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SUMMARY

The inclusion of internet in patient-physician relationship: a necessary reflexion

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The growth of the social importance of the internet among the media is unquestionable. Data from 2015 shows that almost half of the Brazilian population (48%) uses the internet, being driven mainly by the use of smartphones and social media; in addition, 76% of users have daily access and with an average exposure of 5 hours/day. The benefits of this advance can be seen through the existence of countless and varied sources of search available and the consequent emergence of proactive users who, increasingly, assume the position of protagonist agents of the information acquisition process.[1,2]

Concomitantly with the progress of the internet, healthcare has broadened its meaning, translating as a "*state of complete physical, mental and social well-being and not only the absence of affections and diseases*".[3] In parallel to the recognition of healthcare as one of the main concerns of contemporary men and women, there is an increase both in the availability of online information on health-related issues and in the number of users accessing the Internet for the purpose of obtaining information about their own health condition or of a relative or friend, especially if there in cases of installed illness.[2]

Overall, there is a presumptive view that advances in information technology interfere with medical care and is therefore "*replaced by impersonal exchanges around computer screens or smartphones.*" This popularized view must be evaluated insofar as it is refuted by scientific evidence showing the pros and cons of the influence of the internet on doctor-patient relationships.[2,4,5]

In fact, it is believed that there has been, in recent years, the replacement of a passive and uninformed patient with an empowered individual willing to improve his or her own health condition.[5] Modern medicine also encourages patient's participation as a of the pillars that constitute the practice of evidence-based medicine, being seen as an active individual in the decision-making process in the face of diagnostic and therapeutic possibilities offered[6]; the Brazilian Code of Medical Ethics defines this attitude as the principle of autonomy.[7]

The major advantage of online access to infor-

mation in the doctor-patient relationship is that the patient may be more qualified to manage their own health, especially in home-based care, by engaging in partnerships with their physicians. On the other hand, doctors may feel their authority undermined by a patient with a more questioning attitude, in addition to the possible emergence of weaknesses in the trust relationship, if the guidelines given in the doctor's office differ from those found online.[8]

Traditionally, the physician is seen as having greater clinical knowledge when compared to the patient, thus establishing a relationship of power, in which the patient must rely on the precision of the diagnosis and on the doctor's recommendations.[9] However, it is now seen that this professional can establish a collaborative model in the relationship with his/her patient, helping them to choose the method of treatment that they prefers and encouraging them to actively research in reliable and adequate sources information about their health, which positively influences the relationship.[10]

It is worth mentioning that physicians also enjoy the advance of the internet in accessing healthcare information, through research in databases and catalogues of academic journals. In addition to online scientific research, they can inserted themselves in social media (blogs, video sharing sites, social networks, among others), and it is possible to involve and build virtual relationships with patients and the community; in these cases, it is advised that the professional should observe his/her digital privacy, ethical aspects and attitude adopted.[6, 11]

Finally, it is understood that access to healthcare information online is not free from risks such as insecurity and fears, both by patients and physicians. However, the promotion of benefits through the internet, such as the creation of instruments to cope with life threatening situations and emotional relief, is already recognized as a positive effect for certain patients.[12] The cognitive aspect of the patient as a determinant for the interpretation of online health information must be understood; the medical ability to critically evaluate the sources consulted is paramount in conducting the process of reflection and empowerment of people in sharing of knowl-

edge. Thus, recognizing the information age as a social advance is necessary, weighing positive and negative aspects, to continue the endless process of improving communication and the doctor-patient relationship.

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Chronic pain - treatment with spinal cord neurostimulation

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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.

METHODOLOGY FOR EVIDENCE COLLECTION

This guideline followed the pattern of a systematic review with evidence collection based on the movement of Evidence-Based Medicine, in which clinical experience is integrated with the ability of critical analysis, rationally applying scientific information and improving the quality of medical assistance.

We used the structured version of the question synthesized by the PICO process, in which **P** stands for **patients with chronic pain** that have not responded to the conventional treatment; **I** for **spinal cord neurostimulation** intervention; **C** for comparison between **conventional therapy, reoperation, and spinal cord neurostimulation inactive or absent**; and **O** for clinical **outcomes**.

Through the elaboration of five relevant clinical questions related to the proposed theme, based on the structured question, we identified the keywords that served as the basis for searching the source databases: Medline-PubMed and Embase Cochrane Library. Next, the summaries of the studies were analyzed and, after applied the eligibility criteria (inclusion and exclusion), 13 papers were selected to answer the clinical questions (**Appendix I**).

MAIN CLINICAL QUESTION:

Can patients who have not responded to conventional treatment, pharmacological or not (physical therapy, acupuncture, transcutaneous electrical nerve stimulation, psychotherapy), benefit from spinal cord neurostimulation?

SPECIFIC CLINICAL QUESTIONS

1. What is the effectiveness of percutaneous Spinal Cord Stimulation (SCS) when compared to the conventional treatment for treating post-laminectomy syndrome?

2. What is the effectiveness of percutaneous SCS combined with the conventional treatment when compared to reoperation combined with the conventional treatment for treating post-laminectomy syndrome?

3. What is the effectiveness of percutaneous SCS for treating type I Complex Regional Pain Syndrome (CRPS-I)?

4. What is the effectiveness of percutaneous SCS for treating refractory angina pectoris?

5. What is the effectiveness of percutaneous SCS for treating Critical Limb Ischemia (CLI)?

GRADES FOR RECOMMENDATION AND LEVELS OF EVIDENCE

A: Experimental or observational studies of higher consistency.

B: Experimental or observational studies of lower consistency.

C: Uncontrolled case/study reports.

D: Opinion deprived of critical evaluation, based on consensus, physiological studies or animal models.

OBJECTIVE

Identify the best evidence currently available related to the use of spinal cord neurostimulation in patients with chronic pain, assessing its impact on clinical outcomes.

CONFLICT OF INTEREST

There is no conflict of interest related to this review that can be declared by any of the authors.

INTRODUCTION

Based on electrophysiological findings and clinical data, in 1965 Melzack e Wall[1] established the principle of sensory interaction as part of the gate control theory. The theory proposes that the stimulation of structures of the Peripheral Nervous System (PNS) creates impulse patterns that reach the Central Nervous System (CNS), where the information is affected by modulation systems before the perception of pain is evoked. The gelatinous substance of the Posterior Horn of the Spinal Cord (PHSC) acts as a modulation element for the afferent impulses, and the posterior funiculus tracts activate brain structures that, by means of descending fibers, are projected in the spinal cord, interfering with the segmental system activity. Pain and other evoked sensations are the results of the balance between the activities of the primary afferents and the inhibited segmental and suprasegmental pathways. The cells of the gelatinous substance act, thus, as a gate, determining the quality of the stimulus that reaches the cells and originates the suprasegmental projection tracts. The theory suggests the existence of regional inhibition mechanisms that allow the improvement of stimuli identification and offer a physiological basis for correlating the psychological aspects, the attention, and the environmental influences related to pain processing.

The first implantations of spinal electrodes for pain control purposes were carried out in 1967 by means of laminectomy. Initially, the unipolar or bipolar electrodes were implanted in the subarachnoid space. Then, in the subdural compartment and, now, it is preferred to be put in the epidural situation. The current electrodes are quadrupolar and the percutaneous implantation technique is most often employed, since it is safer and simpler.

The electrodes are connected to a battery (like a pacemaker generator) to produce a pain control effect by means of the electrical stimulation of the posterior funiculus of the spinal cord at adequate and established levels, according to the metameres involved and the paresthesia reported by the patient.

The neurophysiological mechanisms for pain relief involve, in addition to the neurophysiological activity, neurochemical elements that explain the lasting effects of analgesics (such as, neurotransmitter modulation, impact on the GABA system, CGRP, etc.)[2].

Spinal cord neurostimulation is intended to reduce the unpleasant sensory experience caused by pain, as well as its functional and behavioral effects.

PRESENTATION OF RESULTS
Spinal cord neurostimulation in neuropathic pain

1. What is the effectiveness of percutaneous Spinal Cord Stimulation (SCS) when compared to the conventional treatment for treating post-laminectomy syndrome?

Patients that underwent Spinal Cord Stimulation (SCS) presented at least 50% of pain relief in the legs (NNT=3) when compared to the conventional treatment, using the Visual Analogue Scale, in 6 months.[3](B)

Patients that underwent SCS did not present any statistically relevant difference in relation to the use of opiates when compared to the conventional treatment (NNT = NS), in 6 months.[3](B)

Patients that underwent SCS presented an improvement (on average) in functional capacity assessed by the Oswestry disability index, in comparison to conventional therapy ($p < 0.001$), in 6 months.[3](B)

Patients that underwent SCS presented statistically relevant ($p < 0.05$) benefits (on average) in quality of life measured by the Short Form-36 (SF-36), in all domains, with the exception of physical performance, in comparison to conventional therapy.[3](B)

After 6 months, 73% of the patients in the control group (conventional therapy) migrated to the intervention (SCS) group, and 10% of the intervention group migrated to control. Due to the risk of bias in

the short-term analysis, we opted for assessing up to 6 months, excluding another publication of the same study that presented a 24-month analysis.[4](B)

2. What is the effectiveness of percutaneous SCS combined with the conventional treatment when compared to reoperation combined with the conventional treatment for treating post-laminectomy syndrome?

Patients that underwent SCS presented 50% of pain relief (McGill Pain Questionnaire checklist) in three years, in comparison to those of reoperation (NNT= 3, CI-95% = 2 a 14).[5](B)

Patients that underwent SCS presented, in three years, a reduction in opioid use, in comparison those of reoperation (NNT = 3, CI-95% = 2 a 15).[5](B)

There were no differences between SCS and reoperation patients regarding the pain related to daily activities or neurological function.[5](B)

These results should be evaluated with caution, because 54% of the reoperation group migrated to the SCS, and 21% of the SCS for the reoperation after 6 months. There are no data available for analysis at 6 months. The analysis was performed per treatment.[5](B)

3. What is the effectiveness of percutaneous SCS for treating type I Complex Regional Pain Syndrome (CRPS-I)?

The authors evaluated the effectiveness of the SCS combined with physical therapy, comparing it to the sole use of physical therapy for treating CRPS-I at 6, 24, and 60 months. The outcomes considered were: reduction of pain intensity (VAS-0 to 10 cm), functional score (function, strength, the amplitude of movement), changes in health-related quality of life (HRQoL). Analysis by Intention to Treat.[6-8](B)

SCS combined with physical therapy was more successful at reducing pain than physical therapy alone, in average, at 6 months (–2.4 cm / 0.2 cm, p<0.001) and at 2 years (–2.1 / 0 cm, p = 0.001), but did not at 5 years (–1.7 cm / –1.0 cm, p = 0.25).[6-8](B)

There was no difference between SCS combined with physical therapy and physical therapy alone with respect to function, strength, and amplitude of movement of the hands and feet (p > 0,05), in the assessments at 6, 24, and 60 months.

There was no difference observed in the assessment of change in health-related quality of life (HRQoL) at 6 months (percent variation in HRQoL:

6% in intervention [SCS] and 3% in control [physical therapy], p = 0.58), nor at 2 years (7% in SCS and 12% in physical therapy, p = 0.41).[6-8](B)

Out of the 36 patients selected for SCS, 24 (67%) were implanted with the device and 12 others (33%), who did not respond to stimulation (paresthesia covering the entire area of pain, 50% of VAS reduction over a period of 4 days), were analyzed by ITT. The sample size calculation, considering a 90% ability to detect a 2.3 cm difference in VAS between treatments with a significance level of 5%, indicated that 34 patients would be needed in the SCS group, as described in the study.[6-8](B)

Spinal cord neurostimulation in ischemic pain

4. What is the effectiveness of percutaneous SCS for treating refractory angina pectoris?

Patients with refractory angina, high-risk surgical patients, without a good prognosis for myocardial revascularization surgery and with contraindication for percutaneous angioplasty (anatomical alterations and others) were included. Thus, when analyzing SCS versus Myocardial Revascularization Surgery (MRS), at 6 months, there was no difference in reduction, on average, of the number of weekly angina attacks between SCS and MRS (p = NS). [9,10](B)

There was no difference in the consumption of short-acting nitrate (dose/week), on average, between SCS and MRS (p = NS). The myocardial revascularization surgery reduced, on average, the consumption of long-acting nitrate (p<0.0001).[9,10](B)

The myocardial revascularization surgery increases the ability to exercise (p = 0.02).

There was no difference in the health-related quality of life between SCS and MRS (Error bars: ±1 SEM) — 'Nottingham Health Profile' (NHP) e 'Quality of Life Questionnaire — Angina Pectoris' (QLQ-AP)[9,10](B)

When analyzing SCS versus Myocardial Revascularization Surgery (MRS), at five years, there was no difference in the quality of life between SCS and MRS (Error bars: ±1 SEM).[9,10](B)

There was no difference in survival (Kaplan-Meier) between SCS and MRS.[9,10](B)

In one study, patients with refractory angina, with no conditions of undergoing percutaneous angioplasty or myocardial revascularization surgery were included and analyzed at 6 weeks.[11](B)

The was no pain reduction, on average, assessed by VAS (0–10 cm) [1.1 cm x 0.2 cm; p = 0.29.[11](B)

In relation frequency of angina attacks (per day), it was reduced, on average, 2.3 x 3.2 (p = 0.01).[11](B)

There was a reduction in nitrate consumption (–48% x 27%, p = 0.03) and an improvement, on average, of the ability to exercise (533 x 427, duration in seconds) (p = 0.03).[11](B)

There was no difference, on average, in the Quality of Life (Linear Analogue Self-Assessment [LASA] scale) (p = 0,10).[11](B)

The sample of the study is small (13 for SCS and 12 for control [inactive SCS]). Considerable Type II Error.[11](B)

The authors included in the study patients with refractory angina to whom the myocardial revascularization surgery was considered inadequate or with no good prognosis, assessed at 8 weeks.[12](B)

The frequency of angina attacks (per week) was reduced, on average, 9.0 x 13.6 (p<0.05) in up to 8 weeks.[12](B) The nitrate consumption (weekly average) was reduced, 1.6 x 8.5 (p<0.05) in up to 8 weeks.[12](B)

There was an improvement, on average, in the ability to exercise (cardiac stress test) [duration of the exercise in seconds: 827 x 694, p<0.002] in up to 8 weeks.[12](B) And the quality of life (HRQoL – daily activity score, including social activity) was improved (p<0.05) in up to 8 weeks.[12](B)

The small sample size of this study (**SCS**=8 and **no SCS**=9) entails a relevant Type II Error. The follow-up time is very short (8 weeks).[12](B)

Patients with refractory angina and reversible myocardial ischemia, however inadequate for conventional revascularization, were analyzed at 3 and 12 months. In relation to the ability to exercise (duration in minutes), there was no improvement, on average, at 3 and 12 months (p>0.05 for both measurements). There was no difference, on average, in the quality of life (p>0.05).[13](B)

5. What is the effectiveness of percutaneous SCS for treating Critical Limb Ischemia (CLI)?

Diabetic patients with atherosclerotic chronic critical ischemia of the lower limbs, lasting over two weeks, with pain at rest and/or ulceration, for which there was an impossibility or failure of revascularization due to poor circulation (analysis at 18 months).[14](B)

- **Pain (VAS)**

It was not possible to assess pain levels at 18 months due to the loss of 80% of the control group for this outcome.

- **Amputation**

SCS did not reduce the number of amputations up to 18 months (NNT = NS).

- **Limb salvage** (revascularization of the ischemic limb)

Limb salvage was not improved (NNT = NS) up to 18 months.

Patients with atherosclerotic peripheral arterial occlusive disease in advanced stage (Fontaine IV [ulcer or gangrene]); not all diabetics; with the impossibility of revascularization and severe pain at rest despite analgesic medication (analysis at 12 months).[15](B)

SCS combined with the use of prostaglandin E1 (intravenously), compared to the exclusive use of prostaglandin E1, did not reduce the number of amputations (smaller and larger) up to 12 months (NNT = NS).[15](B)

Patients with atherosclerotic chronic critical ischemia of the lower limbs, with pain at rest and/or ulceration, for which there was the impossibility of revascularization (analysis at 2 years).[16,17](B)

There was no difference in the pain assessment (VAS, McGill Pain Questionnaire, pain-rating index) (p>0.05). Mortality was not reduced, neither was the number of amputations up to 2 years (NNT=NS). There was no difference in limb salvage up to 2 years (Kaplan-Maier; HR = 1.09, CI95%: 0,59 – 2,03) or in quality of life (*Nottingham Health Profile [NHP] and EuroQol*) (p>0.05).[16,17](B)

FINAL CONSIDERATIONS

Spinal cord stimulation should only be considered as a treatment option after the assessment by a multidisciplinary team with experience in chronic pain assessment.

Spinal cord neurostimulation for treating pain with neuropathic origins

Patients who did not present at least 50% of VAS improvement in pain levels and did not respond to conventional treatment (pharmacological or not [physical therapy, psychotherapy, acupuncture...]) for a period of at least 6 months.

Post-laminectomy syndrome

There is evidence of estimated benefits in using **SCS in comparison to reoperation**, by means

of pain reduction (at least 50% in VAS), [NNT=3]; improvement in functional capacity and in the health-related quality of life (p<0.05) in up to 6 months (Level 2B).

1.2. Complex Regional Pain Syndrome type I

The use of SCS combined with physical therapy compared to the exclusive use of physical therapy as treatment reduces the pain according to the VAS (Visual Analogue Scale) score, [p<0,001]. However, it does not improve the functional assessment (function, strength and amplitude of movement) and the health-related quality of life (p>0.05) up to 2 years.

Spinal cord neurostimulation for treating ischemic pain

2.1. Refractory angina

In patients with refractory angina for whom the myocardial revascularization surgery was considered inadequate, the **SCS, when compared to inactive SCS or no SCS**, in up to 8 weeks, reduced the number of angina attacks and improved the ability to exercise. The assessment of the quality of life is inconclusive, since one study shows improvement and the other does not. Due to the small sample size, the type II error is considerable in both studies.

In patients with refractory angina and reversible myocardial ischemia, however inadequate for conventional revascularization, the SCS compared to laser percutaneous myocardial revascularization does not improve the ability to exercise (p > 0.05) and there is no difference in quality of life (p> 0.05) in up to 12 months.

In patients with refractory angina; high-risk surgical patients; with no good prognosis for myocardial revascularization surgery and contraindication for percutaneous angioplasty (anatomical alterations and others), the **SCS, compared to the myocardial revascularization surgery**, in up to 6 months, did not reduce angina attacks and the consumption of nitrates; it did not improve the ability to exercise or the quality of life (p=NS for all outcomes - average results).

In the 5-year analysis, there was no improvement in the quality of life (p=NS) and in survival (Kaplan-Meier).

2.2. Chronic Critical Limb Ischemia

In diabetic patients with atherosclerotic chronic critical ischemia of the lower limbs lasting for over two weeks, with pain at rest and/or ulceration, for which there was impossibility or failure of revascularization due to poor circulation, the **SCS combined with oral analgesic compared to the exclusive use of oral analgesic** did not reduce the number of amputations nor did it improve limb salvage (NNT=NS) in up to 18 months.

In patients with atherosclerotic peripheral arterial occlusive disease in advanced stage (Fontaine IV [ulcer or gangrene]), not all diabetics, with impossibility of revascularization and severe pain at rest despite the use of analgesic medication, the **SCS combined with prostaglandin E1, compared to the exclusive use of intravenous prostaglandin**, did not reduce the number of amputations (smaller and larger) in up to 12 months.

In patients with atherosclerotic chronic critical ischemia of the lower limbs, with pain at rest and/or ulceration, for which there was impossibility of revascularization, the SCS combined with medical care, when compared to only medical care (analgesics, antithrombotic drugs, vasoactive drugs, local treatment of the ulcer and antibiotics, when necessary) did not reduce the pain (p>0.05); did not reduce the mortality or the number of amputations (NNT=NS); did not improved the limb salvage (HR = 1.09, CI95%: 0.59 – 2.03) and did not improve the quality of life (p>0.05) up to 24 months.

RECOMMENDATION
Use of spinal cord neurostimulation in neuropathic pain

For patients who did not present at least 50% of improvement in pain levels in the VAS score (Visual Analogue Scale) and who did not respond to conventional treatment (pharmacological or not [physical therapy, psychotherapy, acupuncture...]), for a minimum period of 6 months, there is evidence to support the use of spinal cord neurostimulation for post-laminectomy syndrome and complex regional pain syndrome type I.

Use of spinal cord neurostimulation in ischemic pain

There is no evidence to support the use of spinal cord neurostimulation in patients with chronic ischemic pain (refractory angina and chronic critical ischemia of the lower limbs with no possibility of revascularization).

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APPENDIX I
Structured question

P –	Patients with chronic pain who did not respond to conventional treatment
I –	Spinal cord neurostimulation
C –	Conventional therapy, reoperation, spinal cord neurostimulation inactive or absent
O –	Clinical outcomes

Methodology for evidence search
PubMed-Medline

Strategy 1: ((((Electric Stimulation Therapy) AND Spinal Cord) AND Pain))
Strategy 2: with clinical queries filter (Therapy/Narrow[filter]) AND ((((Electric Stimulation Therapy) AND Spinal Cord) AND Pain))

COCHRANE
spinal cord AND *electric stimulation*

Manual search
No papers were selected from manual search.

DATABASE	NUMBER OF PAPERS
Primary	
PubMed-Medline	1,347 / 67(with Cl. Queries filter)
Embase	249
Secondary	
Cochrane Library	2 (System Rev.)

TABLE 1 - No. of papers returned from the search methodology used in each of the scientific databases

Selection of papers

The studies were initially selected by title, then by their summary and, lastly, by their complete text, being the last one subject to critical evaluation and the extraction of all results relating to outcomes.

All studies recovered from the primary and secondary databases were evaluated.

From the primary databases, after the initial critical evaluation, were selected: PubMed-Medline (13), Embase (zero), and Cochrane/Lilacs/BVS (zero).

The papers considered for complete reading were critically evaluated following the inclusion and exclusion criteria, based on study performance, PICO, language and availability of the text in its entirety.

Table 2 presents the number of papers assessed by the clinical situation.

CLINICAL INDICATION	NUMBER OF PAPERS
Post-laminectomy syndrome	3
Complex regional pain syndrome type I	3
Chronic critical limb ischemia	3
Refractory angina	4
TOTAL	**13**

TABLE 2 - No. of papers selected for critical evaluation according to clinical indication

Language
Only studies available in Portuguese, English, or Spanish were included.

According to publication
Only studies with texts available in its entirety were considered for critical evaluation. Out of the 13 papers considered of critical assessment, none was excluded for not being complete.

Inclusion and exclusion criteria
The studies were included according to the PICO components, the language, availability of full text and study design.

The designs included varied according to the clinical question, with the selection of the higher level of evidence for each question.

Studies conducted between 1993 and 2011 were included in the assessment.

Critical evaluation and level of evidence
Only studies with texts available in its entirety were considered for critical evaluation. When, after the inclusion and exclusion criteria were applied, the evidence selected was classified as Randomized Controlled Trial (RCT), it was subjected to a suitable critical evaluation check-list Table 3).

Guide for Critical Evaluation of Randomized Controlled Trials (check-list)	
Study data Reference, study design, Jadad, level of evidence	**Sample size calculation** Estimated differences, power, significance level, the total number of patients
Patient selection Inclusion and exclusion criteria	**Patients** Recruited, randomized, prognostic differences
Randomization Description and blinded allocation	**Patient follow-up** Time, losses, migration
Treatment protocol Intervention, control, and blinding	**Analysis** Intention to treat, analyzed intervention and control
Outcomes considered Primary, secondary, measurement instrument for the outcome of interest	**Results** Benefits or harmful effects in absolute data, benefits or harmful effects on average

TABLE 3 - Guide for Critical Evaluation of Epidemiological Studies (check-list)

The critical evaluation of RCT allows to classify it according to the Jadad score[18], considering Jadad trials < 3 (three) as inconsistent, and those with score ≥ 3 (three) consistent.

Extraction of results

The results regarding the different clinical situations considered will be exposed individually, by means of the following items: clinical question, number of selected works (according to the criteria of inclusion), main reasons for exclusion and synthesis of the evidence available.

References related to studies included and excluded will be arranged in the item References.

For results with available evidence, the population, intervention, outcomes, presence or absence of benefits and/or harmful effects, and controversy will be explicitly defined whenever possible.

In the absence of consistent randomized clinical trials, the synthesis will be limited to the impossibility of sustaining the indication.

Cost-related issues will not be included in the results.

The outcomes considered will be limited to the effectiveness and safety of interventions. The results will be presented, preferably, in absolute data, absolute risk, reduction of absolute risk, and number needed to treat (NNT).

Description of evidence

Based on well-established indications for spinal cord neurostimulation that indicate a better thera-peutic result, this guideline has assessed its use in the treatment of neuropathic pain (Post-laminectomy syndrome [PLS], Complex Regional Pain Syndrome Type I [CRPS-I]) and of ischemic pain (Critical Limb Ischemia [CLI], Refractory Angina [RA]).[19]

The critical reading of each of the studies was conducted, seeking to identify possible biases that could compromise the internal validity of the study. In the absence of serious invalidating biases, the studies were included in the review and its eventual biases and limitations described individually (**Note** at the end of each evaluation).

Important biases found during critical analysis of the studies included in this Guideline for the Use of Spinal Cord Neurostimulation correspond to:

1. Small sample size value in most of the studies, leading to a considerable type II error.

2. Risk of bias in the long-term analysis due to migration, which ranged from 54% to 73% at 6 months.

Only studies that assessed at least one clinical or clinically relevant outcome (for example, pain, functional capacity, quality of life, amputation, limb salvage) were included. When there was more than one publication of the same study, only the one with clinical outcomes considered relevant was assessed.

There was no subgroup analysis, which increases the possibility of random associations.

As with any neuromodulation technique, the therapeutic results of spinal cord neurostimulation may vary over time as the technology is modified.

Detoxification enzymes: cellular metabolism and susceptibility to various diseases

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DETOXIFICATION ENZYMES

Detoxification enzymes act in the cellular metabolism of substances that are strange to the organism (xenobiotic) and endogenous compounds that could cause cellular and tissue damage, such as compounds derived from the oxidative stress. Cellular metabolism occurs in three successive phases: in phase 1, potentially toxic compounds are activated, especially through the action of *P*-oxidases cytochrome (CYP) enzymes.[1] In phase 2, the compounds that were activated in the previous phase are conjugated to substances that will make them more water soluble and easily excreted. In this phase, glutathione S-transferase (GSTs), UDP-glucuronosyltransferases (UGT), Sulfotransferases (SULT) and N- acetyl-transferase (NAT) enzymes are the main players.[2] In phase 3, conjugates compounds are eliminated extracellularly through membrane transporters, which are proteins with ion and molecule transport function through the cellular membrane.[3] Figure 1 shows a scheme of the cellular metabolism by the action of detoxification enzymes.
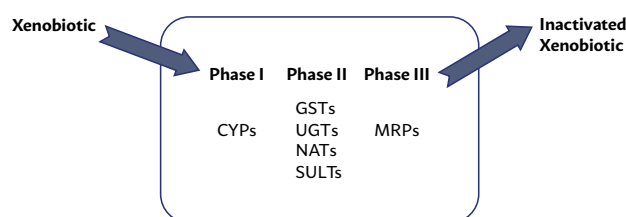
FIGURE 1 Scheme of cellular metabolism by the action of detoxification enzymes. Author: Marcelo S. M. Silva

DETOXIFICATION GENES AND GENETIC POLYMORPHISMS

Detoxification enzymes are proteins produced from the expression of detoxification genes. By default, the gene receives the same acronym of the protein coded by it, however it is written in italic. Polymorphisms in detoxification genes may affect the function of enzymes coded by them, and conse-

quently, the cellular metabolism. Genetic polymorphisms are alterations in the DNA sequence that can increase the organism susceptibility to develop certain diseases. Polymorphisms characterized by the complete deletion of a gene eliminate any functional activity of the enzyme coded by it. On the other hand, polymorphisms that are duplications of a whole gene may result in higher levels of enzymatic activity.[4] There are also replacements of amino acids that originate from the single-nucleotide polymorphisms, better known by the acronym *SNPs*. If the polymorphism is located within the coding region of a gene, there may be the replacement of amino acids in the coded peptide, resulting in protein alterations that may affect the cellular metabolism. An example of that is a single-nucleotide polymorphism that occurs in the apolipoprotein E gene and that is associated with a higher risk for Alzheimer's disease.[5]

POLYMORPHISMS STUDY METHODS

Genetic polymorphisms can be studied through several methods, such as PCR (Polymerase Chain Reaction) DNA amplification, followed by agarose or polyacrylamide gel electrophoresis; DNA sequencing; PCR amplification associated with the use of restriction enzymes (this technique is especially used for *SNPs* investigation), among other methods. In

Figure 2 some methods used for the study of genetic polymorphisms are schematized.

ENVIRONMENTAL FACTORS AND DETOXIFICATION ENZYMES

Environmental factors are biological or non-biological factors found in the environment that affect living organisms. Among the biological factors are the microorganisms, parasites, food consumed, among others. With relation to the non-biological factors (also known as abiotic), there are air and water industrial pollutants, solar radiation, environment temperature, air humidity, etc. In this context, it is important to consider air pollution and its consequence to the populations' health. Both pollution produced by industrial activities and the burning of fuel by transport vehicles, among others, release a variety of toxic compounds in the air. Respiratory diseases, allergies, increased cases of several types of cancer and cardiovascular diseases are among the main health issues that may be caused by the combustion of petroleum products. Among the compounds generated are the nitrogen oxides, particulate matter and ozone.[6]

The influence of environmental factors in the aetiology of several diseases is well known, especially through epidemiologic studies that count on expres-

Biological specimen   **DNA extraction**   **PCR**

Analysis on polyacrylamide gel   **Polyacrylamide gel electrophoresis**
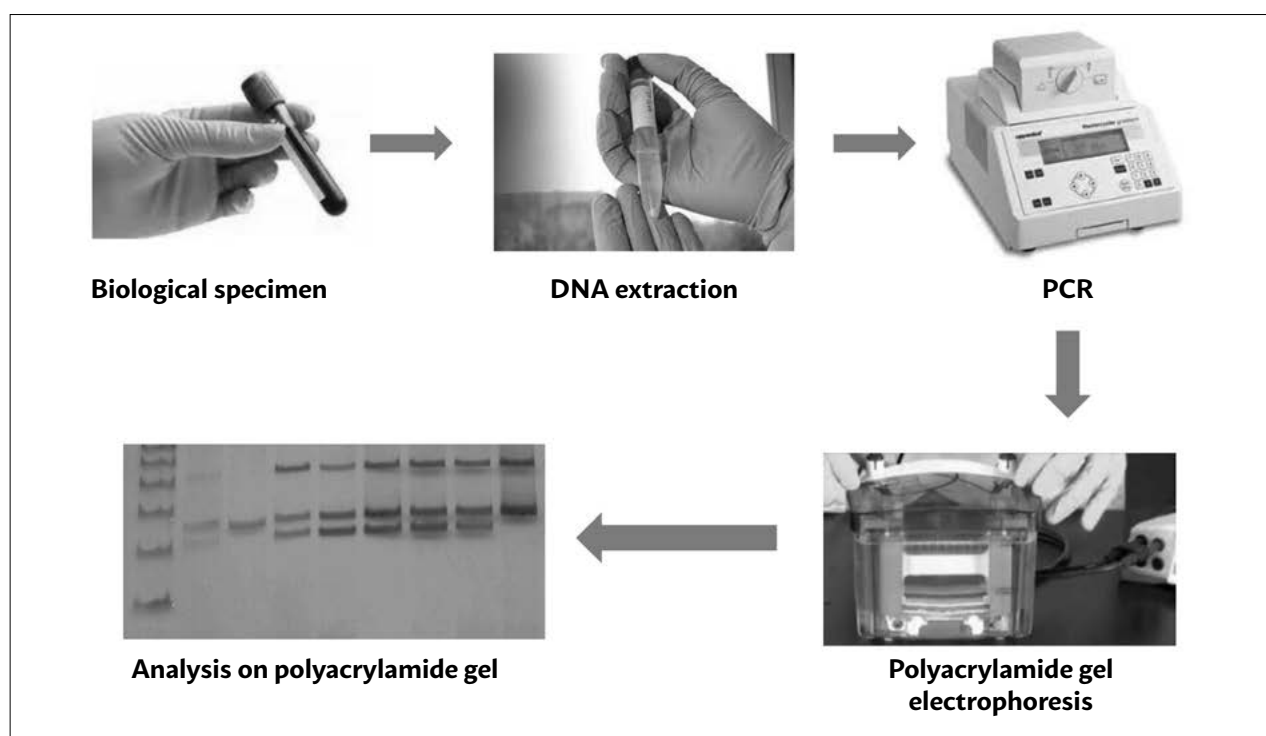
FIGURE 2 Methods of studying genetic polymorphisms. Author: Marcelo S. M. Silva

FIGURE 3 Environmental factors that influence human health. Author: Marcelo S. M. Silva

sive numbers of participants, minimizing possible experimental biases. It can be mentioned as example the association between smoking and lung cancer.[7,8] The close relation between the presence of certain environmental factors and the development of malignant tumours highlights the importance of detoxification enzymes that act to minimize potential damages to the organism. In addition to malignant neoplasia, many other pathologies have been associated to the influence of environmental factors, such as inflammatory bowel disease, respiratory diseases, food poisoning, pesticide poisoning and occupational illnesses. An example of labour disease caused by environmental factor is the green tobacco sickness, which is an acute nicotine poisoning caused by the farmers skin contact with tobacco leaves.[9] Figure 3 shows some environmental factors that affect human health.

The association between detoxification enzymes alterations and the development of some diseases has been investigated in scientific papers. A case-control study carried out in the city of Goiânia with 100 individuals with glaucoma and 52 healthy controls found 84% of a single-nucleotide polymorphism in gene *CYP1A1* (P-oxidase cytochrome A 1) in the glaucoma patients and 46% in healthy individuals.[10] The absence of GSTT1 (glutathione S-transferase theta 1) expression. has been associated in scientific literature with the risk of bladder,[11] oral cavity[12] and lung cancers.[13] A case-control study with 98 participants carried out in Southern Brasil showed the association between the *GSTM1* (glutathione S-transferase mi 1) deletion and the occurrence of breast cancer.[14] A meta-analysis of 23 studies, including 4,065 cases and 5,390 controls, suggested that the *GSTT1* null genotype is associated with the

risk of lung cancer in Asian population.[15] Another meta-analysis including 26,666 cases and 37,210 controls of several ethnicities in different continents suggested that *GSTT1* null genotype is significantly associated with an increased risk of urinary system cancer.[16] An Indian case-control study with 540 participants reported that the *GSTM1* deletion is a decisive risk factor for lung cancer in Northern India population.[17] A meta-analysis with 16 studies, including 3,366 patients and 6,013 controls showed that *GSTT1* null genotype is significantly associated (p < 0.001) with an increased susceptibility to inflammatory bowel disease.[18] A case-control study carried out in South Africa with 202 participants (102 cases and 100 controls) reported association between polymorphisms in genes *GSTM1* and *GSTP1* and coronary artery disease in the studied population.[19]

IMPLICATIONS IN THE DEVELOPMENT OF CANCER AND CHEMORESISTANCE

Articles in scientific literature have addressed the role of detoxification enzymes in chemoresistance.[20,21] For the organism, chemotherapy drugs are xenobiotics and, therefore, must be metabolized and eliminated from the cell. Scientific evidence has established the importance, especially of GSTs, in the patient's response with cancer to the use of chemotherapy. These enzymes are able to metabolize and inactivate anti-cancer agents.[21] GSTP (glutathione S-transferase pi) class is the most abundantly expressed in human cancer and many solid tumours[22] and leukaemia; the high expression of GSTP1 has been associated with chemoresistance, treatment failure and low survival rate of patients.[21]

CONCLUSION

The relevance of detoxification enzymes in processes connected to the metabolism of toxic substances has been confirmed through scientific investigation. The functioning of these enzymes can influence susceptibility to many diseases, as well as resistance to drugs. This knowledge highlights the importance of seeking better understanding, through different types of studies (case-control, meta-analysis, biochemical studies, etc.) of the interaction between environmental factors, detoxification enzymes and health condition of individuals and populations.

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Gluten and Neuroimmunology. Rare association with Myasthenia Gravis and Literature Review

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SUMMARY

As the celiac disease (CD), the non-celiac gluten sensitivity (NCGS) has also been associated with several autoimmune manifestations. It is rarely associated with myasthenia gravis (MG). This paper shall introduce the case of a young female patient, initially presenting a peripheral neuropathy framework. During clinical and neurological follow-up, she began to present symptoms of various immune-mediated morbidities. Diseases related to gluten represent a clinical spectrum of manifestations with a trigger in common, the ingestion of gluten. CD is the most well-known and serious disease of the spectrum, also called gluten-sensitive enteropathy. The NCGS is diagnosed from clinical evidence of improvement in symptoms followed by a Gluten Free Diet (GFD) in patients without signs of enteropathy in duodenal biopsy. There are indications that, although rare, with a prevalence of 1 in 5000, myasthenia gravis (MG) may occur more often when CD is also present. Between 13 to 22% of the patients with MG have a second autoimmune disorder. However, it is often associated with dermatomyositis or polymyositis, lupus erythematosussystemic lupus erythematosus, Addison's disease, Guillain-Barré syndrome and juvenile rheumatoid arthritis. Thus, the symptoms of neuromuscular junction involvement may give a diagnostic evidence of this rare association.

