RAMB

JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

AMB Associação Médica Brasileira

WMA

Volume **64** Number **7** **July 2018**
ISSN **0104-4230**
ISSN **1806-9282** (On-line)

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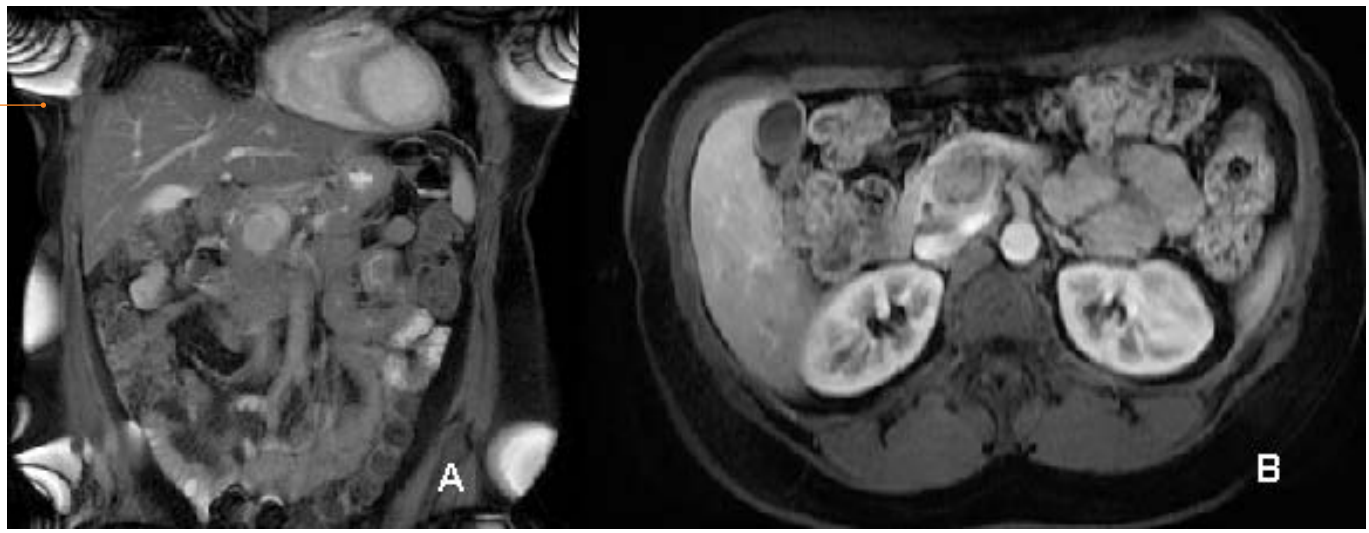

RAMB REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA
JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

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

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

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

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REVIEW ARTICLE

Bariatric surgery in infertile women with morbid obesity: definitive solution?

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http://dx.doi.org/10.1590/1806-9282.64.07.565

Obesity is a global public health problem affecting over 650 million people during all stages of life, especially in the reproductive period[1]. In Brazil, this condition has increased dramatically: in 2006, it affected 11.8% of the population, rising to 18.9% in 2016. The numbers appear to be even worse during reproductive age: in 2013, obesity affected 20.8% of Brazilians over 18 years of age, the percentage being higher among women (24.4%) when compared to men (16.8%)[2].

Clinical comorbidities of obesity, such as systemic arterial hypertension and diabetes mellitus, have an impact on the health and quality of life of this population. However, the effect on male and female fertility is another major concern[3,4]. There are several mechanisms associated with this subfertility, such as chronic anovulation, insulin resistance, reduction of oocyte quality and reduction of embryo implantation rate[5,6]. Obesity is also associated with worse obstetric and perinatal outcomes, such as high risk for preeclampsia, gestational diabetes, macrosomia, and foetal distress[7].

In men, obesity can affect spermatogenesis by increasing testicular temperature and also by elevated serum oestrogen levels, due to the greater peripheral conversion of androgens in adipose tissue, which consequently determines inadequate feedback in the hypothalamic-pituitary-gonadal axis, altering the testicular function[8]. Some researchers have shown reduced concentration and sperm motility in obese patients[9].

Obese female patients are often advised to lose weight before becoming pregnant, but evidence in literature is conflicting when assessing the actual effect of lifestyle changes on the couple's reproductive outcomes. There are several protocols with nutritional guidance and physical activity to reduce preconception weight with an increase in the spontaneous ovulation rate, but without significant repercussions on the number of pregnancies and, especially, on the number of live births[10]. In this sense, Best et al.[11] systematically reviewed the impact of lifestyle changes, including adequate nutritional guidance and physical activity, on fertility. Despite considering randomized clinical trials, they concluded that it may increase the chance of pregnancy, but did not show an increase in

ARTICLE RECEIVED: 23/05/18
ACCEPTED FOR PUBLICATION: 26/05/18
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the live birth rate. Another problem is the difficult adherence to the lifestyle change protocols by the patients, especially those with morbid obesity[12].

Bariatric surgery may be an alternative for morbidly obese women or those with comorbidities who were unsuccessful at attempts to lose weight with behavioural measures and lifestyle changes. This surgical technique aims at reducing the capacity of food intake and/or absorption. Data from literature show a sustainable weight loss over a shorter period of time, and reduction of morbidity associated with obesity[13]. It is an option for morbidly obese women with infertility who have failed with other therapies. In a survey with over 15,000 women who underwent bariatric surgery in the United Kingdom, 53% were between 18 and 45 years old[14].

Bariatric surgery restores the regular menstrual cycle, correcting ovulatory dysfunctions and adjusting the length of the follicular phase (often long in obese patients). In addition, it improves women's self-esteem, having a positive impact on the sexual function[12-17]. However, there are still few studies that have evaluated reproductive outcomes in patients who underwent bariatric surgery. Milone et al.[18] concluded that 58% of women with infertility and submitted to bariatric surgery became pregnant spontaneously, after a systematic review of the literature. This result should be interpreted with caution, since the included studies showed a large variation (22% to 92% of spontaneous gestation) and the evidence quality is still low in many studies[18,19].

Weight reduction after bariatric surgery leads to less need for drugs during assisted reproduction techniques. Tsur et al.[20] found that there was need for lower amounts of gonadotrophins for ovarian stimulation as the body mass index was lower before and after bariatric surgery. Other researchers also found a similar finding and obtained a higher number of oocytes and high quality embryos for transfer[21]. However, other studies have not shown such significant results[22].

In a study of 596 pregnancies of women who underwent bariatric surgery and data compared to 2,356 pregnancies in a paired cohort comprised of obese, non-operated women, there was a higher risk of newborns small for its gestational age (OR = 2.20; 95% CI, 1.64-2.95, P <.001) and higher risk of prematurity between 32 and 36 weeks and 6 days (OR = 1.30, 95% CI, 1.05-1.60) in the women with bariatric surgery. On the other hand, these patients had a lower risk of gestational diabetes (OR = 0.25, 95% CI, 0.13-0.47, P <0.001) and foetal macrosomia (OR = 0.33, 95% CI, 0.24-0.44, P <.001). Therefore, there are negative and positive consequences that should be discussed with patients in the decision for bariatric surgery.

Some considerations should be made when evaluating the impact of bariatric surgery on fertility. First, it must be recognized that there are several techniques and the repercussion of each of them on the reproductive outcomes can also have its nuances and be different. We do not yet know what the preferred technique would be in patients during the reproductive age. In addition, there is uncertainty about the optimal time interval after surgery to attempt to conceive[24,25]. However, some guidelines suggest the minimum interval of 12 months, and others, 24 months. However, the waiting time for women over 35 years old and with low ovarian reserve raises concerns about the feasibility of pregnancy[17-26].

Bariatric surgery may be an alternative for infertile women with morbid obesity but there is still the need for studies to know the ideal type of surgery as well as the time span required to minimize the complications of such procedure on gestation.

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Metastatic colorectal cancer: treatment with panitumumab

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Final version: *October 22, 2016*

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http://dx.doi.org/10.1590/1806-9282.64.07.568

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.

METHOD OF EVIDENCE COLLECTION

This guideline followed the standard of a systematic review with evidence recovery based on the Evidence-Based Medicine movement, where clinical experience is integrated with the ability to critically analyse and rationally apply scientific information, thus improving the quality of medical care. MBE uses existing and currently available scientific evidence with good internal and external validity for the application of its results in clinical practice.[1,2]

Systematic reviews are currently considered the level I of evidence for any clinical issue since they systematically summarize information on a particular topic through primary studies (clinical trials, cohort studies, case-control or cross-sectional studies) using a reproducible methodology, in addition to integrating information on effectiveness, efficiency, efficacy and safety.[1,2]

We used the structured way of formulating the question synthesized by the acronym P.I.C.O., where the **P** corresponds to the patient with **Metastatic Colorectal Cancer**, **I** for intervention with **Chemotherapy with panitumumab**, **C** for comparison of **Chemotherapy without panitumumab and placebo**, and **O** for outcome of **survival and adverse events**. From the structured question, we have identified the descriptors that were the basis of the search for evidence in the databases Medline-PubMed (595 papers) and COCHRANE/Lilacs/BVS (210 papers). Thus, after the eligibility criteria (inclusion and exclusion), 12 papers were selected to answer the clinical questions **(Annex I)**.

CLINICAL QUESTIONS:

Do patients with metastatic colorectal cancer benefit from the use of panitumumab?

Degree of recommendation and strength of evidence

A: Experimental or observational studies with better consistency.

B: Experimental or observational studies with less consistency.

C: Case reports / uncontrolled studies.

D: Opinion with no critical assessment, based on consensus, physiological studies or animal models.

Purpose

The purpose of this guideline is to identify the best evidence currently available regarding the use of panitumumab in patients with metastatic colorectal cancer.

Conflict of interest

No conflict of interest was declared by participants in the preparation of this guideline.

INTRODUCTION

Panitumumab is a fully human recombinant monoclonal IgG2 antibody that binds with high affinity and epithelial growth factor receptor (EGFR) specificity. EGFR is a transmembrane glycoprotein which is a member of a type I receptor tyrosine kinase subfamily including EGFR (HER1/c-ErbB-1), HER2, HER3 and HER4[3]. EGFR promotes cell growth in normal epithelial tissues including skin and hair follicle, and expresses itself in a variety of tumour cells[4].

Panitumumab binds to the binding domain of the EGFR ligand and inhibits the receptor autophosphorylation induced by all known EGFR ligands. This binding results in receptor internalization, inhibition of cell growth, induction of apoptosis and decreased production of interleukin 8 and vascular endothelial growth factor[5,6].

RESULTS OF SELECTED EVIDENCES

Monotherapy - Second or third-line

The results of a multicentre, international (Western Europe, Central Europe, Eastern Europe, Canada, Australia, New Zealand), open-label phase III Randomized Controlled Trial (RCT) in which 463 patients with metastatic colorectal cancer with EGFR expression were randomized to receive panitumumab (6 mg/kg per IV infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity) and "best supportive care" (BSC) [n = 231] or "better supportive care alone" [n = 232]. The study was reported in a major publication[7]**(B)** and five complementary publications[8,9,10,11,12] which are summarized in Table 1. The eligibility criteria included pathological diagnosis of metastatic colorectal adenocarcinoma and radiological documentation of disease progression during treatment or within 6 months after the last administration of fluoropyrimidines, irinotecan and oxaliplatin (second or third-line).

In the BSC group, 176 (76%) of the patients received panitumumab (PAN) according to a crossover protocol. The average crossover time was 7 weeks (6.6 - 7.3 weeks) and the average follow-up after the crossover was 61 weeks (18 - 103 weeks).[7]**(B)**

The median overall survival (OS) values were not given, however, it was reported that there was no difference with statistical significance between groups in the OS analysis (hazard ratio [HR] = 1.00, 95% CI 0.82 – 1.22, p = 0.81). This result may have been affected by the high crossover rate.[8]**(B)**

A retrospective evaluation of the panitumumab efficacy and KRAS status (wild-type [WT] and mutant) showed no statistically significant difference in OS between the treatment groups in either KRAS status.[10]**(B)** HRs for OS were 1.02 (95% CI 0.75-1.39) and 0.99 (95% CI 0.75 of 1.29) for the mutant KRAS and KRAS-WT respectively[10]**(B)**. There was also no difference in median OS. Patients with KRAS-WT treated with panitumumab showed a median OS of 8.1 months compared to 7.6 for those treated with BSC; and patients with mutant KRAS treated with panitumumab showed a median OS of 4.9 months, compared with 4.4 months for those treated with BSC[10]**(B)**.

An improvement in progression-free survival (PFS) was observed in the group of patients treated with PAN + BSC (HR = 0.54, 95% CI, 0.44-0.66; [P < 0.0001]). The difference between the groups was 5 days for the median PFS (56; 95% CI 55 - 59 vs. 51; 95% CI 50 - 54) and 37 days for the average PFS (average [SD]; 96.4 [5.3] vs. 59.7 [3.75]), favourable to PAN + BSC.[7,13]**(B)**

A supplemental analysis for KRAS gene revealed the benefit of panitumumab + BSC in patients with KRAS-WT (non-mutant) codons 12 and 13 (HR = 0.45, 95% CI 0.3 - 0.59), with an increase of 5 weeks in the median PFS (12.3 vs. 7.3). There was no difference in the PFS between treatments in patients with mu-

TABLE 1 - SUMMARY OF MAIN AND COMPLEMENTARY STUDY FOR PANITUMUMAB + BSC VS BSC IN MCRC

Study	Description	Average follow-up (interval) (months)
Van Cutsem et al[7]	PAN + BSC vs BSC main study	8,8 (3,8–19)
Siena et al[8]	Analysis of PFS association with symptoms of colorectal cancer, HRQoL and OS	18 (13–28.3)
Van Cutsem et al[9]	Crossover Extension Study	15.3 (4.5–25,8)
Amado et al[10]	Retrospective analysis of the main study for KRAS	14,1 (for 36 patients remaining at the time of analysis)
Peeters et al[11]	Analysis of the association of skin toxicity severity with PAN efficacy	18 (13–28,3)
Peeters et al[12]	Retrospective analysis of the main study for various genes	__

BSC, best supportive care; PAN, panitumumab; OS, overall survival; PFS, progression-free survival; HRQoL, health-related quality of life.

tations at codons 12 and 13 of the KRAS gene (HR = 0.99; 95% CI 0.73 - 1.36).[10](B)

With this same study, in a retrospective analysis involving 90% (n = 288) of the tumour samples that were available (PAN, n = 147; BSC, n = 141), information was obtained for several genes. Mutation rates for KRAS, NRAS and BRAF were 45%, 5% and 7%, respectively. PAN treatment was associated with higher PFS among patients with KRAS-WT (codons 12/13/61); HR = 0.39 (95% CI 0.28 - 0.56). Among patients with KRAS-WT (codons 12/13/61), treatment with panitumumab showed benefits, increasing PFS in patients who also had NRAS-WT (no mutation; n = 138), [HR = 0.39; 95% CI 0.27 - 0.56; p < 0.001] or BRAF-WT (n = 115), [HR = 0.37; 95% CI 0.24 - 0.55; p < 0.001]. However, there was no such benefit when patients had a mutation in NRAS (HR = 1.94, 95% CI 0.444 - 8.44) .[12](B).

The most common adverse event associated with panitumumab was skin toxicity (90% in the PAN group and 9% in the BSC), although it has been shown that the severity of skin toxicity may be associated with efficacy[11](B). Grade 3 or 4 hypomagnesemia occurred in 3% of patients in the PAN group.

The single arm extension study showed that 92% of the patients had adverse events related to panitumumab (16% had grade 3 and 2% had grade 4 acute renal failure, pulmonary embolism).[9](B)

FIRST-LINE

In a multicentre, open-label, phase III trial that included patients with previously untreated metastatic colorectal cancer (mCRC) and Eastern Cooperative Oncology Group (ECOG) performance status from 0 to 2. Patients (N = 1,183) were randomized to FOLFOX-4 plus panitumumab 6 mg / kg IV for 1 hour, every 2 weeks on day 1 (D1) versus FOLFOX-4 alone. FOLFOX-4 was administered every 2 weeks and consisted of oxaliplatin 85 mg/m² IV infusion on D1 + leucovorin 200 mg/m² (or equivalent) IV infusion D1 and D2 + fluorouracil 400 mg/m² (bolus) + fluorouracil 600 mg/m² (continuous infusion of 22 hours) D1 and D2. KRAS status results were present for 93% of the patients (central and blind laboratory).[14](B)

In patients with mCRC and KRAS-WT (605 patients) an improvement with statistical significance was observed in PFS with FOLOFOX-4 + PAN compared to FOLFOX-4 (HR = 0.80, 95% CI 0.66 to 0.97; p = 0.02). There was an increase of 1.6 months in the median PFS (9.6 months [95% CI 9.2 to 11.1] for FOLFOX-4 + PAN vs 8.0 months [95% CI 7.5 to 9.3] for FOLFOX-4). There was no improvement in OS for these patients (HR = 0.83, 95% CI 0.67 to 1.02, p = 0.072).[14](B)

In patients with exon 2 mutant KRAS (40% of patients), there was a statistically significant reduction in PFS with FOLFOX-4 + PAN compared to FOLFOX-4 (HR = 1.29, 95% CI 1.04 to 1.62; p = 0.02). There was no statistically significant reduction in OS; (HR = 1.24, 95% CI 0.98 to 1.57). The median PFS was 7.3 months (95% CI 6.3-8.0) for FOLFOX-4 + PAN and 8.8 months (95% CI 7.7 - 9.4) for FOLFOX-4.

Subsequently, a retrospective analysis of a predefined subset of data from this study[15](B) evaluated 108 (17%) patients with no mutation in KRAS exon 2 but with additional RAS mutations (KRAS exon 3 or 4, NRAS exon 2, 3, or 4) and 53 (8%) patients with BRAF exon 15 mutation. Patients without any RAS or BRAF mutations had a median PFS greater (10.8 months [95% CI 9.4-12.4] versus 9.2 months [95% CI 7.4 - 9.6] when treated with FOLFOX-4 + PAN and compared with FOLFOX-4 alone, therefore, an increase of 1.4 months in the median PFS.

The most common grade 3 and 4 adverse events known to be associated with anti-EGFR therapy were neutropenia, skin toxicity, diarrhoea, and neurological toxicity.

SECOND-LINE

Patients with mCRC without prior therapy with Anti-EGFR and ECOG performance status from 0 to 2. Patients (N = 1,186) who had not responded to a prior chemotherapeutic treatment (fluoropyrimidine scheme) were randomized to panitumumab 6 mg/kg every two weeks plus FOLFIRI or FOLFIRI alone, until disease progression or intolerability. FOLFIRI consisted of irinotecan 180 mg/m² and racemic leucovorin 400 mg/m² (or L-leucovorin 200 mg/m²) by IV infusion on D1 and 5-fluorouracil (5-FU) 400 mg/m² bolus on D1, followed by 5-FU 2,400 mg/m² administered in continuous infusion over D1 and D2. The KRAS status was available for 91% (55% KRAS-WT and 45% mutant KRAS) of patients. The average follow-up was 10.2-13.3 months for patients with KRAS-WT.[16](B)

When associated with the FOLFIRI regimen as a second-line treatment, patients with KRAS-WT who received panitumumab showed a 2-month increase in median PFS (5.9 months [95% CI, 5.5-6.7] versus 3.9 months [95% CI, 3.7-5.3], p = 0.004). The increase

in median OS of 2 months was not statistically significant (14.5 months versus 12.5 months, p = 0.12).[16](B)

Patients with mutant KRAS did not present differences with statistical significance in PFS and OS evaluations.[16](B)

This same study in a 64-week average follow-up analysis[17](B) for KRAS-WT patients showed similar results. Comparing the addition of panitumumab to FOLFIRI with FOLFIRI alone, there was an increase of 1.8 months in the median PFS (p = 0.023), but the 2 month increase in the median OS did not present statistical significance (p> 0.05).[17](B)

The most common grade 3 and 4 adverse events were skin toxicity, neutropenia and diarrhea.[17](B)

PANITUMUMAB + BEVACIZUMAB

Multicentre open-label RCT that evaluated panitumumab added to bevacizumab associated with chemotherapy based on oxaliplatin and irinotecan as the first-line in non-selected mCRC patients with KRAS mutation. Panitumumab was discontinued after planned interim analysis showed that when it was added to the FOLFOX/bevacizumab regimen, there was a worsening in PFS and increased toxicity compared to the FOLFOX/bevacizumab regimen alone. In both chemotherapy regimens (oxaliplatin and irinotecan), panitumumab was associated with a higher rate of disease progression or death (NNH = 16) and overall mortality (NNH = 11 in oxaliplatin and NNH = 14 in irinotecan).[18](B)

RECOMMENDATIONS

1. PAN + BSC versus BSC (second or third-line monotherapy)

Patients with mCRC with EGFR expression, after confirmation of failure of regimens containing fluoropyrimidine, oxaliplatin and irinotecan.

- There was no statistically significant difference between groups in the analysis of overall survival (HR = 1.00, 95% CI 0.82 - 1.22; p = 0.81).
- Panitumumab showed no statistically significant difference in overall survival (OS) between the treatment groups in any of the KRAS (wild-type or mutant) status.
- There was no difference in PFS between treatments in patients with mutations at codons 12 and 13 of the KRAS gene (HR = 0.99; 95% CI 0.73 - 1.36).
- The difference between groups was 5 days for the median PFS (56 vs 51) and 37 days for the average PFS (average [SD], 96.4 [5.3] vs 59.7 [3.75]), favourable to PAN + BSC.
- There was benefit of panitumumab + BSC in patients with KRAS-WT (non-mutant) codons 12 and 13 (HR = 0.45, 95% CI 0.3 - 0.59), with an increase of 5 weeks in the median PFS (12.3 vs 7.3).
- In patients with KRAS-WT (codons 12/13/61), treatment with panitumumab showed benefit, increasing PFS in patients who also had NRAS-WT (no mutation), [HR = 0.39; 95% CI 0.27 - 0.56; p <0.001] or BRAF-WT, [HR = 0.37; 95% CI 0.24 - 0.55; p <0.001].
- In patients with KRAS-WT (codons 12/13/61), treatment with panitumumab showed no benefit when patients had a mutation in NRAS (HR = 1.94, 95% CI, 0.444-8.44)

2. FOLFOX-4 + PAN versus FOLFOX-4 – First-line

Patients with mCRC untreated for metastatic disease and KRAS-WT:

- There was no increase in OS; (HR = 0.83, 95% CI 0.67 to 1.02).
- There was a statistically significant increase in PFS with FOLOFOX-4 + PAN compared to FOLFOX-4 (HR = 0.80, 95% CI 0.66 to 0.97; p = 0.02).
- There was an increase of 1.6 months in the median PFS (9.6 vs 8.0 months).
- Patients with mRCA and KRAS exon 2 mutant
- There was no difference in OS; (HR = 1.24, 95% CI 0.98 to 1.57).
- In patients with KRAS exon 2 mutant there was a reduction in PFS with FOLFOX-4 + PAN compared to FOLFOX-4; (HR = 1.29, 95% CI 1.04 to 1.62; p = 0.02).
- Patients without any RAS mutations (KRAS exon 2, 3 or 4; NRAS exon 2, 3, or 4) or BRAF exon 15 mutation showed an increase of 1.4 months in the median PFS (10.8 months [95% CI 9.4-12.4] versus 9.2 months [95% CI 7.4-9.6] when treated with FOLFOX-4 + PAN and compared to FOLFOX-4.

3. FOLFIRI + PAN versus FOLFIRI – Second-line

Patients with mCRC who had previously received a fluoropyrimidine chemotherapeutic regimen.

Patients with KRAS-WT:

- The increase in OS median of 2 months was not

statistically significant (14.5 months versus 12.5 months; p = 0.12).
- Patients receiving panitumumab showed a 2-month increase in median PFS (5.9 months versus 3.9 months; p = 0.004).
- Patients with mutant KRAS
- There was no difference in PFS and OS assessments (without statistical significance)

4. PAN + QT based on Oxaliplatin/ bevacizumab or QT based on irinotecan/ bevacizumab versus QT Oxal/bevacizumab or QT Iri/bevacizumab

- In both chemotherapy regimens (oxaliplatin and irinotecan), panitumumab was associated with a higher rate of disease progression or death (NNH = 16) and overall mortality (NNH = 11 in oxaliplatin and NNH = 14 in irinotecan).
- The most common adverse events related to the use of panitumumab, grade 3 and 4 were skin toxicity, neutropenia, diarrhoea, pulmonary embolism, acute renal failure and neurological toxicity.

SUMMARY OF EVIDENCE:

In patients with metastatic colorectal cancer and wild-type KRAS, the addition of panitumumab to the first-line chemotherapy regimen (FOLFOX-4) added 1.6 months to the progression-free survival, but did not show improvement in overall survival. When associated with a second-line chemotherapy regimen (monotherapy or FOLFIRI) in patients with good performance status and adequate organic function, it added 1 to 2 months in progression-free survival without showing a favourable result with an increase in overall survival.

The results of the studies were affected by crossover and sequential treatments. There are also important biases found in the critical analysis of studies such as subgroup analysis and lack of independent evaluator for data analysis.

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ANNEX I

1. Clinical Question

Do patients with metastatic colorectal cancer benefit from the use of panitumumab?

2. Structured Question

P	Patients with metastatic colorectal cancer
I	Chemotherapy with panitumumab
C	Chemotherapy without panitumumab or placebo or supportive care
O	Survival and adverse events (efficacy and safety)

3. Evidence-Seeking Strategy

3.1. PubMed-Medline

#1 – Colorectal Neoplasms
#2 – (Antibodies, Monoclonal OR panitumumab)
#3 – Random*

1st RECOVERY = #1 AND #2 AND #3 = 595

(Colorectal Neoplasms AND (Antibodies, Monoclonal OR panitumumab) AND Random*)

3.2. Cochrane/Lilacs/BVS

#1 – Colorectal Neoplasms
#2 – Antibodies, Monoclonal

2nd RECOVERY = #1 AND #2 = 210

(Colorectal Neoplasms AND Antibodies, Monoclonal)

4. Papers Recovered

Obtaining the evidence to be used followed the steps of preparation of the clinical question, structuring the question, search for evidence, critical evaluation and selection of evidence, exposure of results and recommendations.

The bases of scientific information consulted were Medline via PubMed and Cochrane/Lilacs/BVS. Manual search from references of reviews (narratives or systematic), as well as the selected papers, was performed.

595 recovered papers were recovered until the last search date with the final search strategy.

5. Criteria for inclusion of selected papers

The selection of the studies, evaluation of titles and abstracts obtained with the search strategy in the consulted information bases was carried out by two researchers with skills in the preparation of systematized reviews, independently and blindly, strictly following the inclusion and exclusion criteria established and described in the PICO components, finally separating the papers with potential relevance.

All the papers recovered in the primary and secondary information bases were evaluated. In the primary bases, after the first critical evaluation, we selected PubMed-Medline (12) and Cochrane/Lilacs/BVS (zero). In the manual search, no papers were selected.

5.1 According to the study designs

Only studies with a Randomized Clinical Trial (phase III) study design were included. When the clinical question was considered relevant, the protocol of this review allowed to broaden the search criteria including some evidence with subgroup analysis.

5.2 Language

Studies available in Portuguese, English or Spanish were included.

5.3 According to the publication

Only papers whose complete texts were available were considered for critical evaluation.

6. Method of critical evaluation

The papers considered for full text reading were critically evaluated according to the inclusion and exclusion criteria, by Study design, PICO, language and availability of the full text.

Of 12 papers considered for critical evaluation, none were excluded due to the lack of full text.

The papers included in the evaluation are from between 2007 and 2014.

When, after applying the inclusion and exclusion criteria, the selected evidence was defined as a ran-

TABLE 1 - CRITICAL EVALUATION SCRIPT FOR RANDOMIZED CONTROLLED TRIALS

Study date Reference, Study design, JADAD, evidence strength	**Sample calculation** Estimated differences, power, significance level, total patients
Patient selection Inclusion and exclusion criteria	**Patients** Recruited, randomized, prognostic differences
Randomization Description and blind allocation	**Patients follow-up** Time, losses, migration
Treatment protocol Intervention, control and blinding	**Analysis** Treatment intention, analysed, intervention and control
Considered outcomes Main, secondary, measurement instrument of the outcome of interest	**Result** Benefit or harm in absolute data, average benefit or harm

TABLE 2 - CRITICAL EVALUATION SCRIPT OF COHORT STUDIES

Representativeness of exposed and selection of non-exposed (max. 2 points)	Definition of exposure (max. 1 point)	Demonstration that the outcome of interest was not present at the beginning of the study (max. 1 point)	Comparability on the basis of design or analysis (max. 2 points)	Evaluation of outcome (max. 1 point)	Follow-up appropriate time (max. 2 points)	Evidence level score

domized controlled trial (RCT), it underwent an appropriate critical evaluation checklist (Table 1). The critical evaluation of the RCT allows classification according to the JADAD score[19], considering the JADAD tests < three (3) as inconsistent (grade B), and those with score ≥ three (3), consistent (grade A), and according to the GRADE score[20] (strong or moderate evidence).

When the selected evidence was defined as a comparative study (observational cohorts or non-randomized clinical trial), it was submitted to an appropriate critical evaluation checklist (Table 2), allowing the classification of the study according to the NEWCASTLE OTTAWA SCALE score[21], considering cohort studies with score ≥ 6 consistent, and <6 inconsistent.

7. Exposure of results

For results with available evidence, the population, intervention, outcomes, presence or absence of benefit and/or harm and controversies will be specifically defined, whenever possible.

The results will be preferentially exposed in absolute data, absolute risk, number needed to treat (NNT), or number needed to harm (NNH), and possibly in average and standard deviation (table 3).

TABLE 3 - WORKSHEET USED TO DESCRIBE AND EXPOSE THE RESULTS OF EACH STUDY

Evidence included
Study design
Population selected
Follow-up time
Outcomes considered
Expression of results: percentage, risk, odds, hazard ratio, average

8. Recommendations

The recommendations will be prepared by the authors of the review, with the initial characteristic of the evidence synthesis being submitted to the validation by all authors participating in the preparation of the Guideline.

The degree of recommendation to be used comes directly from the available strength of the studies included according to Oxford[22], and the use of the GRADE[20] system.

Diagnosis and management of hypercalcemia associated with silicone-induced granuloma

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http://dx.doi.org/10.1590/1806-9282.64.07.575

SUMMARY

Hypercalcemia associated with silicone-induced granuloma is a rare disease. Diagnosis can be tricky as it is established after ruling out other hypercalcemia-causing entities. In addition, management is customized depending on the patient's wishes and possible solutions. We present a male bodybuilder, in his thirties, with multiple silicone injections in his upper extremities, who developed hypercalcemia and urinary symptoms. Advanced laboratory tests ruled out various causes of hypercalcemia and CT imaging revealed nephrocalcinosis. A biopsy of the upper arm showed granulomatous tissue and inflammation. The patient necessitated two sessions of dialysis and corticosteroids were given to relieve symptoms and reverse laboratory abnormalities. Silicone-induced hypercalcemia should be on high alert because of the increasing trend of body contour enhancements with injections, implants and fillers. Treatment should be optimized depending on the patient's needs and condition.

KEYWORDS: *Hypercalcemia. Nephrocalcinosis. Dialysis. Granuloma. Resistance training. Silicones/adverse effects. Injections, intradermal/adverse effects.*

A 34-year-old Caucasian male bodybuilder with a history of silicone injections in the shoulders, arms and forearms presented for recurrent left flank pain, dysuria and intermittency for the last 3 months (Figure 1A). He was admitted for the treatment of a urinary tract infection. Lab findings showed hypercalcemia of 13.2 mg/dl (normal range 8.6 – 10.3) and increased creatinine level of 2.3 mg/dl (normal range 0.7 -1.36). An abdominal CT scan showed bilateral nephrocalcinosis. Intravenous hydration was started, and the patient necessitated two sessions of dialysis. Hypercalcemia workup ruled out hyperparathyroidism, Vitamin D intoxication, hyperthyroidism, malignancy, sarcoidosis and multiple myeloma. A biopsy from the right triceps tendon showed fibrosis and sclerosis granulomas (Figure 1B: 1), active granulomas with giant cells (Figure 1B: 2), and fibrous backgrounds with histiocytes (Figure 1B: 3). Magnification with the polarizer showed birefringent bodies corresponding to persistent silicone particles in the tissue (Figure 1C).

Findings supported a diagnosis of hypercalcemia associated with silicone-induced granuloma. Surgical removal of the silicone deposits was not an option. He was started on oral corticosteroids, 40 mg daily for 3 weeks, and was tapered by 5 mg weekly afterwards. Calcium and Creatinine levels gradually returned within range, and symptoms resolved. A repeat blood test, 1-month post treatment showed a Calcium level of 9.1 mg/dl.

Hypercalcemia associated with silicone-induced granuloma is a rare entity with scarce literature. When hyperparathyroidism and malignancy are

DATE OF SUBMISSION: 15-Dec-2017
DATE OF ACCEPTANCE: 25-Dec-2017
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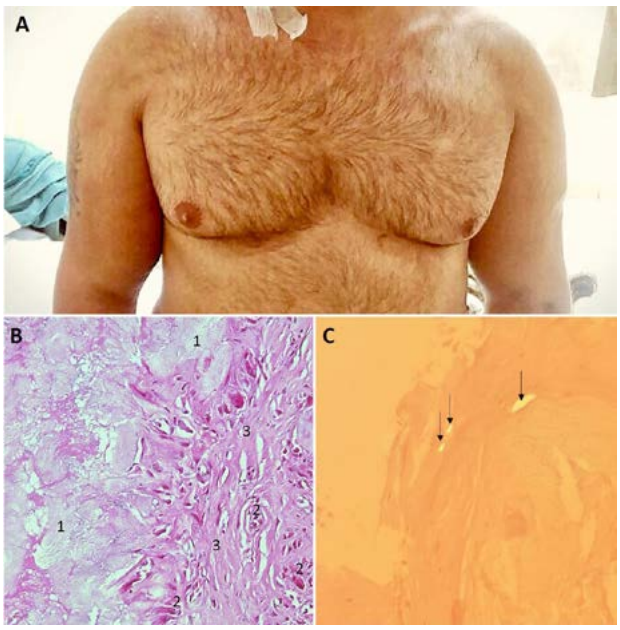

FIGURE 1

ruled out, rare causes of hypercalcemia, which account for less than 10% of cases of elevated serum calcium, need to be entertained[1].

The first case of silicone-induced granuloma was reported in 1964 by Winer et al.[2]. Generally, incidence of granulomatous inflammation in individuals injected with medical grade silicone can reach 20%.[3] Therefore, physicians and public health personnel should educate individuals interested in pursuing such procedures on the possible risks and complications.

The patient necessitated two sessions of dialysis to reverse his lab abnormalities. Similar approach has been adopted in another patient.[4] Urgent dialysis can be lifesaving as bisphosphonates need time to optimize their efficiency.

Resection of the silicone is often problematic. Many surgeons deem excision unsafe and ineffective due to the extent of injections with partial migration.[1] Others, however, opt to resect the granulomatous tissue and it reportedly resolved the silicone-induced hypercalcemia.[5] The patient's wishes should also be respected, and the physician should make sure to explain the risks and complications of each intervention to maintain a healthy physician-patient relationship.[6]

Physicians should be alert, and have a high index of suspicion for silicone-induced hypercalcemia considering the growing popularity of cosmetic silicone in body contour enhancement.

Ethical Approval: Patient granted full permission to share and publish all information present.

Conflict of Interests: None declared.

RESUMO

A hipercalcemia associada ao granuloma induzido por silicone é uma doença rara. O diagnóstico pode ser complicado, pois é estabelecido depois de eliminadas outras entidades que causam hipercalcemia. Além disso, o gerenciamento é personalizado, dependendo dos desejos do paciente e das possíveis soluções. Apresentamos um fisiculturista masculino, com trinta e poucos anos, múltiplas injeções de silicone nas extremidades superiores, que desenvolveu hipercalcemia e sintomas urinários. Testes laboratoriais avançados descartaram várias causas de hipercalcemia e a imagem da TC revelou nefrocalcinoses. Uma biópsia da parte superior mostrou tecido granulomatoso e inflamação. O paciente exigiu duas sessões de diálise e foram administrados corticosteroides para aliviar os sintomas e reverter as anormalidades laboratoriais. A hipercalcemia induzida por silicone deve estar em alerta elevado devido à crescente tendência de aprimoramentos do contorno corporal com injeções, implantes e enchimentos. O tratamento deve ser otimizado de acordo com as necessidades e condições do paciente.

