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Green areas, clean air and cardiovascular health in the city of São Paulo

Áreas verdes, ar puro e saúde cardiovascular na cidade de São Paulo

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This year of 2017 is the inaugural term for most mayors in Brazilian cities, including Mr. João Doria, in the largest city of Brazil, São Paulo. During the electoral period, debate on healthcare issues focused on access, either to medical care or to high-cost examinations. Mr. Doria prioritized access at primary healthcare units, so that people could undergo imaging examinations during the night with the claim of "no queues for examinations"! Mr. Doria's proposal was driven by marketers and not by a serious evaluation of health determinants.

Considering that cardiovascular diseases are the leading cause of death in São Paulo, and most frequently among people living in the poorest districts,[1,2] we have a question: How will Mr. Doria remedy the high and unequal burden of cardiovascular diseases? Will this be achieved through greater access to echocardiography, angiography, nuclear medicine etc.?

Absolutely not. This goal is more likely to be achieved through actions to improve and support cardiovascular health outside of the Health Department. Specifically, the mayor should look towards the Parks & Green Areas and Transportation Departments. We have enough evidence to advocate that increasing the green areas of the city and exchanging diesel-fueled buses for vehicles equipped with cleaner engines will have an impact on the burden of heart diseases and stroke that will benefit all the citizens of this city.

Our proposal is not presumptuous. Rather, it results from knowledge coming from contemporary research on cardiovascular epidemiology, including data from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).[3] The focus within cardiological preventive actions is shifting from only identifying lifestyle and genetic factors that predispose towards high incidence and lethality of cardiovascular diseases, to a more open view of the meaning of risk factors for a population, and not just for individuals.[4] Air pollution, noise and physical inactivity may be consequences of the geography of cities, with long distances from home to work that place strain on accessing education, shopping and leisure activities.[5]

Data from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

ELSA-Brasil is a cohort of 15,105 men and women living in six large cities of Brazil: São Paulo, Rio de Janeiro, Salvador, Belo Horizonte, Porto Alegre and Vitória.[3] It has investigated the association between the subjects' self-perception of the opportunities for physical activity in their neighborhoods (by applying the "walking environment" scales that were originally used in the Multi-Ethnic Study of Atherosclerosis) and their frequency of leisure-time physical activity (LTPA), through the International Physical Activity Questionnaire. The result was that perception that the neighborhood was more walkable was positively associated with engaging in LTPA and doing so for longer periods per week. Compared with subjects who saw their community as less walkable, those who perceived it as more walkable had a 70% greater chance of engaging in LTPA.[6] The favorable effects of LTPA were shown to be a 22% lower possibility of a coronary event for active women than for inactive women and 33% lower for active men than for inactive men, according to the 10-year Framingham Risk Score.[7]

Among the female participants of ELSA-Brasil, there was a higher frequency of hypertension among those who were physically active during their journey to work than among those who were inactive.[8] These associations were maintained after adjustment for LTPA and socioeconomic variables. One speculation to explain the high prevalence of hypertension among individuals who were active during their journey to work in ELSA-Brasil could be their greater exposure to air pollution from traffic, as described in China[9,10] and the United States.[11-13] This has also been described among urban roadway law enforcement officers in Brazil.[14]

In conclusion, location matters because it provides the walkability conditions for leisure-time physical activity, but walking to go to work might be deleterious in Brazilian cities, perhaps because this increases the exposure to air pollutants.

The reality of São Paulo, Brazil

Despite an overall decline in cardiovascular mortality rates in São Paulo, the downward trends have been slower in the poorest areas than in the wealthiest ones, thus widening the social gap regarding these diseases.[1,2] São Paulo is the tenth most populated city in the world, with 96 districts spread over a large area. Working-class people live in neighborhoods that are far from the work sites, and this implies a mean commuting time of longer than two hours per day. Most of them commute by bus, which accounts for 47% of the kilometers traveled, while private motor vehicles account for 29.5%, subway (metro) for 12.8%, walking or cycling for 7% and motorcycles for 4%.[15] Ninety-five percent of the buses have diesel engines that produce exhaust containing combustion-derived particulate matter < 2.5 mm ($PM_{2.5}$). Consequently, the air quality in São Paulo is considered unhealthy during all seasons, with reports of $PM_{2.5}$ concentrations reaching 750 mg/m^3 (30 times the daily threshold for hazardous levels).[16] Moreover, most of these districts have few or no parks for exercise or cultural activities. Particulate material is associated with incidence of heart diseases and mortality due to these diseases.[17] $PM_{2.5}$ leads to increased oxidative stress associated with endothelial dysfunction and, consequently, dysregulation of the autonomic nervous system, which is a putative pathway for high blood pressure.[18]

A proposal for the Mayor and the City Council of São Paulo to reduce cardiovascular deaths

According to data from ELSA-Brasil and several other studies, two important measures can be proposed to the municipality to improve cardiovascular health. Firstly, creation and expansion of the number of green areas in the less affluent areas. This action may be effective for improving cardiovascular health, as demonstrated through the Nurses' Health Study results, which showed that higher levels of green vegetation were associated with decreased cardiovascular mortality.[19]

Secondly, since cardiovascular events and deaths have been strongly correlated with $PM_{2.5}$, and buses are the largest source of these pollutants, we are giving our support to the new bill of law that is currently under discussion in the City Council to progressively restrict the number of buses fueled by diesel until they have been totally replaced by cleaner vehicles.

Please, Mr. Doria, give up your marketing-driven policies and adopt science-driven actions to reduce the burden of cardiovascular diseases.

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Association between asthma and female sex hormones

Associação entre asma e hormônios sexuais femininos

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PALAVRAS-CHAVE:
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Mulheres.
Anticoncepcionais orais.
Citocinas.

ABSTRACT

CONTEXT AND OBJECTIVE: The relationship between sex hormones and asthma has been evaluated in several studies. The aim of this review article was to investigate the association between asthma and female sex hormones, under different conditions (premenstrual asthma, use of oral contraceptives, menopause, hormone replacement therapy and pregnancy).

DESIGN AND SETTING: Narrative review of the medical literature, Universidade Federal do Tocantins (UFT) and Universidade Federal de São Paulo (Unifesp).

METHODS: We searched the CAPES journal portal, a Brazilian platform that provides access to articles in the MEDLINE, PubMed, SciELO, and LILACS databases. The following keywords were used based on Medical Subject Headings: asthma, sex hormones, women and use of oral contraceptives.

RESULTS: The associations between sex hormones and asthma remain obscure. In adults, asthma is more common in women than in men. In addition, mortality due to asthma is significantly higher among females. The immune system is influenced by sex hormones: either because progesterone stimulates progesterone-induced blocking factor and Th2 cytokines or because contraceptives derived from progesterone and estrogen stimulate the transcription factor GATA-3.

CONCLUSIONS: The associations between asthma and female sex hormones remain obscure. We speculate that estrogen fluctuations are responsible for asthma exacerbations that occur in women. Because of the anti-inflammatory action of estrogen, it decreases TNF-α production, interferon-γ expression and NK cell activity. We suggest that further studies that highlight the underlying physiopathological mechanisms contributing towards these interactions should be conducted.

RESUMO

CONTEXTO E OBJETIVO: A relação entre os hormônios sexuais e a asma tem sido investigada em diversos estudos. Esta revisão tem como objetivo descrever a relação entre hormônios sexuais (endógenos e exógenos) e a inflamação nas vias aéreas, especialmente na asma, em eventos diferentes (na asma pré-menstrual, durante o uso de anticoncepcionais, na menopausa, no uso de terapia hormonal e na gestação).

TIPO DE ESTUDO E LOCAL: Revisão narrativa da literatura médica, Universidade Federal do Tocantins (UFT) e Universidade Federal de São Paulo (Unifesp).

MÉTODO: Pesquisamos o Portal de Periódicos Capes, uma plataforma brasileira que fornece acesso a artigos nas bases de dados MEDLINE, PubMed, SciELO e LILACS. Os descritores utilizados foram asma, hormônios sexuais, mulheres e uso de anticoncepcionais, com base no "Medical Subject Headings".

RESULTADOS: As associações entre hormônios sexuais e asma ainda permanecem obscuras. Em adultos, a asma é mais frequente em mulheres do que em homens. Além disso, a mortalidade por asma é significativamente maior no sexo feminino, destacando-se que o sistema imunológico sofre influência de hormônios sexuais, seja porque a progesterona estimula o fator bloqueador induzido pela progesterona e citocinas Th2 ou porque contraceptivos derivados de progesterona e estrógeno estimulam o fator de transcrição GATA-3.

CONCLUSÕES: A associação entre asma e hormônios sexuais femininos permanece obscura. Nós especulamos que as flutuações do estrogênio são responsáveis pelas exacerbações da asma que ocorrem nas mulheres. Devido à ação anti-inflamatória do estrogênio há redução da produção de TNF-α, da expressão do interferon-γ e da atividade das células NK. Sugerimos que sejam realizados novos estudos para esclarecer os mecanismos fisiopatológicos dessas interações.

INTRODUCTION

Asthma is a heterogeneous process that displays considerable phenotypic variability and affects 300 million people globally.[1,2] It is characterized by the presence of inflammation, hyperresponsiveness and reversible airway obstruction. It is considered to be a public health problem that affects 21% of the Brazilian population.[3,4] In Brazil, the mortality rate due to asthma among women is 0.241 per 100,000 inhabitants, whereas among men, it is 0.193 per 100,000 inhabitants.[5] Among adults, epidemiological studies have demonstrated that the prevalence of asthma is higher among females than among males.[6-8]

The relationship between sex hormones and asthma has been evaluated in several studies.[9,10] Sex-related differences in the risk, incidence and pathogenesis of a variety of lung diseases exist in humans.[11] Among children, the prevalence is higher in boys than in girls.[12] Interestingly, after puberty, the frequency and severity of asthma increase among girls, such that it becomes more common among women by the age of 20 years.[13,14] After the menopause, the difference in asthma prevalence between men and women decreases.[14] Thus, in the United States, 65% of all deaths due to asthma occur among women.[11]

The current paradigm for the pathogenesis of asthma is directly related to gene-environment interaction. Production of Th2 cells (T helper 2) involves the 5q32 region, which is located on the long arm of chromosome 5, in a cluster of genes encoding IL-4 (interleukin 4), IL-5 (interleukin 5), IL-13 (interleukin 13) and IgE (immunoglobulin E) levels.[15] The transcription factors that relate to increased Th2 cytokine levels include STAT-5 (signal transducer and activator transducing-5) and GATA-3 (a transcription factor that promotes differentiation of Th2 cells from naïve T lymphocytes). GATA-3 stimulates growth of Th2 cells and inhibits differentiation to Th1 (T helper 1).[16,17] T lymphocytes are important effector cells in relation to asthma, and activation of Th2 cells is considered to be important, especially in cases of asthma relating to atopy. However, immune responses to Th1 lymphocyte activation may be responsible for epithelial changes and activation of airway smooth muscle. In addition, as the disease becomes chronic, it may cause activation of Th1 lymphocytes with increased TNF-α expression (tumor necrosis factor) and IFN-γ (interferon gamma). In non-atopic asthma, a neutrophil inflammatory process may occur.[18]