KEYWORDS: Celiac disease. Glutens. Myasthenia gravis. Autoimmune diseases.

INTRODUCTION

Celiac disease (CD) is an autoimmune disorder accompanied by a variety of neurological manifestations. Within its clinical spectrum, there is the non-celiac gluten sensitivity (NCGS), which presents clinical symptoms similar to those of patients with CD, but without histopathological evidence of enteropathy in duodenal biopsy. Both disorders present extra-intestinal autoimmune manifestations. However, it is rarely associated with myasthenia gravis (MG). In this article, we present a case of an NCGS patient, who developed peripheral neuropathy associated to vitamin B12 deficiency, ataxia related to gluten, epilepsy and later Myasthenia Gravis.

CASE

S.V.B., is a 34-year-old female, born in São Paulo, with an incomplete bachelor´s degree in Psychology, and she is a nun. She started presenting distal paresthesia, in all four limbs accompanied by chronic diarrhea, when she was 20 years old, being diagnosed with NCGS. After a year, she started presenting axial and appendicular ataxia in addition to generalized tonic-clonic seizures, and right tactile hypoesthesia. In the Department of Neurology, it was conducted the hypothesis of ataxia related to gluten, epilepsy and secondary peripheral neuropathy due to vitamin B12 deficiency or NCGS. Brain magnetic resonance imaging (MRI) found a cerebellar atrophy, which was

consistent with the clinical picture. After introducing gluten-free diet (GFD) she had partial improvement of neurological and gastrointestinal symptoms. A year ago, she started to present a progressive asthenia, tetraparesia predominantly proximal, dyspnea, dysarthria, diplopia, dysphonia and bilateral palpebral ptosis. Good therapeutic response with pyridostigmine. She was diagnosed with Myasthenia Gravis. She was already using prednisone and azathioprine due to gastrointestinal alterations.

DISCUSSION

Gluten related diseases represent a clinical spectrum of manifestations with a common factor, ingestion of gluten.[1] The most well-known and serious disease of the spectrum is CD, also called gluten-sensitive enteropathy. Diagnosis of NCGS is made from a clinical evidence of improvement in symptoms followed by a DLG in patients without signs of enteropathy in duodenal biopsy.[2] Both DC as SGNC are responsive to DLG, suggesting a similar physio/pathophysiologic mechanisms.[3] The neurological manifestations of DC and SGNC are similar and occur in up to 10% of patients.[3, 4] Among the most common are peripheral neuropathy in 30% of the cases and cerebellar ataxia in 41% (see graph), both probably related to autoimmune involvement.[2]

In this context, peripheral neuropathy is predominantly distal, sensory motor and slowly progressive and symmetrical. It does not have a unique pathophysiological mechanism defined, but it is believed that the lack of vitamins and nutrients is not the sole cause, and may even be a slightly cause in most cases, since most of the patients do not present a serious enteropathy associated with a malabsorption syndrome.[5] In the case presented, there is vitamin B12 deficiency, despite enteropathy absence, that could have contributed to the onset of neuropathy. It is speculated that there must have an overlap of causes associated with pernicious anemia due to refractivity of the case and development of various immune- mediated morbidities. In addition, according to literature, a free malabsorption syndrome occurs in only 30% of untreated patients and it is not severe in patients undergoing regular and good monitoring therapeutic compliance (like the case of our patient). In general, it is a belief that neuropathy must be immune-mediated just as ataxia related to gluten.

Ataxia usually presents insidiously, with an average age of 53 years, with cases reported in pediatric patients. All affected patients have gait ataxia and most predominantly in the lower limbs. Less than 10% will present any gastrointestinal symptom, only 40% will have evidence of enteropathy. Thus, ataxia has similar evolution to dermatitis herpetiformis, which is a skin disease, triggered by gluten, wherein the gastrointestinal symptoms are not very prominent even in the presence of enteropathy.

In imaging studies of the central nervous system, 60% of patients have cerebellar atrophy, but it can be demonstrated abnormalities to spectroscopy with reduced N-acetyl aspartate / creatinine ratio, primarily affecting the cerebellar vermis in all of them. Postmortem studies of these patients reveal a focal degeneration of Purkinge cells through the cerebellar cortex associated with astrocytic gliosis and diffuse infiltration of T-cells in the white matter. Experimental evidences suggest a cross-reactivity between epitopes of Purkinge cells (and other of the granular layer) and gluten peptides. Such cross-reactivity has been attributed to anti-gliadin antibodies, but with increased evidence of associated involvement of anti-transglutaminase antibodies.

Transglutaminase 6 (TG6), expressed in brain tissue, is described as a target antigen in these patients. Anti TG6 autoantibodies are discarded after introducing gluten-free diet. These probably penetrate the central nervous system by reacting with the cell and granular Purkinje after disruption of the blood-brain barrier triggered by perivascular deposits of IgA.[6] The loss of Purkinje cells after prolonged exposure to gluten is irreversible, so that only the early diagnosis and treatment are able to result in stabilization or clinical improvement.[6,7]

There are indications that, although rare, with a prevalence of 1 in 5000, myasthenia gravis (MG) may occur more frequently when CD is also present.[3] The symptoms of neuromuscular junction involvement can give a diagnostic clue of this rare association.[3, 8] About 13 to 22% of MG patients have a second autoimmune disease. However, it is more often associated with Dermatomyositis or polymyositis, lupus erythematosus, Addison disease, Guillain-Barré syndrome and juvenile rheumatoid arthritis.[8] This combination does not change when we conducted studies for patients with or without thymoma. It is worth mentioning that among the three diseases most associated with MG: Dermatomyositis or polymyositis (myopathies Inflammatory Idiopatic), lupus erythematosusSystemic lupus ery-

thematosus and Adison disease, are all regulated by the haplotype HLA-B8-DR3. More genetic studies are necessary to determine if the combination of these conditions is due to heterogeneity between HLA, interaction between not HLA genes or environmental factors. [9]

In addition to the events listed, there is a close relationship between epilepsy and autoimmune diseases.[10, 11] This association seems to be attributed to the inflammatory part in the underlying disease, shown by consistent histopathological findings in refractory patients undergoing surgery.[10,12] A retrospective cohort study using insurance companies data with more than 2.5 million patients, found an increase of 3.8 times in patients with autoimmune diseases. The same study identified a 2.5-fold increase in adults with celiac disease and five times in patients with myasthenia gravis. Such evidences will further produce new therapeutic options.[10]

Most studies of neurological complications with enteropathy are generally related to celiac disease and have highlighted the central nervous system involvement. However, it is known that the association with neuropathy, myopathy, myasthenia gravis, Stiff person Syndrome (SPS) and, more rarely with celiac disease exists.[2, 13]

Holmes[14] conducted a descriptive study where the frequency of neuropathy was 0.5% and 1.3% in myopathy. In all cases, myopathy was a result of osteomalacia, which is today very unusual in celiac disease, and has a good response to treatment with vitamin D and gluten-free diet.[13,14]

A recent study showed inflammatory cell infil-tration in nerve roots of the spinal cord at a patient with celiac disease and polyneuropathy.[15] The largest series were so far related by Hadjivassiliou et al,[16] who described six patients with sensorimotor axonal polyneuropathy (of which two with a pure motor neuropathy), a patient with multiple mononeuropathy and a patient with Guillain-Barre syndrome.

The results of the studies show that polyneuropathy associated with celiac disease is axonal and affects both motor and sensitive fibers, with greater pain and heat if compared to the group of control. This finding provides further evidences that peripheral nerve fibers, even unmyelinated fibers, have been affected in patients with celiac disease.[13,16]

CONCLUSION

There is a significant overlap between autoimmune disorders, reflecting a similar pathological mechanism. In the context of the celiac disease, the role of DLG in the course of autoimmune diseases has been studied and it is related to some neurological improvement or stabilization. However, there is no consensus in literature considering the clinical course of these entities. In this case, we reported a partial clinical improvement of ataxia, neuropathy, and gastrointestinal symptoms, but control of myasthenia is due to the use of immunosuppressive drugs and cholinesterase inhibitors. There are few reports of this association and limited knowledge about them. A better understanding will be crucial for the establishment of more targeted and effective treatments.
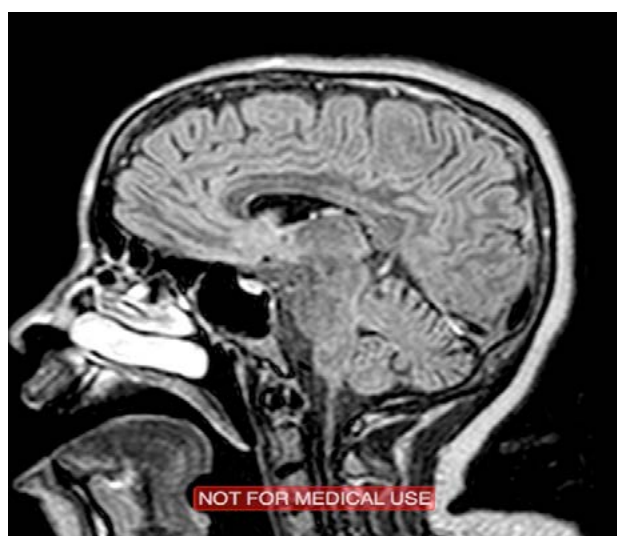
FIGURE 01. MRI Brain: sagittal, respectively, weighted FLAIR and T1 with gadolinium, demonstrating cerebellar atrophy, especially the vermis.

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Exuberant keloid scar associated with skin neoplasia

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INTRODUCTION

Scaring is a complex process that results in the formation of a new tissue for repair of a continuity solution.[1] When there is fibroblast hyperplasia with consequent hyperproduction of collagen fibres, this tissue neoformation becomes elevated and extends laterally in relation to the initial margins of the lesion, characterizing what we called keloid. Additionally, the lesions have variable coloration and continuous or intermittent growth and do not present spontaneous regression, in addition to having a tendency to relapse after drying.[2]

Chronic scaring process like keloid, resulting from the chronic skin inflamation,[3] are mentioned as predisposing factors for the formation of skin neoplasia, with squamous cell carcinoma and the basal cell carcinoma.[4]

We reported an exuberant keloid scar condition associated to lesions of squamous cell carcinoma and basal cell carcinoma in melanodermic patients.

CASE

68-year old melanodermic male patient sought the dermatology department complaining about scars throughout his body associated with vegetative lesion with progressive growth on the scalp with 5-month evolution and ulcerated lesion on the front thorax with 3-year evolution. During the dermatologic exam, he presented extensive keloid lesions that covered most of his body, especially the torso, upper limbs and scalp (FIGURE 1), in addition to an ulcerous-vegetative lesion with approximately 20 cm in diameter in the right occipital region (FIGURE 2) and ulcerated lesion with high and darkened edges on the left hemithorax (FIGURE 3). He reported that the lesions started in his childhood and since he lives in the rural area, he only had access to healthcare services later on, when lesions were already extensive. He claims they were a result of small traumas such as scratches, cuts, and that some of them appeared without any previous perceptive trauma. Some were previously treated with corticoid intralesional injection, as well as surgeries, without any improvement, and that they aggravated the scaring process. He denied any previous pathologies and expressed social limitation due to the unaesthetic character of the lesions.

Biopsies done in the scalp and front thorax lesions indicated, respectively, non-invasive ulcerated moderately differentiated squamous cell carcinoma and nodular basal cell carcinoma. The patient was then referred to the reference centre for treatment of neoplasia with surgical approach of the lesions.
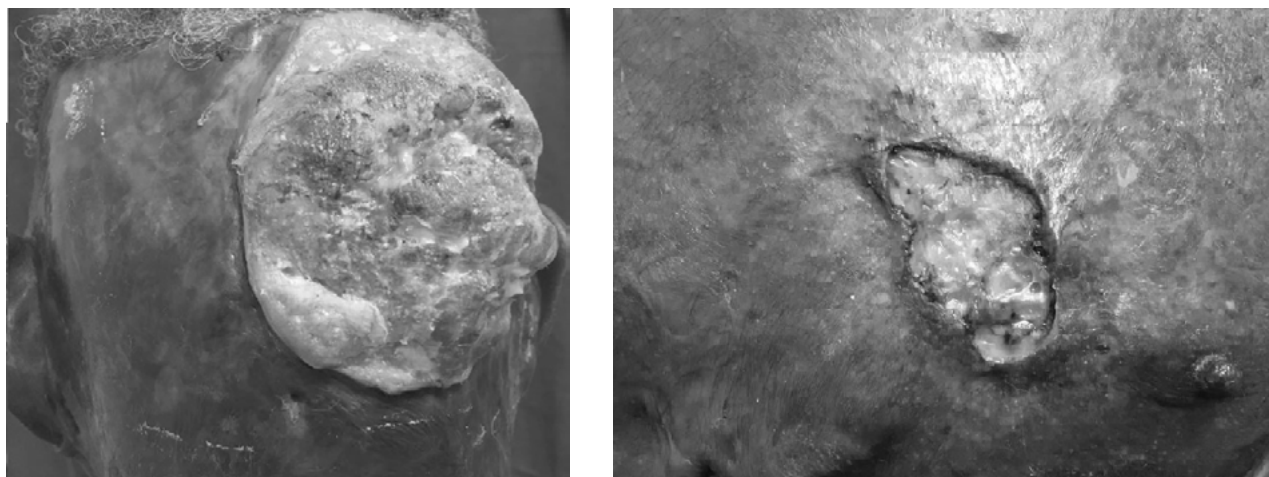
FIGURE 1

FIGURE 2 AND FIGURE 3

DISCUSSION

The scaring of lesions is a dynamic process that leads to the repair or regeneration of tissues in three main phases: inflammatory phase, proliferative phase and remodelling phase.[5] This complex cascade of physiological events involves the integrated action of different cells, cytokines and extracellular matrix. The keloid scar or simply keloid is a fibroproliferative dermic tumour that develops as a result of alterations in this scaring process.[6]

Lesions can affect all ethnical groups; however, they present preponderance in Africans, Asians and dark-skin individuals in general. The most common places affected are the presternal area, back, posterior cervical region, deltoid region and pinna. The disease has a familiar characteristic with little clarified mechanism; however, a recessive autosomal inheritance has been proposed.[1] Some family syndromes like Rubinstein-Taybi Syndrome, Goeminne Syndrome and Conjunctival-Corneal Dystrophy are associated with exuberant conditions of keloid scars often resulting from small trauma[7], as presented by our patient. However, he denied having knowledge of similar condition in family members, in addition to not presenting characteristics for such syndromes. Other differential diagnostics, like Jorge Lobo disease and paracoccidioidomycosis may also manifest with keloid lesions, vegetative lesions and ulcerations.[8,9] Different from the observed in this case, lesions in the Lacaziosis presented erythematous-greyish colour, smooth and glossy surface with telangiectasia, affecting especially lower limbs and ear pinna[8]. As for the skin form of the paracoccidioidomycosis, it initially manifests in the papulopustulosa form or acneiform, and later on evolves to the ulcerated or

ulcerous-vegetative form[9], a morphologic evolution that was not described in the case presented.

The squamous cell carcinoma, an atypical proliferation of cells from the epidermis spinous layer, is the most frequent skin neoplasia in black people, representing 30% of the cancers. As for the basal cell carcinoma, it is the second skin most frequent cancer on black skin: only about 1.8% of the BCC cases affect black individuals. And among the risk factors, in these cases, are the chronic scaring processes.[4]

Despite numerous studies on the scaring process, no uniting hypothesis properly explains the formation of keloids. The numerous modalities of treatments implemented for handling keloids highlight the poor understanding of their pathogenesis.[10] The therapeutic approach is difficult, and becomes extremely complex in cases of extensive lesions and further associated with neoplasia. As well as in the entire medical area, prevention becomes more important than the treatment itself. However, in the impossibility of preventing all cases, knowing the pathology, its variants, as well as possible neoplasia associated, is necessary for the early decision of the best therapeutic treatment and consequent improvement of the patient's quality of life.

PALAVRAS-CHAVE: *Queloide. Cicatriz. Neoplasias cutâneas.*

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Intensity-modulated radiation therapy (IMRT) versus 3-dimensional conformal radiation therapy (3D-CRT) for head and neck cancer: cost-effectiveness analysis

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SUMMARY

BACKGROUND: *A cost-effectiveness analysis of IMRT compared to 3D-CRT for head and neck cancer patients (HNCPs) was conducted in the Brazilian Public Health System.*

METHODS: *A Markov model was used to simulate radiation therapy-induced dysphagia and xerostomia in HNCPs. Data from the PARSPORT trial and the quality-of-life study were used as parameters. The incremental cost-effectiveness ratio (ICER) and cost per quality-adjusted life-year (QALY) gained were calculated.*

RESULTS: *At 2 years, IMRT was associated with an incremental benefit of 0.16 QALYs gained per person, resulting in an ICER of BRL 31,579 per QALY gained. IMRT was considered cost-effective when using the guideline proposed by the World Health Organization (WHO) of three times the national gross domestic product (GDP) per capita (BRL 72,195). Regarding life expectancy (15 years), the incremental benefit of IMRT was 1.16 QALYs gained per person, with an ICER of BRL 4,341. IMRT was also cost-effective using the WHO definition, which states that the maximum cost is equal to the GDP per capita (BRL 24,065).*

CONCLUSIONS: *IMRT was considered cost-effective from the perspective of the Brazilian public health system.*

KEYWORDS: *Head and neck neoplasms. Radiotherapy, intensity-modulated. Radiotherapy, conformal. Cost-benefit analysis.*

INTRODUCTION

The capacity to accurately deliver high doses of radiation to a tumor while reducing the radiation exposure to the neighboring normal tissues has been made possible by the intensity-modulated radiation therapy (IMRT) technique[1, 2]. The advantages of IMRT over 3-dimensional conformal radiation therapy (3D-CRT) include its steeper dose gradient and a more conformal dose delivery[3, 4].

IMRT has been widely used in recent years for the treatment of locally advanced head and neck cancer patients (HNCPs)[5]. Several randomized trials[6-10] and a meta-analysis[11] have confirmed that IMRT has substantial benefits not only related to dosimetric issues but also in terms of reduced treatment toxicity for HNCPs. Specifically, IMRT is associated with less severe xerostomia, dysphagia, acute and late hearing loss, cervical fibrosis and trismus, but it does not compromise local tumor control or overall survival[12, 13].

However, IMRT is challenging due to the complexi-

ty of planning. To ensure secure and satisfactory treatment, additional clinician effort is required to delineate all volumes of interest, and extra time is needed for physicists to provide the more complex quality assurance associated with this method, which increases the apparent incremental costs of IMRT[14, 15].

While IMRT is currently the standard technique for treatment of locally advanced HNCPs, a comparison of the health economic value of IMRT versus 3D-CRT is needed to determine the economic feasibility of this practice, especially in developing countries[16]. The aim of this study, therefore, was to perform a cost-effectiveness analysis of IMRT compared to 3D-CRT for HNCPs in the Brazilian Public Health System.

METHODS AND MATERIALS

Model structure

The perspective of the Brazilian Public Health System was considered. The model structures adopted were similar to that reported by Kohler et al.[17]. A Markov model was used to assess the radiation toxicities (xerostomia and dysphagia) that developed in HNCPs treated with IMRT or 3D-CRT (Figure 1). The starting patient age for our hypothetical cohort was 57 years (corresponding to the mean age of PARSPORT trial[8] patients). The model calculated quality-adjusted life-years (QALYs) and costs associated with the IMRT and 3D-CRT techniques.

The model is based on six states of health, including four combinations of different toxicities (dysphagia and xerostomia), loss to follow-up and death (Figure 1).

Some basic assumptions were formulated for the analyses in this study:

- Xerostomia and dysphagia were dichotomized into severe (grade ≥ 2) and mild (grade 0-1),

based on the PARSPORT trial[8], creating four states of health (1 - low xerostomia/low dysphagia; 2 - low xerostomia/high dysphagia; 3 - high xerostomia/low dysphagia; 4 - high xerostomia/ high dysphagia);
- Overall survival and disease free survival were considered equivalent with regard to radiation therapy techniques (IMRT and 3D-CRT);
- After the second year, patients remain in the same state of health until the end of life;
- It was estimated that 24% of patients would die by the end of 2 years based on the PARSPORT trial[8]; and
- We only considered the cost of radiation therapy. Costs related to dysphagia and xerostomia events could not be calculated.

Health state utility values

Utility values were used to quantify a patient's quality of life related to the disease burden. A utility of zero indicates patient death, while a utility of one represents a patient in full health. Utilities were used for patient health conditions, and their values were combined for dysphagia and xerostomia. The data were obtained from a quality of life study with 396 HNCPs[18] (- Supplementary material 1.).

Treatment costs (IMRT and 3D-CRT)

The 3D-CRT costs are displayed in Supplementary material 2. IMRT is not recognized or permitted in the Brazilian Public Health System. Thus, the IMRT costs for head and neck cancer were estimated based on the opinions of Brazilian Society for Radiation Oncology expert members considering the public health scenario and a relative proportion of 3D-CRT costs.

The IMRT costs were estimated based on following
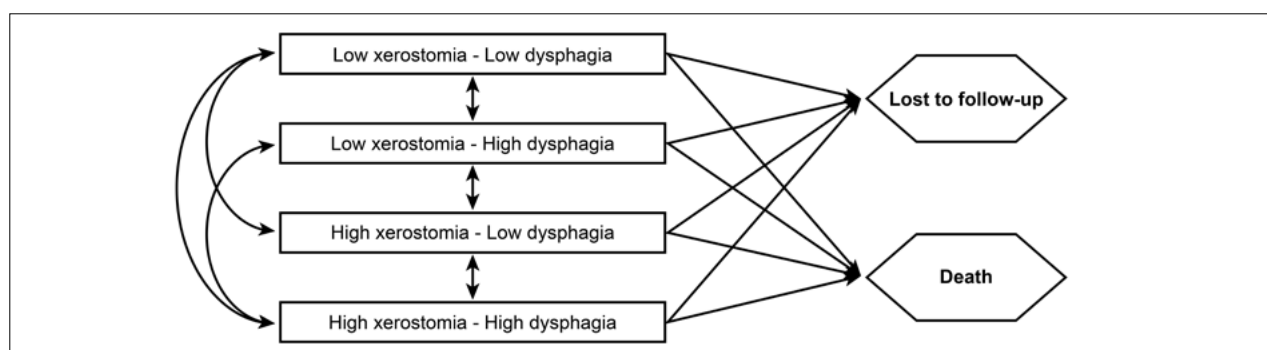
FIGURE 1 – Markov model – Health states. Representation of a Markov model for dysphagia and xerostomia progression of HNCP treated with radiation therapy. Patients might change between health states, become lost to follow-up, or die at each 6-month interval (adapted from Kohler et al. [14]).

items: physician consult, CT simulation, IMRT mask, IMRT planning, IMRT collimator base, port film and nurse consult. A preliminary cost consult in the Brazilian private hospitals that use IMRT for the treatment of HNCPs was performed, and the costs were adapted to the Brazilian Public Health System context. The total IMRT estimated cost was BRL 10,000.

Cost-effectiveness analysis

The comparative results of treatment modalities were measured using an incremental cost-effectiveness ratio (ICER). The ICER describes the cost per QALY gained by one technique compared to another to determine the relative value. The relative value of each radiation therapy technique was calculated using the ICER. The cost-effectiveness analyses were performed in two scenarios; first, patients were followed for a period of two years (the period used by the PARSPORT trial [8]); second, patients were followed for a lifetime period (equivalent to 15 years). The projection over a horizon time of more than 2 years considered that the transition probability of death would be the same from 24 months to the end of the model. The premise of transition probabilities equal to those adopted at 24 months for the remainder of the time horizon (15 years) is based on the results of large observational studies and randomized clinical trials suggesting that after 12-18 months of follow-up, no significant improvement or worsening of the incidence of adverse events is observed [8, 19, 20].

The World Health Organization (WHO) definition for cost-effectiveness assessment was adopted [21].

Sensitivity analyses

Sensitivity analyses were performed to assess overall uncertainty in the outcomes measures. Therefore, it was possible to evaluate how the ICERs were influenced by the adopted assumptions. Univariate and probabilistic sensitivity analyses were performed.

Univariate sensitivity analyses consider variations of a single parameter while other parameters remain constant. In this case, the critical parameters were varied from the base value to the limit values (Supplementary material 3).

Probabilistic sensitivity analyses vary several parameters simultaneously. These analyses simulate a random draw from pre-specified statistical allocations of all input parameters to create a range of potential ICER values. They were calculated with 1,000 itera-

tions. The results were evaluated and classified as follows: Quadrant 1 (incremental effectiveness > 0 and incremental cost > 0); Quadrant 2 (incremental effectiveness < 0 and incremental cost > 0); Quadrant 3 (incremental effectiveness < 0 and incremental cost < 0) and Quadrant 4 (incremental effectiveness > 0 and incremental cost < 0) - Supplementary material 4.

Health state transition probabilities were based on numerous time points of the PARSPORT trial [8] (Supplementary material 5).

RESULTS

The results of the cost-effectiveness analyses are displayed in Table 1. The patient age value was varied in the sensitivity analysis, but significant changes in the final results were not found in the base scenario.

At 2 years, IMRT was associated with an incremental benefit of 0.16 QALYs gained per person, resulting in an ICER of BRL 31,579 per QALY gained compared to 3D-CRT. IMRT was considered cost-effective when using the definition proposed by the WHO, of three times the national gross domestic product (GDP) per capita, which is equivalent to BRL 72,195.

Regarding the lifetime value, the incremental benefit of IMRT was 1.16 QALYs gained per person with an ICER of R$4,341. IMRT was also cost-effective according to the WHO definition of a maximum cost equal to the GDP per capita, which is equivalent to BRL 24,065.

The univariate sensitivity analyses showed that the variables with the greatest effect on the results were utility low xerostomia/low dysphagia (ICER range BRL 25,418 to BRL 36,917); 3D-CRT cost (ICER range BRL 28,483 to BRL 34,674); utility high xerostomia/low dysphagia (ICER range BRL 30.733 to BRL 33.404); utility high xerostomia/high dysphagia (ICER range
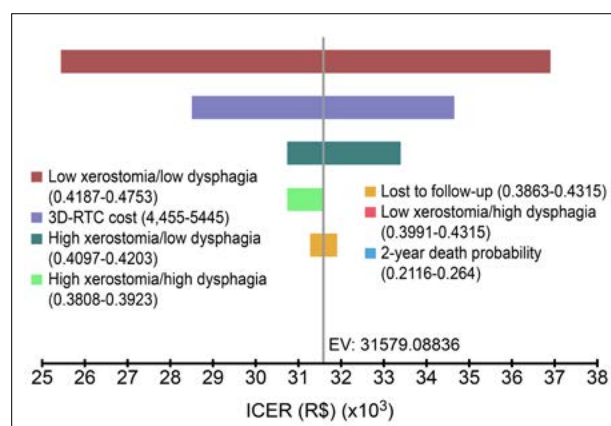
FIGURE 2 – Univariate sensitivity analyses.

BRL 30.731 to BRL 31.579); and utility lost to follow-up (ICER range BRL 31.267 to 31.579) (Figure 2).

The probabilistic sensitivity analyses are presented in Supplementary material 6. A total of 99.1% of results remained in quadrant 1, representing incremental results with greater effectiveness and incremental cost. In addition, approximately 90% of the iterations were below the maximum cost of BRL 72,195.

DISCUSSION

Much effort has been employed to improve HNCP outcomes, especially for locally advanced disease. Different protocols have been attempted to intensify the treatment using induction chemotherapy[22, 23] and/or more advanced surgical techniques[24]. Similarly, IMRT is an advance that has been rapidly implemented for the management of HNCPs worldwide. Based on available evidence from randomized phase III trials[6-10] and a meta-analysis[11], compared to conventional radiation therapy or 3D-CRT, IMRT is associated with less toxicity and improved quality of life without compromising local control and overall survival rates. Nevertheless, this benefit might not balance the higher costs associated with IMRT[25].

In the present cost-effectiveness analyses in the Brazilian Public Health System context, a Markov model was used to evaluate IMRT versus 3D-CRT. IMRT was considered cost-effective for 2 and 15 years of treatment, resulting in ICER values of BRL 31,579 and BRL 4,341 per QALY gained, respectively. These results are relevant because they demonstrate that IMRT is cost-effective during the first 2 years and after long-term follow-up. The sensitivity analyses confirmed that IMRT remains cost-effective.

Other studies have shown similar results. Yong et al.[26] compared the cost-effectiveness of IMRT with 3D-CRT for the treatment of oropharyngeal tumors from the perspective of the Canadian Ministry of Health. IMRT resulted in a gain of 0.48 more QALYs at an extra cost of $2,447, resulting in an ICER of $5,084

per QALY gained. The number of IMRT treatments needed to avoid long-term severe xerostomia was less than 2, resulting in an incremental cost of $4,532, which showed that compared with 3D-CRT, IMRT was cost-effective. Similarly, Kohler et al.[17] performed a cost-effectiveness analysis of IMRT and 3D-CRT from the US health care cost perspective (Medicare). Less than $50,000 per QALY gained was considered cost-effective. In the first 2 years after treatment, IMRT was not considered cost-effective (ICER of $101,100 per QALY gained). However, over a lifetime (15 years), IMRT was considered cost-effective ($34,523 per QALY gained). Of note, in the Yong et al.[26] study, data from a nasopharyngeal trial[6] were used to calculate health state utilities and simulate oropharyngeal cancer patients. Moreover, short-term transitions among toxicity health states were not assessed. Our model is similar to that used in the study by Kohler et al.[17]; different health states reflected diverse stages of dysphagia and xerostomia and distinguished the severity of each disease over time according to the radiation therapy techniques adopted. Thus, this model is a more complete evaluation of the value of IMRT over a range of radiation-induced side effects.

Though not directly evaluated in our study, other benefits of IMRT can result in more robust cost-effectiveness results of IMRT. The longer treatment time of IMRT with the *step and shoot* technique was overcome using IMRT with volumetric modulated arc therapy (VMAT)[27]. VMAT can minimize the radiation delivery period, resulting in a reduced treatment time. Therefore, the cost of IMRT could possibly be decreased with VMAT. Furthermore, long-term costs related to toxicities, such as extra support care and dental assistance, were not considered in our study. Decreases in long-term high-grade dysphagia and xerostomia might translate into lower toxicity-associated costs for HNCPs who receive IMRT rather than 3D-CRT. Hence, HNCPs treated with IMRT would likely have a reduced need for dental care and treatment for xerostomia and dysphagia[28]. This result is

TABLE 1. COST-EFFECTIVENESS ANALYSES – MARKOV MODEL

	2 years			Lifetime (15 years)		
	IMRT	3D - CRT	Incremental	IMRT	3D - CRT	Incremental
Cost per person (R$)	10,000	4,950	5,050	10,000	4,950	5,050
QALYs per person	2.03	1.87	0.16	7.53	6.37	1.16
ICER (R$)		31,579			4,341	

Note: IMRT = intensity modulated radiation therapy; 3D-CRT = conformal radiation therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life; R$ = real.

mainly relevant for the group of patients with a better prognosis and higher overall survival rates, such as those with human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma[29].

It is important to highlight that the costs related to dysphagia and xerostomia could not be calculated in the present study for methodological reasons. Since our analysis aimed to assess the incorporation of IMRT in the Brazilian Health System, the priority of cost estimation was given to national sources. The main source of costs for our analysis is available on DATASUS (*http://datasus.saude.gov.br*). The DATASUS database is used by the Brazilian Federal Government for the reimbursement of public service procedures. In this context, it is not possible to determine a causal relationship between 3D-CRT/IMRT and a need for one of the interventions due to limitations related to patient monitoring and follow-up in the DATASUS system. The inclusion of these costs would clearly make the scenario more favorable to IMRT. However, the non-inclusion of adverse event (dysphagia and xerostomia) costs would make the scenario more conservative. Thus, this study reflected a lower probability of having an overestimated outcome in relation to the economic gains that could be achieved by IMRT incorporation into the Brazilian Health System.

One limitation of our study is that data from patients in the United Kingdom were used[8, 18] because data on radiation toxicities in the Brazilian population are limited. A complete study would include long-term cost and quality of life data in a study of Brazilian HNCPs receiving radiation therapy via different techniques. Hence, it is unknown whether the treatment outcomes would significantly diverge within the Brazilian population in the Public Health System context. Another limitation is that chemotherapy was not officially included in our model. It is important to recognize that our data included patients who did or did not receive concurrent chemotherapy. Therefore, the actual effect on the long-term toxicity of concurrent chemotherapy in HNCPs treated with IMRT or 3D-CRT remains unclear. The last limitation is related to the 3D-CRT and IMRT costs. All cost-effectiveness analyses were performed based on the current and outdated Brazilian Public Health System table of costs (no cost adjustments have been made since 2010). Thus, the costs of 3D-CRT and IMRT are both underestimated.

CONCLUSION

In conclusion, IMRT was considered cost-effective from the perspective of the Brazilian Public Health System. The reductions in high-grade dysphagia and xerostomia made IMRT cost-effective at two years and in the long-term. These results could help to support the implementation of IMRT in Brazilian Public Health Centers.

RESUMO

INTRODUÇÃO: *Foi realizada uma análise de custo-efetividade da radioterapia com intensidade modulada de feixe (IMRT) comparada com a radioterapia conformada para pacientes com câncer de cabeça e pescoço (CCP) no contexto do Sistema Único de Saúde (SUS).*

MÉTODOS: *Foi elaborado um modelo de Markov para comparar os custos médicos diretos e os desfechos de saúde relacionados à qualidade de vida do paciente pós-intervenção radioterápica sofrendo de xerostomia e disfagia. Com essa finalidade, foram usados os dados do estudo PARSPORT e parâmetros de qualidade de vida. Os resultados comparativos das estratégias alternativas de tratamento foram medidos pela razão de custo-efetividade incremental (RCEI). O desfecho analisado foi o de anos de vida ajustados à qualidade (QALY).*

RESULTADOS: *Em um horizonte de tempo de dois anos, a IMRT foi associada com um benefício incremental de ganho de 0,16 QALYs por indivíduo, resultando em um RCEI de R$ 31.579 por QALY ganho. A IMRT foi custo-efetivo, adotando-se o limite máximo de disposição a pagar, proposto pela OMS, de três vezes o PIB per capita nacional, equivalente a R$ 72.195. No horizonte de tempo de 15 anos, o benefício incremental de ganho foi de 1,16 QALYs por indivíduo, com um RCEI de R$ 4.341. A IMRT foi custo-efetivo, adotando-se o limite de disposição a pagar, proposto pela OMS, de uma vez o PIB per capita nacional, equivalente a R$ 24.065.*

CONCLUSÃO: *A IMRT foi considerada um tratamento custo-efetivo na perspectiva do SUS.*

PALAVRAS-CHAVE: *Neoplasias de cabeça e pescoço. Radioterapia de intensidade modulada. Radioterapia conformada. Custo-efetividade.*

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The influence of heel height related on quality of life on the foot in a sample of women

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SUMMARY

Many women have worn high-heel shoes (HHS) at some point in their lives and many wear them on a daily basis, with higher prevalence between 39% and 78% observed in institutional and clinical settings. The purpose of this study was to describe and compare the scores obtained with regard to foot health and health in general in a sample of women that use HHS as opposed to a sample of women without HHS with normalized reference values. A sample of 120 participants with a mean age of 41.94 ± 13.912 came to a health center where self-reported data were registered. The subjects with and without HHS were determined and the scores obtained were compared in the Foot Health Status Questionnaire (FHSQ). This questionnaire is made of 13 questions that assess 4 health domains of the feet, namely pain, function, general health and footwear. The women in the HHS group showed a worse quality of life related to health in general and to foot health specifically. Differences between the two groups were evaluated by means of a t-test for independent samples, showing statistical significance (P<0.01). Women with HHS present a negative impact on the quality of life related to foot health.

KEYWORDS: Foot deformities. Foot diseases. Quality of life. Shoes.

INTRODUCTION

Many women have worn high-heel shoes (HHS) at some point in their lives and many wear them daily basis,[1,2] with higher prevalence between 39% and 78 % observed in institutional and clinical settings[3,4] and representing a huge proportion of the female population.

The increasing popularity of HHS include present day fashion,[5] part of the professional attire,[6] social events,[3] personal expression,[7] source of authority,[8] sexual independence,[9] mark of flaunted femininity,[10] psychological empowerment and joy.[11]

However, there are consequent negative side effects, such as foot problems,[12] sprained ankles,[13] lower back pain,[14] leg disorders,[15] hip pain,[16] knee pain,[17] walking instability,[18] a high risk of falls[19] and venous disease symptoms.[20]

Also, walking in HHS causes many orthopedic conditions (e.g., blisters, bunions, hallux valgus, hyperkeratotic lesions, lesser toe deformities).[21,22]

This kind of disorders represent an important public health issue[22] and have an important economic impact[23] to the affected work and personal activity as it happens to women,[23] all of which can severely impact autonomy, welfare and loss of quality of life.[24]

Despite this, up until now, there are no studies – that have been able to analyze the quality of life related to foot health in women that wear HHS.