PALAVRAS-CHAVE: *Hipercalcemia. Nefrocalcinosis. Diálise. Granuloma. Treinamento de resistência. Silicones/efeitos adversos. Injeções intradérmicas/efeitos adversos.*

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Locoregional recurrence of Frantz' tumor: a case report and review of the literature

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http://dx.doi.org/10.1590/1806-9282.64.07.577

SUMMARY

Frantz' tumours or solid pseudopapillary tumours of the pancreas are rare neoplasms with low malignant potential. Young women in the second to third decades of life are more frequently affected. The treatment of choice is resection of the lesion, which is often curative. The recurrence is uncommon when radical surgical resection is used. Radiological characteristics are important for the correct diagnosis, since the preoperative planning is fundamental to obtain the cure. The objective of this study is to report a rare case of locoregional recurrence and to review the radiological findings of solid pseudopapillary tumours of the pancreas in the literature, as well to know the incidence and risk factors of tumor recurrence. This case report is from a 37-year-old female patient evaluated at an Oncologic Hospital, in the city of São Paulo, Brazil, who presented an uncommon evolution of the disease, characterized by local recurrence despite the complete resection of the primary lesion with free margins.

KEYWORDS: *Pancreatic neoplasms. Recurrence. Magnetic resonance imaging.*

INTRODUCTION

Frantz tumours or solid pseudopapillary tumours (SPTs) of the pancreas are rare. It is estimated that they correspond to 0.3% to 2.7% of all pancreatic tumors.[1,2] Recently there has been an increase in its incidence, which may be related to the greater use of immunohistochemical methods.[3] There are several eponyms to denominate SPTs, such as: Hamoudi Tumor, Frantz Tumor and others. However, according to the World Health Organization (WHO) classification, the most appropriate nomenclature is solid pseudopapillary tumor of the pancreas.[4]

They are tumours of low malignant potential, which predominate in young women in the second to third decades of life.[5,6]

Complete surgical resection is the curative treatment.[7,8] SPTs are usually limited to the pancreas, allowing the resection of the entire lesion. Locoregional recurrence is estimated to occur in less than 10% to 15% of surgical resections.[9] Some factors are related to an increased risk of recurrence, such as lymphatic and vascular invasion, synchronic metastasis, and invasion of the tumor capsule.[10] In these

DATE OF SUBMISSION: 22-Dec-2017
DATE OF ACCEPTANCE: 25-Dec-2017
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cases, a more careful approach to long-term follow-up is needed.[7]

In the imaging service of this oncology reference hospital, located in the city of São Paulo, we evidenced a case of recurrence of an SPT of the pancreas submitted to complete resection of the lesion with free margins. This is a case report obtained from imaging studies conducted in May 2015, before resection of the primary lesion, and in September 2017, after surgery, showing a new lesion.

Considering that SPT is a rare neoplasm, and that recurrence after free-margin resection is uncommon, we report this case with the purpose of reviewing the radiological findings of SPT in the literature, as well as knowing the incidence and risk factors of tumor recurrence.

CASE REPORT

GPSC, a 37-year-old Brazilian female was referred to the imaging department for pancreatic mass screening visualized in an imaging study from another hospital.

Initial nuclear magnetic resonance imaging (MRI) performed at the oncology centre in May 2015 included T1-weighted and T2-weighted images, intravenous paramagnetic contrast injection, fat saturation and diffusion sequences. It was characterized the increase of head/uncinate pancreas process at the expense of a mass, with a heterogeneous solid-cystic aspect, predominating hyposignal in T1, hypersignal in T2 and contrast enhanced, measuring 35 x 25 mm (Figure 1). Such lesion had intimate contact with the proximal portion of the portal vein and spleno-mesenteric junction. No lymphadenopathy or dilatation of the intra- and extrahepatic bile ducts were observed. The remaining pancreatic parenchyma did not show significant changes.

Ultrasound-guided fine needle puncture (Paaf) was performed, which revealed findings compatible with SPT. The patient underwent complete resection of the lesion, with gastroduodenopancreatectomy and lymphadenectomy. Anatomopathological examination confirmed the presence of an SPT. Surgical margins and lymph nodes were free of neoplastic involvement. Immunohistochemical analysis was compatible with SPT.

After two years, another MRI study, performed with the same protocol as the previous examination, a solid, heterogeneous mass was identified with variable signal in T2, intermediate signal in T1, heterogeneous post-contrast enhancement, peripheral and with a tendency to homogenization in the late phases, located in the topography of the head/uncinate process of the pancreas, measuring 44 x 31 mm (Figure 2). This lesion showed proximity to the inferior vena cava and inferior mesenteric vein, but without signs of vascular invasion. The pancreatic duct had dimensions at the upper limit of normality. In view of the appearance of a new lesion after complete resection of the primary lesion, the possibility of tumor recurrence was considered, which was later confirmed by anatomopathological examination.

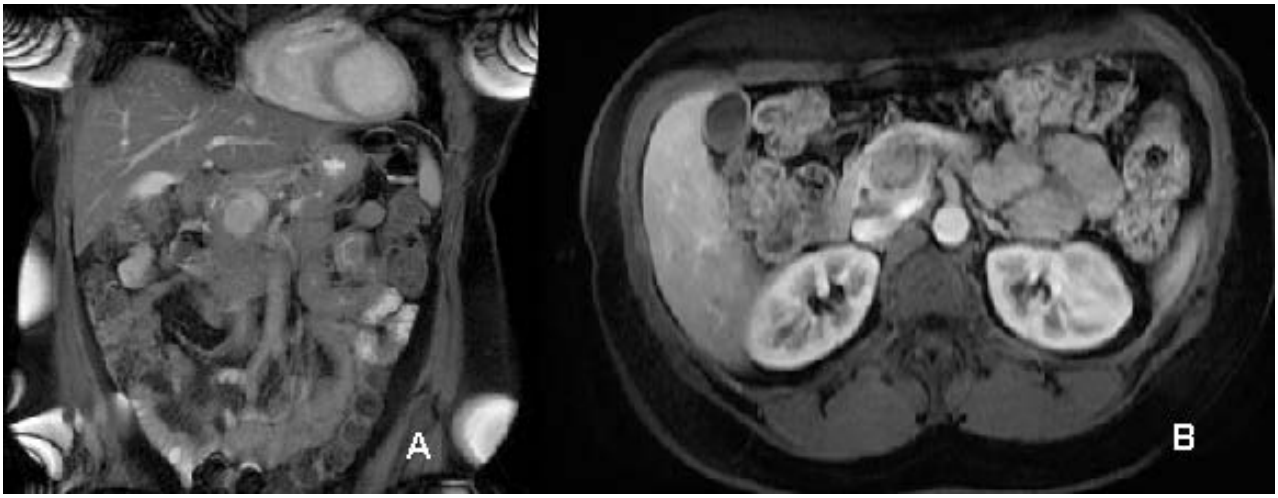

FIGURE 1. 2015 MRI. Coronal section, T2-weighted, shows solid-cystic lesion, with hypersignal in T2, well delimited, in the head/ uncinate process of the pancreas (A). Axial cut, T1-weighted after contrast, characterizing heterogeneous post-contrast enhancement (B).

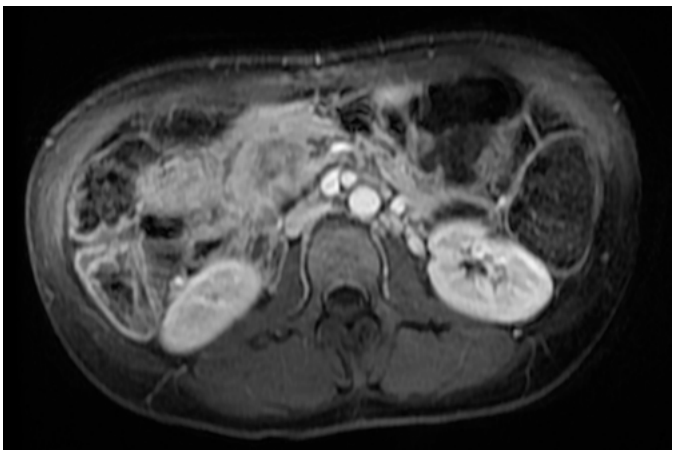

FIGURE 2. 2017 MRI. Axial cut, T1-weighted after contrast, showing a new solid and heterogeneous lesion, with peripheral post-contrast enhancement and with tendency to homogenization in the late phases, on topography of the head/uncinate process of the pancreas.

DISCUSSION

Most SPTs are benign. It is estimated that 10% to 15% are malignant.[11] Recurrence is related to signs of aggressive behaviour, characterized by: lymphatic and vascular invasion, synchronic metastasis and invasion of the tumor capsule.[10] Some studies suggest that tumours with a larger to 5 cm in diameter have greater malignant potential and risk of higher recurrence.[11] The high mitotic rate and nuclear atypia were also related to aggressive behavior[4]. Although these signs are related to the greater risk of relapse, their absence does not exclude the possibility that recurrence occurs in the long term. The most common sites of metastases are liver, portal vein, spleen, regional lymph nodes, omentum and peritoneum.[5,6]

The diagnostic hypothesis is usually made through imaging tests, since the clinical status is nonspecific. Patients may be asymptomatic, report vague abdominal discomfort or symptoms related to the compression of adjacent structures by the tumor.[6]

SPTs have variable presentations on imaging tests. They are more common in the pancreatic tail and head.[5,6] Generally, they are large, well-circumscribed, heterogeneous, solid-cystic masses at the expense of varying amounts of necrosis, haemorrhage, and cystic areas.[5] Calcifications may be present.[12] The solid component shows heterogeneous and progressive contrast enhancement. Dilatation of the biliary tract is rare[12]. MRI provides more information than computed tomography on the resectability and internal characteristics of the lesion, facilitating the identification of purely solid tumours and with smaller dimensions.[13]

Complete surgical resection is the most efficient treatment, even in the presence of metastases or vascular invasion, and should be done for the primary lesion and for metastases if present.[7] Less than 10% to 15% of resections are estimated to evolve with recurrence.[9] In patients with signs of aggression, more careful follow-up is recommended, since recurrences may occur after five years of surgery.[7] In cases of relapse, surgical resection is also the most efficient treatment.[6,7]

SPTs present a favourable prognosis, even when there are metastases, invasion or local recurrence.[7] In such cases, surgery is not a contraindication.[8]

The case report refers to a patient with epidemiological and imaging characteristics compatible with SPT. An ultrasound-guided Paaf was used to distinguish neoplasm from other pancreatic tumours, allowing preoperative planning, since lesion resection is often curative. Despite this, the patient evolved with relapse after two years of surgery.

SPT is a rare neoplasm with few cases of relapse after complete surgical resection. The importance of this case report lies in the correct diagnosis, since resection of the lesion is associated with long-term survival.

RESUMO

Os tumores de Frantz ou tumores pseudopapilares sólidos do pâncreas são neoplasias raras, que apresentam baixo potencial maligno. A maioria acomete mulheres jovens na segunda a terceira década de vida. O tratamento de escolha é a ressecção da lesão, uma vez que é frequentemente curativa. A recidiva é incomum quando é empregada ressecção cirúrgica completa. As características radiológicas são importantes para a hipótese diagnóstica, uma vez que o planejamento pré-operatório é fundamental para a obtenção da cura. O presente estudo tem como objetivo relatar um caso raro de recidiva locorregional e rever na literatura os achados radiológicos dos tumores pseudopapilares sólidos do pâncreas, assim como conhecer a incidência e os fatores de risco da recorrência tumoral. Este relato de caso é de uma paciente do sexo feminino, de 37 anos, avaliada em um hospital de referência oncológica, na cidade de São Paulo, Brasil, que apresentou uma evolução incomum da doença, caracterizada pela recorrência locorregional, apesar da ressecção da lesão primária com margens livres.

PALAVRAS-CHAVE: *Neoplasias pancreáticas. Recidiva. Imagem por ressonância magnética.*

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Behavioural changes caused by diffuse intrinsic pontine glioma

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http://dx.doi.org/10.1590/1806-9282.64.07.581

KEYWORDS: *Glioma. Behaviour. Behavioural symptoms. Brain stem neoplasms.*

This five-year-old girl presented with a history of two weeks of behavioural changes (irritability, aggressiveness and school problems). No underlying cause was found on psychiatric assessment. In the following 5 days, she presented a left sixth nerve palsy and ataxic gait and then she was referred to the neurosurgery team. Magnetic resonance imaging showed a diffuse intrinsic pontine glioma – DIPG – (Figures A and B). Radiotherapy was then started.

DIPG accounts for 10% of childhood brain tumours. Most common signs at presentation include corticospinal tract deficits, cranial nerve palsies and ataxia. The brainstem was not regarded as a structure involved in complex affective behaviour, but today it is well established that cerebrocerebellar and cerebellum-cerebral connections play a role in affective and cognitive behavioural.[1] Actually, behavioural changes are present in only 5% of the cases.[2,3] However, in children with unexplainable behavioural changes, DIPG should be considered as a differential diagnosis.

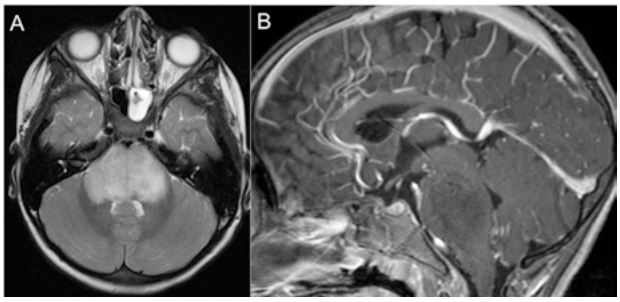

FIGURE. Diffuse intrinsic pontine glioma characterized by a hyperintensity on T2 (A, axial view) and iso-hypointensity on T1 weighted MRI (B, sagittal view). In this case, the lesion did not have significant contrast enhancement.

DATE OF SUBMISSION: 18-Oct-2017
DATE OF ACCEPTANCE: 23-Oct-2017
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PALAVRAS CHAVE: *Glioma. Comportamento. Sintomas comportamentais. Neoplasias do tronco encefálico.*

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Secondary osteoarthritis to ochronotic arthropathy - a diagnostic challenge

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http://dx.doi.org/10.1590/1806-9282.64.07.583

KEYWORDS: *Osteoarthritis. Ochronosis/complications. Alkaptonuria.*

Alkaptonuria is a genetic disorder of the tyrosine metabolism with autosomal recessive transmission, characterized by deficiency of the enzyme homogentisic acid oxidase.[1-4] The disease presents an estimated prevalence of 1:250,000, data being rare in Brazil.[1,5] It predominates in males and usually occurs after the fourth decade of life. The disease may be asymptomatic or lead to ochronosis, characterized by the accumulation of homogentisic acid metabolites in the connective tissues. This deposition leads to several clinical manifestations, such as cutaneous and ocular pigmentation, dark urine, arthropathy and cardiovascular manifestations. A severe form of arthropathy is the most common clinical presentation; however, patients often suffer from cardiovascular disease as well.[2] In this report, we describe the case of a patient with ochronosis presenting with cutaneous, ocular and joint manifestations of the disease.

A 54-year-old stay-at-home female, born in Umari, Ceará, was admitted with chronic weakness and chronic arthralgia in the knees, hip and lumbar region, with a progressive character, with limitation of daily activities. Walking was limited by pain in hip and knee joint, bilaterally, which was worse at the end of the day, and by mobilization. She also presented with diuresis and skin alterations. Family history included consanguineous marriage between the parents, and a daughter with congenital deafness. Over the years, she presented progressive worsening of the joint in the knees, hips and shoulders, evolving ten years ago, with loss of routine daily activities, worsening of locomotion difficulty and reduction of lumbar mobility. She sought medical attention, in which anti-inflammatories and painkillers were prescribed, which she started to use daily. Two years ago, she presented with progressive asthenia, worse at the end of the day, seeking specialized medical attention in January 2015. In view of this situation, the patient was admitted for diagnostic investigation through laboratory tests, imaging and cutaneous biopsy of the lesions pigmented. At physical examination, there were bluish patches on the auricle, the sclera, and the palmar side of the hands.

DATE OF SUBMISSION: 09-Nov-2017
DATE OF ACCEPTANCE: 05-Dec-2017
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Difficulty to walk and reduced lumbar mobility (Schöber test of 1.6 cm) was observed, as well as pain in the mobilization of the right shoulder, hip and knees. Lumbar radiography showed diffuse reduction of intervertebral spaces with disc calcifications in multiple planes. In biopsy of left upper limb skin under microscopy, several degenerate, comma or banana-shaped enlarged collagen beams of golden/brownish colour, present in the superficial and intermediate dermis, with a suggestive aspect of ochronosis, were evidenced. The homogentisic acid test was negative in the urine by the ammonia silver nitrate reduction method, the ferric chloride test and the Benedict reagent reduction test. These methods are not very sensitive. The most sensitive method would be by gas chromatography, but this research was limited due to the unavailability of the test. Anti-inflammatory medications were administered during hospitalization and the patient presented a good response, being discharged in good clinical condition, with improvement of joint pain, and being referred to the Rheumatology outpatient clinic.

DISCUSSION

Patients with alkaptonuria are usually asymptomatic in childhood and as young adults. When the affected individuals age, pigmentation of the sclera and auricular pavilion begins[4,6]. Joint symptoms typically begin in the third and fourth decade of life.[7] Ochronotic arthropathy is characterized by involvement of the spine and large joints and is a rare cause of secondary osteoarthritis. The lumbar spine is generally the most affected anatomical location,[1,2] and the spinal involvement resembles the pattern found in ankylosing spondylitis, but differs from this because it spares the sacroiliac joints. Calcifications of intervertebral discs are the characteristic findings in the spine. In the case reported, the patient presented alterations in the radiographs consistent with the expected for the disease in question. Symptomatic treatment is recommended in the early stages of the disease; in more advanced stages, surgical interventions, such as arthroplasty, may be necessary.[5,6]

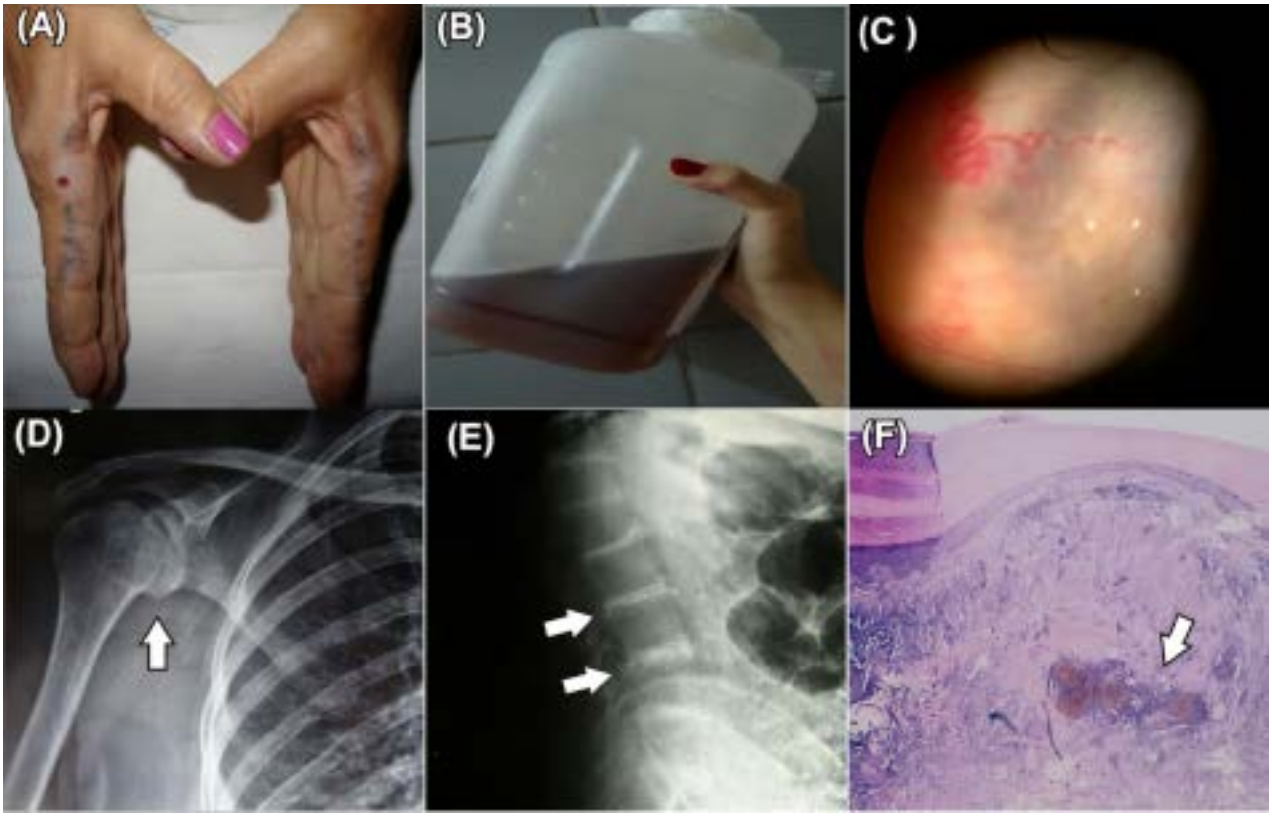

FIGURE 1. (A) Woman, 54 years old, presenting chronic joint pain in knees, hips and lumbar region. She presents ochronotic pigmentation deposit in the blue-blackish colour on hand skin. (B) Dark urine. (C) Dark pigments in the sclera. (D) AP radiography of shoulder evidencing reduction of joint space, sclerosis of subchondral bone. (E) Radiography of lumbar spine in profile evidencing diffuse reduction of intervertebral spaces, with disk calcifications in multiple planes. (F) Biopsy of hand acral region skin (10x Optic microscopy) evidencing degeneration of collagen beams and thick fibres – classic golden-brown colour in comma or banana shape. Ochronosis.

PALAVRAS-CHAVE: *Osteoartrite. Ocronose/complicações. Alcaptonúria.*

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The rs4430796 SNP of the HNF1β gene associates with type 2 diabetes in older adults

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http://dx.doi.org/10.1590/1806-9282.64.07.586

SUMMARY

INTRODUCTION: *The impact of type 2 diabetes mellitus raises interest in understanding its evolutionary-genetic basis, to unveil yet unknown pathways that may have immediate medical relevance. The* HNF1β *gene (hepatocyte nuclear factor-1 beta) is a transcription factor expressed in tissues such as liver, kidney, genital tract and pancreas that is known to be essential for insulin secretion and glucose balance. We tested the association of allelic variants produced by the* HNF1β *gene (rs4430796) variation with the clinical and biochemical profile of elderly Brazilian outpatients with metabolic disorders.*

MATERIAL AND METHODS: *Anthropometry, blood pressure, glycaemia, lipemia and other parameters were assessed in 184 Brazilians aged 60 or older in clinical care settings. Alleles were determined by amplification of the polymorphic site by real time polymerase chain reaction.*

RESULTS: *Analysing variables across the genotypes, a statistically significant difference was noticed in the allele frequencies among diabetic patients, with 30.8% of the A homozygous bearing the condition compared to a prevalence of 12.2% between G homozygotes.*

CONCLUSION: *Our results corroborate the possible protective property of the GG genotype from the rs4430796 variation (already presented in the literature) against occurrence of diabetes mellitus, which appears applicable to elderly individuals as well, even in the context of multiple metabolic disorders so typical in older Brazilians.*

KEYWORDS: *Diabetes mellitus. Polymorphism, genetic. Aged.*

Diabetes is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both[1]. In 2012, an estimated 1.5 million deaths were directly caused by diabetes and another 2.2 million deaths were attributable to high blood glucose[2]. Type 2 diabetes mellitus (DM2) is projected to be the seventh leading cause of death worldwide by 2030. This impact of DM2 has raised concerns and interest in understanding its evolutionary-genetic basis, as well as in discovering underlying, yet unknown pathways that may have more immediate medical relevance [3].

The hepatocyte nuclear factor-1 beta (*HNF1*β) was shown to be a transcription factor involved in the tissue-specific regulation of embryonic development as well as in the gene expression in various organs such as liver, muscle, intestine, kidney, pancreas, and the genitourinary system[4]. *HNF1*β is known to be essen-

DATE OF SUBMISSION: 07-Jan-2018
DATE OF ACCEPTANCE: 13-Jan-2018
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tial for normal glucose-stimulated insulin secretion from the analysis of β-cell-conditional *HNF1*β knockout mice[5]. Besides leading to an impaired glucose metabolism, selective deletion of *HNF1*β in β-cells leads to a variety of islet gene expression dysregulation. Some GWAS revealed that several tag SNPs in the *HNF1*β gene were associated with the susceptibility of DM2 and such associations were well replicated in many countries[6] Thus, *HNF1*β is prominent in the regulation of human insulin gene transcription[7].

The purpose of this study was to investigate the association of allelic variants produced by the rs4430796 variation in the *HNF1*β gene with the glycaemic profile of Brazilian elderly patients as well as with their clinical, biochemical and inflammatory features.

TABLE 1. AVERAGE ANTHROPOMETRIC, CLINICAL AND METABOLIC FEATURES ACCORDING TO GENOTYPES OF THE HNF1β GENE.

	rs4430796		
	A/A (n = 52)	A/G (n= 83)	G/G (n = 49)
Age (years)	73.4 ± 9.7	74.3 ± 8.8	74.9 ± 8.5
Male (%)	46.2	42.2	38.8
BMI (kg/m2)	27.4 ± 4.5	27.6 ± 5.3	27.4 ± 6.0
WC (cm)	97.2 ± 10.2	96.0 ± 11.6	96.9 ± 14.6
SPB (mm Hg)	137.5 ± 18.3	133.9 ± 18.2	137.0 ± 22.6
DBP (mm Hg)	79.4 ± 10.6	79.5 ± 11.6	80.9 ± 11.6
SAH (%)	76.9	75.9	81.6
GLU (mg/dl)	106.0 ± 21.1	102.9 ± 20.3	97.4 ± 15.4
HbA1c (%)	6.1 ± 1.0	6.0 ± 1.0	5.6 ± 0.6 *
DM2 (%)	30.8	31.3	12.2 *
CHL (mg/dl)	187.2 ± 33.9	191.5 ± 39.3	195.8 ± 44.8
HDL (mg/dl)	48.6 ± 10.6	48.6 ± 12.0	48.4 ± 11.1
TGL (mg/dl)	138.4 ± 69.5	131.5 ± 51.5	149.8 ± 74.8
Dyslipidemic (%)	51.9	49.4	51.0
MS (%)	50.0	60.2	65.3
TSH (mU/l)	2.1 ± 1.5	2.7 ± 2.2	2.8 ± 2.5
CRP (mg/dl)	3.6 ± 5.6	3.4 ± 6.0	3.1 ± 3.8
CGault (ml/min)	74.3 ± 28.9	68.4 ± 27.3	67.1 ± 32.1
AST (U/l)	22.2 ± 6.8	20.3 ± 6.2	20.7 ± 5.5
ALT (U/l)	19.1 ± 8.5	18.6 ± 6.7	18.6 ± 7.2
gGT (U/l)	27.3 ± 20.1	33.9 ± 26.0	30.1 ± 22.2
Sedentary (%)	50.0	59.0	63.3
Smoker (%)	31.4	40.2	34.7

Data shown as mean ± SD or frequency within genotype. *π < 0.05 when compared to any other genotypic group. BMI = body mass index; WC = waist circumference; SBP = systolic blood pressure; DBP = diastolic blood pressure; SAH = systemic arterial hypertension; GLU = fasting serum glucose; HbA1c = glycated haemoglobin A1c; DM2 = type 2 diabetes mellitus; TGL = triglycerides; CHL = total cholesterol; HDL = high density lipoprotein; MS = metabolic syndrome; TSH = thyroid stimulating hormone; CRP = C-reactive protein; CGault = Cockcroft-Gault creatinine clearance; AST = aspartate aminotransferase; ALT = alanine aminotransferase; γGT = gamaglutamiltranspeptidase.

For that, a sample of consecutive non-institutionalized patients aged 60 or older were enrolled between 2011 and 2013 at two general geriatrics outpatient clinics located at the metropolitan area of the Federal District, Brazil. The clinics were the Geriatrics Service of the Catholic University of Brasília (HUCB) and the Geriatrics Center of the University of Brasília (UnB). The main inclusion criterion was to spontaneously seek primary or secondary care for circulatory events. Exclusion to integrate these analyses were active inflammatory and/or infectious conditions, malignancies of any kind (current or past) or important kidney impairment (creatinine clearance < 25 ml/min/1.73 m^2) coupled or not with abnormal titers of liver function markers. Patient enrolment was done consecutively, with no active search for particular conditions or events. The study was approved by the institutional research ethics committee and procedures were in accordance with the ethical standards of the Helsinki Declaration, with all participants having signed informed consent before assessments.

Diagnosis of type 2 diabetes included self-report of the condition confirmed by clinical aspect in anamnesis and/or by fasting glycosylated haemoglobin (Hb1Ac) ≥ 6.5%[1]. Practitioners of physical exercises were those exhibiting 30 minutes or over of exercises at any bout for at least four days a week[8], while the smoking habit was defined as report of usual, active consumption of cigarettes[9]. Metabolic syndrome (MS) was identified according to NCEP-ATPIII criteria[10]. For biochemical analysis, the following measures were obtained according to routine clinical biochemistry and expressed in standard units: blood glucose (GLU), glycated haemoglobin (HbA1c), total cholesterol (CHL), and high density lipoprotein (HDL), triglycerides (TGL), C-reactive protein high sensitivity (CRP), thyroid stimulating hormone (TSH), Cockcroft-Gault creatinine clearance (CGault), gamaglutamiltranspeptidase (γGT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

All subjects were submitted to assessments of total body mass (kg), body height (m), and blood pressure (mmHg). Body mass index (BMI; kg/m^2) was defined as usual whereas waist circumference (WC; cm) was measured 2 cm above the umbilicus scar.

Whole blood was obtained during sampling for

biochemical analysis and stored at -20°C until use. Genomic DNA was purified according to standard extraction kits (QIAamp DNA Mini Kit, Qiagen, Brazil). All the patients have been genotyped for the *HNF1*β A/G transition (rs4430796). For the identification of the polymorphisms, we have used the QuantStudio 3 Real-Time PCR System (Applied Biosystems). The reactions have taken place on 96 wells plaques and in 10 µl of total volume that included 2 µl of a DNA preparation (≈ 10-20 ng) and 8 µl of reaction mixture constituted by 5 µl of Universal Master Mix (Applied Biosystems, Foster City, CA), 0,25 µl of TaqMan® SNP Genotyping Assays 40x (Applied Biosystems, Foster City, CA) and 2,75 µl of ultrapure water. The cycling conditions for the Real Time PCR QuantStudio 3 System were 50ºC for 2 minutes (pre-read stage), 95ºC for 10 minutes (hold stage) and PCR stage of 95ºC for 15 seconds and 60ºC for 1 minute for 45 cycles. Results interpretation has been achieved by means of the system QuantStudio™ Design and Analysis Software v1.4.1.

The Kolmogorov-Smirnov test was used to test normal distribution of continuous variables through within-genotype approach. The Hardy-Weinberg equilibrium was tested using chi-square test. Data is expressed as means ± standard deviation (SD) or frequency (%). Analysis of variance (ANOVA) was used to compare means of the continuous variables (e.g.: age) across genotypes. Frequencies of categorical variables (e.g.: gender) across genotypes were compared using the chi-square test. All analyses were performed employing the Statistical Package for Social Sciences (SPSS) for Windows (version 13.0). A p value < 0.05 was considered significant.

Data of the 184 patients was analysed for anthropometric, clinical and metabolic features, with mean values and proportions in Table 1. The overall profile of the patients is compatible with an important frequency of metabolic disorders, with a high prevalence of diabetic (> 30%) dyslipidemic (> 50%) and hypertensive (> 75%) cases as well as of smokers (> 30%) and sedentary individuals (> 50%).

The frequencies of the *HNF1*β rs4430796 alleles in the sample were consistent with the Hardy–Weinberg equilibrium (p value < 0.05). A statistically significant difference was noticed in the frequency of diabetic patients across genotypes, with 30.8% of the A homozygous bearing the condition compared to a prevalence of 12.2% between G homozygotes (χ^2 = 6.04; df = 2; p < 0.05). Genotypes of the *HNF1*β gene associated with no other features of the sample.

Given that the *HNF1*β gene, located on 17q21.3, encodes a transcription factor involved in tissue-specific regulation of gene expression and embryonic development of numerous organs [4,11], and that a total of 30 heterozygous mutations in the *HNF1*β gene have been described so far (including missense, nonsense, frameshift, insertion/deletions, and splice site mutations)[12], we reiterate that our investigation focused on the association of a particular A/G allelic variation (rs4430796) with a range of clinical and biochemical variables in elderly patients, having found evidence for an specific association of the corresponding GG genotype with the occurrence of T2DM. Such an association has already been described elsewhere, as follows.

The major G allele of the rs4430796 SNP of the *HNF1*β gene was associated with decreased risk of T2DM in physically active in contrast to the increased risk in sedentary, pointing out the complexity of the relationship between the gene and diabetes[13]. The evidence for an association is reinforced by the genome-wide association study (GWAS) with a Chinese Hans sample which confirm the association of the *HNF1*β gene rs4430796 with T2DM (OR = 1.19; $p = 1.52 \times 10^{-11}$)[14]. It should be considered that the Brazilian population was formed by an admixture of races[15]. In ancestry-specific GWAS meta-analyses, the rs4430796 polymorphism was also confirmed in association with T2DM (Cochran's Q p-value $3{,}6 \times 10^{-1}$; $p = 8.9 \times 10^{-9}$)[16], as well as in another GWAS that validated this association in European, African and Asian backgrounds and found protective properties of the rs4430796 polymorphism against T2DM (OR= 0.91; $p = 2.7 \times 10^{-7}$)[17].

To our knowledge, this study is the first report to demonstrate that a polymorphism in the HNF1β gene is associated with T2DM in Brazilian elderly patients. In clinical terms, the sample characterization revealed significant prevalence of metabolic disorders compatible with a profile eligible for primary or secondary prevention of vascular conditions. Even so, the analyses showed no association of genotypes with other basic variables apart from the glycaemic traits, rendering this relationship as plausible even in the context of multiple metabolic disorders, typical of older Brazilians[18]. Unfortunately, sample size severely limited statistical power for subgroup analysis. Further thorough investigations with larger sample sizes could confirm our findings.

In summary, we tested the association of allelic

variants from the rs4430796 SNP with the clinical, biochemical and inflammatory profile in elderly patients. Our findings suggest a protective character for the GG genotype in the development of T2DM, which appears applicable to elderly individuals as well. Whether this information will prove useful for targeted prevention or treatment of type 2 diabetes remains to be determined.

Author contributions

W. Machado-Silva carried out the genotyping procedures whereas A.C. Tonet-Furioso performed the biochemical assessments. L. Gomes and C.F. Moraes conducted the clinical/medical component of the study. C. Córdova and O.T. Nóbrega designed and coordinated the study. W. Machado-Silva and O.T. Nóbrega analysed and interpreted results as well as prepared the original manuscript.

Acknowledgments

The research was supported with grants # 445692/2014-6 (CNPq) and # 193.000.967/2015 (FAPDF), with a stipend to W. Machado-Silva (CAPES) and a fellowship for productivity in research to O.T. Nóbrega (CNPq).

Conflict of interest

There is no potential conflicts of interest.

PALAVRAS-CHAVE: *Diabetes* mellitus. *Polimorfismo genético. Idoso.*

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Vasculitis of small and large vessels, a casual association?

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http://dx.doi.org/10.1590/1806-9282.64.07.590

SUMMARY

The authors report a case of a 69-year-old man with idiopathic leukocytoclastic cutaneous vasculitis. For three years, the lesions recurred with progressive worsening and were associated with systemic manifestations of low-grade fever, weight loss and raised inflammatory markers. The patient latter presented a 6th cranial nerve involvement, raising the concern of a possible systemic vasculitis, which was latter evidenced by the development of deep vein thrombosis and angina pectoris. The treatment of the patient witch based on the decreasing of inflammatory activity, by using effective immunosuppressive therapy, with lower toxicity is more important than identifying the type of the vasculitis. This case illustrates the importance of awareness for the systemic involvement that can occur in up to 50% of patients with leukocytoclastic cutaneous vasculitis.