Tregs (regulatory T cells) reduce proliferation and decrease Th2 levels and hence the inflammatory process in asthma cases.[19] Tregs are essential for induction and maintenance of tolerance against antigens.[20] In asthmatic patients, Tregs become reduced in number and function.[20] Recently, other T helper cells were discovered (Th9 and Th17), and these cells are related to the physiopathological process and worsening asthma.[21] The role of IL-17 in asthma is often investigated in patients with non-IgE-mediated non-atopic asthma with a predominance of neutrophils, because Th17 cell levels correlate with disease severity.[22]

Sex hormones play an important role in respiratory health, and hormone fluctuations may be responsible for exacerbations of asthma in women. Hormone fluctuations occur cyclically in reproductive-age women. For four days after menstruation, follicle-stimulating hormone (FSH), luteinizing hormne (LH) and 17-β-estradiol levels are low. During the follicular phase of the menstrual cycle (days 12-16), progesterone levels remain low, while FSH, LH and 17-β-estradiol levels reach a peak. Finally, during the luteal phase (days 24-28 of the cycle), FSH and LH levels are low, whereas progesterone and 17-β-estradiol levels are moderately high.[23] If pregnancy occurs, luteolysis is prevented and the progesterone and 17-β-estradiol levels remain high. After many years, as follicles are depleted and women reaches menopausal status, their sex hormone concentrations decrease to very low levels. In women using oral contraceptives, the progestin component suppresses secretion of LH, and the estrogenic component suppresses secretion of FSH, thus preventing ovulation.[12]

Asthmatic women need to be monitored for hormonal changes.[24] In a study conducted by Scichilone that included eight healthy women, the progesterone levels during the menstrual cycle influenced the concentration of nitric oxide in exhaled air (FeNO) and alveolar exhaled nitric oxide (CANO).[25] There is evidence suggesting that both endogenous and exogenous sex steroids modulate inflammatory processes in the lungs and in smooth muscle tissue during different phases of the hormonal cycle in women.[26,27]

A relationship between sex hormones and inflammatory responses in the lower airways, especially with regard to asthma, has been observed in several studies.[9-14] However, the mechanism for this interaction remains obscure. Thus, it is very important to review the main findings regarding interactions between sex hormones and to understand the pathophysiological mechanisms of this association.

OBJECTIVE

To investigate the association between asthma and female sex hormones, at different conditions (premenstrual asthma, use of oral contraceptives, menopause, hormone replacement therapy and pregnancy).

METHODS

For this narrative review, we searched for articles that addressed association between female sex hormones and asthma regardless of clinical situation, which could encompasse premenstrual period, pregnancy, post-menopause period, use of hormone replacement therapy or oral contraceptives. To do this, we searched the journals in the portal of the Coordination Office for Improvement of High-Education Personnel (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, CAPES). This is a Brazilian platform that provides access to bibliographic sources

from various locations around the world, including the following: MEDLINE, PubMed, SciELO, and LILACS. The following keywords were used (based on Medical Subject Headings: https://www.nlm.nih.gov/mesh/): asthma and sex hormones (for the initial search); and women and oral contraceptives (included to refine the analysis). The inclusion criteria were the following: complete articles, published over the last 20 years and written in English or French. The exclusion criteria were the following: items for which the full content was not available, letters to the editor, editorials and articles published in non-scientific journals.

The search was performed in four steps:

1. Keywords search.
2. Preliminary search to include and exclude articles by using their abstracts.
3. Complete articles were read and additional exclusions were made.
4. Synthesis.

RESULTS

Results from search

In the initial search, we identified 447 references. However, through the preliminary analysis, only 68 references were selected. Only 16 were original articles. The process of study selection is presented in a flow diagram (**Figure 1**).

Results from studies included

Menstrual cycle and asthma

There is little data about airway physiology and hormonal fluctuations.[28] Exacerbation of asthma in the form of premenstrual asthma (PMA) affects 30% to 40% of women with asthma.[29,30] PMA was described for the first time by Frank in 1931, who reported on a woman who experienced severe attacks of asthma that occurred before her menstrual period.[31] Some studies have reported a decrease in pulmonary function during the premenstrual portion of the cycle, with a decreased peak expiratory flow rate.[24] There is also evidence for increased airway inflammation in patients with PMA, as demonstrated by increased levels of eosinophils in sputum and increased levels of fractionated exhaled nitric oxide.[32]

Tan et al. reported on abnormal regulation of beta2-adrenoreceptors, which was proposed as a possible mechanism for PMA during the period of the cycle when progesterone levels are high.[33] The peak incidence of PMA complaints is two to three days before the onset of menstruation, but this phenomenon can also occur during both the menstrual and premenstrual intervals.[31] In a prospective study on 182 female patients with asthma, 46% of all admissions to emergency departments due to acute asthma occurred during the perimenstrual period.[29,34] Murphy reported that use of

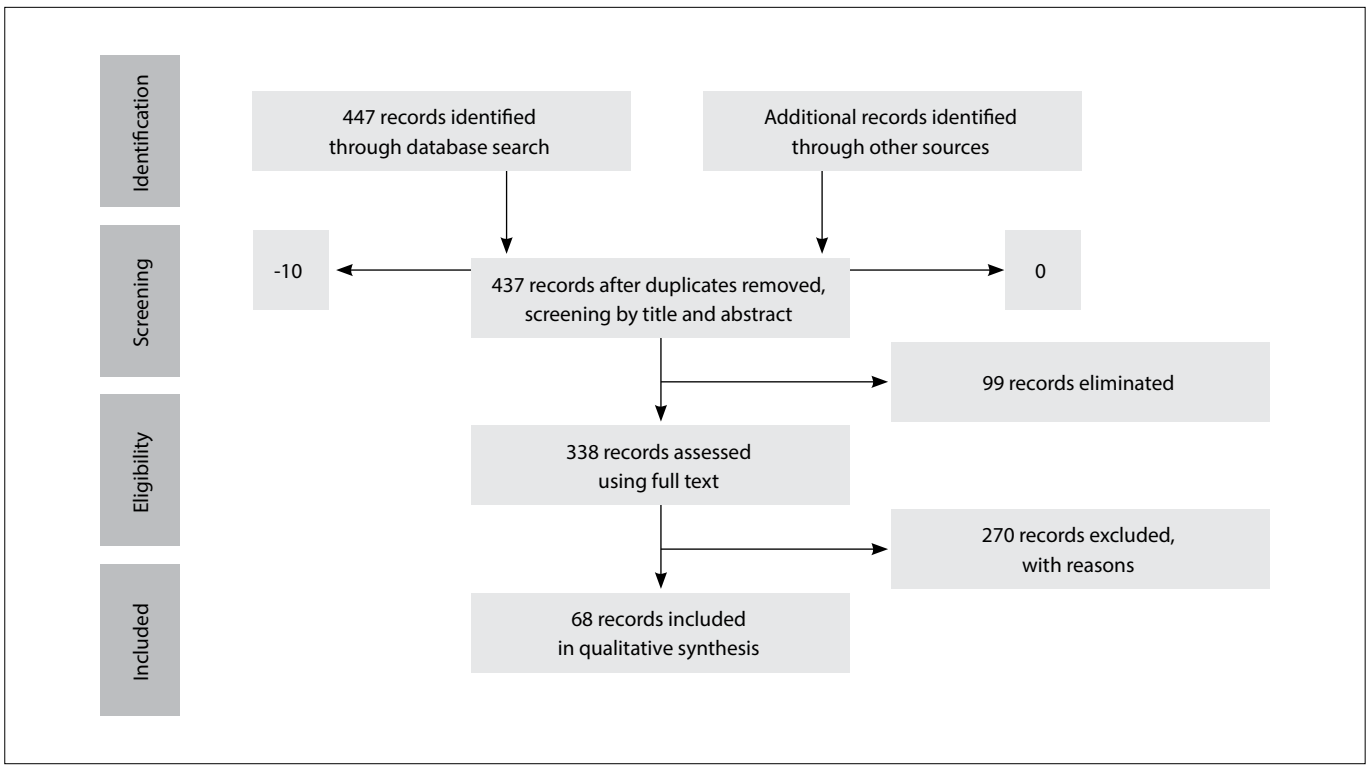

Figure 1. Flow diagram showing study selection for review of studies on association between asthma and female sex hormones.

oral contraceptives was not protective, and further investigation was required to determine the mechanisms involved in PMA.[35]

A few studies have described treatments for PMA, with conflicting results. Several small series have described use of leukotriene receptor antagonists, exogenous intramuscular progesterone, xanthines,[14,24] increased doses of inhaled corticosteroids, addition of long-acting beta2 agonists during the second half of the menstrual cycle, oral contraceptives, a single dose of estradiol (2 mg) during the luteal phase and gonadotropin-releasing-hormone (GnRH) analogues.[29] However, more studies are needed in order to determine the appropriate treatment for PMA.

Use of hormone contraceptives and asthma

Contraceptives have frequently been used over the last 50 years for indications including hirsutism, irregular menstruation, dysmenorrhea, polycystic ovarian disease and contraception. Recently, clinical evidence has suggested that use of contraceptives is associated with impaired lung function.[7,36] Some studies have suggested that use of contraceptives is a risk factor for development or exacerbation of asthma crises.[7,36] The association between asthma and use of combined contraceptives (estrogen and progesterone) is unclear. The findings in the literature are divergent, given that some studies have reported that estrogen and progesterone improve total lung capacity and reduce the exacerbation of asthma symptoms, such as coughing, wheezing and dyspnea.[37-40] In a study by Carlson et al., use of oral contraceptives (combined contraceptives) and unopposed forms of estrogens reduced hormone fluctuations and decreased premenstrual asthma.[41] In a study by Lange, no relationship was found between use of oral contraceptives and asthma.[42]

Erkoçoğlu et al.[45] found in a survey on 487 women by means of a questionnaire that 196 (40.2%) reported using oral contraceptives. This use was associated with higher risk of current wheezing among adolescents and young adults, but only among those who had taken the oral contraceptives recently during the previous year. In a study by Macsali et al.,[7] women taking oral contraceptives had more asthma and allergies, but this association was not present in lean women, and there was an additional association with body mass index (BMI).

