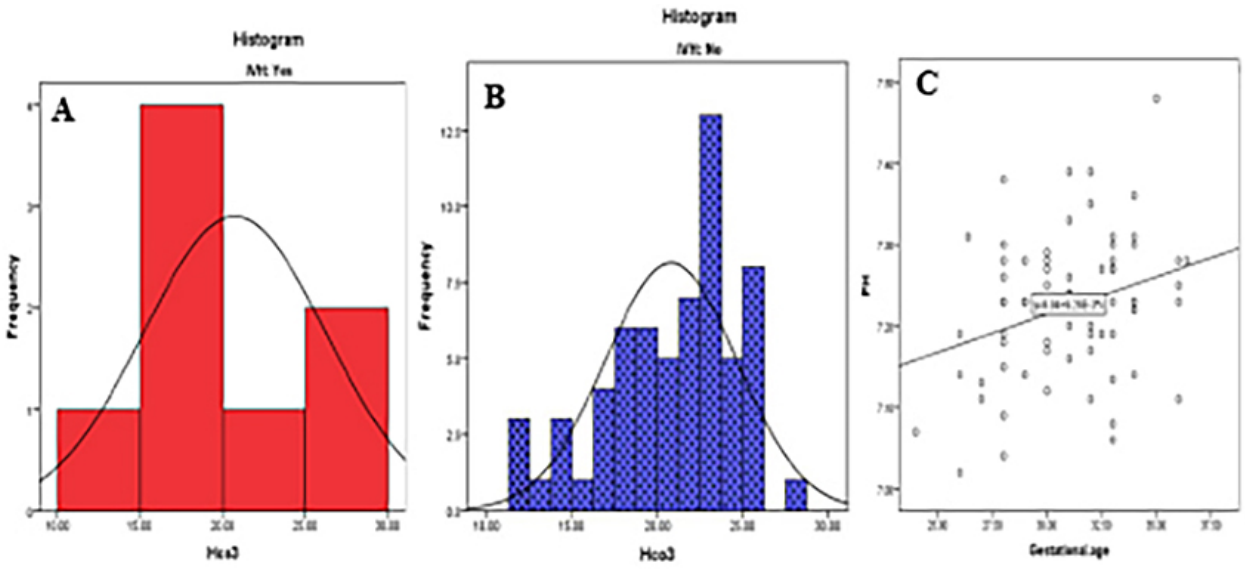


FIGURE 3. A) HISTOGRAM OF BLOOD HCo3 LEVEL IN INFANTS WITH INTRAVENTRICULAR HEMORRHAGE; B): HISTOGRAMS OF BLOOD HCo3 IN INFANTS WITHOUT INTRAVENTRICULAR HEMORRHAGE; C): DISTRIBUTION OF FETAL AGE BASED ON pH IN ALL INFANTS; D): DISTRIBUTION OF EMBRYONIC AGE REGARDING pH IN INFANTS WITH INTRAVENTRICULAR HEMORRHAGE; E): DISTRIBUTION OF FETAL AGE PER WEEK REGARDING pH IN INFANTS WITHOUT INTRAVENTRICULAR HEMORRHAGE.



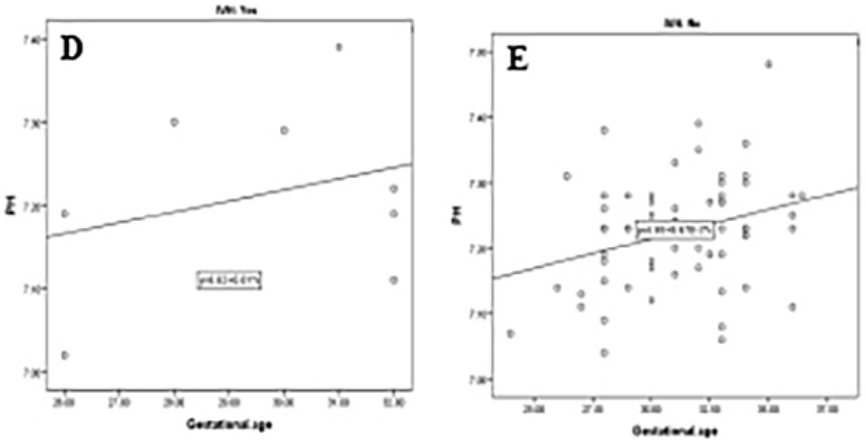


TABLE 1. FREQUENCY OF DISTRIBUTION OF INFANTS PER AGE GROUPS

Age group (weeks)	Frequency
25 ≥	1 infant (4/1%)
29-25	17 infants (9/23%)
32-29	19 infants (8/26%)
36-32	29 infants (8/40%)
36 ≤	5 infants (7%)
Missing	1 infant (4/1%)
Total	72 infants (100%)

TABLE 2. NEONATAL CHARACTERISTICS BASED ON INTRAVENTRICULAR HEMORRHAGE

Variable group	Sex		Type of delivery	
	Male	Female	Cesarean	Natural
Intraventricular hemorrhage	2Neonatals (25%)	6 Neonatals (75%)	6	2
Without intraventricular hemorrhage	40 Neonatals (5/62%)	21Neonatals (4/34%)	46	16
P-value	049/0 *		000/1	

*The statistical test was chi-square and the significance level was 0.05.

TABLE 3. NEONATAL CHARACTERISTICS ACCORDING TO INTRAVENTRICULAR HEMORRHAGE

	Intraventricular hemorrhage	Without intraventricular hemorrhage	P-value
Weight	96/330 ± 25/1416	326/625±37/1621	3/0
Height	46/2 ± 50/27	71/2 ±21/29	09/0
Round the head	64/3±12/41	95/4±94/42	3/0
Round the chest	4/4 ±56/26	05/4 ±64/26	9/0
Apgar Score	32/2 ±37/6	99/1 ±36/7	2/0

TABLE 4. COMPARISON OF CORD BLOOD GASES BASED ON THE INTRAVENTRICULAR HEMORRHAGE

Variable Group	pH	PCo2	HCo3
Intraventricular hemorrhage	11/0 ±21/7	61/12 ±43/54	50/5±71/20
Without intraventricular hemorrhage	08/0 ±22/7	12/11 ±17/52	86/3±79/20
P-value	7/0	5/0	9/0

TABLE 5. COMPARISON OF THE pH OF THE UMBILICAL CORD BLOOD PER PRESENCE OF INTRAVESICAL HEMORRHAGE

Type of delivery Group		Cesarean	Natural	P-value
pH	Intraventricular hemorrhage	09/0 ±23/7	19/0 ±16/7	4/0
	Without intraventricular hemorrhage	07/0 ±22/7	12/0 ±23/7	6/0

TABLE 6. CORD BLOOD pH ACCORDING TO GENDER

Sex Group		Male	Female	P-value
pH	Intraventricular hemorrhage	14/0 ±29/7	10/0 ±18/7	3/0
	Without intraventricular hemorrhage	07/0 ±23/7	08/0 ±22/7	4/0

TABLE 7. pH OF THE UMBILICAL CORD IN THE PRESENCE OF ANOMALIES

P-value	No	Yes	Anomaly Group	
7/0	10/0 ±23/7	13/0 ±20/7	Intraventricular hemorrhage	pH
03/0 *	08/0 ±23/7	07/0 ±16/7	Without intraventricular hemorrhage	

*The statistical test was chi-square and the significance level was 0.05.

RESUMO

OBJETIVOS: *Medimos o nível de gases de pH em bebês prematuros, no nascimento dos neonatos, e examinamos a relação entre a ecografia cerebral no terceiro e no sétimo dia após o nascimento. Um estudo de casos e controles realizados na Unidade de Cuidados Intensivos Neonatais (UCIN) do Hospital Shahid Akbar Abadi durante os anos de 2016-2017, Irã.*

MÉTODOS: *Todos os recém-nascidos prematuros que deram entrada na UCIN foram inscritos no estudo atual. Ao nascer, foi retirada uma amostra de gás em sangue, do sangue do cordão umbilical dos bebês. No terceiro e sétimo dia após o nascimento, um radiologista realizou uma ecografia do cérebro de cada neonato. O cordão umbilical foi avaliado para detectar gases no sangue em 72 neonatos (em sua maioria do sexo masculino).*

RESULTADOS: *Sessenta e seis recém-nascidos tinham ecografia normal e 16.7% (12 casos) tinham anomalias. 75% das 8 crianças com hemorragia intravenosa eram meninas, que foram significativamente diferentes das do grupo não hemodinâmico (62.5% homens) (P.0.049). Contudo, o tipo de parto, o peso médio, a altura, o perímetro cefálico, a circunferência do tórax e a pontuação de Apgar não foram diferentes entre os grupos. O pH médio, HCO3 e PCO2 nas amostras de gás no sangue do cordão umbilical não foram significativamente diferentes entre dois grupos com ou sem hemorragia intraventricular (Hiv). Apesar de não estar relacionado com o gênero e o tipo de parto em recém-nascidos.*

Conclusão: os gases sanguíneos não ajudam a determinar o aparecimento de Hiv nos bebês. Contudo, está associado com a imaturidade e idade fetal.

PALAVRAS CHAVE: *Cordão umbilical. Gasometria. Hemorragia cerebral. Recém-Nascido.*

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ORIGINAL ARTICLE

Aerobic exercise effects in renal function and quality of life of patients with advanced chronic kidney disease

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http://dx.doi.org/10.1590/1806-9282.65.5.657

SUMMARY

BACKGROUND: *To date, the therapeutic effects of exercise have not yet been evaluated regarding renal function parameters and quality of life specifically in patients with advanced chronic kidney disease. Thus, the study aim was to evaluate the effects of aerobic exercise in renal function and quality of life in patients with advanced chronic kidney disease.*

METHODS: *A quasi-experimental prospective study [NCT03301987] was carried out. Nine patients with advanced chronic kidney disease were recruited from a hospital nephrology unit. Kidney function parameters such as creatinine, creatinine clearance, urea clearance, glomerular filtration rate, and creatinine/weight proportion, as well as the Kidney Disease Quality of Life SF-36 (KDQoL-SF36) were measured at baseline and after 1 month of aerobic exercise.*

RESULTS: *Significant increases (P < .05) were observed for creatinine/weight proportion as well as symptoms, effects, charge, and physical domains of the KDQoL-SF36 after 1 month of therapeutic exercise. The other parameters did not show any statistically significant difference (P > .05).*

CONCLUSIONS: *Aerobic exercise may cause improvements in renal function and quality of life of patients with advanced chronic kidney disease. Further studies about therapeutic exercise protocols specifically in patients with advanced stages of chronic kidney disease should be carried out in order to study their effectiveness and safety.*

KEYWORDS: *Exercise. Kidney Diseases. Physical Therapy Modalities. Quality of Life.*

INTRODUCTION

Kidney disease is characterized by the impairment of renal function and causes accumulation of blood metabolites, which alter the electrolyte balance[1], as well as severe comorbidities such as cardiovascular conditions [2] or chronic obstructive pulmonary disease. [3] Indeed, chronic kidney disease (CKD) is considered renal function impairment when it lasts for at least 3 months [4].

Worldwide, CKD is considered a major public health problem [4]. In Spain, this condition may reach up to 9.16% of the total population with a prevalence of 4,300,000 patients with CKD. Indeed, CKD incidence will increase over the next decade as a consequence of other comorbidities such as diabetes and hypertension in conjunction with population aging. The economic burden of CKD is very high and may reach up to $50 billion in the United States and 3% of the total national health burden in Spain[5,6].

DATE OF SUBMISSION: 04-Sep-2018
DATE OF ACCEPTANCE: 24-Nov-2018
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Considering the CKD clinical practice guidelines[1,7], CKD stages are measured according to glomerular filtration [8]. Indeed, albuminuria, measured based on the albumin/creatinine ratio, may be considered as an independent marker of endothelial damage and a risk factor independent from cardiovascular conditions [2]. The averages of urea and creatine clearance (measured at the last 24 hours) are recommended parameters for measurement in patients with advanced CKD, according to the kidney disease guidelines[1,7].

Patients with CKD are more likely to present physical activity limitations and impaired quality of life than the general population [9]. In addition, physical activity may be considered a key predictor of quality of life in these patients[10].

Exercise practice is considered a key therapeutic intervention in patients with CKD and may reduce cardiovascular risk, increase cardiorespiratory, metabolic, neuromuscular, and cognitive functions, as well as improve physical function secondary to muscular tissue increase and minimize the risk of functional impairment through improved quality of life[11].

Consequently, the practice of physical exercise is a key factor for the clinical management of patients with CKD[11], as well as in patients under maintained hemodialysis treatment and patients under peritoneal dialysis intervention[12]. Domiciliary exercise practice has shown to improve renal function in patients with CKD before starting the dialysis treatment[13]. Nevertheless, the effects of therapeutic exercise have not yet been evaluated regarding renal function parameters and quality of life in patients with advanced CKD. Therefore, the aim of this study was to evaluate the effects of aerobic exercise in renal function parameters and quality of life in patients with advanced CKD.

METHODS

Study design

A quasi-experimental prospective study was carried out in order to determine the effects of therapeutic exercise in renal function parameters and quality of life in patients with advanced CKD. A sample of 9 patients with advanced CKD was recruited at the Galdakao Hospital (Spain) from October to December 2017. In addition, this research was conducted according to the Template for Intervention Description and Replication (TIDieR) checklist and guidelines[14]. The Clinical Intervention Ethics Committee from the University of León (Spain; code ÉTICA-ULE-018-2017) approved this study, and subjects signed an informed consent form subjects before the study started. Furthermore, this study was prospectively registered at ClinicalTrials.gov [NCT03301987].

Sample size calculation

The sample size was calculated using the software from Unidad de Epidemiología Clínica y Bioestadística, Complexo Hospitalario Universitario de A Coruña, Universidade da Coruña (available at http://www.fisterra.com/mbe/investiga/9muestras/9muestras2.asp). Considering the prevalence of 4,300,000 patients with CKD in Spain in 2010 [6], the sample size calculation for an α level of 0.05 (confidence interval, α-1 = 95%), a proportion of 5% and a precision of ± 15 %, provided at least n = 8 cases. Also, assuming information loss of 10%, at least n = 9 patients with CKD needed to be included in the study.

Participants

A sample of 9 patients with advanced CKD (for the etiology, comorbidities, and status of CKD in the recruited patients, see Appendix 1) was recruited using a consecutive sampling method. The setting was performed at the Nephrology Unit from the Galdakao Hospital (Spain). The inclusion criteria comprised patients with older than 18 years, who signed the informed consent form, with a diagnosis of stage 4–5 CKD and stable kidney function for at least 1 year[13]. The exclusion criteria comprised not signing the informed consent form, patients with a physical impairment that did not allow for physical exercises, such as uncontrolled hypertension and cardiac failure, motor disorders[13], and dementia, or any degree of cognitive impairment[15].

Intervention

The aerobic exercises were performed according to the recommended Spanish exercise guidelines[1,7]. The patients carried out exercise activities, such as brisk walking (30 min/day) or completing from 8,000 to 10,000 steps/day. The measurement of the physical exercise performed was assessed with an accelerometer pedometer (Kenz Lifecorder, EX 1-axial) with a sensor of acceleration (Suzuken Co-Ltd., Nagoya, Japan). The accelerometer pedometer was continuously used for 1 month and was only removed for

bathing or sleeping. The main physical exercise parameter was the number of steps per day[13].

Outcome measurements

Descriptive data such as sex, age, height, weight, body mass index (BMI), and kidney disease chronicity (years) were extracted from the electronic and paper medical records by the same authorized researcher. The stage of the CKD was determined according to the recommended clinical practice guidelines[1,7]. According to the glomerular filtration [8], the stages of the CKD were established as follows: stage I for values higher than 90 ml/min/m^2; stage II for values from 90 to 60 ml/min/m^2; stage III for values from 60 to 30 ml/min/m^2 (specifically, stage IIIA from 60 to 45ml/min/m^2 and stage IIIB from 45 to 30ml/min/m^2); stage IV for values from 30 to 15ml/min/m^2; and stage V for values lower than 15ml/min/m^2. In addition, CKD was classified in a non-numeric way, considering slight CKD for stages with glomerular filtration higher than 60ml/min/m^2; slight-moderate CDK for stages with glomerular filtration from 60 to 45ml/min/m^2; moderate-severe CDK for stages with glomerular filtration from 45 to 30ml/min/m^2; severe CKD for stages with glomerular filtration from 30 to 15ml/min/m^2; and terminal CKD for stages with glomerular filtration lower than 15ml/min/m^2 [1,7,8].

Kidney function parameters such as creatinine, creatinine clearance, urea clearance, glomerular filtration rate, and creatinine/weight proportion were measured at baseline and after 1 month of therapeutic exercise. The glomerular filtration rate (ml/min/1.73 m^2)[16], which was calculated from the serum creatinine and urinary protein levels, was used as the kidney function index.

The Kidney Disease Quality of Life SF-36 Short Form (KDQoL-SF36™; Spanish Version 1.2; RAND, University of Arizona, Unites States) was measured at baseline and after 1 month of therapeutic exercise. The symptoms, effects, charge, physical and mental domains were registered. The KDQoL™ is a commonly used 134-item instrument designed to assess generic and kidney-disease targeted aspects of quality of life for patients on dialysis[17]. An abbreviated version of the KDQoL™, the KDQoL-SF36™, has been translated to Spanish and used in the United States (rand.org/health/surveys_tools/kdqol.html); it was validated into Spanish by Ricardo et al.[18] for the Spanish population with CKD.

Statistical analysis

The statistical SPSS 22.0 software (IBM SPSS Inc., Chicago, IL, USA) was used for the data analysis. A 95% confidence interval (CI) and a statistically significant difference of *P*-value < .05 were considered. Firstly, the Shapiro-Wilk test was used to assess normality. Secondly, the data were described by means of the mean ± standard deviation (SD) and 95% CI limits (upper and lower limits) for the parametric data (age, height, renal function parameters, and KDQoL-SF36 domains), median ± interquartile range (IR) for the non-parametric data (weight and BMI), as well as frequencies and percentages (%) for the categorical data (sex and kidney disease degree). In paired samples, the Student *t*-test was applied to assess differences before and after the intervention for all the renal function parameters and KDQoL-SF36 domains measurements (due to all of them were parametric data). Box-plots were used to illustrate the KDQoL-SF36 domains differences before and after 1 month of therapeutic exercise.

RESULTS

Descriptive data

A total sample of 9 patients, 3 females (30%) and 6 males (60%), age mean± SD of 66.22 ± 7.08 years, height mean ± SD of 1.66 ± 0.10 m, weight median ± IR of 74.00 ± 11.50 kg, BMI median ± IR of 27.02 ± 6.91 kg/cm^2, with advanced CKD completed the research course. The frequencies (%) of the CKD stages were 5 cases of grade IV (55.5%) and 4 of grade V (44.4%).

Renal function parameters

Regarding Table 1, a statistically significant increase (P = .018) was observed for the creatinine/weight proportion after 1 month of therapeutic exercise. The other renal function parameters did not show any statistically significant difference (P > .05).

Kidney disease and quality of life domains

Regarding Table 2 and Figure 1, statistically significant increases (P < .05) were observed for the symptoms, effects, charge and physical domains of the KDQoL-SF36 after 1 month of therapeutic exercise. Nevertheless, the mental domain of the KDQoL-SF36 did not show any statistically significant difference (P = .972).

TABLE 1 – RENAL FUNCTION PARAMETERS OF PATIENTS (N = 9) WITH ADVANCED CKD BEFORE AND AFTER 1 MONTH OF THERAPEUTIC EXERCISE.

Renal function parameters	Therapeutic exercise	Mean	SD	Lower limit	Upper limit	Mean difference	SD difference	t-test P-value (t)
Creatinine	Baseline	3.41	1.35	2.37	4.45	0.12	0.34	.328 (1.042)
	1 month	3.53	1.58	2.31	4.75			
Creatinine clearance	Baseline	26.92	10.95	18.40	35.24	1.13	5.38	.546 (0.630)
	1 month	27.95	11.10	-3.00	5.27			
Urea clearance	Baseline	10.85	2.72	8.76	12.94	-0.26	1.49	.616 (-0.522)
	1 month	10.59	3.78	8.86	12.32			
Glomerular filtration rate	Baseline	18.66	6.67	13.52	23.79	-0.38	3.39	.743 (-0.3340)
	1 month	19.04	6.61	13.95	24.13			
Creatinine/weight	Baseline	16.23	1.95	14.72	17.74	0.95	0.97	.018 (2.951)
	1 month	17.18	1.60	15.95	18.41			

Abbreviations: CKD, chronic kidney disease. In all the analyses, p < .05 (with a 95% confidence interval) was considered statistically significant.

TABLE 2 – KDQOL-SF36 DOMAINS OF PATIENTS (N = 9) WITH CKD BEFORE AND AFTER 1 MONTH OF THERAPEUTIC EXERCISE.

KDQoL-SF36 domains	Therapeutic exercise	Mean	SD	Lower limit	Upper limit	Mean difference	SD difference	t-test P-value (t)
Symptoms	Baseline	71.96	8.72	65.25	78.67	17.67	9.35	<.001 (5.667)
	1 month	89.64	6.53	84.62	94.67			
Effects	Baseline	75.25	9.31	68.09	82.41	9.23	10.81	.033 (2.563)
	1 month	84.49	9.29	77.00	91.63			
Charge	Baseline	53.47	30.79	29.80	77.14	18.05	20.59	.030 (2.630)
	1 month	75.52	24.22	52.90	90.15			
Physical	Baseline	37.41	10.83	29.08	45.74	4.43	4.79	.024 (2.776)
	1 month	41.85	11.85	32.73	50.96			
Mental	Baseline	48.68	7.50	42.91	54.45	-0.10	8.98	.972 (-0.036)
	1 month	48.57	7.21	43.02	54.12			

Abbreviations: CKD, chronic kidney disease; KDQoL-SF36, kidney disease quality of life SF36. In all the analyses, p < .05 (with a 95% confidence interval) was considered statistically significant.

DISCUSSION

This is the first study to support novel evidence about the effects of aerobic exercise in renal function parameters and quality of life in patients with advanced CKD. Although we prioritized renal function parameters and quality of life, a prior systematic review [19] suggested that exercise improved stress and inflammation biomarkers in patients with CKD.

Likewise Kosmadakis et al.[20], our study obtained improvements after 1 month of aerobic exercise; the same was observed regarding the quality of life and uremic symptom scores. On the other hand, Chang et al. [21]did not observe any improvements in the physical component score of the KDQoL-SF36 after 3 months of intervention. Therefore, this suggests that aerobic exercise may be a key therapeutic factor in the clinical management of patients with CKD, but this is not yet completely clear.

Unlike prior studies [13], our study showed signif-

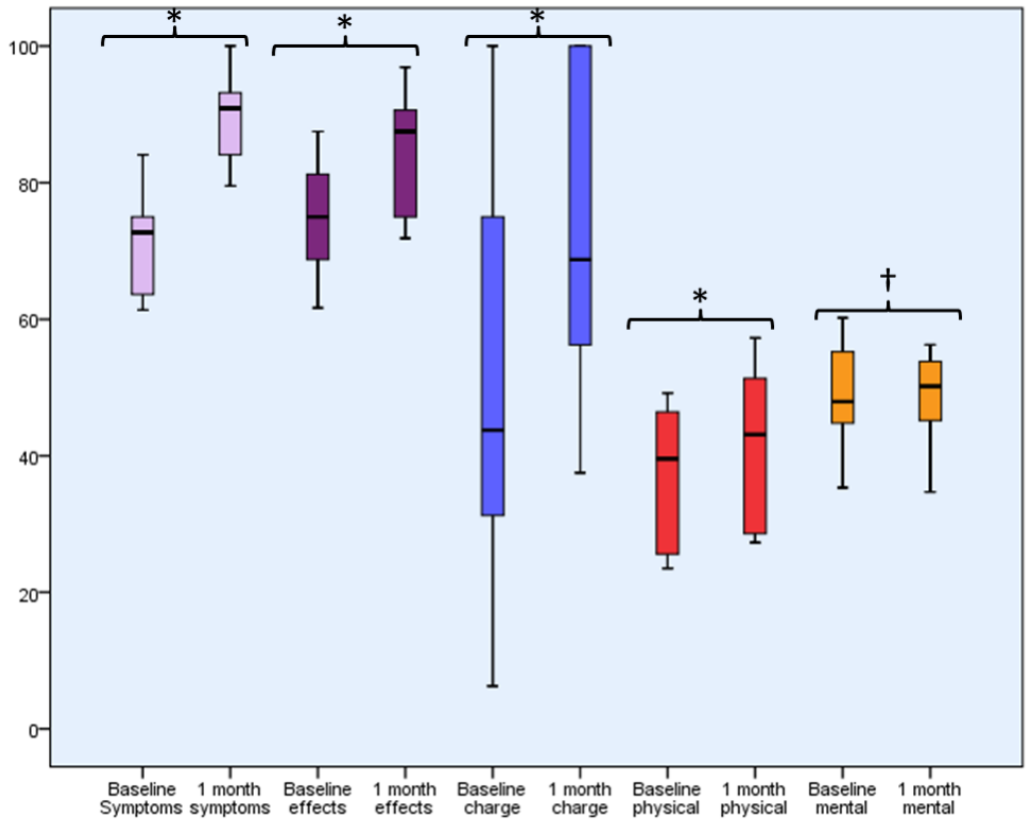

FIGURE 1. Box-plots to illustrate the differences in KDQoL-SF36 domains in patients with CKD before and after 1 month of therapeutic exercise. Abbreviations: CKD, chronic kidney disease; KDQoL-SF36, kidney disease quality of life SF36. *Statistically significant differences with P < .05 (with a 95% confidence interval). †No statistically significant differences with P > .05 (with a 95% confidence interval).

icant improvements in renal function, while others reported improvements in muscle strength, although renal function was not modified. Nevertheless, there is a lack of consensus on the effect of exercise on kidney function. Further research studies are needed to clarify the effect of exercise in the physiopathology of the renal function.

Relevance for physical therapy

Exercise recommendation, prescription, and supervision supported by specialized physical therapists may be effective in helping patients with advanced CKD remove the difficulties to adhere to these kinds of programs. Currently, there is not a unified protocol for prescribing exercise, and there is a disagreement with respect to the prescription moment as well as exercise type, intensity, and duration for these specific patients. In addition, these patients present a high risk of cardiovascular diseases. Consequently, the prescription of exercise should be individualized, and the physical therapist must define the duration and systematic procedure of the aerobic exercise in order to participate actively in the decision making during the prescription of physical exercise.

Regarding the coordination of aerobic exercise care, physical therapists, nephrologists, and physicians play a key role in the adherence of advanced CKD patients to aerobic exercise protocols, which should be supported by multidisciplinary teams.

Limitations

Several limitations should be considered for future studies about therapeutic exercise in patients with advanced CKD. First of all, despite the sample size calculation provided, future studies with a higher precision and sample size should be carried out. Second, despite the prospective trial registry, this study had a case series design. Thus, randomized clinical trials should be carried out with control groups. Finally, the effects of therapeutic exercise must be studied depending on the stages IV and V of advanced CKD.

CONCLUSIONS

In conclusion, aerobic exercise may cause improvements in renal function and quality of life of patients with chronic kidney disease. However, further studies about protocols for therapeutic exercise in patients with advanced stages of chronic kidney disease should be carried out in order to study their effectiveness and safety.

Conflict of interest

The authors declare there are no conflicts of interest.

RESUMO

OBJETIVO: *Até o momento, os efeitos do exercício terapêutico ainda não tinham sido avaliados quanto aos parâmetros de função renal e qualidade de vida em pacientes com doença renal crônica avançada, especificamente. Assim, o objetivo do estudo foi avaliar os efeitos do exercício aeróbico na função renal e na qualidade de vida em pacientes com doença renal crônica avançada.*

MÉTODOS: *Um estudo prospectivo quase experimental [NCT03301987] foi realizado. Nove pacientes com doença renal crônica avançada foram recrutados de uma unidade de nefrologia hospitalar. Parâmetros de função renal como creatinina, depuração de creatinina, liberação de ureia, taxa de filtração glomerular e creatinina/peso, bem como a qualidade de vida da doença renal SF-36 (KDQoL-SF36) foram medidos no início e após um mês de atividade aeróbica.*

RESULTADOS: *Aumentos significativos (P<0,05) foram mostrados para a proporção de creatinina/peso, bem como sintomas, efeitos, carga e domínios físicos do KDQoL-SF36 após um mês de exercício terapêutico. Os demais parâmetros não apresentaram diferença estatisticamente significante (P>0,05).*

CONCLUSÕES: *O exercício aeróbico pode produzir melhorias na função renal e na qualidade de vida de pacientes com doença renal crônica avançada. Especificamente, novos estudos sobre protocolos de exercícios terapêuticos em pacientes com estágios avançados de doença renal crônica devem ser realizados a fim de estudar sua eficácia e segurança.*

PALAVRAS-CHAVE: *Exercício. Nefropatias. Modalidades de fisioterapia. Qualidade de vida.*

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ORIGINAL ARTICLE

Evaluation of predictive measurements of excess weight in brazilian children

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http://dx.doi.org/10.1590/1806-9282.65.5.663

KEYWORDS: *Obesity. Child. Anthropometry.*

INTRODUCTION

Obesity is considered a chronic non-communicable disease (NCD), of multifactor etiology. Its prevalence is rising rapidly, even in children and adolescents; its consequent metabolic changes, which before were only found in the adult population, can already be found in the younger population[1,2]. Among the factors most closely associated with obesity is the change in eating habits and lifestyle. Overall, there has been a change in diet, characterized by the high consumption of high-energy-density foods, rich in simple sugars and fat, combined with a reduction of physical exercises and an increase of screen time[2,3].

The Body Mass Index is the main instrument used to identify obesity. However, the BMI is not able to evaluate central obesity, the main predictor of comorbidities associated with obesity[4]. A measurement that can be used for this purpose is the waist circumference (WC), which is considered a good indicator of visceral fat, presenting a strong relationship with atherosclerotic cardiovascular diseases, insulin resistance, and the metabolic syndrome[5]. Like the WC, the waist/height index (W/H) is also a tool used to measure the deposition of fat in the abdominal region, presenting an important correlation with cardiovascular risk factors[6]. Current research reported that the circumference of the neck (NC) could identify patients with obesity and overweight, which can be directly related to factors associated with metabolic syndrome[7].

The objective of this study is to verify the distribution of body fat using the waist and neck circumference and the W/H index and to compare NC, WC and the N/H index with the BMI of children and adolescents aged 2-14 years treated by the *Projeto Bandeira Científica* in Acreúna (GO) in 2016.

DATE OF SUBMISSION: 18-Jul-2018
DATE OF ACCEPTANCE: 05-Aug-2018
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METHODS

This is a cross-sectional study with children and adolescents aged 2-14 years treated by the *Projeto Bandeira Científica* in the city of Acreúna (GO), between the second and third weeks of December 2016.

The *Projeto Bandeira Científica* project was created in the Medical Faculty of USP in 1957. It is an initiative of university extension led by students from various programs of the University of São Paulo.

The city of Acreúna is a municipality in the Serra do Caiapó mountain range. It has a territorial extension of 1,824 km² and an estimated population of 21,905 inhabitants, of which 5,049 were children between 0-14 years old in 2010. It is a predominantly urban area (86.70%), and its economy revolves around agriculture and services. Its MHDI (Municipal Human Development Index) is 0.686 and has full coverage of the Family Health Program.

The directors of the project made eight previous visits to the city of Acreúna with the objective to learn about the reality of local health, present the initiative and invite the public to participate in the project. A list of people interested in receiving care via the project was drawn up, and they were called on the day the project team started their work. The project team was distributed daily into two different locations, organized every day in different spaces made available by the city hall, in order to facilitate the access of citizens. The units were set up in schools that had enough space for the team and the work material. The selection of the study population was made using an anthropometric assessment in the care units of the Project, where children and adolescents up to 18 years and 11 months old, the elderly and pregnant women were required to go through. A total of 205 children and adolescents were evaluated.

Were excluded from the research children and adolescents who had the following chronic diseases: encephalopathies, lung diseases, heart, liver, and kidney diseases, HIV infection, genetic syndromes, and oncologic diseases. Children aged between 2 and 4 years were characterized as preschoolers; from 5 to 10 years, as schoolchildren; and those from 11 to 14 years old, as adolescents[8].