KEYWORDS: *Vasculitis. Vasculitis, leukocytoclastic, cutaneous. Giant cell arteritis.*

INTRODUCTION

Cutaneous leukocytoclastic vasculitis (VLC) is a common vasculitis in the clinic with no predilection for sex, manifesting in a broad spectrum of ages[1,2]. The lesions can assume several characteristics - nodular, vesicular, bullous or even ulcerated, with dimensions ranging from millimetres to several centimetres. They may be pink or purpuric[3]. Its physiopathology rests on the immune response to invasion by endogenous or exogenous antigens, and the type III reaction of Gel and Coombs is implicated in its pathogenesis.

In order to differentiate from other vasculitis, histologically the dermal lesions will have to present at least two of the three required criteria: presence of perivascular leukocyte infiltrate (neutrophils in the early lesions and lymphocytes in the late phase); vascular destruction with extravasation of blood elements and fibrinoid necrosis[4].

In most cases, VLC occurs in isolation and it is not always possible to clarify its origin. However, in about 50% of cases it is associated with systemic vasculitis. The study of series of patients with greater numerical expressiveness allowed us to conclude that this association is especially common if VLC is late onset (after 65 years old), recurs within a month and is accompanied by neurological manifestations[5,6].

VLC also appears to be associated with drug re-

DATE OF SUBMISSION: 14-Nov-2017
DATE OF ACCEPTANCE: 05-Dec-2017
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actions, infections (HIV), connective tissue diseases and neoplasia.

The 2012 Chapel Hill Consensus Conference on vasculitis highlights that there are two entities with different prognoses - leukocytoclastic vasculitis of an isolated organ with a benign and self-limiting course and that related to systemic diseases, which has a less favourable outcome[6]. Treatment is based on the use of oral corticosteroid therapy for 4-6 weeks, with progressive dose reduction later. If symptoms recur, other drugs, such as azathioprine or methotrexate, may be associated[7].

Temporal arteritis is a vasculitis of large and medium calibre vessels of granulomatous character that preferentially reaches the vessels above the diaphragm and especially the intracranial vessels. There are few references to occasionally monitor about small vessel vasculitis, as is the case for IgA vasculitis, systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's Syndrome[6]. The inflammatory process begins in the adventitia of the vessel after stimulation of the T lymphocytes that trigger the production of interleukin 17 and interferon gamma. These, in turn, lead to an increase in angiogenesis and proliferation of myofibroblasts, culminating in intimal proliferation[8]. Therapy of temporal arteritis is fundamentally based on corticotherapy. In relapses, immunosuppression is used with a variable success percentage[9].

CLINICAL CASE

A 69-year-old man, a retired locksmith, is admitted to a medical ward for the first time in 2012 reporting two months of fever, asthenia, arthralgia, loss of about 5 kg, and nodular erythematous lesions of 3 mm of diameter, slightly itchy, spread throughout his torso. He said that these lesions lasted for several months, appearing and disappearing, giving rise to hyperpigmented zones. Of pathological antecedents to be mentioned, only hypothyroidism and dyslipidaemia, being medicated with levothyroxine and fenofibrate. At the objective examination, the patient had a good general condition, well hydrated, ruddy, feverish (atrial temperature of 38ºC), normotensive, with no signs of poor peripheral perfusion and with symmetrical and large pulses. Cardiopulmonary auscultation showed no alterations. He had no adenomegaly or organomegaly. The wrist and knee mobilization was painful, but no actual signs of arthritis. It was verified the presence of erythematous-nodular lesions with about 3 mm of diameter spread throughout the torso, as well as hyperpigmented macular lesions of smaller diameter. There were no lesions on the palms or plants. Analytically, it should be highlighted the elevation of the inflammatory parameters with sedimentation rate (SV) of 100 mm in the first hour and C-reactive protein (CRP) of 19 mg/dL, elevated ferritin (446.5 ng/dL) and slightly elevated alpha 2 globulin. Coagulation (APTT and prothrombin time), renal function, urinalysis and hepatic enzyme without changes. Normal immunoelectrophoresis. Negative cryoglobulinemia screening. Negative tumour markers (CA 19.9, CA 125, CEA, PSA and beta-2 microglobulin). Complement without alterations, anti-nuclear antibodies (ANA) and negative neutrophil anti-cytoplasmic antibodies (Anca). Normal angiotensin converting enzyme. Negative blood and urine cultures. Serologies for HIV, HCV, HBV and syphilis negative. Imaging tests (chest x-ray and thoracic-abdominal-pelvic CT) did not identify any lesions.

Echocardiogram with good systolic function and no valvular vegetation. Normal upper digestive endoscopy and colonoscopy, and normal positron emission tomography.

He initiated non-steroidal anti-inflammatory therapy (naproxen 500 mg 3 times/day), with fever and arthralgia disappearing and inflammatory parameters decreasing considerably.

He was submitted to skin biopsy, which revealed inflammatory infiltrate and fibrinoid necrosis (Figure 1), allowing the diagnosis of leukocytoclastic vasculitis. He was discharged with an indication for follow-up at a medical appointment.

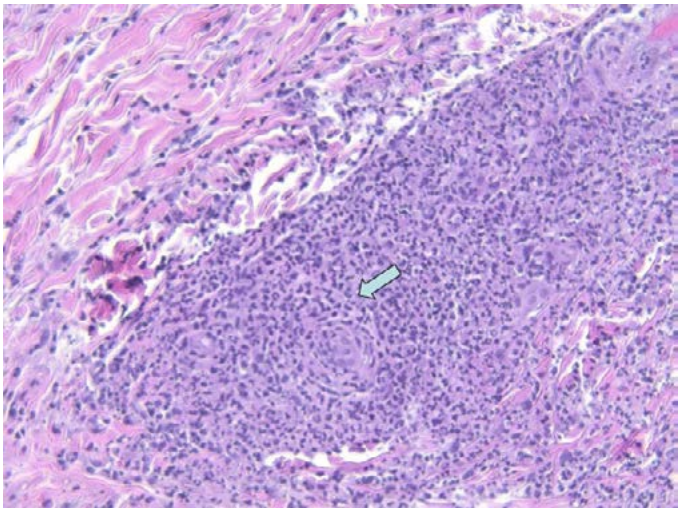

FIGURE 1.

About five months later, the patient was readmitted for sudden diplopia by paresis of sixth left cranial pair, generalized fatigue and asthenia. He denied headache or loss of visual acuity. The analysis revealed normal normocytic anaemia (haemoglobin 9 g/dL), high SV (130 mm in the first hour) and 24-hour proteinuria in the subnephrotic (1,200 g/dL). The remaining study was negative: Anas, Ancas, antiphospholipid antibodies, cytochemical and bacteriological examination of the cerebrospinal fluid (CSF), serologies for Borrelia, herpes virus and Echovirus (blood and CSF), CSF oligoclonal bands test. The MEF gene of the family fever was negative. Cranioencephalic CT, cerebral magnetic resonance angiography and cervical echo-Doppler without changes. Renal ultrasonography did not identify asymmetries in the size of the kidneys, which presented normal cortical-medullar differentiation. The echo-Doppler and magnetic resonance angiography of the renal vessels revealed no alterations. Renal biopsy was normal and did not reveal changes suggestive of vasculitis. Electromyogram of limbs - normal. Given the context of the first hospitalization, and after the exhaustive study excluding other aetiologies, this condition was attributed to probable vasculitis of the vasa nervorum of the sixth cranial pair. He started low dose corticosteroid therapy (30 mg prednisolone day), with total normalization of inflammatory parameters and recovery of ocular movements.

He maintained ambulatory corticosteroid therapy at a dose ranging from 10 mg to 17.5 mg. However, in mid-2013, he started complaints of typical angina again. He underwent an exercise test that proved to be positive and was then submitted to cardiac catheterization, which did not demonstrate occlusive coronary lesions. Once again, it was hypothesized that this is a vasculitis manifestation. The control of dyslipidaemia was intensified and antiplatelet and beta-blocker therapy (nebivolol) was initiated. It was clear that the reappearance of these systemic complaints coincided with the attempt to decrease the dose of corticosteroids. Thus, azathioprine was started as a corticosteroid sparer, but it was not able to lower the dose of prednisolone beyond 17.5 mg without reappearance of symptoms. Methotrexate therapy was then chosen at 15 mg weekly and folic acid 5 mg, with which it had good symptomatic control. However, he had to interrupt due to infectious complication of hepatic abscess. In two more occasions, skin lesions reappeared, biopsies were performed, and the diagnosis of leukocytoclastic vasculitis was again concluded.

In January 2015 he suffered left iliofemoral thrombosis, treated with enoxaparin at a therapeutic dose (1 mg/kg of body weight).

In 2016, he started complaining of lameness of the right leg and pain in the twin region, and critical ischemia at the femoral level was diagnosed. He did a thromboendarterectomy successfully, being later medicated with rivaroxaban.

A few months later, he developed right temporal headache of intense character, fulfilling the clinical criteria for the diagnosis of temporal arteritis, for which he was submitted to biopsy of the temporal artery. This revealed intimal thickening and fibrosis, with focal fragmentation of the internal elastic lamina, without observation of granulomas, giant cells and/or inflammatory infiltrate of the vessel wall - aspects that may correspond to treated temporal arteritis.

At the moment he is preparing to initiate immunosuppressive therapy with mycophenolate mofetil, since he maintains the need for high doses of steroids. This therapy was not started earlier due to the occurrence of a femoral neck fracture after a fall, followed by pneumonia and a long period of motor rehabilitation.

DISCUSSION

In the case presented, at the first hospital stay the patient had palpable, hardened and painful skin lesions. After exclusion of infections, medication and other pathologies, either autoimmune or neoplastic, the diagnosis of idiopathic VLC was confirmed by skin biopsy. However, after a few months, the patient is hospitalized for systemic complaints and for a six-pair cranial monoparesis. After exclusion of embolic and/or neoplastic aetiology, the exclusion of a vasculitis with central involvement became preponderant. Vasculitis that may involve the CNS are Wegener's granulomatosis, polyarteritis nodosa, and microscopic polyangiitis. This effect may be due to direct nerve injury, to the appearance of granulomas in the vicinity of the nerve, or to the vasculitis of the vasa nervorum[5]. The cranial nerves most affected by vasculitis phenomena are the fifth, sixth and seventh pairs[10]. In the case presented, the patient did not present respiratory symptoms

or blood pressure changes. Eosinophilia and the presence of neutrophil anti-cytoplasmic antibodies were not registered. Serologies remained negative. The subnephrotic proteinuria that he presented remained unprovoked, since a renal biopsy was performed, which did not detect the presence of complement, immunoglobulin deposits and/or amyloid deposits. These aetiologies were then excluded, with the hypothesis of open systemic vasculitis being maintained.

In 2013, the patient had an episode of angina. Despite positive exertion evidence, catheterization did not reveal changes. The hypothesis of systemic vasculitis of medium and large vessels is again considered, since no stenotic lesions were seen at the level of the coronary arteries. The vasculitis that frequently present with coronary involvement are Wegener's granulomatosis and Kawasaki's disease, both excluded in the diagnostic investigation. In addition, temporal arteritis reaches the aorta and the supra-aortic trunk. All of the remaining vasculitis induces arrhythmias due to damage to the cardiac or myocardial conduction system, and does not reach the coronary vessels[11].

During the etiological investigation, the patient presented several intercurrences. Deep venous thrombosis and, subsequently, acute ischemia of the right lower limb occurred during a period of elevation of the inflammatory parameters coincident with the reduction of corticotherapy dose. In the literature, there is evidence of increased thrombotic risk in vasculitis, predominantly in those with positive Ancas, which was again excluded in this patient[12].

The development of right temporal headache, with clinic and histology compatible with temporal arteritis, allowed us to conclude that all vascular manifestations present would be related to this type of vasculitis. Giant cell vasculitis or temporal arteritis is a granulomatous vasculitis of large and medium-sized vessels and affects, for the most part, cases of adults over 50 years of age. It preferably involves the extracranial branches of the carotid arteries, such as the temporal artery[9]. The typical symptom of this type of vasculitis is headache, located in the temporal region. Other symptoms include fever, malaise, anorexia, myalgia, and claudication of the jaw, sensitivity of the scalp, diplopia and ptosis. The most feared complication is unilateral/bilateral vision loss due to ischemic optic nerve neuropathy. The aorta and its branches may also be involved in this type of vasculitis, with risk of rupture and/or dissection. Symptoms of polymyalgia rheumatica may coexist[1,5]. Although involving the carotid arteries and their branches, the frequency of strokes in these patients is low[13]. There have been reports of acute atrophy, both of the vessels of the upper limbs and vessels of the lower limbs[14]. The diagnosis of temporal arteritis should take into account all clinical and laboratory assessment, and should not rely solely on biopsy, which may be positive in a small number of cases. Diagnostic criteria are five: age equal to or greater than 50 years old, severe headache, elevated sedimentation rate (SV), temporal artery engorgement and compatible biopsy. It suffices to present three of the five previous criteria for the diagnosis[15]. In the presented case, the diagnosis was made possible by the clinical and analytical evaluation, since the patient is 74 years old, presented severe headache and high SV. The biopsy of the temporal artery was suggestive, presenting features of treated temporal arteritis. This was due to the long-term corticosteroid therapy that the patient performed since the diagnosis of idiopathic leukocytoclastic vasculitis.

Future therapy should be sufficiently effective and safe in order to avoid further recurrences. He will go through, within the current contingencies, the use of monoclonal antibodies or by immunosuppression with oral drugs that, nevertheless, allow a good control of vascular inflammation.

CONCLUSION

Vasculitis is a group of heterogeneous diseases, mostly difficult to diagnose. In many cases, only after several hospitalizations the final diagnosis is established, since they present a complex clinic, easily confused with other pathologies. In addition, the lack of a specific diagnostic test, in addition to the biopsy of the affected tissues, which is often not feasible, contributes to the delay in its early detection. Leukocytoclastic vasculitis is common in clinical practice and does not require, in general, specific therapy. Its recurrence, especially in age groups over 65 years, and CNS attainment may alert to the existence of associated disease. There is no association with temporal arteritis but with systemic lupus erythematosus and IgA vasculitis.

This case may just be a fortuitous association.

At this time, it is important that the patient resume immunosuppressive therapy more effectively and with lower possible infectious risk, since we recognize that the disease still maintains activity, despite apparent symptomatic control under corticosteroid therapy.

Conflicts of interest

The authors declared no conflict of interest.

Acknowledgements

We would like to express our appreciation for the work developed and for the precious help of Dr. João Aranha acting as dermatologist/anatomopathologist.

RESUMO

Os autores reportam um caso de vasculite leucocitoclástica recidivante num homem de 69 anos. Durante cerca de três anos as lesões cutâneas de vasculite leucocitoclástica reapareceram periodicamente, acompanhando-se sempre de um quadro sistêmico caracterizado por febrícula, perda de peso e astenia, assim como aumento de novo dos parâmetros inflamatórios. O aparecimento de parésia do sexto par craniano no decurso de uma dessas recorrências cutâneas levantou a hipótese de estarmos perante uma vasculite mais agressiva, com envolvimento extracutâneo. Esse envolvimento sistêmico foi novamente evidente com aparecimento de angina pectoris e trombose venosa profunda. Atualmente, mais do que a identificação do tipo de vasculite, a abordagem dos doentes com essa patologia assenta na cessação da atividade inflamatória recorrendo a terapêutica imunossupressora eficaz, com a menor toxicidade possível. Destacamos a importância da vigilância do componente sistêmico, que pode ocorrer até 50% na vasculite leucocitoclástica cutânea.

PALAVRAS-CHAVE: *Vasculite. Vasculite leucocitoclástica cutânea. Arterite de células gigantes.*

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Breast cancer: Is grief a risk factor?

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http://dx.doi.org/10.1590/1806-9282.64.07.595

SUMMARY

Cancer is characterized by the disordered growth of cells that have high capacity of invasion to the tissues and organs. One of the types of tumour that has national incidence and high mortality is breast cancer. Studies show that in addition to hereditary factors, lifestyle and environmental factors, there are factors related to emotional distress (mourning), which interfere with the development of breast cancer. Thus, it is necessary to investigate if the experience of mourning can trigger the appearance of the tumour. For this, an integrative review was performed to verify the existence of the relationship between mourning and development of breast cancer, which presented contradictory results. Methodological errors and lack of access to important information, such as alcohol and tobacco use, were pointed out as the main causes of the contradiction found. A possible mechanism involving cortisol release has been proposed, but more research is needed to make it clear whether the association between mourning and breast cancer really exists, and by what path.

KEYWORDS: *Mourning. Death. Risk factors. Breast neoplasms.*

INTRODUCTION

Characterized by a set of more than 100 diseases that have in common the disordered growth of cells that invade tissues and organs, cancer accounts for one of the highest death rates in the world. Among its different types, breast cancer is the one with the highest incidence and mortality among women[1,2].

The causes of this pathology are varied, being external or internal to the organism, both being interrelated. The main factors associated with breast cancer are age, family history, use of contraceptives, alcohol consumption, smoking, previous breast disease, radiation exposure and obesity[3]. In addition, emotional state, stress, depression and bereavement have also been investigated as risk factors for this type of cancer[4].

For Angerami-Camon[5], the conflicts and emotional problems experienced, such as the loss of a relative and separation between spouses may affect emotional health and come to determine the illness. In this sense, research indicates that the appearance of the tumour is attributed to the inadequate way of coping with traumas experienced in the past[4,6]. As reported by the patients, the tumour physically externalized many painfull experiences that were "stored" by them.

As a possible physiological explanation, Li et al.[7] state that the balance of neuroendocrine hormones in women is easily affected by psychological trauma

DATE OF SUBMISSION: 12/03/2017
DATE OF ACCEPTANCE: 06/05/2017
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and that long-term adverse emotional experience can cause hyperplasia in mammary epithelial cells, leading to tumour development. In this sense, the definition of a cellular mechanism that establishes the relationship between these variables (psychological trauma, neuroendocrine hormones and development of breast cancer) will bring new perspectives for the preventive treatment of this disease, and may introduce, in the traditional care plan, special attention to the mourner.

This study aimed to verifying if it is possible to affirm, based on existing data, that there is an association between mourning and breast cancer. In addition, to alert the societies of medicine and psychology to the need for new research on the subject and the inclusion of questions about mourning in the anamnesis of patients with breast cancer.

METHODS

This work was developed from an integrative review, using the descriptors bereavement, grief and mourning, crossed with risk, risk factors and breast cancer to survey the population and define the sample. The database used was PubMed and the population obtained was 39 articles, which were read and analysed (Table 1, page 18). According to the inclusion and exclusion criteria adopted by the study, only nine articles were selected for the sample and one was added by reverse search (Table 2, page 19).

Inclusion criteria were approach to grief as a risk factor for the development of breast cancer and the availability of articles on the internet in its entirety. The exclusion criterion adopted was articles written in languages other than English and Portuguese.

TABLE 1 – SEARCH STRATEGY

Source	Search strategy	Population	Sample
PubMed	*risk factors* AND *breast cancer* AND *bereavement*	13	6
PubMed	*risk factors* AND *breast cancer* AND *grief*	12	4
PubMed	*risk factors* [MeSH Terms] AND *breast cancer* [MeSH Terms] AND *mourning*	7	2
PubMed	((*risk*[MeSH Terms]) AND *breast cancer*[MeSH Terms]) AND *bereavement*[MeSH Terms]	7	3
Articles excluded per repetition	-	-	6
Reverse search	-	-	1
Total	-	39	22*

* The sample was only nine articles since some of them were found in more than one search.

TABLE 2 – ARTICLES SELECTED FOR THE SAMPLE

Author	Title	Year	Source	Reference
Biondi et al.	Can loss and grief activate latent neoplasia? A clinical case of possible interaction between genetic risk and stress in breast cancer.	1996	PubMed	19
Cooper & Faragher	Psychosocial stress and breast cancer: the inter-relationship between stress events, coping strategies and personality	1993	PubMed	9
Hiller	Breast cancer: a psychogenic disease?	1989	PubMed	15
Kvikstad et al.	Death of a Husband or Marital Divorce Related to Risk of Breast Cancer in Middle-aged Women. A Nested Case-Control Study Among Norwegian Women Born 1935-1954	1994	PubMed	10
Lambe et al.	Maternal breast cancer risk after the death of a child	2004	PubMed	13
Li et al.	Cancer Incidence in Parents who Lost a Child	2002	PubMed	11
Li et al.	Cancer survival in parents who lost a child: A nationwide study	2003	PubMed	12
Nakaya	Effect of psychosocial factors on cancer risk and survival	2014	PubMed	20
Wellisch & Cohen	The special case of complicated grief in women at high risk for breast cancer	2010	PubMed	14
Parkes	Coping with loss: Bereavement in adult life.	1998	Reverse search	24

RESULTS

Observations and personal impressions during the 18th century were the basis for the first statistical study conducted by Snow[8] at the London Cancer Hospital. He found that of the 250 cancer patients, 156 reported previous experience with the loss of close relatives. Likewise, Cooper & Faragher[9] identified a correlation between the prevalence of breast cancer and the impact of stress related to emotional trauma, such as mourning. However, Kvikstad et al.[10] did not identify a positive association between the bereavement caused by the husband's death or a divorce and the increased risk of developing breast cancer.

Trauma can be defined as an important and intense event in a person's life, where the inability to react to the event properly is the main factor. This incapacity correlates with the adverse effects that the traumatic event can cause in the psychic organization of the individual, generating an emotional state characterized by an increase in anxieties and fears, as well as an altered perception of the world and yourself[6].

According to Li et al.[11], the belief that psychological stress causes malignancies has a long history, but scientific evidence remains contradictory. This, according to the study, is the result of errors in the methodology used, such as the use of inadequate control, the carrying out of prospective studies with limited observation period due to patient loss, as well as data based on personal reports. Despite the caution with the definition of the methodology, the author clarifies that the lack of access to important information (lifestyle, alcohol and tobacco use) was responsible for the contradiction observed in two of his papers, in which the first one identified the increase for the risk of cancer in mothers who had lost children[11], but not the second one[12].

Lambe et al.[13] found a significant increase in the incidence of breast cancer in women who lost their only children between 1 and 4 years of age. In the study by Grzybowski, Schmidt & Borges[6], breast cancer patients reported believing in the association between the development of neoplasia and previous emotional trauma, such as the death of a loved one. Wellisch & Cohen[14] investigated, in a population of women whose mothers developed breast cancer, bereavement as a risk factor for the disease. The study shows not only the presence of the relationship between chronic mourning and neoplasia, but also the need that this group presents in relation to preventive healthcare.

According to Hiller,[15] for humans, emotional losses appear to be related to the immunosuppressive state. The author reports that clinicians have already described the role of depression, loss, sadness and anxiety in the aetiology of breast cancer in the 19th century. Galen (quoted by HILLER[15]) was the first clinician to report that women who had severe melancholia were more likely to develop breast cancer. Gendron (quoted by HILLER[15]) in 1701 noted that women suffering from depression and anxiety were prone to the development of cancer. Moreover, about 50 years later, Richard Guy (quoted by HILLER[15]) reported the case of a woman who developed breast cancer after a period of depression resulting from the loss of a child.

The observation that there was a personality type prone to the development of cancer and the existence of an association between an emotional state and breast cancer have been reported by other clinicians. The predisposition to the disease seems to be linked to women with a hysterical, melancholic, depressed, sexually inhibited profile and unable to discharge anger; such a correlation was not found when analysing a profile of women who have healthy life habits and who are more emotionally balanced[15].

Cooper & Payne[16] reported that the relationship between psychosocial stress antecedents to the disease has been recognized for centuries. They also stated that most of the research was in the cardiovascular area, but more recently, it has been described in several types of cancer, including gastric, lung, breast and paediatric carcinomas. In addition, Cooper[17] adds that although studies in the area of oncology present methodological errors, they point to an important relationship between the occurrence of previous stress events (within a period of five years) and the subsequent diagnosis of breast disease.

Lerman & Schwartz[18] found that women at increased risk for breast cancer experienced specific or generalized psychological distress. Paget (quoted by BIONDI[19]) reported that the number of cancer patients reporting large losses and depressions prior to breast cancer is high, making clear the presence of an association between mental depression and the development of breast cancer.

However, the contradiction in the results found, coupled with the complexity of the disease and the lack of clarification about the cellular mechanisms

that proved the link between these risk factors and the development of breast cancer, resulted in an interest decline in the research of these psychological factors as cancer risk factor during the 20th century.

The reactivation of interest in the study of the connection between emotional losses and cancer, as well as in the relation between the mind, pathogenesis and progression of this disease, has been attributed to the emergence of research in the areas of psychoneurology and psychoneuroimmunology[17]. According to Li et al.[12], emotional stress can alter immune function and influence tumour growth, metastasis and survival of cancer patients.

According to Nakaya,[20] psychosocial factors, such as personality types and depression, can also alter immune and endocrine function and thus affect the incidence and survival of cancer patients. Studies have reported the reduction of cellular immunity (immunosuppression) in women after the death of the partner[21,21].

The effect on the immune system caused by stress seems to be of particular importance during childhood, at which point the neuroendocrine system is developing. In this sense, an increased risk for the development of cancer was identified among children who lost a close relative during the first 15 years of life, as well as an increased risk of this condition in children exposed to stress during the prenatal period[23]. However, Nakaya[20] did not find data that supported the hypothesis that personality and depression were risk factors for the development of cancer and survival of the patient in the face of the disease. Thay added that, if such an association exists, it is unlikely to have clinical or public health implications.

Parkers[24] and Cohen & Rabin[25] stated that the existence of physiological changes related to depression, particularly pain, induces the development of cancer or becomes a stimulus for the activation of pre-existing cancer (latent pathology). In this sense, Biondi, Constantini & Parisi[19] and Hiller[15] concluded that stress does not generate cancer, but it can activate latent pathology. As for Riley[26], Bammer & Newberry[27] and Newberry, Gordon & Meehan[28], emotional stress interferes with both the onset and progression of cancer.

In an interesting experimental study, Riley et al.[29] used a hybrid strain of female mice, in which the maternal parental line was inoculated with an oncogenic virus. The development of the tumour, for the hybrid mice, only occurs between 8 and 18 months after birth in 80% to 100% of the cases. In the study it is possible to notice that, after stress induction, tumour development was altered in 92% of the animals when compared to the control group and that this result was mediated by the neuroendocrine and immunological systems.

In the present study, the authors report that emotional stress increased plasma corticosterone concentration (from 40 ng/mL to more than 700 ng/mL) and reduced the size of the thymus and number of natural killer (NK) cells, which participate of the body's natural defence against tumour cells[29]. According to Ben-Eliyahu,[30] these factors may lead to increased susceptibility to the development of breast cancer and metastasis.

For Hofer[31] and Irwin[32], in addition to the reduction of NK cells, depression is also related to the constant activation of the hypothalamic-adrenal-pituitary axis and the high concentration of cortisol. It has been shown that neuroendocrine hormones (cortisol, adrenaline, and prolactin, among others) may influence the biology of cancer[33].

Corroborating these results, Biondi et al.[19] verified that psychological stress and depression affect the endocrine and immune systems, and may contribute to neoplastic growth due to increased cortisol, prolactin and oestrogen, or by reducing the number and activity of lymphocytes and NK cells[29,30].

In addition, behavioural studies have shown that people with a upset and depressed emotional state have higher consumption of alcohol and cigarettes, substances widely known as carcinogenic factors, that is, they are substances capable of interacting with the DNA molecule causing changes that allow the development of cancer[34,35].

CONSIDERATIONS AND CONCLUSION

A topic of general interest is the knowledge of how important changes in life may be related to the onset of cancer. Among these changes, to many the loss of a beloved one is experienced intensely, often accompanied by chronic stress and depression, and it has been associated with pathologies.

However, the intensity and duration of the state of stress or depression, as well as the consumption of alcohol and tobacco, whether or not due to this state, are different for each person and have been pointed

out as factors that may confuse and hinder proof of this hypothesis.

Errors in the methodology used, the limitation of the study due to patient loss, studies based on personal observation, inadequate control of confounding factors and the non-inclusion of important information are also pointed out as causes for this difficulty. In addition, stressed individuals are more likely to have health habits that put them at great risk of cancer, such as drug abuse, excessive alcohol consumption, less exercise, and poor diet. The lack of detailed information about individual behaviours such as smoking, physical activity, alcohol consumption and diet, can lead to a wrong association between death and cancer.

Another important point that compromises the validation of this hypothesis is the lack of definition of a cellular mechanism that links mourning to the development of breast cancer, that is, the identification of genetic and molecular changes resulting from this state. This has been attributed to a lack of appropriate technology, but with recent advances in knowledge, new possibilities for advancing this research are emerging.

The proposed biological mechanism for the risk of stress-related cancer includes neuroendocrine changes in the hypothalamic-adrenal-pituitary axis, which regulate the release of glucocorticoids, cortisol levels, catecholamine and reactive species that damage DNA. These substances may alter the cellular immune response to malignant cells, as well as affect tumour angiogenesis and increase the risk of development and progression of the disease. However, despite pointing to a cellular mechanism, the results define only the beginning of a signalling pathway and, therefore, the need for more research.

PERSPECTIVES

The results clearly showed that despite the resumption of research, the relationship between bereavement and risk of breast cancer was not clarified and errors in the methodology continue to be mentioned as the main factor. In this sense, in order to make an effective progress, special attention to the definition of the methodology to be used is necessary. The inclusion of questions about grief in the anamnesis of patients with breast cancer may contribute to the advancement of the research.

Another important point concerns the follow-up by psychologists of patients who face grief, so that they can have support in the process of accepting the loss.

Regarding the mechanism, cortisol seems to be a mediator of several chronic emotional states resulting from bereavement. Therefore, prolonged (chronic) treatment of normal and breast tumour cell may be the way to investigate the cellular mechanism that correlates bereavement to the development of breast cancer and the effect of emotional state on the development of cancer.

RESUMO:

O câncer é caracterizado pelo crescimento desordenado das células que possuem alta capacidade de invasão aos tecidos e órgãos. Um dos tipos de tumour que possui incidência nacional e alta mortalidade é o câncer de mama. Estudos mostram que, além dos fatores hereditários, ambientais e dos hábitos de vida, existem fatores relacionados a um trauma emocional (luto) que interferem no desenvolvimento do câncer de mama. Dessa forma, é necessário investigar se a vivência do luto pode desencadear o aparecimento do tumour. Para isso, realizou-se uma revisão integrativa para verificar a existência da relação entre o luto e o desenvolvimento do câncer de mama, que apresentou resultados contraditórios. Os erros metodológicos e a falta de acesso a informações importantes, como uso de álcool e fumo, foram apontadas como as principais causas da contradição encontrada. Um possível mecanismo envolvendo liberação de cortisol tem sido proposto, mas são necessárias mais investigações para que fique claro se a associação entre luto e câncer de mama realmente existe, e por qual mecanismo ocorre.

PALAVRAS-CHAVE: *Luto. Falecimento. Fatores de risco. Neoplasias da mama.*

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ORIGINAL ARTICLE

Hypertension bearers with high risk/big risk of cardiovascular diseases and socioeconomic and health indicators

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http://dx.doi.org/10.1590/1806-9282.64.07.601

SUMMARY

OBJECTIVE: *To correlate the number of hypertensive patients with high and very high risk for cardiovascular diseases with socioeconomic and health indicators.*

METHODS: *An ecological study carried out from the National Registry of Hypertension and Diabetes (SisHiperDia). The variable "hypertensive patients with high and very high risk" was correlated with the Human Development Index, health care costs and services, average household income per capita, per capita municipal income, number of hospital admissions in SUS, number of medical consultations in the SUS and specific mortality due to diseases of the circulatory system, considering the 27 federative units of Brazil. The data was processed in software IBM Statistical Package for the Social Sciences (SPSS) Statistics, version 22.0Ò. The statistical analysis considered the level of significance p<0.05.*

RESULTS: *Brazilian states with more hypertensive registries in high/very high risk spend more on public health, fewer people reach the elderly age group and more deaths from diseases of the circulatory system (p<0.05). The very high risk stratum correlated with more physicians per population (p<0.05).*

CONCLUSION: *Systemic arterial hypertension has a direct impact on life expectancy and also on the economic context, since when it evolves to high and very high risk for cardiovascular diseases, it generates more expenses in health and demand more professionals, burdening the public health system. Monitoring is necessary in order to consolidate public policies to promote the health of hypertensive individuals.*

KEYWORDS: *Hypertension. Public health. Brazil. Economic indexes. Social indicators.*

INTRODUCTION

Chronic Non-communicable Diseases (NCDs) are the leading cause of death in the world, accounting for a high number of premature deaths. They compromise quality of life, with a high degree of limitation in work and leisure activities, generate economic impacts for families, communities and society in general, as well as aggravate social and health inequities. Approximately 80% of NCD deaths occur in low and middle-income countries. In Brazil, NCDs represent the greatest health problem and correspond to 72% of the causes of death, affecting especially the poor population and vulnerable groups[1].

Among the main NCDs is Systemic Arterial Hypertension (SAH), a serious global public health problem[2]. SAH is an independent risk factor for cardiovascular diseases[3]. This condition is characterized by

DATE OF SUBMISSION: 11-Nov-2017
DATE OF ACCEPTANCE: 14-Dec-2017
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a slow and asymptomatic clinical course, high prevalence, multiple risk factors and control difficulties. When not properly treated, SAH may cause complications in the cardiovascular system[4-7].

It is estimated that one in three adults has SAH, which is equivalent to approximately 1 billion people in the world. As a consequence, there are 9.4 million annual deaths from cardiovascular diseases[5]. At the national level, since the 1960s, the SAH complications have emerged as the main cause of death[4,7]. Average prevalence of self-reported SAH in the population above 18 years of age is 22.7%, being higher in women (25.4%) than in men (19.5%) [6].

Thus, it is necessary to provide appropriate healthcare to the hypertensive. Therefore, stratifying cardiovascular risk can be an effective strategy to plan the most qualified care, depending on the situation of each patient, contributing to reduce the negative repercussions of the disease development. The classification in risk levels allows estimating the probability of developing major cardiovascular events, such as vascular death, myocardial infarction and cerebrovascular accident. This estimate is based on the presence of multiple risk factors, such as gender, age, blood pressure levels, smoking, and cholesterol levels. From the low, moderate, high and very high risk stratification, individuals with a higher chance of complications are selected so that they can benefit from more appropriate interventions[2].

In individuals with high or very high risk, factors such as being more prone to a cardiovascular event; presence of diabetes mellitus or target organ damage such as acute myocardial infarction, cerebrovascular accident/transient ischemic attack, left ventricular hypertrophy, retinopathy and nephropathy are taken into account. Follow-up of hypertensive patients classified in these strata should be judicious, with guidelines on healthy lifestyle and collective activities of healthcare education[2].

Effective care, including cardiovascular risk stratification, is undoubtedly relevant, considering the high morbidity and mortality of SAH, especially deaths caused by cerebrovascular diseases[7]. Therefore, this disease implies considerable impacts for the healthcare sector and society. Its social importance is evidenced, which demonstrates the need to understand the relationship with social, economic factors and health indicators. However, in this context, there are gaps in knowledge, which means the specificities of the subject in question regarding its interface with the social characteristics of the country are now known. And the lack of information about the comprehensiveness, complexity and social, economic and political interrelations of SAH makes it difficult to act on the problem[7-9]. It is of fundamental importance to investigate the relationship between high/very high cardiovascular risk strata and socioeconomic and health indicators, considering that these strata are the most unfavourable and have the largest impact on public health.

In this sense, the studies should describe more clearly the determining factors of the pathology in question, according to a set of sociocultural, economic and geographical characteristics[8,9]. It is expected that knowledge can assist healthcare managers in the challenge of creating and implementing public policies that are consistent with reality, capable of reducing inequalities, quantitatively improving healthcare infrastructure, and making public health universal[10].

The purpose of this study was to correlate the number of hypertensive patients at high and very high risk for cardiovascular diseases with the socioeconomic and health indicators of the Brazilian federative units.

METHODS

This is an ecological, multi-group study, carried out from the unit of analysis "registries of hypertensive stratified at high and very high risk for cardiovascular diseases" of the National System of Registry of Hypertension and Diabetes (SisHiperDia). The data from SisHiperDia were collected through the website of the Department of Informatics of the Brazilian National Health System (DataSUS), in August 2013. The System processes information on patients with SAH and diabetes mellitus, registered in healthcare units or Basic Care teams of the Brazilian National Health System (SUS)[11].