The association between asthma, obesity and sex hormones has been discussed in the medical literature. Obesity has been correlated with higher estrogen levels and with the enzyme aromatase, which in adipose tissue can convert androgens into estrogens.[43,44] The Tucson Children's Respiratory Study showed a significant positive association between obesity and wheezing among women who reached puberty when they were under 11 years of age, while obesity was not associated with wheezing among women in whom puberty occurred after they were 11 years old. In the study by Erkoçoğlu et al., there was no evidence of a relationship between BMI and current wheezing.[45] In a study by Nwaru and Sheikh, hormonal contraceptives reduced exacerbation of asthma and the number of episodes requiring care. That study also showed that overweight and obese women who do not use contraceptives may be at higher risk of asthma.[38] In a study by Dratva et al., oral contraceptives also appeared to have a protective effect, through decreasing bronchial hyperreactivity.[39]

The cohort study by Jenkins et al. was the first to report an association between parity, use of oral contraceptives and the onset of asthma among women. In this study, women without asthma or wheezing by the age of seven years showed a lower risk of developing asthma, and the risk decreased by 7% per year of oral contraceptive pill use, independent of parity history. In this group (women without previous asthma or wheezing), the risk of current asthma increased for each birth (odds ratio, OR: 1.50; CI: 1.03-2.23; P = 0.04). Moreover, in the same group, the risk of current asthma was greater among women who were parous, according to the number of births. Women with one birth were at lower risk than nulliparous women. Among women who did have asthma or wheezy breathing by the age of seven years, neither reproductive history nor oral contraceptive pill use predicted current asthma.[46]

Some authors have suggested mechanisms to explain the complex interaction between hormonal contraceptives and asthma. Velez-Ortega reported on the impact of oral contraceptives on generation of induced regulatory T cells (iTregs).[37] Dysregulation of iTregs plays a major role in the pathophysiology of asthma. In this study, patients taking oral contraceptives showed reduced serum sex hormone levels, and this was associated with higher rates of iTreg induction, better asthma control test scores and a tendency towards lower exhaled nitric oxide (eNO) levels.[37] On the other hand, Guthikonda et al.[47] reported that oral contraceptives and early menarche (via exogenous or endogenous hormones) were associated with the DNA methylation level of the Th2 transcription factor gene and GATA-3 and that they increased the risk of asthma among girls, possibly through interaction with genetic variants. This factor may explain how endogenous and exogenous hormones can, in women, increase the prevalence of asthma after puberty.[47]

Another mechanism was reported by Tan et al., who proposed that exogenous progesterone but not estradiol induces paradoxical downregulation and desensitization of β_2-adrenoceptors in asthmatic women, compared with non-asthmatic subjects.[48,49] Moreover, in another study on eleven women with stable mild to moderate asthma, Tan et al. reported that oral contraceptives did not alter β_2-adrenoceptor regulation and function in stable female asthmatic patients.[33]

Finally, Salam et al.[26] linked oral contraceptive use and asthma, both of which are common in young women. The

outcomes from their study demonstrated that among women without asthma, oral contraceptive use was associated with higher risk of current wheezing. In contrast, in the same study, oral contraceptive use was associated with reduced prevalence of current wheezing among women with asthma. This paradox between hormonal contraceptives and immunologically unclear characteristics of sex hormones emphasizes the need for further research and the importance of knowing a patient's medical history, including the gynecological and hormonal characteristics of asthmatic women.[26]

In **Table 1**, we have summarized the differences between the results from different studies on asthma and hormone contraceptives. In **Table 2**, we have reported the main outcomes from animal model studies on sex hormones and asthma.

Postmenopausal hormone replacement therapy (HRT) and asthma

Among women over 50 years of age, the menopause can either coincide with the onset of asthma or be associated with deterioration of a pre-existing asthma condition.[50] The definition of menopause is the cessation of menstruation for 12 months.[51] The overall incidence of asthma decreases after the menopause,[14] although in the Nurses' Health Study, use of hormone replacement therapy (HRT) approximately doubled the risk of asthma, compared with postmenopausal women without HRT. In that study, a 35% decrease in the incidence of asthma was observed among postmenopausal women without HRT.[10] In a cohort study, Romieu et al. reported that the increase in the risk of asthma onset at the

Table 1. Animal models for sex hormones and airway inflammation

Authors	Method	Results and conclusions
Hellings et al.[63]	BALB/c male mice of 6 weeks of age were sensitized to ovalbumin (Ova) using intraperitoneal injections. Medroxyprogesterone or placebo was instilled daily into the esophagus before and during the inhalatory Ova challenge phase.	Progesterone worsened allergic airway inflammation in Ova-challenged mice. Progesterone increased IL-5 levels and elevated airway eosinophilia. Progesterone did not influence allergen-specific IgE production. Progesterone aggravates the phenotype of eosinophilic airway inflammation in mice by enhancing systemic IL-5 production.
Degano et al.[64]	Ovariectomized seven-week-old female Wistar rats received either placebo or 17β-estradiol (E2) (10 to 100 mcg/kg/day) for 21 days. They were administered an aerosol of saline and increasing concentrations of acetylcholine (Ach) until lung resistance was observed.	Rats treated with low-dose E2 were less responsive to Ach than rats given either placebo or high-dose E2 were. Treatment with E2 had a differential, dose-dependent effect on airway responsiveness to Ach.
de Oliveira et al.[65]	The authors evaluated the roles of estradiol and progesterone in allergic lung inflammation. Female Wistar rats were ovariectomized (Ovx) and then sensitized with ovalbumin (OA). They received estradiol and progesterone.	In Ovx-allergic rats, treatment with estradiol decreased the amount of IL-10 and increased the amount of IL-4 produced by bone marrow (BM) cells. Estradiol increased IL1β and TNFα levels in BAL (bronchoalveolar lavage) cells. Progesterone increased the release of IL-10, IL-1β and TNFα by BAL cells and increased the production of IL-4 by BM cells. The existence of such dual hormonal effects suggests that hormone therapy in asthmatic postmenopausal women and women who suffer from premenstrual asthma should take into account the possibility that these treatments may worsen pulmonary conditions.
Mitchell et al.[66]	Adult female BALB/c mice were ovariectomized and implanted with time-release progesterone pallets. They were housed in filtered air or ETS (environmental tobacco smoke) for 6 weeks and exposed to HDMA (house dust mite allergen) by inhalation.	Progesterone alone did not increase mucous cell mass or abundance of eosinophils, but ETS coupled with progesterone exposure resulted in a significant increase in mucous cell metaplasia and increased accumulation of eosinophils in the asthma model. Progesterone, in the absence of estrogen, exacerbated the airway inflammation and airway remodeling that was induced by the toxicant ETS.
Matsubara et al.[67]	The authors compared sex differences in the development of airway hyperresponsiveness (AHR) following allergen exposure exclusively via the airways. Ovalbumin was administered via nebulization on 10 consecutive days in 8 to 10-week male and female BALB/c mice. After methacholine challenge, significant AHR developed in male mice but not in female mice. Ovariectomized female mice showed significant AHR after 10 days of Ova inhalation. ICI182,780, an estrogen antagonist, similarly enhanced airway responsiveness even when administered 1 hour before the assay.	The results showed that 17 beta-estradiol dose-dependently suppressed AHR in male mice. In all cases, airway responsiveness was inhibited by administration of a neurokinin 1 receptor antagonist. The neurokinin 1 receptor antagonist attenuated the effect that the estrogen receptor antagonist had in enhancing AHR in female mice *in vivo*. Endogenous estrogen may regulate the neurokinin 1–dependent prejunctional activation of airway smooth muscles in allergen-exposed mice.

Table 2. Hormone contraceptives and asthma

Authors and type of study	Method	Results and conclusions
Macsali et al.[7] Cross-sectional survey	Postal questionnaires were sent to subjects in Denmark, Estonia, Iceland, Norway and Sweden from 1999 to 2001 (response rate in women, 77%). The analyses included 5791 women who were 25 to 44 years old, of whom 961 (17%) used oral contraceptives.	Oral contraceptive pills were associated with an increased risk of asthma, asthma with hay fever, wheezing and shortness of breath, hay fever and ≥ 3 asthma symptoms. Associations were present. Women using oral contraceptive pills had more asthma. This was found only in the normal weight and overweight women and not in lean women, thus indicating an interplay between sex hormones and metabolic status in their effects on airways.
Guthikonda et al.[47] Cohort	Blood samples were collected from 245 female participants aged 18 years old.	Subjects with genotype AG showed an increase in the average risk ratio (RR) from 0.31 (95% CI: 0.10 to 0.8) to 11.65 (95% CI: 1.71 to 79.5) when the methylation level increased from 0.02 to 0.12 relative to the risk in genotype AA. A two-stage model that takes into account genetic variants of the GATA-3 gene, oral contraceptive use, age at menarche and DNA-methylation may explain how sex hormones can increase the prevalence of asthma after puberty.
Erkoçoğlu et al.[45] Cross-sectional	The ISAAC questionnaire was provided to 487 women between 11.3 and 25.6 years of age. Questions on oral contraceptives were also asked.	In this study, n = 487 (ages ranged from 11.3 to 25.6 years old), 196 (40%) reported using an oral contraceptive, 7.4% had a diagnosis of asthma from a physician and 10.3% of them were active smokers. Young women taking oral contraceptives had a higher rate of current wheezing, thus suggesting that sex steroids may be important for respiratory health.
Dratva et al.[39] SPALDIA 2 Cohort	571 women aged 28 to 58 years who had menstrual periods without hormone treatment were subjected to methacholine challenge. In a second step, 130 women taking oral contraceptives were subjected to methacholine challenge.	An effect of modification according to asthma status and oral contraceptive use was found, with a lower odds ratio (OR) among subjects without asthma. An OR < 1 was found among woman taking oral contraceptives. Oral contraceptives appeared to have a protective effect through which they decreased bronchial hyperreactivity.
Vélez-Ortega et al.[37] Cohort	Thirteen patients were included in this pilot study. During three distinct phases of their menstrual cycles, the authors measured exhaled nitric oxide (eNO) levels, forced expiratory volume at 1 second (FEV_1), asthma control test (ACT) scores, sex steroid hormone levels in serum, natural Tregs levels in peripheral blood, and the ability of $CD4^+$ T cells to generate iTregs *ex vivo*.	Patients taking oral contraceptives showed reduced serum sex hormone levels in association with higher levels of iTreg induction, better ACT scores and a tendency to have lower eNO levels. The impact of sex hormones on the capacity of T cells to polarize towards a regulatory phenotype suggests that regulation of peripheral T cell lineage plasticity is a potential mechanism that may underlie the beneficial effects of oral contraceptives among women with asthma.
Tan et al.[33] Cohort with intragroup analysis	The study population comprised 11 women aged 19 to 40 years with stable and moderate asthma. The patients were evaluated while on (day 20 to 21) and off (day 5 to 7) oral contraceptives during a 28-day calendar period.	Baseline FEV_1 did not differ between patients who were on and off oral contraceptives. These did not alter beta2-adrenoreceptor regulation or function in stable female asthmatic patients.
Tan et al.[48] Trial	Seven nonsmoking females aged 26 years with mild asthma completed the study. They were evaluated through two successive menstrual cycles during the follicular phase (days 1 to 6). They were randomized to receive single oral doses of either ethinyl estradiol or medroxyprogesterone.	The results showed that exogenous progesterone, but not estrogen, when given during the follicular phase, decreased beta2- adrenoreceptor density and cyclic-adenosine monophosphate (AMP) responses in female asthmatics. The beta2-adrenoreceptor was abnormally regulated in female asthmatics, and this might be a potential mechanism through which premenstrual asthma could be triggered when progesterone levels are high.
Salam et al.[26] Cohort	905 women who had undergone menarche were included. The subjects ranged in age from 13 to 28 years and had participated in the Children's Health Study.	In women without asthma, oral contraceptive use was associated with higher risk of current wheezing. In contrast, oral contraceptive use was associated with reduced prevalence of current wheezing in women with asthma. These associations showed significant trends with duration of oral contraceptive use. Age at menarche was associated with new-onset asthma after puberty. Compared with women who had their menarche after they were 12 years old, women who reached their menarche before they were 12 years old were at higher risk of asthma after puberty. Because women have a higher risk of asthma after puberty, and because oral contraceptive use is common among young women, clinicians should inform women with asthma about the potential effects of oral contraceptives on asthma-related respiratory symptoms.

Continues...

Table 2. Continues...