The methodological instruments used were: a questionnaire for collecting personal, anthropometric, and clinical data, and the following measurements and index:

Weight and height were measured according to the standardized methodology[9]. The NC was measured using an inelastic measuring tape positioned at the middle point of the neck, at the level of the thyroid cartilage, with the individual standing up, looking forward and breathing normally[10]. The WC was measured with a measuring tape by obtaining the smallest circumference between the anterior superior iliac crest and the last costal arch[11]. The index (W/H) is the relationship between waist and height measurements, and the values were separated into two groups: < 0.5 and > 0.5 - the latter indicating an increased risk for cardiovascular diseases[12].

To assess their nutritional status, children and adolescents were classified according to the BMI indicated per age in z-score (BMI/I), using as a reference the growth curves of the World Health Organization[13] and the WHO cut-offs for overweight and obesity risk[14]. The Anthro Plus software, developed by the WHO[15] was used for classifying the nutritional status.

In the statistical analysis, the numerical variables were evaluated using averages and standard deviations and the categorical variables using absolute frequencies. The software used was SPSS Statistics 20. We considered the BMI a outcome variable and the WC, NC, and W/H index predictor variables. Analyses were carried out using Pearson correlation and linear regression between variables and outcome predictors. Then, we made the ROC curve, accuracy, sensitivity, specificity, positive and negative predictive values and precision by age for the variables: W/H index, WC, and NC; the level of significance was set at $p < 0.05$.

The research was approved by the Research Ethics Committee of the Medical Faculty of the University of São Paulo (Process number: 119885/2016), and the parents or guardians signed informed consent for the use of the collected data.

RESULTS

In total, 205 children and adolescents took part in the research, with an average age of 8 years and 2 months (SD = + 3 years and 6 months), 51.20% (n=105) males. Table 1 presents the average anthropometric measurements collected, minimum, maximum, mean and standard deviation, in addition to the classifications according to the z-score.

Regarding nutritional status according to BMI/age, 67.80% were classified as eutrophic, 3.41% as underweight, 4.87% as in risk of overweight, 12.68%

TABLE 1 - CHARACTERIZATION OF THE POPULATION STUDIED ACCORDING TO THE ANTHROPOMETRIC DATA (ACREÚNA, 2016).

	N	Mini-mum	Maxi-mum	Aver-age	Standard deviation
Age (years)	205	2.03	14.99	8.13	3.56
Weight (kg)	205	9.10	82.90	30.69	15.81
Height (cm)	205	81.00	177.20	127.23	22.46
Weight/Age*	134	-3.96	3.44	0.17	1.28
Height/Age	205	-3.66	2.44	-0.03	1.10
BMI/Age (z-score)	205	-3.20	4.26	0.35	1.34
BMI	205	12.30	32.10	17.68	3.86
WC (cm)	205	20.50	99.80	60.32	11.68
NC (cm)	205	16.90	44.50	28.58	3.82
W/H Index	205	0.16	0.65	0.48	0.06

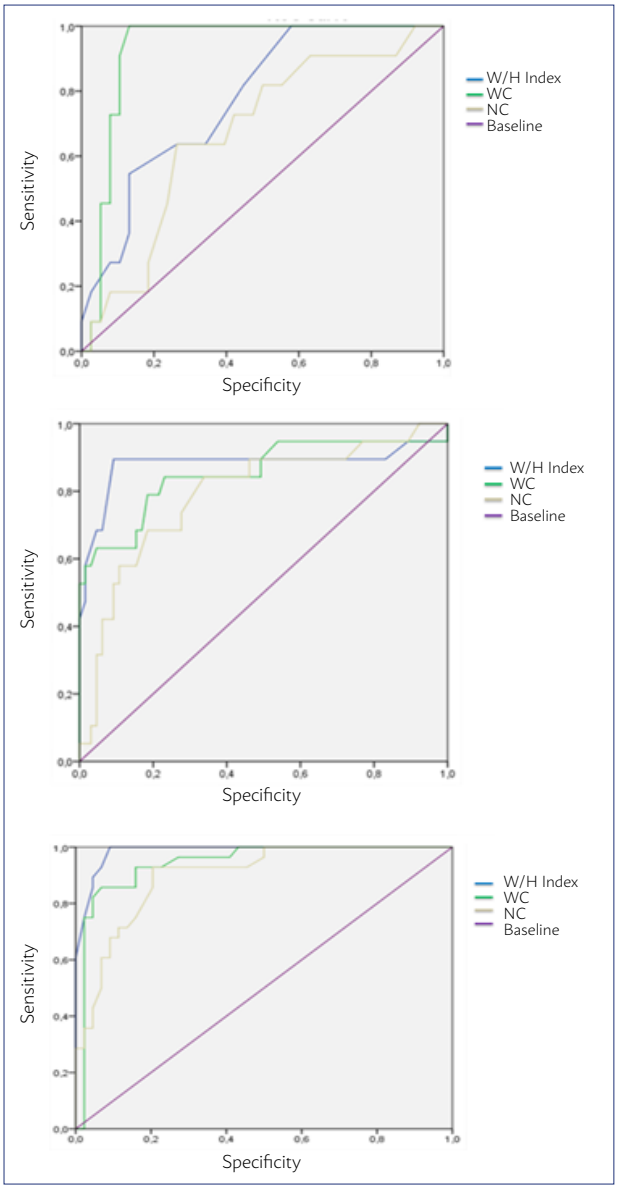
*The classification according to weight/age applies only for children from 0 to 10 years old.

as overweight, and 11.22% as obese (Table 2). Concerning gender, of 100 girls assessed, 29.75% were eutrophic, 1.95% had low weight, 2.44% risk of overweight, 8.78% were overweight, and 5.85% were obese. As to males, 38.04% of the boys were eutrophic, 1.46% had low weight, 2.44% risk of overweight, 3.90% were overweight, and 5.36% were obese (Table 2). The nutritional status of overweight/obesity was more frequent in children over 10 years old than in other age groups.

The average value of neck and waist circumference was 28.56±3.82 cm and 60.32±11.68 cm, respectively. In 66.30% (n=136), the classification of waist circumference per height (W/H) was lower than 0.5 and in 33.70% (n=69) it was greater than this value (Table 2).

The values of the correlation and simple linear

FIGURE 1. ROC CURVES FOR THE W/H INDEX, WC, AND NC IN RELATION TO PEDIATRIC AGE GROUPS.



A. ROC curve for children 2-5 years old. **B.** ROC curve for children 5-10 years old **C.** ROC curve for children over 10 years old

TABLE 2 - CLASSIFICATION OF NUTRITIONAL STATUS ACCORDING TO BMI/AGE IN RELATION TO AGE, GENDER, AND CLASSIFICATION OF THE INDEX W/H INDEX (ACREÚNA, 2016).

		Low weight %(n)	Eutrophy %(n)	Overweight risk %(n)	Overweight %(n)	Obesity %(n)	Total
Age range	2 |– 5	0	18.53 (38)	4.87 (10)	0.48 (1)	0	49
	5 |– 10	1.95 (4)	29.75 (61)	0	4.39 (9)	4.87 (10)	84
	10|–15	1.46 (3)	19.51 (40)	0	7.8 (16)	6.35 (13)	72
Gender	Female	1.95 (4)	29.75 (61)	2.44 (5)	8.78 (18)	5.85 (12)	100
	Male	1.46 (3)	38.04 (78)	2.44 (5)	3.9 (8)	5.36 (11)	105
	<0.5	3.41 (7)	54.63 (112)	0	6.34 (13)	1.95 (4)	136
Classification W/H Index	>0.5	0	13.17 (27)	4.87 (10)	6.34 (13)	9.26 (19)	69
Total		3.41 (7)	67.80 (139)	4.87 (10)	12.68 (26)	11.22 (23)	205

regression between BMI, WC, NC, and W/H Index showed us that the increase in 1 centimeter in WC entails an increase of 0.274 in BMI ($R = 0.830$; $R^2 = 0.688$; $p = 0.001$; $\beta = 0.274$), the increase in 1 centimeter in NC generates an increase of 0.717 in BMI ($R = 0.711$; $R^2 = 0.506$; $p = 0.001$; $\beta = 0.717$) and the increase of 1 millimeter in the W/H Index leads to an increase of 2.770 in BMI ($R = 0.447$; $R^2 = 0.200$; $p = 0.001$; $\beta = 2.770$).

ROC curves were drawn to identify the best instrument for the anthropometric assessment of children and adolescents. To do that, we calculated the areas under the ROC curves (AUC) for WC, NC, and W/H Index per the age ranges. These were statistically significant ($p < 0.05$), except for NC in children up to 5 years old (Figure 1).

Table 3 shows the different cutoff points for WC, NC, and W/H Index and their respective values of accuracy, sensitivity, specificity, positive and negative predictive values, and precision, separated by age and sex. In children aged 2 to 5 years, the WC has proved to be the best instrument (89.8±0.04%), and in children from 5 to 10 years and over 10 years, the W/H Index had the best results (90.1±0.03% and 94.4±0.03%, respectively).

DISCUSSION

This study evaluated the relationship between the WC, NC, and W/H Index variables with the BMI in children and adolescents. The main result found was that the WC of children younger than 5 years and the W/H Index of children older than 5 years have proved to be accurate measurements to identify excess weight.

In the present study, 23.90% of the individuals were classified as having excess weight (12.68% overweight and 11.22% obese), the majority of them females over 10 years old. In the study by Petroski et al.[16], 6.80% of the schoolchildren were classified with excess weight, and there was also a predominance of females over 10 years old. Silva et al.[17] found a higher percentage of overweight among the children analyzed, but lower rates of obesity (14.50% and 8.30%, respectively), and Pelegrini et al.[18] observed that 24.30% of their study population showed excess weight. Such statistical variations are possibly due to regional variations. By analyzing the data from the 2008-2009 HBS, we found that 33.50% of children from 5 to 9 years old are overweight, while in adolescents from 10 to 19 years old the number drops to 20.50%. Thus, the prevalence statistics observed in the present study lies between the HBS values for children and adolescents[19].

Regarding the evaluation per genre, this study found that the prevalence of excess weight is higher in females than in males, with 8.78% of the girls overweight and 5.85% obese, while these number in males are 3.90% and 5.36%, respectively. The data from the 2008-2009 HBS show that excess weight is slightly higher in males: 32% of female children from 5 to 9 years old have excess weight, whereas this value increases to 34.80% in males; in the age range of 10 to 19 years, the HBS data show that the prevalence of excess weight is 19.40% in females and 21.70% in males[19]. The rates of excess weight and obesity are very high. In Brazil, over half of the adult population

TABLE 3 - CUT-OFF POINTS, SENSITIVITY, SPECIFICITY, ACCURACY, POSITIVE AND NEGATIVE PREDICTIVE VALUES FOR WC, NC AND W/H INDEX (ACREÚNA, 2016).

Age range		Entire sample (n=205)	Females (n=100)	Males (n=105)	A (%)	S (%)	E (%)	PPV (%)	NPV (%)	P (%)
2-5 years	W/H Index	0.55	0.55	0.54	80	55	87	55	87	80
	WC (cm)	52.40	52.40	53.00	90	69	100	100	87	90
	NC (cm)	27.50	26.20	26.60	76	40	80	18	92	76
5-10 years	W/H Index (cm)	0.49	0.49	0.49	90	74	97	89	90	90
	WC (cm)	63.00	63.00	65.80	88	80	90	63	95	88
	NC (cm)	29.50	32.00	29.50	82	61	88	58	89	82
Over 10 years	W/H Index (cm)	0.46	0.49	0.46	94	88	100	100	91	94
	WC (cm)	73.00	73.50	73.00	90	89	91	86	93	90
	NC (cm)	30.70	30.90	33.00	85	74	95	93	80	85

A: accuracy; S: sensitivity; E: specificity; PPV: positive predictive value; NPV: negative predictive value; P: precision; WC (waist circumference); NC (neck circumference); W/H Index (waist/height). Values calculated for the total sample.

is overweight[20], a situation that affects both genders similarly.

The increase in ultra-processed food consumption, or even of minimally processed ones, over in natura food, and the increasingly sedentary lifestyle of children and adolescents, characterized by an increase in screen time[3], have been associated with high rates of overweight among children.

The results of the correlation between BMI and NC, WC and W/H Index show that the NC and WC are strongly correlated with the BMI. The W/H Index presented a moderate correlation with BMI (strong positive correlation: r = 0.70 - 0.89) and moderate: r = 0.40 - 0.69). Also, the ROC curves indicate that the AUC of WC was higher in children from 2 to 5 years old, showing it to be the best instrument for indication of excess weight. In children aged 5 to 14 years, the W/H Index proved to be the best instrument. Another point that we were able to observe during the analysis is that WC, NC, and the W/H Index proved to be more significant with increasing age, i.e., there is a proportional and positive relationship with age.

In adults, the WC is a measurement widely used for verification of central obesity, which is related to the risk of cardiovascular diseases. Recently, this parameter has been proposed as an indirect measure of central obesity in children and adolescents[21,22]. The results found allow us to affirm that the WC provides very relevant and consistent information on the central body fat deposition in children when compared with the BMI. Corroborating the findings of this study, the studies of Soar et al.[23] and Ricardo et al.[24] also found a strong correlation between WC and BMI.

The present study showed that 33.70% of children and adolescents had a waist/height ratio over 0.5, i.e., a large fat tissue deposition in the abdominal region. This value is much greater than one found by Ricardo et al.[24], who found that 11.90% of children between 6 and 10 years old had abdominal adiposity and is also greater than the one found in the McCarthy and Ashwell[25] study, in which a 11.70% prevalence was observed. According to Pereira et al.[26], the W/H index can be considered a good indicator of abdominal adiposity, even better than the isolated measurement of waist circumference, because it takes into consideration the height of the individual and allows us to establish a single cut-off point. The AUC shows that the W/H Index is a good tool to identify excess weight, which is confirmed by high sensitivity and specificity values in all age groups. However, according to these results, we observed that, in younger children (2-5 years), this is not the best instrument, which corroborates a study conducted with children in Norway, according to which the W/H Index has lower sensitivity and specificity values in this age group[27].

The NC, a measurement that has been studied as a potential indicator of excess weight, was evaluated in children and adolescents. The results showed a strong positive correlation between NC and BMI, compatible with the findings of Lou et al.[28], Coutinho et al.[29] And Nafiu et al.[10]. In this study, the NC was correlated with BMI and became more significant as a predictor of excess weight as age increased, being indicated as a screening tool in older children. In contrast, the results also indicate that this is a less effective tool than others known since the NC had the lowest values of accuracy, sensitivity, specificity, positive and negative predictive values, and precision when compared with the WC and the W/H Index. The NC may reflect overweight and obesity in children and adolescents, but not in isolation; it needs to be associated with other measurements discussed in this work.

The limitations of our study are related to the gold standard parameter used for the analyses: BMI, which is known to be a high-sensitivity and low-specificity tool in the detection of excess weight. It would be interesting to compare the predictive variables with more reliable parameters of body composition diagnosis, such as densitometry by dual emission of X-rays and bioimpedance, but the dynamics and reality of the project did allow the collection of such data. Furthermore, the data collection was performed by the entire nutrition team who participated in the project in 2016 and, even though they received training to collect anthropometric measures, that did not avoid data collection errors, which are always present in studies such as this one, due to the interpersonal variation. Despite its limitations, this study showed that anthropometric measures such as WC, NC and W/H Index are useful to evaluate the nutritional status of children and adolescents in general.

CONCLUSION

After the analyses, we concluded that the children and adolescents treated by the *Projeto Bandeira Científica* showed a prevalence of 23.90% of excess weight, which is considered a high prevalence. Also, 33.70% had a W/H Index over 0.5, showing that approximately 1/3 had excess abdominal fat, which rep-

resents a risk for developing cardiometabolic diseases.

In the analysis by age groups using the ROC curve, we observed that among children aged 2 to 5 years, the WC presented a higher AUC than the W/H Index and NC. Whereas in children from 5 to 14 years old, the W/H index presented higher AUC than the WC and NC.

In summary, the WC of children younger than 5 years and the W/H Index of children older than 5 years have proved to be accurate measurements to identify excess weight.

Conflict of interest

Nothing to declare.

Source of funding

Foundation of the Medical Faculty and the Public Health Faculty of USP.

Acknowledgments

The *Projeto Bandeira Científica*, for the support offered during the development of this study.

PALAVRAS-CHAVE: *Obesidade. Criança. Antropometria.*

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ORIGINAL ARTICLE

Brazilian Study of Nutrition and Health (EBANS) – Brazilian data of ELANS: methodological opportunities and challenges

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http://dx.doi.org/10.1590/1806-9282.65.5.669

SUMMARY

BACKGROUND: *Epidemiological studies with dietary variables are complex methodologically, being the researcher responsible for anticipating, controlling, reducing and preventing methodological errors. Obesity accounts for almost one-third of the world's population and has consequences for childhood and adolescence. Multifactorial disorder must be faced in several aspects, being food and physical activity, modifiable risk factors. The EBANS aims to perform a diagnosis of the nutritional status of the Brazilian population from 15 to 65 years old, from all regions, and the parameters associated with obesity, with several possibilities of correlating data.*

METHODOLOGICAL PROCESS: *Part of the ELANS study (n = 9218), the EBANS (n = 2000) has a weighted sample and data collection that allows: to evaluate the socioeconomic level of the population; perform a diagnosis of nutritional status (through anthropometric variables); to evaluate food intake (R24h and FFQ for beverages); and evaluate physical activity practice (IPAQ-long and accelerometer).*

METHODOLOGICAL OPPORTUNITIES: *With national coverage, EBANS has the potential to compose regional analyzes, portray the current nutritional epidemiological condition, food consumption and physical activity pattern of the Brazilian population, at different life stages, and may have their data analyzed together or stratified, offering useful subsidies for the formulation of public policies.*

METHODOLOGICAL CHALLENGES: *Each methodological step was designed to reduce errors and biases related to methodological challenges.*

CAAE REGISTRATION: *31670314.8.0000.5567.*

FINAL CONSIDERATIONS: *Of great potential for future data analysis, EBANS tries to contribute to the generation of knowledge to foment policies and actions capable of changing the current obesity scenario.*

KEYWORDS: *Cross-sectional studies. Obesity. Food Consumption. Exercise. Anthropometry.*

DATE OF SUBMISSION: 29-Aug-2018
DATE OF ACCEPTANCE: 01-Sep-2018
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INTRODUCTION

Epidemiological studies in health are quite complex in its methodological design, especially those that involve dietary variables when the data collection instrument are questionnaires or similar protocols, which can cause omission and/or sub-reporting of data[1-3]. After identifying the main sources of error in their study, researchers should anticipate them and be able to propose methodologies that can control, reduce, and even prevent these errors[4]. Scientific and methodological rigor, as well as the application of additional methodologies in order to reduce random and systematic errors, are vital and characterize a methodological differential in epidemiological research[5].

Population studies with the same methodological protocol covering the various stages of life have a high application cost and, consequently, are scarce. The Household Budget Survey (Pesquisa de Orçamentos Familiares POF) aims to map the pattern of consumption, and thus, the expenses of the Brazilian population and is used by researchers as a source of data to identify the pattern of food consumption by Brazilians, which has been undergoing changes over time[6].

Currently, obesity is a public health problem worldwide, classified as an epidemic by the World Health Organization (WHO) and representing almost one-third of the world population[7]. The condition of overweight in the context of public health is determined by several factors, involving from genetic to environmental factors that permeate the lifestyle of the individual. The causes and factors associated with obesity denote that obesity is a multifactorial disorder[8-10]. Nutrition and physical activity are factors that have an important role in the context of obesity and are modifiable risk factors, meaning they may be altered by individual[8,11].

One of the main goals of epidemiological studies on health is producing knowledge and identifying variables related to a determined outcome in order to subsequently act on the variables to change the outcome, avoiding the worsening of a certain health condition[12]. The Brazilian Study of Nutrition and Health (EBANS) proposes an updated diagnosis of the nutritional status of the Brazilian population, as well as of the parameters associated with obesity, such as food consumption and practice of physical activity, with various possibilities of correlation between these data, which brings scientific subsidies related to the diagnosis of the problem so that the fight against the obesity epidemic can be effective.

METHODS

The EBANS is a descriptive, cross-sectional, population-based study part of the Latin American Study of Nutrition and Health/*Estudio Latinoamericano de Nutrición y Salud* (ELANS), which was conducted in eight countries in Latin America (Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Peru, and Venezuela)[13].

All participants signed an Informed Consent Form and/or a Assent Form (for adolescents), and the study is registered in the CAAE under the number: 31670314.8.0000.5567.

Sample size definition and study population

A study of national scope, representative of the Brazilian urban population of all five macro-regions of the country, the EBANS included individuals from 15 to 65 years old, of all socioeconomic levels.

We used systematic random sampling for selecting the cities included. The urban conglomerates were selected in a systematic way, and smaller cities were randomly selected based on their population density. Within the conglomerates, the Primary Sampling Units (PSU), represented by municipalities, districts, and residential areas, were randomly selected, as were the Secondary Sampling Units (SSU), defined as the census sectors. For the selection of the PSUs, we used the probability proportional to size (PPS), with a simple random sampling of the sample size to ensure the principle of statistical independence. Within each PSU allocated in the sample, a sampling point was randomly selected by means using PPS: the SSUs, which were defined based on the cartographic division of the census sectors[14]. In each SSU, the selection of the households was carried out in systematically, with each residential block traveled clockwise by the interviewer, with a sampling interval of three households. Within the households, the selection of individuals was controlled by quotas, always respecting the criteria of selection of half of the individuals with the closest birthday and the other half with the most distant birthday from the date of the interview.

The sample size and level of error calculations of EBANS (confidence level of 95%) adhered to gen-

eral criteria with the guarantee of a minimum basis of cases for disaggregation of data according to the variables of interest. We calculated the number of probable cases to the lowest socioeconomic level, the lowest age range, and for each gender, all obtained from the initial sample universe of 2,109 individuals (Table 1).

The final EBANS sample had 2,000 individuals (Figure 1), and the population of EBANS was characterized as described in Table 1.

Protocol for data collection

Following a standardized ELANS protocol[13], the data collected proposed to (1) diagnose the nutritional status (data measured using anthropometry), (2) evaluate the food consumption and (3) evaluate the practice of physical activity and energy expenditure of the Brazilian population.

The data were collected between October 2014 and July 2015, by means of two visits, respecting an eight-day interval and ensuring at least the collection of one weekend day, as outlined in Figure 2.

Instruments for data collection

Anthropometry

The anthropometric data were measured using standardized procedures in the literature[15], always in duplicate, and whenever there was a difference greater than 0.5 centimeters (cm) or 0.5 kilograms (kg) between them, a third measurement was performed. The measurements were recorded on a form and the data analyzed was the average of the measurements obtained.

The field interviewers, responsible for performing the anthropometric measures, were trained and supervised by anthropometrists in order to ensure better precision and accuracy of the data. Some unforeseen events were anticipated and the interviewers were instructed to make a clarifying note in the form if the individual refused to remove any items of clothing or heavy objects, if they were wearing heavy items of clothing (like jeans), if they refused or were unable to step on the scale or be correctly positioned to have their height measured, or had a hairstyle that could also interfere with the accuracy of the measurement of the neck circumference, if there was a refusal to lift their top for the measurement of waist circumference, and the impossibility of measuring the circumference beyond the maximum extension of the measuring tape and of using the scale to measure weight exceeding 200 kg (in this case, the declared weight was considered).

The measurement of body weight in kg was done with the aid of Sanny® portable scale with a maximum capacity of 200 kg and an accuracy of 0.1 kg, which was placed next to a wall and on a flat surface. The participants were instructed to remove shoes and socks, heavy items of clothing and accessories and objects from their pockets. After stabilizing the scale (with the measurement indicating zero), the participants stepped on the scale and stood still until the weight on the dashboard was fully stabilized.

The height was measured in cm and in whole numbers (rounded down when the measurement was less than 0.5 cm and rounded up when exceeding 0.5 cm) with the aid of a portable Sanny® stadiometer with an accuracy of 0.1 cm and a maximum of 205 cm, which was placed on a flat surface, against a smooth wall without skirting. The participants, barefoot, were positioned with their backs straight,

FIGURE 1. DIAGRAM OF EBANS PARTICIPANTS

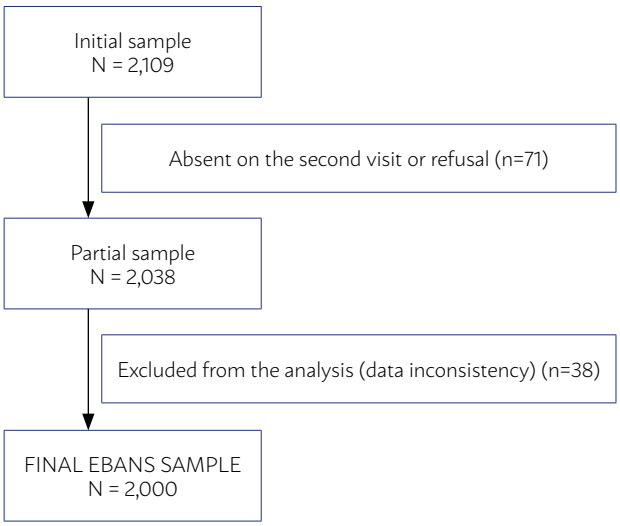


TABLE 1. CHARACTERIZATION AND DISTRIBUTION OF THE EBANS SAMPLE

	SEL*			Age strata				Gender		Error
	High	Medium	Low	15-19.9	20-34.9	35-49.9	50-65.9	Female	Male	
N (%)	169 (8.4)	915 (45.8)	916 (45.8)	235 (11.8)	745 (37.2)	608 (30.4)	412 (20.6)	1,058 (52.9)	942 (47.1)	2.79%

*SEL (socioeconomic level): Critério Padrão de Classificação Econômica Brasil[40]; classified as High (A1, A2, B1 class), Medium (B2, C1 class), and Low (C2, D, E class).

feet together, knees stretched, in the Frankfurt plane (with their head, back, buttocks and heels touching the wall; or with the greatest number of body parts as possible touching the wall). At the time of measurement, participants were instructed to breathe in for the correct measurement of height, and the interviewer was positioned in front of the stadiometer, using a platform to facilitate the reading.

After taking the anthropometric measurements, the average of the measurements obtained was used for calculating the Body Mass Index (BMI) (kg/m^2), according to the equation:

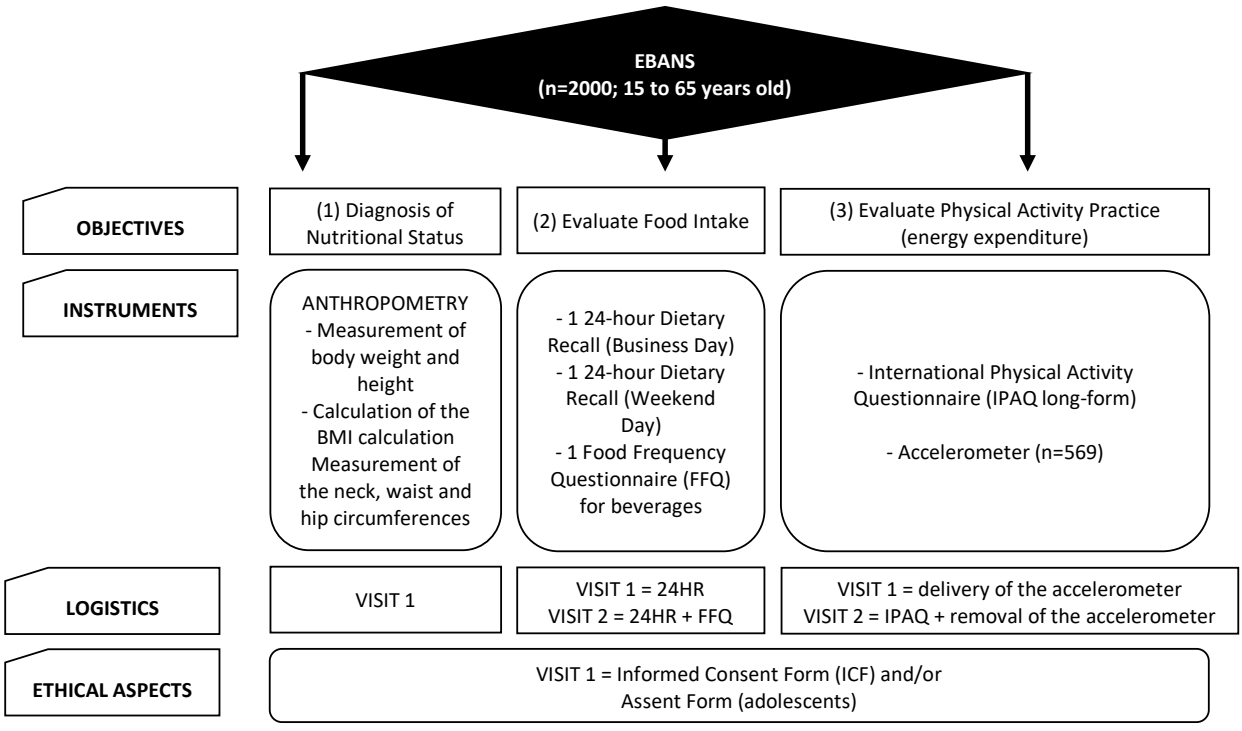
$$\frac{Weight\ (kilograms)}{Height^2\ (meters)}$$

The nutritional status was classified using the BMI calculated according to the parameters established by the WHO for individuals older than 19 years[16] and, for adolescents from 15 to 19 years old, we used the parameters of BMI per gender and age[17].

The measurement of the neck circumference is an anthropometric parameter that has been used and described in the literature for measuring nutritional status, especially as a marker of visceral adiposity and insulin resistance[18,19]. Its measurement is less embarrassing, faster and easier for the interviewers. The neck circumference was measured in cm with the aid of an inelastic Sanny® tape with a precision of 0.1 cm and a maximum length of 200 cm. The tape was positioned horizontally, perpendicular to the axis of the neck, over the thyroid cartilage (point below the larynx) while the individual was in an erect position, looking forward and with their shoulders relaxed[20].

The measurements of waist and hip circumference were also taken in cm using the same instrument, following the parameters recommended by the WHO[16,20]. To measure the waist circumference, the midpoint between the iliac crest and the last rib was located with the interviewer positioned next to the individuals and instructing them to relax their abdomen, outstretch their arms, keep their feet parallel, breath in and hold their breath for a few seconds until the interviewer found the exact point to take the measurement (mid-point of the distance obtained between the iliac crest and the last rib). To measure the hip circumference, the participant was instructed to wear light clothing (for better accuracy), stand upright with their abdomen relaxed, arms at the side of the body, feet together, body weight distributed evenly between both legs — the measurement was

FIGURE 2. GRAPHIC SCHEME OF THE EBANS PROTOCOL FOR DATA COLLECTION



obtained at the point of the greatest circumference on the gluteal region.

Food intake

The data of food intake characterize a very important methodological step in epidemiological studies, since the instrument and the methodology adopted may determine the scientific quality of the data and, consequently, of the entire research. In EBANS, food intake data were collected using two instruments established in the literature: the 24-hour Dietary Recall survey (24HR), which ensures better adhesion of the interviewee since it is faster and requires less memory time of the respondents[3,21]; and the Food Frequency Questionnaire (FFQ) (for beverages), which is widely used in studies with large sample size since it is of easy application, low cost, and the information generated is easy to processing for entry using *software*[22].

Both instruments are based on the self-reporting of the interviewees, so there may be a methodological bias of underreported data[1,2]. However, additional techniques and methodologies were implemented to reduce possible biases and errors related to the variability of the observer, the instrument, and the subject interviewed[5].

The first step was to ensure that the field staff was properly trained for the filling out of the instruments, thus controlling the bias and the intra- and interpersonal variability, minimizing the possible errors assigned to the observer. They were trained with meticulous detailing of the 24HR manual, with constant monitoring of field work by a nutritionist in charge for the immediate detection and correction of possible errors in data collection and the random selection of data for insertion in duplicate.

The 24HR is a tool capable of providing detailed information about the dietary consumption of the previous day or the last 24 hours and, if replicated, can estimate the habitual consumption of the individual. To ensure greater scientific reliability of the data from the 24HR and reduce possible errors related to this instrument, the 24HR was applied in person in two visits, for all participants, ensuring that one 24HR represented a business day and the other a weekend day, thus ensuring the representativeness of all days of the week, randomly distributed. With the purpose of improving the accuracy of the data, we used an auxiliary photo album containing pictures of the sizes of portions and utensils used as homemade measure[22]. Complementary to the data obtained from the 24HR, we used a qualitative FFQ adapted only to investigate the frequency of consumption of beverages ingested (number of times per day/week/month), including alcoholic and non-alcoholic beverages[23].