The classification adopted by the Brazilian Ministry of Health in SisHiperDia represents the result of the stratified risk calculation, identified and broken down according to four levels of stratification, presented in Chart 1.[11]

The variable "hypertensive with high and very high risk" was correlated with the Human Development Index (HDI), expenditures with healthcare actions and services, average household income per capita, municipal income per capita, number of hos-

CHART 1. DESCRIPTION OF THE RISK CLASSIFICATION ADOPTED IN THE NATIONAL REGISTRY SYSTEM OF HYPERTENSION AND DIABETES (SISHIPERDIA).

Stratified risk and quantification of blood pressure prognosis (mmHg)			
Risk factors or disease	Grade 1 Mild hypertension SBP * 140-159 or DBP ** 90-99	Grade 2 Moderate hypertension SBP * 160-179 or DBP ** 100-109	Grade 3 Severe hypertension SBP * ≥180 or DBP ** ≥110
I- No other risk factors.	Low risk	Average risk	High risk
II- One to two risk factors.	Average risk	Average risk	Very high risk
III- Three or more risk factors, or lesions in the target organs, or diabetes mellitus.	High risk	High risk	Very high risk
IV - Associated clinical conditions, including cardiovascular or renal disease.	Very high risk	Very high risk	Very high risk

Source: SisHiperDia.[11] * SBP: systolic blood pressure. ** DBP: diastolic blood pressure.

pitalizations in SUS, number of consultations in the SUS and of medical professionals, and specific mortality due to coronary artery disease (CAD). It considered the records and socioeconomic and health indicators of the 27 federative units (UF) of Brazil grouped into five regions: North, Northeast, Southeast, South and Mid-West.

The HDI of each state, as well as its HDI education and HDI income strata, were collected from the Atlas of Human Development in Brazil, an electronic database developed by the United Nations Development Program (UNDP)[12] from national censuses. The HDI measures the level of human development in the countries and covers three dimensions: education, longevity and municipal income per capita. It ranges from 0 (no human development) to 1 (total human development).

Expenditure on public health actions and services, per capita, refers to the value of the total expenditure per federation unit for each individual, in 2010. This data was determined on the website Ministry of Health/Executive Secretariat/Healthcare and Development Economics Area/Information System on Budgets of the Information System on Public Budgets (Siops)[13].

The average household income, per capita, in 2010, considered the minimum wage at the time, BRL 510.00[14]. The municipal income, per capita, indicates the average income of individuals residing in each state, from the Brazilian Institute of Geography and Statistics (IBGE). It adds up all kinds of income obtained by the residents of the municipalities (including salaries, pensions and government transfers, among others), and the sum is divided by the total number of inhabitants of the state[15].

The number of hospital admissions in SUS per 100 inhabitants in 2010 was obtained from the website of the Ministry of Health/DataSUS - SUS Hospital Information System (SIH/SUS).[16] The source of data on the variable probability of survival up to 60 years was the UNDP (2010)[12].

The number of medical consultations, in the SUS, per inhabitant, in 2010, was verified on a website of the Ministry of Health/SE/DataSUS - SUS Outpatient Information System (SIA/SUS) for 2010[17]. The number of doctors per 1,000 inhabitants, in 2010, followed information from the Ministry of Health/SGTES/Degerts/Conprof - Professional councils. The variable refers to the ratio between the total number of physicians residing in a given municipality and the total number of inhabitants of the same municipality, multiplied by 1,000[18].

CAD-specific mortality, which represents deaths from diseases of the circulatory system, per 100,000 inhabitants, in 2010, was based on the records of the Mortality Information System (SIM). The values are calculated from deaths reported to SIM and IBGE[19].

The database was built on the IBM Statistical Package for the Social Sciences (SPSS) Statistics, version 22.0®. The descriptive analysis considered for each federative unit the total population, the number of hypertensive registries in the system, the percentage of people classified as both high risk and very high risk. The federative units were grouped by Brazilian region (North, Northeast, Southeast, South and Mid-West) and the averaged and medians of registries in SisHiperDia were calculated at high risk and at very high risk. The medians were compared by the Kruskal-Wallism test, according to the Brazilian region. The correlation between socioeconomic and health indicators with high and very high risk hypertensive registries was made according to the Spearman's correlation with correlation coefficient (r) and determination factor (r^2). Non-parametric tests were

adopted, since the Kolmogorov-Smirnov test presented p <0.05. The tests considered the level of significance p <0.05 and the 95% confidence interval.

The study was developed in accordance with National Health Council Resolution no. 466 of December 12, 2012. It was waived of evaluation from an ethics committee in research involving human beings because it was based exclusively on secondary public domain data, without nominal identification.

RESULTS

The percentage values referring to the number of individuals with SAH who were stratified at high and very high risk for cardiovascular diseases, in relation to the total number of hypertensive patients registered, by state, are presented in Chart 2. As for the SAH registries stratified as high-risk, the percentage value in relation to the total number of registries in each Brazilian state ranged from 13.74% for the state of Tocantins (TO), in the North region, to 22.12% for the Federal District (DF), in the Mid-West. For the very high risk registries, the percentage values between states varied from 4.91% to 18.77%, the lowest value for Amazonas (AM) and the highest for Acre (AC), both located in the North region of Brazil. [Chart 2.]

The analysis of the median number of stratified hypertensive patients at high risk per region showed a lower value in the North, 25,897.17, and the highest in the Southeast, 243,308,37, with a statistically significant difference (p = 0.002) among the medians of the five Brazilian regions (Table 1). The median of registries at very high risk was also higher in the South-

CHART 2. REGISTRIES OF SAH AND PERCENTAGES OF HIGH AND VERY HIGH RISK STRATIFICATION PER FEDERATIVE UNIT (UF)

Region	UF	State total population	Number of hypertensive registries in the system	High risk (%)	Very high risk (%)	Total high/ very high risk (%)
North	RO	1,562,409	115,180	14.95	17.20	32.15
	AC	733,559	43,224	15.55	18.77	34.32
	AM	3,483,985	282,282	15.84	4.91	20.75
	RR	450,479	20,383	17.29	15.30	32.59
	PA	7,581,051	256,888	17.55	16.25	33.80
	AP	669,526	18,218	20.29	16.28	36.57
	TO	1,383,445	99,163	13.74	14.85	28.59
Northeast	MA	6,574,789	325,570	16.17	12.95	29.12
	PI	3,118,360	217,443	15.33	11.06	26.39
	CE	8,452,381	342,828	16.76	9.24	26.00
	RN	3,168,027	154.808	18.61	12.85	31.46
	PB	3,766,528	323,639	19.41	14.38	33.79
	PE	8,796,448	400,846	18.51	12.53	31.04
	AL	3,120,494	139,660	19.51	11.52	31.03
	SE	2,068,017	104,283	20.46	12.36	21.82
	BA	14,016,906	932,831	18.15	12.01	30.16
Southeast	MG	19,597,330	1.395,732	15.46	14.99	30.45
	ES	3,514,952	297,709	17.86	15.17	33.03
	RJ	15,989,929	646,829	20.36	16.10	36.46
	SP	41,262,199	1,719,462	20.65	13.13	33.78
South	PR	10,444,526	723,455	15.48	17.46	32.94
	SC	6,248,436	412,357	17.01	17.86	34.87
	RS	10,693,929	598,461	18.78	18.16	36.94
Mid-West	MT	3,035,122	240,928	14.65	16.78	31.43
	MS	2,449,024	148,405	15.44	15.80	31.24
	GO	6,003,788	290,373	14.72	18.26	32.98
	DF	2,570,160	50,493	22.12	15.49	37.61

Source: Prepared by the authors.

east region, 181,698,33, and lower in the Midwest, 30,317.53, with a statistically significant difference (p = 0.003) among the Brazilian regions (Table 1).

The correlation between high risk registries and socioeconomic indicators was positive for HDI and its HDI income and HDI education levels, as well as average household income per capita, but not significant (p> 0.05). Regarding health indicators, there was a positive and significant correlation with public health expenditures per capita (p <0.001) and mortality rate due to CAD (p <0.001). The correlation with the number of medical consultations in per capita public health (p = 0.296), and with the number of medical professionals per capita (p = 0.054), was not statistically significant. However, this last relation was within the limit of the significance assumed in this study, and, therefore, this result should be evaluated with caution. Negative and significant correlation was detected with survival at 60 years old (p = 0.012) (Table 2). Regarding the determination factor between the variable "high-risk SAH registry" and the indicators, the following results were observed: with survival at 60 years old, this factor was 22.5%; with expenditures on public health per capita, 85.7%; number of medical professionals per inhabitant, 14.1%; and with the mortality rate due to CAD, it was 90.6%.

The number of hypertensives at very high risk correlated with socioeconomic indicators identified a positive correlation, not significant, with HDI, HDI income, HDI education and average household income per capita. In the analysis with health indicators, there was a positive and significant correlation with public health expenditures per capita (p <0.001), number of professionals per capita (p = 0.028), and mortality rate due to CAD (p <0.001). The number of medical consultations in public health per capita (p = 0.445) obtained a nonsignificant correlation. There was a negative and significant correlation with survival at 60 years old (p = 0.032) (Table 3). And, regarding the factor of determination between the outcome variable "very high risk SAH registry" and the indicators, the following results were identified: survival at 60 years old was 17.2%; with public health expenditures per capita, 90.4%; number of medical professionals per inhabitant, 17.9%; and with the disease mortality rate due to CAD, this factor was 90.4%.

TABLE 1. AVERAGE AND MEDIAN NUMBER OF HYPERTENSIVE PATIENTS REGISTERED IN SISHIPERDIA ACCORDING TO STRATIFICATION OF HIGH AND VERY HIGH RISK AND BRAZILIAN REGION. BRAZIL, 2013

Risk for cardiovascular diseases	Brazilian region	Average	Median	p*
High	North	29,997.57	25,897.17	0.002
	Northeast	98,502.02	93,417.06	
	Southeast	239,398.21	243,308.37	
	South	145,846.65	143,939.10	
	Mid-West	43,382.76	50,275.47	
Very high	North	20,815.53	14,342.09	0.003
	Northeast	61,357.20	56,005.12	
	Southeast	197,992.15	181,698.33	
	South	101,462.00	115,454.48	
	Mid-West	29,427.12	30,317.53	

Source: Prepared by the authors. *Kruskal-Wallis Test.

TABLE 2. MATRIX OF CORRELATION BETWEEN SOCIOECONOMIC AND HEALTH INDICATORS WITH THE NUMBER OF HYPERTENSIVE PEOPLE REGISTERED AT HIGH RISK. SISHIPERDIA, BRAZIL, 2013

	r	r^2	p
HDI	0.158	0.024	0.432
HDI income	0.125	0.015	0.536
HDI education	0.196	0.038	0.328
Survival at 60 years old	−0.475	0.225	0.012*
Expenditures with public health *per capita*	0.926	0.857	<0.001*
Average household income *per capita*	0.131	0.017	0.516
SUS Admission	−0.088	0.007	0.663
Number of consultations in public health per inhabitant	0.209	0.043	0.296
Number of medical professionals per inhabitant	0.375	0.141	0.054
Mortality rate per coronary artery disease - CAD	0.952	0.906	<0.001*

Source: Prepared by the authors. *Significant at the level of 5%.

TABLE 3. MATRIX OF CORRELATION BETWEEN SOCIOECONOMIC AND HEALTH INDICATORS WITH THE NUMBER OF HYPERTENSIVE PEOPLE REGISTERED AT VERY HIGH RISK. SISHIPERDIA, BRAZIL, 2013

	r	r^2	p
HDI	0.209	0.044	0.296
HDI income	0.181	0.033	0.365
HDI education	0.230	0.053	0.248
Survival at 60 years old	−0.415	0.172	0.032*
Expenditures with public health *per capita*	0.951	0.904	<0.001*
Average household income *per capita*	0.186	0.035	0.354
SUS Admission	−0.159	0.025	0.429
Number of consultations in public health per inhabitant	0.153	0.023	0.445
Number of medical professionals per inhabitant	0.423	0.179	0.028*
Mortality rate per coronary artery disease - CAD	0.951	0.904	<0.001*

Source: Prepared by the authors. *Significant at the level of 5%.

Figure 1 shows the correlation between the number of people registered with very high-risk SAH and the number of deaths due to diseases of the circulatory system, for every 100,000 Brazilians (r = 0.904).

DISCUSSION

The median of SAH registries, both for the high risk and the very high risk strata, in the Brazilian regions were high. In the Brazilian and international scenario, SAH is the main risk factor for cerebrovascular disease, ischemic heart disease and for the global burden of diseases in men and women of all ages. It is the leading cause of preventable death in the world, responsible for 13% of deaths. It is estimated that the global prevalence of SAH will be 29% by 2025, taking into account only population increase and age composition. This percentage equals approximately 1.56 billion people affected. In Latin America, SAH affects over a third of the population.[6,20,21] In Brazil, in 2011, according to the study "Surveillance of risk factors and protection for chronic diseases by telephone survey" (Vigitel), 22.7 % of individuals aged 18 years old reported a diagnosis of SAH.[6]

In the current study, it was observed that in most Brazilian states, about one-third of the hypertensive patients registered were stratified as high/very high risk. It was also found that the largest state population contingent did not necessarily correspond to a higher percentage of people allocated to these risk strata among the registered individuals. On the other hand, the highest medians of registries were obtained in the Southeast region, for all strata of risk, high and very high.

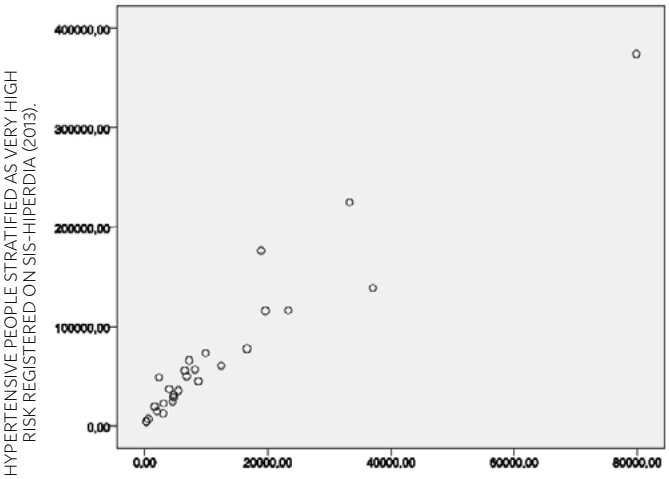
Epidemiological studies corroborate a higher frequency of SAH patients in the Southeast.[6,9] However, because this work is a secondary data analysis, the largest number in the Southeast region may refer to factors such as the effectiveness of the hypertensive registry system and better access to public health services. In this way, undiagnosed fractions of SAH cases may persist, which tend to be reduced by expanding access to healthcare services and organizing care at the basic level. This same hypothesis may explain the higher frequency of SAH in the population of the Southeast and South regions, with an older population and with a greater structure of healthcare services, both in the public sector and in the private sector, for access to the medical diagnosis of SAH.[22]

The results described, with regional differences, may be multifactorial, reflect socioeconomic situations, schooling, income, age distribution and access to healthcare services, resulting in a higher concentration of risk factors in certain regions. Social inequities and living conditions are the main barriers to the progress and improvement of the healthcare situation. And the recognition of these realities can be useful in the definition of healthcare priorities.[23]

Thus, the classic panorama of regional inequalities in Brazil mentioned in other studies is configures.[10,21] A research[21] highlighted a group of eight federation units - seven states in the South/Southeast and the Federal District - with high levels of healthcare development, characterized by the best infrastructure of healthcare resources to provide specialized and more complex care. These units also have a greater coverage of Primary Health Care (PHC) and sanitation indicators are better.[21] This fact indicates the close relationship between health and total expenditure on healthcare per capita and the need to prioritize public policies that overcome these inequities in order to guarantee the principle of healthcare universality in SUS.[10,21]

The results point to some challenges that need to be overcome and which point to the need for continuous investment in PHC, health promotion actions and the search for overcoming healthcare inequities. Government measures for access to medication, such as the implementation of the Popular Pharmacy Pro-

FIGURE 1. CORRELATION BETWEEN NUMBER OF HYPERTENSIVE PEOPLE REGISTERED AT VERY HIGH RISK WITH NUMBER OF DEATHS DUE TO DISEASES OF THE CIRCULATORY SYSTEM.



gram in Brazil, can be beneficial, as long as users do not lose their link with healthcare professionals and are guided and accountable for the care necessary to control the SAH.[21] On the other hand, the increase in the prevalence of a morbid condition, which can be observed in the high prevalence of SAH in the Southeast, can be a positive indicator of access to services, diagnosis and/or reduction of lethality.[24]

It is worth mentioning that in some populations of the Amazon region, the prevalence of SAH is, today, equivalent to that found in medium to large cities. This region is distinguished by the consequences of the entry of its inhabitants into modern life. The use of industrialized foods, withdrawal from extractivism and reduction of physical activity were changes that led to alterations in blood pressure, a fact reported over a decade ago, but which is still important today since it repeats itself. The transition from the rural to the urban lifestyle leads to a higher cardiovascular risk and suggests that the environment played an important role in the relations presented.[25]

In this study, the significant correlation in the high and very high risk strata was present with the health indicator expenditure on public health per capita, with 85.7% of the largest public health expenditures being explained by the greater number of HAS of high risk and 90.4% of expenditures explain the very high risk variation. Thus, the greater variation in public expenditure was better explained by the higher risk variable, that is, where there are more high-risk registries, there are higher public health expenditures per capita.

Thus, the implications of SAH in healthcare services and expenditures are also observed, as verified in the literature.[24,26,27] In another study,[24] the association with this disease and other NCDs was detected with increased hospitalization, in the use of healthcare services, the prevalence of medical consultations, and the risk of having been bedridden and of restricting activities. Moreover, it was found that the inequality of living conditions of the Brazilian adult population, evaluated by years of schooling and by affiliation to private healthcare plans, was associated with different prevalence of chronic conditions, where the higher were, in general, found in socially disadvantaged segments.[24]

In addition, renal dialysis expenditures, one of the consequences of SAH, increased from approximately BRL 600 million in 2000 to BRL 1.7 billion in 2009.[26,27] Faced with this problem, in early 2011, the Ministry of Health expanded the Popular Pharmacy Program, which now offers free basic medicines for diabetes mellitus and SAH, as well as drugs for other chronic diseases, with discounts of up to 90% - funded by government power.[26,27]

It is noted that the impact that health problems have on patients with SAH is very intense, and can lead to death or often impair their quality of life, which makes it a priority to avoid such outcomes.[28] The worsening of disease when diagnosed at advanced stages can cause secondary injuries such as kidney and heart problems; a burden on society with the increase of chronic patients and loss of work force, with leaves and retirements motivated by the incapacity generated by the disease, in addition to the expenses with healthcare services and medication, among others.[29]

It is, therefore, a worrying reality that highlights the need for a better strategic planning of intervention, with the purpose of promoting changes in the lifestyle of at-risk groups.[30] Thus, a concomitant change to the allocation of resources, in relative terms, of hospital treatment and high technology for health promotion and prevention is needed to increase budget support and central coordination for prevention and care of SAH.[27]

Regarding the mortality rate due to CAD, there was a strong positive correlation with the number of registries at high and very high risk, and the variation of high risk registries can be explained in 90.6%, and in the very high, in 90.4%. It should be noted the limitations of this indicator. Since the specific mortality rate is not standardized by age, it is subject to the influence of variations in the age composition of the population, which requires caution in comparisons between geographic areas. However, positive correlation was expected and plausible in the literature.[1,2,5,27,31,32]

Furthermore, in the present study, in the analysis with health indicators, negative correlation was detected with survival at 60 years old for high and very high risk hypertensive patients' registry. This means that sites with more hypertensive registries, at greater risk, have a linear tendency of fewer people reaching the age of 60, the elderly age group in Brazil.

This result is explained in the literature[1,31,32]: demographic aging, urbanization and globalization, as well as the changes in populations' lifestyle, due to these phenomena, have impacted the increase of SAH and other NCDs and, consequently, worldwide mortality. This also implies more patients with SAH in situa-

tions of high/very high cardiovascular risk, with more complications, delicate state of health and, therefore, with greater exposure to the risk of death. There is a concentration of deaths due to SAH, as well as other NCDs, in low and middle-income countries, where there are high numbers of early deaths, especially among people under 60 years of age.[1,31,32]

In view of this reality, high mortality due to CAD and early deaths, it is worth noting that a survey covering the states of Rio de Janeiro, São Paulo, Rio Grande do Sul and its capital cities,[33] which correlated mortality rates by CAD with socioeconomic indicators collected since 1949, revealed that in the past three decades there was a significant reduction in all-cause mortality. This reduction was mainly due to a decrease in mortality due to CAD. The decrease in this mortality was preceded by an improvement in socioeconomic indicators, signalling the importance of improving the living conditions of the population in order to reduce cardiovascular mortality.[33]

The aforementioned study[33] fuels the expectation that the sufficient supply of SUS quality services can significantly reduce social inequalities in the risks of becoming ill and dying. Thus, actions aimed at promoting better living conditions and healthy behaviours are privileged strategies to reduce social inequality in terms of morbidity and mortality.[24] Another study[34] found that individuals with a diagnosis of SAH were more likely to seek healthcare services and were advised to change their behaviours in relation to diet and smoking. It has also been identified a greater chance of survival of those who report less risk behaviour, since positive changes may delay or avoid the appearance of complications commonly associated with SAH mortality.[34]

Being in the hypertensive condition with high/very high risk did not establish a linear association with more medical consultations in the public sector. However, it is known that, in the healthcare system, there is a need for more consultation for the user in that situation, to provide to proper follow-up. On the other hand, in relation to the correlation with the number of doctors per inhabitants, this was positive and significant. Given this result, it is plausible to assume that where there are more physicians there is greater access to the diagnosis and, thus, hypertensive patients classified in the risk strata analysed in this study are identified. In addition, generally, where there are people with more health complications, more healthcare professionals are required. Such demand may have an impact on the increase in expenditures with services, physicians and other healthcare professionals, and on the need for medical professionals to be properly qualified to provide appropriate care to the hypertensive patient.[34,35]

Therefore, it is suggested the development of healthcare actions that promote the access of hypertensive users to healthcare professionals and services, who should offer comprehensive care. This optimizes adherence to treatment and control of blood pressure, with consequent improvement in quality of life and a positive impact on reducing morbidity and mortality.[35] Thus, it is evident the need to carry out policies and practices of harm reduction and promotion of health. To this end, the services of the Family Healthcare Strategy (ESF) should be highlighted, in which the early intake of hypertensive patients should occur, in order to institute appropriate therapeutic measures for each situation, preventing complications and comorbidities.[2,4]

Regarding the limitations of this study, there is a possibility of ecological bias, that is, failure of the ecological associations to reflect the biological effect at the individual level, pertinent to any study of ecological design. Also, the secondary data used are susceptible to errors, for example underreporting of hypertensive registries or technical failure in the stratification of risks for SAH. Therefore, the analyses should consider the limitations of coverage and quality of information of the HiperDia system and other sources consulted in the current research.

CONCLUSION

The correlation between hypertensive patients with high/very high risk for cardiovascular diseases and socioeconomic and health indicators showed that where there are more registries with serious risk, there is more expenditure, per capita, in public health; fewer people reach the age 60 and more people die from diseases of the circulatory system. The increase in the number of physicians was significant for the very high risk strata.

In this sense, the SAH has a direct impact on life expectancy and also on the economic context, since, especially when it develops to high and very high risk of cardiovascular diseases, it generates more expenses in healthcare and requires more professionals, burdening the public health system. In this way, healthcare professionals and managers should mon-

itor SAH cases in order to ensure the effectiveness and consolidation of public policies aimed at prevention and harm reduction, in order to promote health and savings in public health expenditures. Improvements in the quality of the national information system are also necessary to allow the limitations found in the current research to be overcome by new studies, which may provide a more accurate knowledge of the problem investigated.

Institution where the work was carried out: State University of Montes Claros, Montes Claros, MG, Brazil.

Area: Public Health

We declare that there was no conflict of interest in the conception of this work.

Financing: Minas Gerais State Agency for Research and Development (Fapemig) - Process CDS-APQ-00404-13

RESUMO

OBJETIVO: *Correlacionar o número de cadastros de hipertensos com risco alto e muito alto para doenças cardiovasculares com os indicadores socioeconômicos e de saúde.*

MÉTODOS: *Estudo ecológico realizado a partir do Sistema Nacional de Cadastro de Hipertensão e Diabetes (SisHiperDia). A variável "hipertensos com risco alto e muito alto" foi correlacionada ao Índice de Desenvolvimento Humano, gastos com ações e serviços de saúde, renda média domiciliar* ***per capita****, renda municipal* ***per capita****, número de internações hospitalares no SUS, número de consultas médicas no SUS e mortalidade específica por doenças do aparelho circulatório, considerando as 27 unidades federativas do Brasil. Os dados foram processados no* ***software*** *IBM* ***Statistical Package for the Social Sciences*** *(SPSS)* ***Statistics****, versão 22.0Ò. A análise estatística considerou o nível de significância p < 0,05.*

RESULTADOS: *Estados brasileiros com mais cadastros de hipertensos em riscos alto/muito alto gastam mais na saúde pública, menos pessoas alcançam a faixa etária idosa e há mais mortes por doenças do aparelho circulatório (p < 0,05). O estrato de risco muito alto correlacionou com mais médicos por habitantes (p < 0,05).*

CONCLUSÃO: *A hipertensão arterial sistêmica impacta diretamente a expectativa de vida e também o contexto econômico, pois, quando evolui para risco alto e muito alto, para as doenças cardiovasculares, gera mais gastos em saúde e demanda mais profissionais, onerando o sistema público de saúde. É necessário monitoramento, em busca da consolidação das políticas públicas de promoção da saúde dos hipertensos.*

PALAVRAS-CHAVE: *Hipertensão. Saúde pública. Brasil. Indicadores econômicos. Indicadores sociais.*

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ORIGINAL ARTICLE

Risk factors associated with the development of gastric cancer — case-control study

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http://dx.doi.org/10.1590/1806-9282.64.07.611

KEYWORDS: *Stomach neoplasms. Risk factors. Case-control studies.*

INTRODUCTION

It is estimated that about 1 million (952,000) new cases of gastric cancer occurred worldwide in 2012.[1] Except for non-melanoma skin cancer, stomach cancer is currently the fifth most common cancer in the world. The National Cancer Institute (Inca)[2] estimated for Brazil 12,920 new cases of stomach cancer in men and 7,600 in women in the biennium 2016-2017. Adenocarcinoma is the histological type most commonly found in gastric tumours. It accounts for more than 95% of gastric neoplasms, and is practically a synonym of gastric cancer. Other neoplasms found in the stomach include gastrointestinal stromal tumours, leiomyomas, lymphomas, and neuroendocrine tumours.

Risk factors commonly associated with the development of gastric cancer include chronic infection with *Helicobacter pylori (H. pylori)*, low fruit and vegetable intake, high salt intake, smoking, and alcohol consumption[3]. The World Health Organization (WHO) classifies *H. pylori* as a group 1 carcinogen in humans. It is one of the most common infections in the world, with an estimated prevalence of 50%, reaching 90% in developing countries. However, only a small proportion of individuals infected with *H. pylori* develop gastric cancer, indicating the need for interaction of environmental factors, such as smoking and alcohol consumption, in individuals with genetic susceptibility in addition to the variation of the bacterial strain[4]. Since the 1960s, several cohort and case-control studies have been published with the purpose of assessing the association of smoking with the increased risk of developing stomach cancer. The analysis of these publications led the International Agency for Research on Cancer (IARC) to conclude in 2002 that there is sufficient evidence of causality between smoking and gastric cancer[5] (Figure 1).

Although moderate alcohol consumption may bring some health benefits, especially in relation to cardiovascular disease, it is considered one of the ten major risk factors contributing to disease develop-

DATE OF SUBMISSION: 20-Nov-2017
DATE OF ACCEPTANCE: 14-Dec-2017
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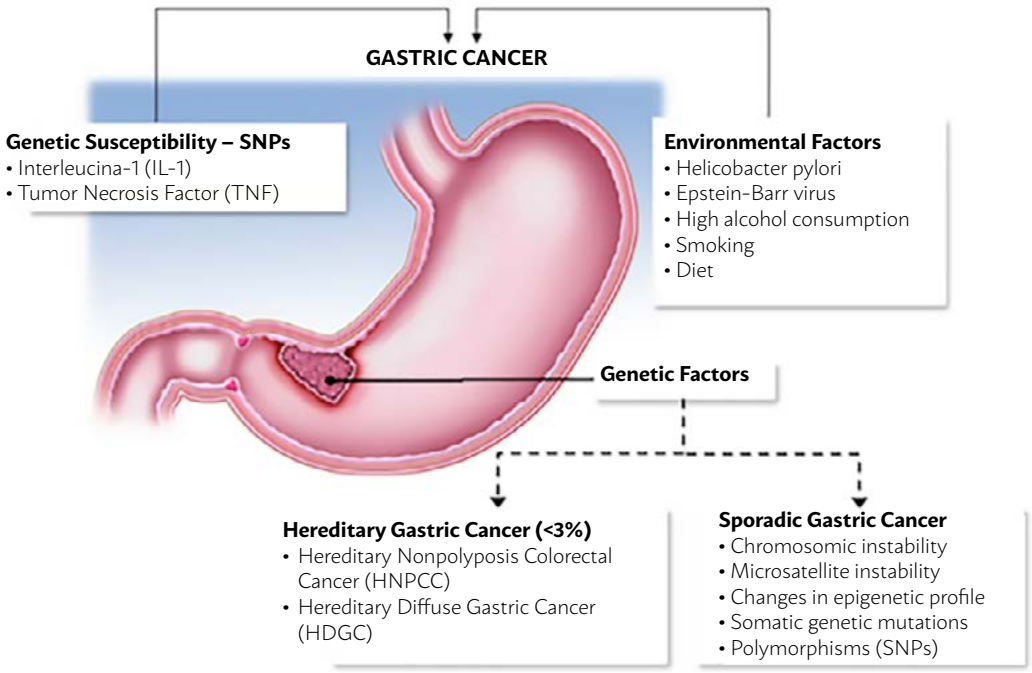
FIGURE 1. RISK FACTORS FOR GASTRIC CANCER



ment globally. Causal association with alcohol consumption was evidenced for some neoplasms, such as the oropharynx, oesophagus, liver, colorectal and breast, confirming alcohol as a group 1 carcinogen. However, the association of alcoholic beverages with gastric cancer was not consistent[6]. The lack of epidemiological evidence may be due to the association of chronic alcohol intake with nutritional deficiencies, unfavourable lifestyle and different patterns of consumption in the populations studied.

Low socioeconomic status is associated with higher incidence and mortality of numerous diseases. Association with the risk of developing gastric cancer may also occur[7]. Although there is no clear justification for the occurrence of this association, a better social condition leads to better working conditions and financial income, favouring the adoption of a healthier lifestyle and broad access to the healthcare system. Populations with low social status also have a higher prevalence of *H. pylori* infection, smoking and diet with nutritional deficiencies, factors commonly related to the development of gastric cancer.

PURPOSES

To assess the risk of gastric cancer associated with smoking, alcohol consumption and level of education. Verify the association of the same factors according to the histological subtype and location of the lesion.

METHODS

This is a hospital-based case-control study that is part of the project "The relationship between the differences in gene expression and the clinical pathological features of human câncer", (Cancer Clinical Genome)[8] conducted between 2001 and 2007. Cases and controls were interviewed in person, using a standardized questionnaire applied by trained healthcare professionals. Patients residing in the metropolitan region of São Paulo (RMSP) for six months or more were included. The cases of gastric adenocarcinoma were diagnosed through anatomopathological examination. They had no previous treatment for the neoplasia and were admitted to the Stomach Surgery Unit of the Hospital das Clínicas - University of São Paulo Medical School

Subjects in the control group were selected from patients admitted to the same hospital with no history or suspected stomach cancer. They were matched to cases by gender and age group, by the expected distribution of cases (frequency matching). The diseases of the patients in the control group should be distributed among several diagnostic categories, so that no illness was represented in excessive num-

bers. Inclusion of cancer patients was restricted, and they should not exceed 15% of the total number of controls. The exclusion criteria adopted was individuals without physical or mental conditions to answer the questionnaire, patients with advanced and terminal stage neoplasms without a therapeutic proposal, gastric neoplasms of histological type other than adenocarcinoma and gastric stump lesions.

The gender variable entered the model dichotomously, and age was divided into six categories (20-39, 40-49, 50-59, 60-69, 70-79 and 80 years or older). The individuals were classified into four categories, according to the level of education: did not attend school and primary education incomplete; completed primary education; secondary education completed and incomplete; university education.

Individuals who smoked at least one cigarette, cigar, or pipe daily for a year were considered smokers. Those who stopped smoking 12 months or more before the interview were classified as former smokers. In order to build a variable that contemplated the total amount of tobacco consumed by each individual and that would allow the comparison among all individuals, it was considered that each cigarette contains one gram (g) of tobacco, 4g for cigars and 3g for pipes. After this transformation, the average daily consumption of tobacco was calculated in grams, which was divided by 20 (amount of tobacco, in grams, of a pack of cigarettes) and multiplied by the number of years of smoking of each individual, therefore finding the pack-year value[9].

The individual who reported drinking at least once a month was considered a current alcohol consumer. Those who stopped drinking alcohol 12 months or more before the interview were classified as former consumers. To calculate the consumption of alcohol, it was considered that beer contains 5% alcohol, wine 12%, cachaça, whiskey, vodka and rum 41%, and liquor 30%. The quantities, in litres of alcohol, found from these percentages were transformed into grams of alcohol, considering that each litre of alcohol contains 798 g. The average daily intake of alcohol was then calculated in grams, which was multiplied by the number of years of consumption of each individual, thus reaching the variable expressed in grams-year of alcohol.

For the analysis of the continuous variable that represents smoking in pack-years and alcohol consumption in grams-year, cases and controls were divided into four categories from cut-off points referring to the quartiles of the variable observed in the control group.

Tumours were classified histologically, according to Laurén's classification for adenocarcinomas, in intestinal and diffuse type[10]. The location of the tumour in the stomach was considered to be distal in cases where the lesion was in the antrum and pylorus, and tumours located in the region of the cardia and fundus were classified as proximal. Diffuse tumours involving the entire stomach and tumours that did not fit into the two major categories were labelled as others.

To estimate the risk of stomach cancer associated with the variables of interest, odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated through non-conditional logistic regression[11] with the Stata® program, version 10 (StataCorp LLC, Texas, United States). Statistical significance was assessed using the likelihood ratio test. The significance level for rejecting the null hypothesis was lower than 0.05. For ordered categorical variables, linear trend tests were performed in the ORs, considering the values of the categories as continuous. Interaction between two variables was analysed by the multiplicative model with the addition of product values. ORs were always adjusted by gender, age, smoking, and alcohol consumption. The study project was approved by the Ethics Committee of HC-FMUSP and the Research Ethics Committee (Protocol no. 222/01), being registered in the Brazil Platform (CAAE: 33009014.0.0000.0065). Only individuals who signed the Informed Consent Term (TCLE – *Termo de Consentimento Livre e Esclarecido*) were included.

RESULTS

The present study included 240 cases of gastric adenocarcinoma confirmed through anatomopathological examination and without previous treatment for neoplasia. Individuals in the control group were selected among patients admitted to HC-FMUSP, totalling 499 individuals. Regarding the diagnosis, the controls were distributed according to several categories of ICD10. It was observed a higher frequency of controls with diseases of the digestive system (21.6%), followed by the category of injuries and external cause poisonings (16.4%). Neoplasms represented less than 10% of controls.

In the case group, 147 individuals were male

(61.2%) and the age ranged from 30 to 93 years, with an average of 63 years old. In the control group, 304 individuals were male (60.9%) and the age ranged from 23 to 96 years, with an average of 58.3 years old. In all age groups, the number of controls was greater than that of cases.

Regarding the level of education, 94 individuals in the case-group did not attend school or did not complete primary education (39.8%) and 187 (37.7%) in the control group. University education was completed by 12 individuals (5.1%) in the case group and 45 in the control group (9.1%). There was no association of education level with an increased risk of stomach cancer (Table 1).