Authors and type of study	Method	Results and conclusions
Jenkins et al.[46] Cohort	681 women aged 29-32 years were randomly sampled from participants who were first surveyed at the age of 7 years in the 1968 Tasmanian Asthma Survey, which was a study of all children born in 1961 who attended school. Current asthma was defined as reporting asthma or wheezy breathing during the past 12 months.	The risk of current asthma in individuals who were parous increased with the number of births, while women with one birth were at lower risk than nulliparous women. Independent of parity, the risk decreased by 7% per year of oral contraceptive pill use. In women who had asthma or wheezy breathing by the age of 7 years old, neither reproductive history nor oral contraceptive pill use predicted current asthma. Parity and decreased oral contraceptive use predicted asthma in women, and these results are consistent with the hypothesis that the asthma that develops after childhood is in part a response to endogenous and exogenous female hormones.
Nwaru and Sheikh[38] Cross-sectional survey	A population-based analysis using serial data from the Scottish general population. A total of 3257 non- pregnant, 16-45-year-old women were included.	The use of any hormonal contraceptive was associated with a reduced risk of current physician-diagnosed asthma. The use of a hormonal contraceptive may reduce asthma exacerbations. Overweight and obese non-contraceptive-using women may be at increasing risk of asthma.
Lange et al.[42] Cross-sectional	Data from a study on women who were selected from the general population were used to correlate the effect of treatment with oral contraceptives and hormonal replacement therapy (HRT) with asthma indications. 377 women were on oral contraceptives (24.5% of the premenopausal women) and 458 were on HRT (15.2% of the postmenopausal women). The age span of the premenopausal women was 21-49 years and of the postmenopausal women, 27-90 years.	A weak association was observed between HRT and self-reported asthma. No relationship was found between the use of oral contraceptives and asthma, although an association was observed between asthma and HRT.

time of the menopause was only significant among women who reported using estrogen alone, especially among those who had never been smokers and those who had had an allergic disease before the onset of asthma. A small increase in the risk of asthma among women who used estrogen/progestogen was found in these subgroups.[52] In a systematic review and meta-analysis, Zemp et al. found that there was no significant association between menopause with asthma prevalence or incidence except for women who reported using HRT.[53]

In a study by Carlson et al., HRT was associated with better lung function and an increase in forced expiratory volume at one second (FEV_1).[41] The mechanisms that link asthma and the menopause are unclear. After the menopause, FSH and LH levels are elevated, and estrogen levels decrease to the levels observed in patients with surgical oophorectomy, who also show extremely low progesterone levels. The incidence of asthma may be associated with decreased estrogen levels and a protective effect against the relative androgen excess that occurs during the menopausal transition.[53,54] Clinical studies have indicated that the menopause is associated with exacerbation of pre-existing asthma. Thus, the onset of asthma is characterized by absence of atopy, absence of a family history and associations with urticaria and/or recurrent sinusitis of high severity.[23] Balzano et al.[55] showed that eosinophil levels were higher in the induced sputum of menopausal asthmatics, but Foschino Barbaro et al. reported that there were high sputum levels of neutrophils and exhaled interleukin (IL)-6 in women with menopausal asthma.[50]

Few studies have explored the link between the menopause and asthma. Hormonal processes and other factors, including genetics and inflammatory and metabolic characteristics, need to be taken into consideration. Studies have indicated that obesity has an effect on the severity of asthma and that this relationship is modified by gender. Estrogen and leptin levels (which have been correlated with increased airway inflammation in animal models)[56] are higher in obese women than in non-obese women.[54] Moreover, obesity has been shown to increase the risk of developing asthma. Interestingly, Gómez Real reported that lean women presented a higher risk of postmenopausal asthma than did obese women using HRT.[57] This phenomenon can be explained by the notion that in lean women without insulin resistance, the pro-inflammatory effect of estrogens may predominate; while in obese women, the pro-inflammatory effects of estrogens are decreased through insulin resistance.[53]

Pregnancy and asthma

Asthma affects 3.7% to 8.4% of all pregnant women in the United States. Maternal asthma is associated with an increased risk of both

maternal and fetal adverse perinatal outcomes,[58] such that 20%-30% of women with asthma experience exacerbations that require medical intervention during pregnancy.[43] There is also evidence of an increased risk of maternal mortality among some asthmatic women.[59]

A number of the physiological changes that occur during pregnancy can affect asthma status, including mechanical, immunological and hormonal alterations. Estradiol and progesterone levels are highest during pregnancy.[60] Moreover, one third of women experience improved asthma, while another third of women retain the same asthma status and the remaining third experience worse asthma. Pregnancy is also marked by a state of Th2 dominance, and asthma is generally characterized by Th2 inflammation. Progesterone receptors are present in large quantities on the surface of lymphocytes, and binding of progesterone to its receptor induces stimulation and release of progesterone-induced blocking factor (PIBF) in a Th2 cytokine expression pattern (IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13). The effects of these proteins are reduced in natural killer (NK) cells, in which expression of IFN-γ is decreased. NK cells are mainly observed in the endometrium of pregnant women.[12,61] During the first trimester of pregnancy, the numbers of circulating and decidual regulatory T cells (Tregs) increase to promote tolerance at the maternal-fetal interface.[62]

Interestingly, fetal sex may influence asthma. Kwon et al. examined pregnant asthmatic women and found that carrying a female fetus was associated with worse maternal asthma than carrying a male fetus was.[60] The mechanism that contributes towards this result is unclear, but there is evidence showing that testosterone potentiates the β-adrenergic-mediated relaxation of bronchial tissues and inhibits responses to histamine. Female sex is associated with higher maternal circulation of monocytes and upregulation of maternal inflammatory pathways.[58]

The mechanisms through which sex hormones influence asthma and the immunological characteristics of pregnancy at the maternal-fetal interface remain obscure, and new studies are needed in order to increase our understanding of and ability to manage asthmatic women.

DISCUSSION

Studies examining the role of hormonal factors in asthma among women have been conducted on human subjects and animal models, and the results have been described in reviews. In an attempt to understand the influence of sex hormones on pulmonary inflammatory responses, we discuss the main immunological aspects of sex hormones here.

Studies using animal models have demonstrated that both progesterone and estrogen can directly affect the lungs.[63-67] Sex steroid hormones influence the immune system by acting on the structure and function of the thymus, thereby modulating the activity of B and T cells, mast cells and natural killer cells (NK cells), and affecting phagocytic cells and cytokine production. These hormones act via a variety of receptors (including the estrogen receptors ERα and ERβ; and the progesterone receptors PR-A and PR-B), and these steroid receptors have been described as nuclear receptors that act as transcription factors to regulate gene expression.[23] However, it has been shown that some steroid receptors are located at the plasma membrane (e.g. membrane-bound G-protein-coupled receptors).[68,69] These receptors are also expressed in the human lungs, such that sex hormones play a role in development of the lungs and androgen receptors are expressed in the mesenchymal and epithelial cells of the lungs.

Gender differences have been observed in relation to development of the lungs. For example, production of surfactants appears earlier in female than in male neonatal lungs, and male preterm infants are at higher risk of experiencing developmental distress syndrome. In addition, before puberty, the prevalence of asthma is higher among boys.[43] Both male and female fetuses express androgen receptors (AR-A, AR-B) in non-reproductive tissues, with significantly higher numbers of AR-B than AR-A receptors expressed in the lungs. However, few studies have examined expression of androgens in inflammatory airways, and testosterone has been shown to cause relaxation of airway smooth muscles.[70] Testosterone may increase apoptosis in T cells, thus resulting in a lower percentage of T lymphocytes in the total pool of lymphocytes in males than in females.[12]

In allergic asthma, airway inflammation is mainly characterized by Th2-mediated processes, including secretion of the cytokines IL-4, IL-5, IL-6, IL-9 and IL-13, secretion of chemokines, regulation of the activation of normal T cells (RANTES), and production of granulocyte macrophage colony-stimulating factor (GM-CSF). In patients with asthma and in allergic animal models (e.g. allergen-challenged mice), bronchoalveolar lavage contains large numbers of eosinophils, M2-polarized macrophages and activated mast cells. In several cases, the numbers of neutrophils in the bronchoalveolar lavage have been found to be higher as a result of Th17-mediated responses and production of IL-8.[68,69] The airway epithelium in asthmatic patients recruits innate and adaptive cells via cytokines, including IL-25 and IL-33, and chemokines such as CCL2, CCL17 and CCL20, and it secretes transforming growth factor beta (TGFβ), which is responsible for airway remodelling.[69]

The transition of monocytes along the monocyte-macrophage axis is accompanied by upregulation of the 46 kDa ERα.[35] Activated monocytes and macrophages show increased tumor necrosis factor-alpha (TNFα) secretion. TNFα is a cytokine produced by Th1 cells and is an important mediator in pro-inflammatory responses. Female reproductive phases also influence the production of TNFα by monocytes. In the luteal phase, higher plasma levels of TNFα have been observed.[12] However, 17β estradiol may decrease TNFα levels via an anti-inflammatory effect caused by estrogen.[71]

Few studies have examined the effects of sex hormones on the bronchial epithelium. The human bronchial epithelium expresses both ERα and ERβ. In patients with asthma, estrogens facilitate dissociation of endothelial nitric oxide synthetase, which results in activation of the NO pathway, vasodilatation and increased inflammation.[72] In another study, treatment of bronchial epithelial cells with 10 nM estrogen induced expression of NOS and production of nitric oxide, thus resulting in bronchodilation.[69,73] In a study by Mandhane et al., among women who were not using oral contraceptives, an increase in progesterone level was associated with an increase in exhaled nitric oxide levels, thus indicating that an inflammatory process was associated with progesterone.[74]

Stimulation of Th2-mediated inflammatory responses and asthma by progesterone has been considered by many studies to represent a typical Th2 disorder.[69,75] In a study by Loza et al., increased accumulation of IL-13^{+}T cells (Th2) was observed in female but not in male asthmatics, and this association was maintained when the analysis was restricted to atopic subjects.[75] In an animal model, ovariectomized or estradiol antagonist-treated mice developed reduced IL-5 dependent eosinophilia during allergic inflammation.[76] However, depending on the concentration of estrogen, it may play dual pro and anti-inflammatory roles.[64,77]

CONCLUSIONS

We have attempted to discuss the characteristics that are affected by sexual hormones during pulmonary inflammatory responses. However, the associations between these factors remain obscure. We speculate that estrogen fluctuations are responsible for asthma exacerbations that occur in women. Because of the anti-inflammatory action of estrogen, as this hormone decreases TNF-α production, it reduces IFN-γ expression, and NK cell activity. We suggest that further studies that highlight the underlying physiopathological mechanisms contributing towards these interactions should be conducted.

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Antidote availability in the municipality of Campinas, São Paulo, Brazil

Disponibilidade de antídotos no município de Campinas, São Paulo

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ABSTRACT

CONTEXT AND OBJECTIVE: The lack of availability of antidotes in emergency services is a worldwide concern. The aim of the present study was to evaluate the availability of antidotes used for treating poisoning in Campinas (SP).

DESIGN AND SETTING: This was a cross-sectional study of emergency services in Campinas, conducted in 2010-2012.

METHODS: The availability, amount in stock, place of storage and access time for 26 antidotal treatments was investigated. In the hospitals, the availability of at least one complete treatment for a 70 kg adult over the first 24 hours of admission was evaluated based on stock and access recommendations contained in two international guidelines.