The subject interviewed represents another source of error in research protocols that do not use direct methods of food intake (such as rest-intake), being necessary to use additional techniques to reduce possible errors linked to the subject interviewed, who may sub-report data due to embarrassment or forgetfulness[1,2]. We used the Multiple Pass Method (MPM), an additional methodology developed by the United States Department of Agriculture (USDA), to assist the respondent in the detailing of his food-intake report, divided into five steps: quick listing, listing of food items usually forgotten, definition of meals and their time, detailing cycle, and final review[24].

After the data collection, another step that requires methodological care is the transfer of data for the analysis by software. After the analysis of data consistency, a team of trained nutritionists converted the quantities reported in household measures into values in grams (g) and milliliters (ml) and inserting them into the Nutrition Data System for Research software (NDS version 2013-R University of Minnesota, MN, USA)[25] for the dietary calculation. Since the NDS-R is an American software, some food items relating to Brazilians culture and habits standardized, according to Kovalskys et al.[26].

A software for statistical modeling using the Multiple Source Method (MSM), available at <https://msm.dife.de/tps/en>, was used for estimating the usual intake, being capable of estimating the usual intake of nutrients, foods and food groups, eliminating intrapersonal variance of consumption, allowing for the estimation of usual intake in both population and individual levels[27,28]. This method requires that you have a repetition of the consumption data (such as the 24HR) in a random subsample of the population to provide estimates of usual intake. It is noteworthy that for the EBANS the replication was made in 100% of the population, and, therefore, the data of the 24HR were used in a quantitative model that is applied to estimate the quantity consumed by means of linear regression. And in a second model, a probability one, which is estimated by logistic regression with random effects, we assumed the probability

of consumption of 100% (i.e., 1), because it is the consumption of nutrients and energy[27,28].

Physical activity

The collection of data of physical activity represents another methodological step that determines the scientific quality of the results if the instrument used is not properly applied, given that physical activity can occur in different contexts and the individual may not report it because they do not believe something is characterized as physical activity[29]. In this scenario, it is crucial that the instrument and the interviewer guide the reasoning and the reflection of the interviewee to describe all activities, whether in leisure, transportation, work and also in guided sports practices. Initially proposed by the WHO, the International Physical Activity Questionnaire (IPAQ long form) is an instrument validated both internationally and nationally[30] and is reliable to measure the energy expenditure of individuals, in particular, those that reside in urban areas. However, it is a subjective measure, since it depends on the interviewee's self-reporting and they usually overestimate the report. Therefore, it is prudent to use direct methods as complements for the higher scientific quality of the data[29].

In addition to the application of the long-form IPAQ, in order to obtain better accuracy of information, in 30% EBANS sample, the level of physical activity was also determined using an accelerometer, which provides a direct and objective measurement. The accelerometer is an instrument that has been used in the laboratory and in real life conditions to measure objectively the level of physical activity[31], mainly for adults. It provides a reliable measure with good validity[32]; however, there are some limitations that may underestimate the result, for example, not being able to measure isometric strength activities and aquatic activities, in addition to its high cost of application, which has limited its use in large epidemiological studies[29].

Always in search of better data precision and accuracy, the field team was trained in completing the long-form IPAQ in its version adapted by Mexican researchers[33], aiming to collect information about the routine practice of physical activity among participants, using as a reference the week before the interview. The field team was monitored by researchers in charge of detecting and correcting possible errors. After the data collection, a *score* for physical activity was standardized multiplying weekly frequency (days/week) by the average time of activity (minutes/day), for each of the domains of physical activity presented in the questionnaire (leisure and transportation), and for each type of physical activity (walking, moderate activity and vigorous activity). For each domain, a *score* of physical activity was obtained (minutes/week). Data were analyzed in accordance with the IPAQ scoring protocol, available at <https://sites.google.com/site/theipaq/scoring-protocol>. IPAQ data are reported as minutes per day of sitting, moderate activity (including walking) and vigorous activity and as MET-minutes of MVPA (minutes of walking x3.3 METS+minutes of moderate activity (excluding walking) x4.0 METS+minutes of vigorous activity x8.0 METS).

Regarding the direct measurement of the level of physical activity, the accelerometers GT3X (ActiGraph, Pensacola, FL) were delivered in the first home visit and the interviewer explained how to use the instrument, always instructing the respondent to attach the accelerometer at the waist using an elastic band over the midaxillary line on the right side of the body, using the instrument at all times while awake, removing it only for bathing or performing aquatic activities. After seven days of continuous use, coinciding with the second home visit, the instrument was collected and then the integrity of the data was verified by the team in charge using the ActiLife software version 6 (ActiGraph, Pensacola, FL).

DISCUSSION

Methodological Opportunities

The EBANS is a survey of national coverage, and its data were obtained from the protocol standardized by ELANS, thus generating a scientific opportunity of direct comparison between the data from research in Latin American participants of the ELANS and allowing for a reflection on a set of information concerning the fight against chronic non-communicable diseases and obesity and originated from different countries, but with similar conditions of being low- and middle-income places[34]. The EBANS data, which compose the ELANS database, can be useful and strategic for the formulation of public policies in the context of the Pan-American Health Organization (PAHO), with a focus on Latin America.

In addition to this broader approach, through analysis at a regional level, the data of the present

study depict the current nutritional epidemiological conditions of food consumption and physical activity pattern of the Brazilian population aged from 15 to 65 years. This allows us to determine the prevalence of excess weight, nutritional inadequacies, and sedentary lifestyle and the implications of the variants that interfere directly on these. The understanding of the size and relevance of this problem in the population is vital so that effective action can be implemented. In Brazil, obesity has grown 60% over the past ten years, the indices of excess weight are increasing over time, and currently, more than half of the Brazilian population presents excess weight[6,35]. The Ministry of Health has the goal to stabilize the prevalence of obesity and contain its growth in the adult population until 2019 by means of intersectoral health policies that cover food and nutritional security[36].

It is widely known that obesity is a multifactorial disorder[8-10] and that lifestyle encompasses factors that can be modified, resulting in significant improvements in various parameters of health and nutritional status[1]. Food consumption and physical activity pattern, therefore, are variables that can be modified by the individual as a result of well-targeted public policies. The EBANS brings data on food consumption and physical activity that can be analyzed together or stratified, generating various methodological opportunities.

Determining the practice of physical activity in a population, to identify individuals who are active or insufficiently active, as well as the implications that lead them to have certain behavior, can give subsidies are useful for formulating public policies capable of changing the backdrop of insufficient practice of physical activity, which seems to be the reality of a large part of the Brazilian population[35,36]. The great methodological differential of EBANS is the possibility of confronting the subjective indicators of physical activity with direct data (obtained using the accelerometer).

Table 2 summarizes the main methodological opportunities of data analyses generated on EBANS and the main methodological challenges linked to the study.

TABLE 2. METHODOLOGICAL OPPORTUNITIES AND CHALLENGES OF EBANS

Methodological Opportunities
1. National and regional coverage (ELANS) → strategic database for public policies with a focus on Latin America
2. Identification of the current nutritional epidemiological condition of the Brazilian population aged from 15 to 65 years
3. Identification of behavior patterns at different ages and stages of life (adolescence until senescence)
4. Data on food intake and physical activity that can be analyzed together or in stratified analyses
5. Identification of active or insufficiently active individuals and the implications of certain behaviors
6. Compare subjective and objective indicators of physical activity

Methodological challenges
1. Inclusion of the adolescent population (individuals biologically vulnerable and impracticality of the logistics to track the stage of pubertal maturation)
2. Approach with adolescents → Assent Form with moral validity
3. Methodological design scientifically robust and in compliance with the objectives of the research
4. Effective training of interviewers for contributing to the quality of the data
5. Definition of each methodological step linked to the careful definition of each instrument in order to reduce errors and biases

Methodological challenges

During the design of EBANS, when defining the study population and the representativeness desired, we initially intended to include children and adolescents under the age of 15 years. However, this intention was characterized as a methodological challenge, given that these populations are biologically vulnerable and, in case of adolescents younger than 15 years old, it would be necessary to check the stage of pubertal maturation[37]. In studies with adolescent population younger than 15 years old, this step is crucial, because, depending on the pubertal stage, the body composition may not faithfully reflect the nutritional status, since this stage of life causes considerable physiological and biological changes in the body[38]. We have chosen to consider 15 years old as the minimum age for inclusion in the study since by then puberty has usually already reached its peak[38]. Another challenging aspect in relation to adolescents was how to approach them since they should understand the purpose of the research and agree to participate through the Assent Form, which needs to be developed and applied in accordance with certain criteria in order to have moral validity[39].

After the challenge of a methodological design that was scientifically robust, the first practical challenge of EBANS was to train the interviewers, since the good relationship between the interviewers and participants could affect the quality of the data, es-

pecially when the research is related to obesity, food consumption, and practice of physical activity, themes that have an emotional impact on individuals due to its various associated aspects.

The data collection instruments elected for each stage of the research were widely discussed by the EBANS team, and each methodological step linked to each instrument was designed from the perspective of reducing errors and biases in connection to the methodological challenges faced, as already explained throughout the article, in the methodological description of the study.

FINAL CONSIDERATIONS

The EBANS is a study with great potential for future data analyses, which can provide various stratified descriptive results and also correlations between variables. Scientifically, it brings many opportunities to aggregate and contributes to the generation of data that may promote policies and effective actions to society. The production of knowledge, as well as the access and the understanding of the population to the information generated about issues that directly affect their lives is essential so that they can make choices and be agents of change of their own habits.

RESUMO

INTRODUÇÃO: *Estudos epidemiológicos com variáveis dietéticas são complexos metodologicamente, e o pesquisador é responsável por antecipar, controlar, reduzir e prevenir erros metodológicos. A obesidade representa quase 1/3 da população mundial e agrega consequências que são observadas na infância e na adolescência. Desordem multifatorial deve ser enfrentada sob diversos aspectos, sendo alimentação e atividade física fatores de risco modificáveis. O EBANS se propõe a realizar um diagnóstico do estado nutricional da população brasileira de 15 a 65 anos, de todas as regiões, e dos parâmetros associados à obesidade, com diversas possibilidades de correlacionar dados.*

PROCESSO METODOLÓGICO: *Parte do estudo ELANS (n=9218), o EBANS (n=2000) tem amostra ponderada e coleta de dados que permite: avaliar o nível socioeconômico da população; realizar diagnóstico do estado nutricional (por meio de variáveis antropométricas); avaliar consumo alimentar (R24h e QFA para bebidas); e avaliar prática de atividade física (IPAQ-longo e acelerômetro).*

OPORTUNIDADES METODOLÓGICAS: *De abrangência nacional, o EBANS tem potencial para compor análises regionais, retratar a atual condição epidemiológica nutricional, de consumo alimentar e padrão de atividade física da população brasileira, em diferentes estágios da vida, podendo ter seus dados analisados em conjunto ou estratificados, oferecendo subsídios úteis para a formulação de políticas públicas.*

DESAFIOS METODOLÓGICOS: *Cada etapa metodológica foi desenhada a fim de reduzir os erros e vieses atrelados aos desafios metodológicos.*

REGISTRO CAAE: *31670314.8.0000.5567.*

CONSIDERAÇÕES FINAIS: *De grande potencial para futuras análises de dados, o EBANS intenta contribuir na geração de conhecimento para fomentar políticas e ações capazes de alterar o atual cenário de obesidade.*

PALAVRAS-CHAVE: *Estudos transversais. Obesidade. Consumo de alimentos. Exercício. Antropometria.*

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ORIGINAL ARTICLE

Successful medical drainage and surgical treatment for vertebral osteomyelitis and bilateral psoas abscess with gas formation caused by *klebsiella pneumoniae* in a diabetic patient

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http://dx.doi.org/10.1590/1806-9282.65.5.678

SUMMARY

OBJECTIVE: *We describe the case of a diabetic patient who developed vertebral osteomyelitis and bilateral psoas abscess with gas formation due to klebsiella pneumoniae.*

METHODS: *A 64-year-old woman with a 4-year history of type-2 diabetes mellitus was admitted to the Emergency Department. The subject had a 2-day history of high-grade fever associated with chills and a 5-hour history of consciousness. She received empirical treatment with febrifuge, after which her fever decreased.*

RESULTS: *Her fever recurred after an interval of three hours. A computed tomography scan of the abdomen revealed vertebral osteomyelitis and bilateral psoas muscle abscess with gas formation. Blood culture and purulent fluid described the growth of the Klebsiella pneumoniae. The patient received antibiotic therapy and bilateral drainage therapy after the drainage catheter was placed into the abscess cavity by CT-guidance. Due to the serious damage to the vertebral column and permanent pain, the patient underwent minimally invasive internal spinal fixation and recovered successfully.*

CONCLUSION: *A case of vertebral osteomyelitis and bilateral psoas abscess with gas formation caused by Klebsiella pneumoniae in a diabetic patient. Antibiotic therapy, drainage, and minimally invasive internal spinal fixation were performed, which enabled a good outcome.*

KEYWORDS: *Osteomyelitis. Psoas abscess. Klebsiella pneumoniae. Minimally Invasive Surgical Procedures. Diabetes Mellitus.*

INTRODUCTION

Vertebral osteomyelitis and bilateral psoas abscess with gas formation caused by *Klebsiella pneumoniae* is a rare but life-threatening infection. It may lead to mortality if early diagnosis and effective management are not carried out. It frequently occurs in a variety of serious complications such as pneumonia, septic shock, and multiple organ failure. In this report, we present a case of vertebral osteomyelitis and

DATE OF SUBMISSION: 26-Jul-2018
DATE OF ACCEPTANCE: 27-Aug-2018
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bilateral psoas abscess with gas formation caused by *Klebsiella pneumoniae* in a 64-year-old woman with poorly controlled diabetes mellitus and review cases previously reported in the literature.

CASE REPORT

A 64-year-old woman with a 4-year history of type-2 diabetes mellitus was admitted to the Emergency Department. The patient had a 2-day history of high-grade fever associated with chills and a 5-hour history of consciousness. She had no history of coronary disease, obesity, and hypertension and was empirically treated with febrifuge, after which her fever decreased. However, her fever recurred after three hours. Upon physical examination, the patient was acutely ill-looking and had consciousness. Her body temperature was 39.2°C, pulse rate was 124/min, respiratory rate was 40/min, blood pressure was 116/76mmHg, and oxygen saturation was 90%. Ulceration of the skin was noticed on her right heel and in the lumbosacral region.

Hemoglobin (HB) level was 11 g/L. White blood cell (WBC) count and blood platelet (PLT) count were within the normal limits. The C-reactive protein level was 200 mg/L, and procalcitonin level was 7.86 ng/ml. Also, the fasting plasma glucose level was 50 mmol/L, arterial blood gas analysis revealed a pH of 7.434, the partial pressure of oxygen was 57.9 mmHg, and serum concentrations of Na+ ion and K+ ion were 159 mmol/L and 2.9 mmol/L, respectively. An electrocardiogram revealed nodal tachycardia. Urine analysis, stool analysis, head magnetic resonance imaging (MRI) and abdominal ultrasound did not reveal any clinical finding. Due to persistent fever and increased C-reactive protein level and procalcitonin level, she received empirical anti-infectious treatment. Abdominal CT revealed osteomyelitis at the L2 vertebral body and bilateral psoas muscle abscess with gas formation (Figure 1). On day three, blood culture yielded *Klebsiella pneumoniae*. Meropenem and moxifloxacin were used to the patient's targeted therapeutic regimen when *Klebsiella pneumoniae* was identified. However, on day five, the patient's fever persisted, and inflammatory markers remained high. At this point, intravenous vancomycin was started. On day 9, a drainage catheter was inserted by CT-guidance due to enlargement of the right psoas abscess (Figure 2), yielding 100 ml of purulent fluid. On day 18, the right drainage tube was taken out. On day 25, the patient was sent to the operating room and received minimally invasive internal spinal fixation due to the worsening of vertebral destruction at the L2 level[1] (Figure 3). The operation was successful. On day 33, due to the enlargement of the left psoas abscess, CT-guided drainage of the left psoas abscess was performed, and purulent material was allowed to flow out. However, cultures of the purulent material were negative. Therapy with ceftazidime was continued, and meropenem and vancomycin were discontinued. On day 40, the left drainage tube was taken out. On day 46, laboratory values were as follows: leukocyte count was 7,900/μL, and C-reactive protein was 10.38 mg/L. MRI revealed that the position of eight pedicle screws fit well. On day 47, the patient was discharged. After one year of follow-up after surgery,

FIGURE 1. ABDOMINAL CT SHOWED OSTEOMYELITIS AT L2 VERTEBRAL BODY AND BILATERAL PSOAS MUSCLE ABSCESS WITH GAS FORMATION.

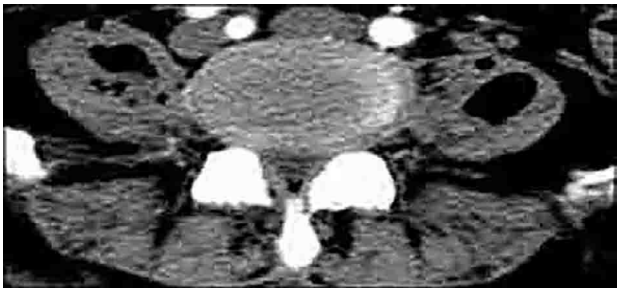

FIGURE 2. A CT-GUIDED DRAINAGE CATHETER WAS INSERTED DUE TO THE ENLARGEMENT OF THE RIGHT PSOAS ABSCESS.

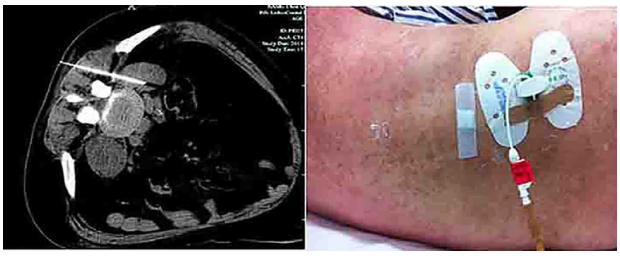

FIGURE 3. MINIMALLY INVASIVE INTERNAL SPINAL FIXATION.

the patient had no evidence of recurrence, and the CT revealed that the bilateral psoas muscle abscess was apparently reduced.

DISCUSSION

Vertebral osteomyelitis and bilateral psoas abscess with gas formation caused by *Klebsiella pneumoniae* is a relatively uncommon disease, and its early diagnosis remains a challenging issue. Diabetes mellitus, immunocompromised conditions, and trauma are major risk factors. Chang et al.[2] has reported seven cases of psoas abscess caused by *Klebsiella pneumoniae*. Results revealed that early recognition, empiric antimicrobial coverage for *Klebsiella pneumoniae*, and aggressive drainage are necessary[2]. *Klebsiella pneumoniae* is a non-spore-forming gram-negative bacillus that is pathogenic for human beings, especially for immunocompromised patients[3]. *Klebsiella pneumoniae* generally infects the lung by directly spreading through the airway and rarely causes infections of the central nervous system, joint, and bone.

Classical symptoms of psoas muscle abscess involve limping, lower back pain and persistent fever with daily spikes[4]. However, the patient had no localized symptom in our presented case. The reported common causative pathogens of psoas muscle abscess in Ricci et al.[5] are *Staphylococcus aureus* (190 cases, 88.4%), *Streptococci* (12 cases, 4.9%), and *Escherichia coli* (seven cases, 2.8%). In our case, gram-positive bacillus and anaerobic bacteria were primarily considered as causative pathogens. However, purulent material and blood culture yielded *Klebsiella pneumoniae*. Ultrasonography is a tool that is readily available but is neither specific nor sensitive. CT is the most sensitive tool for a definitive diagnosis of psoas muscle abscess[3].

Vertebral osteomyelitis is a potentially life-threatening infection[6]. According the report by McHenry et al.[7], *Staphylococcus aureus*, coagulase-negative *Staphylococci*, *Escherichia coli*, *Streptococci*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Salmonella* species, and *Klebsiella pneumoniae* were considered causative pathogens of vertebral osteomyelitis. The diagnoses of vertebral osteomyelitis were based on clinical features, imaging findings, and laboratory examination. Relief of pain, prevention of recurrence, eradication of infection, prevention of neurologic defects and restoration of spinal stability are the general objectives of treatment[8].

Systemic antimicrobial therapy and surgical drainage are the traditional treatment for psoas muscle abscess[9]. Antimicrobial therapy according to drug susceptibility is essential to prevent the emergence of a drug-resistant strain[3]. In the past, abscess drainage was commonly performed using surgical procedures. With the improvement of computer and imaging techniques, percutaneous drainage has become the primary treatment for psoas abscess through CT or ultrasound-guidance, especially when there is a high risk for surgery[10]. Bilateral percutaneous drainage was performed in our case. Conservatively, patients with vertebral osteomyelitis can be treated with intravenous antibiotics. However, surgical treatment is considered when the conservative treatment is unsuccessful. The surgical strategy for vertebral osteomyelitis is currently continuously evolving[8]. Spinal internal fixation is one of the currently used methods for the surgical treatment of vertebral osteomyelitis. In our case, antimicrobial therapy treatment in patients was unsuccessful. Therefore, minimally invasive internal spinal fixation was performed for the treatment of vertebral osteomyelitis due to severe damage to the vertebral column.

In summary, we report a case of vertebral osteomyelitis and bilateral psoas abscess with gas formation caused by *Klebsiella pneumoniae* in a diabetic patient. Antibiotic therapy, drainage, and minimally invasive spinal internal fixation were performed, which enabled a good outcome in our case. *Klebsiella pneumoniae* should be considered a critical pathogen that causes vertebral osteomyelitis and bilateral psoas abscess with gas formation in diabetics. Early and accurate diagnosis should be made to prevent the exacerbation of this disease. Long-term follow-ups are needed to determine its potential for recurrence.

Funding: Medical and Health and Technology Project of Zhejiang Province (2018KY937).

RESUMO

OBJETIVO: *Descrever o caso de uma paciente diabética que desenvolveu osteomielite vertebral e abcesso bilateral do psoas com formação de gás causada por klebsiella pneumoniae.*

MÉTODOS: *Uma mulher de 64 anos de idade, com 4 anos de histórico de diabetes mellitus tipo 2, foi admitida no Serviço de Emergência. A paciente apresentava um quadro de dias de febre alta acompanhada de calafrios e um histórico de 5 horas de consciência. Ela recebeu tratamento empírico com antitérmico, após o qual a febre diminuiu.*

RESULTADOS: *A febre retornou após um intervalo de três horas. Uma tomografia computadorizada do abdome revelou osteomielite vertebral e abcesso bilateral do músculo psoas com formação de gás. A cultura do sangue e o fluido purulento revelaram o crescimento de Klebsiella pneumoniae. A paciente recebeu antibióticos e terapia de drenagem bilateral após o cateter de drenagem ser posicionado na cavidade do abscesso com auxílio de TC. Devido a sérios danos à coluna vertebral e a dor permanente, a paciente foi submetida à fixação vertebral interna minimamente invasiva e recuperou-se com sucesso.*

CONCLUSÃO: *Um caso de osteomielite vertebral e abscesso do psoas bilateral com a formação de gás causada por Klebsiella pneumoniae em uma paciente diabética. Antibioticoterapia, drenagem e fixação vertebral interna minimamente invasiva foram realizadas, o que permitiu um bom resultado.*

PALAVRAS-CHAVE: *Osteomielite. Abcesso do psoas. Klebsiella pneumoniae. Procedimentos cirúrgicos minimamente invasivos. Diabetes Mellitus.*

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ORIGINAL ARTICLE

Profile and scientific output of researchers recipients of CNPq productivity grant in the field of medicine

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http://dx.doi.org/10.1590/1806-9282.65.5.682

SUMMARY

BACKGROUND. *This study aimed to evaluate the scientific production of researchers in the field of Medicine who receive a productivity grant from the CNPq.*

METHODS: *The curriculum Lattes of 542 researchers with active grants from 2012 to 2014 were included in the analysis. Grants categories/levels were stratified into three groups according to the CNPq database (1A-B, 1C-D, and 2).*

RESULTS. *There was a predominance of grants in category 2. During their academic career, Medicine researchers published 76512 articles, with a median of 119 articles per researcher (IQ, interquartile range, 77 to 174). Among the 76512 articles, 36584 (47.8%) were indexed in the Web of Science (WoS database). Researchers in Medicine were cited 643159 times in the WoS database, with a median of 754 citations (IQ, 356 to 1447). There were significant differences among the categories of grants concerning the number of citations in WoS (P <0.001). There was a significant difference in the number of times researchers were cited according to the specialty included in Medicine area. (P < 0.001).*

CONCLUSION. *Strategies to improve the scientific output qualitatively possibly can be enhanced by the knowledge of the profile of researchers in the field of Medicine.*

KEYWORDS: *Research Personnel. Work Performance. Medicine.*

INTRODUCTION

Many evaluations of tenure promotions and grants take into account appraising metrics in order to assess the performance of individual scientists and eventually rank those researchers[2]. Thanks in part to the easier access to interdisciplinary publication and citation databases (such as Web of Science and Scopus), quantitative measuring of the performance of researchers has become even more prevalent, controversial, and influential[2-6].

Every organization that funds research wants to support science that makes a difference for the community. Therefore, quantifying the performance of

DATE OF SUBMISSION: 16-Sep-2018
DATE OF ACCEPTANCE: 02-Oct-2018
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individual scholars, departments, and institutions has become an essential part of decision-making in research policy, funding allocations, awarding of grants, faculty hiring, and claims for promotion[7,8]. In this context, the rationale of performance evaluation is that scientific budget should flow to individuals and institutions with a qualitatively high scientific output. Nevertheless, there is a difficulty in using measurements to evaluate research since there is no simple formula for identifying truly important research. It is clear that a fair and reliable quantification of the 'level of excellence' of individual scientists is a challenging task[9-11]. Thus, to measure the performance of a researcher using objective tools has become one of the major challenges in science. Evaluating individual research performance is a complex task that ideally examines productivity, scientific impact, and research quality [12]. At present, the impact of scientific work is traditionally measured by the balance between the number of papers and the number of times that these publications are cited[13-16]. However, the evaluation system that has been built upon bibliometric indices is very complex and its results are often inconsistent[17-19].

In Brazil, the National Council for Scientific and Technological Development (CNPq) was created in 1951 and, since then, it has been the most important Brazilian agency supporting science and technology[20]. The scientific divisions of this entity are categorized into nine major areas subdivided into several subareas of knowledge. Medicine is one of these major areas and is subdivided into diverse subareas of specialization[21]. In the 1970s, the research productivity grant was implemented as a stimulus to researchers with notable scientific contributions in their respective areas[22]. The area of Medicine had 542 researchers (3.8%) among 14,077 productivity grants in 2014. In order to apply for a grant as a CNPq investigator in Medicine, researchers must fulfill some requirements, and they are ranked according to the criteria established by CNPq. According to the Advisory Committee of CNPq, the criteria for the selection and classification of researchers in Medicine include, among several indicators, scientific production, training of human resources, and contribution to innovation[23]. Therefore, in order to be classified as a CNPq investigator in Medicine, the researcher must meet the following minimum requirements over the previous decade: a) to have published at least 20 papers in scientific journals with IF greater than or equal to 1; b) to have completed the orientation of at least one Ph.D.; and c) to have a defined line of research and a present research project of scientific merit, covering the area of medicine. These researchers are currently classified into two main categories (1 and 2). Category 1 was subdivided into four levels: 1A, 1B, 1C, and 1D, and the first level of category 1 is attributed only to researchers with outstanding scientific productivity [24].

Several studies have examined the profile and the scientific production of CNPq researchers in various areas of knowledge, including pharmacy[20], chemistry[22], computer science[24], neurosciences[25,26], cardiology[27], nephrology[28,29] and clinical medicine[30,31]. However, there is a deficiency of studies concerning the entire area of Medicine with its diverse subareas and specialties. In this regard, the present study aims to describe the profile and the scientific production of recipients of CNPq research productivity grants in Medicine. In addition, we evaluated the ability of the Assessor Committee in Medicine to rank researchers that outstand among their peers as a result of the scientific-technical production developed.

METHODS

Participants

This was a cross-sectional study conducted on 542 investigators registered as recipients of CNPq research productivity grants in Medicine according to a list provided by the agency in February 2013.

Data collection

For this investigation, we used the list of researchers in Medicine from CNPq, with active research productivity grants during the triennium 2012-2014. Using the openly available Lattes curriculum in the CNPq Lattes Platform (http://lattes.cnpq.br/) we elaborated a database with information on each researcher in terms of geographic distribution, institution, time since obtaining the Ph.D., scientific production (published papers), and training of human resources (supervision of undergraduate, master and Ph.D. students). For this data collection, we considered all papers and all student tutoring during the scientific career span of the researcher. We also analyzed the same content for the last five years, considering the period 2008-2012.

Additionally, we searched the database of Web of Science, Thomson Reuters (WoS) at http://apps.

isiknowledge.com/. The database was consulted through the CAPES website (http://novo.periodicos.capes.gov.br/). This database was surveyed with the aim to get the number of times the researchers were cited. The main problem in processing our data was to properly identify authors since the same author can provide his/her name or can be registered in diverse ways [9-10]. Therefore, the scientific name of the researcher primarily used in this investigation was that provided in the Lattes curriculum. Furthermore, there was an intense search for possible variations of researchers' names. Additionally, data were checked with the following filters available on the WoS database: (i) institution; (ii) subject area; (iii) year of publication, and (iv) source titles. We also used the filter called "Document type" and we excluded from the analysis abstracts presented at meetings.

Area of knowledge and medical specialties

For this variable, we considered the expertise area specifically assigned by the investigator in the Lattes curriculum. When this information was missing, we analyzed the researchers' scientific production over the past five years and allocated them to the area of knowledge in which there was a predominance of issues published.

Variables of interest

The following variables, divided into three categories, were analyzed: (1) Demographic variables, including gender and regional distribution; (2) Background information, including affiliation, post-graduate features, and time since obtaining the Ph.D., and (3) Scientific productivity, including mentoring undergraduate, master's, and Ph.D. students, number of articles, and number of papers indexed in the WoS databases. Concerning publications and student supervision, we analyzed all production during the entire scientific career as well as in the last five-year period. Regarding both student supervision and scientific publications, all data were adjusted per time after the researcher's Ph.D., i.e., the average of production and citation per year. Research performance indicators were also included in the analysis: adjusted number of citations, and the number of citations *per* paper[15,32-34]. Research productivity grants categories/levels were classified in the CNPq database as two main categories (1 and 2), with four levels in category 1 (1A, 1B, 1C and 1D). These categories/levels were taken into account for analysis purposes.

Statistical analysis

The SPSS (*Statistical Package for Social Science for Windows, Inc., USA*) version 18.0 for Windows was used to create the database and to perform the statistical analysis. Continuous data were reported as medians and interquartile range (IQ) or means and standard deviation (SD), when appropriate. The non-parametric Mann-Whitney and Kruskal-Wallis (KW) tests were used for comparison of medians and ANOVA was used for comparison of means among groups. Dichotomous or nominal variables were compared using the chi-square test.

RESULTS

The demographic characteristics and the area of knowledge of the researchers are summarized in Table 1. There was an overall predominance of males (63.5%) and grants in category 2 (54.1%). There was a significant difference in the distribution of categories between genders. Among males, 52% had grants in categories 1 (1A-1D), while only 36% of females were included in these categories (P<0.001). Five states of the Federation were responsible for approximately 90% of the researchers, and the State of São Paulo accounted for about 60% of them. Six institutions were responsible for approximately 70% of researchers, with a prominence of USP with about a third of them. Regarding Ph.D., most of the researchers (n=504, 93%) obtained the degree in Brazil and 38 (7%) in institutions abroad. The main institution from which the researchers obtained their Ph.D. was USP (35%). Indeed, six universities accounted for about 80% of the Ph.D. (USP, UNIFESP, UFRGS, UNICAMP, UFRJ, and UFMG).

A total of 35 areas of research were identified with a large dispersion of investigators among the several areas of interest. As shown in Table 1, the five areas of research more frequently assigned as the main area of interest of the researchers include about 45% of the total of the investigators.