Most cases (63.8%) reported being current or past smokers. On the other hand, in the control group, the majority (54.9%) reported never having smoked (Table 2). An increased risk of gastric cancer was found to be more than double for both current and former smokers. All quartiles of consumption analysed were at high risk.

Regarding alcohol consumption, in the control group, less than 30% reported consuming or having consumed, whereas in the case-group, more than half were consumers or former consumers (Table 2). This difference in consumption between the two groups leads to an increased and statistically significant risk for former consumers (OR = 3.81, 95% CI: 2.45-5.91) and current consumers (OR = 2.06, 95% CI: 1.31-3.26). Among the former consumers, 22 cases (68.1%) and 16 controls (74.1%) had stopped drinking more than five years ago. Similarly to smoking, alcohol consumption was associated with increased risk in all quartiles of consumption analysed.

For analysis of the interaction between smoking and alcohol consumption, both current and former consumers were grouped in the same category (Table 2). The risk of gastric cancer in smokers who were only smokers was OR = 1.66; 95% CI: 1.06-2.60) and only alcohol consumers was OR = 1.70; 95% CI: 0.87-3.32). Simultaneous consumption of tobacco and alcohol was associated with high risk of gastric cancer (OR = 12.74, 95% CI: 7.95-20.42).

Regarding the location of the lesion in the stomach, it was considered distal in 168 cases (70%), proximal in 41 cases (17.1%) and the remaining 31 cases (12.9%) were classified as others. Both locations showed an

TABLE 1. ODDS RATIOS OF STOMACH CANCER ACCORDING TO LEVEL OF EDUCATION

EDUCATION1	CASES		CONTROLS		OR (95% CI)2
	n= 236	%	n= 496	%	
Did not attend or did not complete primary education	94	39.8	187	37.7	Reference group
Primary education completed	72	30.5	134	27	1.05 (0.71 – 1.54)
Secondary education completed or incomplete	58	24.6	130	26	1.06 (0.70 – 1.61)
University	12	5.1	45	9	0.62 (0.31 – 1.25)
					Plinear trend=0.54

1 Data ignored in four cases and three controls. 2 Adjusted by gender, age, smoking habits and alcohol consumption

TABLE 2. ODDS RATIOS OF STOMACH CANCER ACCORDING TO SMOKING HABITS AND ALCOHOL CONSUMPTION – INTERACTION ANALYSIS

SMOKING HABITS	CASES		CONTROLS		OR (95% CI)1
	n= 240	%	n= 499	%	
Never	87	36.2	274	54.9	Reference group
Former smoker	93	38.8	141	28.2	2.25 (1.53 – 3.31)
Smoker	60	25	84	16.8	2,67 (1.72 – 4.13)
Pack-years					
Up to 10	43	17.9	63	12.6	2.53 (1.57 – 4.06)
>10 to 21.5	27	11.2	51	10.2	1.88 (1.08 – 3.25)
>21,5 to 38	35	14.6	55	11	2.33 (1.38 – 3.92)
>38	47	19.6	56	11.2	2.81 (1.71 – 4.60)
					Plinear trend<0.001
ALCOHOL CONSUMPTION					
Never	121	50.4	350	70.1	Reference group
Former consumer	69	28.8	62	12.4	3.81 (2.45 – 5.91)
Consumer	50	20.8	87	17.4	2.06 (1.31 – 3.26)
Grams-year3					
Up to 127.6	40	16.7	37	7.4	3.74 (2.21 – 6.33)
>127.6 to 520.75	20	8.3	36	7.2	1.99 (1.06 – 3.73)
>520.75 to 1,540.5	30	12.5	37	7.4	2.74 (1.56 – 4.82)
>1,540.5	25	10.4	36	7.2	2.41 (1.33 – 4.34)
					Plinear trend<0.001
INTERACTION					
None	70	29.2	231	46.3	Reference group
Tobacco only	51	21.2	119	23.8	1.66 (1.06 – 2.60)
Alcohol only	17	7.1	43	8.6	1.70 (0.87 – 3.32)
Tobacco and alcohol	102	42.5	106	21.2	12.74 (7.95 – 20.42)
					γ=1.51 (1.05 – 1.96)

1 Adjusted by gender, age, smoking habits and alcohol consumption. 2 There is no dose information for one case. 3 There is no dose information for four cases and three controls.

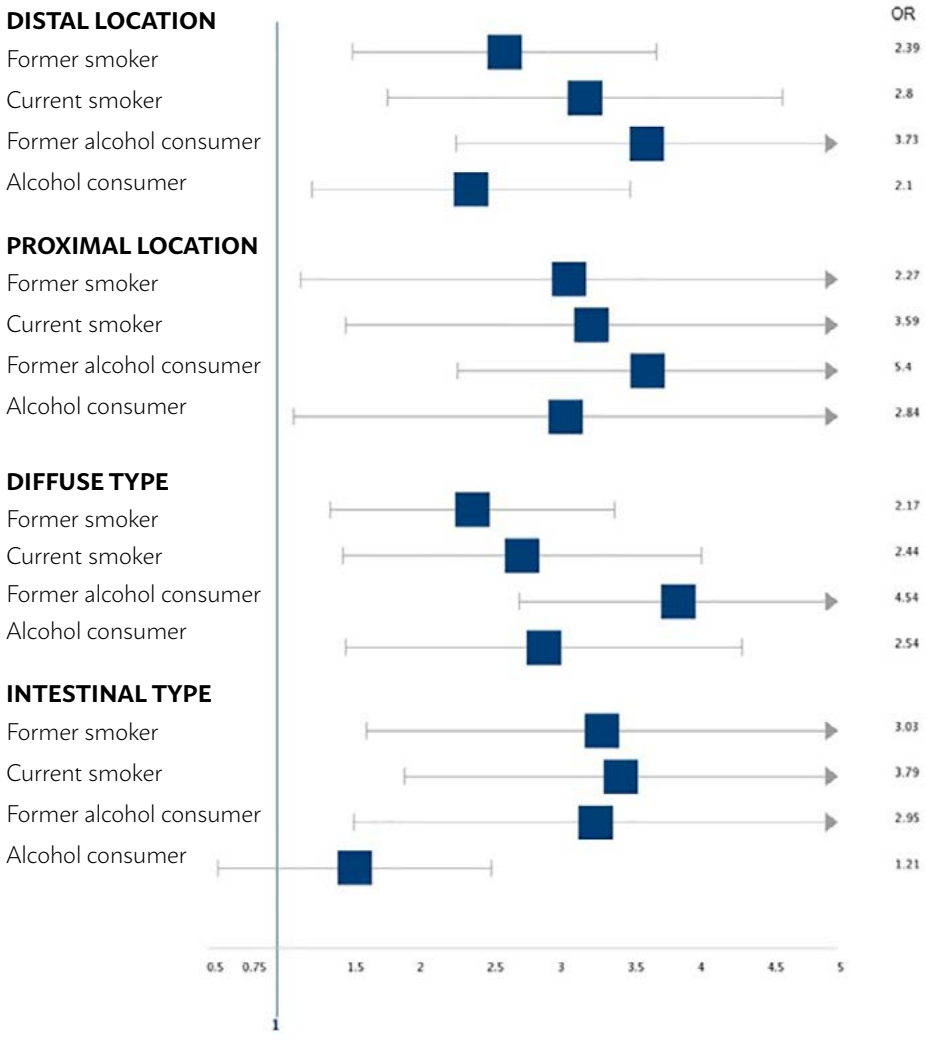
association of smoking and alcohol consumption, both current and previous, with an increased risk of gastric cancer (Figure 2). The association was more evident in proximal tumours in former alcohol consumers (OR = 5.40, 95% CI: 2.29-12.71) and current smokers (OR = 3.59, 95% CI: 1.49-8.67).

The most common histological type of Laurén was diffuse, which occurred in 152 cases (63.3%), while the intestinal type occurred in 83 cases (34.6%). Five cases did not fit into either of the two main histological types. The diffuse type was associated with current and previous smoking (Figure 2). Alcohol consumption was also associated in diffuse tumours, mainly in previous consumers (OR = 4.54, 95% CI: 2.73-7.55). The analysis of intestinal tumours also showed an association with smoking, especially in current smokers (OR = 3.79, 95% CI: 1.91-7.52), but only with former alcohol consumers (OR = 2.94; 95% CI: 1.55-5.57).

DISCUSSION

Several genetic, epigenetic and environmental factors interact in the gastric carcinogenesis. The vast majority appears sporadically, with no evidence of hereditary components. Less than 15% of the cases present clustering in families, but no whitout association with germ mutations, and less than 3% of the cases are part of hereditary cancer syndromes[12]. Tobacco smoke is probably the most important known carcinogen, being associated with the development of tumours in more than 20 different locations. There are more than 5,300 components in tobacco smoke, and more than 60 have already been shown to have a carcinogenic effect on rodents. In addition, for at least a dozen of them there is already sufficient evidence of their ability to carcinogenesis in humans. In the present study, smoking was associated with the risk of gastric cancer for both former smokers and current smok-

FIGURE 2. FOREST PLOT FOR SUBGROUP ANALYSIS ACCORDING TO LOCATION AND HISTOLOGICAL TYPE



ers. In all analyses, current smokers presented a higher risk than former smokers. A recent systematic review[13], which included 32 studies in the analysis, also showed a 60% increase in risk in smokers compared to people who had never smoked.

All quartiles of tobacco consumption analysed were at a higher risk than non-smokers. Individuals classified in the quartile of more intense consumption, greater than 38 pack-years, presented higher OR. However, the intermediate quartiles presented discordant values. The progressive increase in risk with increasing smoking, quantified in pack-years, was not clear. The presence of a dose-effect relationship indicates a biological gradient between exposure and disease, being an important criterion in establishing a cause and effect relationship. Evidence of dose-effect relationship of smoking is contradictory both in relation to intensity and duration of smoking.

Alcohol consumption was also associated with risk of developing gastric cancer. Attention was drawn to the low frequency of individuals who reported being current consumers. In the case-group, 20.8% were current consumers and, among the controls, this value was 17.4%. According to a survey published by the World Health Organization[14], data related to Brazil showed that 20.4% were former consumers and 57.7% were current alcohol consumers. Often individuals may underestimate their consumption while conducting interviews. This can occur simply because of the difficulty in remembering the consumption, remembering that the average age of the case-group was 63 years, or simply due to the belief that the consumption is not relevant. It is very common during a medical consultation the patient says that they do not consume or consume alcohol in small amount and be corrected in detail by a relative. The general knowledge of the population that alcohol is a risk factor for the development of cancer and other diseases is not as widespread as smoking, leading to a lower consumption report[15]. Many patients are also afraid to report current alcohol use during hospital stay, believing that this may disrupt or cancel their treatment. In another hospital case-control study conducted in Brazil[16], it was verified that 31% of the cases and 13% of controls were current alcohol consumers. These values are more similar to those found.

Another interesting result was the fact that former consumers present a higher risk than current consumers. It has been reported that discontinuation of alcohol consumption increases the risk of developing oesophageal cancer in the first two years after cessation of consumption, and then it decreases progressively[17]. With regard to gastric cancer, other studies have also reported an increased risk of development in former consumers compared to current consumers[18]. A possible explanation for the phenomenon of increased risk in the first two years after the suspension is the sick quitter behaviour. In this case, individuals stop drinking alcohol when they have the initial symptoms of the disease. As the diagnosis can still take some time to be done, individuals will report being former consumers at the time of diagnosis. However, in the present study, 68.1% of the cases and 74.1% of the controls classified as former consumers had stopped consumption more than five years ago. Another possible explanation is the inclusion of individuals who were heavy consumers in the former consumer group. Because they showed a significant decrease in consumption, this group ends up reporting being a former consumer even if they still consume alcohol in small quantity.

Several hypotheses have been formulated to explain the possible effects of alcoholic beverages on the genesis of gastric cancer[6]. Alcohol may act as a contributing factor causing chronic irritation of the gastric mucosa or promoting the appearance of intragastric nitrogen compounds by reducing gastric pH. Another possibility is that alcohol is not directly responsible, but other components of alcoholic beverages. Some alcoholic beverages, especially beer, contain nitrosamines, a known carcinogen[18]. Tramacere et al.[19] published in 2012 a meta-analysis encompassing 44 case-control studies and 15 cohort studies. This study found association with gastric cancer only in consumers classified as heavy. In addition, tumours located in cardia and Asian populations presented even lower relative risk.

When two or more independent variables are involved in the outcome of a study, it may be necessary to analyse not only the main effect of each variable, considering that the effect of one variable may depend on the level of exposure to the other. When the combined effect of two variables is greater or less than the simple "sum of the parts", it is possible that an interaction has occurred. The interaction of smoking and alcohol consumption has been reported mainly in cases of head and neck tumors[20].

In the present study, the analysis of the interaction between alcohol consumption and smoking was positive. The biological explanation for this interaction considers that ethanol present in alcoholic beverages may act as a solvent, facilitating the penetration and action of other carcinogens present in the beverage itself or in cigarette smoke.

It is believed that the mechanism of carcinogenesis relating smoking to esophagogastric tumours may involve the direct action of tobacco smoke on the esophagogastric epithelium or due to the ingestion of bronchial mucous secretions containing tobacco particles. Therefore, a greater risk magnitude is assumed in smokers for tumours of the distal and cardiac oesophagus in relation to the gastric distal tumors[21]. However, the overall increase in the incidence of proximal gastric lesions is occurring even with the decrease in the prevalence of smoking. This suggests the need for the interaction of other factors such as gastroesophageal reflux, alcohol consumption, *H. pylori* infection and obesity for the development of proximal gastric tumors[22]. In fact, we found the association of smoking and alcohol consumption stronger in tumours of proximal location, but distal tumours also showed association.

Gastric tumours of the intestinal type are associated with the presence of chronic inflammation of the gastric mucosa, which causes chronic atrophic gastritis and intestinal metaplasia. *H. pylori* is the causal factor most associated with the onset of this inflammation. However, other environmental factors may also contribute[23]. Taking this into account, the intestinal type is expected to be more related to smoking and alcohol consumption. This assumption was not confirmed in our cases, since both types had a positive association. The major prevalence of diffuse tumours, over 63%, and the role of *H. pylori* as a confounding variable may have impaired the analysis of this association.

Low socioeconomic status is associated with a higher incidence and mortality of numerous diseases, including gastric cancer[24]. Level of education is one of the ways to classify the socioeconomic conditions of a population[25]. We did not find association of low level of education with risk of gastric cancer. The study design, with the use of hospital controls that end up presenting more similar socioeconomic characteristics, may have influenced the result found. Another factor to be considered is the high prevalence of *H. pylori* infection in the entire Brazilian population. As in Brazil, and in other developing countries, the infection is not restricted only to those with the most disadvantaged socioeconomic conditions, its role as a causal agent ends up appearing in all socioeconomic strata.

In case-control studies, the selection of participants is a major challenge to minimize the occurrence of any bias. In this study, all individuals in the case-control group were recruited in the same hospital, which is an important reference center. This increases the likelihood of groups being comparable in terms of willingness to participate in the study, willingness to provide information and to answer the questionnaire, as well as their own knowledge of the history of smoking and alcohol consumption. Thus, the occurrence of classification and recall bias may have occurred in a similar way in both groups, leading to a random or non-differential bias. The applied questionnaire was developed in order to facilitate the recall of information and to standardize the quantification of consumption.

In the study of gastric adenocarcinomas, *H. pylori* infection, low fruit and vegetable intake and high salt intake are confounding factors. The prevalence of *H. pylori* infection in the Brazilian population is high, and its research in the control group and characterization of the bacterial strain would imply the performance of other diagnostic tests. The characterization of feeding patterns is difficult and complex and should be evaluated by specific questionnaires[26]. In addition, many patients with gastric tumours alter their eating habits due to the symptoms of the disease. In case-control studies, this fact leads to an important recall bias and incorrect cause associations between diet and tumour development by the participants.

The present study has the merit of having the largest sample in Brazil, with a number of participants comparable to other studies conducted in the world[16,27,28]. The data were collected prospectively as part of a large project related to the study of carcinogenesis that resulted in other studies. Our results are consistent with those found in other studies with consistent values and trends. Discordant values occurred in analyses with subgroups composed of few individuals. Smoking was associated with a higher risk of developing gastric cancer, especially in the proximal location, with current consumption and higher dose. Alcohol consump-

tion also presented higher risk, with the highlight that the risk was higher in former consumers than in current consumers.

The recent classification of gastric adenocarcinomas, based on the molecular profile[29], opened a new possibility for the evaluation of risk factors, such as smoking and alcohol consumption in gastric carcinogenesis. There are already examples of tobacco-related molecular differences that may influence tumour biology, triggering or potentiating carcinogenesis and leading to a change in prognosis[30]. Doubts as to whether this result suggests that smoking-related tumours represent distinct molecular phenotype or whether the changes resulting from smoking in the tumour environment cause such poor prognosis remain open to discussion.

CONCLUSIONS

This study confirmed smoking and alcohol consumption as risk factors for the development of gastric cancer, with no predilection for histological type and location of the lesion. The simultaneous consumption of both potentiates the risk. Level of education has not been shown to be a risk factor.

Based on Marcus F.K.P. Ramos Master's dissertation thesis entitled "Factors associated with the risk of developing gastric adenocarcinoma - case-control study" presented in the Preventive Medicine program at the University of São Paulo Medical School in the year 2017.

It did not have research funding. Presented in the category of oral presentation at the 11th World Congress of Gastric Cancer, São Paulo, 2015.

PALAVRAS-CHAVE: *Neoplasias gástricas. Fatores de risco. Estudos de casos e controles.*

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ORIGINAL ARTICLE

The role of three-dimensional ultrasound in pregnancies submitted to cerclage

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http://dx.doi.org/10.1590/1806-9282.64.07.620

SUMMARY

OBJECTIVE: *Cervical cerclage is the standard treatment for cervical incompetence (CI); however, there is still a high risk of preterm birth for women who undergo this treatment. The aim of this study was to longitudinally evaluate findings on two-dimensional transvaginal ultrasonography (2DTVUS) and three-dimensional transvaginal ultrasonography (3DTVUS) that could be related to gestational age at birth.*

METHODS: *A total of 68 pregnant women who were treated with cerclage were evaluated by 2DTVUS and 3DTVUS in the second and third trimesters of pregnancy. Log-rank tests and Cox regression analyses were used to identify significant findings related to gestational age at delivery.*

RESULTS: *A cervical length lower than 28.1 mm (p= 0.0083), a proximal cervical length lower than 10 mm (p= 0.0151), a cervical volume lower than 18.17 cm^3 (p= 0.0152), a vascularization index (VI) under 2.153 (p= 0.0044), and a vascularization-flow index (VFI) under 0.961 (p= 0.0059) in the second trimester were all related to earlier delivery. In the third trimester, a cervical length lower than 20.4 mm (p= 0.0009), a VI over 0.54 (p= 0.0327) and a VFI over 2.275 (p= 0.0479) were all related to earlier delivery. Cervical funnelling in the second and third trimesters and proximal cervical length in the third trimester were not related to gestational age at birth. The COX regression analyses showed that cervical volume in the second trimester; FI and VFI in the third trimester were significantly associated with gestational age at birth.*

CONCLUSION: *In women treated with history-indicated cerclage or ultrasound-indicated cerclage, 2nd trimester cervical volume and 3rd trimester FI and VFI are independent significant sonographic findings associated with time to delivery.*

KEYWORDS: *Pregnancy. Obstetric labour, premature. Cervix uteri. Cerclage, cervical. Ultrasonography.*

INTRODUCTION

Cervical incompetence (CI) is diagnosed based on an obstetric history of second [1,2] or early third trimester foetal losses [3], following painless cervical dilation, prolapse or membrane rupture, and expulsion of a live foetus despite minimal uterine activity. This condition is implicated in 10% to 25% of second trimester pregnancy losses. [4]

Cervical cerclage is still a standard technique for treating CI, and some reports have estimated that up to 2% of all pregnancies require cerclage procedures [4] Uncontrolled studies have suggested that infant viability is approximately 25% without cerclage but ranges from 75-90% with cerclage.[3]

However, even after this intervention, these women remain at high risk for preterm delivery. Preterm

DATE OF SUBMISSION: 12-Dec-2017
DATE OF ACCEPTANCE: 18-Dec-2017
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birth rates before 36 weeks vary from 20% – 25% in elective cerclages, 27% – 42% in urgent cerclages, and 53% – 77% in emergent cerclages.[2,5]

Historically, women treated with cerclage receive digital or speculum follow-up examinations, although the usefulness of these procedures has yet to be confirmed by controlled studies.[6,7] In contrast, the introduction of two-dimensional transvaginal ultrasonography (2DTVUS) for visualizing the cervix and stitches has improved and facilitated both the diagnosis and follow-up examination of these patients.[8] Many studies about the use of 2DTVUS in women treated with cerclage and the prediction of preterm birth been published.

In addition, three-dimensional transvaginal ultrasonography (3DTVUS) with power Doppler has recently been studied as an option for evaluating the uterine cervix during pregnancy. Previous studies have demonstrated that 3DTVUS can provide more accurate measurements of cervical volume and cervical length than 2DTVUS.[9-11]

There is evidence that angiogenic factors may play a role in cervical ripening and the birth process, and 3DTVUS with power Doppler could provide more information on cervical morphology and vascularization than 2DTVUS.[12] Theoretically, three-dimensional imaging combined with power Doppler enables the quantitative assessment of volume and Doppler signals of the whole target organ. In contrast, 2DTVUS information on vascularization and blood flow is restricted to a single subjectively chosen 2D plane.[13]

The aim of this study was to longitudinally evaluate the findings of 2DTVUS and 3DTVUS with power Doppler that could be related to gestational age at birth in women treated with cerclage.

METHODS

This was a prospective study of women with a singleton pregnancy who underwent elective cerclage (n= 52) between 12 and 16 weeks of gestation or ultrasound-indicated cerclage (n= 16) between 16 and 24 weeks of gestation. The subjects were followed at the Recurrent Miscarriage Clinic of the Department of Obstetrics and Gynaecology of São Paulo University Medical School between June 1, 2012, and October 30, 2015. This study was approved by the University Ethics Committee (CAPPESq 0851/06). All participants in the study provided written informed consent.

The indication for elective cerclage had a history of two or more second trimester pregnancy losses or preterm births with early cervical dilation without uterine contractions. Cerclage was indicated by ultrasound when there was a history of one second trimester pregnancy loss or early preterm delivery and a current cervical length of 25 mm or lower up to 24 weeks of gestation.

All women who were treated with elective or ultrasound-indicated cerclage during this period were invited to participate in this research.

Elective cerclage (n= 52) was placed at 14.06 ± 1.13 weeks, and ultrasound-indicated cerclage (n= 16) was placed at 19.8 ± 2.98 weeks.

Women were included in the study if they met the following criteria: 1) had a singleton gestation of a live foetus; 2) were treated with elective or ultrasound-indicated cervical cerclage; 3) exhibited no uterine anomalies or cervical conisation; 4) received at least 2 serial transvaginal ultrasound examinations for the assessment of cerclage placement and cervical length, one between 20 and 24 weeks (2nd t) and one between 28 and 32 weeks (3rd t); and 5) had available delivery records. Patients who were treated with emergency cerclage due to prolapsed foetal membranes were not included.

All included patients underwent a McDonald cerclage with a second 5 polyester suture 1 cm below the first stich.

The data obtained included the following: maternal age, race, gestational age at cerclage, cervical length, cervical funnelling, proximal cervical length, cervical vascular index (i.e., vascularization index (VI), flow index (FI), vascularization-flow index (VFI)), cervical volume, and gestational age at birth. The presence of cervical funnelling was defined as a protrusion of membranes into the cervical canal ≥ 5 x 5 mm.

All the exams were performed using a 5 - 9 MHz transvaginal transducer with a 146° field of view (GE Healthcare, Zipf, Austria). The following identical pre-installed settings were used for all patients: a frequency of 3-9 MHz, a pulse repetition frequency of 0.6 kHz, a gain of – 5.0, and a low wall motion filter of 1.

Women were examined in the lithotomy position with an empty bladder. The ultrasound probe was slowly introduced into the vagina, and care was taken to avoid undue pressure on the cervix. After a satisfactory grey-scale image of the cervix had been

obtained, the probe was gradually advanced again with only enough pressure to restore a satisfactory image. A sagittal view of the cervix where the internal os, the cervical canal and the external os could all be observed simultaneously was obtained. The cervical length measurements were performed by the first author, who has five years of experience in ultrasounds, as described by Iams et al.[14] In cases of cervical funnelling, the apex of the funnel was considered the beginning of the closed endocervical canal, and the external os was considered the distal end of the endocervical canal. The location of the cerclage was identified as an echo-dense structure in the cervical stroma. The system was switched to the power Doppler mode and then into the 3D mode. The cervix was centralized within the 3D sector appearing on the ultrasound screen, and data were obtained by holding the transducer stationary while its crystals were mechanically rotated across the sector with a sweep angle of 90°. The fast volume acquisition (i.e., low resolution) setting was always used to minimize periodic flashing artefacts arising from uterine artery pulsation and from foetal movements. The scanned volumes were stored digitally for off-line analysis.

Virtual Organ Computer-Aided Analysis (VOCAL™) software, which is integrated into the Voluson E8 ultrasound system, was used to calculate cervical volume (cm^3) and power Doppler flow indexes.

The calculated Doppler indexes were the VI, FI, and VFI. The VI is the ratio between the colour voxels and the total number of voxels in the volume, where a voxel is defined as the smallest unit of each volume; the VI reflects the percentage of the volume consisting of blood vessels. The FI is calculated as the sum of weighted colour voxels divided by the number of colour voxels. The FI reflects the average energy per colour voxel reflected from the blood corpuscles in the vessels of the volume; the more blood corpuscles, the higher the FI values. The VFI is the sum of weighted colour voxels divided by the total number of voxels, and it reflects both the proportion of tissue consisting of vessels and the number of blood corpuscles in the vessels.

The acquired volumes were manipulated to obtain reformatted multi-planar views of the cervix in the mid-sagittal, axial and coronal planes. All cervical measurements were taken on these multi-planar images, and the results were documented on hard copies. The contour mode in the VOCAL™ program was set to manual, and the longitudinal view was used as reference image. The rotation steps were 30°. When drawing the contours, care was taken not to include the lower uterine segment, the vaginal wall, and particularly the large uterine arteries. Once all contours had been drawn, the volume and power Doppler flow indexes of the cervix were computed automatically.

To minimize interobserver variability, a single sonographer performed all the exams.

The threshold for significance was established at $p < 0.05$.

TABLE 1: DEMOGRAPHIC CHARACTERISTICS AND OBSTETRIC DATA.

	n (%)	Average (± SD)	Median (minimum – maximum)
Maternal Age	66 (100%)	29.32 ± 5.7	30 (17 – 43)
Body Mass Index	64 (97%)	28.03 ± 4.2	28.12 (18 – 39)
Race - Caucasian - Non-caucasian	66 (100%) 31 (47%) 35 (53%)	-	-
Obstetric History - Number of gestations - Early miscarriage - 2nd trimester miscarriage - Term delivery - Preterm delivery - Curettage - Cerclage	66 (100%) 66 (100%) 23 (34.8%) 45 (68.1%) 22 (31.8%) 44 (66.67%) 50 (75.7%) 27 (40.9%)	 4.14 ± 2.02 2.28 ± 1.56 1.86 ± 0.94 1.12 ± 0.33 1.76 ± 0.97 2.58 ± 1.45 1.62 ± 1.06	 4 (2 – 12) 1.5 (1 – 5) 2 (1 – 4) 1 (1 – 2) 2 (1 – 5) 3 (1 – 6) 3 (1 – 6)
Gestational Age at Cerclage - Elective cerclage - Ultrasound-indicated cerclage	 50 (75.75%) 16 (24.25%)	 14.06 19.8	 13.8 (12.28 – 17) 19.6 (15.4 – 25,4)
Gestational Age at Delivery - Elective cerclage - Ultrasound-indicated cerclage	 50 (75.75%) 16 (24.25%)	 36.88 ± 3.87 37.50 ± 2.53	 38 (22.71 – 40.28) 38 (32 – 40.42)
Gestational Age at Delivery < 37 weeks Gestational Age at Delivery < 34 weeks	18 (27.27%) 10 (15.15%)		

A Kaplan-Meier Curve was developed for each sonographic characteristic, and the log-rank test was used for continuous variables to form two groups and maximize the differences between them in the survival curves. A Cox regression model was used to identify risk factors related to earlier delivery. The evaluated time periods were analysed separately. The following were considered co-variables for each time periods: funnelling, proximal cervical length, cervical volume, VI, FI, VFI, and cervical length.

RESULTS

68 women referred for cerclage met the study inclusion criteria. Two patients treated with elective cerclage were excluded from the analysis; one was excluded due to spontaneous miscarriage after cerclage at 19 weeks, and the other was excluded due to foetal death at 20 weeks of gestation. The demographic characteristics and obstetric data of the study population are described in table 1.

The average gestational age ± standard deviation at the first and second ultrasound exams was 22.23 weeks ± 1.33 and 29.87 weeks ± 1.46, respectively.

The sonographic findings of 2DTVUS and 3DTVUS with power Doppler are shown in table 2. Cervical funnelling was present in 16 (26%) patients between 20 and 24 weeks and in 16 (27%) patients between 28 and 32 weeks.

Gestational age at delivery was evaluated as a continuous variable. The Kaplan-Meier curves showed an increased frequency of earlier delivery with a cervical length lower than 28.1 mm (p= 0.0083), a proximal cervical length lower than 10 mm (p= 0.0151), a cervical volume lower than 18.17 cm^3 (p= 0.0152), a VI under 2.153 (p= 0.0044), and a VFI under 0.961 (p= 0.0059) in the second trimester (figure 1). In the third trimester, a cervical length lower than 20.4 mm (p= 0.0009), a VI over 0.54 (p= 0.0327) and a VFI over 2.275 (p= 0.0479) were related to earlier delivery (figure 2). Cervical funnelling between 20 and 24 weeks, and cervical funnelling and proximal cervical length between 28 and 32 weeks were not significant predictors.

The COX regression results showed that for the second trimester ultrasound, a cervical volume ≥ 18.17 was an independent variable that was significantly associated with later gestational age at birth. Furthermore, in the third trimester, a FI ≥ 44.336 and a VFI ≥ 2.275 were associated with gestational age at birth (table 3).

TABLE 2: ULTRASONOGRAPHIC FINDINGS FROM 2DTVUS AND 3DTVUS IN THE SECOND AND THIRD

	n	Average	95% CI	SD	Median	Min - Max
2nd t Cervical Length (mm)	61	29.9	27.7 – 32.1	5.1	31.5	9 – 54
3rd t Cervical Length (mm)	59	26.5	24.1 – 29	9.2	28	6 – 45
2nd t Proximal Cervical Length (mm)	56	13	10.7 – 15.2	8.4	14.1	0 – 34
3rd t Proximal Cervical Length (mm)	59	10.4	8.4 – 12.3	7.5	11	0 – 27
2nd t VI (%)	58	4.6	2.9 – 6.3	6.4	3	0 – 3
2nd t FI	58	37.3	35.5 – 39.1	6.9	36.4	26 – 57
2nd t VFI	58	1.6	1 – 2.2	2.3	1	0 – 16
3rd t VI (%)	59	4.3	2.5 – 6	6.7	3.3	0 - 52
3rd t FI	59	37.5	35.4 – 39.6	8	37.5	17 - 57
3rd t VFI	59	1.4	1.1 – 1.7	1.1	1.2	0 - 5
2nd t Cervical Volume (cm3)	59	33.6	29.3 – 38	16.5	29.9	9 - 100
3rd t Cervical Volume (cm3)	59	35.6	31 - 40	17.6	36.2	7 - 90

2nd t: second trimester; 3rd t: third trimester; CI: confidence interval; SD: standard deviation; Min - Max: minimum - maximum.

TABLE 3: COX REGRESSION MODEL FOR ULTRASOUND PARAMETERS IN THE SECOND AND THIRD TRIMESTERS WITH RESPECT TO GESTATIONAL AGE AT BIRTH.

Variable	Estimate	Standard Error	p Value	HR	95% CI for HR	
					Lower	Upper
2nd t Cervical Volume ≥ 18.17 cm^3	-1.029	0.494	0.037	0.357	0.136	0.941
3rd t FI ≥ 44.336	-1.256	0.423	0.003	0.285	0.124	0.653
3rd t VFI ≥ 2.275	1.120	0.421	0.008	0.285	0.124	0.653

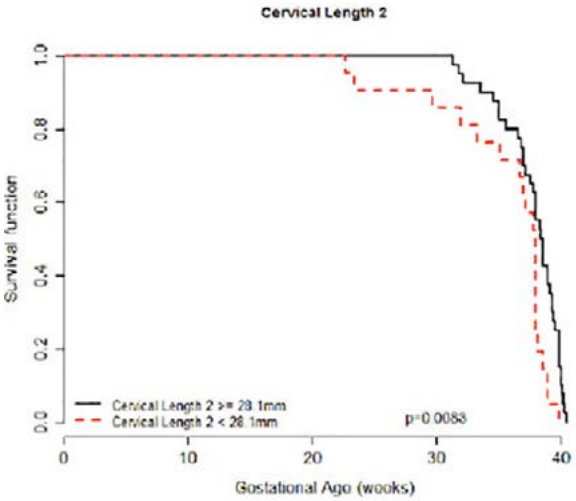

FIGURE 1: Survival curves for gestational age at delivery by cervical characteristics in the second trimester. The p values determined using log-rank tests are p = 0.0083, p = 0.0152, p = 0.0044, p = 0.0059, and p = 0.0151 for a cervical length lower than 28 mm, a cervical volume lower than 18.17 cm3, a VI under 2.153, a VFI under 0.961, and a proximal cervical length lower than 10 mm, respectively.

DISCUSSION

This study aimed at evaluating the usefulness of 2DTVUS and 3DTVUS for investigating gestational age at birth in pregnant women treated with cerclage.

In this group of patients, a second trimester cervical length < 28.1 mm and a third trimester cervical length < 20.4 mm were related to earlier delivery, and these findings are in agreement with current obstetric data. Guzman et al.[15] evaluated 29 women who underwent emergency cerclage at 16 to 26 weeks of gestation and found similar results; these authors found significant differences in postoperative endocervical canal length between patients who delivered at < 36 versus ≥ 36 weeks. Dijkstra et al. [6] studied 32 women treated with elective or ultrasound-indicated cerclage and found a significant relationship between gestational age at delivery and cervical length between 28 and 32 weeks (r= 1.4, p= 0.002). The average cervical length measured between 28 and 32 weeks was significantly different in women who delivered preterm compared with those who delivered at full term (21.0 ± 5.7 compared with 30.3 ± 9.5 mm, respectively; p= 0.002). Song et al.[16] studied a group of 52 pregnant women treated with elective cerclage and found a significant relationship between cervical length after cerclage and gestational age at delivery before 32 weeks. Miller et al.[17] studied 124 women treated with elective cerclage and found a significant relationship between a cervical length of less than 25 mm measured between 18 and 24 weeks and delivery before 34 weeks; however, when these authors considered gestational age as a continuous variable, a cervical length lower than 25 mm was not a significant factor (p= 0.051). In contrast, O'Brien et al.[18], Rust et al.[19] and Hedriana et al.[20] did not find any relationship between cervical length measured after cerclage and gestational age at birth. These findings could be explained by factors of cohort heterogeneity, including a history of second trimester pregnancy loss, a history of diethylstilboestrol exposure in utero, cervical conisation, uterine anomalies and treatment with history-indicated, ultrasound-indicated and emergency cerclage.

A second trimester proximal cervical length < 10 mm was significantly associated with an earlier delivery. Previous studies have already demonstrated this relationship in pregnant women treated with history-indicated[7, 17], ultrasound-indicated[7] and emergency[15] cerclage. However, Hedriana et al.[20] found different results; they measured proximal cervical length at an average gestational age of 26 ± 4.4 weeks (gestational age ± SD) and found that this measurement was not useful for differentiating preterm birth from term birth. The difference between the present study and that study was that we evaluated gestational age as a continuous variable, while Hedriana et al.[20] established the end point as a categorical variable.

A few studies have suggested that compared with 2DTVUS, a 3DTVUS examination would allow a more complete assessment of the cervix.[9, 11] Nevertheless, this is the first study regarding 3DTVUS in women treated with cerclage. Our results showed a significant relationship between a second trimester cervical volume < 18.17 cm^3 and an earlier delivery.