Based on this background and taking into account the existence of unmet care and follow-up care of feet, the purpose of this study was to describe and compare the scores obtained with regard to foot health and health in general in a sample of women that wear HHS as opposed to a sample of women without HHS with normalized reference values.

METHODS
Design and Sample

The overall study was completed in 18 months, from January 2014 to June 2015. The study was carried out among women who have been seen at the Clinic of Podiatric Medicine and Surgery, a facility that provides treatment of diseases and disorders of the foot at the University of A Coruña in the city of Ferrol (Spain).

It was a cross sectional study. Data was collected through a randomized sampling method, the criterion for inclusion being between 18 and 65 years old. All of the participants spent the same amount of time walking at the day, including after-work and weekend. The exclusion criterion was a recent history of ankle injury, including sprain, tendinitis, or any muscular pathology in the lower extremity, as well as those who refused to sign the consent form or were incapable of understanding the instructions necessary to carry out the present study. None of the participants had a neurologic condition affecting the lower limbs.[25-27]

Sample size

Having established a minimal difference score of at least 21 (as clinically relevant) among the groups under study in the FHSQ, and considering that the standard deviation on that scale for the people is around 29[28,29] for a bilateral hypothesis, an alpha risk of 5% and a statistical power of 80%, and a beta error of 20%, at least 47 cases must be studied in each group (n=94).

Procedure

At enrolment, patients were interviewed about general health, demographic characteristics (age and gender) and frequency with which they wore HHS. A single trained examiner performed a standardized clinical exam on all participants measuring height and weight with the subjects barefoot and wearing light clothing. The body mass index (BMI) was calculated from the height (m) and weight (kg²), applying the Quetelet's equation BMI=weight / height².[30]

Then, a measuring tape was used to determine the height of the heel. It was measured vertically from the floor to the top of the heel at the back, including the top piece. The instrument classified the shoes in two groups: with HHS (>3 cm) and without HHS (< 3 cm). Studies have shown that the discomfort increases with the heel height and that a heel height >3 might have adverse effects on the body.[31,32]

Lastly, participants' informants filled out the *Foot Health Status Questionnaire* (FHSQ). This self-administered questionnaire on health-related quality of life is intended specifically for the foot which is recognized as a valid test.[33,34] Foot-specific and general health-related quality of life was assessed by using the Foot Health Status Questionnaire (version 1.03),[35] which comprises three main sections. Section 1 consists of 13 questions reflecting four foot health-related domains (Table 1): foot pain, foot function, footwear, and general foot health. This section has demonstrated a high degree of content, criterion, and construct validity (Cronbach α= 0.89–0.95) and high retest reliability (intraclass correlation coefficient = 0.74–0.92),[36] and it has been shown to be the most appropriate measure of health-related quality of life for women that use high heeled shoes population.[37]

Each domain has a specific number of questions. Four regarding pain, 4 on function, 3 on footwear and 2 on general foot health. The assessment of pain and function is based on physical phenomena; the evaluation of footwear uses practical aspects related to availability and the comfort of the shoes, while the perception of the foot's general health is based on the patients' self-assessment of the state of their feet. Each question allows several answers and these are placed on a Likert-type ordinal scale (words or phrases corresponding to a numeric scale). The descriptors for these scales vary for each domain and the person completing the questionnaire has to choose only one response, whichever is thought to be the most appropriate. The questionnaire does not provide a global score, but rather generates an index for each domain. In order to obtain these indices, the responses are analyzed by a computer program (The FHSQ, Version 1.03) which, after processing the data, gives a score ranging from 0 to 100. A 0 score represents the worst state of health for the foot and 100 is the best possible condition. Furthermore, the software also provides graphical images of the outcomes.

Section 2 includes questions that reflect four general health-related domains: general health, physical activity, social capacity, and vigor. The domains and questions in this section are largely adapted from the Medical Outcomes Study 36-Item Short-Form Health Survey,[38] which has been validated for use in the Australian population.[39]

Section 3 collects socioeconomic status, comorbidity, service utilization and satisfaction informa-

tion and their medical record. This study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (STROBE).[40]

ETHICAL CONSIDERATIONS

This research was approved by the Research Ethics Committee at the University of A Coruña (Spain). All participants gave informed written consent before being included, and the ethical standards in human experimentation contained in the WMA Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine, the UNESCO Universal Declaration on the Human Genome and Human Rights and those of the relevant national bodies and institutions were observed at all times.

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM SPSS Statistics 19.0, Chicago, IL, USA for Windows. Qualitative variables are shown as absolute values and percentages, whilst the quantitative variables described are the mean, median, standard deviation (SD) and maximum and minimum values.

The Kolmogorov-Smirnov test was used to test the normality of the data and were considered normally distributed if $p > 0.05$. The results of these tests indicated that the data were normally distributed and that parametric statistical tests were most appropriate. Independent Student t tests were performed to determine whether there were statistically significant differences in all variables between the two groups.

The Foot Health Status Questionnaire Version 1.03 was used to obtain quality of life scores related to foot health. In all of the analyses, $P < 0.01$ (with a 99% confidence interval) was considered statistically significant. Data analysis was conducted with SPSS software, version 19.0 (SPSS Science, Chicago, Illinois).

RESULTS
Sample characteristics

A total of 120 women completed all stages of the research process. The mean age was 41.94 ± 13.91 years (range 18 to 65) for total population and in table 5 the clinical and sociodemographic characteristics of the participants are showed informants. As can be seen, is relevant that most informants are overweight (BMI = 25.45 ± 4.51 kg/m²). No statistically significant differences were found between the two groups for participant age, height, weight and BMI ($P > 0.01$). The results for the variables measured are shown in Table 1.

In what regards the comparison of the scores obtained with the FHSQ, results appear on Table 2. These scores were lower for the group of women that use HHS, both in the first section of the questionnaire, which assesses the informants' quality of life related specifically to foot health, and in the second section, which assesses the informants' health in general related informants without HHS, with normalized reference values,

The differences between the two groups were statistically significant ($p < 0.05$) for those dimensions in the questionnaire which assessed foot pain and general foot health.

TABLE 1 – SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE SAMPLE POPULATION

	Total Group Mean ± SD Range N= 120	Heel height shoes Mean ± SD Range N= 60	No Heel height shoes Mean ± SD Range N= 60	P Value
Age, years	41.94 ± 13.91 (18-65)	41.25 ± 11.99 (18-63)	42.63 ± 15.66 (20-65)	0.588
Weight (kg)	67.27 ± 12.67 (45-110)	66.05 ± 12.65 (45-110)	68.49 ± 12.67 (48-110)	0.294
Height (cm)	162.49 ± 6.45 (150-176)	163.38 ± 6.225 (150-176)	161.60 ± 6.61 (150-174)	0.130
BMI (kg/m2)	25.45 ± 4.51 (18.66 – 42.97)	24.71 ± 4.52 (18.66 – 41.91)	26.18± 4.42 (19.16 – 42.97)	0.074

Abbreviations: BMI, body mass index; SD, standard deviation. In all the analyses, P < .01 (with a 99% confidence interval) was considered statistically significant. P-values are from Independent student t-test.

DISCUSSION

The purpose of this study was to describe and compare the scores obtained with regard to foot health and health in general in a sample of women that use HHS as opposed to a sample of women without HHS with normalized reference values.

Women people are the predominate wearers of HHS, and the gender that have the highest rate of lower limb health problems, painful and disabling conditions.[41, 42] Although none has focused on the relationships HHS and quality of life related to foot health.

The study outlined in this protocol is, therefore, novel in that it targets a HHS used by those females that spent the same amount of time walking at the day, including after-work and weekend. In our study, participants with HHS present lower scores in quality of life related to health in general on all the dimensions related to foot health specifically: foot pain, foot function, footwear and general foot health and in general on all the dimensions related to general health, physical activity, social capacity and vigor than women without HHS with normalized reference values. Our results are in line with a systematic review of Barnish et al indicating that HHS and musculoskeletal injuries has been strongly associated with poor foot health.[43]

However, our findings need to be interpreted in the context of several methodological limitations that should be acknowledged. First this research excluded people who required custom shoes or custom inserts. Second, our footwear assessment tool was limited to one key feature: HHS and no other characteristics of shoe toe-box shape. Third, a larger and more diverse (individuals from various countries) sample size would be beneficial to improve the strength of the study. Fourth, expanding data collection to other countries may help to identify if there is a culture where this association does not exist and identify the mechanisms involved.

This highlights the need for further research on the presence and severity of HHS and how it influences on the foot in order to improve women's health, quality of life and autonomy. The longitudinal cohort studies may be useful to study the shoes heel effect along the time.

CONCLUSION

This study provides evidence that women who wear HHS have a negative impact on the quality of life regarding foot health. These findings suggest that advising women to minimize their use of HHS may have long-term benefits on general health, and this could be investigated in future studies.

TABLE 2 - FHSQ MEAN SCORES FOR THE CASE AND CONTROL GROUPS.

	Total Group Mean (SD) Range N = 120	Heel height shoes Mean (SD) Range N = 60	No Heel height shoes Mean (SD) Range N = 60	P Value
Foot Pain	71.93 ± 21.39 (0-100)	65.86 ± 22.76 (0-100)	78.00 ± 18.17 (19-100)	0.001
Foot Function	76.56 ± 27.98 (0-100)	66.46 ± 32.19 (0-100)	86.67 ± 18.32 (0-100)	0.001
Footwear	51.46 ± 31.33 (0-100)	45.42 ± 31.12 (0-100)	57.50 ± 30.63 (0-100)	0.034
General Foot Health	56.50 ± 30.21 (0-100)	48.37 ± 28.67 (0-100)	64.63 ± 29.74 (0-100)	0.002
General Health	62.00 ± 27.58 (0-100)	50.00 ± 28.22 (0-100)	74.00 ± 21.08 (20-100)	0.001
Physical Activity	72.45 ± 32.50 (17-100)	60.93 ± 38.58 (0-100)	83.98 ± 19.27 (17-100)	0.001
Social Capacity	72.81 ± 33.39 (0-100)	58.96 ± 37.82 (0-100)	86.67 ± 20.69 (0-100)	0.001
Vigor	61.09 ± 26.38 (0-100)	51.87 ± 25.01 (0-100)	70.31 ± 24.61 (13-100)	0.001

Abbreviations: FHSQ = Foot Health Status Questionnaire Survey;. SD, standard deviation. In all the analyses, P < .01 (with a 99% confidence interval) was considered statistically significant. P-values are from Independent student t-test

DECLARATION OF FUNDING AND ROLE OF FUNDING

None.

CONFLICT OF INTEREST

The authors did not receive any financial assistance and they do not have any personal relationships with any other people or organizations that could inappropriately influence (bias) their work.

AUTHOR CONTRIBUTIONS

All authors: concept, design, analysis, interpretation of data, drafting of manuscript or revising it critically for important intellectual content.

RESUMO

*Muitas mulheres usaram sapatos de salto alto (SSA) em algum momento de suas vidas e muitas usam diariamente, com maior prevalência entre 39% e 78%, observadas em contextos institucionais e clínicos. O objetivo deste estudo foi descrever e comparar os escores obtidos em relação à saúde dos pés e à saúde em geral em uma amostra de mulheres que utilizam SSA em oposição a uma amostra de mulheres sem SSA com valores de referência normalizados. Uma amostra de 120 participantes com idade média de 41,94 ± 13,912 chegou a um centro de saúde onde os dados autorrelatados foram registrados, os informantes com e sem SSA foram determinados e os escores obtidos foram comparados no Foot Health Status Questionnaire (FHSQ). Esse documento tem 13 questões que avaliam quatro domínios de saúde dos pés, nomeadamente dor, função, saúde geral e calçado. As mulheres do grupo SSA apresentaram pior qualidade de vida relacionada à saúde em geral e à saúde dos pés, especificamente. As diferenças entre os dois grupos foram avaliadas por meio de um teste **t** para amostras independentes, mostrando significância estatística (P <0,01). As mulheres com SSA apresentam um impacto negativo na qualidade de vida relacionada à saúde dos pés.*

PALAVRAS-CHAVE: *Deformidades do pé. Doenças do pé. Qualidade de vida. Sapatos.*

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Agreement between dual x-ray absorptiometers using pencil beam and fan beam: indicators of bone health and whole-body plus appendicular tissue composition in adult athletes

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SUMMARY

OBJECTIVE: The current study was aimed to examine intra-individual variation on indicators of bone health in addition to whole-body plus appendicular tissue measurements using two concurrent assessments based on pencil beam and fan beam dual energy X-ray absorptiometry (DXA) systems in adult athletes from several sports.

METHOD: Thirty-two male participants (27.6±10.1 years) were measured on anthropometry including multifrequency bioelectric impedance and air-displacement plethysmography. Bone mineral content (BMC), bone area, fat and lean soft tissue were derived using pencil beam (Lunar DPX-MD+) and fan beam (Lunar iDXA) absorptiometry. Bone mineral density (BMD) was obtained for the femoral neck, trochanter and triangle of ward. Finally, the right thigh was defined as a region of interest (ROI). Analyses comprised intra-class correlation (ICC), Effect size (d) from mean differences of repeated measurements, coefficient of variation (CV)

RESULTS: ICC were >0.900 for all measurements. Intra-individual differences were large for BMC (d=1,312; CV=2,7%), bone area (d=1,761; CV=2,7%), fat tissue (d=1,612; CV=11%) and all indicators of appendicular lean soft tissue (d=1,237-1687; CV=2,0-4,1%). A very large difference (d=4,014; CV=8.4%) was diagnosed for lean soft tissue of the ROI.

CONCLUSION: Although differences among concurrent instruments for BMC and bone area, the effect size of mean differences was negligible for BMD. Fat and lean soft tissue derived from DXA should be interpreted as reference values (not criterion) due to equipment-related variation, more apparently in the ROI values.

KEYWORDS: Absorptiometry, photon. Bone density. Body composition. Athletes.

INTRODUCTION

Assessment of body composition corresponds to a branch of human biology[1, 2] and traditionally, body composition models comprise two compartments,[3] dividing body mass into fat and fat free mass. Technological advancements have allowed the appearance of nondestructive methods of evaluating body composition, being, in general, considered in vivo methodologies. Dual energy X-ray absorptiometry (DXA) assessment is based on a model of body composition evaluation, allowing quantification of fat tissue, lean soft tissue and bone mineral content (BMC), both for the whole body and for standardized segments (head; trunk, subdivided into ribs, pelvis and spine; upper limbs and lower limbs), and it is also possible to obtain the aforementioned components in regions of interest, termed ROI. From the clinical point of view, there is considerable interest in assessment of the proximal femoral area, often the target of prosthesis, by surgery, and additionally the lumbar spine (especially L1-L4), a segment with high informative value regarding the general state of the skeletal structure.

DXA technology has gained popularity over other technologies for its speed, low cost and reduced radiation exposure.[4, 5] Previously, the available technology would use iodine-125 as a source of radiation, the methodology being *single-photon absorptiometry* (SPA), aimed to estimate the mineral content of long bones distal portion, such as radius and ulna, being described as valid.[6] The SPA technology was used to obtain one of the most popular equations to determine the percentage of fat mass from the triceps and subscapular fat folds.[7] DXA technology measures the attenuation of X-rays emitted at frequencies of two different energies, with iodine-125 being replaced by gadolinium-153, which emits radiation at 44 and 100 KeV. There are currently several DXA devices and manufacturers *Hologic* and *Lunar* are the most mentioned ones.[8-10] DXA has been used mainly in the determination of BMC and, consequently, bone mineral density (BMD), by combining BMC and bone area. In fact, this is a criticism of the method, since the BMD should consider BMC by bone volume and not so much by area, assuming that there are inter-individual variations of those observed in relation to thickness measurement. Each of the manufacturers has developed models for reduction of radiological exposure, scanning time and precision gains [either by improving detec-

tors resolution or by the technology of X-ray emission tubes, highlighting procedures "pencil beam" (PB) and "fan beam" (FB)]. DXA, like the generality of the technologies, has assumptions, such as the heating of tissues during the procedures of application of the method, and values of water and carbon dioxide are lost, making it necessary to transform the BMC quantified to obtain the bone mineral itself.[5] Additionally, it is assumed that fat and lean mass have attenuation constants and the exposure of said tissues to low and high voltages allows determining the proportions per unit area, assuming that the thickness in the antero-posterior plane does not affect the estimates.

Most of the studies focus on the comparisons between equipment from different manufacturers (Hologic *vs.* Lunar) or between equipment of the same manufacturer adopting different technologies for X-ray emission, i.e., PB as opposed to FB[11] or even among methodologies: DXA *vs.* computed tomography scan[12-14] or by the methodology of corporal potassium measurement.[15] As a general rule, studies point to an error associated with DXA technology ranging from 1% to 3%.[16, 17] The interest of *Sports Sciences* for body composition is due, in large part, to the search for indices of metabolic efficiency. Recently, studies have emerged to express the oxygen uptakes per unit of fat-free body mass[18] since the fat corresponds to a nonrelevant metabolic tissue, or even considering oxygen consumption in the running pattern expressed per liter of lower limb volumetry (or even mL.L^{-1}.kg^{-1}). The expression per appendicular mass of the lower limb is especially relevant when the movement pattern does not oblige the athlete under evaluation to support the whole body mass and this happens in the cycle ergometer to obtain maximum and average mechanical power[19] or in the dynamometer isokinetic technique to evaluate the moments of maximum strength (peak torques) of the muscles responsible for knee extension and flexion actions.[20] However, the search for informative and noninvasive protocols on limbs volume and body mass has justified a line of study[21-23] devoted to more parsimonious methodologies in terms of costs and morosity (anthropometry) based on geometric models.[24] The interest in total body composition and of particular segments has been especially emphasized for the lower limb or only for the thigh. Despite the popularity of the DXA technology, studies about com-

peting equipment to estimate the determination accuracy of fat tissue, lean soft tissue and BMC are not abundant for the whole body and particular segments. In fact, the possible absence of agreement among equipments shall partially compromise proposals of calibration of new equations.[21-23]

The present study aims to examine agreement among indicators resulting from the application of competing DXA from manufacturer Lunar, namely taking into account *Lunar* DPX-MD+ (PB technology) and *Lunar* iDXA (FB technology), having been carried out with healthy young adults from multiple sports.

METHODS
Procedures and sample

The present study is cross-sectional in nature and adopts procedures recommended for human research[25], having been approved by a Research Ethics Committee (REC) (CE/FCDEF-UC/00102014). The research design comprises several models of body composition assessment and, in the case of DXA, two pieces of equipment from manufacturer *Lunar* (DPX-MD+ and iDXA). All measurements were carried out on the same day and by qualified technicians in duly certified laboratory units. Sample subjects were informed about the study objectives and the nature of the procedures, having signed an Informed Consent Form (ICF). The final sample corresponds to 32 moderately active adult males (27.6 ± 10.1 years) practicing various sport modalities.

Anthropometry

Height and sitting height were measured to the nearest 0.1 cm (stadiometer Harpenden, model 98,603, Holtain Ltd., Crosswell, GB, and Harpenden Sitting Height Table). Lower limbs length was calculated by the difference from previous measurements. Body mass was obtained by a SECA (model 770, Hanover, MD, USA) scale with a reduction of 0.1 kg. All measurements were performed by the same evaluator.

Bioelectric impedance

Participants adopted a standing position, following the manufacturer's instructions. After removing shoes, socks and other clothes, total body water was evaluated by a multifrequency bioelectrical impedance analyzer, 1, 5, 50, 250, 500, 1,000 kHz (*InBody 770 scanner:* In-body Bldg, Seul, Korea).

Plethysmography of displaced air

Information on body volume was obtained through displaced air plethysmography (BODPOD composition system, model BODPOD 2006, Life Measurement, Inc, Concord, CA, USA). Participants were evaluated twice consecutively following the manufacturer's instructions. Body density was calculated by dividing body mass (kg) by body volume (L).

Dual energy x-ray absorptiometry (DXA)

The two DXA instruments used were: Lunar DPX-MD+ (Software: enCORE version 4,00,145, GE Lunar Corporation, 726 Heartland Trail, Madison, WI 53717-1915 USA) and Lunar iDXA (enCORE version 13,60,033, GE Medical Systems Lunar3030, Ohmeda Drive, Madison, WI 53718 USA). For each of the equipments, a full body scanner was carried out. Additionally, area near the femur [information on the BMD of the femur neck, Ward triangle, trochanter and body of the femur (or shaft)] was carried out for each equipment. Subsequently, in the processing phase, an ROI (right thigh) was defined, as described in previous studies.[22, 23] For the whole body and each and every segment, the information includes BMC and bone area to subsequently determine the BMD and the component of the fat tissue and *lean soft tissue*. Calibration was performed on the same day, before the first one, using the model ("*phantom*") and the procedures recommended by the manufacturer.

For the Lunar DPX-MD+ equipment, technical documentation specifies that it is a device with X-ray emission by PB technology, having a potential of 76 kV, with an accuracy of < 1% for BMD (whole body) and also 1% for body composition without specifying whether it applies to both tissues (fat tissue and *lean soft tissue*). In turn, one of the innovations announced in the iDXA technical leaflet concerns the FB issue. Although iDXA has an FB *narrow-angle* device and proceeds to multiple passages, the FB technology is understood as having higher error, which is due to interindividual variation of body size of those evaluated, especially in the sagittal measurements. Reduction of the FB angle and overlapping of scans, successively obtained, supposedly mitigates the error associated with FB equipment with wider angle (*wide-angle* FB). The X-ray in the *Lunar* iDXA equipment presents potential of 100 kV (slightly higher than *Lunar* DPX-MD+) and, beyond the FB *narrow-angle technology* , iDXA

is different from previous equipment by having a high resolution detector (CZT-HD).

Statistical analysis

Analyses comprised descriptive statistics (range, mean, standard error of the mean, confidence intervals of the mean and standard deviation) for the entire sample (n = 32), as well as the verification of normality assumptions. Subsequently, intra-individual differences (time 1 and time 2) have been determined, parallel to the calculation of the technical error of measurement (TEM).[26] Then, and based on TEM, the coefficient of variation was determined (CV %: expressed as a percentage of the combined mean of repeated measurements). Also based on associative statistics, it was possible to determine the intraclass correlation coefficient (ICC) and its 95% confidence interval. The differences of the means of the repeated measurements were evaluated based on the effect size (*Cohen's d*), which have been qualitatively interpreted as follows:[27] < 0.2 (trivial); 0.2-0.6 (small); 0.6-1.2 (moderate); 1.2-2.0 (large); 2.0-4.0 (very large); > 4.0 (extremely large). Statistical procedures were carried out using resources from software IBM SPSS v. 23 for Mac OS software (SPSS Inc., IBM Company, NY, USA).

RESULTS

Table 1 summarizes the characteristics of the sample. BMC, bone area used in determination of BMD, whole body lean soft tissue and whole body fat tissue, are presented in Table 2. Also the outputs related to BMD in the proximal femoral area are presented in Table 2 [femur neck, triangle of ward, trochanter and shaft]. Table 2 includes data from *Lunar DPX-MD+* and *Lunar iDXA*. Violation of assumptions of normal distribution was uniquely noted for fat tissue with regard to the whole body.

Comparison of results by two competing pieces of equipment (Table 3) suggests a substantial intra-individual difference for whole body BMC (mean of intraindividual difference = 110 g, magnitude of the wide effect: d = 1,312) and also for the bone area used in calculating BMD (mean intraindividual difference = 65 cm², effect: d = 1.761). However, for the BMD intraindividual differences were negligible (–0,001 g.cm-²) and the magnitude effect was trivial. In addition, magnitude of the intraindividual difference was large for the fat tissue, with the average being 11.87 kg for equipment *Lunar* DPX-MD+ and 13.56 kg for equipment *Lunar* iDXA, corresponding to a mean of intraindividual differences of 1.70 kg (d = 1.612, magnitude of the wide effect). Differences for the lean tissue were trivial, that is, 0.04 kg.

BMD values for the proximal femoral area showed that for the femoral neck. The variation associated with the equipment corresponded to a trivial intraindividual difference of 0.001 (d = 0.031) and the magnitude of the differences among intraindividual means for the Ward triangle and trochanter was respectively, d = 0.512 (small magnitude) and d = 0.495 (small magnitude). For the shaft of the femur, the magnitude of the differences was moderate (d=0.656).

TABLE 1 DESCRIPTIVE STATISTICS FOR THE TOTAL SAMPLE AND TEST FOR NORMALITY ON ILLUSTRATIVE VARIABLES (N=32)

Variable	Range		Mean			Standard deviation	Normality (Kolmogorov-Smirnov)	
	minimum	maximum	value	standard error	95%CI		value	p
Chronological age (years)	18,60	57,80	27,80	1,75	(24,19 a 31,06)	10,08	0,326	<0,01
Training experience (years)	2,00	47,0	15,5	1,7	(12,2 a 18,8)	9,6	0,185	<0,01
Stature (cm)	155,7	193,0	176,0	1,5	(173,1 a 179,0)	8,6	0,160	0,03
Sitting height (cm)	85,3	100,0	92,4	0,7	(91,1 a 93,7)	3,9	0,107	0,20
Leg length (cm)	70,4	94,6	83,6	1,0	(81,7 a 85,6)	5,7	0,091	0,20
Body mass (kg)	58,4	91,6	73,5	1,6	(70,4 a 76,6)	9,1	0,090	0,20
Whole body volume by ADP (L)	54,414	88,360	69,060	1,574	(65,975 a 72,145)	9,041	0,100	0,20
Whole body density by ADP (kg.L–1)	1,028	1,096	1,065	0,003	(1,060 a 1,071)	0,016	0,168	0,02
Total body water by BIA (L)	38,0	55,0	45,6	0,9	(43,9 a 47,3)	4,9	0,106	0,20

ADP (air displacement plethysmography), BIA (body impedance), 95%CI (95% confidence intervals).

TABLE 2 DESCRIPTIVE STATISTICS AND TEST FOR NORMALITY ON OUTPUTS DERIVED FROM EACH OF THE TWO DUAL ENERGY X-RAY ABSORPTIOMETRY EQUIPMENTS USED IN THE PRESENT STUDY (N=32).

Equipment	Parameter	Units	Range		Média		standard deviation	Kolmogorov-Smirnov	
			minimum	maximum	value	standard error		value	p
DPX-MD+	BMC	g	2294	4303	3370	85	491	0,135	0,14
	Bine area	cm²	2068	3019	2583	40	227	0,134	0,14
	BMD	g.cm⁻²	1,000	1,483	1,293	0,019	0,109	0,071	0,20
iDXA	BMC	g	2368	4147	3260	80	459	0,145	0,08
	Bone area	cm²	2199	2854	2519	31	177	0,112	0,20
	BMD	g.cm⁻²	1,118	1,509	1,293	0,019	0,108	0,141	0,09
DPX-MD+	Lean soft tissue	kg	48,483	66,415	57,508	0,881	5,062	0,104	0,20
	Fat tissue	kg	4,488	28,222	11,865	1,100	6,321	0,171	0,02
iDXA	Lean soft tissue	kg	47,391	66,874	57,466	0,939	5,395	0,101	0,20
	Fat tissue	kg	6,749	27,216	13,564	0,960	5,516	0,17	0,02
DPX-MD+	Femural neck	g.cm⁻²	0,847	1,615	1,218	0,032	0,186	0,092	0,20
	Traingle of Ward	g.cm⁻²	0,636	1,734	1,145	0,038	0,220	0,081	0,20
	Trochanter	g.cm⁻²	0,807	1,322	1,057	0,036	0,147	0,094	0,20
	Shaft	g.cm⁻²	1,119	2,073	1,469	2,073	0,220	0,220	0,09
iDXA	Femural neck	g.cm⁻²	0,843	1,624	1,219	0,031	0,175	0,114	0,20
	Traingle of Ward	g.cm⁻²	0,613	1,704	1,125	0,039	0,225	0,079	0,20
	Femural neck	g.cm⁻²	0,802	1,331	1,041	0,027	0,155	0,104	0,20
	Shaft	g.cm⁻²	1,110	2,069	1,444	0,037	0,215	0,141	0,09
DPX-MD+	LST: trunk	kg	21,923	31,503	26,101	0,472	2,709	0,109	0,20
	LST: upper limbs	kg	5,094	8,536	6,986	0,169	0,974	0,092	0,20
	LST: lower limbs	kg	16,526	23,875	20,406	0,346	1,985	0,113	0,20
	LST: right thigh	kg	3,370	6,348	4,976	0,117	0,672	0,142	0,09
iDXA	LST: trunk	kg	22,567	31,302	26,883	0,441	2,533	0,118	0,20
	LST: upper limbs	kg	5,164	8,940	7,211	0,181	1,038	0,109	0,20
	LST: lower limbs	kg	15,809	23,719	19,886	0,377	2,164	0,126	0,20
	LST: right thigh	kg	4,321	7,203	5,494	0,125	0,717	0,112	0,20

LEGENDS: bone mineral content (BMC), bine mineral density (BMD), LST (lean soft tissue)

For lean soft tissue indicators, differences were observed for all segments and ROI: d = 1.687 (large differences) for the trunk; d = 1.237 (large effect size) for upper limbs; d = 1.402 (also large effect) for the lower limbs. For the ROI, the lean soft tissue showed a vary large variation between equipments (d = 4.014).

With regard to the ICCs, for all measures above, ICC > 0.900 was obtained. The CV % fluctuated between 2.3% and 2.7% for the measures used in cal-culation of BMD. For tissue, CV % is only 1.5% for the lean soft tissue component and 11.2% for the fat tissue component. For the variables of the proximal femoral area, TEM was always less than 5% of the combined mean [i.e., CV % equal to 2.4% for the femoral neck, 2.5% for the Ward triangle, 2.0% for the trochanter and 4.5% for the shaft], the data quality being corroborated by ICC coefficients always higher than 0.950. For lean soft tissue, CV % = 2.1

TABLE 3 COMPARISONS BETWEEN EQUIMENTS (DPXMD+ MINUS IDXA)

Dependent variable	Units	95%LC		Intra-individual mean differences		Effect size		TEM		ICC	
		DPX-MD+	iDXA	value	95%CI	d	qualitative	value	%CV	value	(IC 95%)
BMC	g	(3202;3537)	(3103; 3416)	110	(86 a 134)	1,312	(larga)	91	2,7%	0,995	(0,990 a 0,998)
Bone area	cm²	(2506; 2661)	(2458; 2579)	65	(39 a 91)	1,761	(larga)	69	2,7%	0,966	(0,931 a 0,983)
BMD	g.cm⁻²	(1,255; 1,330)	(1,256; 1,330)	-0,001	(−0,016 a 0,014)	0,000	(trivial)	0,029	2,2%	0,961	(0,922 a 0,981)
Lean soft tissue	kg	(55,781; 59,235)	(55,625; 59,307)	0,04	(−0,395 a 0,478)	0,043	(trivial)	0,85	1,4%	0,986	(0,972 a 0,993)
Fat tissue	kg	(9,709; 14,022)	(11,682; 15,446)	-1,70	(−2,084 a −1,314)	1,612	(larga)	1,41	11,1%	0,992	(0,983 a 0,996)
Femural neck	g.cm⁻²	(1,154; 1,281)	(1,159; 1,279)	0,001	(-0,016 a 0,014)	0,031	(trivial)	0,030	2,4%	0,986	(0,971 a 0,933)
Traingle of Ward	g.cm⁻²	(1,070; 1,221)	(1,048; 1,202)	0,020	(0,008 a 0,033)	0,512	(pequena)	0,028	2,4%	0,994	(0,988 a 0,977)
Trochanter	g.cm⁻²	(1,007; 1,107)	(0,989; 1,094)	0,015	(0,006 a 0,024)	0,495	(pequena)	0,021	1,9%	0,993	(0,986 a 0,977)
Shaft	g.cm⁻²	(1,394; 1,544)	(1,370; 1,517)	0,025	(-0,007 a 0,058)	0,656	(moderada)	0,066	4,5%	0,954	(0,908 a 0,977)
LST: trunk	g	(25,177; 27,026)	(26,019; 27,747)	-0,78	(-1,090 a 0,474)	1,687	(larga)	0,81	2,0%	0,972	(0,943 a 0,986)
LST: upper limbs	g	(6,654; 7,318)	(6,857; 7,565)	-0,23	(−0,352 a 0,098)	1,237	(larga)	0,29	4,1%	0,967	(0,934 a 0,984)
LST: lower limbs	g	(19,728; 21,083)	(19,148; 20,624)	0,52	(0,254 a 0,785)	1,402	(larga)	0,63	3,1%	0,966	(0,932 a 0,983)
LST: right thigh	g	(4,747; 5,205)	(5,250; 5,739)	-0,52	(-0,644 a 0,393)	4,014	(muito larga)	0,44	8,4%	0,931	(0,860 a 0,966)

(Software: enCORE GE Healthcare 2011 version 13,60) and Lunar iDXA (ME+210160 Software: enCORE GE Healthcare 2012 version 15,00), intra-individual mean differences and respective 95% confidence intervals (n=32) and technical error of measurement (TEM), coefficient of variation (%CV) and intra-class correlation coefficient (ICC).

Note: BMC: bone mineral content; BMD: bone mineral density; LST: lean soft tissue; 95%CL: 95% confidence limits; TEM: technical error of measurement; CV: coefficient of variation; ICC: intra-class coefficient of correlation.

and ICC = 0.972 for the trunk, CV % = 4.2 and ICC = 0.967 for the upper limbs; CV % = 3.2 and ICC = 0.966 for the lower limbs were observed. For the ROI, the lean soft tissue showed a higher variation between equipment (CV % = 8.43, ICC = 0.931).

DISCUSSION

In the present study, agreement among indicators resulting from the application of competing equipments used in DXA, one being a PB technology (*Lunar* DPX-MD+) and another, FB (*Lunar* iDXA) was examined. Regarding BMC, the bone area for determining BMD, BMD, fat tissue and lean soft tissue, healthy adults and sportsmen of various sports were assessed. Negligible differences were found for BMD, despite a trend for Lunar DPX-MD+ to produce higher values for BMC and also for the bone area. In a study of women between the ages of 21 and 80,[11] there was a trend for the FB mode to underestimate (by comparison to the PB mode) the bone area used to calculate BMD. This study, previously mentioned, was carried out with the equipment Hologic QDR-2000, that has the possibility of adopting the two modes mentioned above (FB and PB).[5] However, other studies[28, 29] shoed that among FB technology equipment, the subject's thickness constitutes a source of discrepancy. The

Lunar manufacturer's first equipment had a beam angle of about 30 degrees, considering *wide-angle* FB,[30] having been replaced by *narrow-angle* FB equipment (in the *Lunar Prodigy* equipment the angle is 4.5 degrees), and considered several overlapping scans, which takes place in the *Lunar* iDXA (equally a *narrow-angle* FB, with the added advantage of being equipped with a CZT-HD high resolution detector). In the present study, a high ICC was always obtained between the aforementioned *narrow-angle* FB (iDXA) equipment and the PB (Lunar DPX-MD+) equipment.