The overall median time since receiving the doctoral degree was of 18 years (Interquartile range, 13 – 24 years). Female researchers had a median of 17 years of Ph.D. time (13 – 21), while males had a median of 18.5 (13 – 25) (P=0.013). The majority of the researchers (56.3%) had post-doctoral training, predominantly at USA institutions

TABLE 1. DEMOGRAPHIC, BACKGROUND, AND POST-GRADUATE FEATURES OF CNPQ RESEARCHERS IN CLINICAL MEDICINE (N = 542)

Gender	n (%)
Male	344 (63.5)
Female	198 (36.5)
Scholarship categories	
1A	60 (11.1)
1B	52 (9.6)
1C	50 (9.2)
1D	87 (16.1)
2	293 (54.1)
Federation State	
SP	318 (58.7)
RS	62 (11.4)
RJ	55 (10.1)
MG	36 (6.6)
BA	19 (3.5)
Others	52 (9.6)
Researcher Institution	
USP	164 (30.3)
UNIFESP	72 (13.3)
UFRGS	44 (8.1)
UNICAMP	41 (7.6)
UFMG	32 (5.9)
UFRJ	30 (5.5)
Others	159 (29.3)
Area of knowledge	
Psychiatry/Neurosciences	73 (13.5)
Cardiology	47 (8.7)
Gynecology/Obstetrics	44 (8.1)
Endocrinology	39 (7.2)
Pathology	37 (6.8)
Pediatrics	33 (6.1)
Nephrology/Urology	33 (6.1)
Infectious Diseases	27 (5.0)
Hematology/Oncology	26 (4.8)
Medicine/Intensive Medicine	24 (4.4)
Pneumology	20 (3.7)

Area of knowledge (cont.)	n (%)
Ophthalmology	15 (2.8)
Immunology	15 (2.8)
Gastroenterology/Hepatology	14 (2.6)
Rheumatology	13 (2.4)
Genetics/Molecular Biology	13 (2.4)
Others	69 (12.7)
Doctorate country*	
Brazil	502 (92.3)
United Kingdom	12 (2.2)
Germany	10 (1.8)
Canada	6 (0.9)
Japan	3 (0.6)
Netherlands	3 (0.6)
Others	4 (0.8)
Doctorate Institution*	
USP	191 (35.2)
UNIFESP	103 (19.0)
UFRGS	49 (9.0)
UNICAMP	37 (6.8)
UFRJ	35 (6.5)
UFMG	27 (5.0)
Others	100 (18.1)
Time since Doctorate (years)	
Median (IQ range)	18 (13 – 24)
Post Doctorate	
Yes	305 (56.3)
No	237 (43.7)
Post Doctorate country	
USA	144 (47.2)
Brazil	55 (18.0)
United Kingdom	34 (11.1)
Canada	19 (6.2)
France	16 (5.2)
Others	37 (12.1)

*Two researchers without a doctorate

Scientific productivity: human resource training

During their scientific career, CNPq researchers in Medicine have trained 7336 undergraduate research fellows (a program known as scientific initiation at Brazilian universities), with a median of 8 (IQ, 3 – 18) per investigator, 6962 master's students (median of 10, IQ = 5 - 18), and 4962 Ph.D. students (median of 7, IQ = 3 - 13). Table 2 shows the absolute and adjusted (per year of Ph.D.) values considering the mentorship stratified by the grant categories. Concerning the absolute and adjusted values, there was a significant difference among grant categories regarding the number of masters and Ph.D. students, but not regarding undergraduate students (Table 2).

Scientific output: publications

During the entire period of their academic career, CNPq medicine researchers published 76512 articles, with a median of 119 articles *per* researcher (IQ, 77 to 174), ranging from 8 to 992 articles.

There was a significant difference of the median number of publications among the grant categories considering both the absolute and the adjusted number of articles (total of articles, in the last 5 years,

TABLE 2. MENTORING AND SCIENTIFIC PUBLICATION BY CNPQ RESEARCHERS IN MEDICINE ACCORDING TO THE SCHOLARSHIP CATEGORIES (N = 542)

Variables	1A – 1B n = 114	1C-1D n = 136	Level 2 n = 292	p-value*
Undergraduates				
Median (IQ range)	12.5 (3.0 – 26.0)	9.0 (3.0 – 17.0)	7.0 (2.0 – 17.0)	0.03
Undergraduates/year				
Median (IQ range)	0.54 (0.15 – 1.2)	0.48 (0.16 – 1.0)	0.5 (0.16 – 1.0)	0.63
Master degree				
Median (IQ range)	16.5 (9.2 – 17.7)	10.0 (7.0 – 17.7)	3.2 (8.0 – 14.8)	<0.001
Master degree/year				
Median (IQ range)	0.73 (0.42 – 1.2)	0.61 (0.3 – 0.91)	0.57 (0.3 – 0.8)	0.01
Doctorate				
Median (IQ range)	17.0 (10.0 – 23.8)	9.0 (5.0 – 12.0)	4.0 (1.0 – 8.0)	<0.001
Doctorate/year				
Median (IQ range)	0.73 (0.54 – 0.94)	0.43 (0.3 – 0.63)	0.26 (0.12 – 0.4)	<0.001
Mentorship total				
Median (IQ range)	53.5 (36.0 – 75.0)	30.5 (21.0 – 44.8)	21.5 (11.0 – 39.0)	<0.001
Mentorship total/year				
Median (IQ range)	2.3 (1.5 – 3.4)	1.6 (1.2 – 2.4)	1.5 (0.83 – 2.3)	<0.001
Total articles				
Median (IQ range)	193 (155 – 282)	129 (101 – 176)	88 (60 – 126)	<0.001
Total articles/year				
Median (IQ range)	9.4 (6.5 – 12.2)	6.9 (5.3 – 9.4)	5.8 (4.0 – 7.9)	<0.001
Total articles WoS				
Median (IQ range)	108 (87 – 148)	66 (51 – 86)	33 (25 – 49)	<0.001
Total articles WoS/year				
Median (IQ range)	4.7 (3.5 – 7.0)	3.6 (2.4 – 5.2)	2.2 (1.5 – 3.3)	<0.001
Articles last 5 years				
Median (IQ range)	70 (49 - 105)	50 (34 – 66)	36 (26 – 50)	<0.001
Articles last 5 years WoS				
Median (IQ range)	36.5 (26 - 55)	26 (18 – 32)	14 (10 – 21)	<0.001
Increment of Scientific Output (%)				
Median (IQ range)	63.7 (28 – 108)	41.0 (12 – 64)	25.4 (3 – 63)	<0.001

and articles indexed on WoS). There was also a significant difference among grant categories in relation to the increase of scientific publication (Table 2).

During the last five years, the total of articles was 29618 with a median of 44 *per* researcher (IQ, 29 – 63), ranging from 7 to 546. Among the 76512 articles, 36584 (47.8%) were indexed in the WoS database (median per researcher of 53, IQ, 32 - 85). Considering the average number of articles published annually, the majority of researchers (438, 81%) increased their scientific output over the past five years. This increase ranged from 2% to 326% with a median increment of 49.8% in overall scientific production (IQ, 23 to 79).

Regarding the areas of knowledge, there was a significant difference in the increment of the scientific output in the last 5 years ($F = 2.6$, $P < 0.001$). The area of knowledge with the greatest mean percentage of increment was Immunology (64.9% ± 42), followed by Endocrinology (57.5% ± 42.0), Hematology/Oncology (54.7% ±52), Neurosciences/Psychiatry (50.3% ± 51), Pneumology (46.8% ± 51), Surgery (43.8% ± 61), Pediatrics (43.3% ± 51), and Nephrology/Urology (42.5% ± 51). Figure 1 illustrates the increment of scientific output by comparing the mean number of papers/years in the last five years and in the whole scientific career among the researchers in the diverse areas of knowledge.

Scientific production: citations

During their academic career, CNPq researchers in Medicine received 643159 citations in the WoS database, with a median of 754 citations per researcher (IQ, 356 to 1447, ranging from 29 to 12741). The median number of citations *per* article was 13.9 (IQ, 9.5 – 17.5). There were significant differences among the

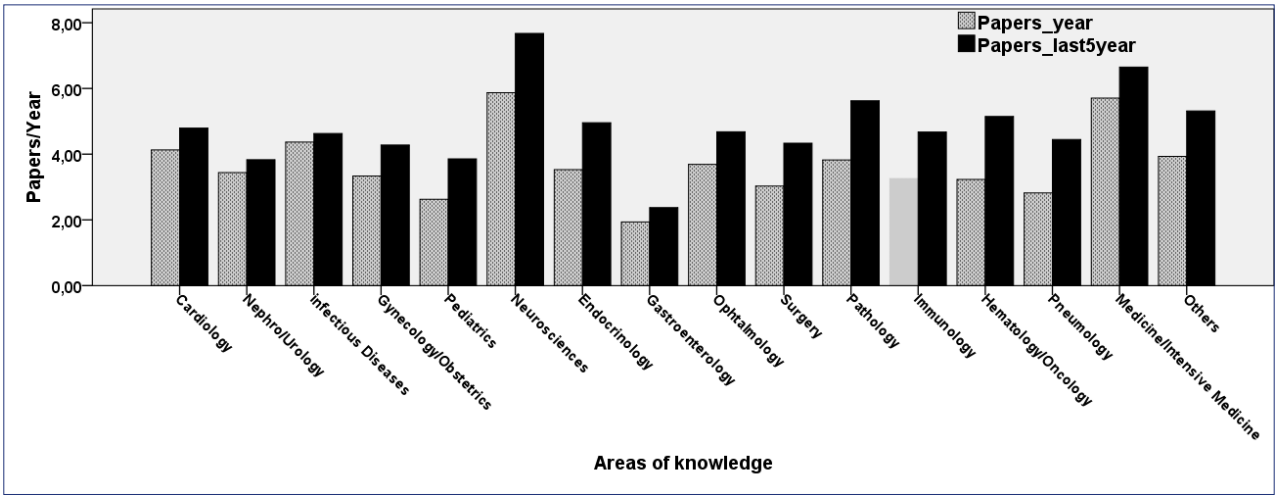

FIGURE 1

grant categories considering the number of citations in WoS (KW = 218.5, P <0.001). CNPq researchers of level 1A-B had a median of 1664 citations (IQ, 1129 – 2292); level 1C-D, 992 citations (IQ, 730 – 1645); and level 2, 425 citations (232 - 752). The difference remained significant even after the adjustment for the time of obtaining the Ph.D. The mean number of citations per year was 105 (SD, 89), 78.4 (SD, 60), and 47 (SD, 83) for levels 1A-B, 1C-D, and 2, respectively (P<0.001). The mean of citations per article was 18 (SD, 9.8) for level 1A-B, 19.6 (SD, 13.4) for level 1C-D, and 15.7 (SD, 14.5) for level 2. There was also a significant difference among grant levels regarding the mean citation per article (P=0.016). Interestingly, there was a moderate positive correlation between the number of papers published in journals indexed on WoS and the number of citations received by the researchers (r=0.66, P < 0.001).

Considering the several areas of knowledge, there was a significant difference in the mean of citations per paper received by the CNPq researchers (F = 5.4, P < 0.001). The area of knowledge with the greatest mean of citations per paper was Cardiology (29.5 ± 29.1), followed by Immunology (22.7 ± 16.9), Pneumology (21.7 ± 13.0), Infectious Diseases (20.3 ± 11.2), Neurosciences/Psychiatry (19.7 ± 12.5), Nephrology/Urology (18.6 ± 13.2), Medicine/Intensive Medicine (16.6 ± 6.5), Hematology/Oncology (16.2 ± 8.8), and Endocrinology (15.9 ± 8.0).

DISCUSSION

A relevant finding that emerges from our cross-sectional study on CNPq researchers in the field of Medicine is the concentration of scientific output in a few Brazilian states. Five of them account for approximately 90% of the researchers, and a single state (São Paulo) for remarkably 60% of the CNPq researchers in Medicine. Notably, this figure is even disproportionately higher than the participation of the State of São Paulo in the Brazilian Gross Domestic Product (GDP), which is about 32% [35]. The findings of this study also show that two institutions in the state of São Paulo (USP and UNIFESP) were responsible for the Ph.D. of about 54% of the researchers. This fact can contribute partly to the concentration of the CNPq researchers in the Southeast region of Brazil[36]. It is important to highlight that only six researchers with a grant in Medicine (1.1%) were from the North and Midwest regions of Brazil, which reinforces the heterogeneous spatial distribution in the country. This finding should subsidize specific government actions to address such regional differences[37].

Our analysis showed that CNPq male researchers have proportionally more grants in category 1 than female researchers. We believe that even though males had a longer Ph.D. time than females, the relatively small difference of 1.5 years cannot explain the imbalance in the grant categories. Concerning the gender disparities in science, Larivière et al.[38] have recently presented a bibliometric analysis confirming that gender inequalities persist in research output worldwide. Moreover, although there are more female than male undergraduate and graduate students in many countries, there are relatively few female full professors, and gender inequalities in hiring, earnings, funding, satisfaction, and patenting persist. As expected, in Brazil the state of affairs is

quite similar, and women are in lower proportion in the higher positions of the academic career, that is, those positions associated with higher income and higher academic prestige[39].

Another point to be emphasized in our study is the assessment of the scientific output by CNPq researchers in Medicine in quantitative and qualitative terms through the analysis of bibliometric indicators. From the quantitative point of the view, our study showed an important scientific output with an expressive number of publications of scientific articles in periodicals indexed at the WoS database. Among the 76512 articles published by the Medicine CNPq researchers, 36584 (47.8%) were indexed in the WoS database. Another point to be emphasized is the increment of the scientific output over the last 5 years, a fact that has also been observed in other areas of knowledge[29-31,40]. CNPq researchers in Medicine had an increase of about 50% in the number of published articles, in comparison to the annual output across the career over the last 5 years. This quantitative increment in scientific production correlates with the general increase in scientific production in Brazil, and possibly reflects the various fostering mechanisms implemented by the various national research support agencies[27,28,41-45]. Unfortunately, the current economic crisis has already resulted in cuts to federal and state science funding. This will probably impair Brazilian research and possibly hamper the scientific output increment over the next years[46].

Another point assessed in our study was the impact of scientific publications by CNPq researchers in Medicine through the analysis of the number of citations. The most widespread method for judging the impact of biomedical articles is citation count, which is the number of citations received[47]. This metric was first introduced by Gross and Gross[48]. It is generally assumed that articles with higher impact receive more citations. Although quantifying the quality of individual scientists is difficult, the general view is that the citation count of a paper (relative to citation habits in its field) has been considered a useful measure of its quality[10]. In our analysis, the median number of citations per researcher and number of citations per article was 754 and 13.9, respectively. There were significant differences among the grant categories regarding the number of citations received in WoS. Nevertheless, it is important to recognize that it takes time for a paper to accumulate its full complement of citations[10]. This fact represents a serious limitation on the value of citation analyses for younger authors, who presumably are the researchers of CNPq grant in category 2.

Another relevant topic that should be pointed out in this study is the remarkable difference in the citation counts among researchers from the diverse subareas of Medicine. In this regard, the areas of Cardiology and Neurosciences stand out with a median of about 12000 citations per researcher. These data emphasize the quality of the scientific output of this group of researchers. In a previous analysis, we have shown that of the 587 journals identified as being used by the CNPq researchers in Cardiology, 340 (58%) are indexed in the Web of Science database, with a median impact factor (IF) of 2.65[27]. It is notable that approximately 16% of these journals have IF > 5. In the database of the Web of Science, there are 97 indexed journals in the area of Cardiology, and only 10 (10.5%) have IF > 5. We have described a similar pattern for the Brazilian researchers in Neuroscience[26]. Among the journals used by the CNPq Neurosciences researcher, 61% were indexed at WoS with a median IF of 2.58. It is noteworthy that approximately 14% of the journals used by researchers in neurosciences have an IF > 5. The same database shows that among 128 journals indexed in the field of Psychiatry and 239 in the field of Neurosciences, only 14 (11%) and 39 (16.3%) had an IF greater than 5, respectively. Therefore, researchers in these areas published papers in indexed journals above the median of the remaining specialties. Interestingly, our data also have shown that there was a positive correlation between the number of papers published in journals indexed on WoS and the number of citations received by the researchers.

Our results should be considered in light of some methodological limitations. In this respect, the possible major weakness was the difficulty to get, in a reliable way, important research metrics, including h-index and m-index. We have tried to recover this information from the Lattes curriculum of each researcher. CNPq has developed the Lattes curriculum system in order to record the scientific output of Brazilian researchers[24]. The current version of the system allows researchers to update their Lattes curriculum vitae (CV) and others to consult the English version of the CVs using a Web system (http://lattes.cnpq.br/english). According to a recent comment in Nature, the Brazilian experience with the Lattes database is

a powerful example of good practice. This provides high-quality data on about 1.6 million researchers and about 4,000 institutions[9]. However, we have found that the information regarding h-index was lacking in about 30% of the CVs in the Lattes platform and, moreover, many researchers have not updated this information in an appropriate way. For this reason, we had to obtain the h-index from WoS by using scientific names informed by each researcher in their Lattes curriculum. Consequently, partially due to these difficulties, we were not able to address some relevant issues regarding the impact of the scientific output of this group of researchers. However, some characteristics of the study may increase the strength of our results, including the strategies mentioned above and the systematic search of the Lattes and WoS databases, according to a well-established protocol.

CONCLUSION

This study of the profile of CNPq researchers in the area of Medicine has shown that the majority of them are males, concentrated in the southeast region of Brazil, particularly in the state of São Paulo. We have shown that CNPq researchers in the field of Medicine have a relevant quantitative and qualitative scientific output, although with a significant discrepancy among the diverse subareas included in this field of knowledge. In this regard, Cardiology and Neurosciences stand out among the several specialties. This overall scientific production has increased significantly in recent years, but again with a relevant asymmetry among the diverse areas.

Finally, our findings suggest that the Assessor Committee in Medicine follows the criteria that were set for awarding productivity grants. According to the objective criteria, including scientific production and human resources training, there is consistency in ranking the grant holders among the diverse grant categories. Nevertheless, it is possible that fine adjustments might still be needed, especially in indices harder to measure, such as leadership and innovation. Further studies addressing some critical issues like research groups' productivity, collaborative efforts, and the impact of the scientific output might contribute to our better understanding of this dynamic area of research.

Acknowledgments

This study was partially supported by CNPq (National Council for Scientific and Technological Development) and FAPEMIG (Research Support Foundation of Minas Gerais).

Conflicts of interest: none.

RESUMO

OBJETIVO: *O objetivo deste estudo foi avaliar a produção científica de pesquisadores da área de Medicina que recebem bolsa de produtividade do CNPq.*

MÉTODOS: *Os currículos Lattes de 542 pesquisadores com bolsas ativas de 2012 a 2014 foram incluídos na análise. As categorias/níveis das bolsas de produtividade foram estratificadas em três grupos de acordo com a classificação do CNPq (1A-B, 1C-D e 2).*

RESULTADOS: *Houve predomínio de bolsas na categoria 2. Durante a carreira acadêmica, pesquisadores da Medicina publicaram 76.512 artigos, com mediana de 119 artigos por pesquisador (Intervalo Interquartil, IQ, 77 a 174). Entre os 76.512 artigos, 36.584 (47,8%) foram indexados no banco de dados da Web of Science (WoS). Pesquisadores em Medicina receberam 643.159 citações no banco de dados de WoS, com uma mediana de 754 citações (IQ, 356 a 1.447). Houve diferenças significativas entre as categorias de bolsas em relação ao número de citações em WoS (P < 0,001). Houve uma diferença significativa no número de citações recebidas pelos pesquisadores de acordo com a especialidade incluída na área de Medicina (P < 0,001).*

CONCLUSÃO: *Estratégias para melhorar qualitativamente a produção científica possivelmente podem ser aprimoradas pelo conhecimento do perfil dos pesquisadores no campo da Medicina.*

PALAVRAS-CHAVE: *Pesquisadores. Desempenho profissional. Medicina.*

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REVIEW ARTICLE

Prevalence of hypovitaminosis D in postmenopausal women: a systematic review

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http://dx.doi.org/10.1590/1806-9282.65.5.691

SUMMARY

BACKGROUND: *Hypovitaminosis D is considered a global public health issue. Knowledge of its true dimensions will allow us to design interventions and plan preventive measures that can have a significant impact on human health.*

OBJECTIVES: *The aim of this study was to evaluate the prevalence of hypovitaminosis D, defined as a serum 25-hydroxyvitamin D concentration < 30 ng/ml, in postmenopausal women around the world, as well as to identify the potential associated factors.*

METHODS: *A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses recommendations. Specific search terms were consulted in Medline, Excerpta Medica, and Latin-American and Caribbean Health Sciences Literature databases, with no restriction for the year or language of publication.*

RESULTS: *Of 451 studies initially identified, 32 were selected for analysis. Collectively, those 32 studies evaluated 21,236 postmenopausal women, of whom 16,440 (77.4%) had serum 25-hydroxyvitamin D concentrations < 30 ng/ml. The reported prevalence of hypovitaminosis D ranged from 29% (in the United States) to 99.4% (in China). In six of the studies, the prevalence was above 90%.*

CONCLUSIONS: *If the criterion is the 30 ng/ml cut-off point, the majority of postmenopausal women in the world could be classified as having hypovitaminosis D. Among the studies evaluated, the lowest prevalence reported was nearly 30%. Neither latitude, region of the world, nor laboratory methodology were found to be associated with the prevalence of hypovitaminosis D.*

KEYWORDS: *Vitamin D deficiency, Vitamin D, Postmenopause, Climacteric, Prevalence*

INTRODUCTION

Vitamin D deficiency represents a major public health problem, not only because its prevalence is high (so high that it is considered a true epidemic) but also because of the considerable clinical repercussions[1-3]. Its importance concerned to calcium homeostasis and bone metabolism are well known, but, following the identification of vitamin D receptors in various cells and organs of the body, including the pancreas, macrophages, endothelium, stomach, epidermis, colon, and placenta[4], vitamin D has been shown to have major extra-skeletal (autocrine and paracrine) effects[5]. Vitamin D treatment has also been associated with reduced rate of falls[6], mobility, worsening of muscle function, an increased risk

DATE OF SUBMISSION: 08-Oct-2018
DATE OF ACCEPTANCE: 29-Oct-2018
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of falls, and cognitive decline, as well as with an increased risk of Alzheimer's disease and depression[1].

Vitamin D is naturally produced by the skin, and exposure to ultraviolet radiation is a key step in its synthesis[7,8]. Factors influencing that exposure, such as geographic location, cultural norms, skin color, use of sunscreen, and the modern lifestyle (more time spent indoors), can affect serum concentrations of 25-hydroxyvitamin D (25[OH]D).

Because human life expectancy has increased, many women live longer after menopause, when hypovitaminosis D can become more severe, not only because of the reduction in intestinal absorption due to the aging process but also because of the inherent hypoestrogenism in the postmenopausal period. In combination, these factors increase the risk of loss of bone mass[9]. From the above, it can be deduced that hypovitaminosis D can affect a large part of the population, and knowledge of its true population frequency can contribute to the formulation of public policies involving preventive measures and interventions[10]. Therefore, the objective of this systematic review was to evaluate the prevalence of hypovitaminosis D in postmenopausal women around the world.

METHODS

We conducted a search for cross-sectional studies that estimated the prevalence of hypovitaminosis D in postmenopausal women. We followed the recommendations established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[11], selecting studies in which the serum concentrations of 25(OH)D had been determined in postmenopausal women and, although measurements over the 20 ng/mL limit are considered normal by important entities[12,13], the 30 ng/ml (75 nmol/L) cut-off point had been used to distinguish between normality and insufficiency or deficiency because this is limit associated with the optimization of intestinal calcium absorption in postmenopausal women[14]. We excluded studies jointly evaluating women of reproductive age and postmenopausal women, studies that did not collect information regarding the menopausal status of the women, cohort studies of women with diseases, and case-control studies. When there was a control group comprising healthy postmenopausal women, data related to those women were included in the review, because the biochemical data from the controls were representative of the general population.

To identify eligible studies, we consulted the Medline, Latin-American and Caribbean Health Sciences Literature, and *Excerpta Medica* databases for entries up to September 2016, using the strategy outlined in Chart 1, without restricting the year of publication or language. The articles were selected through the process described in Figure 1. We also reviewed the publications listed in the bibliographies of the articles selected. The selection, evaluation of the titles, and evaluation of the abstracts of the studies identified in the databases consulted were conducted by two investigators with experience in conducting systematic reviews. The investigators worked independently, strictly adhering to the inclusion and exclusion criteria. To extract data of interest for this review, the investigators then evaluated the remaining articles for information regarding the measurement of serum 25(OH)D concentrations; study locale; participant ages and menopausal status; sample size and selection criteria; and the methods used in the clinical and biochemical analyses. When there was disagreement between the investigators regarding the selection of studies, a third investigator was consulted. The data were compiled into a Microsoft Office Excel spreadsheet. The primary endpoint of interest was the prevalence of hypovitaminosis D, the reference range for serum 25(OH)D concentrations being ≥ 30 ng/ml.

RESULTS

Of a total of 448 articles initially identified, 32 were selected for inclusion in the final analysis (Figure 1). One study was excluded because it presented conflicting results between the prevalence of hypovitaminosis D and the maximum serum concentration of 25(OH)D reported. Most of the studies selected were cross-sectional cohort studies that employed the baseline measures required for inclusion in this review, although a few were case-control studies in

CHART 1 SEARCH STRATEGIES, PER DATABASE

Database	Strategy
Medline/PubMed	"postmenopause"[All Fields] AND "vitamin d deficiency"[All Fields]
Latin-American and Caribbean Health Sciences Literature	postmenopause [words] AND vitamin d deficiency [words]
Excerpta Medica	"vitamin d deficiency" AND "postmenopause" AND "prevalence"

TABLE 1. STUDIES SELECTED

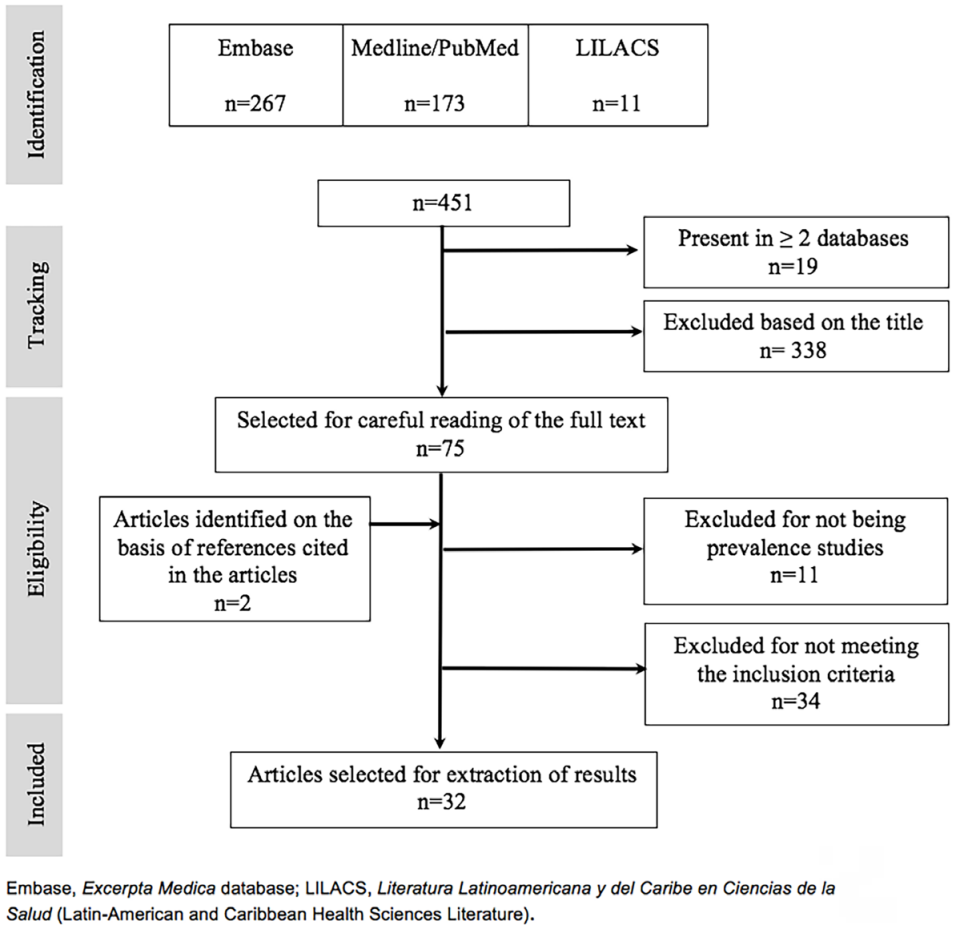
Author and year of publication	Mean age, years	Women	Women with HD	25(OH)D, ng/ml	Latitude	VDS (%)	Locale
	Mean (SD)	N	n (%)	Mean*			
El Maataoui et al., 2016 [32]	59 (8.2)	186	144 (77.4)	20.1	32°N	no	Morocco
Andreozzi et al., 2015 [37]	64.4 (8.4)	62	48 (77.4)	ND	41.87°N	no	Italy
Alipour et al., 2014 [33]	ND	140	113 (80.7)	ND	35.7°N	no	Iran
Godala et al., 2014 [26]	55.4 (3.5)	36	30 (83.3)	23.52 (13.39–45.87)	51.76°N	no	Poland
Cheng et al., 2014 [17]	ND	3345	2727 (81.5)	ND	25–40°N	47.8	USA (40 clinical facilities)
Aloia et al., 2014 [18]	58.8 (4.9)	76	59 (78.0)	25.2	40.44°N	no	USA (Mineola, NY)
Gómez-de-Tejada Romero et al., 2014 [34]	54.8 (11.8)	1221	892 (73.0)	24.3	28.12°N	ND	Spain (Canary Islands)
Hoon et al., 2014 [19**]	ND	605	509 (84.2)	ND	37.56°N	no	Korea
Klisic et al., 2014 [35**]	ND	188	151 (80.3)	ND	42.44°N	ND	Montenegro
Stolarczyk et al., 2014 [27]	70.8 (7.6)	107	95 (88.8)	19.55	52.26°N	no	Poland
Mata-Granados et al., 2013 [38]	5..4 (6.4)	232	217 (93.7)	17.5	37.5°N	no	Spain (Junta de Andalucía)
Asadi et al., 2013 [28]	52.7 (5.0)	110	77 (70.0)	19.28	35.7°N	no	Iran
Casado-Díaz et al., 2013 [42]	57.4 (12.8)	229	190 (83.0)	21.76	37.8°N	no	Spain (Cordoba)
Hacker-Thompson et al., 2012 [15]	63.9 (7.8)	122	36 (29.5)	ND	41°N	82.0	USA (San Francisco, CA)
Hussein et al., 2012 [43**]	ND	223	212 (95.0)	ND	21.29°N	ND	Saudi Arabia
El Maghraoui et al., 2012 [36]	58.8 (8.2)	178	152 (85.3)	15.8 (3.0–49.1)	34°N	no	Morocco
Rudenka et al., 2012 [29**]	63 (7.8)	205	189 (92.0)	ND	53.9°N	62.1	Belarus
Baro; 2011 [44**]	ND	150	119 (79.3)	ND	41.38°N	ND	Spain (Barcelona)
Harinarayan et al., 2011 [20]	53 (0.2)	136	124 (89.7)	ND	13.40° N	no	India
Sternberg et al., 2011 [21**]	61.4	112	65 (57.9)	ND	35°S	ND	Argentina
Zhao et al., 2011 [16]	64.1 (9.2)	1724	1714 (99.4)	13.2 (4.0–35.6)	39.54°N	no	China
Laktasic-Zerjavic et al., 2010 [39]	61.2 (8.8)	120	111 (92.5)	46.94 (10–110.9)	42–46°	no	Croatia
Allali et al., 2009 [30]	55.9 (6.8)	307	282 (92.0)	17.7	33.97°N	no	Morocco
Bobinac et al., 2009 [45**]	ND	720	455 (63.3)	27.33	45.32°N	ND	Croatia
Maddah et al., 2009 [40]	63.4 (8.7)	646	536 (83.0)	19.99	37.12°N	ND	Iran
Poiana et al., 2009 [46**]	58.4	174	144 (82.8)	ND	44.43°N	ND	Romania
Stewart et al., 2009 [22]	54.3 (3.3)	242	153 (63.3)	ND	41.8°N and 38.6°N	53.7	USA (Ames, IA and Davis, CA)
Lee et al., 2009 [23]	58 (8)	254	112 (44.0)	33.3	37.56°N	35.8	Korea
Al-Turki et al., 2008 [24]	56.1 (4.9)	200	110 (55.0)	ND	26.22°N	no	Saudi Arabia
Manicourt et al., 2008 [31]	65 (8)	85	53 (62.0)	25.6	50.85°N	no	Belgium
Bruyère et al., 2007 [25]	74.2 (7.1)	8532	6186 (72.7)	24.04	40.46–55.17°N	24	Belgium, France, Spain, Germany, Hungary, Italy, Poland, and the United Kingdom
Garnero et al., 2007 [41]	62.2 (8.8)	669	490 (73.2)	ND	45.76°N	ND	France

HD, hypovitaminosis D; VDS, Vitamin D supplementation; ND, no data. *Plus minimum and maximum values, where provided. **Published in poster form.

which the control group was representative of the population of interest. We also included eight poster publications that presented the necessary minimum information (Table 1).