Most studies about cervical volume during pregnancy are related to low-risk patient[7, 12, 21] parity and previous delivery modes[22]. Rovas et al.[12] found no differences in the cervical volume of 677 women during low-risk pregnancy; however, their data showed a significant difference in cervical volume between parous and nulliparous pregnant women. Park et al.[23] found an inverse association between cervical volume measured at 20-24 weeks of gestation and the risk for spontaneous preterm birth before 36 weeks of gestation in pregnant women at a low risk for preterm birth. Similar to our results, they found that the smaller the cervical volume, the higher the likelihood of preterm birth. In a study of 28 pregnant women hospitalized for preterm labour, Rozenberg et al.[24] reported that

cervical volume increases the positive predictive value of preterm birth. This study reported that the optimal cervical volume cut-off point for differentiating full term and preterm birth was 20 mm^3. In contrast, Hoesli et al.[25] did not find a significant difference in cervical volume between pregnant women with low and high risk for preterm birth.

When examining gestational age as a continuous variable, the Kaplan-Meier curves showed that the VI and VFI in the 2nd trimester and the VI and VFI in the 3rd trimester were related to gestational age at birth. We noted that a reduced VI and VFI in the 2nd trimester were related to earlier delivery, in contrast with an increased VI and VFI in the 3rd trimester. Rovas et al.[12] and Yilmaz et al.[21] did not find differences in these cervical indexes when analysing low-risk pregnant women in relation to gestational age at delivery.

There are few studies about cervical vascular indexes and gestational age at delivery. To our knowledge, this is the first study using 3DTVUS with power Doppler to examine women treated with cerclage. De Diego et al.[26] studied 29 women with an asymptomatic short cervix in the 2nd trimester of pregnancy and 71 women with threatened preterm labour; they compared these two groups of women in relation to cervical length, cervical volume, VI, FI and VFI. In the group of women admitted for preterm labour, there was a difference in cervical length (18.3 versus 14.9 mm, p= 0.014) between those with at full term and preterm delivery, respectively, but no differences were found in cervical volume, VI, FI or VFI. The authors also found that cervical volume was lower in women with threatened preterm labour than in asymptomatic women with the same cervical length; in addition, VI and VFI were higher in women with threatened preterm labour, which reinforced the idea that the cervix increases its vascularization and flow to prepare for labour. The different results we found regarding cervical vascular indexes could be due to the cerclage stitch. Cox regression analyses were used to identify which ultrasound variable could be considered a risk factor for preterm birth; the results showed that a cervical volume ≥ 18.17 cm^3 in the 2nd trimester and a FI ≥ 44.336 in the 3rd trimester reduced the risk for preterm birth, whereas a VFI ≥ 2.275 in the 3rd trimester was associated with earlier delivery. While this behaviour was unexpected for FI, it could be explained by the fact that FI is not an indicator of perfusion and cannot provide information on the volume of blood being pumped through a vessel during a particular period. The real meaning of the FI is unclear, and the FI is less predictable than the VI and VFI.[27] Furthermore, Park et al.[23] have already reported an association between small cervical volume (≤ 20 cm^3) and preterm birth

In our study, standardized equipment settings were used to avoid significant effects on our results, and the use of a transvaginal probe to evaluate the cervix theoretically reduces the influence of attenuation on the vascular index.

A methodological difficulty when estimating cervical volume and vascularity using 3D ultrasound is defining landmarks when drawing the contours of the cervix. Rovas et al.[12] and Hoesli et al.[25] have also noted this difficulty. The delineation between the cervix and the lower uterine segment is particularly difficult, especially during early pregnancy and at mid-gestation, when the lower uterine segment is thick and the cervix is often curved. It may also be difficult to clearly distinguish the cervix from the surrounding vaginal tissue.

While we found that according to Kaplan-Meyer curves, the VI and VFI were significantly associated with earlier delivery in women treated with cerclage, the clinical importance of these findings for the vascularization of the cervix has yet to be fully understood.

CONCLUSION

In women treated with history-indicated cerclage or ultrasound-indicated cerclage, 2nd trimester cervical volume and 3rd trimester FI and VFI are independent significant sonographic findings associated with time to delivery.

COMPLIANCE WITH ETHICAL STANDARDS:

The authors declare that they have no conflict of interest.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the author

Informed consent was obtained from all individual participants included in the study. TF Borghi: Data collection, data analysis, manuscript writing;

MHB Carvalho: Protocol/project development; data analysis; Manuscript writing/editing, supervisor AG Amorim Filho: Protocol/project development; data analysis; S Martinelli: Data collection RPV Francisco: Manuscript writing/editing; M Zugaib: Manuscript writing/editing, supervision

RESUMO

OBJETIVOS: *Determinar quais características ultrassonográficas obtidas por meio da ultrassonografia transvaginal bidimensional (USG TV 2D) e tridimensional (USG TV 3D) associam-se ao parto prematuro em gestantes submetidas à cerclagem profilática e terapêutica.*

MÉTODOS: *Sessenta e seis gestantes com feto único submetidas à cerclagem profilática ou terapêutica e acompanhadas no ambulatório de Aborto Habitual da Clínica Obstétrica do Hospital das Clínicas da Faculdade de Medicina da USP, entre 1º de juho de 2012 e 30 de outubro de 2015, foram avaliadas longitudinalmente, por meio das US TV 2D e US TV 3D associadas ao power Doppler para avaliação do VI, FI e VFI , nos três trimestres da gestação. Os resultados foram avaliados em relação ao parto em idade gestacional (IG) menor que 34 semanas e maior ou igual a 34 semanas, assim como em relação à idade do parto como variável contínua.*

RESULTADOS: *O comprimento do colo uterino (CC) e a distância do ponto de cerclagem ao orifício interno do colo uterino (POI) diminuíram de forma significativa entre o segundo e terceiro trimestres da gestação. O CC, o POI e o afunilamento cervical no terceiro trimestre da gestação tiveram relação com a ocorrência de parto em IG<34 semanas. Na análise de regressão de COX, em que a variável de interesse foi o tempo até o parto, o volume do colo uterino no segundo trimestre e o FI e VFI no terceiro trimestre foram significativos.*

CONCLUSÃO: *Foi possível identificar parâmetros ultrassonográficos do colo uterino bi e tridimensionais que se correlacionam com a idade gestacional do parto.*

PALAVRAS-CHAVE: *Gravidez. Trabalho de parto prematuro. Colo do útero. Cerclagem cervical. Ultrassonografia.*

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ORIGINAL ARTICLE

Translation and cultural adaptation of the Breast Cancer Treatment Outcome Scale (BCTOS) into Brazilian Portuguese

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http://dx.doi.org/10.1590/1806-9282.64.07.627

SUMMARY

BACKGROUND: *Breast conservative treatment (BCT) is safe when it is performed in association with radiotherapy. The number of referral for BCT has increased, and it has become an important treatment modality. Patients who undergo BCT present some characteristics that are associated with better quality of life compared with patients who undergo mastectomy without reconstruction. Instruments that measure the quality of life specifically used in cases of BCT are limited. One of these instruments is the* Breast Cancer Treatment Outcome Scale *(BCTOS), which has not yet been translated into Brazilian Portuguese. It contains 22 questions and four domains (functional, aesthetic, breast sensitivity and oedema).*

METHODS: *We performed the translation and cultural adaptation process using Beaton's and EORTC translations process. In summary, the translation process is based on Portuguese translation, translation summary, reverse translation into English, expert committee, pre-test (10 patients), questionnaire review and test of the final version (6 patients).*

RESULTS: *All 16 patients were submitted to quadrantectomy and mammary radiotherapy. Lymphedema was present in 4, altered strength in 5, and altered shoulder mobility in 6 patients. Considering the questionnaire, the reconciled version determined change in 2 items. Pre-test evaluation showed difficulties in 3 patients, but the questionnaire did not change. Test evaluation showed no problems.*

CONCLUSION: *The translation of BCTOS into Portuguese will help us to evaluate the quality of life in BCT patients evaluating treatment-related sequelae and may be useful for oncoplastic surgery evaluation.*

KEYWORDS: *Breast neoplasms. Quality of life. Surveys and questionnaires. Mastectomy, segmental. Conservative treatment.*

INTRODUCTION

For over 20 years, studies that have focused on the breast treatment conservative have shown that the procedures are safe as long as they are associated with radiotherapy[1,2]. The initial indications of BCT were for tumours under 3 cm, but over the years, the allowable tumour size has increased. Currently, the concept of the breast/tumour ratio is accepted, which allows the resection of larger tumours as long as the associated margins are tumour-free. Despite a higher rate of local recurrence in this group of patients, such numbers were found to be acceptable[3]. Radiotherapy is systematically used in BCT since it reduces the risk of local recurrence[2]. We have recently witnessed the development of oncoplastic surgery, but this term has since become very broad. Oncoplastic surgery is also as-

DATE OF SUBMISSION: 15-Dec-2017
DATE OF ACCEPTANCE: 25-Dec-2017
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sociated with multiple techniques and is used both for BCT and for mastectomies with skin preservation or late reconstruction.

Early diagnosis and multiple therapeutic modalities have increased the number of patients who are submitted to conservative treatment and the survival rate of patients with breast cancer[3]. Recently, the quality of life of these patients has been questioned, and multiple quality of life questionnaires have been created[4,5]. Thus, general cancer questionnaires (EORTC QLQ C30; FACT-G) were initially created, followed by general questionnaires for breast cancer (EORTC BR23, FACT-B), with specific questionnaires associated with breast reconstruction (MBROS, BREAST -Q)[6]. Patients who undergo conservative treatment generally present higher scores in the domains related to breast satisfaction and sexual well-being compared with patients who undergo mastectomy[7]. Therefore, when patients who exclusively undergo BCT are required to be evaluated, we now have the BCTOS (*Breast Cancer Treatment Outcome Scale*[8]). The BREAST-Q questionnaire was initially developed for breast reconstruction. To evaluate conservative treatment there was a module related to mastopexy[6,9], and more recently (2016), a module related to BCT was added[10], but it has not been translated into Portuguese. No particular questionnaire is specifically used in oncoplastic surgery. We began to question the cosmetic results of BCT and its association with oncoplasty and quality of life due to the limited studies in this subject area[11] and due to the lack of a specific instrument that can be used in Brazilian Portuguese.

Created in 2001, the BCTOS is based on a review of the literature and expert opinion and is an unconventional instrument that is used in the evaluation of quality of life in patients who undergo BCT[6,8]. Many questionnaires have already been translated and validated into Brazilian Portuguese[9,12,13]; however, the BCTOS questionnaire is an instrument that has not been translated and adapted to this language.

TABLE 1. PATIENTS' CHARACTERISTICS

Variable	Category	Version 5 (n = 10)	Version 6 (n = 6)	Total
Patient's characteristics				
Age	Average (SD)	57.9 ± 9.5	59.9 ± 10.6	58.6 ± 9.6
Follow up time	Average (SD)	42.2 ± 36.7	44.9 ± 43.0	43.2 ± 35.5
Side	Right	7	2	9 (56.2%)
	Left	3	4	7 (43.8%)
Education	Absent/primary	10	4	14 (87.6%)
	High School/Higher Education	0	2	2 (12.4%)
Treatment performed				
Oncoplastic surgery	Absent	8	4	12 (75.0%)
	Present	2	2	4 (25.0%)
Axillary surgery	Lymphadenectomy	4	3	7 (43.8%)
	Sentinel lymph node	6	3	9 (56.2%)
Breast RXT	Present	10	6	16 (100%)
Fossa RXT	Absent	6	4	10 (62.5%)
	Present	4	2	6 (37.5%)
Patients' Sequelae				
Lymphedema	Absent	9	3	12 (75.0%)
	Present	1	3	4 (25.0%)
Change in Shoulder Mobility	Absent	7	3	10 (62.5%)
	Present	3	3	6 (37.5%)
Change in Hand Strength	Absent	8	3	11 (68.8%)
	Present	2	3	5 (31.2%)

SD = standard deviation; RXT = radiotherapy

MATERIALS AND METHODS

This study was methodological in nature and was initially part (translation and cultural adaptation) of a larger psychometric validation study. This research was approved by the Research Ethics Committee of the Cancer Hospital of Barretos under number 782/2014 and was conducted using patients who underwent BCT. As inclusion criteria, we selected female patients with ECOG (Eastern Cooperative Oncology Group) scores of 0 and 1 who had unilateral breast cancer and who underwent surgical treatment of breast and axilla. Radiotherapy treatment was performed for more than 12 months prior to study inclusion. All patients underwent treatment exclusively in this hospital and had the mental capacity to answer the questionnaire. The patients' characteristics are reported in Table 1.

Patients were evaluated on lymphedema, hand muscle strength and shoulder range of motion (Table 1; Figure 1). The range of motion was evaluated statically through photogrammetry with Image J® software. To measure the shoulders motion range, participants were positioned in front of Sanny Posture grids for postural evaluation, in the orthostatic position, 3 meters away from the camera used to capture the images. The camera was a SONY, model DSC-H300 and resolution of 20.1 mega pixels, fixed to a tripod level[14]. Patients were positioned, and after postural compensations, patients have done the maximum movement of flexion, abduction and extension. They were photographed bilaterally to evaluate both treated and untreated sides. Minimum change values of 10º observed were considered as sequela. The evaluation of hand muscle strength was performed with hand hydraulic dynamometer model Saehan SH5001. To perform the test, patients remained seated with their spine erect, maintaining the angle of knee flexion at 90°, shoulder positioned at adduction and neutral rotation, elbow flexed at 90°, forearm at half pronation and neutral grip, up to 30 degrees of extension, following the guidelines of the American Society of Hand Therapists[15]. Three measurements were performed, maintaining the palmar hold for 5 seconds, 60 seconds between each measurement, alternately in each hand. Patients did the palmar grip contraction using a verbal command, which was issued to indicate the beginning and end of contractions and to encourage the contraction as strong as possible[16]. The greatest measure (Kgf) of the three measurements of each member was noted[17]. It was considered a change in force a minimum difference of 12% between the affected side and the unaffected side[18]. For evaluation of lymphedema, volumetry of the upper limbs was performed through the displace-

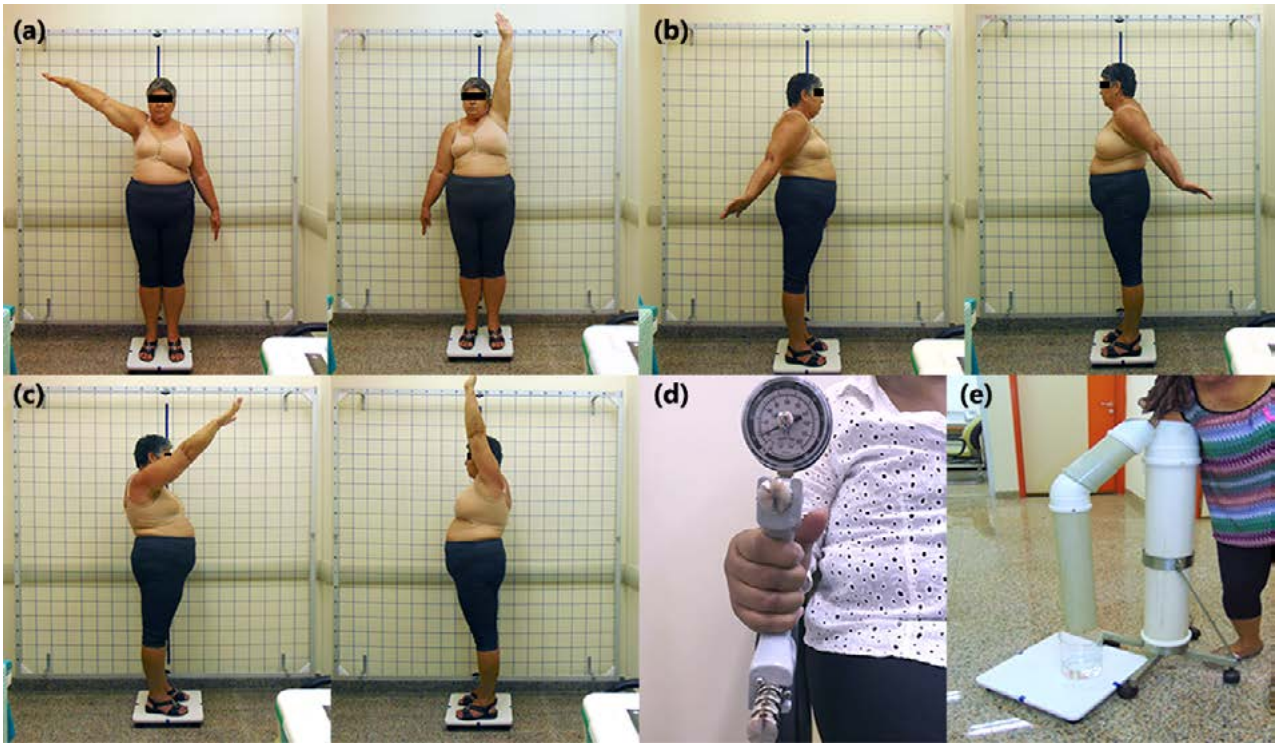

FIGURE 1. Patient's sequelae evaluation. (a) Abduction; (b) extension; (c) flexion; (d) strength of hand; (e) volumetric evaluation

ment of water proposed by Lette[19]. Before performing the volumetry, patients were marked every 5 cm from the cubital fossa on both arms to ensure that both limbs were submerged on the same level. Patients were instructed to position themselves next to the equipment and place the arm at low speed until the highest possible marking and the same procedure is performed on the other limb. The water displacement in each arm was recorded by a Becker vessel in millimetres. It was diagnosed when the difference in volume of the affected arm to the contralateral arm was higher than or equal to 200 milliliters[20].

Author (Annette L. Stanton) provided the BCTOS quality of life instrument used in this study to the research group, whose aim was to translate the instrument into the Portuguese for use in Brazil. The questionnaire consists of 22 questions and uses a 4-point Likert scale, which seeks to compare the outcome of cancer treatment in treated breast versus untreated breast. According to this scale, "1" indicates no difference, while "4" indicates a large difference between treated and untreated breast. Subsequently, calculations are performed for four domains (functional, aesthetic, specific breast pain and oedema), and the final score is the mean of all values.

For translation of the BCTOS, the methodology of translation and cultural adaptation proposed by Beaton et al.[21], which is divided into 5 phases, was used and is summarized in Figure 2. The process follows the steps described below:

- Phase 1: Translation from English into Brazilian Portuguese by two bilingual (Portuguese-English) Brazilian translators with fluency in English. The first translator is an English teacher [version 1 (v1)], while the second translator is a physician with international experience (v2);
- Phase 2: Summary of the translation by a committee of experts represented by the primary researchers (RACV, CEP): v12.
- Phase 3: Reverse translation from Portuguese into English, as performed independently by two Brazilian services for scientific translation (Editage and Scientific), with versions: v3 and v4; and

- Summary of the English version: v34.

- Phase 4: The Expert Committee (RACV, CEP) sought to compare the initial English language version with the final version, and sought to make adjustments in the Portuguese language version, which resulted in an intermediate version (v5). The researchers then independently evaluated the semantic/idiomatic, conceptual and cultural equivalences using a standardized form and an equivalence scale based on

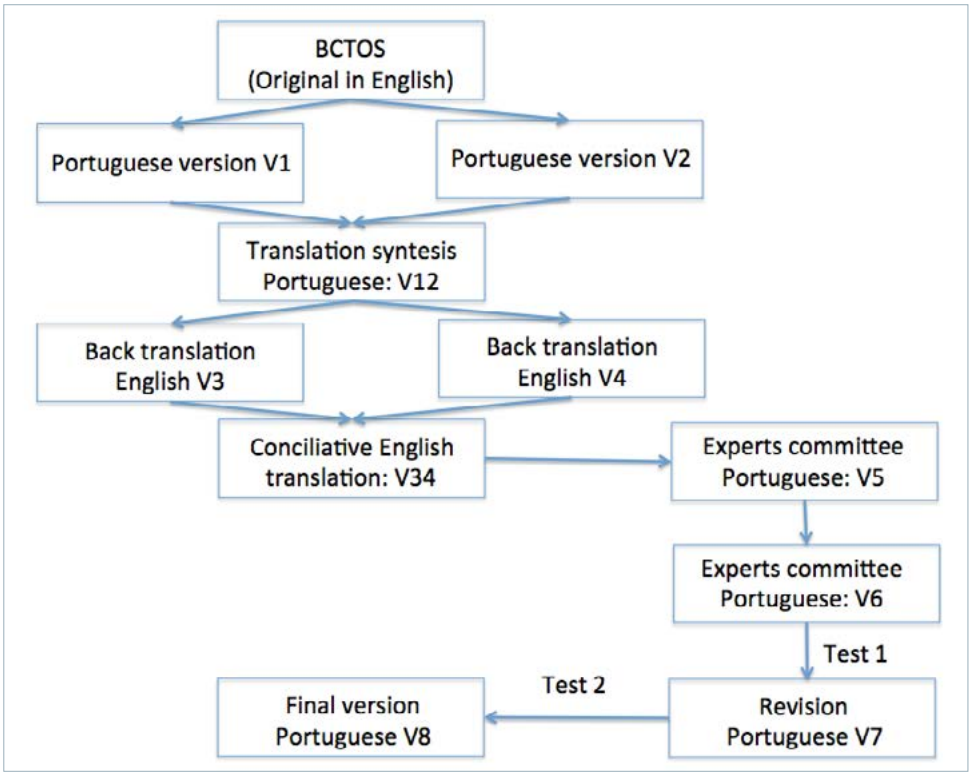

FIGURE 2. Translation process of the quality of life questionnaire according to Beaton *et al*[21].

non-equivalence (-1), impossible to evaluate (0) and equivalence (+1), by which the version was scored and suggestions were made. The intermediate version was revised, and the initial Brazilian Portuguese language version (v6) was obtained.

- Phase 5: The pre-test consisted of application of the questionnaire to 10 patients and aimed at evaluating the patients' understanding of the questionnaire using an independent evaluator (MESS), who was previously trained in the application of quality of life questionnaires. The patient's understanding, possible change suggestions and presence of an item that caused embarrassment were investigated. The interviewer evaluated understanding according to a scale, namely: I. Confused; I.II doubt; I.III. difficulty, I.IV other; II. Embarrassed; III. Need to correct or change; and IV. No understanding.

- The committee of experts reviewed the questionnaire, evaluated doubts and suggested terms to be adjusted. This resulted in version 7, which was applied by the same evaluator (MESS) to 6 patients.

- The version was revised, and the need for terms modification was evaluated, which resulted in the final version of the questionnaire (v8).

RESULTS

In the reconciled version (v5), non-equivalence was observed in relation to items 2, 10 and 13, and changes were made in items 10 and 13; this resulted in version 6, which was initially applied to 10 patients.

Table 1 presents the characteristics of the groups in the pre-test (v6) and test (v7). All patients underwent quadrantectomy and mammary radiotherapy. The average age was 58.6 years (ranging from 44.0 to 79.4 years old), and up to 87.6% of patients did not complete elementary school. In all, 56.2% of the tumours were on the right side, and fossa radiotherapy was performed in 37.5% of the patients. With respect to sequelae, 25.0% (n = 4) presented lymphedema, 37.5% (n = 6) presented with altered shoulder mobility, and 31.3% (n = 5) presented with altered strength.

In version v6 applied to the first 10 patients, difficulties were observed in 3 patients, where each patient indicated 1 or 2 nonconformities, with questioning of score (difficulty to understand the term "moderado") in item 19 (difficulty in understanding the term "rigidez"; the term "braço endurecido" was suggested), item 21 (difficulty in understanding the term "sensibilidade da mama"; the term "mama sensível" was suggested) and item 22 (difficulty in understanding the term "ajuste"). Despite the considerations indicated by the patients, this questionnaire was not altered (v7) and was once again applied to 6 patients, where no questioning was observed; this was considered the final version (v8), but versions v6, v7 and v8 remained similar. Tables 2 and 3 show the original version and the final version in Brazilian Portuguese.

DISCUSSION

The BCTOS was first published in 2001[8] and aimed at evaluating the quality of life after BCT and radiotherapy based on aesthetic measurements (breast shape) and functional status (pain and mo-

TABLE 2. TEXT FROM THE ORIGINAL ENGLISH VERSION AND FINAL PORTUGUESE (BRAZIL) VERSION.

Original/ English	Portuguese Translation
We are interested in your evaluation of your physical appearance and functioning since your breast surgery. Please rate the following items on this four-point scale, according to your evaluation at this point in time. (Note: If you have had bilateral surgery, complete the items with regard to the difference between the right and left side.)	Estamos interessados na sua avaliação em relação à aparência e funcionamento de seu corpo, desde a sua cirurgia da mama. Por favor, avalie os itens abaixo e, entre as quatro opções de resposta, escolha uma delas. Considere, para responder, como você está neste momento. (Nota: Se você operou as duas mamas, escolha a resposta considerando a diferença entre o lado direito e o lado esquerdo).
1 = no difference between treated and untreated breast and area	1 = nenhuma = nenhuma diferença entre a mama (ou a área da mama) tratada e a mama não tratada
2 = slight difference between treated and untreated breast and area	2 = leve = leve diferença entre a mama (ou a área da mama) tratada e a mama não tratada
3 = moderate difference between treated and untreated breast and area	3 = moderada = moderada diferença entre a mama (ou a área da mama) tratada e a mama não tratada
4 = large difference between treated and untreated breast and area	4 = grande = grande diferença entre a mama (ou a área da mama) tratada e a mama não tratada

bility) after treatment. Initially, the questionnaire was associated with three domains (cosmetic, functional and breast pain)[8]. The methodology used for its creation was the literature review, expert opinion, and development of conceptual model, which differs from the current model, where the patient interview was associated with the generation of the items[6]. This questionnaire was initially presented to 301 patients in the form of personal or telephone interview, with a participation rate of 66%; in total, 185 patients were eligible for the study[8]. The primary questionnaire was applied to individuals with a high level of education (average of 14.4 years, standard deviation 2.75 years), which is contrary to our study, where due to the characteristics of the service, women with a low level of education represented the majority of patients. Despite the apparent disadvantage of population with a low level of education, questionnaires that are validated in this type of population have a higher reproducibility rate for the entire population. Little difference was observed in age (58.6 x 61.6 years of age), but a significant difference was observed in relation to time after treatment (43.0 x 73.6 months).

Based on the population in the original article, 54 patients underwent lymphedema evaluation (> 2 cm difference) and clinical examination of the breast; oedema was observed in 18%, and 30% of reasonable and negative aesthetic outcomes, respectively. The aesthetic evaluation was based on the sum of the differences in size, symmetry, fibrosis and telangiectasia. Convergent validity showed objective and subjective associations with cosmesis and functional status as well as patients with lymphedema. In our population, 25% (n = 4) presented with lymphedema, and 37.5% (n = 6) presented with altered shoulder mobility, which were sequelae included in the questionnaire.

In the initial version, questions about "arm swelling" and "breast swelling" were not maintained in later versions since these questions had a low impact factor in the composition of the domains. Due to their clinical importance in relation to oedema, two items were added: "arm heaviness" and "fit of shirt sleeve"; the oedema domain was then included in further studies[22,23].

The 22-item version was translated into German and published in 2010, but the oedema domain was not evaluated. In addition to the BCTOS, the QLQ BR23 questionnaire was prospectively applied in the immediate postoperative period. A comparison was

TABLE 3. QUESTIONS FROM THE ORIGINAL ENGLISH VERSION AND FINAL PORTUGUESE (BRAZIL) VERSION.

Question	Original/ English	Portuguese Translation
1	Breast size	Tamanho da mama
2	Breast texture (hardening)	Textura da mama (endurecimento)
3	Arm heaviness	Peso do braço
4	Nipple appearance	Aparência do mamilo
5	Shoulder movement	Movimento do ombro
6	Arm movement	Movimento do braço
7	Breast pain	Dor na mama
8	Ability to lift objects	Capacidade de levantar objetos
9	Fit of shirt sleeve	Ajuste da manga da camisa
10	Breast tenderness	Mama dolorosa ao toque
11	Shoulder stiffness	Rigidez do ombro
12	Breast shape	Formato da mama
13	Breast elevation (how high the breast is)	Elevação da mama (o quão alta a mama está)
14	Scar tissue	Cicatriz
15	Shoulder pain	Dor no ombro
16	Arm pain	Dor no braço
17	Arm swelling	Inchaço do braço
18	Breast swelling	Inchaço da mama
19	Arm stiffness	Rigidez do braço
20	Fit of bra	Ajuste do sutiã
21	Breast sensitivity	Sensibilidade da mama
22	Fit of clothing	Ajuste das roupas

Functional domain: Items 5,6,8,11,15,16,19. Cosmetic domain: Items 1,2,4,12,13,14,20,22. Specific breast pain: Items 7,10,21. Oedema: Items 3,9,17,18

then made between the QLQ BR23 domains and the three BCTOS domains, and a correlation between all the scales was observed. An analysis of covariates identified that young patients exhibited a worse quality of life in all BCTOS scales[24]. In this study, a factorial analysis[24] was performed, and the same findings of the original study were observed. A later study with 138 patients evaluated the impact of quality of life on the immediate postoperative period and again one year after surgery using the same questionnaires. A similar correlation was observed between the questionnaires for the period analysed, where aesthetic and functional status were correlated with global health, and older age and poor functional status were predictors of decline in overall quality of life one year after surgery[25].

To compare the BCTOS questionnaire with objective measurements, a software for breast aesthetics evaluation was associated with the BCCT.core (breast cancer conservative treatment cosmetic results), which was used to assess 128 patients during the period prior to surgery, around the time of surgery and after a year of follow-up. It was observed that the Kappa agreement between the BCCT.core and the BCTOS was 0.34, which indicates that patients judged their aesthetic result better than the software[26].

The cross-cultural adaptation process allows the adaptation of the questionnaire to a new country and/or language, and allows the equivalence between the initial questionnaire and the version adapted to the new language. The translation should not only be linguistic, but there must also be equivalence of meaning between both questionnaires. We used the model proposed by Beaton et al.[21], with little differences in relation to the translation model used by the European Organization for Research and Treatment of Cancer (EORTC)[27], which has many of its questionnaires presented in English and several other languages. Heil et al.[24] used the model proposed by the EORTC, but in their article, the translated version in German is not presented. Access to the translated questionnaire facilitates the realization of new studies in different languages, which reflects a policy adopted by the EORTC. In this context, although BCTOS was originally written in English and translated into German, we present the Brazilian Portuguese version, which will facilitate future studies using this questionnaire.

We present the first questionnaire to be applied in Brazilian studies in patients who undergo BCT; this will serve as a foundation for studies that will evaluate the oedema domain, which was not evaluated in previous studies, the comparison with objective measures of evaluation as well as the impact of oncoplastic surgery and/or symmetrisation on the quality of life of patients who undergo BCT.

Conflict of interest: The authors declare no conflict of interest

Acknowledgments: We thank Annette L Stanton, who have kindly sent us the questionnaire for translation, Wilson Marçal Vieira Neto and Walker de Albuquerque Félix who have helped us in the translation and linguistic evaluation.

P.S.: This study was performed based on the author authorization. Nowaday for clinical use or to perform studies with BCTOS questionnaire, please contact Map Research Trust for the authorization.

RESUMO

INTRODUÇÃO: *O tratamento conservador da mama (TCM), desde que associado à radioterapia, é seguro. As indicações inicialmente utilizadas para o TCM se elevaram, sendo importante modalidade de tratamento. Novas modalidades, como a oncoplastia associada ao TCM, tornam-se cada vez mais presentes no cotidiano. Pacientes submetidas ao TCM apresentam alguns parâmetros associados a uma melhor qualidade de vida em relação às pacientes mastectomizadas sem reconstrução. Há limitados instrumentos de qualidade de vida a serem utilizados especificamente no TCM, sendo um deles o* ***Breast Cancer Treatment Outcome Scale*** *(BCTOS), questionário este não traduzido e adaptado para a língua portuguesa/Brasil. O BCTOS contém 22 perguntas e quatro domínios (funcional, estético, sensibilidade mamária e oedema).*

MÉTODOS: *Realizamos a tradução e adaptação cultural utilizando a metodologia proposta por Beaton e pelo EORTC. Em resumo, consiste de tradução para o português, resumo da tradução, tradução reversa para o inglês, comitê de especialistas, pré-teste (dez pacientes), revisão do questionário e teste da versão final (seis pacientes).*

RESULTADOS: *As 16 pacientes foram submetidas a quadrantectomia e radioterapia. Linfedema esteve presente em quatro, alteração da força em cinco e alteração da mobilidade em seis pacientes. Avaliando o questionário, a versão de conciliação modificou dois itens. O pré-teste mostrou dificuldades em três pacientes, mas o questionário não se alterou, fato que não se observou no teste final.*

CONCLUSÃO: *A tradução do BCTOS para o português nos ajudará a avaliar a qualidade de vida em pacientes submetidas a tratamento conservador da mama, avaliando as sequelas relacionadas ao tratamento, podendo ser útil na avaliação da cirurgia oncoplástica.*

PALAVRAS-CHAVE: *Neoplasias da mama. Qualidade de vida. Inquéritos e questionários. Mastectomia segmentar. Tratamento conservador.*

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REVIEW ARTICLE

Relationship between microcephaly and Zika virus during pregnancy: a review

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http://dx.doi.org/10.1590/1806-9282.64.07.635

SUMMARY

AIM: *the present study analysed the association between Zika-virus and microcephaly during the gestational period of women in Brazil. Methodology: Systematic reviews of intervention research, current publications of clinical investigations were used systematic search strategies in three electronic databases PubMed, SciELO and Google academic. The following keywords were used: Microcephaly, gestation, Zika-virus to perform the search, and 1020 articles were obtained after exclusion, 45 were left and 35 were eligible. The collection period was from 2004 to 2017. Results: Epidemiological data suggest a temporal association between the quantitative increase and the Zika-virus epidemic, especially in Northeast Brazil. It is not consensual to measure the cephalic perimeter curve to be considered. Conclusion: Given this, the application of techniques to accurately diagnose the relationship between causes and effects in the pathogenesis of Zika virus infection in the central nervous system should be prioritized.*

KEYWORDS: *Epidemics. Zika vírus. Microcephaly. Pregnancy.*

INTRODUCTION

It is of expressive importance to know about the transmission process and ways to combat Zika fever, as well as how to explore the possibility of it being related to neurological diseases[1]. In summary, the Zika (ZIKV) spread in Brazil was caused by the migration of the vírus from the French Polynesia during the Confederations Cup in 2013 with the Tahitian delegation; this fact is confirmed by the genetic similarity of the viruses found in the mentioned countries and by the promotion of inappropriate sanitary conditions, the occurrence of several events with significant migratory activities, such as the 2014 World Cup, the rapid urbanization process and deforestation[2].

Due to the progressive increase in incidence, the World Health Organization (WHO) launched an alert to declare an international emergency because of the increase in microcephaly in endemic zones with ZIKV virus proliferation[3]. The possible relationship between intrauterine infection by ZIKV and early microcephaly was first reported by physicians in the Brazilian Northeast. The sudden increase in these incidences was observed in the birth of children with

DATE OF SUBMISSION: 16-Nov-2017
DATE OF ACCEPTANCE: 14-Dec-2017
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microcephaly, and the arrival of this virus was then identified in the country. However, further evidence on the relationship between cause and effect is still necessary,[4,5] but the fact is that when ZIKV enters the central nervous system (CNS), it breaks the protection of the blood-brain barrier, and this has already been demonstrated in animal studies[1,6].

Other means of virus transmission have recently been discovered, in addition to the bite of the infected insect, through sexual contact or secretions (saliva, urine), which, together with the lack of vaccines or specific treatment, cause an important alarm in the population. Together, the absence of biological markers of exponential duration that make it possible to confirm the diagnosis, it increases the number of suspected cases and, consequently, false positive records[1,7].

Microcephaly was established as a neonatal cephalic perimeter equal to or greater than 2 SD below the average in relation to gestational age and the gender of the child at birth. It is difficult to confirm the infection retroactively, considering that immunological and serological tests have the possibility of indicating a cross-reaction with other flaviviruses, especially the dengue virus[8]; there is also a remote possibility that microcephaly is not a consequence of Zika fever, as the pathophysiological gears by which the Zika virus has destabilized the central nervous system have not yet been completely unveiled, although there is an increasing epidemiological evidence that they are related, but one cannot be sure that it exists[9].