For measurements of the proximal femoral area, which are widely used in clinical settings, BMD presented differences between equipment which fluctuated between trivial and moderate, although CV % and ICC confirmed a certain idea of data quality, especially for the femur neck, trochanter and Ward triangle, revealing shaft as a more problematic parameter. The literature confirms this trend for variation in the discrepancy between FB and PB modes, namely in a study of 63 women[11] which made it possible to conclude that there was an overestimation of +1.5% by FB in the lumbar spine, in parallel with an underestimation of −0.7% in the femoral neck and −1.8% in the trochanter. In the latter region, a correlation of +0.36 was found among the residuals of the two modes (FB/PB) and the body mass of the women

BONE MINEARAL DENSITY
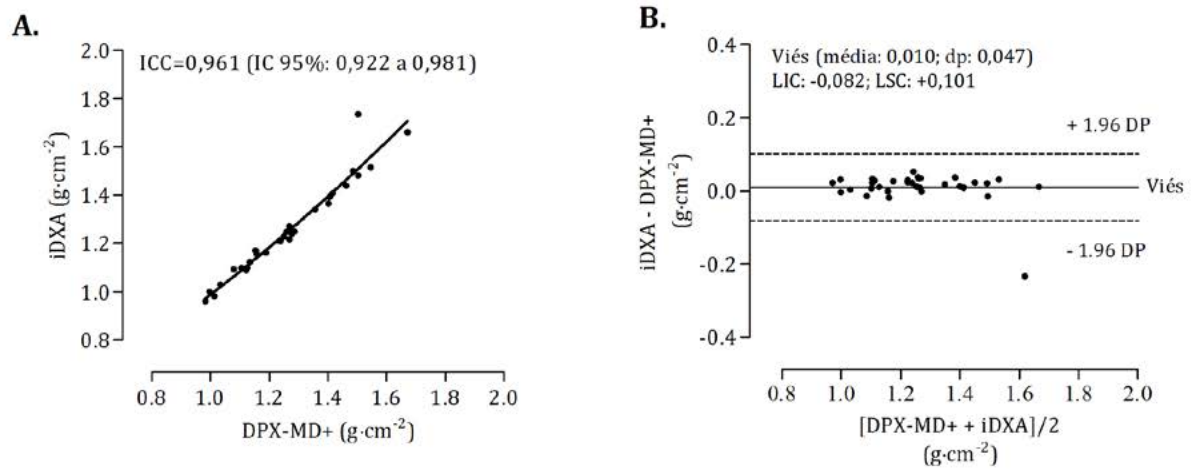
LEAN SOFT TISSUE
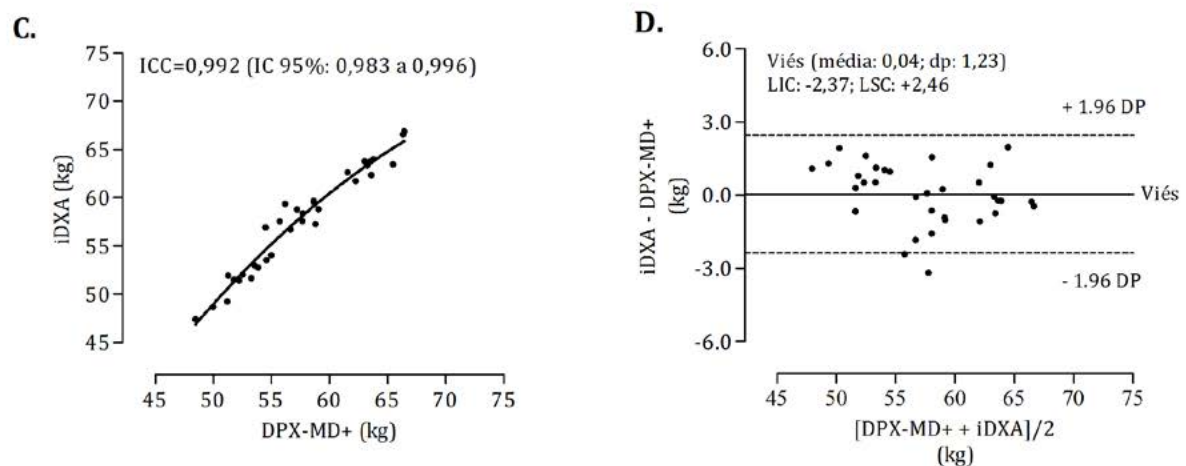
FAT TISSUE
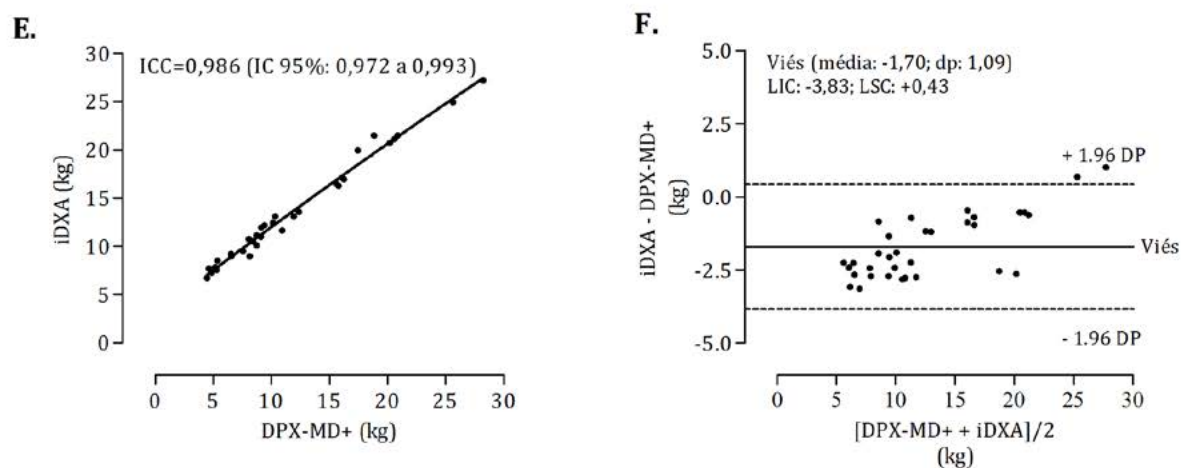
evaluated. Also, in another study with 40 postmenopausal women, accuracy of repeated BMD measurements was 1.1-1.6% for the lumbar spine and 2.2-2.5% for the femoral neck, with intraindividual variation being highest for obese women.[31]

For fat tissue, it is possible that variations in energy and data processing associated with each of the equipments contribute to a substantive intraindividual difference and caution is recommended for the acceptance of fat mass data, expressed in kg, from the DXA technology. In the present study, this variable showed the highest value for CV % (11.2%) and the magnitudes of intraindividual differences were large. Regarding lean soft tissue, the data between DXA-MD+ and iDXA appeared to be in agreement, except for ROI, where it is considered an additional source of error, that is, the error introduced by the observer, also involving data processing and not just acquisition. Use of DXA for determination of trunk fat, combined with measurements and thickness of subcutaneous fat folds, was tested as a protocol to obtain an intra-abdominal fat quantification using computed tomography[14], having explained 91% of the interindividual variance, although with a CV % of 14.8%.

Appendicular composition has also been of interest in several studies using DXA technology. For example, a study of 41 male rugby players (16.3 to 20.7 years old) calibrated the geometric models by anthropometry to determine the lower limb volumetry, based on data obtained by DXA (Hologic, Explorer W, Waltham, Massachusetts, USA, software QDR version 12.4) to obtain data on fat mass and fat-free mass of the lower limb.[21] Thus, it was possible to determine correlation coefficients of 0.81 and 0.90 between the anthropometric method and the DXA reference. More recently, the same researchers[22] has calibrated the geometric models based on two conical structures (only for the thigh) in 168 school-age children using the DXA equipment (Hologic Explorer W, Waltham, Massachusetts, USA, software QDR version 12.4). In this last study, the appendicular thigh volume corresponded to an ROI defined between the transverse planes that pass between two anthropometric references: ischium and suprapatellar. Finally, another study[23] has been carried out with 42 adolescent volleyball players (14.0-17.9 years) aiming at anthropometric calibration of thigh volumes obtained by anthropometry and DXA (Lunar DPX NT/Pro/MD+/Duo/Bravo). However, intra-observer reliability for the same equipment has not been determined, particularly with regard to ROI, which requires more expertise from the observer.

CONCLUSIONS

In general, the various parameters revealed good reproducibility and allowed to confirm a certain idea of the quality of the indicators resulting from the application of competing DXA equipment (Figure 1). Negligible differences were found for BMD, despite a trend for equipment Lunar DPX-MD+ to produce higher numbers for BMC and also for the area. It is recommended, however, that measurements of whole body fat tissue and in the case of lean soft tissue in the thigh, when obtained by DXA, be not taken as a criterion, but rather as a reference. Such an understanding has implications for the interpretation of intraindividual discrepancies that would comprise measurement error in each of the competing variables and not only in the predictive variable.

CONFLICT OF INTEREST

The authors declare having no conflict of interest.

RESUMO

OBJETIVO: *O presente estudo examinou a concordância entre os indicadores de saúde óssea e composição tecidual resultantes da aplicação de equipamentos concorrentes de absorciometria de raios X de dupla energia (DXA).*

MÉTODO: *A amostra (n = 32), com 27,6 ± 10,1 anos de idade avaliados antropometricamente, inclui impedância bioelétrica com multifrequência e pletismografia de ar deslocado. O conteúdo mineral ósseo (CMO), a área de tecido ósseo, o tecido magro e o tecido gordo de corpo inteiro foram obtidos considerando o modo* pencil beam *(Lunar DPX-MD+) e o* fan beam *(Lunar iDXA). Para cada um dos equipamentos, foi efetuado um* scanner *proximal do fêmur, sendo produzida informação sobre a densidade mineral óssea (DMO) do colo, nomeadamente triângulo de Ward, trocanter e haste. Na fase de processamento, foi definida uma região de interesse (ROI; coxa direita). As análises compreenderam a diferença de médias de medidas repetidas com cálculo da magnitude de efeitos (d), coeficiente de correlação intraclasse (CCI), coeficiente de variação (CV).*

RESULTADOS: *Foram obtidos CCI>0,900 para todas as medidas, com diferenças intraindividuais largas apenas para CMO (d = 1,312; CV = 2,7%), área de tecido ósseo (d = 1,761; CV = 2,7%), tecido gordo total (d = 1,612; CV = 11%) e tecido magro em todos os segmentos (d = 1,237-1,687; CV = 2,0-4,1%). A massa magra da ROI apresentou uma variação intraindividual muito larga (d = 4,014; CV = 8,4%).*

CONCLUSÃO: *Foram encontradas diferenças negligenciáveis para a DMO de corpo todo. As medidas de massa gorda e massa magra obtidas por DXA não devem ser tidas como critério, mas antes como referência, muito especialmente quando se delimita uma ROI.*

PALAVRAS-CHAVE: *Absorciometria de fóton. Densidade óssea. Composição corporal. Atletas.*

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Public social security burden of musculoskeletal diseases in Brasil- Descriptive study

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SUMMARY

BACKGROUND: *To present data on the social security burden of diseases of the musculoskeletal system and connective tissue (DSOTC) in Brasil in 2014, and evolution of these social security expenditures between 2009 and 2014.*

METHOD: *Compilation and analysis of data on the granting of disability pensions and sickness benefits in the year 2014, available on the official website of Social Security, classified according to ICD 10. It was evaluated the evolution between 2009 and 2014, using the F test to compare the curves with the growth of the active age population (PIA).*

RESULTS: *Among the 22 disease groups classified according to ICD-10, the DSOTC group led benefits grants in 2014, with 19% of the sickness benefits and 13.5% of the disability pensions. The main causes of sickness benefit and disability retirement were, respectively: dorsopathies (43.3% and 41.2%), soft tissue diseases (27.3% and 19.7%), osteoarthritis (7.6% % And 27.8%) and chronic inflammatory arthropathies (2.8% and 7.9%). In the evolution of the number of sickness benefits granted between 2009 and 2014, both INSS and DSOTC totals showed an increasing tendency (35.9 and 35.3%, respectively, with p = 0.000 for both). As for disability retirement, there was a 5.9% increase in the INSS total (p = 0.039), while for the DSOTC there was a decrease of 7.6% (p = 0.005).*

CONCLUSIONS: *These data point to a progressive increase in the granting of sickness pensions and disability benefits in the country, superior to the growth of the PIA, as well as a high participation of DSOTC in these benefits.*

KEYWORDS: *Social security. Musculoskeletal system. Insurance benefits. Salaries and fringe benefits.*

INTRODUCTION

The Brazilian Social Security System, managed by the National Institute of Social Security (PS/INSS), is heading towards collapse given the huge gap between expenses and collection.[1] Government strategies aimed at preventing or at least mitigating this negative balance have reached maximum attention and disclosure, constituting one of the main economic and social topics of discussion in the country[1].

Partial data for June 2016 indicate a 12-month accumulated expenditure of BRL 438.16 billion, corresponding to 7.42% of GDP, with a negative social security balance of BRL 112.8 3 billion in the period.[2]

Between 2009 and 2014, for example, there was a 203% increase in the number of sickness benefits and 27.8% in the number of disability pensions granted. Considering all types of INSS benefits, there was an increase of 76.7% in those five years.[3] The fact that the growth of the economically active population in this period was only 10% is noteworthy.[4] Also, benefits granted by the INSS in the same period had a cost increase of 508.8%[1], while inflation stood at 213.4%.[5] These data are alarming, as they reveal a progressive and disproportionate increase in the indirect cost of health care system for the country.

Economic issues have been increasingly high-

lighting the health care system in the international scenario. This panorama is particularly relevant in relation to diseases of the musculoskeletal system and connective tissue (DSOTC, in the Portuguese abbreviation) due to their high prevalence. Reinforcing this assertion, the World Health Organization and the United Nations, in a joint action, have declared the period between 2000 and 2010 as the "Decade of Bone and Articulations".[6] The main objective of this initiative was to identify and assess the DSOTC economic burden in the world, calling on governments to prioritize this group of diseases in their political agendas.

Academic circles also address the impact of these diseases on health, social and economic issues using publications in scientific journals,[7-10] but not yet with the magnitude that the problem demands.

Data on social security expenditures are available on the Brazilian Social Security Web Portal,[2] but in a dispersed and fragmented way in several subdivisions. The objective of this study is to present this information filtered, grouped and tabulated in order to facilitate its registration and interpretation, as well as to evaluate its evolutionary behavior.

METHODS

The main source was the Historical Social Security Database,[2] containing statistical yearbooks, available on the official social security web portal. Benefits were analyzed in the year 2014, whose data were the most recent available on the web portal at the time of the study. An analysis of the evolution of the granting of benefits between 2009 and 2014 was also made. Two types of benefits were considered: sickness benefits and disability pensions, since they are directly associated with health. The International Classification of Diseases [ICD; its full official name is International Statistical Classification of Diseases and Related Health Problems and it is maintained by the World Health Organization (WHO)] in its last version was used as a search filter (ICD 10),[11] which has 22 chapters representing groups of diseases, maintaining the terminology of this one in the presentation of results. Six groups were considered for analysis: DSOTC encompassing ICDs M00 to M99, specific interest of the study, and, for comparison purposes, diseases of the circulatory system, neoplasia, diseases of the respiratory system, infections and mental disorders, as they

are among the diseases of higher prevalence in our environment.

In the DSOTC group were considered individualized ICDs or, in some cases, grouped according to similar characteristics of the diseases in question.[12, 13] Based on this criterion, the following groups were defined: inflammatory spondyloarthritis, which included ICDs M02 (reactive arthropathies), M03 (postinfectious arthropathies), M07 (psoriatic and enteropathy arthropathies), M45 (ankylosing spondylitis) and M46 (other inflammatory spondylopathies); dorsopathies, consisting of the sequence of ICDs M40 to M54, except those of inflammatory spondylopathies (M45 and M46), which comprised the spondyloarthritis group; soft parts (ICDs M60 to M79); microcrystalline arthropathies (ICDs M10 and M11); osteoarthritis (ICDs M15 to M19) and rheumatoid arthritis (ICDs M05 and M06). ICDs M32 to M36, which include lupus, dermatopolymyositis, systemic sclerosis and other systemic connective tissue diseases were grouped under the denomination of diffuse connective tissue diseases. A group named "others" was established, encompassing diagnoses that in individual analysis were numerically minor, being grouped to facilitate the presentation of results. This group covers osteometabolic diseases (ICDs M80 to M90), juvenile idiopathic arthritis (ICDs M08 and M09), vasculitis (ICDs M30 to M31), infectious arthropathies (ICDs M00 and M01), other arthropathies (ICDs M12 to M14), deformities of the musculoskeletal system (ICDS M20 and M25), chondropathies (ICDs M91 to M94) and miscellaneous (ICDs M95 to M99).

Assessment of the potential for permanent disability was established by the ratio of the number of permanent (retired) disabled persons to the total number of temporary and permanent disabled people (sick pay and disability retirement) for each ICD or set of ICDs, as defined above. With the aim of quantifying the evolution of the number of benefits granted between 2009 and 2014 in each disease or group of diseases evaluated, the simple linear regression analysis technique was used[14] to obtain a predictive line of the number of cases per year and consequent analysis of the (growth or decline) trend of the volume of interest. Finally, evolutionary trends (or slopes of a straight line) of the benefits granted to sickness or group of sicknesses with the evolutionary trend of the working-age population (WAP)[15] in the same period in order to be able to propose specif-

ic research on a certain disease or group of diseases with out-of-expected behavior for the population as a whole. The WAP was chosen because it contained the individuals exposed to occupational outcomes addressed (population between 15 and 64 years of age).[4] This comparative analysis was performed by an F-test between the slopes of the WAP straight lines and each disease or group of diseases. The year 2009 was adopted based on 100[16] so that the differences observed would not be due to discrepancies among the values and also so that trends (or inclinations) could be identified.

RESULTS

Considering the benefits accruing, in 2014, 2,328,151 sickness benefits were granted, which accounted for 43.6% of all benefits (including social security, welfare and accident benefits) from the National Institute of Social Security. In that year, 189,651 new disability pensions were registered or 3.5% of the total benefits.

Analyzing ICD 10 main groups of diseases, the most represented in the benefits granted in 2014 was that of DSOTC, responsible for 19.0% of the total sickness benefits. By comparison, mental disorders, corresponding to 9.0%, diseases of the circulatory system, 7.4% and neoplasms, 6.9%, were next. In terms of disability pensions, DSOTC accounted for 13.5% of total benefits granted in 2014, followed by diseases of the circulatory system (13.4%), respiratory diseases (12.6%), neoplasias (7.6% %) and mental disorders (6.3%).

When the search parameter in the Social Security web portal was the individualized ICD, the most prevalent benefits in number were: back pain – M54 (108852), leg fractures – S82 (87591), hand and wrist fractures – S62 (71623) and disorders of intervertebral discs – M51 (64018). It is important to note that the website recorded 90,242 cases with "ignored" diagnosis (written as 999 in the ICD search). Using the same search system for disability pensions, back pain – M54 continued as the most prevalent ICD, with 4,566 grants, followed by disorders of intervertebral discs – M51 (4,337), stroke – I64 (3,686) and knee arthrosis – M17 (3,602). For this type of benefit, the website records 72,677 grants with "ignored" ICD.

Considering only the group of diseases of the musculoskeletal system and connective tissue, dorsopathies remained the main causes for granting sickness benefits, with 43.3%, followed by soft tissue diseases (27.3%), osteoarthritis (7.6%) and chronic inflammatory arthropathies (2.8%) (Figure 1). Also within the DSOTC, the dorsopathies group accounted for 41.2% of disability pensions (Figure 1). On the other hand, osteoarthritis was the second most common, with 27.8% of the pensions, followed by soft tissue diseases (19.7%) and chronic inflammatory arthropathies (7.9%, especially rheumatoid arthritis, with 4.5%) (Figure 1).

Granting disability retirement in relation to the sickness benefit

The ratio of the number of invalidity pensioners to the sum of the number of sickness benefit recipients and the number of disability pensioners in 2014 was

FIGURE 1. SOCIAL SECURITY DISABILITY INSURANCE X STATUTORY SICK PAY

Social security disability insurance

Statutory sick pay
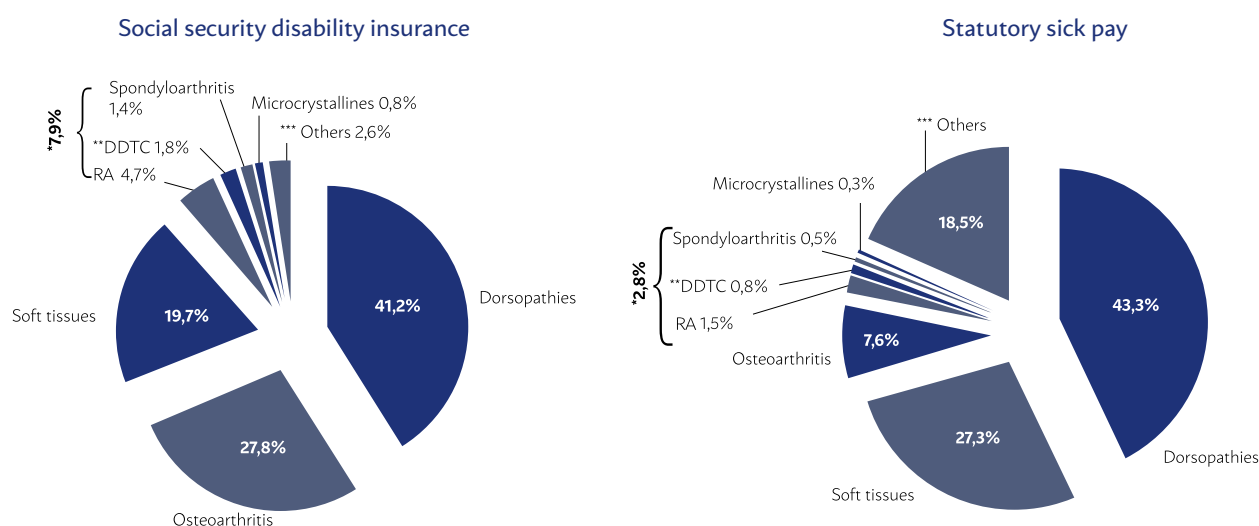
7.53% for the total benefits granted by the INSS. For the DSOTC, the ratio was 5.52%. The ratio for other large groups was: diseases of the circulatory system, 12.83%; neoplasias, 8.28%; diseases of the respiratory system, 91.69%; infections, 6.38%, and mental disorders, 5.42%. As for most of the diseases of the DSOTC group, the ratio was higher than that observed in the INSS total: systemic sclerosis, 25.05%; osteoarthritis, 17.55%; rheumatoid arthritis, 15.28%; myopathies, 15.12%; vasculitis, 14.40%; spondyloarthritis, 13.16%; juvenile idiopathic arthritis, 7.93%; osteoporosis, 11.81%, and lupus, 10.03%. Exceptions were the dorsopathies and soft tissues subgroups, which present a much lower ratio (5.12% and 2.84%, respectively), but together represent approximately 70% of the total benefits for musculoskeletal and connective tissue and their values end up determining the values of the average of 5.52% of the DSOTC group.

Evolution of benefits between 2009 and 2014

For sickness benefits, both INSS and DSOTC groups showed a growing trend between 2009 and 2014 (35.9% and 35.3%, respectively, p = 0.000 for both) (Figure 2). These rates mean an average increase of 132,199 cases of sickness benefits per year in the total INSS and 22,429 more cases per year for DSOTC. This increase was higher than the growth of the working-age population (WAP) in the period, which was 6.5% (p = 0.000 for total INSS benefits and for DSOTC) (Figure 2). Separately considering the subgroups of diseases within DSOTC, soft tissue rheumatism, spondyloarthritis and osteoarthritis presented an increasing trend, and that of microcrystalline arthropathies, a decreasing trend (Table 1). All these trends remained significant when compared to WAP growth in the period (Table 1). In the case of dorsopathies and rheumatoid arthritis, despite a numerical increase, variation was not significant.

Disability pensions as a whole showed an increase of 5.9% in the period or an average of 2,352 more cases per year (p = 0.039 for trend), while for the DSOTC there was a decreasing trend of 7.6% with an average of 394 fewer cases per year (p = 0.005) (Table 1). Subgroups of spondyloarthritis, rheumatoid arthritis, dorsopathies and osteoarthritis showed a significant reduction trend, whereas connective tissue diseases and

FIGURE 2
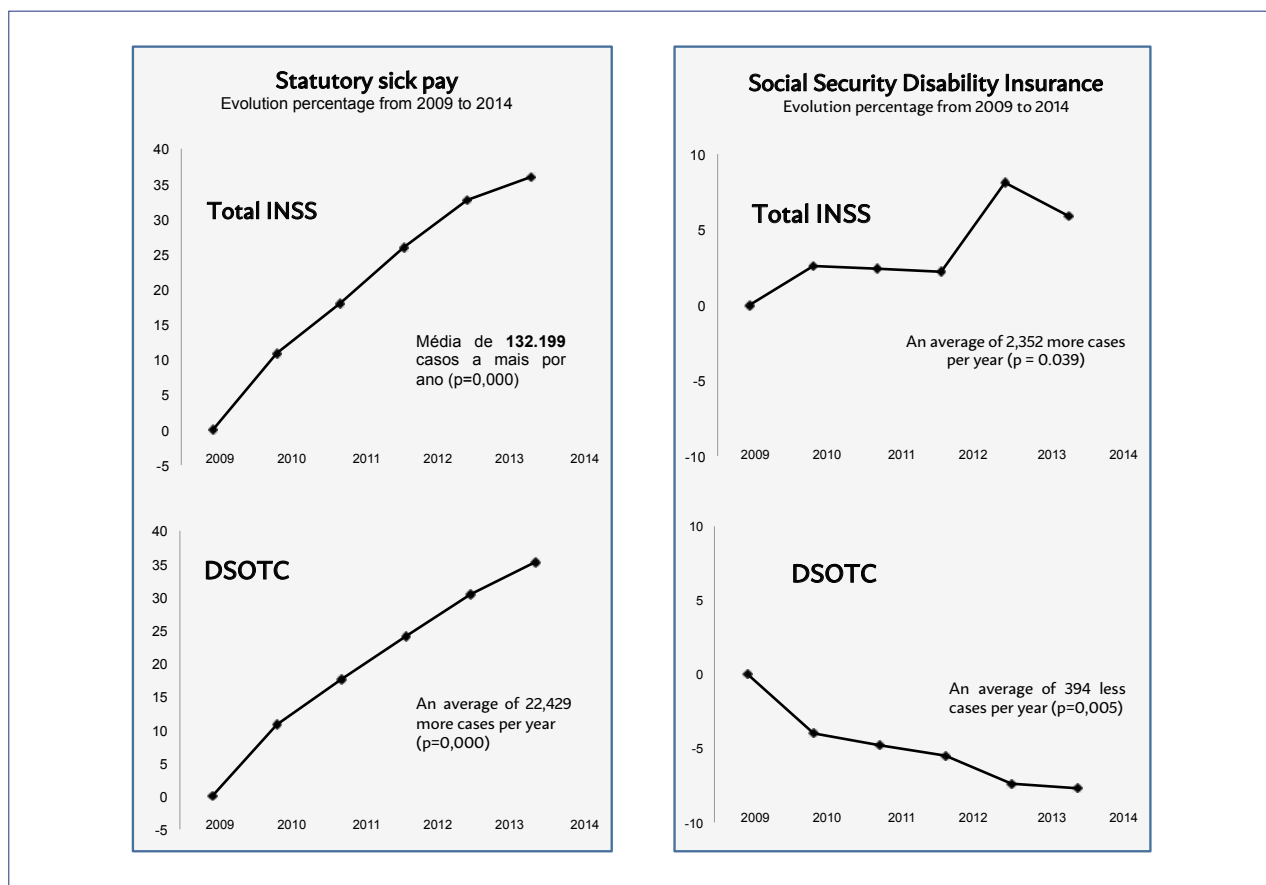
microcrystalline arthropathies showed numerical reduction without configuring trend. On the other hand, soft tissue diseases showed an increasing trend (Table 1). Once again all these trends remained significant when compared to WAP growth in the period (Table 1).

DISCUSSION

Evaluation of public health care system data in Brasil shows that the DSOTC were the main responsible ones for social security benefits in the health care sector in the year of 2014 analyzed.

By comparison, in Italy, a country with a public pension system similar to the Brazilian one, that is, where social security costs are borne by the government, the DSOTC, although quite expressive, corresponded to the third cause of short-term absenteeism and only in the tenth place in the generation of

permanent benefits (similar, respectively, to sickness benefits and to disability retirement in Brasil).[9]

Obviously, there are limitations to the interpretation of the data inherent to the descriptive nature of this study but it is possible to formulate hypotheses for the prevalence of DSOTC in social security claims. Increase in their impact could basically be due to the phenomena of demographic transition (mortality and birth rate, culminating in an aging population, a range in which the prevalence of degenerative diseases of the locomotor system is greater) and epidemiological transition from morbidity and mortality in emerging countries, from infectious to chronic-degenerative diseases).

Regarding evolutionary behavior, INSS's sickness benefit and disability pension as a whole presented growth higher than that verified in the working-age population (WAP) between 2009 and 2014. Choice of

TABLE 1

STATUTORY SICK PAY

Disease	Variation	Tendency	P	Comparison to PIA
Total INSS	+35,9%	↑	0,000	
DSOTC	+35,3%	↑	0,000	0,000
DDTC	+45,0%	↑	0,001	0,000
Soft tissues	+42,9%	↑	0,000	0,000
Dorsopathies	+32,3%	-	0,740	-
Spondylarthritis	+34,9%	↑	0,046	0,049
Rheumatoid arthritis	+18,2%	-	0,197	-
Osteoarthritis	+13,2%	↑	0,001	0,001
Microcrystallines	-7,7%	↓	0,022	0,000

SOCIAL SECURITY DISABILITY INSURANCE

Disease	Variation	Tendency	P	Comparison to PIA
Total INSS	+5,9%	↑	0,039	
DSOTC	-7,6%	↓	0,005	0,001
Spondylarthritis	-54,3%	↓	0,021	0,003
Rheumatoid arthritis	-16,7%	↓	0,003	0,000
Dorsopathies	-13,3%	↓	0,001	0,000
DDTC	-13,0%	-	0,439	-
Microcrystallines	-8,4%	-	0,407	-
Osteoarthritis	-7,3%	↓	0,003	0,000
Soft tissues	+21,8%	↑	0,008	0,015

this indicator as a reference is due to the fact that it covers individuals exposed to occupational outcomes addressed (population between 15 and 64 years of age).[4] Also for comparison, Italy has shown decrease in granting short-term benefits in a recent period.[9] In the field of hypotheses, it can be speculated that in Brasil there might be pressure generated by precariousness and low labor remuneration and rising unemployment associated with some culture of seeing the State as a provider (the financing of social security in Brasil follows the arrangement of partition and not capitalization).[17] These propositions could lead individuals to seek social security benefits more often.

Interestingly, in the DSOTC group, while the sickness benefit has shown an upward trend, following the profile of INSS benefits, disability pensions have decreased. Again explanations for the phenomenon are in the field of hypotheses: greater rigor in expert procedures, greater control of these diseases, with lower ratio of patients evolving to permanent disability. Another possibility would lie in the heterogeneous nature of DSOTC. This last aspect has been explored in the evaluation of the percentage ratio between disability pensions and the sum of pensions plus sickness benefits. From this perspective, it has been found that many diseases in the DSOTC group, such as connective tissue diseases and vasculitis, had a higher ratio than the INSS mean, signaling a greater incapacitating potential, although they are less prevalent. On the other hand, dorsopathies and soft tissue rheumatism, although less disabling, drag down the evolutionary trend of the group over time because they are much more frequent.

Osteoarthritis is the single most commonly diagnosed illness-related disability, accounting for more than a quarter of disability pensions. This profile may be due to its high prevalence in the population (in Brasil, 4.1% at 36 years and 15.8% at 55 years),[18] leading to an expressive number of patients for permanent incapacitation. As for lupus, although much more severe, it can occur with periods without clinical activity in response to treatment, leading to a relatively lower number of individuals for permanent disability. Dorsopathies and soft tissue rheumatisms constitute a group with such a large and heterogeneous number of diseases that they deserve careful interpretation, based on more data than those presented here.

Tabulation and availability of data by the INSS represent an important instrument for better understanding the socioeconomic dimension of public health care. However, there are still gaps to be filled. There was, for example, an unexpected and high occurrence of "neglected" ICD, which may have influenced the relative distribution of benefits across the different disease groups. In addition, there is no information on the time spent away in cases of sickness benefits or the individual cost of each benefit so that the exact financial size of the disease groups could be obtained. In this way, it is not possible to analyze, for example, which categories of diseases lead to a longer period of remoteness and are more costly for the system. Regarding the temporal aspect, the INSS only provides the complete, tabulated and organized data of a given year long after they were generated, limiting this study to the data obtained until 2014 (available at the time of this study). Finally, it must be taken into account that the descriptive nature of the data does not allow their more in-depth and critical interpretation.

It is important to note that, although Brasil adopt a basically public pension system, there are other financing patterns. Thus, based on information obtained from NATLEX,[19] a global database with information on social security, labor and human rights, maintained by the International Labor Organization, some authors[20] have compared the social security system of 22 countries with regard to short-term absenteeism (*paid sick day* – about five days) and in the long term (*sick leave* – 50 or more days). Australia, Norway, New Zealand, the Netherlands, Switzerland and the United Kingdom leave the payment of both benefits to the employer. Nor does the United States impose such an obligation. Austria, Belgium, Canada, Finland, Germany, Iceland, Luxembourg, Japan, Sweden and Spain offer social security only for long-term cases (most of them help the employer to pay the long term one). Only Denmark, France, Ireland and Italy offer state social security for both departures, similar to the Brazilian system.

In conclusion, the data presented in this study point to a progressive and higher increase in the evolution of the working-age population (WAP) in granting sickness and disability benefits in Brasil, as well as a high participation of diseases of the musculoskeletal system and connective tissue. It is plausible that this situation can be modified with policies that improve the resolution and comprehensiveness of medical care to the population, as well as improving mechanisms for evaluating and granting benefits to recipients.

RESUMO

OBJETIVOS: *Apresentar dados sobre o ônus previdenciário das doenças do sistema osteomuscular e tecido conjuntivo (DSOTC) no Brasil no ano de 2014, e sua evolução entre 2009 e 2014.*

MÉTODO: *Compilação e análise de dados sobre a concessão de aposentadorias por invalidez e auxílios-doença no ano de 2014 disponíveis no portal oficial da Previdência Social, classificados segundo o CID 10. Avaliação da evolução entre 2009 e 2014, utilizando-se o teste F para comparar as curvas com o crescimento da população em idade ativa (PIA).*

RESULTADOS: *Entre 22 grupos de doenças classificados de acordo com o CID 10, o das DSOTC liderou as concessões de benefícios em 2014, com 19% dos auxílios-doença e 13,5% das aposentadorias por invalidez. As principais causas de concessão de auxílio-doença e aposentadoria por invalidez foram, respectivamente: dorsopatias (43,3% e 41,2%), doenças de partes moles (27,3% e 19,7%), osteoartrite (7,6% e 27,8%) e artropatias inflamatórias crônicas (2,8% e 7,9%). Na evolução do número de auxílios-doença concedidos entre 2009 e 2014, tanto o total do INSS quanto o do grupo DSOTC apresentaram tendência crescente (35,9 e 35,3%, respectivamente, com p = 0,000 para ambos). Já para aposentadoria por invalidez, houve aumento de 5,9% no total do INSS (p = 0,039), enquanto que para as DSOTC houve um decréscimo de 7,6% (p = 0,005).*

CONCLUSÕES: *Verificou-se uma elevação progressiva na concessão de auxílio-doença e aposentadoria por invalidez no País, superior ao aumento da população em idade ativa. As DSOTC foram o grupo com maior participação relativa nesses benefícios.*

PALAVRAS-CHAVE: *Previdência social. Sistema musculoesquelético. Benefícios do seguro. Salários e benefícios.*

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Abdominal obesity and reduction of glomerular filtration

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SUMMARY

The objective was to evaluate the association between nutritional status and the glomerular filtration rate (GFR) in remaining quilombolas. Cross-sectional study carried out on 32 remaining quilombola communities in the municipality of Alcântara-MA. The nutritional indicators (IN) used were: body mass index (BMI); Waist circumference (WC); Waist-to-hip ratio (WHR); Waist-to-height ratio (WHtR); conicity index (CI) and estimated visceral adipose tissue (VAT). GFR was estimated from the CKD-EPI creatinine-cystatin C formula. The Shapiro Wilk test was used to evaluate the normality of the quantitative variables. In order to compare the second IN sex, the chi-square test was applied. The Anova or Kruskal-Wallis tests were used to verify the association between IN and GFR. Of the 1,526 remaining quilombolas studied, 89.5% were black or brown, 51.2% were women, 88.6% belonged to economic classes D and E and 61.2% were farmers or fishermen. Clinical investigation revealed 29.2% of hypertensive patients, 8.5% of diabetics and 3.1% with reduced GFR. The BMI revealed 45.6% of the remaining quilombolas with excess weight. When compared to men, women presented a higher prevalence of overweight by BMI (56.6% vs 33.8%, p <0.001) and abdominal obesity CC (52.3% vs 4.3%), WHR (76,5% vs 5.8%), WHtR (82.3% vs 48.9%) and VAT (27.1% vs 14.5%) (p <0.001). Comparing the means of IN according to the GFR, it was observed that the higher the mean value of the IN lower the GFR (p <0.05). The GFR reduced with increasing mean values of nutritional indicators of abdominal obesity, regardless of sex.

KEYWORDS: Nutritional assessment. Obesity. Glomerular filtration rate. African Continental Ancestry Group.

INTRODUCTION

Obesity is a non-transmissible chronic disease, characterized by the excessive accumulation of body fat to such an extent that it causes damages to individuals' health.[1]

Its association with kidney disease is complex. Excess fat is a site of active production of several cytokines responsible for the higher level of inflammation and oxidative stress with deleterious renal effects. Several observational studies have demonstrated a consistent association between obesity and the risk of chronic kidney disease (CKD). However, the role of body fat in its development is still unclear.[2]

The pattern of body fat distribution appears to be some more important risk factor in morbid process-

es than total obesity. In this sense, the accumulation of adipose tissue in the abdominal region is associated with several morbidities.[3] Abdominal fat, specifically visceral fat, is related to high blood pressure, insulin resistance and dyslipidemia,[6] risk factors for the development of chronic kidney disease.[4]

For some authors, the association between obesity and CKD occurs indirectly through the influence of risk factors such as diabetes, hypertension and metabolic syndrome.[5, 6] Others, however, have suggested a direct link between obesity and kidney disease.[7, 8]

With regard to ethnic-racial inequalities, the situation of quilombola (descendants of Afro-Brazilian slaves and residents of quilombos) groups deserves special mention because it is a group in a situation of social vulnerability. Scholars show that blacks have a higher incidence of disease and die early, at all ages.[9] In addition, the prevalence of obesity is significantly higher among blacks when compared to whites.[10]

The cause of the increased susceptibility of blacks to the development of CKD has not yet been well established. Some authors attribute this fact, in addition to genetic factors, to the higher rates of hypertension and type 2 diabetes mellitus found in this population, which characterize the major causes of reduction of the glomerular filtration rate in the world.[11] However, in Brasil, information on renal disease in remnant quilombola populations is scarce.