Table 1 shows the information obtained from the selected studies[15-46]: the names of the authors and year of publication; the mean ages of the participants; the number

FIGURE 1



Embase, *Excerpta Medica* database; LILACS, *Literatura Latinoamericana y del Caribe en Ciencias de la Salud* (Latin-American and Caribbean Health Sciences Literature).

of subjects with serum 25(OH)D concentrations < 30 ng/ml; the prevalence of hypovitaminosis D; the mean 25(OH)D concentrations, with minimum and maximum values when available; and the latitude and locale of the study. Collectively, the selected studies evaluated 21,236 women, 16,440 (77.4%) of whom had serum 25(OH)D concentrations < 30 ng/ml. Sample sizes ranged from 36 to 8,532, the prevalence of hypovitaminosis D ranging from 29.5% (in San Francisco, CA) [15] to 99.4% (in Beijing, China)[12]. The laboratory techniques used were radioimmunoassay, in nine studies[17-25]; chemiluminescent immunoassay, in six[26-31]; electrochemiluminescence, in six[16,32–36]; high-performance liquid chromatography (HPLC), in three[15,37,38], ELISA, in two[39,40], and competitive protein-binding techniques, in one[41]. In five studies, the laboratory technique employed was not reported[42–46].

In six of the 32 studies, the prevalence of hypovitaminosis D was above 90%[16,29,30,38,39,43]. In the study conducted in Beijing[16], only 10 of the 1,724 women evaluated had serum concentrations of 25(OH)D above 30 ng/ml. The prevalence of hypovitaminosis D was above 90% in seven other cities around the world: 95.0% in Jeddah, Saudi Arabia[43]; 93.7% in Junta de Andalucía, Spain[38]; 92.5% in Zagreb, Croatia[39]; 92.0% in Minsk, Belarus[29]; and 92.0% in Rabat, Morocco[32]. Even at the sites where the prevalence of hypovitaminosis D was lowest, it was relatively high: approximately 30% in San Francisco, CA[15]; 44.0% in (one of the studies conducted in) South Korea[23], and 55.0% in Saudi Arabia[24].

Stratifying the results by continent, we found that the prevalence of hypovitaminosis D in North America, Europe, Africa, the Middle East, and Asia was 78.6%, 73.6%, 86,1% 81.5%, and 90.4%, respectively. The fact that the prevalence was highest in Asia was due to the study conducted in Beijing, which involved 1,724 women, almost all of whom had hypovitaminosis D[16]. With the search strategy adopted, only one study from South America was selected, a study conducted in Argentina and involving 112 women, in

which the estimated prevalence of hypovitaminosis D was 57.9%[21].

Multiple studies carried out in a single country presented very different results. In a study conducted in South Korea in 2009 and involving 254 women[23], the prevalence of hypovitaminosis D was 44.0%, compared with 84.2% in another, more recent study involving 605 women evaluated in that same country[19]. In the studies conducted in the United States, the reported prevalence ranged from 29.5%[15] to 81.5%[17]. In two studies conducted in Saudi Arabia, one in the city of Al Khobar in 2008[24] and the other in the city of Jeddah in 2012[43], the reported prevalence was 55.0% and 95.0%, respectively.

Although comparisons were made among latitudes and continents, we identified no factors that could explain the differences observed. The reported prevalence of hypovitaminosis D was high even in populations in which the rate of vitamin D supplementation was near 50%[19], or even above 60%[29], although it was lower in the studies in which women receiving vitamin D supplementation were excluded[24]. We identified no association between the prevalence of hypovitaminosis D and the laboratory techniques employed.

DISCUSSION

One of the most important aspects of this review is the fact that, to our knowledge, this is the first study to show the worldwide distribution of the prevalence of hypovitaminosis D according to the laboratory technique employed, specific geographic location, and latitude. Another important aspect was the selection of studies involving healthy postmenopausal women, with the objective of avoiding biases caused by treatments or diseases concerning the serum concentrations of 25(OH)D. We chose to include studies in which a portion of the population was using vitamin D supplementation, as long as the samples were representative of the local population of healthy postmenopausal women.

In this review, we did not find the prevalence of hypovitaminosis D to be associated with geographic location, latitude, use of vitamin D supplementation, or the laboratory technique employed. We identified considerable variation among studies conducted in the same country, in terms of the prevalence of hypovitaminosis D. Between the two studies conducted in South Korea, the one conducted in 2009[23], in which the prevalence of hypovitaminosis D was 44.0%, included women under treatment for osteoporosis or menopause, which could account for the difference in relation to the 2014 study[19], which involved only women not receiving such treatment and in which the prevalence was 84.2%. It is of note that both of those studies were conducted in the city of Seoul. For the 2009 study[23], if only the women not receiving vitamin D supplementation (n = 91) were evaluated, the prevalence would be 56%. In addition, the women evaluated by those authors were under treatment at a referral center for hormone replacement therapy or osteoporosis. Those treatments could have generated behavioral changes that had a positive influence on serum concentrations of 25(OH)D (engaging in outdoor activities, increased exposure to the sun, and consumption of foods rich in vitamin D). Similarly, in the United States, the prevalence of hypovitaminosis D ranged from as high as 81.5%, in a multicenter study[17], to as low as 29.5%, in the study conducted in San Francisco[15]. Those two studies, however, were quite different. The first was an assessment of baseline serum 25(OH)D concentrations measured at the start of the follow-up of the Women's Health Initiative Observational Study, involving a total of 3,345 postmenopausal women followed at 40 clinical institutions throughout the United States, where approximately 50% of the participants were receiving vitamin D supplementation. The second study, conducted by Hacker-Thompson et al.[15], involved a much smaller sample, comprising 122 participants, 82% of whom were receiving vitamin D supplementation. In addition, the laboratory technique used in both studies was HPLC, a technique described as being highly sensitive[1,4]. In Saudi Arabia, blood samples were collected between January and May 2008 in the study conducted in the city of Al Khobar[24], whereas they were collected throughout 2011 in the study conducted in the city of Jeddah[43]. However, the latter study provided no information on the laboratory technique used.

The countries of Europe were represented in 15 studies, the largest of which involved more than 8,500 postmenopausal women in nine countries[25]. In that study, serum 25(OH)D concentrations were determined by radioimmunoassay, although all of the laboratory techniques described in this review were used in at least one of the studies conducted in Europe. The prevalence of hypovitaminosis D was the lowest (62.0%) in Belgium and the highest (92.5%) in

Spain. The high prevalence in the study conducted in Spain was not explained by geographic location or laboratory technique, and the most sensitive technique, HPLC, was used in that study. Morocco, the only African country represented in this review, accounted for three of the studies evaluated[30,32,36], among which the prevalence ranged from 77.4%, in a study using electrochemiluminescence and collecting samples between November 2008 and October 2009[32], to 92.0%, in a study using chemiluminescent immunoassay and collecting samples between June and August of an unspecified year[30]. These data did little to explain the difference found, given that the prevalence was higher in the study conducted only during the months of maximum solar radiation in that country[30]. Five of the studies selected had been conducted in the Middle East, three in Iran[28,33,40] and two in Saudi Arabia[24,43]. The lowest and highest values for the prevalence of hypovitaminosis D in the Middle East (55.0% and 95.0%, respectively) were both reported in studies conducted in Saudi Arabia[24,43]. Researchers working in countries where Islam is the predominant religion often cite cultural and clothing issues as major factors inhibiting the endogenous production of vitamin D. In this review, we found that the mean prevalence of hypovitaminosis D in the Middle East was 78.6%, lower than that found in North America (81.4%), where the culture is very different from that of Muslim countries and the clothing designed for women does not necessarily cover their entire bodies. Therefore, we can't assume that the low serum concentrations of 25(OH)D reported for Muslim countries correlate with the type of clothing used.

Studies about hypovitaminosis D in postmenopausal women brings knowledge about a factor strongly associated with osteoporosis, which is particularly prevalent in this group. The knowledge about other population groups, such as premenopausal women, however, is desirable to allow comparisons that improve the understanding of hypovitaminosis D and its possible triggers.

This review has some limitations. The lack of standardization of the laboratory technique employed in the measurement of serum 25(OH)D concentrations and the different times of year during which the blood samples were collected made it difficult to compare the results across studies. Also, some studies with large sample sizes had to be excluded, some because they evaluated women with diseases such as osteopenia or osteoporosis and others because they did not present serum 25(OH)D concentrations with a cut-off point of 30 ng/ml. Furthermore, in some countries, a large part of the postmenopausal population use vitamin D supplementation, which creates a situation in which the potential vitamin D status of those populations could be masked. Nevertheless, we believe that this review has achieved its primary goals, showing the available information on the prevalence of hypovitaminosis D in postmenopausal women around the world and providing a global perspective on the problem.

CONCLUSION

The analysis of the selected studies revealed that the prevalence of hypovitaminosis D is high among postmenopausal women, affecting a large part of the population, even in the regions where that prevalence is lowest. Given the importance of vitamin D in women's health, further studies are needed in order to determine the actual impact of this finding.

RESUMO

INTRODUÇÃO: *A hipovitaminose D é considerada um problema de saúde pública global. O conhecimento de suas verdadeiras dimensões nos permitirá projetar intervenções e planejar medidas preventivas que possam ter um impacto significativo na saúde humana.*

OBJETIVO: *O objetivo deste estudo foi avaliar a prevalência de hipovitaminose D, definida como concentração sérica de 25-hidroxivitamina D <30 ng/ml, em mulheres na pós-menopausa em todo o mundo, bem como identificar os potenciais fatores associados.*

MÉTODOS: *Uma revisão sistemática foi realizada de acordo com as recomendações de Itens de Relatórios Preferenciais para Revisão Sistemática e Meta-Análises. Os termos de pesquisa específicos foram consultados nas bases de dados Medline, Excerpta Medica e Literatura Latino-Americana e do Caribe em Ciências da Saúde, sem restrição para o ano ou idioma de publicação.*

RESULTADOS: *Dos 451 estudos inicialmente identificados, 32 foram selecionados para análise. Coletivamente, esses 32 estudos avaliaram 21.236 mulheres na pós-menopausa, das quais 16.440 (77,4%) apresentavam concentrações séricas de 25-hidroxivitamina D <30 ng/ml. A prevalência relatada de hipovitaminose D variou de 29% (nos Estados Unidos) a 99,4% (na China). Em seis dos estudos, a prevalência foi superior a 90%.*

CONCLUSÕES: *Se o critério é o ponto de corte de 30 ng/ml, a maioria das mulheres na pós-menopausa no mundo poderia ser classificada como tendo hipovitaminose D. Entre os estudos avaliados, a menor prevalência relatada foi de quase 30%. Nem latitude, região do mundo, nem metodologia laboratorial foram encontrados para ser associados com a prevalência de hipovitaminose D.*

PALAVRAS-CHAVE: *Deficiência de vitamina D; Vitamina D; Pós-menopausa; Climatério; Prevalência.*

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REVIEW ARTICLE

Repercussions of melatonin on the risk of breast cancer: a systematic review and meta-analysis

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http://dx.doi.org/10.1590/1806-9282.65.5.699

SUMMARY

Breast Cancer is common in women, but its etiology is not yet fully understood. Several factors may contribute to its genesis, such as genetics, lifestyle, and the environment. Melatonin may be involved in the process of breast cancer. Therefore, the aim of this study is to evaluate the influence of the levels of melatonin on breast cancer through a systematic review and meta-analysis. We performed a systematic review according to PRISMA recommendations. The primary databases MEDLINE, Embase, and Cochrane were consulted. There was no restriction on the year of publication and language. Data of systematic reviews from April 2017 to September to 2017 were analyzed. The meta-analysis was conducted using RevMan 5.3 software provided by the Cochrane Collaboration. From a total of 570 articles, 9 manuscripts were included in this review. They analy onzed women with breast cancer and control patients, of which 10% and 90% were in the reproductive period and after menopause, respectively. The lowest level of melatonin was found in approximately 55% of studies with breast cancer in post-menopause. The metanalyses of the studies demonstrated low levels of melatonin in breast cancer patients (n=963) compared with control patients (n= 1332), with a mean difference between the studies of -3.54 (CI -6.01, -1.06). Another difference found was in the comparison between smoking patients, with an average difference between 1.80 [0.97-2.63]. Our data suggest that low levels of melatonin might be a risk factor for breast cancer.

KEYWORDS: *Melatonin. Breast Neoplasms. Review. Risk factors. Meta-Analysis.*

INTRODUCTION

The pineal gland is an endocrine organ that, among other functions, produces the melatonin hormone. Its production reaches its maximum at night and is regulated by the biological clock (suprachiasmatic nucleus)[1,2]. In humans, melatonin secretion increases during darkness hours and peaks between 2 and 4 a.m. with a subsequent gradual decrease during the rest of the night[1,2]. Disturbances on the melatonin production may have consequences on the organism and influence cancer genesis and growth[3].

The mechanisms of melatonin action are generally through receptors (MT1 and MT2). MT1 is associated with the G receptor protease family, and MT2 is related to the hydrolysis of phosphoinositide and

DATE OF SUBMISSION: 18-Oct-2018
DATE OF ACCEPTANCE: 04-Nov-2018
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calcium[4]. After the action of receptors, the intracellular signaling of melatonin involves the calmodulin, which in turn activates transcription factors, such as NFAT (Nuclear factor of activated T-cells). This transcription factor regulates the immune system and influences tumor growth as well as cell cycle genes[5]. This system is also implicated in breast cancer[6]. In addition, melatonin interplays with estrogen signaling pathways: a) interferes in estrogen synthesis by the reducing the gonadotropin action[7]; b) disrupts the activation of estradiol receptors on breast tumors; c) regulates the enzymes involved in the biosynthesis of estrogens in other tissues (selective estrogen enzyme modulator). Those mechanisms may justify the protective effect of melatonin on tumor growth.

Studies *in vitro*[8] and *in vivo*[9] showed that melatonin is a potent antioxidant modulator that may prevent DNA damage and control tumor growth. Another function of melatonin is the destabilization of levels of HIF-1alpha (Hypoxia-inducible factor 1-alpha) that increases the reactive oxygen species induced by hypoxia and angiogenesis. Therefore, melatonin protects from potential damage through this mechanism and decreases the expression of VEGF in tumor[10].

Breast cancer (BC) is one of the most common malignancies and the first cause of cancer-related mortality among women[11]. However, the mechanism involved in the genesis of this tumor is not totally clear. Night-shift female workers have a significantly increased risk of BC compared to women with normal sleep duration[12]. The decrease in melatonin levels may be related to enhancing the BC incidence in night worker[s13]. Therefore, the propose of our study is to evaluate if low levels of melatonin are related to breast cancer through systematic review and meta-analysis.

METHODS

A systematic review was carried out to evaluate whether melatonin levels are associated with breast cancer in women during the reproductive period and after menopause. This review was conducted according to the recommendations established by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis)[14].

In the selection of the studies, only those which analyzed the levels of melatonin and its relationship with breast cancer in women during the reproductive years (pre-) and after menopause (post), as well as studies that also had a control group, were included in our study. The retrieval of the relevant articles was conducted using the strategy described in Table 1 on Medline, Embase, and Cochrane primary databases and the search was completed in September 2017 without restricting the year of publication and language[15]. Studies, which did not provide access to the full text and duplicates were excluded from the analysiss. References related to the topic identified in the retrieved articles were also included.

Two researchers conducted the process of selecting the studies and the evaluation of the titles and abstracts with the ability to elaborate systematic reviews (E.C.V. and R.S.S.) independently and blindly, following the inclusion and exclusion criteria. The selected articles were critically evaluated to be included or not in the review. When there was disagreement over the selection of studies among the investigators, a third reviewer was consulted (J.M.S.J.). In order to analyze the methodological quality of the articles included, the New Castle Ottawa scale was used considering those with a score > or equal to 9. The PICO was: P = patients with breast cancer; I = collected blood or urine for melatonin measurements; C = normal patients without cancer; O = correlation between levels of melatonin and breast cancer frequency.

The information obtained from the studies selected for the systematic review was set out in a table, and the following characteristics were described: author's name and year of publication, study design, case series, patient's age, melatonin collection method, melatonin level, and outcome. (Table 1). For the meta-analysis, RevMan version 5.3 (Cochrane Collaboration, Oxford, UK)[25] calculated the relative risk of incidence of contralateral breast cancer and distant metastasis. The random effect model was used in the heterogeneity period. The inclusion criteria for the meta-analysis were the methodology of urine collection, with the detection of creatinine, women who were in menopause, and the homogeneity of the results.

RESULTS

The search, identification, and selection process are presented in Figure 1. From the search strategies elaborated, 25 papers were selected from 572 abstracts and tiles. Among those studies, nine were finally selected for inclusion in the systematic re-

view [16-24]. The total number of women evaluated was 6.389, of whom 963 had breast cancer and 1332 did not. The majority of patients were post-menopausal (90%), and only 10% were of reproductive age.

The age range was very heterogeneous: a) from 25-56 years old still in the reproductive period; b) from 45-80 years old post-menopausal. The levels of melatonin in the studies were measured through blood and mainly by urine. Although studies of Schernhammer et al.[19] 2005, Brown et al.[23], Devore et al.[24] collected urine for 24 hours, the others measured melatonin from the first urine in the morning. Also, Schernhammmer et al.[20], Schernhammer et al.[21], Schernhammer et al.[22] divided nocturnal melatonin secretion into four quartiles during the night, and the last one was the most representative because it shows peak levels of melatonin.

In all studies, only stage IV breast cancer was not included. A total of 55% of the studies (5/9) presented low melatonin levels in patients with breast cancer compared to the control group in the reproductive period (n=2 studies, 17, 22) and post-menopausal (n=3, 19-21) (Table 1).

The meta-analysis demonstrated that in the two studies analyzed, there was a significant difference in the melatonin means in breast cancer post-menopausal patients (n = 963) and control patients (n = 1332); the mean difference was -3.54 (CI: -6.01, -1.06) (Figure 2). Figure 3 shows the results of the meta-analysis in premenopause patients; the meta-analysis was in relation to body mass index, and the results refer to alcohol consumption per day (g/day) among patients and melatonin levels in smoking patients. Other studies were not included in the meta-analysis because their standard deviations were very heterogeneous, making it impossible to reach a homogeneous result in a meta-analysis.

DISCUSSION

Breast cancer is still a challenge for medicine because the genesis of the tumor is still unknown[26]. Experimental studies (in *vivo* and *in vitro*) have been shown that melatonin may exert an anti-proliferation action that interferes in cancer risk[27]. the lLow levels of melatonin probably influence breast cancer risk.

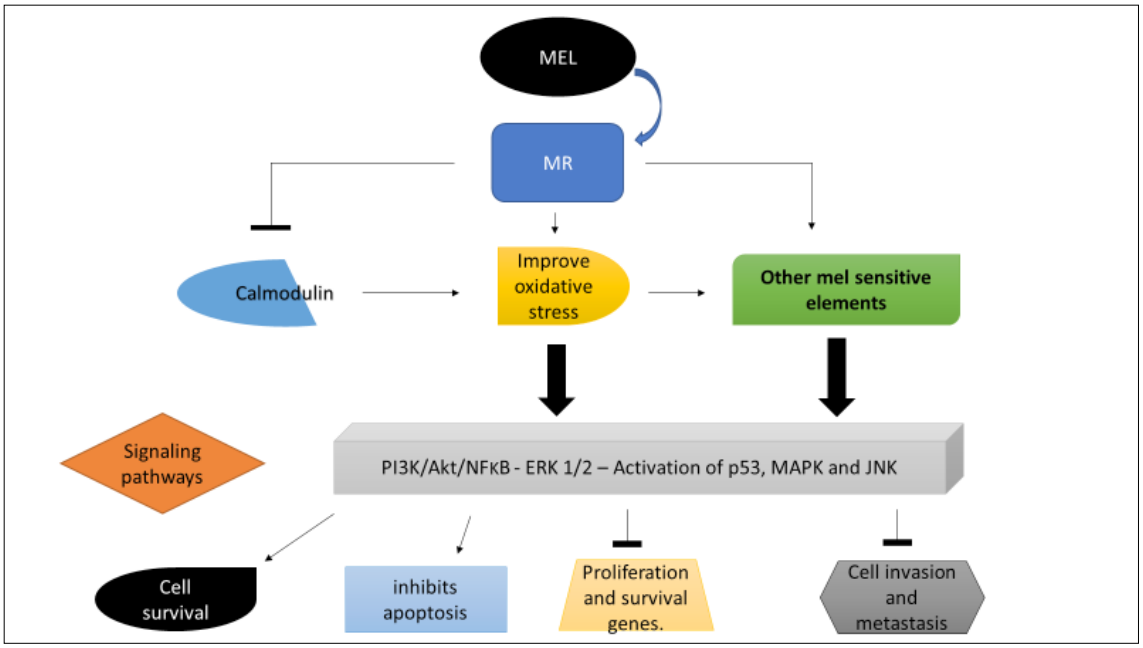
Some studies had a few methodological problems. In the first studies[16-18], the number of patients was meager for finding a statistical difference between breast cancer patients and the control group. Also, those studies measured melatonin directly from urine and not 6-sulfatoxymelatonin, which is the more stable metabolite of melatonin. Therefore, it may not reflect the exact amount produced because of the degradation of melatonin[16-18]. That is probably the explanation why they did not find any significant differences between breast cancer patientsand healthy ones.

TABLE 1. AUTHOR AND YEAR OF THE STUDY, CASE STUDY, AGE OF PATIENTS, METHOD OF COLLECTION AND LEVEL OF MELATONIN.

Authors	Study design	groups (n)*	Menopause	Age**	Methods	Outcome
Bartsch et al.1981	transversal	BC (10) C (10)	Post	57.0 ± 7.71	Urine	NS
Danforth et al. 1985	transversal	BC (37) C (33)	Pre	34.0 ± 7.21	Blood	NS
Holdaway et al. 1991	transversal	BC (20) C (9)	Pre	40.4 ± 6.03	Blood	NS
Schernhamm et al 2005	cohort, prospective	BC(194) C (384)	Pre	44.4 ± 2.8	Urine/Blood	Decreased
Schernhammer et al. 2008	cohort, prospective	BC (178) C (710)	Post	52 ± 24.04	Urine	Decreased
Schernhammer et al. 2009	cohort, prospective	BC(357) C (533)	Post	67.2 ± 6.7	Urine	Decreased
Schernhamm et al 2010	cohort, prospective	BC(180) C(683)	Pre	43.4 ± 4.3	Urine	Decreased
Brown et al. 2015	cohort, prospective	BC(600) C(786)	Pre	48.9 ± 30.5	Urine	NS
Devore et al. 2016	cohort, prospective	BC (606) C (799)	Post	42.2 ± 17.7	Urine	Decreased

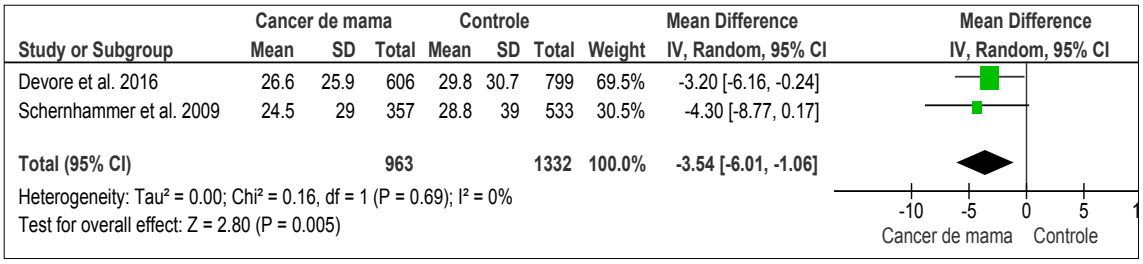
*n= number of patients; BC – breast cancer patient; C – control women; **mean ± standard deviation; Decrease: indicates that melatonin levels in control patients are higher than melatonin levels in patients with breast cancer.NS – indicates that there were no differences between levels of melatonin in patients with breast cancer x control patients.

FIGURE 2. MECHANISMS OF MELATONIN ACTION IN BREAST CANCER CELLS.



Mel – melatonin; MR – Melatonin receptors; Calmodulin; PI3K – phosphatidylinositide 3-kinases; Akt – Protein kinase B; NFKB – Nuclear factor kappa light chain enhancer of activated B cells; ERK 1/2 – Extracellular signal-regulated kinase 1/2; MAPK – mitogen-activated protein kinase; JNK – c-Jun N-terminal kinase; melatonin binds to its melatonin receptors and blocks the action of calmodulin resulting in the improvement of oxidative stress and other melatonin-sensitive elements that activate the PI3K/Akt/NFKB -ERK 1/2, MAPK and JNK signaling pathways that result in cell survival and inhibitory apoptosis, acts on proliferation and activation of survival genes and block cell invasion and metastasis on breast cancer cells.

FIGURE 3. META-ANALYSIS OF MELATONIN LEVELS IN RELATION TO BREAST CANCER PATIENTS AND POST-MENOPAUSAL CONTROL PATIENTS.



The detection method improved a lot in recent years. The majority of studies that found low levels of melatonin used 6-sulfatoxymelatonin measurements and normalized by creatinine levels. This is probably the most accurate method for detecting the levels of this hormone[26,27] because this metabolite is more stable than melatonin[28]. The studies that have found low levels of melatonin applied this method.

The estrogen hormone state is another problem, because estrogen levels may interfere with melatonin production and action[11]. Therefore, the phase of the menstrual cycle is important for comparison. This fact may explain the reasons why some studies did not find any differences during the reproductive period even studying a significant number of patients[23].

Among the pathways of intracellular signaling, we can highlight the rupture of the calcium homeostasis produced by the inhibition of calmodulin, the improvement of oxidative stress, and the signaling cascade that leads to a lower rate of apoptosis. Among the proteins that are part of this pathway are the PI3K / Akt / NFkB pathway, the pathways involving the ERK 1/2 proteins and the activation of p53, MAPK, and JNK. The results obtained are a higher rate of survival of healthy cells and inhibition of cell proliferation and their genes in addition to a lower rate of cell invasion in cells with breast cancer and a reduction in the angiogenesis of tumor cells[11,29,30].

Regardless of the results, melatonin is considered a tumor inhibitor[29]. Also, the melatonin reduces the estrogen receptor in tumors[24,28,31] and interferes in the immune system, favoring the combat against breast neoplasia[30]. There are other melatonin mechanisms: a) it blocks estrogen receptors binding to DNA and

transactivation functions[32]; b) it has anti-angiogenic and antioxidant actions (ref) and; c) it induces apoptosis in tumors[31,32].

The clinical application of our data is on the night workers who are exposed to long periods of light and low levels of melatonin[16,33]. Therefore, this is a risk population for breast cancer due to the fact that their light/dark cycle is interrupted. Currently, night jobs are essential in hospitals, law enforcement, trade, and industry. There are also other risk factors, such as family history of cancer, use of hormone therapy, and smoking [27,34-36]. Perhaps, health public policies for evaluating melatonin levels or even taking melatonin supplementation might be necessary for preventing the risk of developing breast cancer. However, further studies are necessary to prove that this procedure would be beneficial for these patients.

Finally, our data suggested that a lower amount of melatonin may be a risk for breast cancer or at least, influences tumor growth.

Acknowledgments

This study was supported by grants from CAPES, FAPESP, and CNPq.

Competing interests

The authors declare that they have no competing interests.

AUTHOR´S CONTRIBUTIONS

1. ECAV – Made substantial contributions to the concept and design of the study and the definition of intellectual content, were involved in literature search, data analysis, statistical analysis, manuscript preparation, drafting the article or revising it critically for important intellectual content and giving final approval of the version to be published.
2. RS – Were involved in the literature search, data analysis, statistical analysis, and final approval of the version to be published.
3. VEV – Were involved in the literature search, data analysis, statistical analysis, and final approval of the version to be published.
4. JCN – Made substantial contributions to the concept and design of the study and the definition of intellectual content, were involved in literature search, data analysis, statistical analysis, manuscript preparation, drafting the article or revising it critically for important intellectual content and giving final approval of the version to be published.
5. LCA – Made substantial contributions to the concept and design of the study and definition of intellectual content, were involved in literature search, data analysis, statistical analysis, manuscript preparation, drafting the article or revising it critically for important intellectual content and giving final approval of the version to be published.
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10. JMSR – Made substantial contributions to the concept and design of the study and definition of intellectual content, were involved in literature search, data analysis, statistical analysis, manuscript preparation, drafting the article or revising it critically for important intellectual content and giving final approval of the version to be published.

RESUMO

O câncer de mama é comum em mulheres, mas sua etiologia ainda não é totalmente compreendida. Vários fatores podem contribuir para sua gênese, genética, estilo de vida e meio ambiente. A melatonina pode estar envolvida no processo de câncer de mama. Portanto, o objetivo deste estudo é avaliar a influência dos níveis de melatonina no câncer de mama por meio de uma revisão sistemática e meta-análise. Realizamos uma revisão sistemática de acordo com as recomendações do Prisma. Os principais bancos de dados, Medline, Embase e Cochrane, foram consultados. Não houve restrição quanto ao ano de publicação e idioma. Os dados de revisão sistemática obtidos de abril de 2017 a setembro a 2017 foram analisados. A meta-análise foi conduzida pelo programa RevMan 5.3 fornecido pela Cochrane Collaboration. De um total de 570 artigos, nove foram incluídos nesta revisão. As análises foram conduzidas em mulheres com câncer de mama e pacientes controle, dos quais 10% e 90% estavam no período reprodutivo e após a menopausa, respectivamente. O nível mais baixo de melatonina foi encontrado em aproximadamente 55% dos estudos com câncer de mama na pós-menopausa. As meta-análises de estudos demonstraram os baixos níveis de melatonina em doentes com câncer da mama (n=963), em comparação com os pacientes de controle (n=1.332), sendo a diferença de médias entre os estudos da −3,54 (CI −6,01, −1,06). Outra diferença é demonstrada nas comparações entre pacientes fumantes, sendo a diferença da média entre 1,80 [0,97-2,63]. Nossos dados sugerem que baixos níveis de melatonina podem ser um fator de risco para câncer de mama.

PALAVRAS-CHAVE: *Melatonina. Neoplasias da mama. Revisão. Fatores de risco. Meta-análise.*

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REVIEW ARTICLE

Neurophysiological, cognitive-behavioral and neurochemical effects in practitioners of transcendental meditation - A literature review

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http://dx.doi.org/10.1590/1806-9282.65.5.706

SUMMARY

The term meditation can be used in many different ways, according to the technique to which it refers. Transcendental Meditation (MT) is one of these techniques. TM could serve as a model for research on spiritual meditation, unlike the meditation techniques based on secular knowledge. The purpose of the present study is to conduct a bibliographic review to organize scientific evidence on the effects of TM on neurophysiology, neurochemistry, and cognitive and behavioral aspects of its practitioners. To conduct this critical narrative review of the literature, we searched for scientific papers on the PubMed database of the National Center for Biotechnology Information. The keywords used in the search were Transcendental Meditation, Neuroscience of meditation e Meditation and behavior. We selected 21 papers that analyzed different aspects that could be altered through meditation practice. We concluded that TM has positive and significant documentable neurochemical, neurophysiological, and cognitive-behavioral effects. Among the main effects are the reduction of anxiety and stress (due to the reduction of cortisol and norepinephrine levels), increase of the feeling of pleasure and well-being (due to the increase of the synthesis and release of dopamine and serotonin), and influence on memory recall and possible consolidation. Further studies are needed using creative and innovative methodological designs that analyze different neural circuitry and verify the clinical impact on practitioners.