RESULTS: 14 out of 17 functioning emergency services participated in the study, comprising pre-hospital services such as the public emergency ambulance service (SAMU; n = 1) and public emergency rooms for admissions lasting ≤ 24 hours (UPAs; n = 3), and 10 hospitals with emergency services. Six antidotes (atropine, sodium bicarbonate, diazepam, phytomenadione, flumazenil and calcium gluconate) were stocked in all the services, followed by 13 units that also stocked activated charcoal, naloxone and diphenhydramine or biperiden. No service stocked all of the recommended antidotes; only the regional Poison Control Center had stocks close to recommended (22/26 antidotal treatments). The 10 hospitals had almost half of the antidotes for starting treatments, but only one quarter of the antidotes was present with stocks sufficient for providing treatment for 24 hours.

CONCLUSION: The stock of antidotes for attending poisoning emergencies in the municipality of Campinas is incomplete and needs to be improved.

RESUMO

CONTEXTO E OBJETIVO: A carência de disponibilidade de antídotos nas salas de emergência é uma preocupação mundial. O objetivo foi avaliar a disponibilidade de antídotos usados no tratamento de pacientes intoxicados no município de Campinas (SP).

TIPO DE ESTUDO E LOCAL: Trata-se de estudo transversal de serviços de emergência de Campinas, realizado de 2010-2012.

MÉTODOS: A disponibilidade, quantidade estocada, local de armazenamento e tempo de acesso a 26 tratamentos antidotais foi investigada. Nos hospitais, foi avaliada também a disponibilidade de pelo menos um tratamento completo para um adulto de 70 kg nas primeiras 24 horas da admissão, com base em recomendações de estoques e acesso contidas em duas diretrizes internacionais.

RESULTADOS: 14 dentre 17 serviços de emergência em funcionamento participaram do estudo, que incluiu serviços pré-hospitalares, como o Serviço de Atendimento Móvel de Urgência (SAMU, n = 1) e três Unidades de Pronto Atendimento (UPAs, internação limitada até 24 horas), além de 10 hospitais com emergência. Seis antídotos (atropina, bicarbonato de sódio, diazepam, fitomenadiona, flumazenil e gluconato de cálcio) estavam estocados em todos os serviços, seguidos de 13 que também estocavam carvão ativado, naloxona, difenidramina ou biperideno. Nenhum serviço tinha estoque de todos os antídotos recomendados; somente o Centro de Controle de Intoxicações regional tinha estoque próximo ao perfil recomendado (22/26 opções terapêuticas). Os 10 hospitais tinham quase metade dos antídotos necessários para iniciar tratamento, mas somente um quarto dos antídotos estava em estoques suficientes para oferecer tratamento por 24 horas.

CONCLUSÃO: O estoque de antídotos para atendimento de emergências toxicológicas no município de Campinas é incompleto e deve ser melhorado.

INTRODUCTION

The lack of adequate and readily available antidotes in emergency services is a worldwide concern.[1-9] Various factors have been correlated with antidote unavailability, including product shelf-life, the high cost of certain antidotes, the classification of some antidotes as orphan drugs (i.e. drugs of low commercial interest that qualify for incentives such as tax relief, depending on each country's policy) and difficulty in importing antidotes from certain countries.[8]

Guidelines may help to organize antidote stocks in emergency services in acute hospitals.[1-4,9,10] The United Kingdom (UK) guidelines, which were initially published in 2008 and are regularly revised and updated, stipulate that antidote stocks should be sufficient for the initial treatment of a 70 kg adult patient and for treatment during the first 24 hours. In these guidelines, antidote stocks are also classified according to availability, i.e. antidotes held in emergency departments for immediate use, antidotes held in hospital pharmacies or dispensaries for use in emergency departments within one hour of patient admission, and antidotes that are rarely used or for which the time interval until use in emergency departments is not critical, with stocks held in a supraregional center.[3,10]

The United States (US) guidelines also classified antidotes based on their optimal access time.[4] This list of antidotes and their minimum stocks was defined based on a systematic review of the literature followed by evaluation by a panel of experts, who assessed the efficacy, safety, influence of access time on subsequent treatment and dose required to treat a 100 kg-individual.[4] Based on antidote guidelines, verification of antidote stocks in Canada had a beneficial impact on antidote availability in acute hospitals.[1,2] In that context, two audits were held: one year before and one after the publication of antidote stockpile guidelines. In the second audit, conformity was found to have significantly increased, reaching at least 62% of the recommended stock for each antidote. To date, assessments of antidote availability in the Brazilian context are still lacking.

OBJECTIVE

In this study, we assessed the availability of antidotes used to treat poisoning at the emergency services of the municipality of Campinas, in the state of São Paulo, southeastern Brazil. The analysis included both pre-hospital services and acute care hospitals.

METHODS

Study design and setting

This investigation was a cross-sectional study conducted among emergency services in Campinas, São Paulo, from April 2010 to April 2012. Campinas had an estimated population of 1.15 million inhabitants in 2014.[11]

We identified 17 emergency services registered in the National Registry of Healthcare Establishments of the Department of Information of the Brazilian National Health System (Sistema Único de Saúde, SUS): 10 private and seven public.[12] We attempted to include the universe of eligible participants, and thus no sample size was predetermined.

Participants

All emergency services in the municipality were eligible for this study: public pre-hospital services (the emergency ambulance service [Serviço de Atendimento Móvel de Urgência, SAMU] and emergency rooms with limited capacity for admission, i.e. admission for up to 24 hours [Unidade de Pronto Atendimento, UPA]); and any hospital that had inpatient beds and could be required to treat a poisoned patient (emergency hospitals, also referred to as acute hospitals).

Variables

The primary endpoint was the frequency of antidotal treatment availability in the emergency service that was surveyed (pre-hospital or hospital). The secondary endpoints were the adequacy of the stockpile for the initial and subsequent 24 hours of treatment for an adult of 70 kg in the emergency departments.

We considered "antidote" to be one or more medicine that is appropriate for treating a case of poisoning. As a result, the list has more medicines than antidotes.

The variables of the institutions were their nature (public/private), complexity, number of beds and educational attainment of the pharmacy director. With regard to the antidotes, the variables were the availability of each medicine, amounts available in the main storage and in the emergency room, and time taken to make the medicine available in the emergency room (< 1 hour or ≥ 1 hour).

Data sources and measurement

The list of recommended antidotes was based on the UK (2008) and US (2009) guidelines (**Table 1**).[3,4] We excluded the antidotes recommended for stocking in supraregional centers, since these do not need to be available in all emergency rooms. We also excluded phentolamine, which was recommended in only one guideline; and potassium iodide, because of lack of clinical demand within the Brazilian context.

The antidote doses and quantities recommended for the initial treatment of a 70 kg adult patient over the first 24 hours after exposure were obtained from the UK guidelines and from standard texts of clinical toxicology.[3,13] These were then adapted for the pharmaceutical preparations available on the Brazilian market, as shown in **Table 1**. This led to 26 antidote options, corresponding to 30 different medicines. For comprehensiveness, from this point onwards, we will call these antidote options simply the "antidotes".

The availability on the Brazilian market was defined from a previous study and from the authors' expertise in this field.[8] In cases

in which the antidote was not commercially available, we considered the possibility of extemporaneous preparation or importation.

We elaborated a semi-structured questionnaire in order to gather data on the institutions and antidotes. The person responsible for the pharmacy of the emergency service answered the questionnaire, which was provided on paper.

We did not assess antivenin stockpiles for treating bites/stings caused by native venomous animals. The National Program for Control of Venomous Animals, of the Brazilian Ministry of Health, supplies the stockpiles of antivenin based on the notifications of cases. In Campinas, antivenin stockpiles are available from the regional Poison Control Center.[14]

Control of bias

To avoid selection bias, we invited all the eligible emergency services to participate, by means of a written invitation and further follow-up calls. We gave assurances of confidentiality by stating that the analysis would be performed in an aggregated manner and that no healthcare service would be negatively exposed through identification in the study.

Two experienced clinical toxicologists (FB, EMDC) reviewed the questionnaire. In this step, the physicians assessed its comprehensiveness and compatibility with Brazilian clinical settings. Although the list of antidotes was based on international guidelines (because of the lack of national standardization), it was adapted to

Table 1. Pharmaceutical preparations and recommended stock for the antidotes evaluated in this study based on sufficient amounts for the initial and subsequent 24 hours of treatment of a 70 kg adult patient in the emergency room

Item	Antidote, route	Pharmaceutical preparation	Recommended stockpile	Clinical indication*
1	Acetylcysteine, IV Acetylcysteine, PO	100 mg/ml; 3 ml ampoule 600 mg sachet	70 ampoules 155 sachets	Paracetamol
2	Activated charcoal, PO	10 g, 25 g or 50 g sachets	300 g (e.g., 6 x 50 g sachets)	Adsorbent for gastrointestinal decontamination
3	Anti-digoxin antibodies, IV	38 mg vial	10 vials	Cardioactive steroids
4	Atropine, IV	250 µg/ml; 1 ml ampoule	300 ampoules	Cholinesterase inhibitors
5	Calcium folinate, IV	300 mg vial; 50 mg vial; 3 mg/ml; 1 ml ampoule	3 x 300 mg vials, or 16 x 50 mg vials, or 240 ampoules	Methotrexate; methanol, formic acid
6	Calcium gluconate, IV	10% (100 mg/ml); 10 ml ampoules	12 ampoules	Calcium channel blockers, hydrofluoric acid
7	Calcium gluconate, topic	gel 2.5%; 25 g pack	1 pack	Hydrofluoric acid burns
8	Dantrolene, IV	20 mg vial	35 vials	Neuroleptic malignant syndrome
9	Desferrioxamine, IV	500 mg vial	12 vials	Iron salts
10	Diazepam, IV	5 mg/ml; 2 ml ampoule	4 ampoules	Convulsions, agitation and precordial pain
11	Dimercaprol, IM	100 mg/ml; 1 ml ampoule	15 ampoules	Mercury, arsenic, gold
12	Diphenhydramine, IV Biperiden, IV	50 mg/ml; 1 ml ampoule 5 mg/ml; 1 ml ampoule	4 ampoules 4 ampoules	Dystonic reactions
13	Flumazenil, IV	100 µg/ml; 5 ml ampoule	4 ampoules	Benzodiazepines
14	Fomepizole, IV Ethanol, IV	5 mg/ml; 20 ml ampoule 100%; 10 ml ampoule	25 ampoules 30 ampoules	Methanol, ethylene glycol
15	Glucagon, IV	1 mg vial	50 vials	Beta blockers, calcium channel blockers, tricyclic antidepressants
16	Hydroxocobalamin, IV Sodium nitrite, IV and sodium thiosulfate, IV	5 g pack 3% (30 mg/ml); 10 ml ampoule 25% (250 mg/ml); 10 ml ampoule	2 packs 1 ampoule 8 ampoules	Cyanide
17	Methylene blue, IV	1-2 mg/ml; 5 ml ampoule	3-6 ampoules	Methemoglobin-inducing agents
18	Naloxone, IV	0.4 mg/ml; 1 ml ampoule	25 ampoules	Opioids
19	Octreotide, IV	0.1 mg/ml; 1 ml ampoule	2 ampoules	Oral hypoglycemic agents
20	Physostigmine, IV	1 mg/ml; 2 ml ampoule	2 ampoules	Anticholinergic agents
21	Phytomenadione (vitamin K), IV	10 mg/ml; 1 ml ampoule	1 ampoule	Coumarin anticoagulants
22	Polyethylene glycol 3350, PO	Sachets, reconstituted with water (2 l)	12 sachets	Iron salts, lithium, packs of cocaine or heroin (body packers)
23	Pralidoxime, IV	1 g vial	5 vials	Organophosphates insecticides
24	Protamine sulfate, IV	10 mg/ml; 5 ml ampoule	1 ampoule	Heparin
25	Pyridoxine, IV	100 mg/ml; 10 ml ampoule	5 ampoules	Isoniazid
26	Sodium bicarbonate, IV	8.4%; 250 ml vial	750 ml (3 vials or 75 ampoules)	Tricyclic antidepressants, serum and urinary alkalization

*In cases of treatment for a specific type of poisoning, only the name of the agent is shown.
IV = intravenous; IM = intramuscular; PO = per oral.

the Brazilian context through the empirical knowledge of these clinicians. Five other healthcare professionals (three physicians and two pharmacists) tested and approved the questionnaire in order to assure understanding (SLSM, ILG, RJV, MY, SMM). The pharmacy director of each service filled out the questionnaire to ensure correctness. These measures were aimed at limiting potential measurement bias.