In view of the complex relationship between obesity and CKD and the increased prevalence of both, especially in black individuals, the present study has aimed to evaluate the association between abdominal obesity and reduction of glomerular filtration rate in adult quilombolas in the Brazilian municipality of Alcântara, MA.

METHODS

This is a cross-sectional study carried out on 32 remaining communities of quilombos in the Brazilian municipality of Alcântara, MA. This research is linked to the project "PrevRenal – prevalence of chronic kidney disease in the Brazilian municipality of São Luís, MA, and in quilombolas communities in the Brazilian municipality of Alcântara, MA".

PrevRenal is a population-based cohort of 1,539 remaining quilombolas from the municipality of Alcântara, in the north of Brazilian state of Maranhão, between August 2012 and April 2013.

Selection of participants was performed by a ran-dom probabilistic sampling process in two stages, in which the quilombos represented the first stage and the households the second stage. All adult residents of the households that were randomly selected were invited to participate in the survey.

Patients younger than 18 years of age, pregnant patients with chronic constipation disease, hematological disease, autoimmune disease, infection, chronic or acute renal disease in dialysis and those on immunosuppressive drugs or having thyroid disorders based on clinical history and physical examination of the individuals.

For constitution of the group investigated in this study, all individuals in the PrevRenal database were selected, being excluded those who presented incomplete information. The sample was finalized in 1,526 individuals.

Prior to the beginning of the survey, interviewers received training addressing the project basic procedures, as well as the need for confidentiality of the information.

The data were collected in two stages. The first stage occurred in the households through the application of an individual questionnaire for the adults present. The questionnaire consisted of the following topics: social, demographic and economic characteristics, clinical data, lifestyle, blood pressure, comorbidities and medication intake.

At the end of the interview, the participants' blood pressure (BP) was measured and they were told to fast for 12 hours for blood collection the following day, as well as to have their anthropometric measurements checked.

Blood pressure was measured using an indirect method and a digital sphygmomanometer (Omron®) with an appropriate cuff. Measurement was performed on the right arm with the individual sitting and at rest. Measurements were performed in triplicates, with an interval of 10 minutes, using the mean of the three measurements. Criteria proposed by the VI Brazilian Guidelines for Hypertension were adopted for BP classification.

In the second stage, on the following day, blood was collected and anthropometric measurements were checked. Such procedures were carried out by the research team in public schools or community health care clinics.

Biochemical analysis was performed by a tertiary referral laboratory with automated dosages and standardized methodology.

Anthropometric data were measured by nutritionists and included weight, height and waist circumference (WC) and hip circumference (HC).

Weight was measured in portable electronic scales (Plena®) with a capacity of 150 kg and a variation of 50 g. Height was measured using a portable stadiometer (*Alturezata*®) with a variation of 0.1 cm. For weight and height measurement, subjects were barefoot, wearing light clothing and in an orthostatic position.

Waist circumference (WC) was obtained at the midpoint between the last rib and the iliac crest at the time of expiration and the hip circumference (HC) in the area of greater prominence of the buttocks, using inextensible tape.

Anthropometric indicators used to assess the nutritional status were: body mass index (BMI), waist-hip ratio (WHR), waist-to-height ratio (WHtR), conicity index (CI), and estimated visceral adipose tissue (eVAT).

BMI was calculated using the ratio between body weight and height squared and the cutoff used for adults was that of the World Health Organization (WHO).

WHR and WHtR were calculated for the ratios between WC and, respectively, HC and height. From the measurements of weight, height and WC, the CI was calculated. The eVAT was estimated using the predictive equation of adipose tissue[12] and WC variables for men and WC and age for women.

Cutoff points of the anthropometric indicators used for men and women were, respectively: CI = 1.25 and 1.18[13]; WC ≥ 88 cm and ≥ 102 cm; WHR ≥ 0.85 and ≥ 1.0, according to criteria proposed by the World Health Organization (WHO). For WHtR = 0.50[14] and eVAT ≥ 150 cm[3, 15] for both genders.

Blood samples obtained were used for biochemical evaluation of lipidogram, uric acid (UA), fasting glycemia (FG), creatinine (Cr) and cystatin C (CysC). In biochemical analysis, the following cutoff points were considered as normal serum levels: total cholesterol (CT) < 200 mg/dl; (high-density lipoproteins) HDL-cholesterol (HDL-c) > 60 mg/dl; (low-density lipoprotein) LDL-cholesterol (LDL-c) < 100 mg/dl; triglycerides (TG) < 150 mg/dl; GJ < 100 mg/dl; UA for men < 7.2 mg/dl and women < 6.0 mg/dl; Cr > 1.4 mg/dl and CysC > 1.09 mg/dl.

The estimated glomerular filtration rate (eGFR) was obtained from the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration equation) formula using the creatinine and cystatin C values as references for the calculation. Serum creatinine was previously measured in a reference laboratory using the modified Jaffe reaction method. Serum cystatin C was measured by automated immunoturbidimetric assay using the *Roche-Hitachi Cobas 6000* analysis platform. Individuals with reduced eGFR (< 60 mL/min/1.73 m²) were referred to the Center of prevention of renal diseases of the university hospital at Brazilian university Universidade Federal do Maranhão.

The Shapiro–Wilk test was used to evaluate the quantitative variables normality.

Association of nutritional indicators and gender was tested with the chi-squared test. Analysis of variance, followed by Bonferroni correction or Kruskal-Wallis tests were used to verify the association between anthropometric indicators and GFR.

To ensure that the association between eGFR and obesity was independent of the presence of HBP (high blood pressure) and DM (diabetes mellitus), an unadjusted logistic regression with eGFR as a dependent variable and anthropometric indicators as independent variables were performed. HBP and DM were considered in an adjusted model for each anthropometric parameter investigated.

Level of significance adopted was 5%. The data were analyzed in the general-purpose statistical software package Stata 12.0.

The present study complies with all the precepts listed in Resolution 466/12 CNS/MS (National Health Council of the Brazilian Ministry of Health), which deals with guidelines and norms regulating research involving human beings. PrevRenal was approved by the Research Ethics Committee (REC) at the university hospital at Brazilian university Universidade Federal do Maranhão (consolidated opinion 41,492/2012) and all participants in the study signed an Informed Consent Form (ICF).

RESULTS

Of the 1,526 quilombola remnants surveyed, 89.5% were black or dark-skinned, 51.2% were women, mean age was 44.4 ± 17.3 years. Eighty-nine percent belonged to the less favored economic classes D and E, 61.2% had farming and fishing as their main occupation and 83.8% lived without a fixed income or received up to a minimum wage. As for schooling, 86.0% were illiterate or had at most elementary education.

When it came to lifestyle, 10.8% smoked and 42.1% drank. Clinical investigation revealed that 29.2% of the sample were hypertensive, 8.5% diabetic and 3.1% had a reduced estimated glomerular filtration rate (eGFR).

Evaluation of nutritional status showed, through BMI, prevalence of 45.6% of overweight. Women, when compared to men, had a higher prevalence of overweight by BMI (56.6% vs. 33.8%; p < 0.001) and abdominal obesity evidenced by the WC (52.3% *vs.* 4.3%; p < 0.001); WHR (76.5% *vs.* 5.8%; p < 0.001); WHtR (82.3% *vs.* 48.9%; p < 0.001) and eVAT (27.1% *vs.* 14.5%; p < 0.001) (Table 1).

Regarding the biochemical evaluation, it showed elevated serum levels of total cholesterol, 38.0% of the remaining quilombolas, of triglycerides, 23.7% and LDL-c, 31.7%. With reduced HDL-c, 42.8% of the sample were found (Table 1).

Markers of renal function revealed 4.9% of the individuals studied as presenting high values of uric acid, 1.3% of creatinine and 7.7% of cystatin C (Table 1).

Women, when compared to men, had a higher prevalence of high serum levels of total cholesterol (47.8% *vs.* 27.6%; p < 0.001) and reduced of HDL-c (53.7% *vs.* 31.4%; p < 0.001) (Table 1).

TABLE 1. ANTHROPOMETRIC AND BIOCHEMICAL CHARACTERISTICS OF REMAINING QUILOMBOLAS, ACCORDING TO GENDER. ALCANTARA - MA, 2013.

VARIABLES	GENDER						p. value*
	GENERAL		Men		Women		
	n	%	n	%	n	%	
ANTHROPOMETRIC							
Body Mass Index							< 0,001
Malnutrition	50	3,3	24	3,2	26	3,3	
Eutrophia	783	51,3	469	63,0	314	40,1	
Overweight	508	33,3	217	29,2	291	37,3	
Obesity	185	12,1	34	4,6	151	19,3	
Waist Circumference							
Altered	441	28,9	32	4,3	409	52,3	< 0,001
Waist-to-Hip Ratio							
Altered	641	42,0	43	5,8	598	76,5	< 0,001
Waist-to-Height Ratio							
Altered	1.008	66,0	364	48,9	644	82,3	< 0,001
Conicity Index							
Altered	1.032	67,6	490	65,9	542	69,3	0,150
Visceral Adipose Tissue							
Altered	320	21,0	108	14,5	212	27,1	< 0,001
BIOCHEMICAL							
Total Cholesterol							
High	570	38,0	201	27,6	369	47,8	< 0,001
Triglycerides							
High	362	23,7	161	21,6	201	25,7	0,062
HDL Cholesterol							
Low	652	42,8	233	31,4	419	53,6	< 0,001
LDL Cholesterol							
High	484	31,7	219	29,4	265	33,9	0,062
Uric Acid							
High	75	4,9	42	5,6	33	4,2	0,200
Creatinine							
High	20	1,3	14	1,9	6	0,8	0,056
Cystatin C							
High	118	7,7	67	9,0	51	6,5	0,069

*Chi-square.

TABLE 2. ASSOCIATION BETWEEN NUTRITIONAL INDICATORS AND GLOMERULAR FILTRATION RATE OF REMAINING QUILOMBOLAS, ACCORDING TO GENDER. ALCÂNTARA – MA, 2013.

NUTRITIONAL INDICATORS	Glomerular Filtration Rate (mL/min/1.73m²)			p. value*
	≥ 90	60 - 89	< 60	
	Average ± DP	Average ± DP	Average ± DP	
MEN				
Body mass index (kg/m2)	23,77±3,06	24,20±3,56	24,28±4,23	0,238*
Waist circumference (cm)	82,18±9,04ᵃ	85,37±10,19ᴬ	87,69±12,58	< 0,001*
Waist-to-hip ratio	0,88±0,06ᵃ	0,91±0,07ᴬ	0,94±0,07ᴬ	< 0,001*
Waist-to-height ratio	0,50±0,05ᵃ	0,53±0,06ᴬ	0,55±0,08ᴬ	< 0,001*
Conicity index	1,20±0,07ᵃ	1,25±0,08ᴬ	1,29±0,10ᴬ	< 0,001*
Estimated visceral adipose tissue (cm3)	69,81±57,58ᵃ	90,12±64,91ᴬ	104,87±80,13ᴬ	< 0,001*
WOMEN				
Body mass index (kg/m2)	25,80±4,61	26,58±5,31	27,60±6,49	0,028#
Waist circumference (cm)	87,18±11,77ᵃ,ᵇ	91,06±12,18ᴬ,ᵇ	94,95±15,10ᴮ	< 0,001*
Waist-to-hip ratio	0,89±0,07ᵃ	0,92±0,07ᵃ	1,08±0,84ᴬ	< 0,001*
Waist-to-height ratio	0,57±0,08ᵃ,ᵇ	0,60±0,08ᴬ,ᵇ	0,64±0,10ᴮ	< 0,001*
Conicity index	1,27±0,10ᵃ,ᵇ	1,32±0,09ᴬ,ᵇ	1,37±0,0808ᴮ	< 0,001*
Estimated visceral adipose tissue (cm3)	75,27±65,11ᵃ,ᵇ	143,05±58,92ᴬ,ᵇ	202,50±61,85ᴮ	< 0,001*

Anova / *Bonferroni* (A > a), (B > b); DP- Standard Deviation; *#Kruskal Wallis*

When comparing the means of nutritional indicators according to the glomerular filtration rate (GFR), it was observed that the higher the mean value of nutritional indicators, the lower the eGFR, and this difference was statistically significant in all nutritional indicators. This condition was not observed in relation to BMI in men (Table 2).

The adjusted logistic regression analysis for DM and HBP revealed that all nutritional indicators assessing abdominal obesity were associated with reduced GFR regardless of whether the subjects were hypertensive or diabetic. BMI did not demonstrate this association (Table 3).

DISCUSSION

Results of this study showed that quilombola remnants with higher mean values of nutritional indicators of obesity presented lower GFR. It was observed that women showed average values of higher nutritional indicators.

Nowadays, one aspect that has attracted attention in research on obesity is the distribution of body fat. Abdominal obesity has been considered an independent risk factor for several morbidities, representing a different risk when compared to other forms of body fat distribution.[3]

Some authors point out that the association between obesity and reduction of the glomerular filtration rate happens indirectly through the influence of risk factors such as diabetes, hypertension and metabolic syndrome.[5, 6] Others, however, have suggested a direct link between obesity and kidney disease.[7,8] Obesity may lead to an increase in glomerular size and abnormalities in glomerular function. In addition, it can also lead to segmental and focal glomerulosclerosis, which worsens the scenario of proteinuria and makes even faster the loss of renal function.[16]

It was also observed that all nutritional indicators of abdominal obesity evaluated in this study were associated with the reduction of GFR regardless of the presence of diabetes and/or hypertension.

Research indicates that anthropometric indicators of abdominal obesity such as WC, WHR and WHtR are more sensitive predictors for GFR reduction, as well as evaluation of metabolic effects and risk factors associated with obesity.[17, 18] It is worth noting that BMI, although being the most frequently used anthropometric indicator in research to classify obesity, is not able to distinguish lean mass from ad-

TABLE 3. LOGISTIC REGRESSION OF NUTRITIONAL INDICATORS AND GLOMERULAR FILTRATION RATE OF REMAINING QUILOMBOLAS ADJUSTED FOR ARTERIAL HYPERTENSION AND DIABETES. ALCÂNTARA – MA, 2013.

VARIABLES	RP	Confidence Interval (95%)	p. value*
Body mass index			
Eutrophia	1	-	-
Malnutrition	1,71	0,38 – 7,75	0,48
Overweight	1,21	0,61 – 2,39	0,59
Obesity	1,52	0,66 – 3,50	0,33
Waist circumference			
Normal	1	-	-
Altered	1,91	1,04 - 3,51	0,03
Waist-to-hip ratio			
Normal	1	-	-
Altered	2,15	1,15 - 4,03	0,01
Waist-to-height ratio			
Normal	1	-	-
Altered	2,96	1,14 - 7,68	0,02
Conicity index			
Normal	1	-	-
Altered	3,34	1,17 - 9,55	0,02
Estimated visceral adipose tissue			
Normal	1	-	-
Altered	4,40	2,29 - 8,45	< 0,001

RP: ratio of prevalence.

ipose mass, to differentiate the distribution of body fat or to detect the increase of fat that occurs with the advancement of age.[19]

Corroborating the findings of this study, researchers from a cohort of 3,107 Iranians found that abdominal obesity assessed by WC was associated with a higher risk of CKD regardless of BMI values.[20] Similarly, another cohort study with elderlies in the United States has shown that increased WC was associated with faster decline in GFR.[18] Dutch researchers who evaluated 7,676 subjects[17] and Americans who evaluated 13,324 subjects[8] have demonstrated a correlation of abdominal obesity, measured by WHR, and reduction of GFR. França et al.[21], evaluating 241 hypertensive patients in the Brazilian city of São Luís, MA, showed that GFR was lower in women with higher amount of estimated visceral adipose tissue.

A multicenter cohort study by Grubbs et al. (2014)[22] with 2,839 blacks and whites without renal disease at baseline has assessed the association of total obesity with GFR reduction over 10 years and found that the highest BMI was associated with a greater decline in renal function. On the other hand, Minoo et al. (2015)[23], evaluating the relationship between obesity severity and the presence of renal injury in 186 individuals in Tehran (the capital of Iran and Tehran Province), have not observed a correlation between BMI and renal injury.

Thus, the association between obesity and renal disease is a complex relationship that is not yet completely understood.[2] Increase in body weight may result in a greater expression of angiotensinogen in the adipocyte, with higher formation of angiotensin II in the circulation and, consequently, greater stimulus to lipogenesis. This mechanism leads to alteration of pressure homeostasis, which can also lead to changes in glomerular homeostasis.[24] Obesity also affects the renal medulla structure, since adipose tissue of the renal capsule, which is more developed in individuals with excess weight, can penetrate the renal medulla. With this, there is a compression of the glomerular and tubular fil-

tration systems, leading to an increase of arterial pressure in order to compensate the compression of nephrons, resulting in an increase of GFR, with consequent hyperfiltration and increased tubular reabsorption of sodium.[25, 26]

The nutritional profile of the quilombola remnants researched in this study was characterized by a high prevalence of overweight and abdominal obesity and prevalence among women was particularly alarming. These results indicate that abdominal obesity is an important health problem in quilombola communities and, more specifically, among women.[27] However, despite the greater amount of abdominal fat evidenced in the remaining quilombola women, some authors have shown that black women present smaller amounts of visceral fat when compared to white women.[28]

The greater amount of abdominal fat in women may reflect the accumulation of fat in the abdomen area due to occurrence of pregnancy, in addition to metabolic and hormonal changes throughout life.[29] Another possible explanation for this difference between genders is that the men who participated in the study worked harder in farming and fishing, developing more intense physical labor activities with little or no technological input, resulting in higher energy expenditure, while the women reported being more involved in household chores.

Corroborating the results, Soares and Barreto,[29] in quilombola communities in the Brazilian state of Bahia, have concluded that overweight and abdominal obesity are important health problems, especially among women. These same authors,[30] in a more recent study, have detected a high prevalence of nutritional risk for chronic noncommunicable diseases (NCDs), especially among women.

In the present study, prevalence of reduced glomerular filtration rate was considered low when compared to other studies conducted in Brasil, which found prevalence of CKD between 8.4% and 9.6%[31, 32] and with research involving Afro-descendant North Americans, which showed a prevalence of 19.4%.[32] This data can be explained by the fact that it is a predominantly young population (44.4 ± 17.3 years), in a phase in which renal changes are still in the early stages.

The study has some limitations. The first one is related to its cross-sectional design, which precludes conclusions about the impact of the variables evaluated on the reduction of glomerular filtration and the occurrence of CKD. Secondly, as a highly specific group of patients was evaluated, the results can not be automatically extrapolated to the entire remaining Brazilian quilombola population. On the other hand, the main positive aspect is the fact that it is the first study to evaluate the association between nutritional indicators of obesity in remaining quilombola communities in Brasil, filling a gap in relation to the topic.

CONCLUSION

Excess weight and abdominal obesity are an important health problem in remaining quilombola women. Glomerular filtration rate was reduced with increased abdominal obesity, regardless of gender.

RESUMO

O objetivo foi avaliar a associação entre o estado nutricional e a taxa de filtração glomerular (TFG) em remanescentes quilombolas. Estudo transversal, realizado em 32 comunidades remanescentes de quilombolas, no município de Alcântara – MA. Os indicadores nutricionais (IN) utilizados foram: índice de massa corporal (IMC); circunferência da cintura (CC); relação cintura-quadril (RCQ); relação cintura-estatura (RCEst); índice de conicidade (Índice C) e tecido adiposo visceral estimado (TAVe). A TFG foi estimada a partir da fórmula do CKD-EPI creatinina-cistatina C. O teste Shapiro Wilk foi utilizado para avaliar a normalidade das variáveis quantitativas. Para comparar os IN segundo sexo foi aplicado o teste qui-quadrado. Os testes Anova ou Kruskal-Wallis foram usados para verificar a associação entre os IN e a TFG. Dos 1.526 remanescentes quilombolas estudados, 89,5% eram da cor preta ou parda, 51,2% eram mulheres, 88,6% pertenciam às classes econômicas D e E e 61,2% eram lavradores ou pescadores. A investigação clínica revelou 29,2% de hipertensos, 8,5% de diabéticos e 3,1% com TFG reduzida. O IMC revelou 45,6% dos remanescentes quilombolas com excesso de peso. Quando comparadas aos homens, as mulheres apresentaram maior prevalência de excesso de peso pelo IMC (56,6% vs. 33,8%; p <0,001) e obesidade abdominal CC (52,3% vs. 4,3%), RCQ (76,5% vs. 5,8%), RCEst (82,3% vs. 48,9%) e TAVe (27,1% vs. 14,5%) (p<0,001). Comparando as médias dos IN segundo a TFG observou-se que, quanto maior o valor médio dos IN, menor a TFG (p<0,05). A TFG foi reduzida com o aumento dos valores médios dos indicadores nutricionais de obesidade abdominal, independentemente do sexo.

PALAVRAS-CHAVE: *Avaliação nutricional. Obesidade. Taxa de filtração glomerular. Grupo com ancestrais do continente africano.*

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The effect of hemodialysis on the body composition and cardiovascular disease markers in recently diagnosed end stage renal disease patients

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SUMMARY

AIM: *Uremic toxins and excess fluid contributes to increased cardiovascular (CV) risk. We aimed to determine the body fluid status in patients who are just starting hemodialysis (HD) and to determine the effects of excess fluid removed by HD on the CV system.*

METHODS: *A total of 52 patients with chronic kidney disease (CKD) who had just started HD were included. Before the HD, the left atrial diameter was measured, the volumes were calculated, the pulse wave velocity (PWV) and the augmentation index (AIx) were measured, the bioimpedance analysis (BIA) was performed, the blood was taken for brain natriuretic peptide (BNP). When patients reached their dry weight with HD, the same measurements were repeated.*

RESULTS: *Measurements were made to determine the volume status, and all parameters except the fat tissue index decreased significantly after HD. With the removal of fluid by HD, there was an average weight reduction of 4.38 kilograms. Positive correlations between PWV and age and cardiothoracic ratio (CTR) before HD were determined. Negative correlations were found between PWV and lean tissue mass (LTM) and intracellular water (ICW) before HD. At the end of the last HD, PWV was positively correlated with age, CTR, central pulse pressure Correlation between pulse wave velocity and LTI was negative*

CONCLUSIONS: *HD significantly improves PWV in patients reaching dry weight. Reduction of fluid excess by ultrafiltration in HD patients may reduce CV mortality by reducing arterial stiffness.*

KEYWORDS: *Pulse wave analysis. Natriuretic peptide, brain. Kidney diseases. Kidney failure, chronic. Electric impedance. Renal dialysis. Body composition.*

INTRODUCTION

The incidence and prevalence of chronic kidney disease (CKD) has increased day by day and has become an important public health problem.[1] The most important cause of mortality and morbidity in patients with CKD is cardiovascular disease (CVD). Inadequate ultrafiltration (UF) will cause patients to be exposed to fluid and pressure loads, while excessive UF will cause undesirable side effects, particularly hypotension, during dialysis.[2] In this study, we aimed to investigate the effect of reducing the fluid excess and correcting the uremic state on the cardiovascular system in patients with end-stage renal disease (ESRD) (with new onset dialysis). For this reason, echocardiography, arterial stiffness, pro-BNP and bioimpedance were used to assess CVD and volume status of patients before dialysis. The same parameters were repeated after the patients reached dry weight.

MATERIALS AND METHODS

A total of 52 patients (18-75 years old) who were admitted to the nephrology outpatient clinic and the emergency department for ESRD and who had just started HD were included in the study. Participants who were informed about the study were voluntarily included in the work after their signed approval. In our study, the exclusion criteria are listed below: Patients with cardiac arrhythmia, patients with coronary artery disease, patients with peripheral arterial disease, patients who have had stents in coronary arteries or underwent bypass surgery, patients with metal lid, stent, metal suture or metal prosthesis, patients with malignancy, patients with active infection during the study, pregnancy, patients who are not hemodynamically stable during the use of the device.

Detailed medical histories were obtained from all the subjects studied, general physical examination was performed, heart rate and arterial blood pressure recorded. Measurements of height and weight, body composition and volume, arterial stiffness, and echocardiographic measurements were performed. The body mass indexes were calculated by dividing the weight of the patients in kilograms by the height of the body in meters. [Body mass index (kg / m^2) = weight / (height) ^{2}]. Body surface area (BSA) was calculated using the DuBois formula by the patients' height (cm) and weight (kg) [BSA (m2) = (height 0.425 x weight 0.725) x 0.007184]. Age, gender, primary renal disease, hypertension, presence or absence of DM, medication usage, smoking status were recorded for all the subjects who were taken into the study.

LABORATORY ANALYSIS

BNP levels were measured before and after HD. BNP levels above 100 pg / mL were assessed in relation to heart failure. Hemoglobin, hematocrit, leukocyte, thrombocyte, total protein, albumin, globulin, sodium, potassium, calcium, phosphate, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, PTH, CRP, ferritin and serum iron levels were measured using Architect System Kits (With the Abbott II2000SR model Architect plus (serial number ISR0746).

Arterial Stiffness Measurement

A single-armed arteriograph device (Mobil-O-Graph PWA model pulse wave analyzer, branded by İ.E.M. GmbH), which has proven to be reliable for the measurement (user-independent, measuring with oscillometric method) was used. Patients included in the study were allowed to rest for 10 minutes before measurement. They were asked not to smoke or drink caffeinated beverages within the 30 minutes prior to the measurement. For each individual, date of birth, height, weight, smoking information was entered into the program of the device. While the patients were sitting, a suitable cuff was placed in the upper arm on the non-arteriovenous fistula. Three consecutive measurements were taken automatically with 30 seconds of duration. Measurements were made just before the first hemodialysis treatment on admission and after the last hemodialysis treatment before the discharge. As a measurement principle, the device was inflated so that the cuff could be at least 35 mm Hg above the currently detected systolic pressure. Thus, occlusion of the brachial artery was performed and blood flow was stopped for approximately 8-20 seconds during the measurement period. It is important to point ou that in the stop-flow condition, a membrane is formed in the brachial artery at the upper border of the inflated cuff. As air in the cuff is evacuated, arterial movement causes pressure changes in the cuff.[3] Pressure fluctuations become noticeable in the diaphragm when the central pressure changes and early (direct, P1) and late (reflected P2) systolic and diastolic waves reach the occlusion region. These small, weak pressure changes can be detected by the high-resolution pressure sensors of the arteriography, which are then amplified and scanned with a special tonometer. These changes were then evaluated by a computer. Systolic pressure, rapid increase of oscillations, average pressure, the most acute point of oscillations and diastolic pressure, all showed the point where oscillations disappeared rapidly.[4] This way, peripheral blood pressures, central systolic blood pressure, central diastolic blood pressure, central pulse pressure, cardiac output (CO), augmentation index and pulse wave velocity could be measured. Similar to the measurements made with the central pressure catheter, subclavian, axillary and brachial arteries act as cannula to transmit the central pressure changes to the sensor. The signals obtained through the oscillometer were transmitted to the computer via infrared, wireless communication network.[5]

Body Composition and Volume Measurement

Bioimpedance is based on the principle that an

alternating current is applied to the human body and a vector size called impedance (Z) is measured. Volume status and body composition were measured using a portable multifrequency bioimpedance spectroscopy device (BCM® Fresenius Medical Care D, GmbH).[6] Those involved in the study were placed in a flat lying position on the back. When bioimpedance measurements were made, the arm without arteriovenous dialysis fistula was used. A total of 4 special electrodes were attached and connected to the device. Electrodes were attached to the proximal side of the dorsal face of the hand and ankle, on the same side. The device makes measurements based on changing the conductivity and insulation property of the cell membrane by sending current in 50 different frequencies (between 5 and 1000 kHz). Measurements were completed for 1-2 minutes after entering age, weight, height data for each individual. The data was transferred to the computer via patient cards and analyzed using the fluid management system. Measurements were made just before the first HD treatment and after the last HD treatment before the discharge.

Echocardiography

Echocardiographic evaluations of all patients were performed immediately before beginning the first HD treatment and 2 hours after the last HD treatment before discharge. For the echocardiographic evaluation, services were received from the Adnan Menderes University Medical Faculty Hospital. Echocardiographic examination was performed by a single investigator with Philips brand model no HD11XE ultrasound system SN 2010-10 USD 10778319 with probe S3-1. After a 10-minute rest, the patient was recorded in the device's memory at the lateral decubitus position, at the end of the expiration, when necessary at short-term apnea periods, at a rate of 100 mm / sec. Averages of 3 consecutive measurements were taken in the assessments and

recorded on the patient registration forms. Left atrial dimension was measured in the parasternal long axis plane. The left atrial dimension was measured at the end of the ventricular diastole and where the left atrium was largest. Atrial diameters were measured by 2D echocardiography in apical 4 space, 2 space and long axis planes and atrium volume was calculated according to the formulas specified (LA Volume= 0.85XA1XA2 /L, where A1 and A2 were areas measured in 2ch and 4ch views, respectively. L was the linear measurement acquired in two different ways, parallel to atrial septum or perpendicular to mitral annulus).[7-9] To calculate the left atrium volume, measurements were made at the end of the left ventricular diastole at the time of the greatest left atrium just before opening the mitral valve.

Statistical Methods

Statistical Package for Social Sciences for Windows version 17 (SPSS Inc; Chicago, IL, USA) was used in statistical evaluations. Descriptive statistics were expressed as number (n, %) and mean ± standard deviation. The normal distribution suitability of the variables was examined by the Kolmogorov-Smirnov Test. T-test was used for independent groups and ANOVA for repeated measures was used to compare normal distribution variables. The Friedman ANOVA test was used to compare the variables without normal distribution. Multiple regression analysis was used to determine the factors affecting the AIx and PWV variables. The relationship of variables to each other was examined by Pearson Correlation Coefficient. $p < 0.05$ was considered significant.

Ethics Committee Approval

Our study was presented to Adnan Menderes University Faculty of Medicine Clinical Investigation Ethics Committee and it was approved by 7th decision of B.30.2.ADÜ.0.20.05.00 / 050.04-149 dated 14.06.2012.

TABLE 1: DEMOGRAPHIC DATA

	Gender		Total
	Male	Female	
Number of patients (n, %)	37 (71,2 %)	15 (28,8 %)	52 (100 %)
Age (years)	56,54 ± 12,81	62,27 ± 11,96	58,19 ± 12,73
Height (cm)	167,56 ± 7,60	151,73 ± 7,55	163 ± 10,44
Weight (kg)	73,43 ± 13,96	67,46 ± 18,13	71,71 ± 15,35
Body Mass Index (kg / m²)	26,17 ± 4,36	29,27 ± 7,67	27,07 ± 5,62

RESULTS

Newly diagnosed patients with end-stage renal insufficiency and who planned to undergo renal replacement therapy were included in the study. Among the 52 patients diagnosed with end-stage renal failure, 71.2% (n = 37) were male and 28.8% (n = 15) were female. The mean age of all patients, male and female patients was 58,19 ± 12,73 (years old), 56,54 ± 12,81 (years old) and 62,27 ± 11,96 (years old), respectively. The distributions of age, height, weight and body mass index values according to sex are shown in Table 1. CKD etiologic cause was hypertension in 44% of our patients, diabetes in 29%, glomerulonephritis in 7% and amyloidosis in 6% of our patients. Etiological cause could not be determined in 6% of patients. Volumetric status, vascular access, medical treatment, cigarette use, hepatitis and HIV serological status of the studied patients are given in patient characteristics section.

PATIENT CHARACTERISTICS

Vascular access route: Transient HD catheter, arteriovenous fistula (AVF) and permanent HD catheter ratios were 50%, 19.2% and 30.8%, respectively. Number of HD sessions reached dry weight (%); specified below: Dry weight was reached in 4 sessions (13.5 %), 5 sessions (46.2%,), 6 sessions (19.2%), 7 sessions (13%) and ≥ 8 sessions (7.6%). Pretibial edema status (%), specified below: 36.5% of the patients had no edema, 15.4% of the patients had edema in the

amount of trace, 1 + edema, 2+ edema, 3+ edema and 4+ edema status were, 15,4 %, 21,2 %, 9,6 % and 1,9 %, respectively. Diuretic treatment status (%), specified below: 46.2% of the patients were using diuretics and 53.8% were not using diuretics. Oral sodium bicarbonate intake status, (%); specified below: 90.4% of the patients were using oral sodium bicarbonate while 9.6% were not using oral sodium bicarbonate. Smoking status (%); While 19.2% of the patients were already smoker, 28.8% quit smoking, 52% were never smoker. HBsAg / Anti-HCV / Anti-HIV status (%); The rates of HBsAg positive, anti-HCV positive and anti-HIV positive patients were 7,7%, 0% and 0%, respectively. The laboratory data of the patients were given below: The mean urea, creatinine, uric acid, total protein, albumin and bicarbonate (HCO3) values of the patients were 184,54±62,48 mg/dl, 6,41±2,70 mg/dl, 8,18±2,52 mg/dl, 6,19±0,86 g/dL, 3,08±0,61 g/dL and 20,23±7,11 mEq/L, respectively. The mean sodium, potassium, calcium, phosphorus, ALP and PTH values were 136,15±5,83 mEq/L, 4,45±0,69 mEq/L, 7,97±1,16 mg/dL, 5,51±1,86 mg/dL, 110,73±67,46 U/L and 443,53±454,66, respectively. The mean hemoglobin, hematocrit, ferritin and CRP values were 9,21±1,52 g/dL, 28,47±4,76 %, 237,68±232,20 ng/mL and 52,26±61,12 mg/L, respectively. The mean total cholesterol, triglyceride, HDL and LDL cholesterol values were 174,67±45,05 mg/dL, 142,60±72 mg/dL, 33,08±11,64 mg/dL and 112,57±33,53 mg/dL.

Biochemical and body composition parameters that could be affected by body fluid status were compared before and after treatment (Table 2). Significant changes were detected in hemoglobin, hematocrit and sodium. In the body composition measurement to determine the body fluid state, all parameters except the fat tissue index decreased significantly after HD treatment (Table 2). PWV measurements made with mobilograph for arterial stiffness were found to be 8,84 m / s before the first HD treatment and 8,38 m / s after the last HD. It decreased significantly (p = 0.001). Before the first HD and after the last HD treatment, arterial stiffness and echocardiographic parameters were compared. PWV, MAP, CO, pulse pressure, central systole, central diastole and central pulse pressures were also significantly correlated. There was a significant decrease in CTI, LA diameters and volumes after treatment (Table 3). Correlations between PWV and age and CTI were positive (r = 0.865 p <0.001 and r = 0.301 p = 0.030, respectively) before HD treatment. Before HD treatment,

TABLE 2. BIOCHEMICAL AND BODY COMPOSITION PARAMETERS AFFECTED BY BODY FLUID STATUS

	Before the HD	After treatment	p Value
Hemoglobin (g/dL)	9,21±1,52	9,87±1,68	0,008
Hematocrit (%)	28,47±4,76	30,44±5,35	0,009
Sodium (mEq/L)	136,15±5,83	134,15±3,20	0,012
Albumin (g/dL)	3,08±0,61	3,17±0,65	0,164
BNP	443,10±584,06	560,64±2316,70	0,705
Weight	71,82±15,20	67,44±14,96	<0,001
Overhydration	2,52±3,28	0,39±1,62	<0,001
LTI	11,98±3,13	11,07±2,74	<0,001
FTI	13,98±7,06	14,12±6,65	0,556
BCM	17,14±6,81	15,37±6,02	<0,001
TBW	33,38±6,44	29,64±5,71	<0,001
ECW	16,82±3,45	14,10±2,64	<0,001
ICW	16,65±3,85	15,54±3,50	<0,001

LTI: Lean Tissue Index, FTI: Fatty Tissue Index, ECW: Extra Cellular Water, ICW: Intra Cellular Water.

negative correlations between PWV and LTM, ICW were detected (r = -0,408, p = 0,003 and r = -0,444, p = 0,001, respectively). In the analysis of the measurements performed after the last HD, positive correlations were found between PWV and age, CTI, central pulse pressure (r = 0,884 p <0,001, r = 0,348 p = 0,012, r = 0,641 p <0,000, respectively) and negative correlation with LTI.