KEYWORDS: *Meditation. Mind-body therapies. Complementary therapies. Neurophysiology.*

INTRODUCTION

The term meditation can be used in various ways, according to the technique to which it refers. According to Johnson[1], meditation can be defined as: "The wide range of activities that seek to expand and emphasize the mind's reach and its possible functioning, achieved mostly by methods of sensory-motor discipline, such as remaining seated in silence, relaxing, closing one's eyes, breathing consciously and adopting an object of consciousness [...] it is first and foremost a technique, a way of developing consciousness." Transcendental Meditation (TM) is one of these meditation techniques, like those associated

DATE OF SUBMISSION: 06-Aug-2018
DATE OF ACCEPTANCE: 09-Jan-2019
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with yoga, tantra, Tibetan Buddhism and Zen Buddhism[2].

During meditation, mental activity is naturally installed while attention is maintained or even increased. Studies show that meditation produces a specific pattern of physiological responses that involve several biological systems. More frequent mechanisms suggest that meditation produces effects that are beneficial for the autonomic, endocrine, neurological, cardiovascular, and psychological metabolism[3].

Transcendental meditation was brought to the west by the Indian Maharishi Mahesh Yogi. It became very popular in the 1960s, and in the 1970s scientific research linking its practice with the physiological effects caused was presented for the first time[4]. This practice has been described as a simple and natural method to establish a peaceful and deep rest, so there is full mental awareness[5].

While Western psychology describes three states of consciousness (sleep, dream, and wakefulness), in eastern philosophy and mystical traditions, another state is considered the "fourth state of consciousness," which could be achieved through the practice of meditation[6]. The purpose of meditation is the elimination or reduction of thought processes, the deceleration of the inner dialog of the mind. This reduction of the thought process aims to increase this state of higher consciousness and, thus, could lead to a great sense of physical and mental tranquility[7].

Meditation has a history of association with religious and spiritual practices and disciplines. Practitioners of TM affirm that they do not adhere to any specific religious practice but emphasize the spiritual dimension of this specific technique[8].

There are several understandings about what spirituality is. Unruh et al.[9] analyzed concepts of spirituality in research on the area of health and observed that the notions of transcendence and sense of connection were at the center of the understanding of spirituality in this field of study. Transcendence refers to the idea of an experience field outside the material existence of everyday life, and connectedness refers to the perception of being connected to people, nature, the cosmos - the ability to have an intrapersonal, interpersonal, and transpersonal connection.

The spiritual characteristic inherent to the practice of TM aims to maintain the practitioner less involved in physical and mundane concerns, focusing on something greater, their own position within a universe, a notion that relates to the concept of transcendence. In this context, TM can be regarded as a model for research on spiritual meditation, unlike meditation techniques based on a secular understanding[8].

In a meta-analysis that examined meditation techniques, beneficial effects were found more consistently after the use of TM, which is a practice spiritually substantiated, than in individuals who used techniques of secular meditation or relaxation[10].

The range of positive effects reported after the practice of TM is wide and include reduction of anxiety[11], increase of self-accomplishment[12], increased creativity and concentration[13], increased in autonomic stability[14], significant decrease of cortisol and norepinephrine plasma levels[15], increased serotonin and dopamine[16], blood pressure control[17], among others.

TM is a technique that has been little studied if compared to standardized secular practices, such as mindfulness-based stress reduction (MBSR). The results of these studies are scattered in different publications, and some are ignored by many scholars due to the significant lack of knowledge on the existence of this particular technique. Thus, the objective of the present study was to conduct a literature review to organize the scientific evidence on the effects of MT on neurophysiology, neurochemistry, and cognitive and behavioral aspects of its practitioners. The study also aims to propose a conceptual model to provide bases for future studies on possible mechanisms of MT.

Transcendental meditation presents a differential, which is the fact that it does not require disciplined postures and breathing, or even the control of concentration. The technique flows naturally and spontaneously, so it is not an exhaustive or uncomfortable practice. It consists of meditation induced by mantras and dismisses the classical postures and the need for absolute concentration, which are found in other meditative techniques; thus, it can be practiced at any place and time.

METHODS

For this critical narrative review of the literature, we searched scientific articles in the PubMed database of the National Center for Biotechnology Information (NCBI) in June 2018. The keywords used for the search were *Transcendental Meditation*, *Neuroscience of meditation*, and *Meditation and behavior*. The

inclusion criteria were studies that reported the neurophysiological and behavioral effects of the practice of transcendental meditation. After selecting the articles, they were grouped and described in three different sections: neurophysiological, neurochemical, and cognitive/behavioral aspects.

The articles were read, evaluated, and described in relation to aspects of methodological quality and other parameters, such as techniques used, factors for the inclusion of participants and, finally, the results obtained. We found 21 articles relating neurophysiological, neurochemical, cognitive and behavioral aspects with practices of transcendental meditation. These studies analyzed different aspects that could be altered by meditative practice (Table 1).

Five aspects of the methodological quality of the studies were assessed, as described in Table 2.

It is observed from Table 2 that, of the 20 articles analyzed, 19 had a control group. In these, the controls were individuals randomly selected who did not have the habit of practicing transcendental meditation and who remained at rest with their eyes closed; the experimental groups were meditation practitioners.

RESULTS & DISCUSSION

Neurochemical and neurophysiological aspects

Electrophysiology experiments showed that MT promotes greater stimulation in alpha waves in the prefrontal and temporal areas[19], which are related to concentration, sense of social responsibility, and decision-making. This higher cortical stimulation in the prefrontal region added to an increase in the glutamatergic synthesis and release, results in the stimulation of the arcuate nucleus in the hippocampus, an area mediated by circulating hormones and metabolites, in addition to receiving direct stimulation of the lateral and paraventricular nuclei of the hypothalamus. The lateral nuclei interact based on afferencies from the dopaminergic reward system, stimuli related to memory, motivation, and learning, signals from the nucleus accumbens, amygdala, and nucleus pallidus; these nuclei are directly correlated with the production of neurotensin, orexin, hypocretin, histamine, melatonin, and beta-endorphins with the arcuate nucleus.

Electroencephalography experiments have shown that in MT there is an increase in the activation of the prefrontal cortex and anterior cingulate gyrus[20]. Using positron emission tomography, a decrease in blood flow in the prefrontal cortex (PFC) was observed, apparently associated with the attention to the mantra[21]. Some imaging studies suggest that the PFC, especially the right hemisphere, is related to attention-dependent activities[22]. The cingulate gyrus also features a similar function and is involved in focusing attention[23]. Studies have shown that, after the practice of meditation, the bilateral activity of the CPF and the cingulate gyrus presented increased activity[24].

Several studies have demonstrated that the CPF can directly stimulate the thalamic reticular nucleus[25], this activation may be related to the production and release of glutamate, the main excitatory neurotransmitter[26]. The thalamus, considered the sensory station, uses the glutamate released by activating the synapses it has with other structures[27]. During meditation, the increased activity of the CPF promotes the concomitant increase in the activity of the reticular nucleus, which in turn secretes the neurotransmitter gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter, in the lateral posterior and geniculate nuclei, increasing the activation of the reticular nucleus via the superior parietal lobe (PSPL)[28,29].

Some studies have shown the increase in GABAergic concentration during meditation[30], resulting in a possible reduction of external stimuli to the visual cortex and PSPL, increasing the sensation of focus.

TABLE 1. ARTICLES DIVIDED BASED ON THE ASPECTS ADDRESSED

Aspect addressed	Yes
Cognitive aspects	3
Neurochemical aspects	6
Neurophysiological aspects	12
Behavioral aspects	7

TABLE 2. EVALUATION OF THE METHODOLOGICAL QUALITY OF THE STUDIES FOUND

Studies selected	Yes
Was there randomization?	21
Was there a control group?	20
Was it double-blind?	21
Was the dropout rate described?	21
The time of the evaluation of results was similar in all groups?	21

(Source: Based on Berger & Alperson[18]).

It is important to emphasize that the dopaminergic system participates in the adjustment of the glutamatergic system by means of the basal ganglia and interacts with the PFC and subcortical structures. In a imaging study (such as positron emission tomography [PET]) it was found that during meditation, there is a significant increase in dopamine levels[31].

Another important effect observed after the practice of transcendental meditation was a decrease in sensitivity to pain[32-34]. The studies compiled showed that practitioners of the transcendental technique present a significant reduction in blood pressure and heart rate. The significant changes in blood pressure (systolic and diastolic) may be related to changes in the levels of psychological distress, such as anxiety, depression and the ability of social confrontation. This physio-behavioral relationship became a study model, in which psychological distress triggers a heightened activation of the sympathetic autonomic nervous system and the activation of the hypothalamic-pituitary-adrenal axis[35].

It appears that transcendental meditation promotes the reduction of stress and anxiety levels, which can be explained by the significant decrease in cortisol[36] and 37 noradrenaline levels, along with increasing concentrations of dopamine plasma dopamine and serotonin [39 38] (Table 3). The increase of the serotonergic activity can be related to the stimulation of the lateral hypothalamus; the hypothalamic innervation in the pineal gland contributes to the increase in the synthesis and release of serotonin.

The decrease of cortisol and noradrenaline and the dopaminergic increase are associated with the decrease of cardiac and respiratory frequency[40], taking into account that during the meditative practice there is less sympathetic stimulation and more parasympathetic stimulation. The increased activity of the parasympathetic system would result in a lower inhibition of the GABAergic system at a bulbar level, triggering changes in blood pressure, respiratory frequency, motility, and functioning of the gastrointestinal system, improved memory, decreased anxiety and improvement in the sensation of well-being, due to the dopaminergic increase.

Cognitive/behavioral aspects

The effect of the meditative techniques has been studied in different health conditions, such as depression, anxiety, eating disorders and problems caused by the use of psychoactive drugs[42.43]. The influence of meditation on stress reduction, in the prevention of psychosomatic disorders, in the control of changes in blood pressure and other metabolic diseases[44], in the control of chronic pain, respiratory, musculoskeletal, and skin problems are also the object of current studies[45].

In spite of the few studies that relate the effects of meditative techniques with cognitive and behavioral aspects, it is already known that its practice can have a positive influence on the improvement of cognitive functions [in] attention [46,47] and promote the improvement of verbal fluency and memory[48].

Some of the studies included in this review claim that the association of transcendental meditation practice and the use of medicines for anxiety promotes greater clinical improvement in general when compared to the use of medication alone. Other studies show that practitioners of TM exhibit greater autonomous stability, which can be inferred from experiments that evaluate the spontaneous dermal resistance[49]. The systems activated in meditation have direct influence in the increase of cerebral perfusion in the prefrontal, parietal and auditory cortex regions[48], a protective effect on the thickness of the gray mass[50] in elderly patients, greater stimulation in the areas involved with attention[51], increase in the strength of cognitive circuits[52]. In addition, meditation can improve the process of myelination or restructuring of the white matter, associated with the anterior cingulate cortex. Another effect of medita-

TABLE 3: CHANGES IN NEUROTRANSMISSION AND STRUCTURAL SYSTEMS IN THE CNS

Neurotransmitter	Change	Structure in the CNS	Reference
Gaba	Increase	Thalamus / inhibitory structures	Guglietti et al.[30], 2013
Cortisol	Decrease	Paraventricular nucleus	MacLean et al.[36], 1997
Glutamate	Increase	Diffuse in the CNS	Armony & Ledoux[27], 1999
Serotonin	Increase	Raphe nuclei	Bujatti & Biederer[38], 1976
Noradrenaline	Decrease	Locus coeruleus	Mills & Farrow[40], 1981
Dopamine	Increase	Substantia nigra	Infante et al.[39], 2001

(Source: Based on Newberg & Iversen[41], 2003).

tion is neuroprotection; with the decrease in the synthesis and release of cortisol, there is stress reduction, which may be associated with the volume of the hippocampus region in meditation practitioners[53].

Transcendental meditation practitioners showed better musical and textual memory [54.55], which may be justified by the possible activation of the amygdala and hippocampus, possibly resulting in better memory consolidation and learning. Finally, meditation practitioners feel a positive impact on the decrease of oxidative stress, which can reduce the risk of neural vascular diseases as well as Alzheimer[56].

Other studies have shown that in other types of meditation, such as mindfulness, Buddhist and yoga there is a consistent effect on activation in several regions related to the limbic system that reflect on behavior, such as the caudate nucleus, putamen, thalamus, hippocampus, posterior and anterior cingulate cortex, precuneus, Insular lobe, fusiform gyrus, orbitofrontal cortex, occipital lobe, cerebellum, regions of the parietal and temporal gyrus, among others[57].

The practice of meditation is effective for the significant decrease of the severity of symptoms in patients with obsessive-compulsive disorder, decreasing the obsessions, anxiety and depression episodes[58]. There is also a significant effect in relation to family, social, and professional relationships and in the quality of life of patients who adhered to the practice of meditation in addition to psychotherapeutic treatment. Other studies also show that there is less activation of the amygdala, an area known to play an important role in the processes related to emotional stimuli, which may justify the improvement in the quality of life[59].

This article seeks to present the philosophical origins and some of the current scientific evidence regarding transcendental meditation and its neurophysiological, cognitive/behavioral, and neurochemical effects on practitioners. Some current mind-body approaches have been increasingly integrated into health care. However, in TM, the spiritual aspects are part of its very nature since this practice is based on eastern spiritual traditions.

The present study presents a small but growing number of well-conducted experimental studies. Additional research is needed to understand in more detail what are the mechanisms of action involved in TM. There is great heterogeneity in meditation techniques, and there are few studies that compare these different methods. The meditation techniques can have different effects on the brain and, consequently, in neurophysiology and cognition[6]. Despite this, it is possible to observe that transcendental meditation techniques are a promising health intervention, alone or as a complement to conventional treatment, given the benefits described in this review.

Future challenges

Further studies are needed to improve the understanding of this area. It would be important to explore innovative and different study designs, as well as examine meditation practitioners in different contexts and conditions.

A recent study examined the brain of a single individual isolated in a retreat for 5.5 weeks. A highlight of this study was its experimental design adapted to observe the response of a single-case study, comparing neuroimaging data pre- and post-intervention. Conventional studies, which analyze groups, take into account the variability between subjects in the statistical analyses, while this approach considered variability in a single subject during the sessions. Repeated observations were required to consider the measurement of errors that could occur for different reasons, such as lack of homogeneity of field or subtle head movements. As a result, the neuroimaging data showed reductions in visual cortices, Brodmann area, and anterior cingulate cortex; the amplitude of low-frequency fluctuations increased in the dorsolateral prefrontal cortex[60].

This study investigated differences in functional connectivity of the neural network in default mode between frequent practitioners of meditation and non-practitioners in relation to the focus of attention. The participants were instructed to name the color of simple words presented visually in a task called the Stroop Word-Color (SWCT), adapted for functional magnetic resonance (fMRI). The task was performed when the participants were not formally meditating. The logistic analysis based on neuroimaging studies showed that the connectivity between the right and left posterior cingulate cortex and the parietal lobes helps differentiate frequent meditation practitioners from non-practitioners since it may represent a higher degree of interference and distraction during the SWCT in non-practitioners compared with frequent practitioners[61].

There is another line of research on the modulating impact of meditation on age-related changes in

the macrostructure of the brain that suggests that meditation can slow down the degeneration of the brain related to age[62.63]. Some studies show less pronounced negative correlations between the chronological age and brain measurements (for example, volumes of local and global gray matter, or indicators of the integrity of fiber from the white matter) in meditation practitioners than in controls[64.65]. However, because these are cross-sectional studies, it is not possible to infer whether meditation induced the differences observed if the differences existed before the individuals initiated the practice, or whether the differences were due to more complex interactions with other factors.

In the studies mentioned above, which are innovative, different techniques of meditation were used. It would be appropriate to check if these results are reproduced by comparing them with the practice of transcendental meditation. There are few studies comparing different meditation techniques.

CONCLUSION

It is concluded that the TM produces documentable neurochemical, neurophysiological, and cognitive-behavioral effects in its practitioners, both positive and significant. Among the main effects are decreased anxiety and stress (due to the decrease in cortisol and noradrenaline levels), increased sensation of pleasure and well-being (due to an increase in the synthesis and release of dopamine and serotonin) and influence on the recall and possible consolidation of memory. Further studies are needed using creative and innovative methodological designs that analyze different neural circuitry and verify the clinical impact on practitioners.

RESUMO

O termo meditação pode ser utilizado de diversas formas, de acordo com a técnica a que se refere. A meditação transcendental (MT) é uma dessas técnicas meditativas. A MT pode ser um modelo para pesquisas de meditação espiritual, diferentemente de técnicas de meditação baseadas em uma compreensão secular. O presente estudo objetiva realizar uma revisão bibliográfica para organizar as evidências científicas sobre os efeitos da MT sobre a neurofisiologia, neuroquímica e aspectos cognitivos e comportamentais dos seus praticantes. Para a realização desta revisão narrativa crítica da literatura, foi realizado um levantamento dos artigos científicos presentes na base de dados PubMed do National Center for Biotechnology Information. As palavras-chave utilizadas na busca foram Transcendental Meditation, Neuroscience of meditation e Meditation and behavior. Foram selecionados 21 artigos que analisavam diferentes aspectos que poderiam ser alterados pela prática meditativa. Conclui-se que a MT produz efeitos neuroquímicos, neurofisiológicos e cognitivo-comportamentais documentáveis em seus praticantes, de caráter positivo e significativo. Entre os principais efeitos estão a diminuição da ansiedade e do estresse (via diminuição nos níveis de cortisol e noradrenalina), aumento na sensação de prazer e bem-estar (em decorrência ao aumento na síntese e liberação de dopamina e serotonina) e influência na evocação e possível consolidação da memória. São necessários mais estudos utilizando desenhos metodológicos inovadores e criativos, analisando diferentes circuitos neurais e verificando o impacto clínico sobre os praticantes.

PALAVRAS-CHAVE: *Meditação. Terapias mente-corpo. Terapias complementares. Neurofisiologia.*

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REVIEW ARTICLE

Isthmocele: an overview of diagnosis and treatment

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http://dx.doi.org/10.1590/1806-9282.65.5.714

SUMMARY

An isthmocele, a cesarean scar defect or uterine niche, is any indentation representing myometrial discontinuity or a triangular anechoic defect in the anterior uterine wall, with the base communicating to the uterine cavity, at the site of a previous cesarean section scar. It can be classified as a small or large defect, depending on the wall thickness of the myometrial deficiency. Although usually asymptomatic, its primary symptom is abnormal or postmenstrual bleeding, and chronic pelvic pain may also occur. Infertility, placenta accrete or praevia, scar dehiscence, uterine rupture, and cesarean scar ectopic pregnancy may also appear as complications of this condition. The risk factors of isthmocele proven to date include retroflexed uterus and multiple cesarean sections. Nevertheless, factors such as a lower position of cesarean section, incomplete closure of the hysterotomy, early adhesions of the uterine wall and a genetic predisposition may also contribute to the development of a niche. As there are no definitive criteria for diagnosing an isthmocele, several imaging methods can be used to assess the integrity of the uterine wall and thus diagnose an isthmocele. However, transvaginal ultrasound and saline infusion sonohysterography emerge as specific, sensitive and cost-effective methods to diagnose isthmocele. The treatment includes clinical or surgical management, depending on the size of the defect, the presence of symptoms, the presence of secondary infertility and plans of childbearing. Surgical management includes minimally invasive approaches with sparing techniques such as hysteroscopic, laparoscopic or transvaginal procedures according to the defect size.

KEYWORDS: *cesarean section; hysteroscopy; laparoscopy; uterine bleeding.*

INTRODUCTION

The World Health Organization recommends as ideal a cesarean section (CS) rate of 10-15% of all births.[1] However, the percentages of CS delivery in South America (42.9%), Latin America (40.5%), North America (32.3%) and Europe (25%)[2] are well above this number. This has led to a worldwide discussion about the complications and consequences of the procedure, which are also increasing in number.[3] Some of them, such as scar dehiscence, placenta praevia and accreta are already established and studied. Others, however, are only recently gaining more importance,[4] which is the case of the cesarean scar defect, isthmocele or niche.

The isthmocele is a myometrial defect resembling a pouch on the anterior wall of the uterine isthmus, over a previous cesarean scar.[5,6] This defect contrib-

DATE OF SUBMISSION: 01-Nov-2018
DATE OF ACCEPTANCE: 31-Dec-2018
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utes to pathologic changes that may predispose the emergence of symptoms like menorrhagia,[7] abnormal uterine bleeding (AUB),[8] pelvic pain, dysmenorrhea, cesarean scar pregnancy and secondary infertility.[8,9]

Guidelines for diagnostic criteria and treatment of isthmocele are still unclear. Currently, the treatment options include conservative treatment based on combined estrogen and progesterone therapy and hysteroscopic, laparoscopic, or transvaginal surgical repair.[10]

The objective of this review is to present an overview of the current literature on isthmocele, approaching its classification, predisposing factors for the niche development, clinical symptoms, diagnostic methods, and the current treatment options, focusing on minimally invasive approaches.

DEFINITION, CLASSIFICATION, AND PREVALENCE

a. Definition

There is no universal definition of isthmocele or standard characterization that clearly indicates its location and size.[11] Several authors have proposed definitions in an attempt of establishing a universal concept. Overall, most studies refer to isthmocele, cesarean scar defect, niche or diverticulum as a myometrial discontinuity or a hypoechoic triangle in the myometrium of the anterior uterine wall at the site of hysterotomy presented in transvaginal ultrasound (TVUS) or sonohysterography (SHG) examination in non-pregnant women.[3,4,8,11] Other studies, nonetheless, describe the pouch as a myometrial thinning, an anechoic defect >1mm or a defect of the myometrium of >2mm at the place of a cesarean scar.[12-14] Even so, the defect usually presents abundant and ectatic vessels, covered in smooth mucosa and menstrual blood often fills the pouch.[15] Gubbini has described that the site of the defect varies according to the site of the CS, which relates to the stage of labor, uterine cervix changes, and the surgical technique.[5]

b. Classification

Some authors classified the findings according to the size of the defect:[4] a large defect is described as a myometrial reduction of >50% of the wall thickness[14] or even >80% by some authors.[4,16] A large defect may also be classified as residual myometrium (RM) <2.2mm by TVUS and <2.5mm by SHG.[17] For management purposes, Marotta et al.[18] adopted the cutoff of RM <3mm as a large defect and a RM ≥3mm as a small defect. These radiologic findings can be found incidentally in the absence of symptoms or be associated with clinical symptoms. Therefore, they can also be classified as asymptomatic or symptomatic when presenting AUB, pelvic pain, and infertility, for example.[8]

c. Prevalence

The exact prevalence of isthmocele is unknown and is related to the method used to assess the defect.[12] In a recent systematic review, Tulandi and Cohen[4] have found that the prevalence of isthmocele rages from 24% to 70% in TVUS examination and from 56% to 84% in SHG in women with 1 or more previous CS.[3,4] When compared with asymptomatic patients, the prevalence is higher in those with symptoms, ranging according to the literature, from 19.4% to 84%,[13,19] with postmenstrual spotting as the main symptom.[4,20]

ETIOPATHOGENESIS AND RISK FACTORS

Several risk factors have been related to the development of the isthmocele; however, there are few associations proven to date. Ofili-Yebovi et al.[14] first presented an association between isthmocele and multiple previous CS, retroflexed uterus, and failure to identify all CS scars during repeat CS of multiple CS, later corroborated by several authors.[20]

Tulandi and Cohen[4] also reviewed predisposing factors recently, stating that even though several risk factors have been linked to isthmocele, multiple CS is the principal risk factor for its development. Although demonstrating inconclusive results, Bij de Vaate et al.[3] hypothesized in a systematic review that duration of labor, dilatation, stage of the presenting part, and a lower position of the CS hysterotomy may be potential predisposing factors for the development of a niche. A CS conducted in active labor and cervical dilatation >5cm is related to larger isthmoceles.[3,4] The association of different uterine sutures and the prevalence of isthmocele is still unclear. Although the single-layer myometrial closure appears to increase the risk of isthmocele development when compared to double-layer closure,[21] it is not significantly associated with larger defects.[4]

Concerning the etiology, four hypotheses have been postulated by Vervoort et al.[11] on causes of isthmocele, depending mostly on surgically induced factors and patient factors. The first hy-

pothesis concerns the location of the hysterotomy, proposing that a low incision in the cervical part of the uterus is made through cervical tissue, which contains mucous glands, and the mucus produced during the healing could dilate the sutured rims of the myometrium.[11] This theory is corroborated by several studies that have associated a higher prevalence of isthmocele and patients with cervical dilatation >5cm, longer duration of labor (>5h) or lower station.[3,6,16,22] In addition, a high prevalence of isthmocele and CS performed in active labor suggests that an incision made through cervical tissue due to an effaced cervix is more difficult to distinguish from the uterine wall.[11,23,24]

The second hypothesis is related to surgical technique, concerning an incomplete closure of the uterine wall.[11] The improper closure, or even no closure, of the deeper muscular layer, usually unintentional or related to non-perpendicular sutures and endometrial saving techniques, may lead to an irregular myometrium closure, thus causing the development of isthmocele.[11,23]

The third hypothesis relates to early adhesion development in the hysterotomy scar and the anterior abdominal wall, pulling the edges of the wound and impairing the healing due to those counteracting forces on the uterine scar.[11,23] This mechanism is even more exuberant in a retroflexed uterus, in which those counteracting forces are increased, potentially decreasing blood flow to the healing tissues.[23,24]

The final hypothesis involves patient factors, suggesting the presence of an individual/genetic predisposition contributing to an impaired wound healing, poor hemostasis, inflammation or adhesion formation, which may influence isthmocele development.[11]

CLINICAL SYMPTOMS

In general, most isthmoceles are asymptomatic, being found incidentally on ultrasound.[23] However, over the last decades, with the rising rates of CS, there has been an increase of sequelae reported after this procedure. Symptoms including abnormal uterine bleeding, postmenstrual spotting, dysmenorrhea, pelvic pain, and infertility[12,13,20] have now been associated with isthmocele. Obstetric complications of isthmocele were described in the literature, such as placenta accrete, placenta praevia, scar dehiscence, uterine rupture, and ectopic pregnancy in cesarean scar defects.[8,24]

Gynecologic Complications

Abnormal uterine bleeding (AUB), mostly characterized as postmenstrual bleeding, is the main symptom related to the presence of an isthmocele, being present in 28.9% to 82%[12,13,22,25] women with isthmocele.[4]

The presence of isthmocele may predispose a deposit of blood and menstrual debris within the defect, associated to reduced contractility of the uterus due to fibrotic tissue around the scar, slowing the drainage of the menstrual flow and causing AUB.[13,26] Pathology findings of free erythrocytes in the scar tissue suggesting a recent hemorrhage lead Morris[7] to propose that the blood could also be produced in situ, also causing intermittent spotting. Regardless of the source, the presence of blood in the isthmocele is also associated with a higher mucus secretion, which could contribute to postmenstrual AUB.[6]

Also, an association between the isthmocele size and postmenstrual bleeding has been established.[20] Postmenstrual spotting is more frequent in patients with larger defects than in patients with smaller defects.[12]

Dysmenorrhea and pelvic pain have also been described in isthmocele in studies over the last decade. Wang et al.[20] stated a correlation concerning the isthmocele size and pelvic pain and dysmenorrhea. Morris[7] suggested that those pain complaints were related to inflammatory infiltration, fibrosis and anatomic disruption of the lower uterine segment.

Although these symptoms of AUB, dysmenorrhea and pelvic pain are a common complaint in the gynecological office, isthmocele has grown as a differential diagnosis in women who underwent a CS.[8] Tulandi and Cohen[4] found an increase from 63.8% to 82% in the rate of isthmocele in women presenting postmenstrual bleeding who underwent TVUS or SHG due to gynecologic symptoms. Therefore, if a patient with previous CS presents any of the symptoms such as above, symptomatic isthmocele should be part of the differential diagnosis and thus investigated.[23]

The association between isthmocele and secondary infertility has been reported in the literature with a high prevalence.[6,8] The presence of blood in the isthmocele could affect the cervical mucus and sperm quality, obstruct sperm transport and make embryo implantation more difficult, therefore impairing fertility.[27,28] Several studies have evaluated the fertility outcomes after isthmocele treatment,[28]

demonstrating that the repair of the defect is associated with high rates of restoring fertility.[6]

Obstetric Complications

The presence of an isthmocele is associated with an increased risk of complications during pregnancy, including placenta previa, accrete/increta/percreta, scar dehiscence, uterine rupture, and cesarean scar ectopic pregnancy.[24] The risk of an isthmocele becoming deficient is related to multiple CS.[14,17] The overall rate of uterine rupture during a posterior pregnancy does not exceed 2%, however, in larger defects, this risk increases to 5%.[24] It appears that scar thickness in ultrasonographic assessment has no practical use as a prognostic marker of uterine rupture.[14,24]

One of the rarest obstetric complications, the cesarean scar ectopic pregnancy, occurs when the embryo is implanted in the myometrium of the cesarean scar defect. Over the last decades, there has been a rise in the prevalence of the cesarean scar ectopic pregnancy, as well as the CS and therefore isthmocele rates.[29]

DIAGNOSIS

There are no definitive criteria for the diagnostic of isthmocele.[4,8,19] Various imaging methods including ultrasonography, sonohysterography, hysterography, hysteroscopy, and magnetic resonance imaging can be used to assess the anterior uterine wall and diagnose isthmocele.[18]

Transvaginal ultrasound (TVUS) is the initial and most usual method described to assess the integrity of the uterus wall in non-pregnant patients.[8,18] Because the principal symptom is postmenstrual bleeding, the early proliferative phase best shows the deposit of blood within the isthmocele, allowing its identification even without the necessity of saline or gel infusion[4] and there is minimal chance of pregnancy.[23,30] The defect has been described on TVUS as an anechoic triangle defect in the myometrium with the base communicating to the uterine cavity, or a deformity (wedge, shape, concavity or sacculation) on the anterior isthmus.[22,31]

The prevalence of isthmocele in sonohysterography (SHG), when compared with TVUS, appears to be higher (56%-84% against 24%-70%). Nevertheless, SHG is more sensitive than TVUS,[4,12,13,16,17,32] and the defect seems larger or deeper by SHG.[12] Therefore, the saline infusion sonohysterography (SIS) is more sensitive and specific for the identification of isthmocele[26] by filling the defect and providing contrast.[8] When compared to the TVUS, SIS presented better results by detecting more defects and more often classifying them as larger on average of 1 to 2mm.[32] Gel instillation sonography (GIS) also presents a higher prevalence in detecting the defect when compared to TVUS (49.6% against 64.5%).[12] Furthermore, similarly to SIS, the defect shown on GIS was larger and the RM smaller comparing to TVUS only.[12] This effect on prevalence and defect size diagnosed by SHG is a consequence of a pressure increase inside the uterus, which causes an enhancing on the defect size.[4]

Hysterography (HSG) can also assess the isthmocele; however, it cannot measure the myometrial thickness, which is a limitation of this method. Moreover, if blood or mucus is accumulated in the isthmocele, HSG may not clearly identify the defect.[23]

Using magnetic resonance imaging (MRI) allows determining the RM thickness of the isthmocele on the sagittal T2-weighted views. Nevertheless, Marotta et al.[18] found that RM measurements in MRI were related to those assesses through TVUS.

Hysteroscopy enables direct visualization and confirmation of the isthmocele.[19,22] Usually described as a pouch or a discontinuity of the anterior uterine wall,[6,22] hysteroscopy allows for visualization and potential treatment; however, it may not assess de RM thickness.

TVUS and SHG can both be performed in the office, are more affordable than MRI, less invasive than hysteroscopy and produce reliable measurements.[23] If an isthmocele is suspected, several authors[6,8,23] recommend SIS as a diagnostic study based on its greater sensitivity and specificity for planning surgery and research purposes.

6. Treatment

The treatment of isthmocele ranges from clinical management with expectant or pharmacological treatment, surgical treatment, and hysterectomy to sparing techniques including hysteroscopic, laparoscopic, laparotomic, or transvaginal procedures limited to the defect site.[9] The decision to treat takes into consideration the size of the defect, presence of symptoms, secondary infertility and plans of pregnancy.[8,19,23]

In the case of incidental diagnosis of asymptomatic isthmocele and no plans for future childbearing, clinical observation and no surgical intervention are

usually recommended.[18,23] In symptomatic women with either AUB, pelvic pain, or secondary infertility, the course of treatment depends upon the size of their defect. There are a great number of studies proposing different surgical approaches and techniques to the correction of the cesarean scar defect.[9,18,23,33,34]

Clinical Management

Expectant treatment is an option for women with small isthmoceles (RM≥3mm).[18] However, in a recent study, Vervoort et al.[35] randomized symptomatic women with small defects ≥3mm into expectant treatment or hysteroscopic resection, achieving a decrease in the number of postmenstrual spotting and spotting-related discomfort in women submitted to the procedure.