SOURCE OF DATA

This article, with a descriptive qualitative character, based the research on data available in digital collections, mainly through scientific articles published in an online environment.

The parameters for the eligibility and constitution of the synthesis were based on systematic reviews of intervention research, current publications of clinical investigations. Narrative reviews, overviews, essays, and meta-analyses were not included.

Systematic search strategies were used in three electronic databases: PubMed, SciELO and Google academic. The collection period was from December 2016 to January 2017, using the keywords microcephaly, gestation and Zika virus as descriptors, and articles were included in the English and Portuguese languages. As a result, 1,020 articles were obtained, and the repeated articles were subsequently excluded. The selection of articles was started by reading the abstracts to choose the ones of interest. Subsequently, the articles were read entirely by two reviewers for the analysis.

SYNTHESIS OF DATA

EPIDEMIOLOGY OF THE ZIKA VIRUS

The Zika virus (ZIKV) is a flavivirus mainly transmitted by the *Aedes aegypti* mosquito. Since May 2015, an outbreak of ZIKV infection has been identified in Brazil, associated with the growth of congenital microcephaly in new-borns (NB) in affected regions[10].

The ZIKV RNA virus was found in the brain of a foetus with congenital microcephaly (11); in addition, it was also found in the amniotic fluid of two women with foetuses who had congenital microcephaly identified on prenatal ultrasound (3). These occurrences have raised concerns about the possibility that congenital microcephaly may be associated with the recent outbreak of ZIKV infection in Brazil, but only image data restricted to cerebral anomalies are available that may be linked to intrauterine infection by ZIKV[12].

In West Africa and Asia (Southeast Asia), although the virus has been found in monkeys (*Cercopithecus aethiops and Erythrocebus patas*), serological investigations point to a possible circulation in several species of vertebrate animals, along with large mammals such as orangutans, elephants, zebras, buffaloes and rodents[3].

Incidents and the geographical spread of outbreaks without identifying the incidence in non-human primates strengthens the premise that humans show essential importance as hosts that amplify the ZIKV transmission cycle. However, there are still several gaps in the stages of ZIKV transmission to be understood, both in urban and wild environments, and although there are signs of infection, with detection of ZIKV-specific antibodies, and it has been verified in rodents, there is no evidence that there are other non-primate reservoirs[13].

DIAGNOSTIC METHODS OF THE ZIKA VIRUS

The test for ZIKV is within the measures determined by the Ministry of Health in the protocol that establishes the preliminary procedures to be adopted for the surveillance of cases of microcephaly in Brazil[10]. In most cases, at the laboratory level, the haemogram shows no changes, and may possibly indicate leukopenia, lymphocytosis and thrombocytopenia. The definitive diagnosis is made through costly and rarely available tests, in some reference centres only, by the reverse tran-

scriptase reaction followed by the polymerase chain reaction (RT-PCR)[7].

The Elisa technique (serology) can be effective after the symptomatic period of the disease, gaining relevance as a retrospective diagnosis for epidemiological purposes. However, it should be noted that serology may have a diminished characteristic in regions where distinct flaviviruses occur, and in this context, RT-PCR is of greater importance. The Brazilian government has invested efforts in the perspective of providing serological tests for suspected cases of the disease[7].

However, there are no systematized forms of treatment guidance and performing them depends on considering the reports of other epidemics (Asian and African) and the experience with other arboviruses12. Treatment of ZIKV fever is based on resting, hydrating and symptomatic treatment. In this case, the use of non-hormonal anti-inflammatory drugs is contraindicated, and those that are frequently used for rheumatologic diseases should be re-evaluated[12].

Because of the juxtaposition of symptoms in distinct arboviruses, the characteristic diagnosis of ZIKV in tropical regions presents a challenge. In addition, during the rainy season, other diseases should also be observed, such as leptospirosis[12,13]. For healthcare teams, it is essential that they have specific training and greater attention to signs and symptoms that indicate an atypical evolution or greater severity of the infection, besides the availability of a continuing medical education on the subject, since a large part of the patients are conducted clinically by general practitioners with maximum capacity being reached at emergency rooms[14].

Stages of intrauterine development of the central nervous system (CNS) and microcephaly-associated disorders

The development of the central nervous system in humans begins in the period of gastrulation, around the 14th embryonic day, when a thickening of the ectodermal membrane occurs, which will give rise to the neural plaque. From there, two sequential processes will occur: neural tube formation and forebrain growth[15].

The proliferation phase is extremely complicated and extensive. It begins from the 2nd to the 4th month of gestation with the proliferation of neurons and the formation of glial radial cells, extending from the 5th month and until the first year of life. The beginning of the process is characterized by the stem cells of the germinal matrix dividing symmetrically, forming the neural-glial proliferative units, which, in turn, are distributed in the periventricular zone15. Then an asymmetric division begins, in which each stem cell gives rise to another stem cell and a postmitotic neuronal cell. It is the asymmetrical division that establishes the dimension of the proliferative unit16; the postmitotic neurons migrate to the extension of the radial glia to form the various layers of the cerebral cortex. Approximately 1/3 of the neurons do not use the radial glial frame and migrate tangentially in the cortical direction[14].

In the course of the migration, neurons transit through neurons that are in position in the cortex, leading to a lamination in which the last neurons that return in the cortical zone take position on the outermost surface of the cortex. This final order with six layers, histologically different, aggregates an exceptional plurality of neuronal subtypes, which have the utility of blocks for the constitution of a powerful neural circuit[14].

Modifications of the cerebral cortex development are like a grouping of differentiated malformations with pathogenesis still undefined, and among the cortical malformations a subset of pathologies has been linked to changes in cellular migration and to neurodifferentiation, among them the lysencephaly, polymicrogyria and focal cortical dysplasia[14].

Several environmental factors have already been detected as responsible for cortical malformations; disorders in cortical development of the foetus may occur due to the mother's exposure to agents such as ethanol, some acids, anticonvulsant drugs, mercury, radiation and viral agents, among others, in the gestational phase[17].

STAGES OF INTRAUTERINE DEVELOPMENT OF THE CENTRAL NERVOUS SYSTEM (CNS) AND MICROCEPHALY-ASSOCIATED DISORDERS

The development of the central nervous system in humans begins in the period of gastrulation, around the 14th embryonic day, when a thickening of the ectodermal membrane occurs, which will give rise to the neural plaque. From there, two sequential processes will occur: neural tube formation and forebrain growth[15].

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AETIOLOGY AND DIFFERENTIAL DIAGNOSIS OF MICROCEPHALY

It is more pertinent to approach microcephaly, due to the diverse forms, aetiologies and clinical expressions. The pathogenesis of microcephaly is heterogeneous, including genetic causes in environmental factors that have a possible impact on neurodevelopment and thus end up influencing brain enlargement. Thus, any factors that may interfere in cell proliferation and/or differentiation and cell death may lead to microcephaly; these factors can only reach the development of the brain or compromise other parts of the body, determining dimorphisms (syndromic microcephaly)[18,19].

In order to simplify the clinical investigation and the differential diagnosis of microcephaly, one can first classify them based on the moment when the diagnosis is made. Thus, microcephaly can be listed in two categories: congenital and postnatal, which develops generally in the first two years of life[18,19].

Microcephaly can be either genetic or acquired, comprehending exponentially damaging external/environmental factors to the brain. In acquired congenital microcephaly, the most aggressive factors play a role throughout the development of the brain in the intrauterine phase, including maternal infections (herpesviruses, cytomegalovirus, rubella, toxoplasmosis, syphilis, HIV and now possibly ZIKV conjugation), exposure to drug/substance toxicity (emphasis is placed on the mother's consumption of alcoholic beverages, foetal alcohol syndrome), irradiation, disruptive factors that end up interrupting normal brain growth, for example, hypoxic-ischemic syndrome, ischemia, haemorrhage, traumatic brain injury and nutritional deficiency (maternal malnutrition, placental insufficiency, hypothyroidism or folate deficiency in the mother)[18,20].

Genetic congenital microcephaly may be linked to chromosomal diseases or to specific genes, such as in microcephaly primary hereditary (MCPH), historically known as microcephaly vera, in which at least 12 genes were detected as centrosome-associated proteins encoding[21,22]. In this case, the term primary microcephaly corresponds to those in which the decrease of cerebral volume is first due to the reduction of the neuronal population along the neurogenesis[23,24].

Among the genetic postnatal microcephaly linked to mutations (duplication, deletion mutation, fusion, insertion, circumstantial changes of amino acids) are those that derive from congenital metabolic errors, neurodegenerative diseases and distinct syndromes, such as: Pitt-Hopkins, Rubinstein-Taybi and Christianson's syndromes, Angelman's syndrome, and disorders related to MECP2 (Rett's syndrome)[23].

NEUROIMAGING AND ZIKV

It was reported through a cranial CT scan that 23 children, 13 of them female, were affected by congenital microcephaly, with clinical and epidemiological data compatible with ZIKV congenital infection with TTC between September and December 2015, in Pernambuco, Brazil[25]. Cerebrospinal fluid samples were available for serological testing in seven children out of 23, and the IgM antibody enzyme-linked immunosorbent assay for ZIKV was positive in the seven samples collected. The conclusions about the serological analyses of Torch infection (toxoplasmosis, rubella, cytomegalovirus and herpes simplex and others [syphilis, varicella, parvovirus and human immunodeficiency virus]) were negative in all 23 children[25].

In the CT-scan images an average age of 36 days after birth (ranging from 3 to 5 months) was identified; intracranial calcifications were observed in all children, especially in the frontal lobe (69% to 78%) and the parietal lobe (in 83% to 87%)[26]. Calcifications were found mainly at the corticomedullary junction (53% to 86%), with basal ganglia (in 57% to 65%) and in the thalamus (39% to 43%); the configuration of the calcifications was basically punctate (72% to 100%), distributed in the band format (in 56% to 75%); ventriculomegaly was found in all children and classified as severe in the majority of cases (53%), and it covered only the lateral ventricles in 43% [25].

The children, in their totality, had an overall reduction in the constitution of gyri of the severe cerebral cortex in 78% of the cases; cerebellar hypoplasia was present in 17 of the children (74%), involving only one cerebellar hemisphere in three children, in which, in two of them, the brainstem was globally hypoplastic. Abnormal hypodensity of the white matter occurred in all children and in 87% of them there was diffuse involvement of all the cerebral lobes; chronic encephalomalacia alterations of ischemic stroke were identified in the vascular territory of the left middle cerebral artery[25].

Intrauterine infection by ZIKV is associated with potential brain abnormalities, including calcifications, global reduction of cortical gyri constitution, ventriculomegaly, and white matter abnormalities, although it is not possible to definitively determine whether ZIKV infection occurred during the foetal development in the 23 children observed [25].

The results achieved are non-specific and may be observed in other congenital viral infections; the fact that there is an overall reduction in the constitution of cortical gyri and hypermyelination of the white matter or dysmyelination in all infants and cerebellar hypoplasia in most of them suggests that ZIKV may be related to an interruption in brain development rather than destruction of the brain itself.[27]

RELATIONSHIP BETWEEN ZIKV AND MICROCEPHALY

The attention given to the association of this infection is due to the increase of incidences of apparent microcephaly in foetuses born to mothers infected with ZIKV[11] and to numerous studies reporting this association (Table 1). This fact can be identified in the case report of a pregnant woman who was affected by a febrile illness with eruption, already at the end of the first trimester of pregnancy, during her stay in Brazil[11,28].

An ultrasonography was performed when she crossed the period corresponding to 29 weeks of pregnancy, revealing microcephaly with calcifications in the foetal brain and placenta. After the mother's request for pregnancy termination, the foetal autopsy was performed and microcephaly (anomalously small brain) was identified, with near-integral agitation, hydrocephalus and multifocal dystrophic calcifications in the cortex and subcortical white matter, associated with cortical displacement and mild focal inflammation; ZIKV was found in foetal brain tissue in the RT-PCR assay, with accurate results when placed under electron microscopy, that is, the complete genome of ZIKV was reconstituted from the foetal brain[11].

Another finding occurred with the discovery of cases in the Northeast of Brazil, a region in which the Ministry of Health declared a state of emergency. Occurrences were identified in women in the first months of gestation of children diagnosed with microcephaly, whose correspondence is equivalent to the highest occurrence levels in the region and were not correlated with family history of genetic inheritance or standardized tests of other infections[26].

The Ministry of Health, through the Evandro Chagas Institute (IEC), made the causal link when it isolated the ZIKV from the brain by identifying it in the CSF, brain and fragments of various viscera (heart, lung, liver, spleen and kidney) of a new-born child who died after its birth[26].

To clarify the causal association, we analysed the amniotic fluid of two pregnant women from Paraíba with a history of exanthematous disease and foetuses detected with microcephaly on foetal ultrasonography[29].

From there, additional studies have been carried out to fully sequence the virus isolated from amniotic fluid, in which phylogenetic analysis has shown that the virus shares between 97% and 100% of its genomic identity with Asians isolated in the outbreak of French Polynesia, and that the findings of the viral genome in the patients for a few weeks after the acute phase suggest that the intrauterine viral load results from a persistent response[30].

As described above, genomic alterations of the virus should be considered as a possibility of a new cause until more cases with greater evidence are identified and diagnosed, since the possibility of other aetiologies cannot be disregarded[11].

DISCUSSION

The population has been alarmed about the possibility of an association between ZIKV disease in women in the gestational phase and the development of microcephaly[13,28]. It is a disorder that occurs in the stage of neuronal dissemination, which processes early during gestation (3rd and 4th month) and, in specific cases, appears to coincide with the symptoms of maternal infection. The criteria for definitively certifying microcephaly have not been used uniformly, and since there are clear sub-notifications of these occurrences in Brazil, it is not easy to determine

TABLE 1 - DESCRIPTION OF THE MAIN STUDIES ON THE ASSOCIATION BETWEEN ZIKA VIRUS AND MICROCEPHALY INCLUDED IN THIS RESEARCH

Name of the author	Purpose of the study	Conclusion
Bell et al. Zika virus infection of the central nervous system of mice, 1971.	To verify the correlation between the virus and microcephaly by intracerebral inoculation of 5-week old new-born mice with zika virus.	It identified that the replication of the astroglial cells is associated with the destruction of the neurons indicating the infection.
Schuler-Faccini et al. Possible association between Zika virus infection and microcephaly, 2015.	Task force report to investigate association between microcephaly and zika virus during gestation from registry with incidence (cephalic circumference ≥ 2 standard deviations [SD] below average for gender and gestational age).	Four limitations were identified: the historical prevalence of children with microcephaly in Brazil was lower than the estimates; before the alert, despite descriptions of congenital anomalies reported, the cephalic perimeter was not routinely recorded; there were cases in which there was no laboratory confirmation, resulting in an incorrect classification and, finally, there are no comments on other characteristics of the intrauterine infections.
Broutet et al. Zika virus as a Cause of Neurologic Disorders, 2016.	To analyse how and through which mechanisms zika virus infections can affect the nervous system.	Causal relationships cannot be substantiated in epidemiological studies, but these factors help to identify the strength of possible causal links.
Hazin et al. Computed Tomographic Findings in Microcephaly Associated with Zika Virus, 2016.	To investigate the association between progressive incidences of new-borns with congenital microcephaly in regions affected by ZIKV in Brazil.	Intrauterine ZIKV infection appears to be associated with severe brain anomalies, including calcifications, cortical hypogria, ventriculomegaly, and white matter abnormalities, although we cannot determine with certainty when ZIKV infection may have occurred during foetal development.
Jernej et al. Associação entre Zika Vírus e Microcefalia, 2016.	Case report on the vertical transmission of zika virus (ZIKV) in a woman probably infected with ZIKV in the Northeast of Brazil at the end of the first trimester of pregnancy. Discussion includes imaging details and foetal pathological and virological analyses.	Foetal body weight of 1,470 g (percentile 5), length 42 cm (percentile 10), cephalic perimeter 26 cm (1st percentile). The only external anomaly noted was microcephaly; placenta weighing 200 g, resulting in weight ratio of foetal placenta of 0.136 (<percentile 3). Macroscopic examination of the CNS revealed microcephaly with a total brain weight of 84 g (4 standard deviations below average).
Mlakar et al. Zika virus associated with microcephaly, 2016.	Research the association through the increased incidence of microcephaly in foetuses born to mothers infected with ZIKV.	Near-complete agitation and internal hydrocephalus of the lateral ventricles were observed with numerous calcifications of variable size in the cortex and subcortical white matter in the frontal, parietal and occipital lobes.
Oliveira et al. Zika virus intrauterine infection causes foetal brain abnormality and microcephaly: tip of the iceberg?, 2016.	Case report to prove the relationship between zika virus and microcephaly.	Similar to other intrauterine infections, it is possible that the reported cases of microcephaly represent only the most affected children and that in new-borns of lesser severity, it affects not only the brain but other organs and it has not yet been diagnosed.
Tetro JA. Zika and microcephaly: causation, correlation, coincidence? 2016.	Research on the increase in incidence in the State of Pernambuco.	Reduced brain size indicates microcephaly, although the mechanisms of the zika virus pathogenesis appear to be in line with the requirements. There is no concrete evidence.
Ventura et al. Ophthalmological findings in infants with microcephaly and presumable intrauterus Zika virus infection, 2016.	Research based on the report of a 20-fold increase in the prevalence of microcephaly in Brazil, in which the Ministry of Health associated this abnormal prevalence with the transmission of the maternal-foetal zika virus (ZIKV).	Patients presented normal anterior segment and important abnormalities of the macular nerve and optic nerve. Other studies will evaluate the visual significance of these changes.

An ultrasonography was performed when she crossed the period corresponding to 29 weeks of pregnancy, revealing microcephaly with calcifications in the foetal brain and placenta. After the mother's request for pregnancy termination, the foetal autopsy was performed and microcephaly (anomalously small brain) was

exactly whether the incidence of this pathology has really increased[18,21]. In addition, accessible neuroimaging studies show that other malformations of foetal cortical development are also present, as well as diffuse calcifications (neuronal death), suggesting an extended duration of the virus pathogenesis in the CNS or a vulnerability of more phases of cortical development[4,15, 16, 29].

If we consider the widespread diffusion of *Aedes aegypti* in the country and that the methods adhered to control the growth of the vector are slow to show results, it is expected that the incidence of ZIKV infection requires prioritizing the search for more integrated knowledge about the pathology and the etiological agent. Current studies suspect that changes in the molecular components of ZIKV, especially protein E, which is on the surface of the virus, could be correlated with an exponential worsening of ZIKV, thus reinforcing its neurotropism and its ability to affect humans[31].

The situation requires multiple interpretations and multidisciplinary actions to control the vector and the infection by the ZIKV, through the awareness of the people (the paediatrician plays a leading role in this process). It is true that ZIKV can overcome placental blockage and affect amniotic fluid and foetal tissues32; however, it is a priority to calm pregnant women, since it cannot be said that this increase in microcephaly reports is only associated with the virus, since many suspicious cases at the beginning have already been ruled out[11].

The cases confirmed in the laboratory are inferior in comparison to the large index of notifications. Regardless, the means of prevention are still essential and should be identified, but the tests available for laboratory diagnosis of ZIKV infection in the acute or subsequent phase are still very limited. The difficulty of confirming or excluding infection still hinders the understanding of the natural history of the disease, its association with microcephaly and Guillain-Barre syndrome[33].

Because of the extreme worldwide attention to the teratogenic potential of the Zika infection, there is a greater commitment to the development of more affordable and more specific tests, such as serology that represent a lower risk of cross-reactivity[34].

In short, it is evident that there is a temporal association between the quantitative increase in the notification of cases of microcephaly and the ZIKV epidemic, especially in Northeast Brazil. However, the advancement of diagnostic techniques that reaffirm the relationship between cause and effect, the mechanism and infectious pathogenesis of ZIKV in the central nervous system and the diagnostic parameters more specifically established to identify the cases to be recognized should still be investigated with priority[33].

ASSOCIATES

GRB dos Santos and FBA Aragão contributed to the construction of the object of study, definition of objectives and methodology, data collection, processing, analysis and writing of the article. LMR de Andrade and FR Lima participated in the study and their specific contribution was in the drafting of the manuscript and in its critical review regarding the content. WJM Lobão and QR Furtado participated in the analysis and interpretation of the results and in the proofreading. JE Batista participated in the study design, in the preparation and orientation of the research, in the critical review and in the approval of the final version of the article submitted for publication.

RESUMO

OBJETIVO: *O presente estudo analisou a associação entre Zika vírus e microcefalia durante o período gestacional de mulheres no Brasil.* METODOLOGIA: *Revisões sistemáticas de pesquisas de intervenção, publicações atuais de investigações clínicas. Foram utilizadas estratégias de buscas sistemáticas em três bases de dados eletrônicos: PubMed, SciELO e Google acadêmico. Utilizaram-se as palavras-chave microcefalia, gestação e Zika vírus para realizar a busca, sendo obtidos 1.020 artigos. Após a exclusão, restaram 45 e na elegibilidade, 35. O período da coleta foi de 2004 a 2017. Resultados: Os dados epidemiológicos preconizam uma associação temporal entre a ampliação do quantitativo e epidemia de Zika vírus, especialmente no Nordeste do Brasil. Não é consensual a mensuração da curva de perímetro cefálico a ser considerada.* CONCLUSÃO: *Visto isso, deve ser priorizada a aplicação de técnicas para diagnosticar com precisão as relações entre causas e efeitos na patogênese da infecção pelo Zika vírus no sistema nervoso central.*

PALAVRAS-CHAVE: *Epidemias. Zika vírus. Microcefalia. Gestação.*

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REVIEW ARTICLE

Use of active metabolites of vitamin D orally for the treatment of psoriasis

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http://dx.doi.org/10.1590/1806-9282.64.07.643

SUMMARY

Objective: The objective of this study was to analyse the existing bibliographic production on clinical trials related to the use of vitamin D for oral treatment of psoriasis. Method: A literature review of clinical trials related to the use of vitamin D for oral treatment of psoriasis, published in the LILACS, Scielo, Medline, PubMed and Cochrane Library from 1986 to 2013. The search included the following terms: "Psoriasis and oral Vitamin D"; "psoríase e vitamina D oral".Results: After analysing the titles and summaries, 10 articles met the eligibility criteria. Discussion: According to the literature, most tests were made in moderate psoriasis with doses ranging from 0.25 to 2µg, demonstrating improvement with this treatment modality. Some studies suggest the use of high doses, but the biggest concern is hypercalciuria as a side effect.Conclusion: The use of active metabolites of vitamin D orally for the treatment of psoriasis showed efficacy and safety.

KEYWORDS: *Administration, oral. Review literature as topic. Psoriasis. Vitamin D.*

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease that affects about 2% of the world's population and 3 million people in Brazil. It is characterized by erythematous and scaly papules or plaques, usually located in the elbows, knees, feet, hands, sacral region, and scalp or even throughout the body, with periods of exacerbations, remissions and recurrences. According to the location or characteristics of the lesions, it can be classified as plaque, guttate, inverted, pustular (generalized and localized), palmoplantar, scalp, nail, erythrodermic and arthropathic psoriasis (Figures 1, 2 and 3). Although psoriasis does not affect survival, it has a negative impact on the patient's physical and psychosocial well-being, as the appearance of the lesions is a cause for stigma[1].

The pathophysiology of psoriasis defines it as an immune-mediated systemic disease involving helper T lymphocytes type 1 (Th1). Cytokines of the Th1 pathway - interferon gamma, interleukins 2 and 12 and TNF-alpha - predominate in the psoriatic plaques, as well as interleukin-17, which induces the expression of chemoattractant in the lesion. Therefore, an unknown stimulus activates the dendritic cells that present antigens of the skin, which will lead to the activation of the helper T cells, and, finally, the release of a cascade of inflammatory cytokines. This cascade results in the recruitment and activation of other cells, such as neutrophils and endothelial cells, chemokines and growth factors that will induce keratinocyte proliferation. A chronic condition, there-

DATE OF SUBMISSION: 29-Nov-2017
DATE OF ACCEPTANCE: 06-Dec-2017
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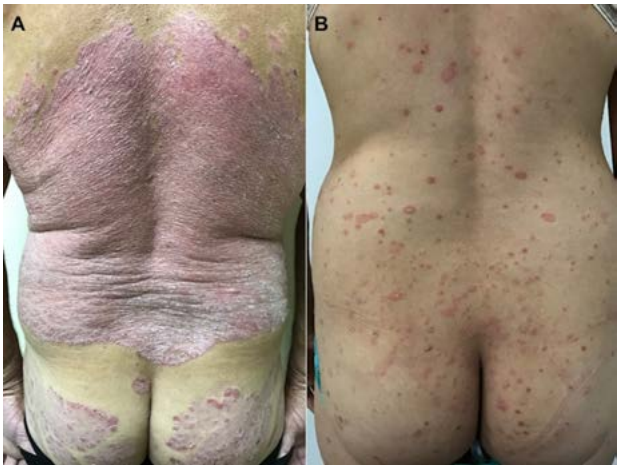
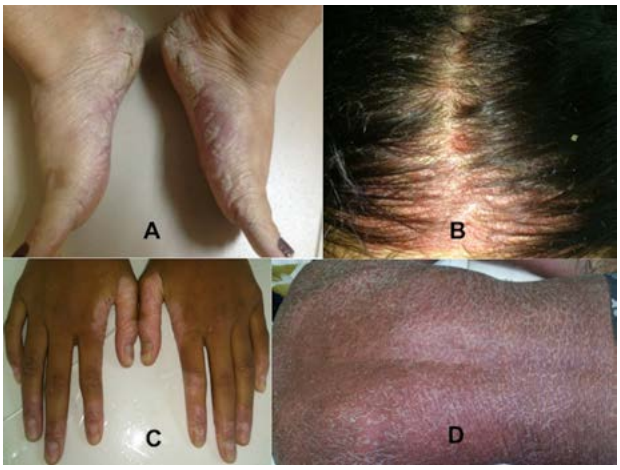
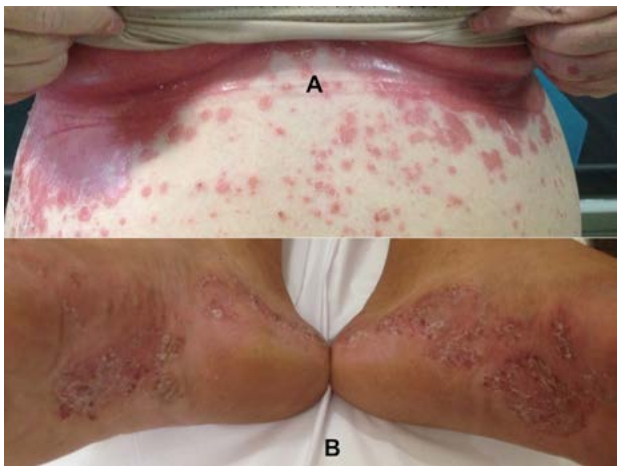
fore, guarantees and leads to the formation of skin lesions in psoriasis[2].

In addition, psoriasis is nowadays associated with vitamin D deficiency. A study by Gisondi et al.[3], which analysed the vitamin D status in patients with chronic plaque of psoriasis, demonstrated that vitamin D deficiency is common in these patients, regardless of age, gender, body mass index, Psoriasis Area Severity Index (Pasi), parathyroid levels (PTH) and blood collection time.

FIGURES 1, 2 and 3







Vitamin D - or cholecalciferol - is a steroid hormone that has endogenous formation in cutaneous tissues after exposure to ultraviolet B radiation. Cholecalciferol circulates in protein-bound blood and, when it reaches the liver, undergoes hydroxylation, forming 25-hydroxyvitamin D or 25(OH)$D_{3,}$ which in spite of being biologically inert, represents the circulating form in greater amounts of vitamin D. Blood levels of 25(OH)D3 correspond in proportion to the amount of vitamin D that is ingested or produced on the skin. The final stage of production of the hormone is its hydroxylation in the kidney, where the biologically active form of vitamin D, calcitriol or 1,25(OH)D_3 will be synthesized. The main function of vitamin D in the body is to participate in calcium homeostasis, stimulating the active transport of this ion in enterocytes[4]. In addition, many cell types involved in immune responses not only express vitamin D receptors, but also have all the enzymatic machinery for the local synthesis of 1,25 (OH)2 D3; these sites of synthesis in cells related to immunity are of great importance for the regulation and control of various immune responses[5]. Thus, the existence of extra-renal hydroxylation of vitamin D, with autocrine or paracrine action, has the function of inhibiting cell proliferation, promoting cell differentiation and regulating immunological mechanisms[4], such as the control of the inappropriate activation of interleukin-17, which participates in the pathogenesis of multiple inflammatory and autoimmune diseases[6].

Topical vitamin D derivatives have immunomodulatory effects on monocytes, macrophages, T lymphocytes and dendritic cells. Thus, topical vitamin D products have been widely used in monotherapy or in combination with steroids[3]. The latter alternative is considered first-line therapy for the majority of patients with mild to moderate psoriasis, demonstrating efficacy and safety in treatment of patients with plaque psoriasis[7].

However, evidence that psoriasis is a systemic disease, involving many comorbidities, suggests the importance of analysing the treatment of this disease with oral vitamin D, given the few studies investigating this modality in patients with psoriasis[2]. Doses of oral vitamin D can be expressed in microgram or International Unit (IU), with 1 microgram corresponding to 40 IU[8]. In addition, when the literature is observed, the forms of vitamin D used for oral treat-

ment may be: 1,25(OH)D_3, which is the biologically active form of this hormone or 1α(OH)D_3, which is a precursor 1.25(OH)D_3[9-16].

OBJECTIVE

This study aims at analysing the literature on the clinical trials related to the use of vitamin D for oral treatment of psoriasis. It will be analysed especially the type of psoriasis in which the treatments were applied, results, side effects and doses used in this therapeutic alternative.

METHODS

This is a bibliographic review research using the online databases Lilacs, SciELO, Medline, PubMed and Cochrane Library, consulted from the portal of free and restricted databases of the virtual library of the Universidade do Oeste Paulista.

Thus, a search was initially made on the production of knowledge regarding the oral use of vitamin D for the treatment of psoriasis.

In the search, the titles and abstracts of the articles were considered for the broader choice of probable papers of interest, being selected the articles that provided complete texts. The descriptors used were "Psoriasis and oral Vitamin D"; "psoríase e vitamina D oral".

At the end of the research, ten articles were selected for the study, covering the period between 1986 and 2013.

RESULTS

The research strategy was to analyse the titles and abstracts of the articles. According to the topic of interest, ten articles, published in the period between 1986 and 2013, were used to carry out the literature review.

DISCUSSION

The therapeutic use of vitamin D in psoriasis dates back to the 1930s when the compound was used as an oral agent to treat osteoporosis in a patient with psoriasis where subsequently the improvement of psoriatic skin lesions was observed[9,10].

In 1986, Morimoto et al.[11], in an open-label clinical trial, and Takamoto et al.[12], in a pilot study, selected patients with psoriasis vulgaris, resistant to topical corticosteroid therapy, and administered 1 µg/day of 1α(OH)D3 for six months. The authors demonstrated that the biologically active metabolites of vitamin D3 are effective in therapy of the disease and do not cause apparent side effects.

Smith et al.[13] studied 14 patients with psoriasis from moderate to extensive lesions. They administered 1,25-(OH)2D3, at the initial dose of 0.25 µg, once or twice daily. Patients should limit daily calcium intake to less than 800 mg. If they had normocalciuria at the follow-up, the dose was increased to a maximum of 2 µg/day; if hypercalciuria occurred, therapy was discontinued. Hypercalciuria was observed when fractionated doses of vitamin D exceeded 0.75 µg/day. To avoid this effect, the dosage was changed to only one dose of 0.25 to 0.5 µg before bedtime: the authors believe that the influence of 1,25-(OH)2D3 on the absorption of calcium by the intestine is lower at night; therefore, higher doses administered before bedtime possibly cause a lower risk of hypercalciuria. In this study, 13 of the 14 patients improved with two months of treatment and continued to improve up to 6-8 months after the initial improvement was observed.

El-Azhary et al.[14], in a pilot study, treated eight patients with psoriasis vulgaris, presenting more than 25% of body involvement at an initial dose of 1,25-(OH)2D3 of 0.5 µg before bedtime. This dose was beneficial for one patient, who had psoriatic plaques completely resolved within two months and no side effects. Patients receiving dosages greater than 1 µg/day showed an increase in calcium excretion in the urine for 24 hours. Considering this, they do not recommend the use of doses above 1 µg/day. The research also shows that serum vitamin D levels do not correlate with disease activity.

Perez et al.[15] conducted a clinical trial to test the safety and efficacy of oral calcitriol to treat psoriasis in 85 patients with at least 15% of the body affected by the disease. The initial dose was 0.5 µg/day of vitamin D before bedtime and was subsequently increased by 0.5 µg/day every two weeks, with laboratory control of serum calcium and urine for 24 hours; while these tests remained within normal range, the dose of vitamin D would be increased. The treatment lasted between 6 and 36 months; the maximum tolerated dose was 4 µg/day and the average dose ranged from 2.1 +/- 0.8 µg/night for treatments lasting 24 months and 2.4 +/- 0.6 µg/night for treatments of 36

months. The results were 88% of patients improved their clinical condition, 26.5% had complete improvement, 36.2% had moderate improvement and 25.3%, slight improvement.

Huckins et al.[16] performed an open-label trial using 1,25-(OH)2D3 for the treatment of psoriatic arthritis in ten patients at an oral dose of 2 µg/day for six months. More than 50% achieved substantial improvement and 25% improved moderately. The conclusion of the study was that high doses of vitamin D could be used as a therapeutic agent of psoriatic arthritis.

Werner de Castro et al. (2012)[17] mention the resolution of a psoriasis case, induced by the use of adalimumab, in a woman with rheumatoid arthritis, after using high doses of vitamin D to treat the deficient rates of this vitamin.

A pilot study by Finamor et al. (2013),[6] evaluated the effect of prolonged oral administration of high daily doses of vitamin D in the clinical course of 16 patients with vitiligo and 9 patients with psoriasis, using 35,000 IU per day for six months. This study suggested that high daily doses of vitamin D might be particularly critical for controlling the activity of autoimmune disorders. Cumulative data from the past 30 years, reviewed by the authors, establish a regulatory effect of vitamin D on the innate and adaptive immune response, with circulating levels of 25 (OH)D3 - the main circulating form of vitamin D - inversely related to autoimmune disease activity. They state that doses of up to 40,000 IU per day of vitamin D3 are probably safe for healthy individuals and that in patients with autoimmune disorders, polymorphisms that affect vitamin D metabolism enzymes may increase their tolerability. They also point out that hypervitaminosis D are associated with the positive regulation of intestinal vitamin D receptors and increased dietary calcium absorption; a calcium-deficient diet protects against vitamin D toxicity not only by reducing calcium available for intestinal absorption but also by facilitating vitamin D inactivation at sites related to calcium metabolism. In the pilot study, all patients had clinical improvement of the cutaneous condition without side effects: serum calcium concentrations (total and ionized) were measured and did not differ significantly from baseline values after six months of high treatment doses with vitamin D3. The urinary excretion of calcium increased considerably, but remained within the normal range. The dose chosen by the authors of 35,000 IU was selected arbitrarily, as well as other interventions that have already been applied to treat autoimmune disorders using high doses of vitamin D3, however it is suggested that PTH may be the best biological indicator for the individual establishment of the optimal dose of vitamin D3 for the treatment of autoimmune disorders. The magnitude of reduction in PTH serum concentration from baseline to the level reached after the treatment period may provide a reasonable estimate of how much the initial daily dose of vitamin D3 should be increased to reduce serum PTH levels below reference range.

TABLE 1: STUDIES EVALUATING THE EFFICACY OF USING THE ACTIVE METABOLITES OF ORAL VITAMIN D FOR THE TREATMENT OF PSORIASIS.