DISCUSSION

CV complications are the most important cause of death in ESRD. In the emergence of this complication, classical atherosclerosis risk factors as well as factors of chronic renal failure (CRF) play an important role. In the course of CRF, vascular calcification, arterial stiffness, and accelerated atherosclerosis often develop prior to the stage of dialysis and transplantation. Vascular calcification and arterial stiffness are independent determinants of CVD risk in CRF. AIx, pulse pressure and PWV are the most important parameters showing arterial stiffness. It has been shown that central AIx and aortic PWV may be a more sensitive marker of arterial aging in younger individuals, and in those over 50 years of age, respectively.[10] Patients on dialysis had better arterial stiffness parameters than predialysis stage 5 CKD patients, indicating that dialysis can improve arterial stiffness in patients with uremia.[11] Progression of renal failure decreases the renal sodium excretion capacity and increases the incidence of hypertension due to extracellular volume increase.[12] Volume expansion is one of the most important factors that results in higher levels of blood pressure in patients with CKD.[13] Beyond causing hypertension, chronic fluid overload leads to an increase in PWV, an indicator of arterial stiffness, and left ventricular hypertrophy, which is closely related to mortality.[14] It has been shown that excess fluid plays an important role in the development of arterial stiffness in dialysis patients by increasing arterial distension and systolic blood pressure.[15] Both volume overload and angiotensin II may contribute to the decreased arterial compliance and increased AIx in HD patients.[16] Aortic stiffness in HD patients is thought to be due, in part, to a reduction in aortic compliance associated with excess volume (which can be reversible). Öğünç et al.[17] evaluated the changes occurring in PWV and AIx during a single HD ses-

sion. The measurements obtained at 15-minute intervals showed a significant decrease in PWV that started at 135 minutes during HD and continued until 30 minutes after the end of the dialysis. Di Iorio et al.[18] reported that PWV in HD patients underwent cyclic changes in a period of 1 week; PWV, hydration status, and blood pressure decreased during dialysis and increased in the interdialytic period. In our study, we aimed to investigate the effect of reducing the fluid excess and correcting the uremic state on the CV system in patients who reach dry weight after dialysis is started. The correlation of PWV with age and CTI before the first and after the last HD was determined. This is consistent with the fact that age is an independent variable in arterial stiffness. There was a decrease in all volumetric indicators with HD and a positive correlation between PWV and CTI was detected. HD treatment significantly improves PWV, which is indicative of arterial stiffness, in patients reaching dry weight. Decreased volume with ultrafiltration is associated with a decrease in all echocardiographic parameters. Benetos showed that elderly men with high lean mass and low-fat mass exhibit the best arterial profile with the lowest arterial stiffness in general population.[19] In our study, there was a negative relationship between PWV and LTM (before HD) and PWV and LTI (after

TABLE 3. ARTERIAL STIFFNESS AND ECHOCARDIOGRAPHIC PARAMETERS BEFORE AND AFTER TREATMENT.

	Before treatment	After treatment	P Value
Heart rate	83,58±14,52	88,60±16,16	0,054
Pulse wave velocity	8,84±1,82	8,38±2,07	0,001
Augmentation Index	26,5±12,61	30,31±12,52	0,078
Augmentation Pressure	9,48±7,63	7,50±5,65	0,18
MAP	107,15±17,37	97,35±21,71	0,007
CO	4,91±2,39	4,20±0,83	0,040
Peripheral Resistance	1,35±0,33	1,29±0,19	0,289
Cardiac Index	2,56±0,53	2,45±0,60	0,184
Pulse Pressure	54,67±17,25	45,61±18a,27	0,004
Central Systolic Pessure	122,35±22,42	109,02±26,12	0,002
Central Diastolic Pressure	85,27±15,12	78±17,75	0,019
Central Pulse Pressure	38,75±13,43	31,02±13,25	<0,001
CTI	55,2±7,82	48,31±5,48	<0,001
LA diameter	3,70±0,51	3,46±0,46	<0,001
LA volume – Elliptic	46,12±17,90	34,39±12,64	<0,001
LA volume – Biplane	60,78±31,93	44,88±22,54	<0,001

MAP: Mean arteriel pressure, CTI: Cardiothoracic index

HD); Indirectly, reduction in muscle mass may be important in increasing PWV and affecting arterial stiffness. This data supports the argument that better uremic clearance and better volume control can have positive results in arterial stiffness.[17] In our study, removal of excess fluid by ultrafiltration also led to an increase in hematocrit levels. Anemia usually develops during the course of CKD and may be associated with adverse outcomes. Anemia can lead to negative cardiac outcomes by inducing hypoxia and establishing the basis for LVH, ischemic heart disease, congestive heart failure. Early detection and effective treatment of anemia due to the development of CVD and adverse effects on mortality is important in preventing these adverse events. In patients with ESRD, known classical CV risk factors are insufficient to explain the development of early atherosclerosis. Effective treatment of modifiable risk factors in patients with CRF may reduce morbidity and mortality due to CVD. Therefore, recognition of the factors affecting the development of early LVH are more common in patients with CKD due to the presence of excess fluid and anemia. Correct determination of dry weight of patients is an important parameter in preventing heart failure development. In addition, BNP levels increase as the progression of heart failure progresses. It is known that BNP levels begin to increase before an apparent volume expansion occurs. Volume expansion is an important problem in patients with initial HD treatment. Interdialytic fluid intake has been shown to be associated with mortality. Long-term dialysis treatments are thought to reduce mortality by eliminating uremic toxins as well as providing volume balance. In patients with CKD, the risk of CVD can be reduced by preserving residual renal functions by salt and fluid restriction. In HD patients without residual renal function, the contribution of volume load to arterial stiffness can be prevented by correctly determining the volume status of the patient. By means of routine use of arterial stiffness measurement and bioimpedance devices, the volume status of patients can be controlled. Thus, CVD in patients with CKD can be detected and treated in advance and their development slowed down. Reduction of fluid excess by ultrafiltration in HD patients may reduce CV mortality by reducing arterial stiffness. Routine follow-up of arterial stiffness and bioimpedance parameters besides echocardiography may be helpful in determining cardiovascular risk in patients undergoing HD.

CONCLUSION

Routine measurement of arterial stiffness and bioimpedance parameters may play an important role in monitoring the cardiovascular risks of hemodialysis patients.

Acknowledgement

RESUMO

INTRODUÇÃO: *Em pacientes com doença renal crônica (DRC), toxinas urêmicas e hipervolemia contribuem para aumentar o risco cardiovascular. Nosso objetivo foi determinar o estado de hidratação em pacientes com DRC iniciando hemodiálise (HD) e avaliar os efeitos da correção da hipervolemia sobre o sistema cardiovascular.*

MÉTODOS: *Foram incluídos 52 pacientes que haviam acabado de iniciar HD. Antes do início da sessão, foram determinados o diâmetro e o volume atrial esquerdo, a velocidade de onda de pulso (VOP) e o índice de amplificação sistólica ("augmentation index", AI). Além disso, realizamos análise da composição corporal por bioimpedância elétrica (BIA) e mensuramos os níveis plasmáticos de peptídeo natriurético tipo B. Os mesmos procedimentos foram repetidos após os pacientes alcançarem o "peso seco".*

RESULTADOS: *O peso corporal dos pacientes foi reduzido, em média, em 4,38 kg. Na BIA, todos os parâmetros, exceto o índice de gordura corporal, foram significativamente reduzidos após a hemodiálise. Antes da HD, a VOP se correlacionou positivamente com idade e razão cardiotorácica (RCT), e negativamente com a massa magra e a água intracelular. Ao final da hemodiálise, a VOP se correlacionou positivamente com idade, RCT e pressão de pulso central, correlacionando-se negativamente com a Lean Tissue Index (LTI).*

CONCLUSÃO: *A hemodiálise melhora a VOP por meio da redução da volemia. O controle da hipervolemia via ultrafiltração pode reduzir a mortalidade cardiovascular por meio da redução da rigidez arterial.*

PALAVRAS-CHAVE: *Análise de onda de pulso. Peptídeo natriurético encefálico. Nefropatias. Falência renal crônica. Impedância elétrica. Diálise renal. Composição corporal.*

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Expressions of TOLL-like receptor 4 (TLR-4) and matrix metalloproteinase 9 (MMP-9)/Tissue inhibitor of metalloproteinase 1 (TIMP-1) in pulmonary blood vessels with chronic obstructive pulmonary diseases and their relationships with pulmonary vascular remodelling

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SUMMARY

OBJECTIVE: This study aims at investigating the expressions of TOLL-like receptor 4 (TLR-4) and matrix metalloproteinase 9 (MMP-9)/ tissue inhibitor of metalloproteinase 1 (TIMP-1) in pulmonary blood vessels with chronic obstructive pulmonary disease (COPD) and their relationships with pulmonary vascular remodelling (PVR).

METHODS: 60 para-tumour tissues were divided into the COPD group and the control group (n=30); the inflammations, pulmonary artery wall area/total artery area (WA%), and wall thickness/vascular outer diameter (WT%) were compared. The expressions of TLR-4, MMP-9/TIMP-1, and PCNA in pulmonary vascular smooth muscle cells were detected, and their relationships with PVR were then analysed.

RESULTS: The inflammations (1.6±0.8), WA% (44.0±6.4), and WT% (27.3±3.3) in the COPD group were higher than in the control group (0.3±0.5, 26.1±2.8, 15.6±1.8), and the expressions of TLR-4 (31.4±14.7) and MMP-9/TIMP-1 (2.2±2.6) were increased compared to the control group (4.7±4.5, 1.9±1.2). Correlation analysis: TLR-4 and MMP-9/TIMP-1 were positively correlated with the inflammations (r=0.18, P<0.01), WA% (r=0.68, P<0.01), and WT% (r=0.73, P<0.01), as well as positively correlated with the expression of PCNA (r=0.44, P<0.01); the upregulation of TLR-4 was positively correlated with the expressions of MMP-9 and TIMP-1.

CONCLUSIONS: The upregulation of TLR-4 in the pulmonary arterial smooth muscle cells of COPD patients could promote the in-flammations and the MMP-9 expression, thus causing abnormal degradation of extracellular matrix, so it played an important role in the process of PVR.

KEYWORDS: Lung diseases. Pulmonary disease, chronic obstructive. Matrix Metalloproteinase 9. Myeloid differentiation factor 88. Tissue inhibitor of metalloproteinases. Remodelling.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has become an increasingly serious global health issue, and the World Health Organization (WHO) estimates that COPD will rank the fifth of the worldwide disease burdens by 2020; multi-regional epidemiological surveys in China showed that the prevalence rate of COPD in people over 40 years old was 8.2%, and the prevalence increased significantly in older people.[1] As a progressive disease, its main characteristics are inflammations and lung function deterioration, and the pathological fea-

tures are mainly emphysema, mucus hypersecretion, chronic inflammations in airway and vessels, and remodelling. TOLL-like receptors (TLR) are an important class of pattern recognition receptors, as the main receptors mediating the lipopolysaccharide or endotoxin signal transductions, which originate from the outer membrane of the cell wall of Gram-negative bacteria, TLR could activate signal transduction pathways, induce the expressions of a variety of immune responsive genes, and is involved in the occurrence and development of COPD and other inflammatory diseases.[2-5] It has been proven that the high expression of TLR-4 could cause lung cells to produce a variety of inflammatory cytokines, interfere the Th1/Th2 balance, thus inducing such common respiratory diseases characterized by bronchial spasm, obstruction, inflammatory cell infiltration and destruction; furthermore, it could regulate the expressions of matrix metalloproteinase 9 (MMP-9)/tissue inhibitor of metalloproteinase 1 (TIMP-1) in multiple ways.[6-12] MMP-9 is an important enzyme regulating the synthesis and degradation of extracellular matrix, and TIMP-1 is the specific inhibitor of MMP-9, synthesized and secreted by macrophages, endothelial cells, fibroblasts, tumour cells, etc., and could inhibit the activities of MMP-9 mainly by blocking the self-activation of pro-matrix metalloproteinases, and specifically binding with Zn^{2+}, located in the catalytic activity centre of MMP-9 and forming stable complex. The ratio imbalance between these two was closely related with the persistent activation of chronic airway inflammations, tissue damages, repairing and remodelling, and revascularization.[13-15] Currently, studies are mostly focused on airway inflammation, oxidative stress, and airway remodelling, etc., and less on pulmonary vascular remodelling (PVR); furthermore, these studies used more animals or in vitro cultured pulmonary arterial smooth muscle cells, which are different from human specimens, so the results would be different. This study used human specimens as subject, aiming at reflecting the actual expression situations of COPD-related factors. By detecting the expressions of TLR-4 and MMP-9/TIMP-1 in pulmonary vascular smooth muscle cells, combined with detecting the related indexes, this study explored the roles of their expressions in the PVR process, thus providing new theoretical basis for further clarifying the mechanisms of PVR in COPD.

MATERIALS AND METHODS
Study population

The lung tissues were sampled from male patients with well-differentiated squamous cell carcinoma in the department of thoracic surgery of our hospital from January 2012 to May 2013. After measuring the lung functions before surgery, all patients were divided into the COPD group and the control group (30 cases each) according to the diagnosis and treatment standards of COPD.[16] Patients with lung malfunctions caused by airway-obstructing tumour were excluded, and the enrolled COPD patients had no other lung disease or chronic disease in other systems. The patients in the COPD group were in a stable stage, and the age difference between the two groups was not significant; no other systemic disease existed. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the Qingdao University. Written informed consent was obtained from all participants.

The normal periphery tissues that were over 5 cm away from the lung tumour and not infiltrated were selected, followed by formalin fixation, ethanol dehydration, xylene hyalinization, paraffin embedding, and preparation of 3 μm paraffin slices. The tissue specimens' properties were confirmed by pathologists.

Hematoxylin-Eosin (HE) staining

The pulmonary morphological and structural changes were observed under an optical microscope, and 100-500 μm in diameter arteries were selected for semi-quantitatively evaluation of the levels of arterial wall and surrounding inflammatory cell infiltration. Scoring criteria: no inflammatory cell infiltration: 0 point; minor inflammatory cell infiltration: 1 point; more inflammatory cell infiltration with uneven distribution: 2 points; more inflammatory cell infiltration and even distribution, but not gathered into clumps: 3 points; many inflammatory cell infiltration gathered into clumps: 4 points; five small pulmonary arteries with relatively round cross-section were then randomly selected for Dotslide imaging and measurement of inner and outer diameters of pulmonary arterioles, wall thickness, and wall area, and then WT% and WA% were calculated.

Immunohistochemically staining

The PV two-step method of immunohistochemically staining was used, and the operations were performed strictly according to the kit instructions. Rabbit anti-human MMP-9 polyclonal-antibody, rabbit anti-human TIMP-1 polyclonal-antibody and mouseanti-human PCNA were obtained from ZSGB-BIO (Beijing, China), rabbit anti-TLR4 antibody was obtained from BIOSS (Beijing, China). All other chemicals used were of the best commercially available grade. Each slice was randomly collected, five pulmonary arteries with 100~500 μm in diameter (×400): the positive expression of MMP-9 and TIMP-1 was characterized as brown cytoplasm, and that of TLR4 was buffy cytoplasm and/or cell membrane; the percentage of the cells with positive MMP-9, TIMP-1 and TLR-4 to the overall pulmonary vascular smooth muscle cells were then observed and counted. Proliferating Cell Nuclear Antigen (PCNA) was synthesized in nuclei, and the cells appearing brown granules were proliferating; the percentage of the cells with positive PCNA to the overall pulmonary vascular smooth muscle cells were then counted. The overexpression of PCNA indicated active cell proliferation and apoptosis reduction.

Statistical analysis

The data was analysed using SPSS17.0 statistical software. The measurement data was expressed as mean±standard deviation ($\bar{x}$±s). The intergroup comparison method used the t test, and the related indicators were compared using the Pearson correlation analysis, with $P<0.05$ considered statistically significant.

RESULTS
Characteristics of the study groups

All the patients were male, and there was no statistically significant age difference ($P>0.05$). The lung function, percentage of the first second forced expiratory volume to the estimated value (FEV1%), percentage of the first second forced expiratory volume to the forced vital capacity (FEV1/FVC%) in the COPD group were significantly lower than in the control group ($P<0.01$) (Figure 1).

Comparison of HE staining results

Under light microscope, the pulmonary vascular wall in the control group was complete and not thickened, without or with rare inflammatory cells around; the bronchial mucosa was intact, and the alveolar structures were normal. The lung vascular wall and surrounding tissues in the COPD group exhibited the infiltration of a large number of monocytes and lymphocytes, and the pulmonary vascular wall was significantly thickened. Compared with the control group, the patients in the COPD group exhibited significant inflammatory cell infiltration in pulmonary artery lumen and surrounding tissues, and the inflammation score was significantly higher ($P<0.01$); meanwhile, the arterial wall was thickened, the lumen was narrowed, and smooth muscle proliferation and collagen deposition appeared significantly; WT% and WA% in the COPD group were significantly higher than in the control group ($P<0.01$) (Table 1).

FIGURE 1

Basic information

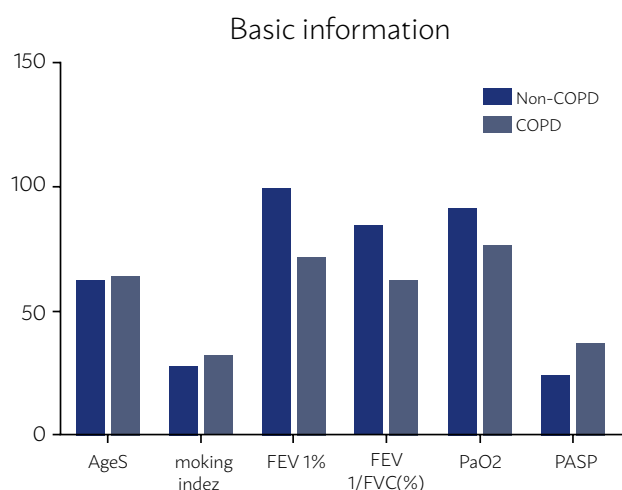**Figure 1.** Comparison of basic situation and lung functions between the two groups ($\bar{x}$±s).

TABLE 1. RESULTS OF LUNG TISSUE IMAGE ANALYSIS IN THE TWO GROUPS (X±S)

Group	Cases	Inflammation score	WT%	WA%
Control	30	0.3±0.5	15.6±1.8	26.1±2.8
COPD	30	1.6±0.8	27.3±3.3	44.0±6.4
T		−7.824	−17.140	−13.949
P		<0.01	<0.01	<0.01

TABLE 2. IMMUNOHISTOCHEMICALLY POSITIVE CELL RATIOS IN THE TWO GROUPS (X±S)

Group	Cases	TLR4 (%)	MMP-9 (%)	TIMP-1 (%)	MMP-9/TIMP-1 (%)	PCNA (%)
Control	30	4.7±4.5	5.5±6.1	4.1±4.2	1.9±1.2	9.4±4.8
COPD	30	31.4 ±14.7	39.2±24.0	32.8±22.4	2.2±2.6	26.8±15.6
T		-9.6	-7.5	-6.9	-0.65	-5.9
P		<0.01	<0.01	<0.01	<0.01	<0.01

Comparison of immunohistochemically results

The immunohistochemically results showed that the expression levels of TLR4, MMP-9, TIMP-1, and PCNA in the pulmonary vascular smooth muscle cells of the COPD group were significantly higher ($P<0.01$) (Table 2).

Correlation analysis

The expression of TLR-4 in pulmonary vascular smooth muscle cells was positively related with the PVR-associated indicators (WT%, WA%) (r=0.73, 0.68, $P<0.01$), PCNA (r=0.44, $P<0.01$), inflammations (r=0.48, $P<0.01$), and MMP-9/TIMP-1 ratio (r=0.18, $P<0.01$) (Table 3).

DISCUSSION

Chronic pulmonary vascular inflammations caused inflammation injuries, and repair-caused extracellular matrix increasing, proliferation of smooth muscle cells, hypertrophy of pulmonary artery muscles, stenosis, and blood vessel elasticity decreasing would cause PVR and pulmonary hypertension, as well as eventually result in the occurrence of ventricular remodelling and pulmonary heart disease. Chronic inflammations play an important role in PVR. Researches had shown that mild COPD patients without hypoxia and long-term smokers not meeting the diagnostic criteria already had significant pulmonary vascular inflammations, and abnormal pulmonary vascular structures and PVR could also be seen.[17] This study found many inflammatory cells

TABLE 3. CORRELATION BETWEEN TLR4(%) AND WT%,WA% PCNA(%), MMP-9/TIMP-1, INFLAMMATION SCORE.

R (P<0.01)	TLR4 (%)
WT %	0.73
WA %	0.68
PCNA (%)	0.44
MMP-9/TIMP-1	0.18
Inflammation score	0.48

existing around the pulmonary vessels in the COPD group, and the inflammation score was significantly higher than in the control group, consistent with other researches.[17] Sustained inflammation activation would release a variety of inflammatory mediators, thus promoting the activation of a variety of inflammatory cells; the interactions among cells could produce a variety of cytokines, which would then act on the pulmonary vascular smooth muscle cells and endothelial cells, promoting the proliferation of stromal cells, repetitively carrying out injury-repair processes, and involved in PVR. It was confirmed that the increased inflammatory cells in lung tissues were positively correlated with the destruction degree of lung parenchyma, as well as closely related to the degree of airflow restriction. With the aggravation of the disease and the declining of the lung functions, the number of inflammatory cells in lung tissues were increased.[18] This study showed that the pulmonary vascular wall and surrounding tissues of COPD patients exhibited a large number of inflammatory cell infiltration, the pulmonary vascular wall was significantly thickened, the smooth muscle cells exhibited significant hypertrophy, the intercellular substances were increased, and the lumen was narrowed, namely exhibiting significant PVR. Image analysis showed that, compared with the non-COPD group, the inflammation score, WT%, and WA% in the COPD group were significantly higher ($P<0.01$), and the inflammation score was positively correlated with WT% and WA% ($P<0.01$). The inflammations in pulmonary vessels might occur in early COPD stage, and the inflammatory cells might migrate from the bronchial arteries, thus directly or indirectly contributing to PVR.

Vascular inflammations were also closely related with the expression of TLR-4. Toll-like receptors (TLRs) belong to the recognition receptors of pathogen-associated molecular patterns (PAMPs), and could recognize PAMPs, thus activating the intracellular signalling pathways, promoting the release of inflammatory factors, and closely relating to the human innate

immunity and acquired immunity. Presently, TLR4 has been much studied; TLR4 is the main receptor of Gram-negative bacterial lipopolysaccharide, and its high-expression is associated with a variety of diseases; it could promote inflammations thus exacerbating disease severities. The TLR4 signal transduction pathways could be divided into the myeloid differentiation factor 88 (MyD88)-dependent and non-dependent pathways, in which the former is mainly through activating NF-κB, and then starting gene transcriptions and promoting the expressions of inflammatory factors; the latter is through binding the TLR-4 intracellular Toll-IL-1 receptor domain with the respective molecules, thus inducing the interferon regulatory factors to enter the nuclei, followed by promoting the maturation of dendritic cells and the expression of interferon.[19,20] The overexpression of TLR-4 gene in pulmonary cells might be caused by producing interferon and various inflammatory cytokines, thus participating in the chronic inflammations of COPD, inducing the influx of inflammatory cells, changing the lung vascular permeability, promoting the increasing of matrix metalloproteinase and other active substances, and further exacerbating the injury-repair process. The inflammatory cytokines produced by a variety of inflammatory cells, as well as the pathological changes of vascular endothelial cells, smooth muscle cells, fibroblasts, etc., are the leading cause for PVR. The accumulation of inflammatory cells and the production of inflammatory cytokines are closely related to the expression of TLR4. This study showed that the expression of TLR-4 in the COPD group was significantly increased, and the inflammatory cell infiltration was more significant; its expression level was positively correlated with WA% and WT%, and closely related to the expression of PCNA, suggesting that TLR-4 participated in the COPD inflammation, and was closely related to the proliferation of lung vascular smooth muscles. Some scholars found that simvastatin could inhibit the protein expressions of NF-κB, MUC5AC, and TLR-4 in the airway and lung tissues, thereby reducing the roles of airway inflammations and airway mucus hypersecretion.[21]

The upregulation of TLR-4 and its ligands could affect the metabolic balance of extracellular matrix, and participate in PVR. TLR-4 could induce the apoptosis of matrix-producing cells by the Fas-associated death domain pathways, resulting in the reduction of extracellular matrix; on the other hand, TLR-4 could induce macrophages to secrete MMP-9 so as to break down extracellular matrix.[22] MMP-9 is one member of the matrix metalloproteinases family, with its substrates mainly as gelatine, elastic fibres, and type IV, V, VII, and X collagens. MMP-9 could regulate cell adhesion, act on extracellular components or other protein components, thus involved in pathophysiological processes as angiogenesis, tissue remodelling, embryogenesis, or wound healing.[23] The results of this study showed that the expression of MMP-9 in the COPD group was significantly increased, and positively correlated with the expression of TLR-4; TLR-4 regulated the expression of MMP-9 via the NF-κB activation pathway.[6] The increased expression of MMP-9 in vascular smooth muscle cells would disturb the metabolism of extracellular matrix in vascular walls, promote the proliferation and migration of vascular smooth muscles, thus resulting in the vascular wall thickening and lumen stenosis. TIMP-1 is the specific inhibitor of MMP-9, and could be synthesized and secreted by a variety of inflammatory cells and lung structural cells; it might inhibit the MMP-mediated endothelial cell migration, and inhibit the angiogenesis. Since it has cell growth factor-like effects, it could promote the collagen synthesis and fibroblast proliferation, inhibit the extracellular matrix (ECM) degradation, and promote its deposition. The increased ratio of MMP-9/TIMP-1 was found to be related with a variety of lung diseases.[24] Some scholars found the imbalanced MMP-9/TIMP-1 ratio in the sputum of COPD patients, which was significantly increased in acute exacerbation, suggesting that it was related to the lung tissue remodelling.[25,26] The results of this study showed a significant increase of the MMP-9/TIMP-1 ratio in the COPD group, as well as the high expressions of MMP-9 and TIMP-1 in the wall smooth muscle cells, indicating that in the vascular wall of COPD patients there was the imbalance of proteases - anti-proteases; due to the imbalance of these two, the pulmonary vessels were damaged, and the repairing balance was also destroyed. Therefore, the occurrence and development of PVR were accelerated. Some scholars also found that in the rat model with monocrotaline-induced right ventricular hypertrophy, the degrees of pulmonary arterial muscularization and collagen deposition were related with the high expressions of MMP-9 and TIMP-1-proteins,[27] consistent with the results of this study.

The etiology and pathogenesis of PVR in COPD are involved in many factors, and the specific mechanisms are not fully understood, yet. This study

showed that inflammations might be the initiating factor of PVR appearing in early COPD, and the upregulation of TLR-4 might exacerbate the inflammations, as well as promote the expression of MMP-9 to be increased. Therefore, the MMP-9/TIMP-1 ratio was significantly increased, followed by the metabolic disorders of ECM in vascular walls and the induced proliferation of pulmonary vascular smooth muscles, which all played important roles in the process of PVR. This study used human specimens, unlike animal-only studies. Patients with severe COPD could not tolerate surgeries due to their fragile hearts and lung functions, so their lung tissues are difficult to obtain. Therefore, this study still lacked the corresponding expression data of the above pulmonary vascular smooth muscle cell-associated factors. Meanwhile, this study was only in mild-moderate COPD patients, so it had some limitations; however, through further studying the mechanisms of PVR in COPD, this study provided more evidence for the treatment of PVR. When inhibiting inflammatory responses, physical or chemical methods could be performed to intervene the expression of TLR-4, and this might become an effective way towards the prevention and treatment of PVR, pulmonary hypertension, and pulmonary heart disease.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

RESUMO

OBJETIVO: Este estudo tem como objetivo investigar as expressões de TOLL-like receptor 4 (TLR-4) e metaloproteinase 9 da matriz (MMP-9)/inibidor de tecido da metaloproteinase 1 (TIMP-1) em vasos sanguíneos pulmonares com doença pulmonar obstrutiva crônica (DPOC) e suas relações com o remodelamento vascular pulmonar (PVR).

MÉTODOS: Sessenta tecidos paratumorais foram divididos em grupo COPD e o grupo controle (n = 30). Foram comparadas as inflamações, área da parede da artéria pulmonar/área da artéria total (WA%) e espessura da parede/diâmetro externo vascular (WT%). As expressões de TLR-4, MMP-9/TIMP-1 e PCNA em células de músculo liso vascular pulmonar foram detectadas, e suas relações com PVR foram então analisadas.

RESULTADOS: As inflamações (1,6 ± 0,8), WA% (44,0 ± 6,4) e WT% (27,3 ± 3,3) no grupo COPD foram maiores que no grupo controle (0,3 ± 0,5; 26,1 ± 2,8; 15,6 ± 1,8). E as expressões de TLR-4 (31,4 ± 14,7) e MMP-9/TIMP-1 (2,2 ± 2,6) foram aumentadas em relação ao grupo controle (4,7 ± 4,5, 1,9 ± 1,2). Na análise de correlação, TLR-4 e MMP-9/TIMP-1 foram positivamente correlacionadas com as inflamações (r = 0,18; P <0,01), WA% (r = 0,68; P <0,01) e WT% (r = 0,73; P <0,01), bem como correlacionadas positivamente com a expressão de PCNA (r = 0,44; P <0,01). A elevação da TLR-4 foi correlacionada positivamente com as expressões de MMP-9 e TIMP-1.

CONCLUSÕES: A regulação positiva do TLR-4 nas células do músculo liso arterial pulmonar de pacientes com DPOC poderia promover as inflamações e a expressão de MMP-9, causando assim uma degradação anormal da matriz extracelular, por isso desempenhou um papel importante no processo de PVR.

PALAVRAS-CHAVE: Pneumopatias. Doença pulmonar obstrutiva crônica. Metaloproteinase 9 da matriz. Fator 88 de diferenciação mieloide. Inibidores teciduais de metaloproteinases. Remodelação.

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Metabolic syndrome and psoriasis: a study in 97 patients

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SUMMARY

BACKGROUND: *Psoriasis is associated with higher prevalence of metabolic syndrome (MS). The prevalence of MS varies according to the studied population as it suffers influence of genetics, aging, sedentary behaviour and diet.*

OBJECTIVE: *To study the prevalence of MS in local psoriasis patients and the influence of psoriasis variables on its appearance.*

METHODS: *A group of 97 psoriasis patients were studied for MS and compared with 97 controls. Psoriasis type, nail involvement, psoriasis extension measured by PASI (Psoriasis Area and Severity Index) were obtained through physical examination and history of previous myocardial infarction, angina and stroke were obtained through chart review.*

RESULTS: *Comparison of MS prevalence in psoriasis patients (49.4%) with controls (35.0%) showed difference with p=0.04; OR=1.8 (95%CI=1.02-3.23). Patients with psoriasis had higher body mass index (p=0.02), higher systolic blood pressure (p=0.007), lower HDL cholesterol (p=0.01), higher glucose (p=0.04), higher waist circumference (p=0.003) and more angina pectoris (p=0.03;OR=2.5; 95% CI=1.04-6.15) than controls. When psoriasis sample with and without MS were compared, those with MS were older (p=0.0004), had disease onset at older age (p=0.02), more tobacco exposure (p=0.02), and a tendency to have less scalp involvement (p=0.06) in univariate analysis. Logistic regression showed that only age and scalp involvement were independently associated with MS in the psoriasis sample.*

CONCLUSION: *In our psoriasis sample, MS prevalence is high and the items that deserve more attention are central obesity, low HDL, hypertension and smoking habits. In the psoriasis group, MS was associated independently with older age and less scalp involvement.*

KEYWORDS: *Psoriasis. Metabolic syndrome X. Metabolic diseases.*

INTRODUCTION

Psoriasis is a chronic and complex immune-mediated skin disorder.[1] The systemic nature of the inflammatory process involved in its etiopathogenesis is responsible for several co-morbidities, which themselves have a considerable impact on the patient's quality of life and mortality.[1] Myocardial infarction and stroke are considered to be increased in patients with psoriasis when compared with the general population.[2] Hence, the effective treatment of this disease includes not only care with the skin and nail manifestations but also attention to the associated conditions. A meta-analysis including 12 other studies showed that patients with psoriasis were 2.2 times more likely to have metabolic syndrome (MS) than the general population[2] and some authors found that there is a positive correlation between severity of

psoriasis and the presence of MS.[3] The exact mechanism for this interaction remains uncertain but the link between them may be the effects of pro-inflammatory cytokines and adipocytes on glucose regulation, lipid status, and endothelial function.[1]

MS is a clustering of several medical conditions such as central obesity, arterial hypertension, glucose intolerance, high serum triglycerides and low high-density lipoprotein (HDL) levels (4). It has been recognized as a pro-inflammatory, prothrombotic state associated with elevated levels of C-reactive protein (CRP), interleukin (IL)-6, and plasminogen activator inhibitor (PAI)-1.[5,6] This syndrome lies in the background of the association of psoriasis, cardiovascular risk and type 2 diabetes mellitus. The prevalence of MS varies according to the studied population as it suffers influence of genetics, aging, sedentary behaviour and diet. [7,8]

In the present study, we aimed at identifying the prevalence of MS in psoriasis patients from a single dermatology centre in Southern Brasil, and its relationship to the clinical profile of the skin disease.

METHODS

The local Committee of Ethics in Research approved this study and all participants signed a consent form. It is a cross sectional observational study that includes a convenience sample of 97 individuals formed by all psoriasis patients that came for regular consultations during a twelve-month period and that agreed to participate. All of them were from a single Dermatology Outpatient Clinic of a Tertiary Care Hospital. Patients under 18 years of age, pregnant women and patients with uncontrolled hypothyroidism were excluded. As control, 97 individuals were included, paired according to gender and age that came for an ophthalmologic appointment to test refraction and for routine gynaecological exams without chronic inflammatory diseases.

Epidemiological information (age, ethnic background, disease duration, tobacco use and age at disease onset), clinical aspects of psoriasis (psoriasis type, nail involvement, treatment), history of diabetes mellitus and high blood pressure treatment, previous history of myocardial infarction, angina and stroke were obtained through chart review and upon direct questioning. Data on PASI (Psoriasis Area and Severity Index) (9), arterial blood pressure, body mass index (BMI) and abdominal circumference were obtained through physical examination. Blood was drawn for fasting glucose (by automated enzymatic method), total cholesterol, HDL (high-density lipoprotein) cholesterol, LDL (low-density lipoprotein) cholesterol and triglycerides (by enzymatic/colorimetric methods); ESR (erythrocyte sedimentation rate by the Westergren method), uric acid (by fasting automated enzymatic method) and CRP (C reactive protein by immunoturbidimetry) were determined.

The metabolic syndrome diagnosis was done according to the guidelines developed by the 2001 NCEP ATP III and updated in 2005 in a statement from the American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI) (4,10). Current ATP III criteria define metabolic syndrome as the presence of any three of the following five traits:

- Abdominal obesity, defined as a waist circumference in men ≥102 cm and in women ≥88 cm ;
- Serum triglycerides ≥150 mg/dL or drug treatment for elevated triglycerides;
- HDL cholesterol <40 mg/dL in men and <50 mg/dL in women or drug treatment for low HDL cholesterol;
- Blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure;
- Fasting plasma glucose ≥100 mg/dL or drug treatment for elevated blood glucose.

STATISTICAL ANALYSIS

Data was collected in frequency and contingency tables. Data distribution was studied through the Kolmogorov Smirnov test. Central tendency was expressed in mean and standard deviation (SD) for parametrical data and median and interquartile range (IQR) for non-parametric data. Comparison studies were carried out through Fisher and chi-squared test when data were nominal and Mann Whitney and unpaired t test when data were numeric. Correlation studies were carried out through the Spearman test.

Data that showed association/correlation with p <0.1 with MS in univariate analysis were further studied through logistic regression (MS as dependent variable) to access the variables independence.

The adopted significance level was 5%. Calculations were done with the help of the software Medcalc 12.0.

RESULTS

Pairing data and sample description:

In the 97 psoriasis patients, 48/97 (49.4%) were female with age range between 20 and 80 years old (median=52; IQR=42-59 years); in the 97 individuals from the control group, 49/97 (50.5%) were female (p=0.94); with age range between 20 and 81 years old (median=52; IQR=31.5-60; p=0.44).

In the psoriasis group, the age of disease onset varied from 6-72 years old (mean 30.9±16.2 years) and the disease duration was of 1-43 years (median 13.0; IQR=8-21.5 years). Tobacco exposure was found in 61.8% of them. Tobacco use was more common in psoriasis patients (28.8% smokers and 32.2% former smokers) than controls (6.2% smokers and 23.7% former smokers) with p<0.0001.

In 81/97 (83.5%) the psoriasis was in plaques; in 10/97 (10.3%) it was gutatta; in 5/97 (5.1) it was pustular, in 4/97(4.1%) involved genital area; in 33/97 (34.0%) involved scalp; in 10/97 (10.3%) had articular involvement. Nail involvement was found in 27/97 (27.8%) ranging from 1 to 20 fingers (median 5.0; IQR=2-12). PASI varied from 0 to 49.8 (median=3.4; IQR=1.6-10.0). This sample was treated with cyclosporine in 3.0%; acitretin in 7.2%; methotrexate in 28.8%; ustekinumab in 7.2% and anti TNF-α drugs in 17.5%. About 34.0% used just topical treatment.