Clinical management has been described to have failed to reduce symptoms in most of the subjects treated with oral contraceptives, as observed by Thurmond et al.[26]. However, Tahara et al.[36] presented a preliminary report with positive results in eliminating intermenstrual bleeding after three cycles of oral contraceptives in relatively higher doses. Despite the contrasting results, the current data present as the first choice of treatment for symptomatic isthmocele the resection of the defect due to its minimally invasive approach and good therapeutic results.[5,15,19,37]

Hysteroscopy

Hysteroscopic resection of isthmocele is a minimally invasive, non-time-consuming and low morbidity procedure, allowing visualization and repair of the defect.[9] Despite the great variety of technique among the authors, the surgical technique overall consists of the resection of fibrotic tissue from the defect, presented like a flap underneath the triangular pouch. The resection of the niche edges setting the wall in continuity to the cervical canal improves the flow drainage and prevent the retention of menstrual blood.[6,9] Fulguration of the base of the pouch, either globally or targeting visible vessels, enables the removal of the inflamed and congested tissue, preventing the in situ production of fluid and blood.[8] In a systematic review, Abacjew-Chmylko et al.[9] presented favorable outcome rates of hysteroscopic resection of 85.5%, ranging from 59.6% to 100%, completely solving AUB symptoms in 72.4% of the cases. Uterine perforation and bladder injuries are the major risks of the hysteroscopic procedure. Therefore, in order to reduce this risk, the resectoscope treatment by hysteroscopy is recommended to be performed if the remaining myometrial thickness is >3mm.[18]

Laparoscopy

A laparoscopic approach has been advocated for large defects (RM <3mm), in the presence of symptoms and desire to maintain fertility.[18] Laparoscopic isthmocele repair consists in the resection of the isthmocele edges, in order to excise the scar tissue, closing the defect in two-layer sutures.[4] Laparoscopy enables a better visualization to identify the defect, allowing repair and thus increasing the myometrial thickness.[23]

Donnez et al.[33] described large isthmocele (RM <3mm) laparoscopic repair outcomes in thirty-eight symptomatic women. The surgical technique used was laparoscopic excision of the isthmocele with CO2 laser. A Hegar probe was used after the excision of the defect to preserve uterine continuity through the canal. The excision was repaired in three layers, the first two closed with separated Vicryl sutures, and the peritoneum closed with Monocryl in a running suture. In the case of a retroflexed uterus, a shortening of the round ligaments was done to decrease the counteracting forces that may impair the wound healing, as suggested by Vervoort et al.[11] Hysteroscopy was then conducted to assert the repair. The mean myometrial thickness raised from 1.43±0.7 to 9.62±1.8mm in 3-month follow-ups. A total of 93% of the patients were symptom-free, and among women with infertility, 44% achieved pregnancy and delivered healthy full-term babies.[33] The significant increase in myometrial thickness demonstrated the effectiveness that a laparoscopic isthmocele repair has on restoring the anterior uterine wall integrity.[23]

Vervoort et al.[37] recently published a large prospective study with 101 women with symptomatic isthmocele <3mm submitted to laparoscopic repair under hysteroscopic control. The defect was resected by monopolar hook and the fibrotic tissue excised with a cold scissor, guided by hysteroscopy. The defect was then closed in two-layered suture in full-thickness including endometrium. Hyaluronic acid adhesion barrier was then added. In cases with an extreme retroflexed uterus, the round ligaments were also shortened. Hysteroscopy was performed to evaluate the anatomic result repair. In this study, 80 women had symptoms improved or resolved, and the RM significantly increased in follow up. Of the women with presence of fluid in the uterine cavity,

this was solved in 86.9% after the repair, and, in the overall, 83.3% of women were (very) satisfied with the results.[37]

The combined use of hysteroscopy and laparoscopy offers many advantages. During the laparoscopy, the bladder can be mobilized to offer superior visualization of the isthmocele and thus minimize the risk of bladder injury. Moreover, the cavity can be assessed for diagnosis and possible immediate surgical treatment of other conditions that can cause pain or infertility, such as chronic pelvic inflammatory disease or endometriosis. The hysteroscopy light source transilluminates the pouch providing guidance in identifying the defect by laparoscopy, and the hysteroscopy can also confirm the laparoscopic repair afterward .[10]

Vaginal Procedure

The vaginal procedure to isthmocele repair, although minimally invasive and effective, has fewer reports in the literature.[38,39] Zhang[40] compared the transvaginal repair to the laparoscopic approach in a retrospective study finding similar outcomes between the two techniques. This technique is described as a dissection of the bladder from the cervix and uterus, opening the vesicovaginal space with the identification of the isthmocele. The defect is excised, and the hysterotomy is closed in two layers. The transvaginal isthmocele repair was found to be cost-effective with shorter operation time and comparably more effective than laparoscopy.[40] This approach, however, demands the surgeon be greatly experienced in vaginal surgery in order to avoid damage to adjacent structures and accurately locate the isthmocele in the limited surgical view.[30,38]

Hysterectomy

Hysterectomy is the curative management for large symptomatic isthmocele in women who do not wish to conceive anymore.[18] Yet, hysterectomy is a major procedure when compared to other minimally invasive approaches available.

ISTHMOCELE AND PREGNANCY

The assessment of the RM in the lower uterine segment (LUS) by ultrasound can be used to predict the occurrence of cesarean scar dehiscence or rupture in future or ongoing pregnancies.[41,42] Although several studies have classified LUS in values of higher or lower risk of scar dehiscence, no cutoff value has been universally defined. A meta-analysis of 2013 presented LUS thickness of 3.1-5.1mm and RM of 2.1-4.0mm as a strong negative predictive value for the occurrence of dehiscence or uterine rupture during a trial of labor, and RM of 0.6-2.0 provided a strong positive predictive value for the occurrence of a defect.[43]

Therefore, until newer studies can determine precise values and their implications the clinical practice, the antenatal evaluation of the LUS can be used, as a complementary data alongside other clinical variables, such as number of previous CSs, time between pregnancies, previous vaginal delivery, maternal age, among others, in the decision of a trial of labor after CS or performing a repeat CS.[44] However, when performed in nonpregnant women who wish future pregnancies, the RM assessment allows the possibility to identify the defects at higher risk, enabling the possibility of correcting the defect before the next pregnancy.[41]

STRENGTHS AND LIMITATIONS

The relevance of this study lies, above all, on the high and increasing incidence of isthmocele and its complications. We were able to summarize most aspects regarding this condition, reaching epidemiology, etiopathogenesis, methods of diagnosis and methods of treatment.

However, there was some divergence on the information we found. There is no consensus about the definition of isthmocele, its classification, and prevalence. There are also only hypotheses. Thus, nothing has been proven, to date, about its etiology. Moreover, there are different surgical approaches and techniques recommended in each study.

Therefore, our article contemplates the most important concepts about isthmocele and summarizes the different information we found in the multiple up-to-date studies reviewed.

CONCLUSION

The increasing prevalence of isthmocele, thus its gynecological and obstetric complications, led by the rising number of CS deliveries performed worldwide is alarming. Postmenstrual spotting, pelvic pain, and secondary infertility are common complaints in gynecologist practice, and isthmocele

should figure as a differential diagnosis in women with previous CS deliveries, especially in those with risk factors of multiple previous CSs and retroflexed uterus. Diagnosis of isthmocele by TVUS and especially by SIS are cost-effective and have good specificity and sensitivity. Treatment should be offered according to the presence of symptoms, secondary infertility, defect size, and plans for childbearing. The defect can be minimally invasively repaired with sparing techniques by hysteroscopy for small defects, and by vaginal approach, laparoscopy, and combined laparoscopy and hysteroscopy for larger defects.

Financial support

The authors declare no financial support.

Conflict of interest

The authors declare no conflicts of interest and nothing to disclose.

RESUMO

A istmocele ou nicho uterino é representada por uma descontinuidade miometrial ou um defeito anecoico triangular na parede uterina anterior, com a base se comunicando com a cavidade uterina no local de uma cicatriz anterior de cesárea. O defeito pode ser classificado como pequeno ou grande, dependendo da espessura da parede miometrial deficiente. Embora geralmente assintomático, seu principal sintoma é o sangramento uterino anormal ou pós-menstrual; a dor pélvica crônica também pode ocorrer. Infertilidade, placenta acreta ou prévia, deiscência de cicatriz, ruptura uterina e gravidez ectópica em cicatriz de cesárea prévia também podem aparecer como complicações dessa condição. Os fatores de risco para desenvolvimento da istmocele comprovados até o momento incluem útero retroverso e múltiplas cesarianas. No entanto, fatores como localização mais inferior de uma cesárea prévia, fechamento incompleto da histerotomia, aderências precoces na parede uterina e predisposição genética também podem contribuir para o desenvolvimento de um nicho. Como não existem critérios definitivos para o diagnóstico de uma istmocele, vários métodos de imagem podem ser usados para avaliar a integridade da parede uterina e, assim, diagnosticar uma istmocele. Entretanto, ultrassonografia transvaginal e sono-histerografia com infusão salina surgem como métodos específicos, sensíveis e custo-efetivos para o diagnóstico de istmocele. O tratamento inclui manejo clínico ou cirúrgico, dependendo do tamanho do defeito, da presença de sintomas, da presença de infertilidade secundária e de planos de gravidez. O manejo cirúrgico inclui abordagens minimamente invasivas como histeroscopia, laparoscopia ou transvaginal, de acordo com o tamanho do defeito.

PALAVRAS-CHAVE: *Cesárea. Histeroscopia. Laparoscopia. Sangramento uterino.*

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REVIEW ARTICLE

National scientific production on Burnout Syndrome in ICU nurses and physicians: a bibliometric study

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http://dx.doi.org/10.1590/1806-9282.65.5.722

SUMMARY

OBJECTIVE: *To analyze the scientific production on Burnout Syndrome in physicians and nurses of ICU in Brazil.*

METHOD: *Bibliometric study, documentary, with quantitative approach. We selected articles published in Brazil on Burnout Syndrome in the ICUs, in the VHL and Portal Capes, from 2000 to 2018.*

RESULTS: *40 articles were identified, predominantly from the Southeast. Prevalence of those published in the Brazilian Journal of Intensive Care and in the Journal of Nursing UFPE online. The B2 Qualis periodical is the most prominent. The most prevalent descriptors were: Intensive Care Units, Burnout Syndrome, Burnout and Professional Exhaustion.*

CONCLUSIONS: *Nurses are more interested in publishing this issue. Burnout Syndrome studied in intensive physicians would contribute to identifying its prevalence in these professionals.*

KEYWORDS: *Burnout, Professional. Physicians. Nurses. Intensive Care Units.*

INTRODUCTION

Burnout Syndrome is characterized as a process of responding to an overload caused by the work environment, resulting in exhaustion of the worker. The deterioration of the fundamental relationship that the individual has with their work negatively affects the job performance, interpersonal relationships, and organizational commitment, posing a risk to their health.[1,2] It is the stress caused by the work activity, which involves negative behavior in relation to users, customers, and work organization and causes emotional and practical damage to the worker and the organization. These negative conducts and attitudes imply directly in a loss of enthusiasm for the work activity. Whereas traditional stress is a per-

DATE OF SUBMISSION: 26-Nov-2018
DATE OF ACCEPTANCE: 29-Nov-2018
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sonal depletion interfering in the life of the individual but is not necessarily related to work[3,4].

The Ministry of Health considers Burnout Syndrome, or Syndrome of Professional Exhaustion, a disease whose etiologic agent would be a prolonged response to chronic stress that arises from work, and this is the description found in the list of International Statistical Classification of Diseases and Related Health Problems (ICD-10)[3].

The burnout phenomenon was mentioned for the first time in the United States in the 1970s, in the Freudenberger studies, whose findings showed the harmful physical and mental situation of workers of a Detox Clinic, which included symptoms such as exhaustion, irritation, and cynicism towards patients[4]. In addition, it is also possible to mention Maslach and Jackson[5], who classified the syndrome in three dimensions: *Emotional Exhaustion*, *Depersonalization* and *Low Personal Fulfillment*.

Thus, some instruments are used to evaluate Burnout Syndrome, among them, the MBI (Maslach Burnout Inventory), drawn up by Christina Maslach and Susan Jackson, which is the most used for the measurement of the syndrome. Another instrument employed is the Cesqt (Síndrome de Quemarse por el Trabajo), developed by Gil-Monte et al.[6], which adds the study of guilt, not previously investigated in the MBI.

Burnout Syndrome is defined as a response to chronic stress associated with work and consists of four dimensions: *Work Illusion*, *Psychic Wear*, *Indolence* and *Guilt*, thereby establishing two profiles[6]. Profile 1 represents a moderate form of malaise; profile 2 represents the harmed state due to the syndrome, with the addition of a guilt feeling.

The subject of burnout has been the object of research in various countries and is considered a global problem. Therefore, the frequency and distribution of Burnout Syndrome have become something of global concern, which is why it has been the object of research. In Brazil, according to surveys by the Isma-BR (International Stress Management Association in Brazil) [7]. 32% of workers suffer from Burnout Syndrome (devastating level of stress), with similar proportions to the United Kingdom. It should also be pointed out that in Germany, even with a reduced workload among the developed countries, 8% of the workforce shows signs of burnout. In this context, mental illnesses associated with work rank third among the reasons why Brazilian workers receive disability insurance from INSS[8].

In the context of Brazil, in 1987, the cardiologist Hudson Hubner France published a paper on Burnout Syndrome, the subject started to be discussed [9]. Accordingly, research showed the prevalence of the syndrome among physicians and nurses[10-12], among whom the presence of this phenomenon is critical, being observed in 23.1% of doctors, with a score of high degree.

Health professionals, due to their need of keeping direct contact with their clients, are more vulnerable to exhaustion through work[13]. Other studies[14,15] add that nurses in Intensive Care Units (ICU), due to the tense and exhausting nature of their work activities, are in a position of vulnerability to occupational stress. Moreover, they also point out that the professional intensivists tend to suffer from stressors linked to the environment, the number of work hours, and the high degree of demands related to their skills and abilities, all of which can cause physical and/or psychological illness.

Thus, it should be noted that the hospital environment constitutes a peculiar site to the occurrence of burnout, in view of its very nature, which heightens occupational stressors[16]. ICU is no different, especially for professionals who work there.

In this context, this study sought to answer the following question: what scientific productions available in online journals address Burnout Syndrome in physicians and nurses in Intensive Care Units in the national context? In this perspective, this research has the objective to analyze the scientific production on the Burnout Syndrome in physicians and nurses in Intensive Care Units in Brazil.

METHODS

This is a bibliometric study with a quantitative and documental approach. The bibliometric method is defended for its functionality in the analysis of science universally, and the long period of time it investigates, by means of databases of citations, allows for a multidisciplinary investigation of the social and cognitive changes in science[17], with the possibility to pinpoint indicators of scientific production in different areas and themes.

For the preparation of this study, we selected articles that focused primarily on the phenomenon of Burnout Syndrome in Intensive Care Units, on the following online libraries: *Biblioteca Virtual de Saúde* and Capes Portal. The data collection took place in July 2018.

The search for articles in the databases was performed using the health care terminology available in the Medical Subject Headings (MeSH), and the terms discussed among the keyword in Health Sciences (DeCS) were subsequently consulted, with the keywords: *Burnout, Professional; Physicians; Nurses;* and *Intensive Care Units* combined with the Boolean operator "*and*" to improve the search and select the studies in accordance with objective of this research.

To select the sample, we adopted the following inclusion criteria: publications in the form of articles, with free-access full texts, available online, from 2000 to 2018, which addressed Burnout Syndrome in doctors and nurses from Care Units in Brazil. In the initial stage, we retrieved 48 publications; then eight studies were excluded because only their abstracts were available. The study sample consisted of 40 articles, organized according to the databases in which they were located.

The timeline established for the study was justified for two reasons: firstly, it is subsequent to the inclusion of burnout in the ICD 10 list and, consequently, subsequent to its recognition in Brazil as a labor disease by the Decree-Law 6.042/2007 of Social Security in 1999. The second reason relates to the meager number of studies available from earlier periods; therefore, their inclusion would not be meaningful to the results of this research.

In the next step, the data were organized according to the desired variables: year of publication, region, periodical, *Qualis Periodical*, and keywords. The data were analyzed using descriptive statistical analysis, through the calculation of simple frequency in absolute numbers and percentage of variables, using Microsoft Excel® 2010.

A concept map (CM) was prepared from the descriptors of the publications selected and the thematic classes that emerged after the selection of keywords, without hierarchy, and considering only the conceptual thematic affinity between them[18]. Based on this understanding, the conceptual maps are extremely valid as graphic organizers that reproduce knowledge, helping in the learning process, and is of especially high relevance for presenting the keywords of the articles.

RESULTS

Between 2000 and 2018, 40 articles were found that focused on Burnout Syndrome in ICU physicians and nurses and met the predetermined criteria. Of these, 15% (6 articles) were published in 2017, followed by 12.5% (5 articles) in 2011 and 2013, indicating the years of higher production. Then come the years of 2009 and 2014, each with 10% (4 articles). The years 2010, 2015 and 2016 had, each, 7.5% (3 articles); and 2008, 2012, and 2018 produced 5% of publications (each with two articles). In 2004, there was only one publication (2.5%). In the years 2000, 2001, 2002, 2003, 2005, 2006 and 2007, there were no records of publications related to the study.

As for the region where the studies were carried out, it appears that the Southeastern region, with 22 (55.0%) studies, represents a significant predominance in relation to other regions, whose representations of regional publications were: Northeast, with 12 (30.0%); South, three (7.5%), Central-West, two (5.0%), and North, one (2.5%). It is noteworthy that

TABLE 1 - DISTRIBUTION OF SCIENTIFIC PRODUCTION ON BURNOUT SYNDROME IN ICUS PHYSICIANS AND NURSES, PER PERIODICALS, BRAZIL, 2000 TO 2018 (N=40). AUTHOR: KELY C. C. AZEVEDO

Periodical	N	%
Journal of Nursing UFPE on-line	05	12.5
Revista Brasileira de Terapia Intensiva	05	12.5
Revista Latino-Americana de Enfermagem	03	7.5
Revista de Pesquisa: cuidado é fundamental	02	5
Revista da Escola de Enfermagem da USP	02	5
Revista Brasileira de Enfermagem	02	5
Acta Paulista de Enfermagem	02	5
Trends in Psychology	01	2.5
São Paulo Medical Journal	01	2.5
Revista Texto & Contexto Enfermagem	01	2.5
Revista Psicologia: Ciência e Profissão	01	2.5
Revista Gaúcha de Enfermagem	01	2.5
Revista de Psicologia	01	2.5
Revista de Enfermagem da UFSM	01	2.5
Revista de Enfermagem Centro Oeste Mineiro	01	2.5
Revista da Universidade Vale do Rio Verde	01	2.5
Revista da Spagesp	01	2.5
Revista da Rede de Enfermagem do Nordeste	01	2.5
Brazilian Medical Association Periodical	01	2.5
Revista Ciências em Saúde	01	2.5
Revista Ciência, Cuidado e Saúde	01	2.5
Revista Brasileira de Educação Médica	01	2.5
Online Brazilian Journal of Nursing	01	2.5
Enfermería Global	01	2.5
Ciência & Saúde Coletiva	01	2.5
Caderno de Saúde Pública do Rio de Janeiro	01	2.5
Total	40	100

one of the studies addressed five capital cities located in five regions of the country; however, the amount of research on the theme from the North and Central-West regions are still meager.

With respect to the periodicals involved in publications, we found that the *Revista Brasileira de Terapia Intensiva* and the *Revista de Enfermagem da UFPE on-line* are the most representative, with 12.5% (n=5) of publications each, followed by the *Revista Latino-Americana*, with three publications 7.5% (n=3). The heterogeneity of different journals involved is imperative. Thus, we obtained only one study per journal (see Table 1).

In relation to the *Qualis Periodical*, in accordance with the classifications of journals from the quadrennium 2013-2016, in the area of nursing, we identified that they are distributed in strata, ranging from the highest, A1 with only one publication (3.8%), to B4, with two publications (7.7%), respectively, in the following journals: *Revista Latino-Americana*, *Revista Ciências em Saúde*, and *Revista da Universidade Vale do Rio Verde*. However, it is worth pointing out that the B2 stratum was the most prominent, corresponding to nine studies (34.6%).

In Table 2 it is possible to verify that, regarding the classification of journals in the area of medicine, the periodical entitled *Cadernos de Saúde Pública* stood out: its *Qualis* B2 corresponded to the largest stratum of evaluation among the 26 journals listed in this study.

In relation to the keywords, we observed that the ones used most often in the articles were: Intensive Care Units, Burnout Syndrome, Burnout, and Professional Burnout. From the recognition of the keywords, the concept map was developed (Figure 1).

DISCUSSION

Considering the scientific production on Burnout Syndrome in various areas of knowledge is in a clear

TABLE 2 – SYNTHESIS OF SCIENTIFIC PRODUCTION ON BURNOUT SYNDROME IN ICUS PHYSICIANS AND NURSES, PER QUALI PERIODICALS IN MEDICINE AND NURSING, BRAZIL, 2000 TO 2018 (N=40). AUTHOR: KELY C. C. AZEVEDO

Qualis Periodicals	Medicine	Nursing
Journal of Nursing UFPE on-line	-	B2
Revista Brasileira de Terapia Intensiva	B3 (I, II, III)	B2
Revista Latino-Americana de Enfermagem	B3 (II, III)	A1
Revista de Pesquisa: cuidado é fundamental	B4 (II)	B2
Revista da Escola de Enfermagem da USP	B4 (II, III)	A2
Revista Brasileira de Enfermagem	B3 (II, III)	A2
Acta Paulista de Enfermagem	B3 (II, III); B5 (I)	A2
Temas em Psicologia	-	B2
São Paulo Medical Journal	B3 (I, II, III)	B1
Texto & Contexto Enfermagem	B3 (II); B4 (I)	A2
Revista Psicologia: Ciência e Profissão	B4 (II)	B2
Revista Gaúcha de Enfermagem	B3 (III); B4 (I, II)	B1
Revista de Psicologia: teoria e prática	B5 (I, II)	B3
Revista de Enfermagem da UFSM	-	B2
Revista de Enfermagem Centro Oeste Mineiro (Recom)	-	B2
Revista da Universidade Vale do Rio Verde	B5 (II)	B4
Revista da Spagesp	-	B3
Revista da Rede de Enfermagem do Nordeste	B4 (II); B5 (III)	B1
Brazilian Medical Association Periodical	B3 (I, II, III)	B1
Revista Ciências em Saúde	-	B4
Ciência, Cuidado e Saúde	B5 (II)	B2
Revista Brasileira de Educação Médica	B4 (II, III); B5 (I)	B2
Online Brazilian Journal of Nursing	B4 (I, II)	B1
Enfermería Global	B4 (I, II)	B1
Ciência & Saúde Coletiva	B3 (I, II, III)	B1
Cadernos de Saúde Pública	B2 (I, III); B3 (II)	B1
Total	26	100

expansion, it is noteworthy that, when the study is directed at ICU professionals, the numbers are still small, a phenomenon that has been occurring for nearly two decades (2000 to 2018), the period chosen for this study.

In relation to the year of publication of articles, the data obtained from the analysis of this indicator shows that from 2008, there was publication in every subsequent year. However, the growth curve is inconsistent — at times, the number of published articles increases, other times, it decreases, and we could not find an even pace for its expansion, especially concerning the years 2017, 2013 and 2011.

A study conducted by Silva et al.[19] showed the prevalence of burnout syndrome in 55.3% of ICU nurses. Corroborating this finding, in the nursing team that works in the ICU of a school hospital of Minas Gerais, the presence of occupational stress was observed in half the team, as well as in intensivists that showed proportions of burnout near or above 50%[20,21]. Although the investigations indicate the presence of the phenomenon in health professionals, the timeline reveals a still unimpressive number of national studies that focus on the scenario of the ICU.

On this matter, it important to mention a national study[22] whose evidence indicated a reduced amount of research on burnout in health professionals and identified the need for studies that emphasize preventive and therapeutic measures directed at this problem.

According to the Brazilian geographic regions in which health professionals were investigated, we found that the Southeast region is the one that stands out the most, followed by the Northeast region. On the other hand, the North and Midwest regions have little representation, which could be explained by the poor distribution of ICU beds in Brazil. In this perspective, an analysis of the Federal Council of Medicine[23], which mapped the distribution of ICU beds per states and capitals, revealed that the Southeast region alone concentrates 54% of the ICUS in the country; whereas the North region has the lowest proportion, with only 5% of all ICU beds.

The 40 studies found on this topic are distributed in various journals, and the ones that presented the greatest number of scientific publications were: *Revista Brasileira de Terapia Intensiva* and *Journal of Nursing* - UFPE on-line. Then there is the representativeness of the *Revista Latino-Americana de Enfermagem*.

The larger number of articles published in these journals enabled us to identify that the *Revista Brasileira de Terapia Intensiva* focuses its studies on research based on discussion, distribution, and promotion of information in this area of knowledge, which is aimed at intensivists. In particular, the name of the magazine already makes it inviting for investigations in Intensive Therapy.

In relation to the journal entitled *Journal of Nursing - UFPE online*, it is understood that it is an international scientific journal of master's and doctoral programs in Nursing, of the Federal University of Pernambuco. Although it is an *online* journal, it is located in the Northeast region of Brazil, which ranks in second among the studies selected studies, thus catching our attention to the scientific publications in this journal, in addition to focusing on research aimed at nursing and its team.

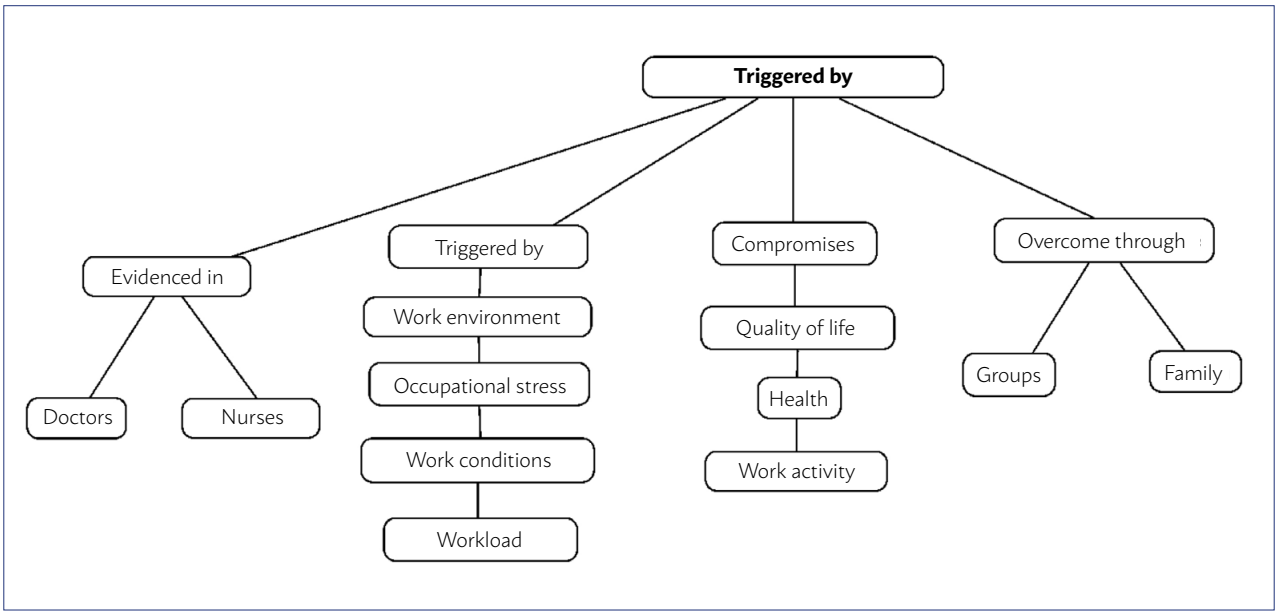
The dynamics of the variable analysis of the *Qualis Periodical* has its great value by projecting and giving visibility to quality scientific production. *Qualis* grades the quality of articles and other types of production based on the analysis of the quality of the means of publication, i.e., scientific journals, classifying them into eight categories: A1, A2, B1, B2, B3, B4, B5, and C[24].

According to the *Qualis Periodical*, based on the assessment of the Nursing area, it appears that there was a greater representativity of scientific production in journals classified in category B2; the second *Qualis* of higher expression was A2. Thus, we can see that the scientific production in this great area of Nursing presents a positive trend of publications in *Qualis* A, either A1 or A2, although some indicators demonstrate certain known difficulties in publishing in upper strata of *Qualis*. A survey[25] confirms the challenges faced by professional nurses to publish in periodicals of quality, affirming that it is necessary not just to conduct research, to develop quality knowledge.

In general, publications on Burnout Syndrome in medical journals indicate a limitation related to quantitative studies and the low level of classification of scientific production from Brazilian postgraduate programs published in journals.

It is important to highlight the variety and similarity of terms when consulting DeCs in relation to the theme Burnout Syndrome. They range from *Burnout*, *Professional Burnout, Professional Wear, Professional Stress, Occupational Stress, Emotional and*

FIGURE 1: CONCEPTUAL MAP PRODUCED FROM THE KEYWORDS OF THE ARTICLES AND THE THEMATIC CLASSES ON BURNOUT SYNDROME IN NURSES AND DOCTORS OF INTENSIVE CARE UNITS (N=40). AUTHOR: KELY C. C. AZEVEDO



Physical exhaustion, which makes it evident that this issue is in the process of construction. The concept map illustrated in Figure 1 is a graphical representation of concepts that organize themselves, establishing relationships between them and allowing us to reflect on its content[26].

From the conceptual map, it was possible to identify four thematic groups: professionals affected by the syndrome, factors related to its development, aspects of the professional life that are compromised, and ways to overcome the pathology.

As for the group of professionals affected by Burnout Syndrome, the publications presented the following keywords: *health professionals, physicians, nurses,* and *nursing team.* Based on these keywords, studies[27,28,29] indicate that the nursing work in ICUs faces stressful processes worldwide since the hospital environment is crucial for treating people increasingly diseased and senile[30]. In addition, it has been found that the prevalence of *burnout* in pediatricians of a public hospital in the South of Brazil was 53.7%[31]. This result is similar to that of another study that identifies the presence of the syndrome in intensivists of the state of Sergipe, which found that over 40% of participants were affected by it[32].

As for the factors related to the development of Burnout Syndrome in these professionals, the publications used the following keywords: *occupational stress, work conditions,* and *work environment.* Categorically, these keywords refer to elements of the organizational model of work. However, the causes of Burnout Syndrome occur at three different levels: individual, organizational, and social. On this subject, studies[33.34] indicate that burnout is determined by inadequate work organization, which causes an overload, lack of autonomy and support for carrying out tasks. In addition, negative factors in the work environment, such as the lack of structural resources, work organization, and conflicting interpersonal relationships increase the risk of undesirable consequences for health professionals, such as burnout.

In relation to the commitment of some aspects of the professional life of the individual, the following descriptors stood out: *quality of life, work activity*, and *health*. The quality of life at work is determined by individual situations, as well as those which emerge from the working environment itself. In addition, authors[35.36] argue that work is where people seek excellence in service due to feeling well, in a healthy environment, to accomplish their tasks. It is inferred that the compromise on the quality of life is reached when individuals are expected to reach scores of productivity and primacy, with harmful effects on the body and the mind of public servers.

Quality of life has been the object of research in various areas, especially in the context of health when associated with work. Studies[37.38] on nurses who work on surgical centers suggest that, in terms

of health-related quality of life, the physical, emotional and pain domains are the aspects most seriously compromised.

The fourth group of keywords used to portray the ways of tackling Burnout Syndrome in health workers were: *groups* and *family*. In this sense, it is necessary to contemplate a definition[39] that says that effective interventions are those that act positively, causing changes in the individual by following these steps: overcoming the resistance to change and preparing for it to occur; transitioning to a different position and remaining in this the newly changed state. In this context, it is vital to mention a research[40] that presented an intervention based on group meetings with professional ICU nurses of a university hospital, whose results revealed that groups could help the coexistence of professionals in the work environment. In terms of interpersonal relations, the support of family members is fundamental to mitigate the risk of developing Burnout syndrome in the work environment, since strained relations and conflict are reflected on work. In this context, there are some strategies for intervention, which are grouped into three categories: individual, group, and organizational strategies.