In cases involving incomplete questionnaire that was returned, we assumed that the antidote in question was not available.

Statistical methods

The data were entered into an Excel (Microsoft Office 2010) spreadsheet and were analyzed using simple descriptive statistics. We did not perform statistical testing or produce adjusted analyses because of the small sample size.

Ethical aspects

This study was approved by the institutional Research Ethics Committee of the School of Medical Sciences, State University of Campinas (protocol no. CEP 121/2010). All participants signed a free and informed consent statement.

RESULTS

Out of the 17 emergency services that were running at the time of the study, 14 (7 public and 7 private) agreed to participate in the study. These emergency services were classified either as pre-hospital (SAMU, n = 1; and UPA, n = 3, 8-21 beds) or as acute hospitals (total of 10, of which: < 50 beds, n = 1; 50-250 beds, n = 8; and > 250 beds, n = 1). The three services not included in this survey were all private: one large and two small hospitals. The reasons for exclusion were refusal (one large hospital); no person responsible for the pharmacy at the time of data collection (one small hospital); and no response and subsequent hospital closure (one small hospital).

Table 2 shows the list of available antidotes according to the emergency service characteristics. All the emergency services stocked 6 out of the 26 recommended antidotes: atropine, sodium bicarbonate, diazepam, phytomenadione, flumazenil and calcium gluconate. Thirteen emergency services also stocked activated charcoal, naloxone and diphenhydramine or biperiden (thus totaling 9/26). None of the emergency departments stocked all of the antidotes surveyed and none had anti-digoxin antibodies, fomepizole, hydroxocobalamin, physostigmine or pralidoxime.

Table 2. List of antidotes available in Campinas according to the emergency service profiles

Antidotes*	Pre-hospital services		Emergency hospitals			Total n = 14
	SAMU (ambulance) n = 1	UPA (8-21 beds) n = 3	Small (< 50 beds) n = 1	Medium (50-250 beds) n = 8	Large (> 250 beds) n = 1	
Atropine	1	3	1	8	1	14
Calcium gluconate 10%	1	3	1	8	1	14
Diazepam	1	3	1	8	1	14
Flumazenil	1	3	1	8	1	14
Phytomenadione (vitamin K)	1	3	1	8	1	14
Sodium bicarbonate	1	3	1	8	1	14
Activated charcoal	0	3	1	8	1	13
Diphenhydramine or biperiden	1	2	1	8	1	13
Naloxone	1	2	1	8	1	13
Acetylcysteine	0	0	1	8	1	10
Dantrolene	0	0	1	8	1	10
Methylene blue	0	0	1	8	1	10
Octreotide	0	0	0	7	1	8
Protamine sulfate	0	0	1	5	1	7
Calcium folinate	0	0	0	3	1	4
Ethanol†	0	0	0	3	1	4
Polyethylene glycol 3350	0	0	0	3	1	4
Calcium gluconate gel	0	0	0	0	1	1
Desferrioxamine	0	0	0	0	1	1
Dimercaprol	0	0	0	0	1	1
Pyridoxine	0	0	0	0	1	1
Sodium nitrite and sodium thiosulfate‡	0	0	0	0	1	1
Glucagon	0	0	0	1	0	1

*No emergency service had anti-digoxin antibodies, physostigmine or pralidoxime; †fomepizole was not available; ‡hydroxocobalamin was not available.
SAMU = Serviço de Atendimento Móvel de Urgência (public emergency ambulance service); UPA = Unidade de Pronto Atendimento (public emergency rooms with a limited capacity for admission, usually less than 24 hours).

Only the hospital at which the regional Poison Control Center is run had antidote stocks close to the recommendation (excluding the five antidotes mentioned earlier and also glucagon); at this service, 100% ethanol was provided instead of fomepizole and sodium nitrite/sodium thiosulfate instead of hydroxocobalamin.

All the emergency hospitals had 12 antidotes with which they were able to start treatment within one hour of admission (diazepam, phytomenadione, flumazenil, calcium gluconate, diphenhydramine or biperiden, sodium bicarbonate, methylene blue acetylcysteine, atropine, activated charcoal, naloxone and dantrolene) (**Table 3**). To continue the treatment for the first 24 hours in the hospitals, the stockpile was adequate for seven antidotes (diazepam, phytomenadione, flumazenil, calcium gluconate, diphenhydramine or biperiden, sodium bicarbonate and methylene blue).

DISCUSSION

The pre-hospital and hospital emergency services of Campinas have one quarter of the recommended antidotes available for treating poisoning. In the hospital setting, all the emergency departments stocked almost half of the antidotes for starting treatment, but with regard to continuing it for 24 hours, the stockpiles were insufficient for 75% of the antidotes. Only the reference service, which is located in the largest hospital in the city, had an antidote stock that approached the recommended stock profile. This situation is similar to that described in the literature, in which larger hospitals generally have larger, more diversified antidote stocks.[2,5,6]

Since no Brazilian recommendations for antidote supply are available, the diagnosis provided by the present study was based on international guidelines. Although the US and UK guidelines for antidote stockpiles can provide a useful starting point, the recommendations may not be realistic from a clinical or economic perspective within our context.

To better address this issue, we compiled a list of the most prevalent poisonings handled by the Campinas Poison Control Center in 2014 (**Table 4**). Our findings suggest that even the pre-hospital

Table 3. Antidotes available at ten emergency departments (emergency hospitals) in the municipality of Campinas, based on the time required for accessing them and the adequacy of the stock for the initial and subsequent 24 hours of treatment for a 70 kg adult patient

Antidotes	Availability in ED (n = 10)	
	< 1 hour	Adequate stock
Diazepam	10	10
Phytomenadione (vitamin K)	10	10
Flumazenil	10	10
Calcium gluconate 10%	10	10
Diphenhydramine or biperiden	10	10
Sodium bicarbonate	10	10
Methylene blue	10	10
Acetylcysteine	10	8
Atropine	10	6
Activated charcoal	10	5
Naloxone	10	5
Dantrolene	10	4
Octreotide	8	7
Protamine sulfate	7	7
Calcium folinate	4	4
Polyethylene glycol 3350	4	2
Ethanol*	4	2
Pyridoxine	1	1
Calcium gluconate gel	1	1
Desferrioxamine	1	1
Dimercaprol	1	1
Sodium nitrite and sodium thiosulfate†	1	1
Glucagon	1	0

*Fomepizole was not available; †hydroxocobalamin was not available. ED = emergency department.

Table 4. Most frequent toxic exposures among 5,362 patients followed up by the Campinas Poison Control Center in 2014

Exposures (n = 5,362)*	n	%
Pharmaceuticals		
Sedatives/anticonvulsants	761	14.2
Benzodiazepines	468	8.7
Carbamazepine	113	2.1
Phenobarbital	61	1.1
Antidepressants	403	7.5
Selective serotonin uptake inhibitors	220	4.1
Tricyclic antidepressants	112	2.1
Antipsychotics	236	4.4
Risperidone	45	0.8
Quetiapine	36	0.7
Analgesics and antipyretics	242	4.5
Paracetamol	120	2.2
Dipyrone	96	1.8
Histamine H_1-receptor antagonists	183	3.4
Venomous animal bites/stings		
Scorpion stings	398	7.4
Snake bites	68	1.3
Spider bites	71	1.3
Caterpillars	69	1.3
Cleaning substances (household)		
Cleansers/detergents/soaps/softeners	366	6.8
Bleaches	139	2.6
Pesticides		
Rodenticides (anticoagulants)	150	2.8
Pyrethroids	122	2.3
Illegal rodenticides *("chumbinho")*†	74	1.4
Organophosphates/carbamates	66	1.2
Abused drugs		
Cocaine	125	2.3
Ethanol	91	1.7

Exposures could be for one or more agents; †"Chumbinho"* = illegal rodenticide used in Brazil since the 1990s containing cholinesterase inhibitors, mainly carbamates such as aldicarb.

services have sufficient amounts of antidotes to provide the initial medical treatment in most situations. The epidemiological pattern of poison exposure usually has low variation in terms of the agents,[15] which was the reason why we chose to present this epidemiological data with further updating.

The following additional limitations of the present survey relating to the source of the data should be noted. The information on local stocks was supplied solely by the pharmacist responsible for the emergency services, with no crosschecking of the data to assess reliability. Some fields in the questionnaire were left blank, which was conservatively considered to represent stock unavailable. Not all of the emergency services in Campinas participated in the study, even though the response rate was above 80%. The study scope was essentially regional, but it represents the first report of antidote availability in emergency services in Brazil.

Making an antidote available does not in itself ensure safety and effectiveness in treating cases of poisoning. Flumazenil, which was found in all stocks, requires judicious evaluation before use for treating benzodiazepine poisoning, since it is contraindicated for concomitant treatment with central nervous system depressors such as tricyclic antidepressants and carbamazepine.[7,16] Single-dose activated charcoal can be considered for use in cases involving potentially toxic doses of substances that are adsorbed by activated charcoal; however, there is no evidence that activated charcoal improves the prognosis for patients affected by these substances.[17] Timely administration is another restriction on the effectiveness of activated charcoal, which should be done within 60 minutes of poison ingestion. Multiple-dose activated charcoal might prevent absorption of some drugs that persist in the gastrointestinal tract (e.g. modified-release preparations), or increase elimination in the postabsorptive phases (enterohepatic or enteroenteric recirculation), and should be considered in cases of ingestion of high doses of carbamazepine, phenobarbital, dapsone, theophylline or quinine, all of which may be life-threatening.[18]

Although dantrolene was stocked by the ten acute hospitals with surgical centers, as recommended by the Brazilian Society of Anesthesiology,[19] in most cases the stocks held were insufficient.