Comparison of psoriasis patients and controls according to metabolic profile:

The MS prevalence, its components as well as its cardiovascular repercussions in the psoriasis group compared with controls are shown in **Table 1**. In this table, it is possible to see that psoriasis patients had higher rate of MS, higher BMI and waist circumference, higher systolic blood pressure and glucose level, lower HDL cholesterol and higher number of individuals with angina pectoris.

Comparison between psoriasis patients with and without MS:

When psoriasis patients with and without MS were compared, we noticed that those with MS were older, had higher exposure to tobacco, disease onset at older age and tendency towards less involvement of scalp as shown in **Table 2**.

When psoriasis variables associated with MS with p <0.1 were studied through logistic regression, age (OR=1.08; 95% CI=1.06-1.16) and scalp involvement (OR=0.23; 95%CI=0.06-0.87) were independently related to MS.

DISCUSSION

The results of the present study have shown that psoriasis patients from our region have 1.8 times

TABLE 1 - COMPARISON OF METABOLIC SYNDROME, ITS COMPONENTS AND ITS CONSEQUENCES BETWEEN PSORIASIS PATIENTS (N=97) AND CONTROLS (N=97).

Variable	Psoriasis patients	Controls	P
Metabolic syndrome – n (%)	48/97 (49.4)	34/97 (35.0)	0.04* §
Mean body mass index and SD - (kg/m2)	28.4±5.09	26.8±4.68	0.02*
Median systolic blood pressure and IQR - (mm Hg)	130(120-140)	120(110-130)	0.007**
Median diastolic blood pressure and IQR - (mm Hg)	80 (70-90)	80 (70-90)	0.99**
Median waist circumference and SD (cm)	99 (92-108)	94 (86-104)	0.003#
History of hypertension - n (%)	37 (38.1)	43 (44.3)	0,38*
History of dyslipidemia- n (%)	23 (23.7)	23 (23.7)	1.00*
History of diabetes mellitus	10 (10.3)	10 (10.3)	1.00*
History of angina pectoris	18 (18.5)	8 (8.2)	0.003*§§
History of stroke	0	1 (1.03)	1.00##
History of myocardial infarction	4 (4.1)	5 (5.1)	1.00*
Median fasting blood glucose and SD (mg/dL)	89 (80-98.5)	91.7 (87-101)	0.04##
Median total cholesterol and IQR (mg/dL)	181(160-203)	180(160-212)	0.52**
Median HDL cholesterol and IQR (mg/dL)	42 (37.0-50.5)	47 (39.0-59.5)	0.01**
Median LDL Cholesterol and IQR (mg/dl)	196.4(84-129.9)	104 (86-126)	0.37 **
Median triglycerides and IQR (mg/dL)	118 (78-164.5)	119.2(87-168)	0.39**

*- chi squared test; ** Mann Whitney test; # unpaired t test; ## - Fisher test; SD= standard deviation; IQR= interquartile rate;n=number. § - OR = 1.8 (95%CI=1.02-3.23); §§ - OR=2.5, 95%CI=1.04-6.15).

more chances of having MS than controls, a result similar to the findings of a meta-analysis done by Armstrong et al[2] that included 41,853 patients. When comparing psoriatic patients with controls, the MS components that predisposed to this finding were body weight, waist circumference and high systolic blood pressure. Low HDL cholesterol and higher glucose levels were also a finding. Studies of the relationship between the individual components of MS with psoriasis are contradictory. Madanagobalane and Anandan[3] reported a higher prevalence of obesity in psoriasis patients than in controls as we did, but Nisa and Qazi[11], contrasting with our findings, did not observe a difference in the occurrence of central obesity. Finding a higher prevalence of central obesity is important in this context because it has become clear that the distribution and function of adipose tissue, rather than the amount of fat per se, exerts an important impact in MS.[12] A strong genetic component influencing fat distribution has been described and

may be responsible for the contradictory findings in populations with different ethnic backgrounds.[13]

Hypertension is another component of MS. While some studies have shown an association between hypertension and psoriasis, others have not[3,14-18]. In our study, the number of patients with hypertension was the same in controls and psoriasis but systolic blood pressure was higher in the psoriatic group.

Low HDL serum levels contribute to cardiovascular risk in this context as this particle has multiple anti-atherogenic properties.[15,19] Low serum HDL level may result in decreased activity of lipoprotein lipase, secondary to insulin resistance[20]. HDL anti-atherogenic properties are believed to be mediated by its role in the elimination of cholesterol from macrophages in a mechanism called "macrophage cholesterol efflux".[19] It also hinders the thrombotic component of atherosclerosis[21] and helps maintain the endothelial function.[22] Its serum levels are inversely related to stroke risk, need for coronary revascular-

TABLE 2 - COMPARISON OF PSORIASIS PATIENTS WITH (N=48) AND WITHOUT (N=49) METABOLIC SYNDROME (MS).

Variable	With MS	Without MS	P
Gender (female/male)	23/25	25/24	0.75 *
Mean age and SD (years)	54.9±10.6	45.9±13.3	0.0004#
Median age at disease onset and IQR (years)	44 (33-63)	31 (16-43.5)	0.002**
Median disease duration and IQR (years)	12(4.5-22.5)	13 (8-21.5)	0.72**
Ethnic background (A/C)	6/42	9/40	0.57*
Tobacco users - n (%)	35 (72.9)	25 (51)	0.02*
Median ESR and IQR (mm)	25 (10-42)	20 (9-33)	0.39**
Median CRP and IQR (mg/dL)	11.6 (6-17.5)	9.5 (5,2-19.3)	0.65**
Mean uric acid and SD (mg/dL)	5.2±1.1	4.9±1.1	0.14#
Presence of nail psoriasis – n (%)	16 (33.3)	12 (24.4)	0.33*
Median number of involved nails and IQR	5 (3.2-11.2)	6 (2-12)	0.76##
Vulgar psoriasis - n (%)	40 (83.3)	41 (83.6)	0.96*
Psoriasis guttata – n (%)	3 (6.2)	7 (14.2)	0.31 ##
Pustular psoriasis – n (%)	4 (8.3)	1 (2.0)	0.20##
Genital involvement – n (%)	1 (2.0)	3 (6.1)	0.61 ##
Scalp involvement – n (%)	12 (25)	21 (42.8)	0.06 *
Articular involvement – n (%)	5 (10.4)	5 (10.2)	1.0 ##
Median PASI and IQR	3.4(1.2-7.3)	3.5(1.6-10.0)	0.51**
Treatment			
Cyclosporine – n (%)	1 (2.0)	2 (4.0)	1.0 ##
Acitretin – n (%)	4 (8.3)	3 (6.1)	0.71 ##
Methotrexate – n (%)	16 (33.3)	12 (24.4)	0.33*
Ustekinumab – n (%)	2 (4.1)	5 (10.2)	0.43##
Anti TNF-α - n (%)	8 (16.6)	9 (18.3)	0.82*
Only topic treatment – n (%)	16 (33.3)	17 (34.6)	0.88*

*- chi squared test; ** Mann Whitney test; # unpaired t test; ## - Fisher test; SD= standard deviation; IQR= interquartile rate; n=number; ESR= erythrocyte sedimentation rate; CRP= S reactive protein; A/C= Afrodescendants/Caucasians; PASI =Psoriasis Area Severity Index.

ization, myocardial infarction and death from cardiovascular causes.[15,19] Beneficial effects of psoriasis treatment on HDL composition and function were observed in a small uncontrolled study.[23]

Smoking habits have a close relationship with psoriasis: it is associated with higher prevalence and severity of this skin disease.[24] The present study shows that, not only psoriasis patients smoke more than controls, but also that the prevalence of this practice was more common in psoriatic patients with MS. This practice certainly worsens the scenario. Smoking increases levels of triglycerides (TG) and lowers HDL cholesterol [25]; it also releases large amounts of free radicals causing oxidative stress.[23] Smokers were found to have the largest waist circumference and reduced insulin sensitivity.[26] The effect of smoking on metabolic disorders lasts up to 20 years after quitting the habit. [27]

Several authors have noted an association of progression of skin involvement[2,3,28] and presence of the arthropatic form[29] with SM. In our sample, it was not possible to link the presence of MS neither with the extension of the skin disease nor with articular manifestations. Our sample of patients with psoriatic arthritis was small and may not have had the strength to prove such association. Psoriatic arthritis occurs in 33% of psoriasis patients in our region[30] but it was present in roughly 10% of the studied sample. Concerning the occurrence of MS, according to the degree of skin involvement, it is important to note that categorizing severity of disease based on the percentage of affected body surface area may be a poor marker of the degree of systemic inflammation[18], especially when all types

of psoriasis are studied together. Most studies in the literature were done exclusively in patients with psoriasis vulgaris not including others forms as we did.

A curious feature in the present analysis was the negative association of scalp psoriasis with MS. In our sample, only one patient had isolated scalp involvement; all others had association with plaque psoriasis. We did not find data from others studies to compare with and this finding is a contribution of the authors to this issue.

In the current study, it was also not possible to prove that the medications used for treatment modified the scenario, including the use of biologic agents. Biological drugs may have a beneficial effect in this context [31]. The low sample number may have precluded this finding.

This is a transversal study with a small number of patients and all the limitations that this type of study has but it does show the urgent need for a holistic view in the care of psoriatic patients.

Concluding, in the studied sample, MS prevalence is high in the psoriasis patients and findings that deserve more attention are central obesity, low HDL, hypertension and smoking habits. As psoriasis is quite a common disease, with estimated prevalence of 2.5% in the general population in our country[32], this brings a great opportunity for the dermatologist to act as a transforming agent by improving the survival rate of this group of patients.

CONFLICT OF INTEREST

None.

RESUMO

OBJETIVO: Estudar a prevalência de SM (Síndrome metabólica) em pacientes com psoríase de nossa localidade, assim como a influência das variáveis da psoríase no seu aparecimento.

MÉTODOS: Noventa e sete pacientes com psoríase foram estudados para SM e comparados com 97 controles. Dados sobre o tipo de psoríase, envolvimento de unhas e extensão da lesão cutânea medida pelo PASI (Psoriasis Area and Severity Index) foram obtidas por meio de exame físico. Dados de infarto do miocárdio, angina pectoris e acidente vascular cerebral prévios foram coletados por meio de revisão de prontuários e questionamento direto.

RESULTADOS: A comparação da prevalência de SM em pacientes com psoríase (49,4%) com controles (35,0%) apresentou diferença com p = 0,04; OR = 1,8 (IC95% = 1,02-3,23). Pacientes com psoríase apresentaram maior índice de massa corporal (p = 0,02), maior pressão arterial sistólica (p = 0,007), menor colesterol HDL (p = 0,01), maiores valores de glicose (p = 0,04), maior circunferência da cintura (p = 0,003) e mais angina pectoris (p = 0,03; OR = 2,5; IC95% = 1,04-6,15) do que controles. Quando os pacientes de psoríase com e sem SM foram comparados entre si, aqueles com SM eram mais velhos (p = 0,0004), apresentaram início da doença em idade mais avançada (p = 0,02), tinham maior exposição ao fumo (p = 0,02) e tendência a ter menor envolvimento no couro cabeludo (p = 0,06) quando comparados com os sem SM na análise univariada. A regressão logística mostrou que apenas a idade e o envolvimento do couro cabeludo foram independentemente associados à SM na amostra de psoríase.

CONCLUSÃO: *Na presente amostra de pacientes com psoríase, a prevalência de SM é alta e os itens que merecem mais atenção são obesidade central, baixo HDL, hipertensão e hábito de fumar. No grupo da psoríase, a SM foi associada de forma independente com idade mais avançada e menor envolvimento no couro cabeludo.*

PALAVRAS-CHAVE: *Psoríase. Síndrome metabólica. Doenças metabólicas.*

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Evolution of incidence, mortality and cost of non-traumatic abdominal emergencies treated in Brasil in a period of nine years

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SUMMARY

OBJECTIVE: *To evaluate the incidence, mortality and cost of non-traumatic abdominal emergencies treated in Brazilian emergency departments.*

METHODS: *This paper used DataSus information from 2008 to 2016 (http://www.tabnet.datasus.gov.br). The number of hospitalizations, costs - AIH length of stay and mortality rates were described in acute appendicitis, acute cholecystitis, acute pancreatitis, acute diverticulitis, gastric and duodenal ulcer, and inflammatory intestinal disease.*

RESULTS: *The disease that had the highest growth in hospitalization was diverticular bowel disease with an increase of 68.2%. For the period of nine years, there were no significant changes in the average length of hospital stay, with the highest increase in gastric and duodenal ulcer with a growth of 15.9%. The mortality rate of gastric and duodenal ulcer disease increased by 95.63%, which is significantly high when compared to the other diseases. All had their costs increased but the one that proportionally had the highest increase in the last nine years was the duodenal and gastric ulcer, with an increase of 85.4%.*

CONCLUSION: *Non-traumatic abdominal emergencies are extremely prevalent. Hence, the importance of having updated and comparative data on the mortality rate, number of hospitalization and cost generated by these diseases to provide better healthcare services in public hospitals.*

KEYWORDS: *Emergencies. Mortality. Cost and cost analysis. Abdominal pain. Pancreatic diseases. Digestive system diseases. Cholelithiasis. Stomach ulcer*

INTRODUCTION

Historically, in emergency departments, trauma is the most frequent pathological condition (20.1%), followed by cardiopulmonary disorders (13.8%) and gastrointestinal problems, including abdominal pain and digestive symptoms (13.6%)[1]. Acute abdominal pain is one of the most common causes for referral to the emergency department (9.1%) and to emergency surgery, in addition to being the most common cause for non-trauma-related hospital admissions[1-3]. Patients that arrives with this symptom as main complaint in the admission is subjected to a series of complementary exams, such as abdominal radiography (30.1%), abdominal ultrasound (43.9%), CT scan (16.3%), blood testing (90.4%) and urine analysis (18%), which increase hospital costs. Furthermore, 35% of these patients with acute abdominal pain are admitted.[3]

There is a high prevalence of abdominal emergencies of non-traumatic origin treated worldwide; however, there are only a few studies on this topic in our community.

This is a national database study with the purpose of assessing the evolution of incidence, mortality and cost of non-traumatic abdominal emergencies treated in Brazilian emergency departments.

METHODS

This paper used information from DataSUS from 2008 to 2016 (http://www.tabnet.datasus. gov.br/cgi/deftohtm.exe?sih/cnv/niuf.def). In order to obtain the data, it was necessary to access the link of the Hospital Information System (SIH) and insert the CID 10 of the following diseases: acute appendicitis, acute cholecystitis, acute pancreatitis, gastric and duodenal ulcer, inflammatory bowel disease and acute diverticulitis. From there, the following variables were analysed: number of admissions, average of hospital stay, mortality rate and average admission cost (AIH). Each one of these diseases and their variables were assessed between 2008 and 2016.

Data was exposed in Excel spreadsheets, displayed in charts and compared against one another in relation to the diseases and variables assessed. The statistical analysis was carried out through Qui-square, considering p<0.05 as significant.

The research project was submitted for appreciation and approval of the Research Ethics Committee from the Universidade Anhembi Morumbi.

RESULTS

In descending order, non-traumatic abdominal emergencies with higher incidence treated in Brazilian emergency departments were cholelithiasis and cholecystitis, appendix diseases, acute pancreatitis, gastric and duodenal ulcer, diverticular disease and inflammatory bowel disease.

Analysing the data on Figure 1, it is possible to notice that until 2013, cholelithiasis and cholecystitis led the number of admissions, followed by appendix diseases. However, this relation reversed in the last years, with larger number of appendix diseases. However, the disease with higher growth in number of admissions was the diverticular disease, with an increase of 2,954 cases a year (68.2%), comparing 2008 with 2016. Appendix diseases and acute pancreatitis had similar percentage increases in this period, 34,630 (45.7%) and 9,004 (42.8%), respectively. These three diseases were the ones that had a growth proportionally higher than the Brazilian population in this period, and the diverticular disease had a growth significantly higher than the others did (p<0.001). Cholelithiasis and cholecystitis had a growth of 11,901 (11.9%) and inflammatory bowel disease, 160 (4%) in the same period. On the other hand, there was a decrease of 6,700 (40%) in admissions due to gastric and duodenal ulcer.

Over the eight years, there were no major variations in the hospital stay average. The disease with higher increase was the gastric and duodenal ulcer, with a growth of 0.81 day (15.9%), followed by inflammatory bowel disease, with an increase of 0.55 day (8.15%); pancreatitis, with an increase of 0.5 day (7.41%); cholelithiasis and cholecystitis, with an increase of 0.31 day (7.9%); diverticular disease, with a decrease of 0.45 day (7%), and appendix disease, with a decrease of 0.47 day (12%) (Figure 2).
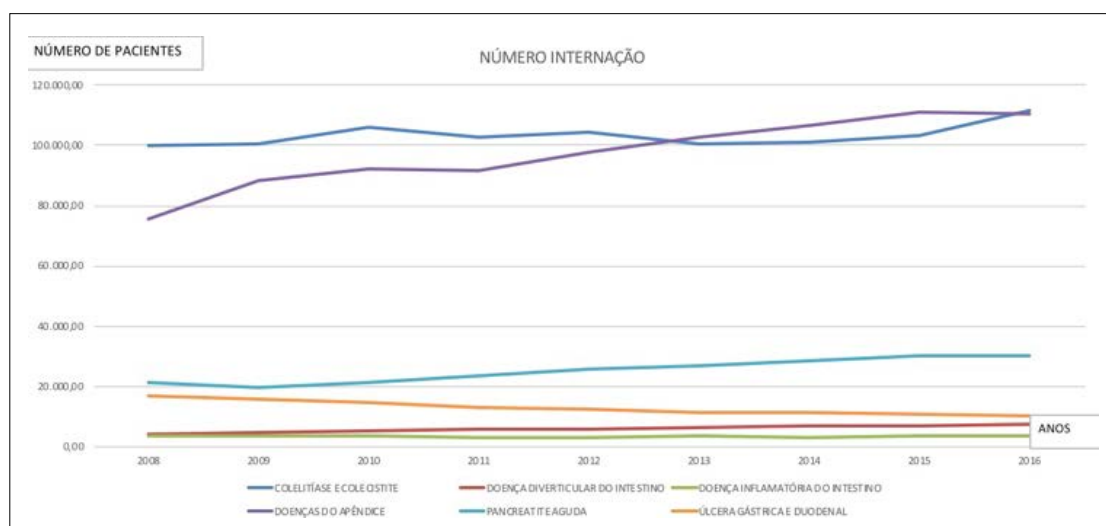
Among these diseases, mortality rate due

FIGURE 1. Number of admissions per non-traumatic abdominal diseases between 2008 and 2016.
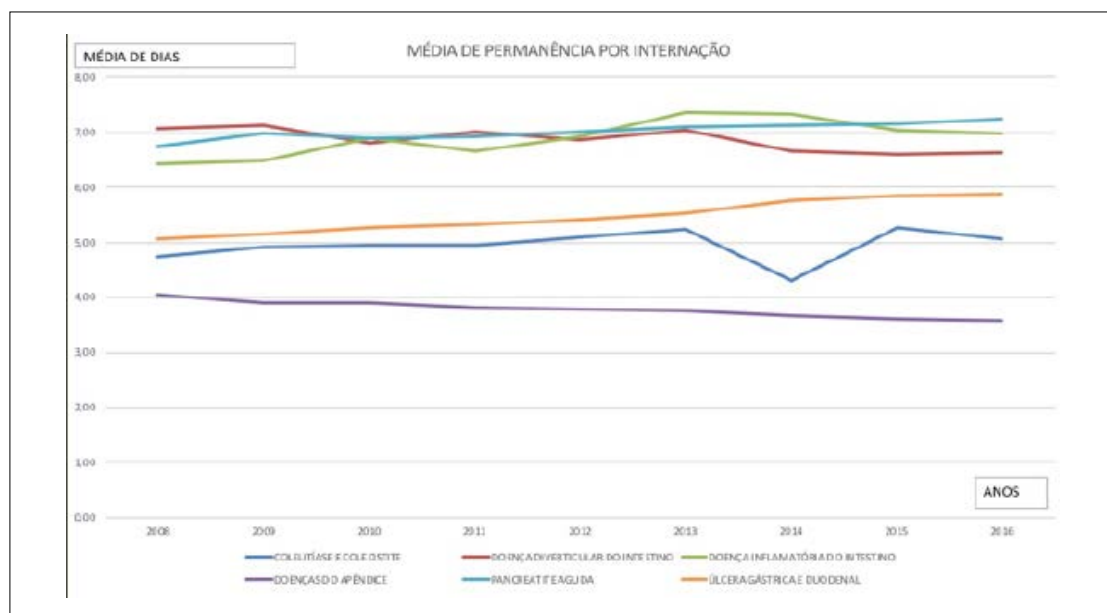
FIGURE 2. Average of hospital stay per non-traumatic abdominal diseases between 2008 and 2016.

to gastric and duodenal ulcer was the only one that presented a significant increase, with 4.6 deaths/1,000 people (95.63%), when compared to the other diseases: cholelithiasis and cholecystitis, with an increase of 0.16 (10.3%); acute pancreatitis, with an increase of 0.05 (0.9%); acute diverticulitis, with a decrease of 0.37 (4.7%); inflammatory bowel disease, with a decrease of 0.22 (7.4%) and appendix disease, with a decrease of 0.11 (24%), when comparing 2008 and 2016 (Figure 3).

All diseases assessed had their average admission cost (AIH) increased between 2008 and 2016, and diverticular disease maintained the highest value. However, the one that had the highest proportional increase over the last eight years was gastric and duodenal ulcer, with an increase of BRL 555.4 per admission (85.4%) (p<0.001), followed by inflammatory bowel disease, with an increase of BRL 234 per admission (42%); acute pancreatitis, with an increase of BRL 224.95 per admission (41.1%); diverticular disease, with an increase of BRL 454 per admission (36.9%); cholelithiasis and cholecystitis, with an increase of BRL 190 per admission (34.5%) and lastly, appendicitis, with an increase of BRL 150.86 per admission (30.3%) (Figure 4).

DISCUSSION

Abdominal emergencies of non-traumatic origin are extremely prevalent in emergency departments worldwide, with a significant impact on mortality rate, on number of hospital admissions and on costs. This is a national study that correlates the main gastroenterological emergencies of non-traumatic origin with variables assessed.

Diverticulosis is a phenomenon that depends on age, affecting up to 60% of adults over 60 years old, which justifies it being the disease with the higher growth in number of admissions (68.2%), once the elderly population is the one presenting the higher growth projection worldwide[4]. This projection, added to the increase in morbidities (obesity, diabetes mellitus), also makes cholelithiasis, a disease already with large prevalence in the population, lead the number of hospital admissions.[5]

Appendicitis shares the leadership in number of admissions with cholecystitis, since even though it is more prevalent children and young adults, it is the intra-abdominal pathological condition that most requires surgical interventions in the emergency room, resulting in a high number of hospital admissions.[2,6]

The availability of proton-pump inhibitors and their more frequent use, in addition to the *H. pylori* treatment, have contributed to a reduction of gastric and duodenal ulcer prevalence, and the ulcer cases admitted represent only the severe cases (10% of the total peptic ulcer cases), which is related to a lower average of hospital stay.[7]

On the other hand, the mortality rate of gastric and duodenal ulcer had an increase of 95.63%, since it takes into account that admissions represent the complicated ulcer cases that 15% evolve to a diges-
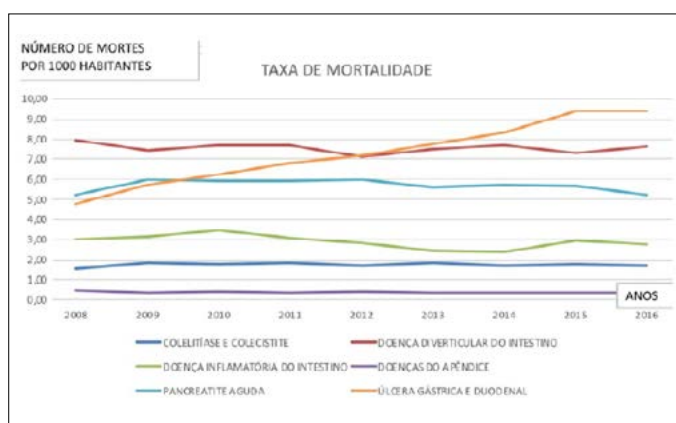
FIGURE 3. Mortality rate per non-traumatic abdominal diseases between 2008 and 2016.
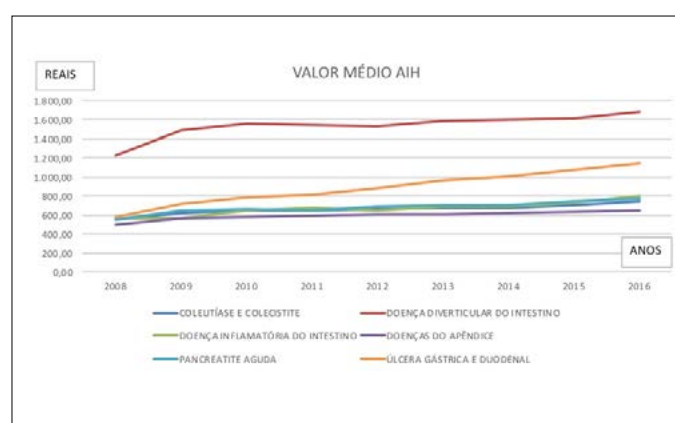

FIGURE 4. Average costs in Brazilian expenses per admission of non-traumatic abdominal diseases between 2008 and 2016.

tive bleeding, 7% to perforation and less than 2%, to obstruction.[7]

Appendix diseases had a decrease of 24% in the mortality rate, probably due to an early and more appropriate treatment. Furthermore, the use of laparoscopic appendectomy, a minimally invasive method associated with less incidence of post-surgery complications, had a significant growth in past years[6]. According to a study carried out by Santos et al.[6], the mortality rate was 57.1% lower in the laparoscopic method when compared to the open appendectomy, a statistically significant difference, however taking into account that this study did not compare the access methods stratified by severity[6]. On the other hand, the literature is clear when stating the advantages of the laparoscopic method such less post-surgery pain, early return to activities and better aesthetic result.[8-10]

The diverticular disease remained with the highest AIH value due to the complexity of its treatment. In studies carried out by the Johns Hopkins University School of Medicine, it was noticed that from 310,983 visits to the emergency department for diverticulitis, 53% resulted in hospitalization and 6% in surgical intervention. From those 6%, 75% had a rectosigmoidectomy and 16% had a left hemicolectomy, justifying the high hospital costs.[4, 11]

In this study, the disease that had the highest proportional cost increase in the period of nine years was the gastric and duodenal ulcer, with an increase of 85.4% due to the higher severity of the cases and to the need for complex procedures. Taking into account the inflation of 74.79% in this period, the only disease that had a cost increase above the inflation rate was the gastric and duodenal ulcer. All others

presented cost reduction when compared to the inflation. This can be explained by the complexity of the presentation forms of the gastric and duodenal ulcer, such as bleedings and perforation.

It is believed that a portion of the population does not have access to ulcer diseases treatment, with difficult access to gastroenterologists, exams such as endoscopy and drug treatment, even though the distribution of proton-pump inhibitors by the government is free. This scenario causes the sick person, in lower number, to present the severe complications of peptic ulcer disease, thus requiring prolonged admissions, blood transfusions, emergency endoscopies and sometimes, surgical procedures, which increases its cost.

Appendix diseases were the ones with lower increase in AIH average value, even with a higher use of the laparoscopic method.[6]

This paper presents limitations since DataSUS information spreadsheets have a limited number of data, preventing analyses that are more complex. However, this study shows the main cases of non-traumatic abdominal emergencies in the Country, with results that can guide healthcare policies and hospital emergencies cost analysis in Brasil.

CONCLUSION

There was an increase in the number of admissions of all the non-traumatic abdominal diseases, except for the gastroduodenal ulcer. There was a significant increase of mortality by gastroduodenal ulcer. Treatment costs have increased for all non-traumatic abdominal diseases, especially for the gastroduodenal ulcer.

RESUMO

OBJETIVO: *Avaliar a evolução da incidência, mortalidade e custo das urgências abdominais não traumáticas atendidas nos serviços de emergência do Brasil durante o período de nove anos.*

MÉTODOS: *Este trabalho utilizou informações do DataSus de 2008 a 2016, (http://www.tabnet.datasus.gov.br). Foram analisados número de internações, valor médio das internações (AIH), valor total das internações, dias de permanência hospitalar e taxa de mortalidade das seguintes doenças: apendicite aguda, colecistite aguda, pancreatite aguda, diverticulite aguda, úlcera gástrica e duodenal, e doença inflamatória intestinal.*

RESULTADOS: *A doença que teve o maior crescimento do número de internações foi a doença diverticular do intestino, com o valor de 68,2%. Ao longo dos nove anos não houve grandes variações da média de permanência hospitalar, sendo que o maior aumento foi o da úlcera gástrica e duodenal, com crescimento de 15,9%. A taxa de mortalidade da doença por úlcera gástrica e duodenal teve um aumento de 95,63%, consideravelmente significante quando comparada com as outras doenças. Todas tiveram seus valores de AIH aumentados, porém, a que proporcionalmente teve o maior aumento nos últimos nove anos foi a úlcera gástrica e duodenal, com um acréscimo de 85,4%.*

CONCLUSÃO: *As urgências abdominais de origem não traumática são de extrema prevalência, por isso a importância em ter dados atualizados e comparativos sobre a taxa de mortalidade, o número de internações e os custos gerados por essas doenças, para melhor planejamento dos serviços públicos de saúde.*

PALAVRAS-CHAVE: *Emergências. Mortalidade. Custos e análise de custo. Dor abdominal. Pancreatopatias. Doenças do sistema digestório. Colelitíase. Úlcera gástrica.*

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Spine surgery in patients with ankylosing spondylitis

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SUMMARY

INTRODUCTION: *Ankylosing spondylitis (AS) is an idiopathic seronegative spondyloartropathy that involves mainly the axial skeleton and the sacroiliac joints. AS promotes biomechanical changes in the spine that predispose to fractures, spinal deformity and spondylodiscitis. The aim of this article is to report the clinical and laboratorial characteristics of patients with AS who underwent spinal surgery at our Institution.*

METHODS: *Retrospective review of medical charts of patients who had AS and underwent spinal interventions.*

RESULTS: *Nine patients were found and eight were included in the present study. There were three men and six women and the patients' mean age was 57 years old. All patients had pain at the involved spinal level and one patient had tetraparesis due to cervical myelopathy. Acute-phase proteins were positive in six patients (75%), and HLA-B27 was found in two patients (25%). Four patients had the radiological diagnosis of spondylodiscitis (50%) and underwent a spinal disc biopsy. They were all characterized as having aseptic spondylodiscitis. Three patients were free of pain with analgesics in their last follow-up and one patient had only partial solution of his pain. Three additional patients had spinal fractures surgically treated (37.5%) and one patient was operated because of a cervical kyphotic deformity (12.5%). There were no deaths or surgical complications in this series.*

CONCLUSIONS: *the majority of our clinical and laboratories findings were discrepant with the medical literature. These differences may be secondary to regional characteristics or by the fact that our population included only those patients who underwent spinal surgery.*

KEYWORDS: *Spondylitis, ankylosing. Fractures, bone. Discitis.*

ABBREVIATIONS: *MRI = magnetic resonance imaging; CT = computed tomography, AS= Ankylosing spondylitis, HLA=Human leukocyte antigen, ASAS= Assessment of Spondyloarthritis international society, SpA= Spondyloarthitis, NSAIDSs= Nonsteroidal anti-inflammatory drugs.*

INTRODUCTION

Ankylosing spondylitis (AS) is an idiopathic seronegative spondyloartropathy that involves mainly the axial skeleton and the sacroiliac joints. The disease has an estimated prevalence of 0.1 to 1.4% of the adult population, typically affecting men and with clinical symptoms starting at 20-30 years of age.[1]

There is a rough correlation between the prevalence of HLA B27 and the incidence and prevalence of AS.[2] Although 6-10% of the world population is positive for HLA B27, only 5% of them will develop AS. However, almost 90% of the AS patients are positive to HLA B27.[1,3,4] There are no laboratorial findings that define AS, and in contrast to other systemic inflam-

matory diseases, acute-*phase* proteins are frequently in the normal range.

The diagnosis was first defined using the modified New York criteria.[4, 5] These criteria presented high sensibility and specificity; however they were not useful for early diagnosis or prevention. Because of that the most recent ASAS classification criteria for axial spondyloarthritis were developed for early and established cases and include the MRI technique (to depict active inflammation) as an important tool for early diagnosis (Table 1).[6]

AS has a caudo-rostral progression, altering the biomechanical properties of the spine and diminishing its resistance through a process of remodeling, which involves ligamentary ossification, vertebral joint fusion, osteoporosis and finally, spinal deformity. The ankylosed spine is prone to fractures even after minor traumas; additionally, fractures are often unstable and require proper treatment to avoid primary and secondary neurological injury, disability, and progressive deformity.[7,8,8,10]

Other possible complication is the occurrence of spondylodiscitis, especially for those patients who receive medicaments such as biologic agents or tumor necrosis factor antagonists, who may increase the chances of infections. It is radiologically suspected by the combination of narrowing of the disc space and erosions at the terminal plates summed to peripheral sclerosis, most of the times with gadolinium enhancement at the MR. Of note, it may also be aseptic, secondary to AS disease itself.[9, 10,11,12,13]

The aim of the present manuscript is to analyze the patients with AS who underwent spinal surgeries at our tertiary University Hospital.

TABLE 1 - ASAS CLASSIFICATION CRITERIA FOR AXIAL SPONDYLOARTHRITIS (SPA)

In patients with ≥ months back pain and age onset < 45 years	
OR	
Sacroiliitis on imaging and ≥1 SpA feature	HLA B27 positive and ≥2 other SpA features
Spa features:	Sacroiliitis on imaging
Inflammatory back pain Arthritis Enthesitis (heel) Uveitis Dactylitis Psoriasis Crohn´s / colitis Good response to NSAIDs Family history of SpA HLA B27 Elevated C reactive protein	Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA Definite radiographic sacroiliitis according to Modified New York criteria

METHODS

A retrospective study at the University Hospital of the State University of Campinas, São Paulo, Brasil, was performed. The medical charts of all patients with the diagnosis of AS that had spine surgery, were reviewed. Institutional Review Board approval was obtained under the number 17337313.7.0000.5404.

The inclusion criteria were: patients with diagnosis of AS established by the internal medical department of our institution that underwent a spinal procedure by any reasons in our hospital. All procedures were performed by the same spine surgeon (AFJ).

The exclusion criteria were: lack of medical or radiological data or lack of postoperative follow-up.

The following variables evaluated were:

Clinical information: gender, age, time of disease progression, clinical manifestation, neurological status at diagnosis, description of the surgical procedure and clinical evolution, conventional criteria to evaluation of AS (peripheral arthritis, enthesopathy, uveitis), comorbidities, and history of trauma.

Laboratorial information: *acute-phase* proteins results, presence of antigen HLA B27, results of hemocultures and biopsy results

Radiological findings: reported on spine MRI and CT scans.

RESULTS

Nine patients were found (three males and six females), but one patient was excluded due to the lack of data in the medical charts. Eight patients were included in the present study and were fully evaluated.

The male/ female ratio was 1:3; the mean age was 57 years, ranging from 30 to 73 years; the mean time of disease progression was 9.5 years, ranging from five to 20 years. The most common clinical presentation of spinal disease was pain in the affected segment, present in all cases.

Considering the neurological status, only one patient had incomplete neurological deficits (Frankel C) (12.5%). This patient was diagnosed with spondylodiscitis at C45 and C67 disc and had a concomitant myelophaty and tetraparesis. He underwent an open anterior cervical disc biopsy, and the tetraparesis improved spontaneously after a few months. No bacteriological origin was confirmed. All the remaining patients were neurologically intact.

Peripheral arthritis was documented in 50% of the cases, entesopathy in 25% of them and uveitis

FIGURE 1 – Sagittal T2 sequence thoracic spine MRI showing vertebral body edema at T1112 and T12L1 in the intervertebral discs. This 57 years-old man underwent a spinal needle biopsy at the T1112 disc due to persistent back pain. Final result was compatible with a chronic inflammatory process without bacteriological evidence. This patient improved his pain in the following three months without any additional spine intervention.

was not reported in the included patients. The most common comorbidities were arterial hypertension and diabetes that presented concomitantly in three patients. Two patients were smokers.

The laboratorial findings *showed that acute-phase* proteins were positive in six patients (75%), and HLA-B27 was found in two patients (25%).

Four patients had the diagnosis of spondylodiscitis (50%). One case at L5S1, one case at C45 and C67 (with myelopathy, as mentioned above), one case at T12L1 disc, and the last case at T1112. The clinical presentation was limiting pain in the affected segment in all cases, and the cervical case had some degree of cervical myelopathy in the affected segment. All of them presented negative hemocultures and urocultures, but two of them had elevated acute phase proteins. After that, a percutaneous needle spine biopsy was performed in three cases and one had an open spinal biopsy. The results revealed unspecific chronic inflammatory process in all cases, without positive identification of the etiological agent, characterizing aseptic spondylodiscitis. Treatment consisted in a short-term empiric antibiotics treatment,

pain medication and physical therapy. The outcome was complete pain resolution in three patients, and one patient had partial resolution of the pain in the following months.