CONCLUSION

From the bibliometric perspective, the analysis of the scientific production on the Burnout Syndrome in ICU nurses and physicians, based on the databases investigated, showed that nurse researchers have a greater interest in publishing on this theme, in comparison to physicians. Thus, there are some concerns that arise, since studying Burnout Syndrome in intensivists would help to identify their prevalence in these professionals, in addition to being an important indicator of quality in the context of work in health organizations.

It is a fact that the scientific production on Burnout Syndrome in Intensive Care Units has advanced. However, it is considered that there is a low number of publications by medical professionals, hindering the dissemination of knowledge among the medical class. This aspect is relevant to point out the need to develop new studies addressing this phenomenon, especially because it is a major occurrence in the context of mental health.

We found that the Southeast region plays an important role by being the greatest publisher of information in the scientific community, regarding the number of articles published with a focus on *burnout* in ICU. In addition, the choice of the journal that will feature each discovery is understood to be of great value.

Therefore, considering the vast number of journals available, those who stood out had a though out approach, especially in regards of the scope of the subject (intensive care), with greater visibility in the universe of nursing. However, although the theme studied focuses on the psychosocial nature of the impacts caused, in respect to the *Qualis Periodical*, the discussions are often not able to be published in journals of greater prominence.

The contribution of this study suggests an attention to the development of more complex research on Burnout Syndrome in the context of Intensive Care Units, which has affected comprehensively Brazilian health workers, especially nurses and intensivists.

RESUMO

OBJETIVO: *Analisar a produção científica sobre a Síndrome de Burnout em médicos e enfermeiros de UTI no Brasil.*

MÉTODO: *Estudo bibliométrico, documental, com abordagem quantitativa. Foram selecionados artigos publicados no Brasil sobre a Síndrome de Burnout nas UTIs, na BVS e Portal Capes, entre 2000 e 2018. Foi elaborado um mapa conceitual de modo a organizar o eixo temático.*

RESULTADOS: *Foram identificados 40 artigos, predominantemente do Sudeste. Prevaleceram os publicados na Revista Brasileira de Terapia Intensiva e na Revista de Enfermagem UFPE on-line. O Qualis periódico B2 é o de maior destaque. Os descritores encontrados com maior prevalência foram: Unidades de Terapia Intensiva, Síndrome de Burnout, Burnout e Esgotamento Profissional.*

CONCLUSÕES: *Enfermeiros apresentam maior interesse em publicar nessa temática. A Síndrome de Burnout estudada em médicos intensivistas contribuiria para identificar a sua prevalência nesses profissionais.*

PALAVRAS-CHAVE: *Esgotamento profissional. Médicos. Enfermeiras e enfermeiros. Unidades de Terapia Intensiva.*

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COMMENTARY ON ARTICLE

"National scientific production on the Burnout Syndrome in ICU physicians and nurses: a bibliometric study"

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http://dx.doi.org/10.1590/1806-9282.65.5.730

Burnout Syndrome is significantly studied worldwide due to the severity of its symptoms and increasingly high prevalence rates in various professional categories. The vulnerability of health professionals, especially of doctors and nurses, to this syndrome is already well documented in the literature, with particular attention to those who work in Intensive Care Units (ICU). They have the highest rates of Burnout Syndrome, and its prevalence is attributed to the particularly stressful environment of this type of hospital unit.

The relevance of Burnout Syndrome as the object of research is evident since it is an important mental health problem that has been gaining prominence in Brazil over the years. However, most Brazilian studies on Burnout Syndrome in health professionals aim to identify prevalence rates and risk factors. Given this scenario, the study "National scientific production on Burnout Syndrome in ICU physicians and nurses: A bibliometric study"1 stands out because it investigates Burnout Syndrome under the perspective of a bibliometric study, conducting a chronological, geographic, thematic, and authorial mapping of Brazilian articles published.

Bibliometric studies are widely used in health due to its impact on future research and contribution to the development of specialized areas of knowledge. Thus, the article brings a significant contribution by quantifying and measuring the quality of national scientific production on Burnout Syndrome in intensive care doctors and nurses, allowing the scientific community to compare it with the extensive international literature and identify the aspects that still need to be investigated.

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REVIEW ARTICLE

Depression, anthropometric parameters, and body image in adults: a systematic review

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http://dx.doi.org/10.1590/1806-9282.65.5.731

SUMMARY

OBJECTIVE: *To evaluate the association between depression, anthropometric parameters and body image in adults through a systematic review of the literature.*

METHOD: *Medline, Lilacs and PsycInfo databases were searched by two independent reviewers up to August 2018, without language restriction, including cross-sectional, case-control, and cohort studies in adults (18-65 years), of both genders. The quality of the studies was assessed using the Newcastle-Ottawa Scale instrument. The PRISMA standards were adopted for the conduct of this review, whose protocol is registered in PROSPERO, number CRD42018105248.*

RESULTS: *The search resulted in 1,770 articles; however, a total of 5 articles were included in this review, whose designs were transversal. Quality scores ranged from 8 to 9 points. The association between depression, anthropometric parameters, and body image was found in all included studies, regardless of the different statistical methods employed. Women perceived their body larger than it really was by idealizing a lean body, whereas in men the perception of being underweight or dissatisfaction was observed by idealizing a larger body, both conditions were associated with the presence of depression or depressive symptoms and body mass index in the same time.*

CONCLUSION: *Depression, anthropometric parameters and body image were associated. It is necessary to conduct other studies, especially longitudinal studies to elucidate the relationship among depression, weight, body image, and other associated factors.*

KEYWORDS: *Body image. Depression. Body mass index. Obesity. Review.*

INTRODUCTION

Body image is one of the components of personal identity and can be defined as the figure that one has on their own anthropometric measurements, shapes, and contours of the body, and the feelings related to these factors that influence the satisfaction with the body shape or specific parts of the body[1]. Cultural, social, cognitive, affective, and biological aspects, as well as individual attitudes in relation to weight and body shape, and the presence of psychopathologies should also be considered in the assessment of body image[2].

The dissatisfaction with body image (IIC) has been attributed to a discrepancy between the perception of body shape and its idealized image[3], with an association to characteristics such as sex[4,5], nutritional state[6], eating disorders[7], in addition to other unfavorable outcomes in health, such as the presence of depressive symptoms[8].

Depression and obesity are public health problems that have bidirectional association[9,10]. Both can influence the perception of body image and promote or aggravate comorbid clinical conditions, such as worse general health conditions or eating

DATE OF SUBMISSION: 23-Oct-2018
DATE OF ACCEPTANCE: 09-Jan-2019
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disorders[11-14]. Obese individuals are generally more dissatisfied with their body image[13], while those with depression tend to distort it negatively[11]. Only a Dutch study has investigated the joint role of overweight and the severity of the depressive episode in the self-assessment of body image. A higher diagnosis and severity of depression and Body Mass Index (BMI) are associated with dissatisfaction with body image (DBI), both in isolation and in comorbidity[14].

Most studies about body image and health have been conducted with adolescents[15-18] with the assumption that the perception of body image is affected by pubertal development. However, the physical changes that occur in adulthood also have the potential to affect body image, since, in this stage, body shape can move away from the aesthetics of sociocultural ideals of physical beauty[19].

Thus, we identified the need to better understand what are the factors that influence the perception of body image among adults and how these factors relate among themselves. The objective of this study is to evaluate the association between depression, anthropometric measurements, and body image in adults, from a systematic review of the scientific literature.

METHODS

The present study is a systematic review of the literature, and its protocol is registered in the Prospero International Prospective Register of Systematic Reviews under CRD42018105248. We adopted the standards of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for conducting the study and obtaining and presenting the results[20].

The process of searching and evaluating the articles was conducted independently by two reviewers (DAS and LOF) and, in case of inconsistencies, a consensus was reached between them, or they sought the opinion of a third reviewer (MCV).

The databases consulted were Medline, Lilacs, and PsycInfo using boolean operators (*and/or*) for the combination of the following keywords: *body image, adults, depression*, body mass index, body size, body weights, and measures*. There was no restriction of language or date, and the process was conducted in August 2018, contemplating articles published until the date of the search.

The inclusion criteria adopted were studies with adults (18 to 65 years old), of both sexes, and with cross-sectional, case-control, or cohort design. We excluded studies performed with specific groups or that included individuals with associated medical and clinical conditions, pregnant women, women in postpartum, and hospitalized population. We also excluded interventional studies, letters, editorials, case reports, databases of theses and dissertations, summaries of congresses, and opinion articles.

The selection process comprised the identification of titles, the evaluation of abstracts, and the reading of the studies in full. Subsequently, information identifying the authors and year of publication, place of study, population, form of assessment of body image and depression, anthropometric parameter investigated, objectives of the study, measures of association evaluated, and main results were extracted from the studies selected.

The quality of the studies included in this review was assessed using the Newcastle-Ottawa Scale (NOS), which comprises the assessment of selection, comparability, and outcomes of each study[21,22]. The total score assigned corresponded to the number of positive items in the NOS, with a maximum of 10 points.

RESULTS

The search process resulted in 1,770 scientific articles, of which 620 were from Medline, 1,142 from PsycInfo, and 8 from Lilacs. After the assessment by means of the inclusion and exclusion criteria, 12 studies were read reading in full and, of these, five were included in this systematic review[12,14,23-25]. The reasons for exclusion were: studies that evaluated the three factors of interest simultaneously (3/7), focused on the role of self-esteem (1/7) or stigma (1/7), presented a mean age at the stage of adolescence (1/7) and had an experimental design (1/7). The process of selection of articles is described in Figure 1.

The characterization and the main methodological aspects of the five studies included in this review are presented in Table 1. We observed that all publications started in 2010, and two were published in 2018. Also, we found that two studies were conducted in the United States of America (USA).

The methods for analyzing body image was different among studies. One used an instrument validated and specific for each sex[14], and in four studies, the assessment was performed by means of a specific question, and in only one[25] body image was compared with BMI, calculated from measurements taken. Thus, two dimensions of body image were

studied: the perception of body image and satisfaction with body image, and one of the 14 studies investigated both (Table 1).

The instrument most often used for the assessment of depression was the Patient Health Questionnaire (PHQ). All studies used BMI as an anthropometric indicator and, in most of them (3/5), this index was calculated from the weight and height measured (Table 1).

The quality scores of the studies ranged from 8 to 9 (Table 1). The item "description of the response rate or characteristics of respondents and non-respondents" was the evaluation criterion with lower scores.

Objectives, measures of association, and the main results of the studies are described in Table 2. It is noteworthy that two of the five studies had as objective to investigate the mediating role of DBI in the association between depression and obesity[23,24], and most presented results separated by sex. The measure of association most often employed was the Odds Ratio.

It is important to emphasize that, with the exception of Richard et al.[12] and gaskin et al.[24], all the other studies excluded individuals with BMI<18.5 kg/m², classified as low weight, due to the possible association with eating disorders, small sample size, or for considering it a specific group with different characteristics from those with normal weight or excess weight.

An association between depression, anthropometric indicators, and self-image was found in all studies included, although the variables and methods of statistical analysis employed differed among them. Regarding the method for analyzing the association between depression and anthropometric indicators and

TABLE 1. CHARACTERIZATION OF THE STUDIES INCLUDED IN THE SYSTEMATIC REVIEW REGARDING DESIGN, PROCEDURES, ASSESSMENT TOOLS AND SCORE OF THE METHODOLOGICAL QUALITY.

Author/Year	Country	Study design	Population	Self-body image and dimension evaluated	Depression	Anthropometric indicator	NOS score
Gavin et al.[23] (2010)	USA	Cross-sectional	4,543 women enrolled in the *Group Health Cooperative*, 40 years old or older	Score of 0 (always) to 5 (never) to the statement "I feel satisfied with my body shape" Satisfaction with body image	PHQ-9	BMI (self-reported weight and height)	8
Gaskin et al.[24] (2013)	USA	Cross-sectional	13,548 participants from Nhanes, 18 years old or older	"Do you consider yourself to be underweight, overweight or with an appropriate weight?" Self-perception of body image	PHQ-9	BMI (weight and height measured)	8
Richard et al.[12] (2016)	Switzerland	Cross-sectional	15,975 participants from SHS, 18 years old or older	"Are you satisfied with your body?" Satisfied (absolutely satisfied or very satisfied) and dissatisfied (rather dissatisfied or absolutely dissatisfied) Satisfaction with body image	PHQ-9	BMI (self-reported weight and height)	8
Kim et al.[25] (2018)	Korea	Cross-sectional	Participants of Knhanes VI-2 from 19 to 65 years old	"How would you describe your body image?" (Very thin/slightly thin, normal, slightly/very obese) Comparison of body self-image with BMI measured: Accurate perception (perceived weight = measured); Overestimation (perceived weight > measured) and underestimation (perceived weight < measured). Self-perception of body image	PHQ-9K (Korean version)	BMI (measured weight and height)	8
Paans et al.[14] (2018)	Netherlands	Cross-sectional	1,452 participants of the Wave 9 of Nesda, 18 to 65 years old	Stunkard Adult Figure Rating Scale, specific for sex, containing 9 figures (very thin=1 and very heavy=9) -Circle the figure that shows your body today (Self-perception of body image) -Circle the figure that shows the body that you would like to have (idealized body image) Categories: 1) Individuals who would like to have a larger silhouette; 2) Individuals who were satisfied with their body; 3) Individuals who would like to have a smaller silhouette Satisfaction with body image	Cidi for diagnosis of depression IDS-SR for assessing the severity of depression	BMI (measured weight and height)	9

USA: United States of America; Nhanes: National Health and Nutrition Examination Survey; Knhanes VI-2: Sixth Korea National Health and Nutrition Examination Survey; Nesda: Netherlands Study of Depression and Anxiety; SHS: Swiss Health Survey; PHQ: Patient Health Questionnaire; Cidi: Composite International Diagnostic Interview (Cidi), BMI: Body Mass Index, NOS: Newcastle-Ottawa Scale.

TABLE 2. OBJECTIVES, MEASURES OF ASSOCIATION, AND MAIN RESULTS OF THE STUDIES INCLUDED IN THE SYSTEMATIC REVIEW.

Authors	Objectives	Measure of Association	Main Results
Gavin et al.[23] (2010)	-To evaluate the association between obesity and depression in a population sample of middle-aged women -To evaluate if the dissatisfaction with body image has a mediator role in this association and whether this varies with the level of formal education	Odds Ratio (OR)	Obesity and Depression -Adjusted by dissatisfaction with body image and stratified by level of formal education <16 years of formal education: OR= 1.81; CI 95% 1.15; 2.86* >=16 years of formal education: OR= 1.25; CI 95% 0.85; 1.85 -Adjusted by dissatisfaction with body image and other sociodemographic co-variables and smoking, stratified by level of formal education <16 years of formal education: OR= 1.75; CI 95% 1.11; 2.77* >=16 years of formal education: OR= 1.15; CI 95% 0.77; 1.72
Gaskin et al.[24] (2013)	-To evaluate the strength of the association of depression with weight and the self-perception of body image -To evaluate whether the relationship between excess body weight and depression was mediated or confounded by the perception of body image	Odds Ratio (OR)	Women -Depression and BMI adjusted for self-perception of body image Obesity (vs eutrophy): OR= 1.72; CI 95% 1.01; 2.92* Overweight (vs eutrophy): OR= 1.62; CI 95% 1.01; 2.60* Low weight (vs eutrophy): OR= 0.92; CI 95% 0.19; 4.42 -Depression and self-perception of body image with adjustment for BMI Overweight (vs eutrophy): OR= 1.73; CI 95% 1.14; 2.61* Low weight (vs eutrophy): OR= 2.75; CI 95% 1.47; 5.14* Men -Depression and BMI adjusted for self-perception of body image Obesity (vs eutrophy): OR= 1.24; CI 95% 0.62; 2.49 Overweight (vs eutrophy): OR= 0.77; CI 95% 0.39; 1.50 Low weight (vs eutrophy): OR= 0.46; CI 95% 0.13; 1.63 -Depression and self-perception of body image with adjustment for BMI Overweight (vs eutrophy): OR= 1.47; CI 95% 0.81; 2.67 Low weight (vs eutrophy): OR= 2.80; CI 95% 1.42; 5.54*
Richard et al.[12] (2016)	-To evaluate the association between dissatisfaction with body image and depression among men and women of different age subgroups	Odds Ratio (OR)	Dissatisfaction with body image and depression -Adjusted by BMI and other sociodemographic and clinical variables, stratified by sex Total sample: OR= 2.04; CI 95% 1.66; 2.50* Men: OR= 1.85; CI 95% 1.34; 2.56* Women: OR= 2.25; CI 95% 1.71; 2.96* -Adjusted by BMI and other sociodemographic and clinical variables, stratified by age range Young people: OR= 1.78; CI 95% 1.16; 2.74* Adults: OR= 2.10; CI 95% 1.61; 2.74* Elderly: OR= 2.34; CI 95% 1.30; 4.23* -Adjusted for sociodemographic and clinical variables, stratified by nutritional state Low weight: OR= 5.2; CI 95% 1.77; 15.26* Eutrophy: OR= 1.89; CI 95% 1.39; 2.59* Overweight: OR= 2.0; CI 95% 1.41; 2.83* Obesity: OR= 1.97; CI 95% 1.1; 3.51*
Kim et al.[25] (2018)	-To investigate the association between perception of body weight and depressive symptoms among Korean adults and potential differential association by gender	Regression coefficient (β)	Women -Underestimation of weight status (vs accurate perception) and depressive symptoms Total sample: β =0.19; CI 95% -0.40; 0.76 Obese: β =-1.25; CI 95% -2.44; -0.01* Eutrophic: β =0.14; CI 95% -0.55; 0.84 -Overestimation of weight status (vs accurate perception) and depressive symptoms Total sample: β =0.45; CI 95% 0.10; 0.79* Obese: not informed Eutrophic: β =1.00; CI 95% 0.54; 1.45* Men -Underestimation of weight status (vs accurate perception) and depressive symptoms Total sample: β =0.14; CI 95% -0.25; 0.52 Obese: β =0.01; CI 95% -0.62; 0.64 Eutrophic: β =0.30; CI 95% -0.25; 0.85 -Underestimation of weight status (vs accurate perception) and depressive symptoms Total sample: β =-0.09; CI 95% -0.62; 0.44 Obese: not informed Eutrophic: β =-0.21; CI 95% -0.78; 0.38
Paans et al. (2018)	14 -To examine whether depressive disorder, depressive symptoms, and BMI are associated with the self-perception of body image and dissatisfaction with body image -To evaluate the association between depression and obesity along with body size, perception of body image, and dissatisfaction with body image	Regression coefficient (β)	Depression and self-perception of body image (Outcome 1) -Diagnosis of depression, adjusted for BMI Healthy controls: Reference Patients in remission: β=0.07 p=0.25 Patients with current depression: β=0.14 p=0.08 -Severity of depression, adjustment for BMI: Severity of depression: β=0.07 p=0.007* Depression and dissatisfaction with body image (Outcome 2) -Diagnosis of depression, adjustment for BMI Healthy controls: Reference Remitted patients: β=0.12 p=0.01* Current patients: β=0.21 p=0.001* -Severity of depression, adjustment for BMI Severity of depression: β=0.11 p< 0.001*

body image, only one of the papers[25] considered the combination of the assessment of body image and nutritional state (derived from the calculation of the BMI) to build the variable of interest related to the accuracy of self-perception of body image, according to the results presented in Table 2.

In general, women perceived their body as larger than it really was or were dissatisfied with their body image, possibly due to the idealization of a slimmer body, and both the distortion of body image as the DBI were associated to the presence of depression. In the case of men, the perception of being underweight or the DBI due to the idealization of a larger body proved to be associated with the presence of depressive symptoms. A study found there was a reduction of depression scores among obese women who underestimated their body weight[25] (Table 2).

Paans et al.[14] analyzed two outcomes, the perception of body image and dissatisfaction with body image, both evaluated through the identification of silhouettes. The associations with depression and BMI were tested in two multivariate models, whereas, in one of them, the diagnosis of depression was considered and, on the other, the severity of the clinical condition. In the first model, only BMI was associated with a body image considered large. In the second model, this association was observed for both the highest severity of depression and high values of BMI. However, when DBI was evaluated, significant associations were obtained in the two models, both with the diagnosis of depression and BMI, as well as with the severity of depression and BMI[14], showing that the presence of depression and greater severity of clinical manifestations appear to be more related to the dissatisfaction with body image, regardless of BMI, than with the perception of a large silhouette, which seems to be a reflection of the BMI.

Among the studies that performed analyzes stratified by age[12.25], one[12] identified a significant association between DBI and depression (with adjustment for BMI) in all age ranges studied, with increasing magnitude of OR with increasing age (Young individuals: OR= 1.78; CI 95% 1.16; 2.74; Adults: OR= 2.10; CI 95% 1.61; 2.74; Elderly: OR= 2.34; CI 95% 1.30; 4.23). In contrast, Kim et al.[25] found that, in individuals with normal weight, the magnitude of the association between overestimation of body image (*vs.* accurate perception) and depression was higher in younger individuals (19 to 40 years) than among older individuals (41 to 65 years) (average PHQ score of 1.04, 95% CI: 0.49-1.60 and mean PHQ score of 0.63, 95% CI, 0.22-1.05, respectively; values that were not described in Table 2, since the objective of the study did not include the evaluation per age).

Another study[23] conducted analyses stratified by level of formal education to investigate the association between depression and obesity, with models adjusted for DBI only and including other covariates. An association was found only among those with less formal education in both models (adjustment only for DBI: OR=1.81; 95% CI 1.15; 2.86; adjustment including other covariates: OR= 1.75; CI 95% 1.11; 2.77). In participants aged 16 years or with more years of formal education, there was no association between depression and obesity in the analysis adjusted for body image[23].

DISCUSSION

This systematic review identified associations between depression, anthropometric indicators, and body image in adult individuals with differentiated standards for different sexes. Among women, the associations found were between depression, higher BMI or overweight/obesity, and dissatisfaction with body image due to excess weight or the perception of being overweight. In men, there were also associations identified, but with dissatisfaction due to low weight or the perception of being underweight. These differences in the pattern of DBI between sexes, in which women often idealize a slim body while men value a muscular body, have been reported in the literature[26.27].

It is important to highlight that this is the first systematic review to investigate, in adults, the association between depression, anthropometric indexes, and body image combined. We included studies published in different databases, without restrictions on language and date of publication, contemplating population-based samples representative of different parts of the world.

A slim body is, as a rule, revered as the standard of beauty and dissatisfaction with body image is observed even among eutrophic individuals[28]. In addition to the lack or excess weight, other forms of dissatisfaction with the body could be observed, such as dissatisfaction with body structure, size of certain parts of the body, or fat distribution.

Dissatisfaction with one's own body and with its self-perception can become even more intense in the presence of depression since negative self-per-

ception, and low self-esteem are part of the clinical scenario of the disease. In addition, changes in appetite may also be present, both as part of the symptoms, as resulting from the treatment of the disease, with consequent changes in weight and nutritional status[29]. Atypical depression, more frequent among women, often presents as increased sleepiness and appetite and, consequently, weight gain, and has been shown to be associated with overweight and obesity[30]. Thus, it is supposed that the atypical depression can also be more associated with DBI than other subtypes of depression. However, no studies were found that assess subtypes of depression and body image in adults, highlighting the need for research with that purpose.

There was a reduction in magnitude or absence of the association between depression and body image (when adjusted for BMI) and between depression and BMI (when adjusted for body image), which may explain the differences found among the studies[23,24,31]. There is no consensus on the role of body image in the relationship between depression and BMI, nor of BMI in the relationship between depression and body image, being regarded as mediators in some studies and confounding variables in others. Following the Directed Acyclic Graph (DAG), mediating variables should not be included as an adjustment in causal models[32]. It is also possible that BMI and body image are indicators (manifest) of a same condition (latent variable) and that, in association with depression,

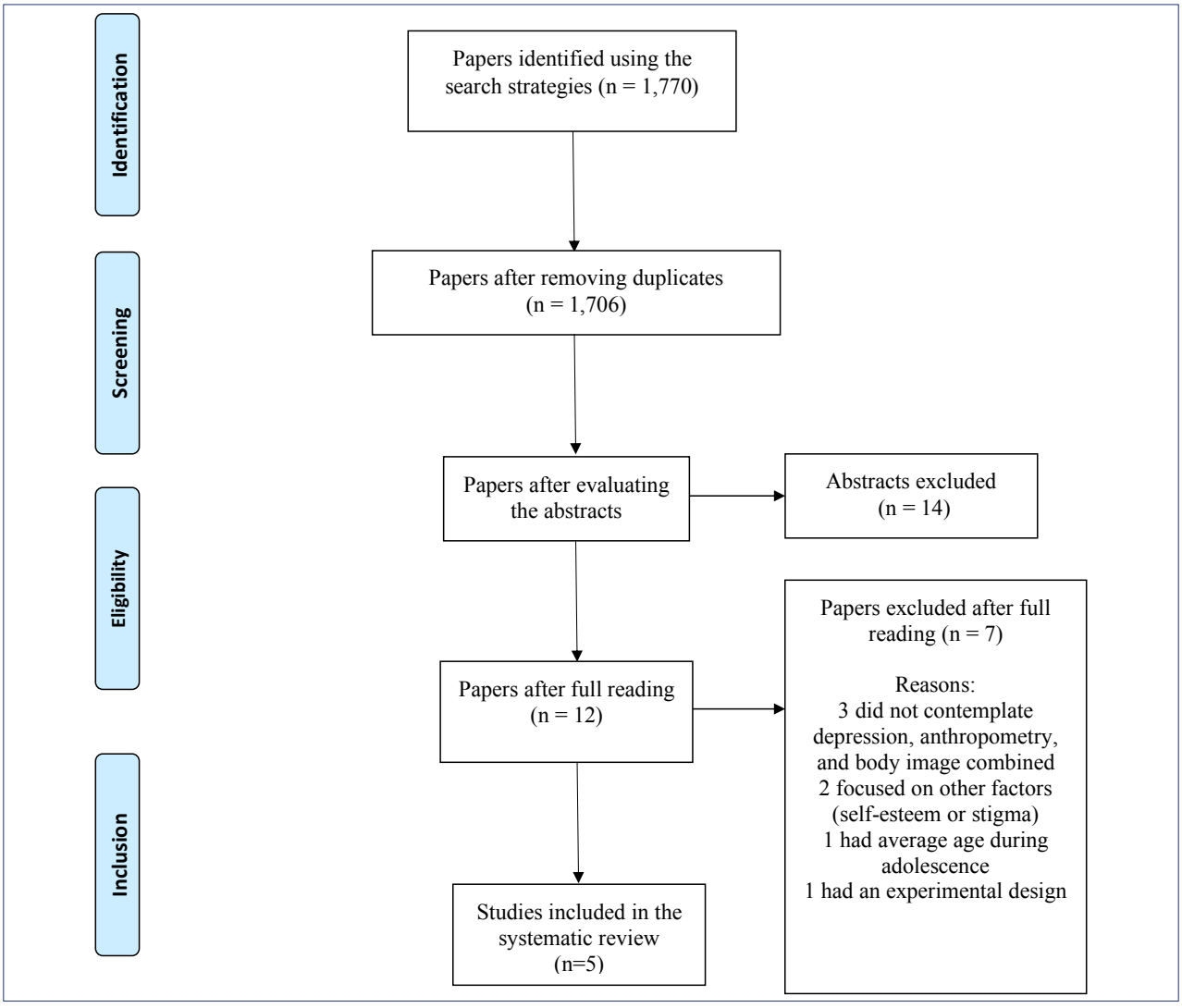

FIGURE 1. FLOWCHART OF THE PROCESS FOR SELECTION OF PAPERS: IDENTIFICATION, SCREENING, ELIGIBILITY AND INCLUSION OF SCIENTIFIC PAPERS IN THE SYSTEMATIC REVIEW, BASED ON PRISMA (2019).

can operate in different ways in different groups, for example, in the presence of obesity and in individuals with normal weight.

In most of the studies included in this review, the magnitude of the associations between depression and self-perception or dissatisfaction with body image was more robust than between depression and the actual nutritional state, obtained from BMI, which demonstrates the importance of subjective aspects in the investigation of the association between depression and weight[24,25,33]. In this sense, it was observed that an accurate perception of weight among obese women might represent a marker of increased risk of depression[25].

This systematic review had as limitations the weaknesses of the studies selected, such as the method for obtaining anthropometric data, since some studies used self-reported measurements, and the assessment of body image, which was investigated in several studies by means of just one question. Furthermore, most studies excluded individuals with BMI<18.5 kg/m², preventing the verification of the association of depression and body image in these individuals. The studies included in this review are cross-sectional, which does not allow the identification of the temporal sequence of the variables studied, emphasizing the need for longitudinal research on the subject.

We observed a good methodological quality of the articles included in this study, guaranteeing the reliability of the results obtained. All articles were published less than a decade ago, which shows recent in-depth interest on this topic regarding the adult population since most of the previous studies had been conducted on adolescents. The scarcity of studies on adults is reported by several authors[12,24,34] and, moreover, discrepant results have been found when the role of other variables, such as gender, age, and formal education, among others, were investigated[12,25]. Thus, the relevance of this study and the need for future investigations is highlighted.

The negative impact of depression and obesity on social life, work, life habits, and health of individuals is already well documented[14,29,35,36]. In situations where both conditions are present, the severity could be even greater, associated with other clinical conditions, such as eating disorders or cardiovascular diseases[9,29,37].

Considering the obesity epidemic worldwide[38], the estimate that depression will contribute to the greatest global burden of diseases in the year of 2030,[39] and the bidirectional association between depression and obesity[9,10], it is essential and urgent that resources are invested allowing for the planning and implementation of interventions in public health and clinical practice with the purpose of preventing and controlling these diseases.

CONCLUSION

This review identified an association between depression, anthropometric indicators, and body image on representative samples of adults from different parts of the world, with specific patterns for different sexes.

We found a recent interest in the study of this topic in adults and the need of other studies, especially of a longitudinal design, for greater understanding of the relationship between depression, weight, body image, and other associated factors.

RESUMO

OBJETIVO: *Avaliar a associação entre depressão, indicadores antropométricos e autoimagem corporal em adultos por meio de uma revisão sistemática da literatura.*

MÉTODOS: *Foi realizada busca nas bases de dados Medline, Lilacs e PsycInfo por dois revisores independentes, até agosto de 2018, sem restrição de idioma, incluindo estudos de delineamento transversal, caso-controle e de coorte, avaliando adultos (18-65 anos), de ambos os sexos. A qualidade dos estudos foi aferida por meio do instrumento Newcastle-Ottawa Scale. Esta revisão sistemática foi conduzida de acordo com as normas do Prisma e foi registrada no Prospero (CRD42018105248).*

RESULTADOS: *A busca resultou em 1.770 artigos, dos quais cinco foram incluídos nesta revisão, todos de desenho transversal. Os escores de qualidade dos estudos variaram de 8 a 9 pontos, num total de 10. A associação entre depressão, medidas antropométricas e autoimagem corporal foi encontrada em todos os estudos incluídos, independentemente dos diferentes métodos estatísticos empregados. No geral, as mulheres percebiam o seu corpo maior do que realmente era ou estavam insatisfeitas por desejarem ter um corpo mais magro, enquanto que, entre os homens, a percepção de estar abaixo do peso ou a insatisfação com a imagem corporal foram observadas, principalmente, por desejarem ter um corpo maior. Tanto a percepção distorcida ou a insatisfação com a imagem corporal se mostraram associadas à depressão e ao índice de massa corporal conjuntamente.*

CONCLUSÃO: *Depressão, indicadores antropométricos e autoimagem corporal se mostraram associadas. Destaca-se a necessidade da condução de outros estudos, especialmente de desenho longitudinal, para maior elucidação desta relação.*

PALAVRAS-CHAVE: *Imagem corporal. Depressão. Índice de massa corporal. Obesidade. Revisão.*

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Erratum

http://dx.doi.org/10.1590/1806-9282.65.5.739

Regarding the article "Subtar arthroscopic debridment for the treatment of sinus tarsi syndrome: case series", with DOI number: http://dx.doi.org/10.1590/1806-9282.65.3.370, published in Journal of the Brazilian Medical Association, 2019;65;03, page 370:

Where was written: "Subtar arthroscopic debridment"
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