During the data collection period, none of the emergency departments had any of the first-option antidotes: anti-digoxin antibodies, hydroxocobalamin or fomepizole.[7,13] However, some less expensive antidotes may be used as alternatives. For example, sodium nitrite and sodium thiosulfate (methemoglobinizing agents and activators of the rhodanese system), instead of hydroxocobalamin, are also effective for treating cyanide poisoning. However, use of methemoglobinizing agents can be deleterious in poisonings resulting from inhalation of toxic gases containing high concentrations of carbon monoxide and cyanide, especially in urban fires.[7,13] In such situations, the first-option emergency antidote is hydroxocobalamin.[7,13]

Ethanol is an effective alternative to fomepizole for treating methanol/ethylene glycol poisoning. On the other hand, despite the high cost of fomepizole, it is much simpler to use than ethanol.[7,13] Fomepizole is particularly useful for treating methanol poisoning caused by massive consumption of adulterated spirits.[20] Indeed, fomepizole was included in the list of essential antidotes published by the World Health Organization.[21]

Pyridoxine (a first-choice antidote for treating isoniazid poisoning) and dimercaprol (a first-choice antidote for treating acute arsenic poisoning) were stocked in the regional reference service. Since Brazil is among the countries with high incidence and prevalence of tuberculosis,[22] access to isoniazid is widespread and this increases the risk of toxic exposure. Poisoning due to isoniazid is uncommon, but may result in seizures that are very difficult to control and that improve with high doses of pyridoxine.[13] Acute poisoning with arsenic is rare nowadays and cases that do occur are generally intentional (attempted suicide and homicide), with serious fulminant complications, hence justifying maintenance of stocks of dimercaprol in the regional reference service.[4,23]

Although not investigated in this study, other antidotes should be considered for antidote stocks. These antidotes include lipid emulsions for dealing principally with systemic poisoning by local anesthetics;[7,24] cyproheptadine for treating serotoninergic syndrome;[25] continuous infusion of high doses of insulin and glucose as inotropic medicines to counteract poisoning due to myocardial depressors such as β-blockers and calcium channel blockers, instead of glucagon;[7,26] and L-carnitine for severe poisoning caused by sodium valproate and valproic acid.[27] All of these antidotes are stocked in the regional reference service.

Although the cost of some antidotes may appear to be rather high in the context of Brazil's healthcare system, acquisition of high-cost antidotes could be included in the strategic pharmaceutical assistance component of the Brazilian Ministry of Health, which deals with neglected situations and market availability. Such inclusions would markedly reduce the cost of importation of various antidotes and allow the demands of a greater number of states and municipalities to be met. In this regard, in 2014, at the time when the soccer World Cup was being organized in Brazil, the Campinas Poison Control Center received a supply of hydroxocobalamin sufficient for ten treatments, and the equivalent of four treatments of pralidoxime. Treatment for cyanide poisoning with hydroxocobalamin has been approved by the Brazilian Ministry of Health, with publication of an official guideline and further incorporation in SUS in 2016.[28,29] It is valid to say that tragic events, especially the Santa Maria fire in 2013, played an important role in the approval of this antidote in particular. The conclusion of a previous paper in this field remains up-to-date: "Procrastination, fragmentation of responsibilities and improvisation in this area need to be tackled. A policy that anticipates great commotion events or calamity in public health is a pressing need".[8]

As shown here, this discussion needs to be expanded to define stocks in relation to the immediate needs of emergency rooms and the local epidemiology of poisonings. A recent advance in this regard has been the implementation of an "antidote policy" by the Secretary of Health in the state of Santa Catarina, southern Brazil, based on the strategy adopted in the UK. This policy was formulated in partnership with the local Poison Control Center to incorporate it into the state emergency care network.[30] This policy and its implementation could provide a basis for creation of similar systems in other Brazilian states or even a basis for a national policy.

In the present survey, we only considered antidotes that are essential for appropriate emergency care of poisoning cases. In low-resource settings, the need for all acute hospitals to stock all of the available recommended antidotes may be unrealistic because of economic constraints. In these situations, strategies such as inter-hospital transfer of antidotes may be effective for treating acute poisonings that require expensive, rarely used antidotes, such as anti-digoxin antibodies. With this system in operation, it would perhaps be irrelevant whether only one or two local hospitals had all of the recommended antidotes. Indeed, these approaches have frequently been used in Campinas, coordinated by the local Poison Control Center, such as the interchange of affordable antidotes like acetylcysteine, ethanol 100%, dimercaprol and antivenins.

CONCLUSION

In conclusion, the antidote stocks in the emergency services of the municipality of Campinas are incomplete and need to be improved. Our situational awareness can be useful as a starting point in other contexts. For clinical practice, the present findings emphasize the need for an antidote access policy. Further investigations should focus on a national consensus for minimum antidotes and regular stockpile surveys.

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Academic performance of students who underwent psychiatric treatment at the students' mental health service of a Brazilian university

Desempenho acadêmico de alunos que se submeteram a tratamento psiquiátrico no serviço de saúde mental para estudantes de uma universidade brasileira

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KEY WORDS:
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PALAVRAS-CHAVE:
Transtornos mentais.
Aconselhamento.
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Estudantes.
Saúde mental.

ABSTRACT

CONTEXT AND OBJECTIVE: University students are generally at the typical age of onset of mental disorders that may affect their academic performance. We aimed to characterize the university students attended by psychiatrists at the students' mental health service (SAPPE) and to compare their academic performance with that of non-patient students.

DESIGN AND SETTING: Cross-sectional study based on review of medical files and survey of academic data at a Brazilian public university.

METHODS: Files of 1,237 students attended by psychiatrists at SAPPE from 2004 to 2011 were reviewed. Their academic performance coefficient (APC) and status as of July 2015 were compared to those of a control group of 2,579 non-patient students matched by gender, course and year of enrolment.

RESULTS: 37% of the patients had had psychiatric treatment and 4.5% had made suicide attempts before being attended at SAPPE. Depression (39.1%) and anxiety disorders/phobias (33.2%) were the most frequent diagnoses. Severe mental disorders such as psychotic disorders (3.7%) and bipolar disorder (1.9%) were less frequent. Compared with non-patients, the mean APC among the undergraduate patients was slightly lower (0.63; standard deviation, SD: 0.26; versus 0.64; SD: 0.28; P = 0.025), but their course completion rates were higher and course abandonment rates were lower. Regarding postgraduate students, patients and non-patients had similar completion rates, but patients had greater incidence of discharge for poor performance and lower dropout rates.

CONCLUSION: Despite the inclusion of socially vulnerable people with severe mental disorders, the group of patients had similar academic performance, and in some aspects better, than, that of non-patients.

RESUMO

CONTEXTO E OBJETIVO: Estudantes universitários geralmente estão na faixa etária típica do início de transtornos mentais que podem afetar seu desempenho acadêmico. Tivemos como objetivos caracterizar os estudantes atendidos por psiquiatras em serviço universitário de saúde mental para alunos (SAPPE) e comparar seu desempenho acadêmico com o de alunos não pacientes.

DESENHO E LOCAL: Estudo transversal baseado em revisão de prontuários e levantamento de dados acadêmicos em uma universidade pública brasileira.

MÉTODOS: Prontuários de 1.237 estudantes assistidos por psiquiatras do SAPPE entre 2004 e 2011 foram revisados. Seu coeficiente de rendimento (CR) e status acadêmicos em julho de 2015 foram levantados e comparados aos de um grupo de controle com 2.579 alunos não pacientes, pareados por sexo, curso e ano de matrícula.

RESULTADOS: 37% dos pacientes tiveram acompanhamento psiquiátrico e 4,5% fizeram tentativas de suicídio prévios ao atendimento pelo serviço. Os diagnósticos mais frequentes foram depressão (39,1%) e transtornos fóbico-ansiosos (33,2%). Transtornos mentais graves, como o psicótico (3,7%) e o bipolar (1,9%), foram menos frequentes. Entre os pacientes dos cursos de graduação, o CR médio foi levemente inferior (0,63; desvio padrão, DP: 0,26; *versus* 0,64; DP: 0,28; P = 0,025) que o de não pacientes, mas suas taxas de conclusão do curso foram maiores e as de evasão, menores. Na pós-graduação, as taxas de conclusão foram semelhantes, mas pacientes tiveram maior frequência de desligamento por baixo desempenho acadêmico e menor de desistência.

CONCLUSÃO: Mesmo incluindo pessoas socialmente vulneráveis e com transtornos mentais graves, o grupo de pacientes teve desempenho acadêmico semelhante e, em alguns aspectos melhor, do que o de não pacientes.

INTRODUCTION

Admission into university is indicative of certain capabilities among young adults, which allowed them to complete high school and pass the entrance examinations. Those conditions are not limited to cognitive traits, but also include access to information and an evolved state of internal and external mental organization and structures. On the other hand, this phase of life brings new challenges such as living away from family, making new friends and adapting to a new level of academic requirements. It is also an age at which outbreaks of various mental disorders frequently occur.[1-3] For such reasons, since the beginning of the twentieth century, a number of universities in the United States and Europe have created internal services for student mental health care.[4] Such concerns have also motivated several institutions in Brazil to establish their own services for the same purpose.[4]

Campinas State University (Universidade Estadual de Campinas, Unicamp) is a Brazilian public university, founded in 1966.[5] In 2011, the university had 27,783 regular students, of whom 60.04% were undergraduates.[7] The university's Psychological and Psychiatric Service for Students (Serviço de Assistência Psicológica e Psiquiátrica ao Estudante, SAPPE), which is the mental health service on the campus, was created in 1987. The service is structured such that psychiatrists provide medical support for psychological treatment, thus attending to the most severe cases. During the survey period of the present study, psychiatric consultations accounted for around 15% of all attendance provided by the service.[6,7]

A study conducted within SAPPE[8] reviewed the medical files of all students who sought the service between 1987 and 2003. It found that students who were dependent on scholarships and those living in student housing belonging to the university were overrepresented in relation to the total number of university students. This indicated that mental care on the campus was more important to students whose economic conditions were unfavorable. Another study conducted in 2011[9] surveyed the group of students who sought the service for a second time after completing the initial treatment. It identified unfavorable economic situation, academic difficulties, early seeking of the service for first attendance and low self-esteem as the main factors associated with returning to the service.

In 2005,[6] the university debuted its Affirmative Action and Social Inclusion Program (Programa de Ação Afirmativa e Inclusão Social, PAAIS), a series of measures following federal government guidelines for expansion of social inclusion programs. Initially, it was intended to cover 30% of new undergraduate students, but was recently expanded to 50% of entrants.[10] In the light of previous studies, it is reasonable to expect that the resulting growth of the vulnerable university population will imply an expansion of the number of students who are dependent on healthcare services provided by the university.

OBJECTIVE

Our aim was to characterize the patients treated by psychiatrists at SAPPE, describing some of their socioeconomic and clinical attributes, and to compare some of their academic performance indicators with those of their colleagues who were not assisted by the service. Our purpose was to move a few steps further forward in gathering inputs for planning, not only of the mental health services themselves, but also of broader strategies that may be needed to address the ongoing changes affecting the student population.

METHODS

The National Commission for Research Ethics (Comissão Nacional de Ética em Pesquisa, CONEP) approved this descriptive, retrospective study based on medical file review. We reviewed the medical files of all undergraduate and postgraduate students attended by the mental health service of the campus between January 2004 and December 2011 and identified 1,237 cases in which a student underwent psychiatric consultation, comprising 769 undergraduate and 468 postgraduate students.