Three patients had spinal fractures (37.5%), associated with minor trauma and one woman had a cervical kyphotic deformity that precluded her from looking horizontally when walking (12.5%). The cervical kyphotic deformity was treated by posterior instrumented cervical fusion (C2T3) with a pedicle subtraction osteotomy of c7.

The three patients with thoracic fractures were treated by a posterior instrumented fusion and had an AO type B3 injury with anterior distraction (T1011; T910 and T89 fractures). All of them had a posterior instrumented fusion two segments above and two segments below the involved level with a reasonable clinical improvement of their pain.

DISCUSSION

Our spine surgery division performs around 150 procedures each year. However, in the period between 2011 and 2016, only nine patients had the diagnosis of AS, with an estimated incidence of one per 100 patients who underwent a spinal procedure at our institution.

Regarding gender, our study found a predominance of the female population, with a male/female ratio of 1/3. The literature estimates about two men for each women affected by AS.[8,13] Some authors suggested an overestimation of male prevalence due to lighter forms of presentation in women, leading to sub notification of those cases.[1,5]

The laboratory findings in our patients also diverged from the reported in the literature.[1,14,15] In our series, most patients (62.5%) presented positive acute phase proteins, and the minority (25%) presented positive antigens HLA B27. These differences may be secondary to regional characteristics of our patients or by the fact that our population included only those patients who underwent a spinal procedure.

The majority (50%) of our evaluated patients was diagnosed with an aseptic spondylodiscitis also known as Andersson's lesions (described for AS). This data diverges from the literature which suggests that discitis is a rare presentation in the setting of AS. However, its incidence may be underestimated due to the asymptomatic presentation of some cases of aseptic spondylodiscitis.[11] Of note, the biopsy of
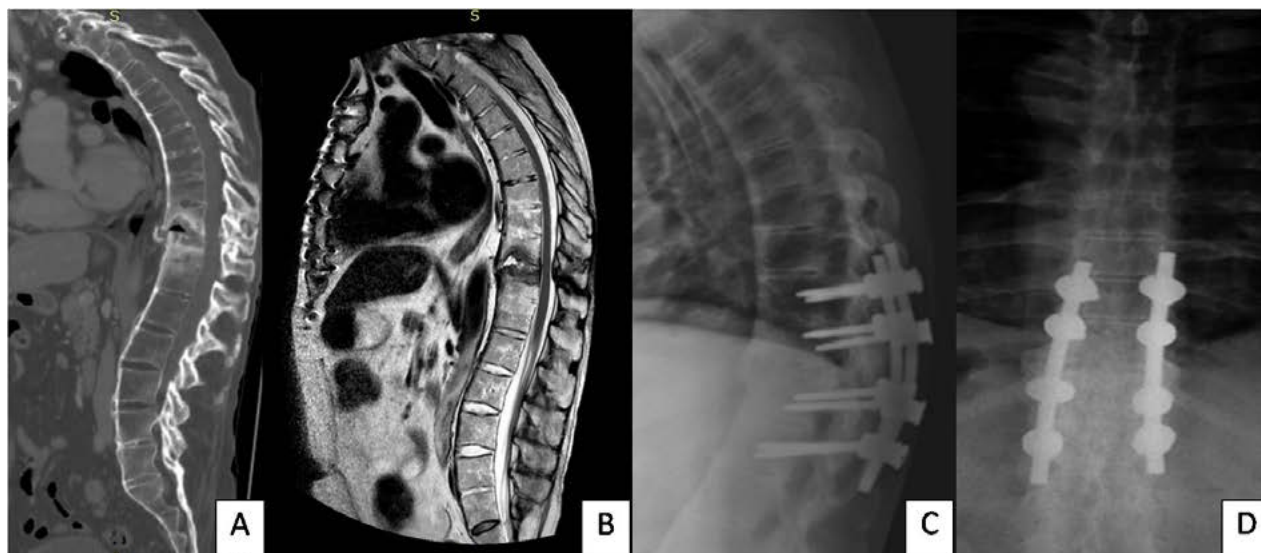
FIGURE 2 – This 54 patient had a fall from the height 2 months before, developing chronic low back pain. Figure 2A - A sagittal T2 sequence thoracic spine MRI shows a T1011 fracture with anterior vertebral elements distraction. Figure 2B - The CT scan documented the fracture and also gas inside the intervertebral disc. A T9101112 pedicle screw fixation was performed with total pain relief (Figure 2C with the plain radiographs after surgery).

patients with spondylodiscitis may not identify any infectious agent, leading to false negative results. This should be taken into account as a potential bias of our high rate of aseptic spondylodiscitis.

The incidence of surgically treated fractures was low, corresponding to only three cases (37.5%). The only segment fractured in our small sample was the lower thoracic spine. Both data disagree with the literature in occurrence and location, which presents the majority of the cases in the cervical spine.[11] The progressive cervical kyphotic deformity present in these patients results in major susceptibility to cervical fractures in comparison to the other segments. Other factors involved in the vulnerability of the cervical segment are: small vertebral bodies, oblique articular facets and the mobility of the heavy skull on the cervical spine.[11,12] Therefore, the most common level of fractures is the cervical level. Westerveld et al.[11] reviewed 93 articles and found 280 (81.2 %) cases of cervical fractures in a total of 345 patients with AS and diagnosis of spinal fractures However, our series does not include conservatively managed patients, which may also change the epidemiological presentation of spinal fractures.

Although limited by the small case number, and retrospective nature, our retrospective study provides unique information about AS patients treated for spinal diseases in a Brazilian university hospital.

CONCLUSIONS

This series displays epidemiological differences in clinical and laboratorial findings, with a high incidence of aseptic spondylodiscitis, when compared to the literature. The regional features of surgically managed patients with diagnosis of AS, could be used as future reference for the management of patients in our country.

RESUMO

INTRODUÇÃO: *A espondilite anquilosante (EA) é uma espondiloartropatia soronegativa, caracterizada principalmente pelo envolvimento do esqueleto axial e das articulações sacroilíacas. A EA promove alterações biomecânicas que predispõem a coluna a fraturas, deformidades e à espondilodiscite. O objetivo do presente estudo é reportar as características clínicas e laboratoriais dos pacientes com EA que foram submetidos a procedimentos cirúrgicos na coluna vertebral em nossa instituição.*

MÉTODOS: *Estudo retrospectivo com revisão de dados médicos dos pacientes com EA que foram submetidos a intervenções na coluna vertebral.*

RESULTADOS: *Nove pacientes foram encontrados e oito incluídos no presente estudo. Três pacientes eram homens e seis mulheres, com média de 57 anos de idade. Todos os pacientes apresentavam dor no segmento da coluna acometido pela doença e um paciente tinha tetraparesia por mielopatia cervical. Seis pacientes (75%) apresentaram proteínas de fase aguda com níveis séricos elevados*

e dois eram HLA-B27 positivos. Em quatro pacientes houve o diagnóstico radiológico presumido de espondilodiscite e estes foram submetidos à biópsia de disco (três por via percutânea e um com biópsia aberta) – em nenhum deles houve identificação de agente infeccioso. Desses, três pacientes tiveram melhora total da dor durante o seguimento, enquanto um deles mantinha dores leves. Houve três casos de fraturas tratadas cirurgicamente (37,5%) e um caso de deformidade cervical cifótica grave (12,5%). Não houve mortes ou complicações relacionadas às cirurgias nessa série.

CONCLUSÕES: *A maioria dos dados clínicos e laboratoriais de nosso estudo divergiu da literatura. Essas diferenças podem ser atribuídas às características regionais de nossa população ou pelo fato de incluirmos apenas pacientes que foram submetidos à intervenção cirúrgica.*

PALAVRAS-CHAVE: *Espondilite anquilosante. Fraturas ósseas. Discite.*

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Neuroaxial anesthesia for gynecological surgeries: meta-analysis

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INTRODUCTION

Major surgical procedures increase the risk of fatal events. For this reason, influence of anesthetic techniques employed is discussed.[1] Anesthesia has the potential to induce physiological changes that may influence patients' morbidity and mortality. Despite this, several studies have shown that there is a tendency of decrease in mortality rates related to anesthesia.[2]

Neuraxial anesthesia (NA) refers to the use of local anesthetics in the vicinity of the spinal cord in order to abolish the perception of painful stimuli.[3] General anesthesia (GA) refers to the use of drugs that lead to loss of consciousness and, consequently, to the abolition of the perception of painful stimuli.[3] Anesthetic techniques have not undergone major changes in recent decades, except for the appearance of new drugs as well as new therapy strategies for pain and control of postoperative nausea and vomiting.[4]

A systematic review attempts to gather all the empirical evidence that fits into prespecified inclusion criteria to answer a specific research question.[5]

Due to the lack of articles proving effectiveness and safety of neuraxial anesthesia in general in major gynecologic surgeries, this systematic review of randomized clinical trials aims to determine effectiveness and safety of NA compared to GA for major gynecologic surgeries, assisting anesthesiologists in choosing the technique to be used.

METHODS

The study has not been submitted to the Research Ethics Committee (REC) because it is research with analysis of secondary data that are available in databases of medical literature as well as in libraries of laboratories and scientific journeys and events involving the topic of this research.

Protocol

A protocol has been developed for the present research and is available with the author, in case there is need of analysis. This systematic review is in agreement with the items proposed in *The Preferred*

Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[6]. The journal, the institution where the study was conducted and the researchers have not influenced the results obtained.

Inclusion criteria

Types of participants: Female patients, older than 18 years, who have undergone some major gynecologic surgery.

Type of study: Randomized controlled trials have been used.

Types of intervention: The intervention group was submitted to NA. The control group was submitted to GA.

Exclusion criteria

Duplicate articles, articles with incomplete data and those not obtained in full were excluded.

Identification of studies

Search strategies were developed to identify original articles from randomized clinical trials related to the topic in the databases selected for this research. Electronic bases selected were: Embase (Excerpta Medica dataBASE), available on: <http://aplicacao.periodicos.saude.gov.br/> (1974 a agosto de 2017); LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde), available on: <http://regional.bvsalud.org/php/index.php> (1982 to August 2017); MEDLINE® (Medical Literature Analysis and Retrieval System Online), via free search engine PubMed (1966 to August 2017) and freely accessible web search engine Google Scholar (August 2017 2017).

A search strategy was created for the PubMed database. The strategies of all databases were based on the PubMed search strategy. The search strategy on Embase was: "'general anesthesia'/exp OR 'spinal anesthesia'/exp OR 'epidural anesthesia'/exp AND rand* AND 'gynecologic surgical procedures' /exp". The search strategy used on Lilacs was "general anesthesia OR spinal anesthesia OR epidural anesthesia OR gynecologic surgery OR controlled trial." The search strategy used on Google Scholar was "'general anesthesia', 'spinal anesthesia', 'epidural anesthesia', 'gynecologic surgery', 'randomized controlled trial' OR 'controlled clinical trial'". There were no restrictions on language, date and format of the document. The search strategy used in PubMed is as follows:

(("general anaesthesia"[All Fields] OR "anesthesia, general"[MeSH Terms] OR ("anesthesia"[All Fields] AND "general"[All Fields]) OR "general anesthesia"[All Fields] OR ("general"[All Fields] AND"anesthesia"[All Fields])) OR (neuraxial[All Fields] AND ("anaesthesia"[All Fields] OR "anesthesia"[MeSH Terms] OR "anesthesia"[All Fields])) AND ("gynaecological surgery"[All Fields] OR "gynecologic surgical procedures"[MeSH Terms] OR ("gynecologic"[All Fields] AND "surgical"[All Fields] AND "procedures"[All Fields]) OR "gynecologic surgical procedures"[All Fields] OR ("gynecological"[All Fields] AND "surgery"[All Fields]) OR "gynecological surgery"[All Fields]) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields])).

Selection of studies

Titles, abstracts or both, identified through the search strategy in each electronic database, were independently analyzed by two researchers (CAJAIBA, L. S.; REIS, M. R.). Articles that met the eligibility criteria were obtained in full for reading. Contact through e-mail correspondence was tried with some authors to clarify doubts about the study variables, unsuccessful though.

The authors recorded the data extracted from the randomized controlled studies in standardized forms, including: method used, number of participants, inclusion and exclusion criteria, age, country where the study was developed, description of interventions of control and intervention groups, continuous and dichotomous variables and references of the studies. In addition, a scale of quality registered in each form was applied. Disagreements were resolved through consensus meetings.

METHODOLOGICAL QUALITY

The validation of randomized controlled trials was done independently by two authors (CAJAIBA, L. S.; REIS, M. R.) using the Quality Scale[7] and disagreements resolved at a consensus meeting. Criteria for the quality scale evaluation used in this research were: randomization, double-blind masking and set of losses and exclusions.

For randomization: the random sequence generation method was considered appropriate when it allowed each study participant to have the same chance of receiving each intervention and when the investiga-

tor could not predict what the next treatment would be. For double-blind masking: studies were considered double-blind when the double-blind expression was used. The method was considered appropriate when neither the patient nor the data collector were able to identify the type of treatment given to each one or, in the absence of this statement, whether the use of identical placebos or imitations was mentioned. For losses and exclusions: participants who entered the study but did not complete the observation period or who were not included in the analysis and were described by the authors of the original articles. The number and reasons for losses in each group have to be stated. When there are no losses, this should also be stated in the article. When there was no description of losses, zero was assigned to this item.

Maximum of five points could be obtained through this scale, where: one point for each yes, one additional point for an appropriate method of randomization and one additional point for an appropriate method of masking. When the double-blind term was not mentioned but there was a description of the masking of the patient and the researcher of the variables, there was a score on this item in the quality scale. A study was considered of poor quality when it received two points or less in the quality scale.

Variables

Primary variables were mortality, quality of life and degree of satisfaction. Secondary variables include the need for postoperative analgesia, complications in anesthetic recovery room, length of hospital stay, length of stay in post-anesthesia care unit, length of ICU stay, surgical wound infection, other infection sites and blood transfusion.

Data analysis

Statistical analysis was performed with data from the original articles included and referring to the variables of interest to this systematic review. Statistical analysis was performed using the RevMan 5.1 software.[8] For dichotomous variables, the relative risk (RR) and the 95% confidence interval (95% CI) were calculated using the Random Effect Model(REM); and for continuous variables, mean and standard deviation were used to generate mean difference (MD) and 95% confidence interval using REM.

Statistical heterogeneity was quantified by means of the I^2 test. When the I^2 test values were greater than 50%, results were considered heterogeneous.

### Analysis of sensitivity and homogeneity

Sensitivity analysis was performed comparing the studies results with good and poor methodological quality. The heterogeneity research was performed by means of successive meta-analyses, with one study being withdrawn at a time until identification of the heterogeneity source. The research was performed in the meta-analyses that presented I^2 test greater than 50%.

RESULTS
Selection of studies

A flowchart demonstrating the selection process of articles relevant to this systematic review is shown in Figure 1. 2,189 titles were analyzed after applying the research strategy, of which 13 were identified as relevant in the process.[9-21] Four of these were later excluded.[18-21] Reasons that led to the exclusion are set out in Figure 1. Nine articles were identified as potential to answer the research question.[9-17] 224 references from these nine selected papers were also analyzed but no study was added because they did not respond to the research question or had already been included. In total, 2,413 titles and abstracts were screened.

FIGURE 1. FLOWCHART DEMONSTRATING PROCESS OF SELECTION OF STUDIES
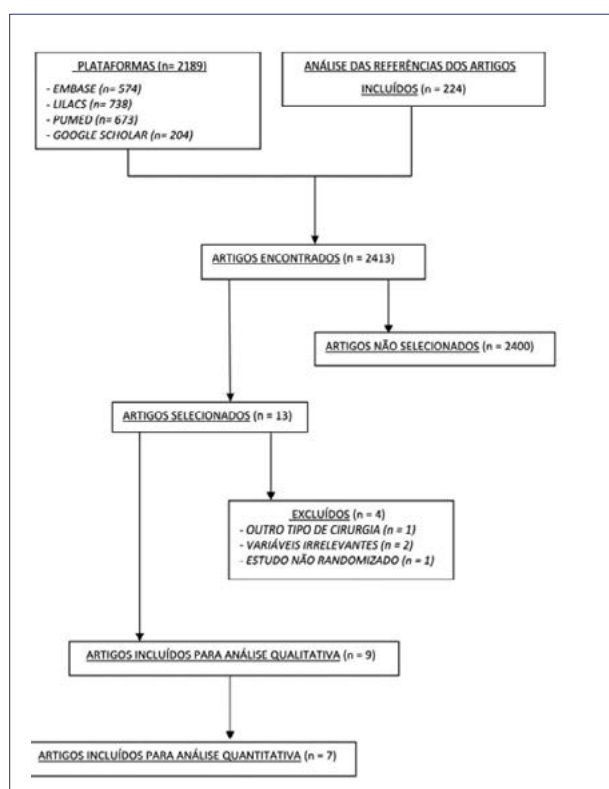
QUALITY OF STUDIES

Quality analysis of the randomized controlled trials selected for this systematic review showed that: seven articles received three points by the applied quality scale[9-13, 15, 16], one article received two points[14] and another article[17] only one point. One study has not had the method of randomization described.[17] Six studies have not mentioned double-blind masking.[10, 12-14, 16, 17] Three studies justified the impossibility of performing double-blind masking.[9, 11, 15] The quality score and main characteristics of the studies are presented in Table 1.

TABLE 1. MAIN CHARACTERISTICS OF STUDIES SELECTED

Authors (Year of publication)	Type of anesthesia	N	Type of surgery	Main results	Quality score	Comments
Purwar et al.[9] (2015)	AN	31	Vaginal surgery: Vaginal prolapse; Urinary incontinence	– There was no statistically significant difference between groups regarding nausea, quality of life, as well as duration of PACU, need for postoperative analgesia and length of hospital stay.	3	– Follow-up time: February 2012 to May 2013. – NA pharmaceuticals: Hyperbaric bupivacaine and fentanyl.
	AG	29				
Segal et al.[10] (2014)	AN + AG	20	Robotic sacrocolpopexy: Vaginal prolapse	– Need for analgesia in percentage in the NA + GA group was 33% and in the GA group was 53% (P < 0.042). – Average satisfaction level was 9.8 ± 0.5 in the NA + GA group and 8.7 ± 1.5 in the GA group (P < 0.014). – The median in relation to the length of hospital stay was equal in both groups: two days.	3	Use of analgesics in the first 24 hours after surgery was lower in the NA group. – Follow-up time: August 2011 to September 2012. – NA + GA pharmaceuticals: Fentanyl and morphine.
	AG	20				
Castro-Alves et al.[11] (2011)	AN	35	Abdominal hysterectomy (Benign diseases)	– The median difference in the overall QoR-40 score in 24 hours between NA e GA groups was 17 (11 to 21.5) (p < 0.001). – Patients in the NA group had better scores on recovery quality (P < 0.005). – There was a linear inverse relationship between opioid intake and operative recovery quality in 24 hours, $r^2 = 0.67$ (p < 0.0001, 95% CI of 0.77 to 0.51) and in 48 hours, $r^2 = 0.58$ (p < 0.0001, 95% CI of 0.72 to 0.42). – The median for nausea in the first 24 hours was 11 in the GA group and 4 in the NA group (P = 0.03).	3	NA provides better recovery quality than GA. *Opioid-sparing* effects in NA were associated with better recovery quality. In the absence of contraindications, neuraxial anesthesia seems to be an anesthetic plan for these patients. – Follow-up time: September 2010 to March 2011. – NA pharmaceuticals: Hyperbaric bupivacaine and morphine.
	AG	35				
Wodlin et al.[12] (2011)	AN	91	Abdominal hysterectomy (Benign diseases)	– Neuraxial anesthesia reduced the need for postoperative opioids. - Episodes of vomiting were reported mostly during the first day in the NA group.	3	NA with intrathecal morphine has advantages over postoperative symptoms and recovery after abdominal hysterectomy. – Follow-up time: March 2007 to June 2009. – NA pharmaceuticals: Hyperbaric bupivacaine and morphine.
	AG	89				
Wodlin et al.[13] (2011)	AN	91	Abdominal hysterectomy (Benign diseases)	– Medians related to the length of hospital stay were, in the NA and GA groups, 46 and 50 hours (P = 0.4004), respectively. – NA was associated with lower opioid use and higher prevalence of vomiting.	3	Length of hospital stay was < 50 hours, regardless of the type of anesthesia. NA reduced the need for analgesia when compared to GA. – Follow-up time: March 2007 to June 2009. – NA pharmaceuticals: Hyperbaric bupivacaine and morphine.
	AG	89				
Massicotte et al.[14] (2009)	AN	20	Abdominal hysterectomy	– Morphine intake in the NA and GA groups at 48 h was 19 ± 16 and 81 ± 31 mg (p < 0.0001), respectively. – Nausea at the 6th hour in the GA group had a median of 1. – Times in PACU in the NA and GA groups were 52 ± 9 and 73 ± 11 minutes (P < 0.0001), respectively. – Hospital stay time was 2.2 ± 0.4 and 3.3 ± 0.7 days (P = 0.01).	2	Intrathecal morphine 0.15 mg with 15μg fentanyl reduced postoperative pain and morphine intake in patients with controlled analgesia without increase of adverse reactions in women submitted to abdominal hysterectomy. – Follow-up time: not described. – NA pharmaceuticals: Hyperbaric bupivacaine, fentanyl and morphine.
	AG	20				

Authors (Year of publication)	Type of anesthesia	N	Type of surgery	Main results	Quality score	Comments
Sprung et al.[15] (2006)	AN	45	Vaginal hysterectomy	– Morphine intake (mg) in the PACU in the NA and GA groups was 1.0 ± 3.0 and 9.0 ± 7.3 (P < 0.001), respectively. – Morphine intake (mg) in the first 12 hours after discharge from the PACU was 7.9 ± 8.3 and 14.8 ± 11.2 (P < 0.001), respectively. – Frequency of nausea in the PACU was lower in the NA group than in the GA group (P = 0.021). – In 2 weeks of follow-up, 69% of the NA patients and 48% of the GA group were painless (P = 0.044).	3	There was no significant difference in the length of patients' hospital stay or postoperative functional status between the two groups. – Follow-up time: April 2001 to February 2005. – NA pharmaceuticals: Hyperbaric bupivacaine, clonidine and morphine.
	AG	44				
Kuramochi et al.[16] (2004)	AN	14	Laparoscopic surgery for infertility treatment	– Mean hospital stay time was 1 day in both NA and GA groups.	3	NA, when used in laparoscopic surgery for infertility treatment, has advantages over GA in terms of analgesic effects, postoperative respiratory function and return to daily preoperative activities. – Follow-up time: not described. – NA pharmaceuticals: Mepivacaine and fentanyl.
	AG	9				
Vofsi et al.[17] (2004)	AN	8	Gasless laparoscopy	– Significant differences were not detected between the groups during the operative and postoperative periods, except for lower need for analgesics in the AN anesthetic recovery unit.	1	– Follow-up time: not described. – Pharmaceuticals used: Bupivacaine and fentanyl.
	AG	8				

NA = neuraxial anesthesia; GA = general anesthesia; N = number of participants; PACU = post-anesthesia care unit.

VARIABLES

Analysis of the studies allowed us to perform meta-analyses of the following variables: nausea and vomiting, need for postoperative analgesia, length of hospital stay and time in post-anesthesia care unit. Meta-analysis was not possible for the following variables: mortality, quality of life, degree of satisfaction, length of ICU stay, surgical wound infection, other infection sites and blood transfusion. The reasons are described below.

Mortality: One study has mentioned mortality.[15] The authors reported that there were no cases of death and it was not possible to perform statistical analysis of this variable. Only with one study it is not possible to perform a meta-analysis.

Quality of life: Two studies presented this variable.[9, 15] Two scales were used. In both studies, the SF-36 questionnaire was applied and in one of them[9] was also used the *International Consultation on Incontinence Questionnaire on Vaginal Symptoms* (ICIQ-VS). As only one used ICIQ-VS, meta-analysis is not feasible, since at least two studies are necessary to perform it. The number of patients who presented satisfactory quality of life in articles using SF36 was not identified.

Degree of satisfaction: Two studies presented this variable.[10, 15] In these, different units of measure were used. In one, a verbal scale of 0 to 10 was used.[10] In another, the scale was classified as Very Satisfactory, Satisfactory, Somewhat Satisfactory and Unsatisfactory in relation to anesthesia and post-procedure analgesia.[15]

Length of ICU stay: No studies were found with this variable. However, one study reported that two people needed ICU admission, one in the NA group, representing 1.2%, and another in the GA group, representing 1.3%.[13] And another states that there was no admission to ICUs.[15]

Blood transfusion: In only one study, this variable was addressed.[13] How many patients needed blood transfusion was mentioned. In patients submitted to GA, three of them had blood transfusion, which represented 3.8% of these individuals. Of those submitted to NA, no patients needed it. Only with one study it is not possible to perform a meta-analysis.

Infection of operative wound and infection in other sites: No studies were found with these variables.

Nausea and vomiting: This variable was analyzed in six studies.[9, 11-15] Meta-analysis was only possible with two.[11, 13] No significant statistical difference was

found among studies (RR = 1.48; 95% CI: 0.49 to 4.48; P = 0.48; two studies; 230 participants). Of the four articles in which it was not possible to perform the meta-analysis[9, 12, 14, 15], the first one presented the number of people who needed treatment for nausea, being for the NA group 32 people, representing 71% and for the GA group 30 people (68%).[15] The second one presented the number of people in the median who evolved with nausea at different times in hours after the procedure (6h, 12h, 18h, 24h, 48h), obtaining a non-zero result only at the first moment (6h) for the GA group, equal to 1.[15] The third one presented the number of people who evolved with nausea from a four-level verbal scale (without nausea, mild, moderate, severe) at different times.[9] And the fourth one presented the number of vomiting situations in days (day 0, day 1 and day 2) in the different groups.[12] It was observed that there was significant statistical heterogeneity (I^2 = 65%; X^2 = 2.86; P = 0.09). It was not possible to identify the source of the heterogeneity since meta-analysis is only possible with at least two articles.

Need for postoperative analgesia: Five studies have analyzed this variable.[10, 13-15, 17] Meta-analysis was possible with two of them.[10, 17] There was no statistically significant difference in the analysis (RR = 0.76; 95% CI: 0.11 to 5.12; P = 0.78; two studies; 54 participants). Of the three studies that did not participate in the meta-analysis, two presented mean in milligrams of the amount of analgesic drugs[14, 15] and one presented this data in median[13]. It was observed that there was significant statistical heterogeneity (I^2 = 88%; X^2 = 8.19; P = 0.004), and, therefore, it was not possible to identify the source of heterogeneity.

Length of hospital stay: This variable was analyzed in five studies.[9, 10, 14-16] Meta-analysis was possible with two studies.[14, 15] There was no statistically significant difference (MD = -0.50; 95% CI: –1.67 to 0.68; P = 0.41; two studies; 129 participants). Of the three articles in which it was not possible to perform the meta-analysis, the first one presented the variable in median, being for the NA + GA group equal to 2 and for the GA group equal to 2.[10] The second one presented the mean in hours, being for the NA group 36.4 ± 36.7 and for the GA group 52.6 ± 53.2.[9] The third one presented the average in days, being for the NA and GA groups equal to 1. Nevertheless, the standard deviation was not informed.[16] It was observed that there was significant statistical heterogeneity (I^2 = 96%; X^2 = 26.16; P = 0.00001). It was not possible to identify the source of heterogeneity.

Time in a post-anesthesia care unit: Five studies analyzed this variable.[9, 13-15, 17] It was possible to perform meta-analysis with four of them.[9, 14, 15, 17] There was no statistically significant difference (MD = –4.81; 95% CI: –24.02 to 14.39; P = 0.62; four studies; 205 participants), as shown in Figure 2. In the study in which it was not possible to perform meta-analysis, the variable was analyzed as median hours and for the NA group it was 3.6 and for the GA group, 4.3.[13] It was observed that there was statistical heterogeneity (I^2 = 78%; X^2 = 13.55; P = 0.004). The heterogeneity test was performed by withdrawing each study successively. One study was identified as a source of heterogeneity.[14] Analysis without this study did not result in a statistically significant difference (MD = 5.17; 95% CI: –8.16 to 18.50; P = 0.45; three studies; 165 participants).
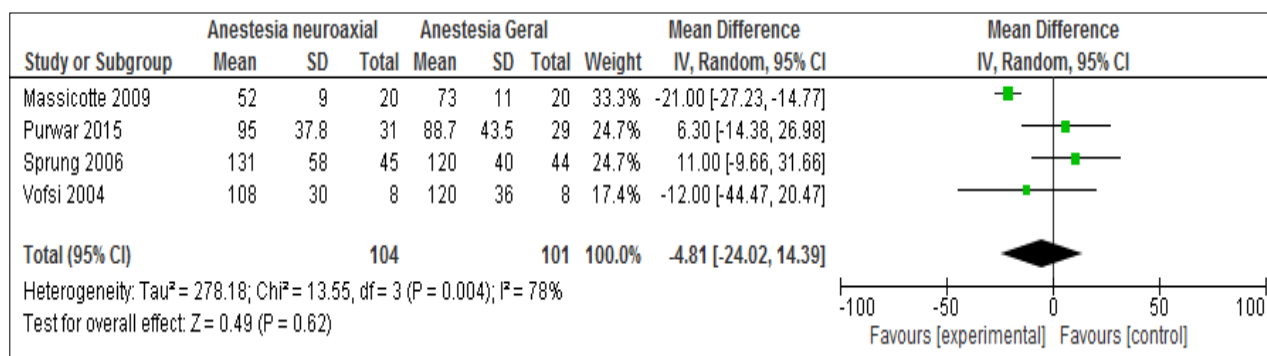
Included in the figure below:
Massicotte et al.[14], 2009
Purwar et al.[9], 2015
Sprung et al.[15], 2006
Vofsi et al.[17], 2014

FIGURE 2. FOREST PLOT OF VARIABLE TIME IN POST-ANESTHESIA CARE UNIT.

DISCUSSION

Although some studies point to NA as a good option for postoperative pain control, the impact of this technique on mortality and surgical morbidity is not yet evident.[22] This systematic review was unable to prove greater effectiveness and safety of neuraxial anesthesia compared to general anesthesia for major gynecologic surgeries, since primary variables were not addressed by most of the studies selected.

Some limitations were identified in this systematic review. There were discrepancies in the units of measure and scales presented for variables quality of life, satisfaction, need for postoperative analgesia, length of hospital stay and nausea and vomiting, which made it difficult to perform the meta-analyses. In some cases, contact with the authors was attempted but no answers were obtained. Statistical heterogeneity was identified in the analyses. Exploration was carried out to find the source of this heterogeneity. However, some variables were analyzed with only two articles and results were kept in the text for readers' appreciation.

Variables nausea and vomiting, need for analgesia, length of hospital stay and time in the post-anesthesia care unit were not statistically significant. The small number of events in the studies and a small number of participants identified with these variables may have been some of the limiting factors for analysis.

RR in nausea and vomiting was 1.48, demonstrating that there was no difference between the groups. A systematic review in 2005 evaluated that the GA group had more episodes of nausea than the NA group.[23] Another study reported the lower incidence of postoperative nausea and vomiting in subjects submitted to NA.[24] The two articles used for meta-analysis presented clinical heterogeneity that justified the absence of statistical significance, such as the number of discrepant samples between them.[11, 13]

RR in need of analgesia was 0.76, demonstrating that there was no difference between the groups. The studies used for meta-analysis showed clinical heterogeneity that may have influenced the analysis, such as different surgical techniques, anesthetic approach[10, 17] and a higher mean age in one of the studies[17]. There was discrepancy in the presentation of the data among the articles of meta-analysis and the others[14, 15] that addressed this variable.

The mean difference in hospital stay time was –0.50, demonstrating that there was no significant statistical difference between the groups. A systematic review of 2016 found that the use of NA significantly reduces length of hospital stay.[25] The studies used in the meta-analysis[14, 15] showed clinical heterogeneity that may have influenced the analysis, such as different surgical techniques, mean age in one of the studies[15], drugs used in the anesthetic approach and number of samples. In both articles, the authors found that there was no significant difference between the NA and GA groups.

The mean difference in post-anesthesia care unit was -4.81, demonstrating that there was no significant statistical difference between the groups. The studies used for meta-analysis showed clinical heterogeneity that may have influenced the analysis, such as types of surgical techniques, mean age of patients, drugs used in anesthetic approach and sample size.[9, 14, 15, 17]

The mortality variable did not generate meta-analysis. However, the only primary study showed that no cases of death were recorded during the research.[15] It is not the authors' consensus to evaluate this variable. A systematic review in 2000 showed that neuraxial anesthesia reduces mortality and other types of severe postoperative complications.[1] Another systematic review conducted in 2016 found that the association of NA with GA, when compared to the use of GA, does not have a significant difference in mortality.[26]

The blood transfusion variable[13] has not generated meta-analysis either. However, the only primary study demonstrated that 3.8% of patients in the GA group required transfusion and 0% in the NA group. It is noted that it is not the authors' priority to analyze this variable.

The quality of life variable, reported in two studies, was expressed in two different scales and in both studies there was no significant statistical difference between the groups.[9, 15] SF-36 is a multidimensional questionnaire that seeks a generic measure of health status consisting of 36 items inserted in eight domains (functional capacity, physical aspects, pain, general health, vitality, social aspects, emotional aspects and mental health).[27] ICIQ-VS is a module of the ICIQ which consists of a comprehensive assessment of severity and impact of vaginal symptoms and related sexual issues, particularly those attributed to pelvic organ prolapse, in order to characterize the severity of these symptoms to measure their impact and evaluate the treatment

outcome.[28] As the studies analyzed the same variable, however in a different way and with different questionnaires, it is impossible to carry out a meta-analysis for comparative effect.

The degree of satisfaction variable, reported in two studies, was expressed in different scales for evaluation, and in both there was no significant statistical difference between the groups in relation to satisfaction in pain management.[10,15] As the studies analyzed the same variable, but in a different way and with different questionnaires, it is impossible to carry out meta-analysis for comparative effect.

It is necessary to carry out more randomized controlled trials of good quality and with greater number of participants so that the influence of anesthetic techniques on the variables proposed in this review can be analyzed and, in this way, to guide conducts in the medical area. Based on assumptions of 5% mortality in the general anesthesia group, 1% mortality in the neuraxial anesthesia group, 80% power and 5% level of significance, 284 participants shall be required in each group for future studies in order to answer this research question.

In light of these results, suggestions for future research can be offered. Analysis of mortality, quality of life, degree of satisfaction, complications in the post-anesthesia care unit, length of ICU stay, surgical and other wound infection and blood transfusion are proposed so that it is possible to evaluate the impact of different anesthetic techniques in gynecologic surgeries.

This systematic review has not presented definitive results. Therefore, previous training and daily practical experience over the years shall allow professionals to choose the most effective and safe technique to be employed.

CONCLUSION

To date, evidence assessed from the studies included is insufficient to ensure that neuraxial anesthesia has greater effectiveness and safety compared to general anesthesia for major gynecologic surgeries.

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28. Price N, Jackson SR, Avery K, Brookes ST, Abrams P. Development and psychometric evaluation of the ICIQ Vaginal Symptoms Questionnai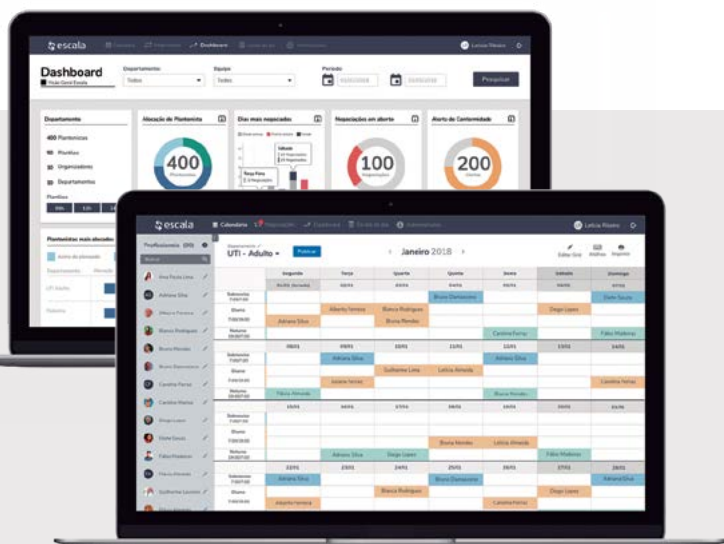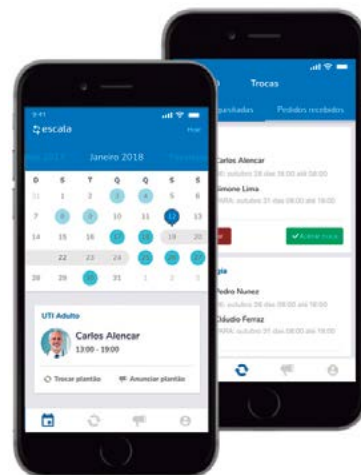re: the ICIQ-VS. BJOG. 2006;113(6):700-12.