Author/ Year	Type of Study	Number of patients	Clinical presentation of psoriasis	Initial Dose	Study Contribution
Morimoto et al. (1986)	Open-label clinical trial	17	mild to moderately refractory psoriasis	1 µg/day	It demonstrated the efficacy of using active metabolites of vitamin D3, with no apparent side effects.
Takamoto et al. (1986)	Pilot Study	7	psoriasis vulgaris for more than 6 months and refractory	1 µg/day	It demonstrated the efficacy of using active metabolites of vitamin D3, with no apparent side effects.
Smith et al. (1988)	Double-blind Clinical Trial	14	moderate to severe psoriasis vulgaris	0.25 to 0.5 µg/day	Dosage should be 1 dose before bedtime to avoid hypercalciuria.
Huckins et al. (1990)	Open-label clinical trial	10	psoriatic arthritis	2 µg/day	High doses of vitamin D may be useful for psoriatic arthritis therapy.
El-Alzhari et al. (1993)	Pilot study	8	moderate to severe psoriasis vulgaris	0.5 µg/day	It does not recommend doses higher than 1 µg/day.
Perez et al. (1996)	Open-label clinical trial	85	moderate to severe psoriasis vulgaris	0.5 µg/day	Maximum tolerated dose of 4 µg/day.
Finamor et al. (2013)	Open-label clinical trial	9	moderate to severe psoriasis vulgaris	35.000 UI/ day	High doses of vitamin D may be safe and effective for treating psoriasis.

According to Gisondi et al. (2011)[3], the toxicity of vitamin D supplementation is very rare to occur and consists mainly of acute hypercalcemia, which usually results from doses exceeding 10,000 IU per day.

On the other hand, Trémezaygues and Reichrath (2011)[5] affirm that only supraphysiological doses lead to a clinical improvement of psoriasis, therefore, the use of vitamin D analogues in dermatology was considered, decades ago, limited due to the occurrence of serious effects related to calcium metabolism.

Furthermore, Smith et al. (1988)[13], in the literature review they did to compare the results obtained in their clinical trial, report that in the 1930s and 1940s there were studies in which extremely high doses of vitamin D (around 100,000 IU) were administered to treat a variety of skin disorders such as scleroderma, eczema, acne and psoriasis. Although some responses were favourable, the doses required were very toxic, and since vitamin D is biologically inert, successive hydroxylation is required in the liver and later in the kidneys, in order to form 1,25-(OH)2D3 and thus have biological activity. They conclude that increased intake of vitamin D has few beneficial effects.

PRACTICAL ASPECTS OF THIS REVIEW

According to the literature, oral vitamin D testing was primarily performed on moderate to severe vulgar psoriasis. Most studies have shown that the active metabolites of vitamin D3 - 1,25-(OH)2D3 or 1α(OH)D_3 (synthetic analogue of 1,25-(OH)2D3) - provide favourable results in the evolution of psoriasis and cause few side effects, and may be a therapeutic alternative for the treatment of this disease. The most worrying adverse effect that can occur is acute hypercalciuria, which can be avoided by restricting daily calcium intake (less than 800 mg per day), by administering vitamin D at night - before bedtime - and by properly monitoring, throughout the treatment, urinary calcium levels; if the patient has hypercalciuria, the use of vitamin D should be stopped. The doses that can be used vary from 0.25 µg to 2 µg per day, but recently, a higher dose (35,000 IU) has shown therapeutic safety and efficacy, and PTH is the best biological indicator for the establishment of the vitamin D3 dose.

CONCLUSION

The review of the literature revealed that there are still few studies that have tested the use of oral vitamin D active metabolites for the treatment of psoriasis, in addition to the fact that the sample studied in all of them is small and the follow-up time is very limited. However, existing data suggest that such a therapeutic alternative is safe and effective. Therefore, more studies are needed, in the long term and in larger cases, to try to establish an adequate protocol of treatment and thus to reach a consensus as to the doses and time that should be employed, since this alternative is low cost and apparently safe, even at high doses, unlike most systemic drugs currently used in psoriasis, the adverse effects of which are significant and many of them are costly.

RESUMO

OBJETIVO: *O objetivo deste estudo foi analisar a produção bibliográfica existente sobre os ensaios clínicos relacionados ao uso da vitamina D para tratamento por via oral da psoríase.* MÉTODOS: *Revisão de literatura de ensaios clínicos relacionados ao uso de vitamina D para tratamento por via oral da psoríase publicados no Lilacs, SciELO, MedLine, PubMed e Biblioteca Cochrane no período de 1986 a 2013. A pesquisa incluiu os seguintes termos: "Psoriasis and oral Vitamin D"; "psoríase e vitamina D oral".* RESULTADOS: *Depois de analisar os títulos e resumos, dez artigos preencheram os critérios de elegibilidade.* DISCUSSÃO: *Segundo a literatura, a maioria dos ensaios foi realizada na psoríase moderada, com dose que varia de 0,25 a 2 µg, demonstrando melhora com esta modalidade terapêutica. Alguns estudos sugerem o uso de doses elevadas, porém a maior preocupação é a hipercalciúria como efeito colateral.* CONCLUSÃO: *O uso de metabólitos ativos de vitamina D por via oral para o tratamento da psoríase demonstrou eficácia e segurança com relação aos efeitos colaterais.*

PALAVRAS-CHAVE: *Administração oral. Literatura de revisão como assunto. Psoríase. Vitamina D.*

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REVIEW ARTICLE

Effectiveness of harmonic scalpel in patients submitted to total thyroidectomy: systematic review with meta-analysis

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http://dx.doi.org/10.1590/1806-9282.64.07.649

SUMMARY

OBJECTIVE: *The objective of this study was to evaluate the efficacy and safety of the harmonic scalpel compared to the conventional technique in patients submitted to total thyroidectomy.*

METHOD: *This is a systematic review with inclusion of randomized controlled trials (RCTs) that compared both techniques. An electronic search was carried out in the Medline and Lilacs databases until June 2017. The outcomes analysed were operation time, intraoperative bleeding, surgical morbidity, and costs.*

RESULTS: *Data from 31 primary studies were included. The use of the harmonic scalpel correlates to a shorter operation time (p <0.001) and a lower volume of intraoperative bleeding (p <0.001). There were no differences in the risk of transient (p = 0.53) and permanent (p = 0.70) hypocalcaemia, transient (p = 0.61) and permanent (p = 0.50) dysfunctions of the inferior laryngeal nerve and hematoma (p = 0.14).*

CONCLUSION: *Total thyroidectomy using a harmonic scalpel is effective and safe compared to the conventional technique.*

KEYWORDS: *Thyroidectomy. Haemostasis, surgical/methods. Ultrasonic surgical procedures. Review.*

INTRODUCTION

Thyroidectomy is the most performed operation by head and neck surgeons and is considered a safe procedure, with virtually no mortality. Due to the rich vascularization of the thyroid gland, its resection is based on haemostasis both to prevent bleeding that can become fatal and to keep the surgical field clean and facilitate the visualization of noble structures such as the laryngeal nerves and the parathyroid glands[1,2].

In order to provide bleeding control, haemostatic devices have been developed to try to make the operation even safer. One of the most studied is the harmonic (or ultrasonic) scalpel, which consists of the use of high frequency wave that is converted into mechanical energy and simultaneously promotes the sealing and sectioning of blood vessels, as well as fibrous and muscular tissue structures, providing adequate haemostasis at temperatures lower than those of mono- and bipolar scalpels[3,4].

The objective of this study was to perform a systematic review to evaluate the efficacy and safety of the harmonic scalpel compared to the conventional technique in patients submitted to total thyroidectomy.

DATE OF SUBMISSION: 05-Dec-2017
DATE OF ACCEPTANCE: 06-Dec-2017
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METHOD

Selection criteria

We selected all randomized and controlled clinical trials comparing the use of harmonic scalpel with the conventional ligature technique in patients submitted to total thyroidectomy. The studies were selected from the reading of the respective titles and abstracts. When it was not possible to identify whether the study would be included or not, the full text was requested for the detailed analysis.

Studies that included patients with thyroid gland disease, regardless of the nature of the diagnosis (benign or malignant), who underwent total thyroidectomy were included. Studies that included patients submitted to total thyroidectomy, associated with other concomitant procedures, and with a history of previous surgery and/or cervical irradiation were excluded.

The intervention group included patients who used the harmonic scalpel during the surgical procedure, while the control group underwent conventional ligation surgery. At first, there was no restriction on the description of the harmonic scalpel technology used.

The outcomes analysed were operating time, intraoperative bleeding volume, incidences of inferior laryngeal nerve injury (temporary and permanent), hypocalcaemia (temporary and permanent), and hematoma requiring surgical intervention and procedure costs.

SEARCH STRATEGY

The electronic databases Medline (via PubMed) and Lilacs were consulted for identification of the primary studies. These were closed in June 2017.

For the recovery of the primary articles, the search strategy (thyroidectomy OR thyroid surgery) AND (electrocoagulation OR ultrasonic surgical procedures OR ligation OR constriction OR surgical haemostasis OR suture techniques OR harmonic OR ultrasonic OR surgical instruments OR) was used.

In addition, the references of the selected studies and of published reviews were consulted through manual search to select articles that were not included in the electronic searches.

STATISTICAL ANALYSIS

The measures of effectiveness or damage expressed in absolute numbers were analysed through the relative risk difference adopting a 95% confidence interval. For all statistically significant results, the numbers needed to treat (NNT) and numbers needed to harm (NNH) were calculated. The continuous data were analysed when the average and its standard deviation of the final measurements were presented. The weighted average difference between groups was used.

Inconsistencies between clinical trials were estimated by the chi-square test (Chi^2) of heterogeneity and quantified using the I^2 test. Values above 50% were considered as high heterogeneity.

A sensitivity analysis was carried out regarding the methodological risk, which was established according to the Jadad criteria[5].

RESULTS

Results of electronic searches

Electronic and manual searches resulted in a total of 2,137 studies. After reading the respective titles and abstracts, 2,099 studies that clearly did not fit the proposed theme were excluded. Thirty-eight studies potentially eligible for inclusion were selected for reading the full texts. After this step, seven studies were excluded, since four did not separately describe the results regarding total and partial thyroidectomy[6-9], one was not a randomized clinical trial[10], one was published in duplicate[11] (the most recent article was considered) and one included only 7% of the sample submitted to total thyroidectomy[12]. Thus, the results of this review are based on data from 31 studies.

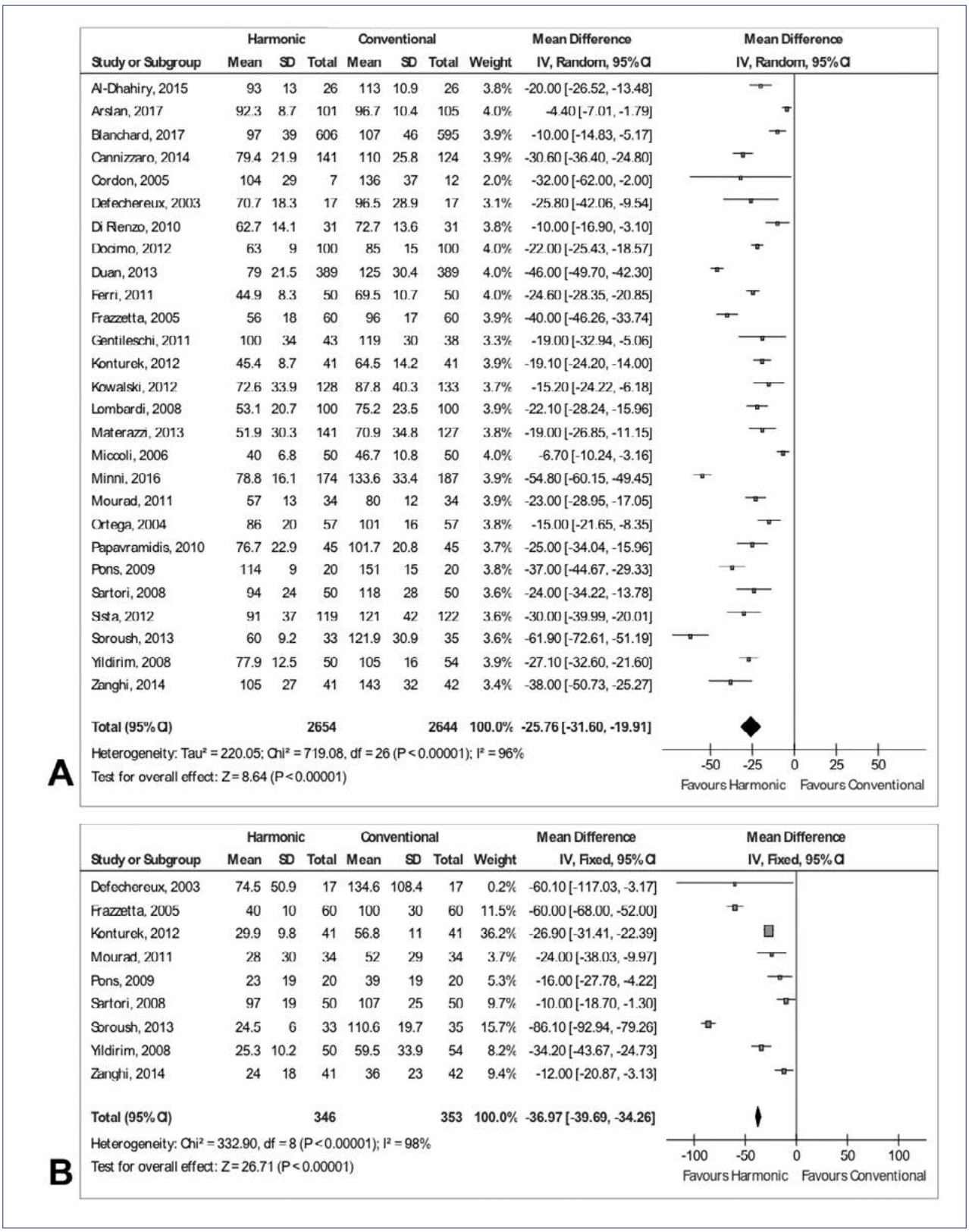
Assessment of methodological risk of primary studies

All primary studies were described as a randomized clinical trial. Of the 31 studies, only ten adequately described the randomization and allocation of patients[14,16,22,24,28,30,33,34,42,43]. In 17 studies the method of randomization was not described[15,17-20,25,26,27,29,31,32,35-39,41] and in another four it was considered inappropriate[13,21,23,40].

Since it is a surgical study, double blinding is very difficult to apply. Only one study was described as double-blind[25], while other nine[18,20,23,29,34,35,37,42,43] applied blinding only in the patients. In the remaining 21 studies, there was no blinding.

Whenever present, loss of follow-up or protocol break were described, and accounted for less than 20% in all studies.

FIGURE 1. META-ANALYSIS ON (A) OPERATION TIME AND (B) INTRAOPERATIVE BLEEDING COMPARING THE HARMONIC SCALPEL WITH THE CONVENTIONAL TECHNIQUE.



Operation time

Twenty-seven primary studies evaluated the operation time of total thyroidectomy comparing the harmonic scalpel to the conventional technique. Two studies did not provide the standard deviations of the averages and were not included in the overall analysis of the result.

For the calculation of the meta-analysis the random effect method was used due to the high heterogeneity of the results (I^2 = 96%). Patients submitted to total thyroidectomy with the aid of the harmonic scalpel showed a reduction of approximately 26 minutes in the operation time when compared to the conventional group (95% CI 19.91 to 31.60, p <0.001, Figure 1A).

Volume of intraoperative bleeding

Ten primary studies evaluated the intraoperative bleeding volume of total thyroidectomy comparing the harmonic scalpel to the conventional technique. One study was excluded because it did not present the standard deviations of the averages[22]. All studies showed a statistically significant reduction in bleeding volume in the group submitted to thyroidectomy with the aid of a harmonic scalpel. The overall analysis results in a decrease of approximately 35 ml of bleeding (95% CI 16.31 to 54.35, p <0.001, Figure 1B).

Incidence of postoperative complications

Hematoma requiring surgical revision was studied in 18 primary studies presenting an incidence of 0.83%, 13 cases (0.60%) in the harmonic scalpel group and 23 cases (1.06%) in the conventional group. There was no significant difference between the groups (95% CI -0.01 to 0.00, p = 0.14 and I^2 = 0%).

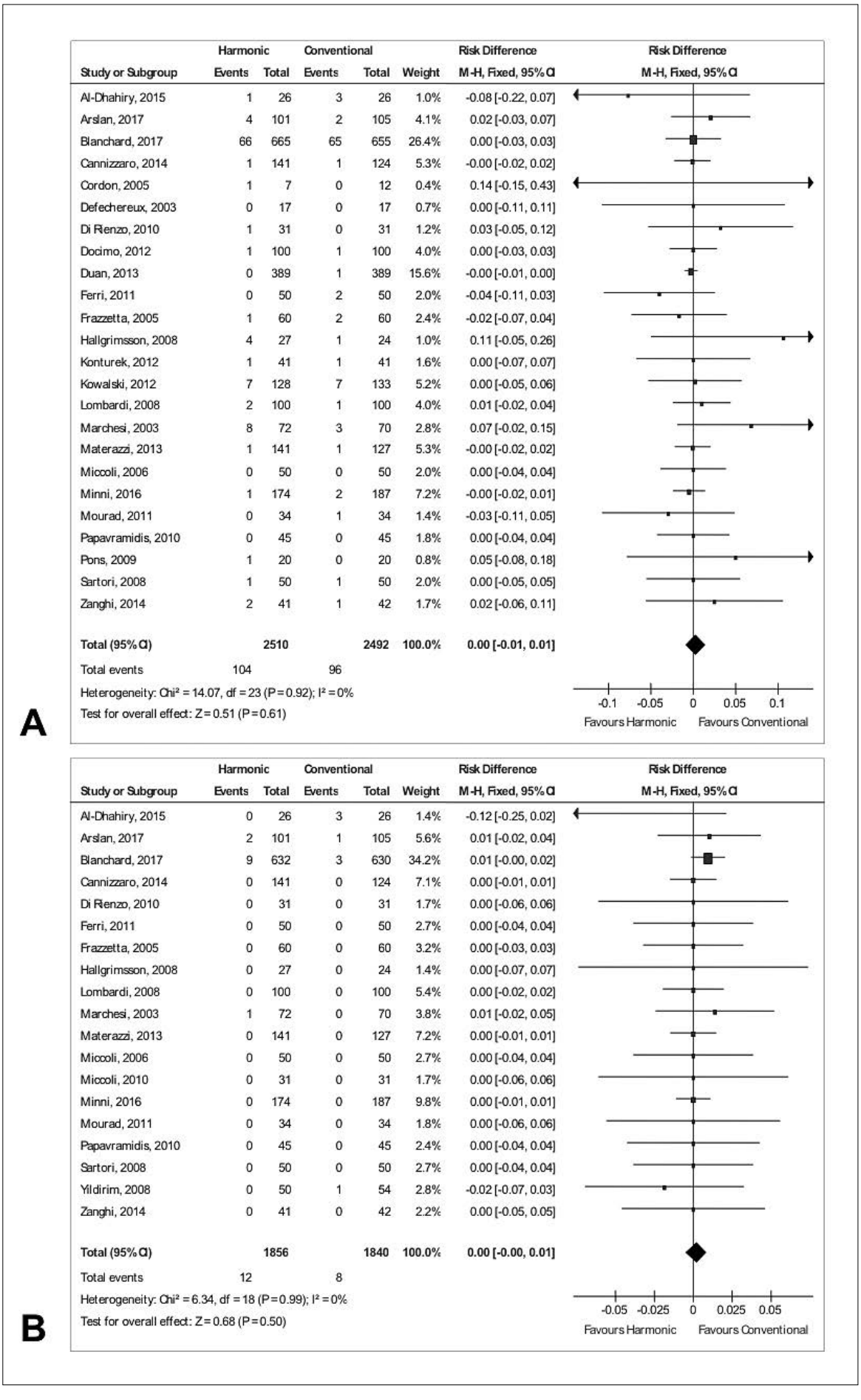
The incidence of transient inferior laryngeal nerve dysfunction (24 studies) occurred in 200 patients, 104 cases (4.1%) in the harmonic scalpel group and 96 cases (3.9%) in the conventional group. There was no significant difference between the groups (95% CI -0.01 to 0.01, p = 0.61 and I^2 = 0%, Figure 2A). In relation to permanent dysfunction (19 studies), there was also no significant difference between the groups (0.6% x 0.4%, 95% CI --0.00 to 0.01, p = 0.50 and I^2 = 0 %, Figure 2B).

Transient hypocalcaemia (25 studies) occurred in 15.3%. In the group with harmonic scalpel, the incidence was 14.9%, while in the conventional group it was 15.6%. There was no significant difference between the groups (95% CI -0.04 to 0.02, p = 0.40 and I^2 = 56%, Figure 2C). Excluding the primary studies responsible for the high heterogeneity (I^2 = 56%)[18,21,29], the same effect of the previous analysis was maintained (95% CI -0.03 to 0.01, p = 0.53 and I^2 = 0%).

TABLE 1. DESCRIPTION OF PROCEDURES COSTS COMPARING TOTAL THYROIDECTOMY WITH AND WITHOUT THE USE OF HARMONIC SCALPEL

Study	Expenses considered	Harmonic	Conventional	Difference between averages	p
Ortega, 2004*	Medications; Operating room time; Materials; Hospitalization period	985.77 ± 107.08	1,148.40 ± 153.25	−162.6	<0.001
Frazzetta, 2005*	Materials; Operating room time; Medications; Human Resources	978.6 ± 120	1,328.7 ± 105.7	−350.1	<0.001
Lombardi, 2008*	Human Resources; preoperative tests; Medications; Operating room time; Materials; Admission/Discharge	2.238.1 ± 406.5	2,368.1 ± 489.9	−130.0	0.04
Hallgrimsson, 2008*	Materials; Operating room time	2,040 (1,614 – 3,214)	2,413 (922 – 3,798)	−373.0	-
Pons, 2009#	Materials; Human Resources; Medications	2,486 ± 153	2,571 ± 296	−85.0	0.25
Ruggeri, 2012*	Medications; Operating room time; Materials; Hospitalization period; Human Resources; Admission/Discharge	2,292.52	2,411.49	−118.9	-
Kowalski, 2012#	Operating room time; Materials; Medications; Hospitalization time	2,554.7 ± 525.1	2,470.1 ± 923.9	+84.6	0.36
Konturek, 2012*	Operating room time; Materials; Hospitalization time	666.2 ± 32.1	718 ± 27.2	−51.8	<0.001
Blanchard, 2017*	Operating room time; Hospitalization period; Human Resources; Materials	3,954 ± 792	3,728 ± 831	+226	<0.001

* Values in euros; # Values in US dollars


Harmonic
Conventional
Risk Difference
Risk Difference
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Al-Dhahiry, 2015 1 26 3 26 1.0% -0.08 [-0.22, 0.07]
Arslan, 2017 4 101 2 105 4.1% 0.02 [-0.03, 0.07]
Blanchard, 2017 66 665 65 655 26.4% 0.00 [-0.03, 0.03]
Cannizzaro, 2014 1 141 1 124 5.3% -0.00 [-0.02, 0.02]
Cordon, 2005 1 7 0 12 0.4% 0.14 [-0.15, 0.43]
Defechereux, 2003 0 17 0 17 0.7% 0.00 [-0.11, 0.11]
Di Renzo, 2010 1 31 0 31 1.2% 0.03 [-0.05, 0.12]
Docimo, 2012 1 100 1 100 4.0% 0.00 [-0.03, 0.03]
Duan, 2013 0 389 1 389 15.6% -0.00 [-0.01, 0.00]
Ferri, 2011 0 50 2 50 2.0% -0.04 [-0.11, 0.03]
Frazzetta, 2005 1 60 2 60 2.4% -0.02 [-0.07, 0.04]
Hallgrimsson, 2008 4 27 1 24 1.0% 0.11 [-0.05, 0.26]
Konturek, 2012 1 41 1 41 1.6% 0.00 [-0.07, 0.07]
Kowalski, 2012 7 128 7 133 5.2% 0.00 [-0.05, 0.06]
Lombardi, 2008 2 100 1 100 4.0% 0.01 [-0.02, 0.04]
Marchesi, 2003 8 72 3 70 2.8% 0.07 [-0.02, 0.15]
Materazzi, 2013 1 141 1 127 5.3% -0.00 [-0.02, 0.02]
Miccoli, 2006 0 50 0 50 2.0% 0.00 [-0.04, 0.04]
Minni, 2016 1 174 2 187 7.2% -0.00 [-0.02, 0.01]
Mourad, 2011 0 34 1 34 1.4% -0.03 [-0.11, 0.05]
Papavramidis, 2010 0 45 0 45 1.8% 0.00 [-0.04, 0.04]
Pons, 2009 1 20 0 20 0.8% 0.05 [-0.08, 0.18]
Sartori, 2008 1 50 1 50 2.0% 0.00 [-0.05, 0.05]
Zanghi, 2014 2 41 1 42 1.7% 0.02 [-0.06, 0.11]
Total (95% CI) 2510 2492 100.0% 0.00 [-0.01, 0.01]
Total events 104 96
Heterogeneity: Chi² = 14.07, df = 23 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.51 (P = 0.61)
-0.1 -0.05 0 0.05 0.1
Favours Harmonic
Favours Conventional

A

Harmonic
Conventional
Risk Difference
Risk Difference
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Al-Dhahiry, 2015 0 26 3 26 1.4% -0.12 [-0.25, 0.02]
Arslan, 2017 2 101 1 105 5.6% 0.01 [-0.02, 0.04]
Blanchard, 2017 9 632 3 630 34.2% 0.01 [-0.00, 0.02]
Cannizzaro, 2014 0 141 0 124 7.1% 0.00 [-0.01, 0.01]
Di Renzo, 2010 0 31 0 31 1.7% 0.00 [-0.06, 0.06]
Ferri, 2011 0 50 0 50 2.7% 0.00 [-0.04, 0.04]
Frazzetta, 2005 0 60 0 60 3.2% 0.00 [-0.03, 0.03]
Hallgrimsson, 2008 0 27 0 24 1.4% 0.00 [-0.07, 0.07]
Lombardi, 2008 0 100 0 100 5.4% 0.00 [-0.02, 0.02]
Marchesi, 2003 1 72 0 70 3.8% 0.01 [-0.02, 0.05]
Materazzi, 2013 0 141 0 127 7.2% 0.00 [-0.01, 0.01]
Miccoli, 2006 0 50 0 50 2.7% 0.00 [-0.04, 0.04]
Miccoli, 2010 0 31 0 31 1.7% 0.00 [-0.06, 0.06]
Minni, 2016 0 174 0 187 9.8% 0.00 [-0.01, 0.01]
Mourad, 2011 0 34 0 34 1.8% 0.00 [-0.06, 0.06]
Papavramidis, 2010 0 45 0 45 2.4% 0.00 [-0.04, 0.04]
Sartori, 2008 0 50 0 50 2.7% 0.00 [-0.04, 0.04]
Yildirim, 2008 0 50 1 54 2.8% -0.02 [-0.07, 0.03]
Zanghi, 2014 0 41 0 42 2.2% 0.00 [-0.05, 0.05]
Total (95% CI) 1856 1840 100.0% 0.00 [-0.00, 0.01]
Total events 12 8
Heterogeneity: Chi² = 6.34, df = 18 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.68 (P = 0.50)
-0.05 -0.025 0 0.025 0.05
Favours Harmonic
Favours Conventional

B

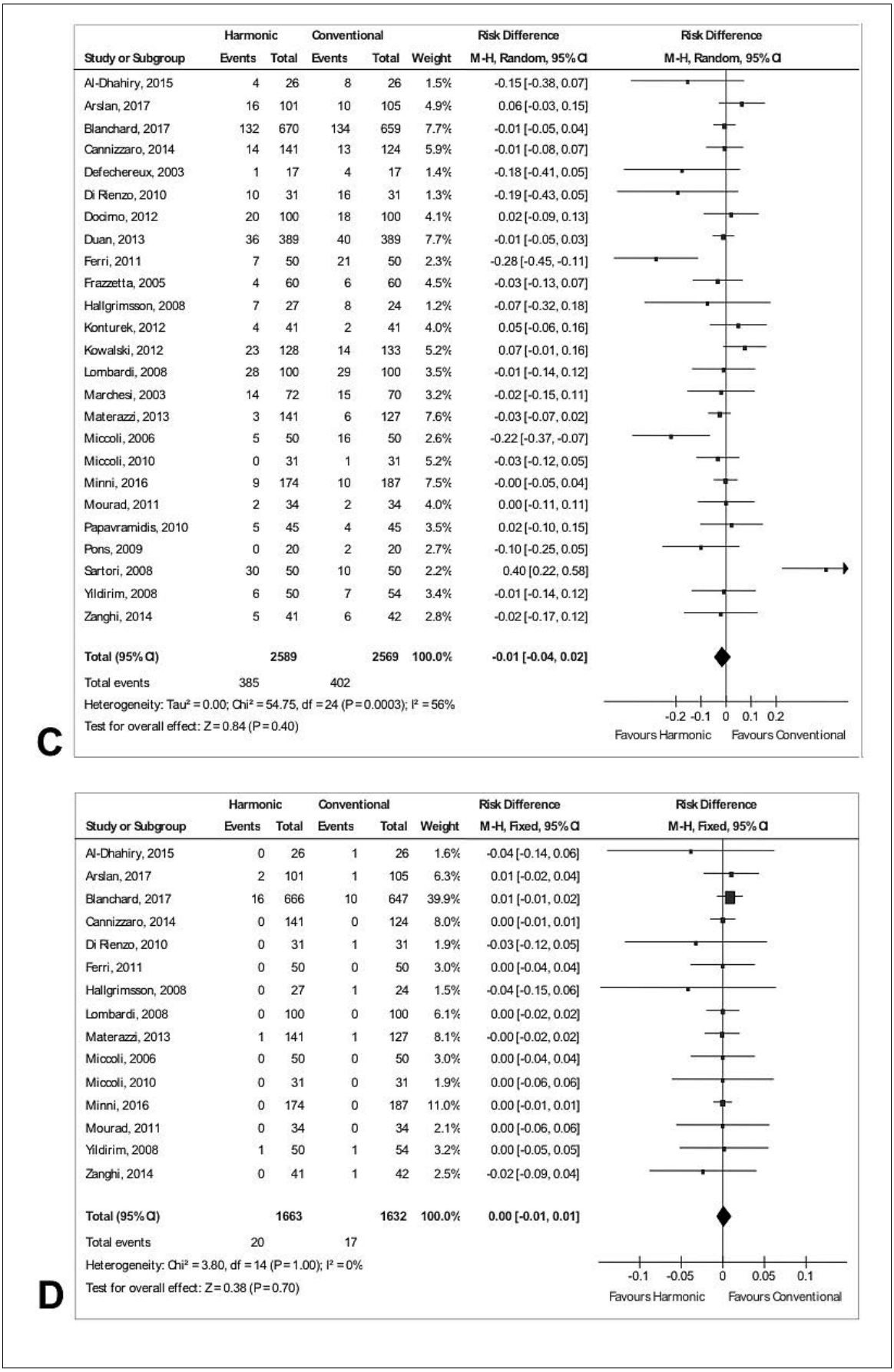


FIGURE 2. META-ANALYSIS ON POSTOPERATIVE COMPLICATIONS COMPARING THE HARMONIC SCALPEL WITH THE CONVENTIONAL TECHNIQUE. A) TEMPORARY DYSFUNCTION OF THE RLN; B) PERMANENT DYSFUNCTION OF THE RLN; C) TRANSIENT HYPOCALCAEMIA; D) PERMANENT HYPOCALCAEMIA.

Regarding permanent hypocalcaemia, there were no significant differences between groups (1.2% x 1.0%, 95% CI -0.01 to 0.01, p = 0.70 and I2 = 0%, Figure 2D).

COST ASSESSMENT

Nine primary studies assessed the costs of the treatments comparing the use of the harmonic scalpel to the conventional technique. Data is shown in Table 1. Two studies did not provide the values of standard deviations and were not analyzed[22,33]. Four studies showed a significant decrease in hospital costs,[15,17,20,34] in one study there was a significant increase in costs[43] and in two others[23,30] there was no difference between the groups.

Sensitivity analysis

A sensitivity analysis was performed for all outcomes related to the methodological risk of primary articles, excluding those at high risk. There was a significant difference in operation time (17.3 minutes, p <0.001) and intraoperative bleeding volume (-26.8 ml; p <0.001) in the group of patients submitted to surgery using a harmonic scalpel. There was no significant difference in the incidence of hematoma (p = 0.16), permanent and temporary paralysis (p = 0.66 and p = 0.10, respectively) and transient and permanent hypocalcaemia (p = 0.33 and p = 0.31).

DISCUSSION

Since the first thyroidectomy documented by Abu al-Qasim in 952, until the mid-19th century, with the experience of Theodor Billroth, surgery on the thyroid gland was considered virtually prohibitive[1,2]. It was only at the beginning of the 20th century, with the improvement of anaesthetic and aseptic techniques and a better knowledge of haemostatic techniques, that Emil Theodore Kocher obtained satisfactory results, making thyroidectomy a safe surgery, with mortality around 0.5%. Since then, the surgical technique has changed very little[1,2].

The success of thyroid surgery is primarily based on adequate haemostasis both to prevent bleeding, which can become fatal, and to keep the surgical site clean and facilitate dissection of tissues, especially vital structures such as the lower laryngeal nerve and parathyroid glands. Given this premise, the results of this review show that there is a statistically significant decrease in intraoperative bleeding volume (35 ml). However, this data was not correlated with the reduction of perioperative complications.

In attempting to make thyroidectomy an even safer and more efficient procedure, haemostatic devices were developed with the purpose of adequate haemostasis without the need for numerous ligatures, which theoretically could save time. One of the most studied is the harmonic scalpel, which consists of mechanical energy in the form of ultrasonic vibrations (up to 55,000 Htz) that seal the blood vessels by breaking the hydrogen and protein bonds of the tissues and vessels and creating endovascular clot[3,4]. One of the theoretical benefits of using the harmonic scalpel is that it acts under lower temperatures (50° C-100° C), resulting in decreased heat transfer by adjacent tissues and, consequently, less thermal trauma[3,4]. Moreover, it does not transmit any type of current to the patient[3,4].

One of the most frequent and feared complications during thyroidectomy is injury to the inferior laryngeal nerve, which occurs due to surgical trauma, either mechanical (manipulation, traction or section) or thermal trauma. Experimental studies in pigs with histological analysis have demonstrated that the use of the ultrasonic scalpel in the dissection of adjacent tissues (1 mm) to the inferior laryngeal nerve does not cause thermal nerve damage[44,45]. In another experimental pig model, it was concluded that there is thermal lesion of the inferior laryngeal nerve by lateral heat dissipation in dissections that are distant <1 mm from the nerve[46]. The dissipation of heat to adjacent tissues is directly related to the power and time used by the harmonic scalpel. Studies show that the use of the harmonic scaler for more than 5 seconds with 4/5 intensities or for more than 20 seconds with lower intensities can generate thermal trauma to the tissues[47,48]. In this review, no significant difference was observed in the incidence of both temporary and permanent inferior laryngeal nerve dysfunction, comparing surgeries with and without harmonic scalpel.

Voice quality is a poorly assessed outcome in clinical trials that examine the efficacy of various haemostatic devices. Two prospective randomized studies have demonstrated that there are no significant differences in voice quality (objective and subjective) of patients undergoing thyroidectomy with the aid of the harmonic scalpel compared to the conventional technique[41,49].

All new technology that is developed must present, in addition to proven efficacy through comparative

studies with proper methodology, also an economic analysis that assesses its implementation costs. For this, there are specific economic assessment tools and methodologies. Studies based on the concepts of cost-effectiveness, cost-benefit and cost-utility should be encouraged in order to obtain better information for decision-making on the incorporation or not of a new technology. In this review, the cost analysis was not considered a primary outcome and was not explored in detail, but there was a tendency to decrease costs in operations with the aid of the harmonic scalpel. This economy was mainly due to the shorter operating time observed in this group, which was directly related to lower operating room and human resources costs. A systematic review with meta-analysis on hospital costs, published in 2016, has shown that there is an absolute reduction of approximately US$ 229 in harmonic scalpel surgeries[50].

This systematic review updates the data available in the literature with published clinical trials up to the mid-2017. The clinical data found in this study are in line with the latest published reviews on the subject[51-54] and show that there is apparently no doubt about the actual efficacy and safety of the harmonic scalpel, questioning only the cost-effectiveness of the implementation of this technology in thyroid surgery.

CONCLUSION

In patients submitted to total thyroidectomy, the use of the harmonic scalpel is effective, reducing operation time and intraoperative bleeding volume when compared to the conventional technique. There is no difference in the incidence of postoperative complications with the aid of the technology.

PALAVRAS-CHAVE: *Tireoidectomia. Hemostasia cirúrgica/métodos. Procedimentos cirúrgicos ultrassônicos. Revisão.*

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