Through examination of the records, we obtained the following: sociodemographic information consisting of gender, age, marital status, origin and type of income; prior clinical information consisting of prior psychiatric care, assistance by hospital psychiatric services and suicide attempts; and information gathered during treatment, comprising the ascribed diagnosis and prescribed medications, assistance or hospitalization by the hospital psychiatric service and suicide attempts. The data collection was carried out between August 2014 and February 2015.

The university's academic board (Diretoria Acadêmica, DAC) provided the academic data. The information referred to the first half of 2015 and consisted of the academic status and the academic performance coefficient (APC). The APC is an index used by the university to measure students' overall academic performance along the course, calculated from the grades obtained and the number of credits in each subject of the course. It is similar to the grad-point average (GPA), except that it is scaled from -1.0000 to 1.0000 for undergraduate courses and from 0.0000 to 4.0000 for postgraduate courses. The APC is best suited for evaluating the performance of undergraduate students, given the heterogeneity of master's and doctorate programs in terms of structure and evaluation methods. Therefore, we assessed those two education levels (undergraduate and postgraduate) separately and for postgraduate students, we analyzed only academic status.

With regard to establishing parameters for evaluating academic indicators, we asked DAC to set up a control group through random selection of at least two other students from the same course and from the same semester of enrollment for each patient of the service. They were also asked to preserve the same gender proportion found in the group of assisted students.

Specifically for the undergraduate courses, we compared 769 assisted students with a control group of 1,514 students who did not receive assistance from SAPPE, and then, separately, 468 assisted postgraduate students with a control group of another 1,065 postgraduate students who did not attend this service. Within the control group, the proportions of students affected by mental diseases and of students already subject to mental health care outside of SAPPE are unknown to us. The reason for selecting a comparison group with twice the number of students was to mitigate the distortions that might have arisen from that factor. We performed the comparisons separately according to course level (undergraduates and postgraduates), using the chi-square test for categorical variables and the Mann-Whitney test for comparisons of APC. The latter was calculated only for undergraduates.[11,12] The level of significance was 5%.

RESULTS

Sociodemographic data

The average age of the students when they were first assisted by psychiatrists at SAPPE was 25.3 years, with standard deviation (SD) of 5.8, median of 24.0, minimum of 17 and maximum of 60 years. They were mostly women (56.9%), singles (81.8%), from the state of São Paulo (71.8%) and living in dwellings shared with other students (*repúblicas*) (35.3%). A scholarship was the main source of income for 41.1% of the students, while 31.5% lived supported by family resources and 18.8% from their own savings. Only 20.8% of these students attended night classes.

Table 1 shows some of the sociodemographic attributes, as well as some general academic data such as the fields of study and the distribution between undergraduates and postgraduates.

Clinical data

When the students sought psychiatric care at SAPPE for the first time, 37.0% (n = 454) of them had undergone some prior psychiatric treatment and 2.8% (n = 34) had already gone through hospital psychiatric services. The data showed that 4.53% (n = 56) of the students had made suicide attempts before seeking the service. Among these, 19 (1.5%) had made more than one attempt. During the period of treatment at SAPPE, 1.78% (n = 22) attempted suicide. Six students made more than one attempt. The majority of the students assisted by psychiatrists (74.6%; n = 923) were also under simultaneous psychotherapeutic care (**Table 2**).

The most frequent diagnoses were depressive episodes (n = 480; 38.8%); anxiety and phobic disorders (n = 407; 32.9%); abuse of and/or dependence on psychoactive substances (n = 76; 6.2%); schizophrenia and other psychotic disorders (n = 46; 3.7%); and affective bipolar disorder (n = 23; 1.9%).

The drugs most prescribed were antidepressants, prescribed to 80.2% of the patients (n = 992), followed by benzodiazepines, prescribed to 20.5% of the patients (n = 253). The average number of psychiatric consultations per student was 8.3 (SD = 9.5; median = 5).

Table 1. Characteristics of mental health campus service clients

	Frequency n = 1237	Percentage (%)
Female	704	56.90
Singles	1012	81.80
Source		
Students from São Paulo state	888	71.80
Students from Brazilian states other than São Paulo	316	25.50
Students from other countries	33	2.70
Living in the campus residence hall	165	13.30
Undergraduate students	769	62.20
Postgraduate students	468	37.80
Study field		
Exact sciences	612	49.50
Human sciences	318	25.70
Life sciences and health professions	227	18.40
Art	79	6.40
Source of income		
Scholarship	508	41.10
Own savings	188	15.20
Family resources	390	31.50

Table 2. Clinical attributes

Variable	Frequency n = 1237	Percentage (%)
Previous clinical history		
Prior psychiatric care	454	37.00
Passage through hospital psychiatric service	34	2.80
Attempted suicide	57	4.50
Clinical data during care by the service		
Attempted suicide	22	1.80
Attempted suicide with clinical complications	4	0.30
Death by suicide	1	0.08
Passage through hospital psychiatric service	20	1.60
Diagnoses		
Depressive episode	480	38.80
Phobic and anxiety disorders	407	32.90
Schizophrenia or other psychotic disorders	46	3.70
Bipolar affective disorder	23	1.90
Abuse and/or dependence of psychoactive substance	76	6.20
Medication		
Antidepressants	992	80.20
Benzodiazepines	253	20.50

Academic performance of the assisted students compared with that of those who did not attend the service

The undergraduate students who received psychiatric care at SAPPE had slightly lower mean academic performance coefficient (APC) when compared to the control group of non-patient students (0.63, SD = 0.26, versus 0.64, SD = 0.28). Although small, this difference was statistically significant (P = 0.025, Mann-Whitney test).

By the end of the first half of 2015, among the group of undergraduate patients, 515 students (67.0%) had completed their courses, 128 (16.7%) had abandoned the course; 82 (10.7%) had been discharged because of low academic performance, and 42 students (5.5%) had courses still in progress. In the undergraduate control-group, the rate of course completion was significantly lower (57.9%), and the rate of course abandonment higher (27.8%), chi-square test, P < 0.0001 (data presented in **Table 3**).

Among postgraduate students assisted over the surveyed period, only 17 students (3.7%) were still enrolled in their courses at the end of the first half of 2015. Just over two-thirds (69.0%; n = 321) had completed the course, while 6.7% (n = 31) had left the course before its conclusion. Among the latter, seven students did so because they transferred to another course. This number also accounts for direct progression from a master's to a doctoral course. Around one in five of the assisted postgraduate students (20.6%; n = 96) was clearly discharged for poor academic performance. Three were cut off from their programs but rejoined later on, solely to defend their dissertation or thesis, as allowed by Unicamp's master's and doctoral program statutes. In the postgraduate control group, the course completion rate was very similar (68.9%); the rate of drop-out was a little higher (9.13%) and the rate of discharge due to poor academic performance, a little lower, but no significant difference was found (chi-square test, P = 0.3538) (**Table 3**).

DISCUSSION

To the best of our knowledge, this is the first study conducted in Brazil to address the academic performance of university students who underwent psychiatric treatment. This study also examined the association between psychiatric disorders in general and academic performance.

With regard to gender distribution at the university during the period 2004-2011,[6] men formed the majority (55%) of the total student population of the university. This indicates that there was female overrepresentation among the clientele served by SAPPE. This finding is consistent with other studies that correlated demand for mental health care and gender.[8]

Admittance to campus halls of residence follows socioeconomic selection criteria and extends to only about 3.0% of the university students.[6] About 13% of the assisted students were resident there: a clear overrepresentation that is corroborated by previous studies carried out in this service.[8] The same applies to the overrepresentation of students whose main source of income was scholarships.

The inverse relationship between mental disorders and economic standard of living is one of the most consistent results from epidemiological population studies and studies on primary care, not only in Brazil but also internationally. However, the relationship between mental health/illness and social vulnerability is very complex and requires deep reflection and contextualization in order to be understood. A simplistic form of logic that correlates "madness" and "poverty", thereby reinforcing stigma and prejudice with regard to the least favored population, is a pitfall to be avoided.[13]

The fact that a considerable number of students underwent psychiatric care before seeking the service for the first time is open to several interpretations. It could be an indication of greater severity, but could also be a consequence of reduction of stigma, which would stimulate an earlier search for care and might possibly have contributed towards success in being admitted into the university.

The most frequent diagnosis was depressive episodes, followed by anxious and phobic disorders. Among the studies conducted in Brazil, we did not find any centered on students who underwent psychiatric treatment that allowed us to establish direct comparisons regarding the prevalence of different mental disorders. The majority of the studies to which we had access screened either the general population or some specific group (mostly healthcare-related courses) for the prevalence of mental disorders. Some other published papers have pointed out that

Table 3. Academic status by the end of the first half of 2015

	Undergraduate students		Postgraduate students	
	Assisted students	Control group	Assisted students	Control group
	n = 765	n = 1509	n = 465	n = 1062
Academic status				
Course completed	515 (67.3%)	874 (57.9%)	321 (69.0%)	732 (68.9%)
Ongoing course	42 (5.5%)	84 (5.6%)	17 (3.7%)	32 (3.0%)
Left the course	128 (16.7%)	420 (27.8%)	31 (6.7%)	97 (9.1%)
Discharged due to low performance	80 (10.5%)	131 (8.7%)	96 (20.6%)	201 (18.9%)
	Chi-square test P < 0.0001		Chi-square test P = 0.0043	

only a relatively small proportion of the students affected by mental disorders seek and receive clinical attention.[14-17] This applies especially to substance-related disorders[18] and might explain the somewhat low prevalence of those disorders in our sample. Also at lower proportions, we found students with diagnoses commonly regarded as severe mental disorders, such as schizophrenia and other psychotic disorders, along with bipolar disorder. The prescription records relating to different classes of psychopharmacological drugs showed a good proportional relationship to the distribution of diagnoses found.

The frequencies of suicide attempts and instances of care provided by hospital psychiatric services during the course of psychiatric treatment at SAPPE were lower than those reported previously to the treatment at the service (1.78% and 1.5% versus 4.53% and 2.8%, respectively). Whether this decrease might be attributable to a potential protective effect from the psychiatric and psychotherapeutic care received is a question that we cannot positively answer without further research.

The comparisons of academic parameters show that the assisted undergraduate students had an academic performance coefficient (APC) that was only slightly below their colleagues in the control group. Taking into account both the negative impact of mental illness on academic performance[19] and the fact that there was an overrepresentation of students in economically and socially vulnerable situations among the clients at SAPPE, we consider that this result is a very positive outcome. We might interpret it as suggestive of the effectiveness of providing mental health care on the university campus. Nevertheless, caution is required given that we are unable to make any assertions regarding the proportion of students in the control group who might have been affected by mental illness without receiving treatment either within or outside of our service.

We were positively surprised by the fact the assisted undergraduate students presented a higher course completion ratio than the control group. A study in 2010[19] evaluated the independent associations between psychiatric disorders among college freshman and the failure to complete the college course. Five diagnoses were positively and significantly associated with failure to graduate: bipolar I disorder, marijuana use disorder, amphetamine use disorder, cocaine use disorder and antisocial personality disorder. The authors suggested that the benefits of prevention, detection and treatment of psychiatric illness might therefore include higher college graduation rates. The fact that the students attended by psychiatrists at SAPPE performed well, concerning dropout rates in comparison with their colleagues in the control group, might also be considered to be a good outcome, given that graduation from a university course can generally be considered to be an important achievement. It needs to be borne in mind, however, that at an individual level, academic dropout is not necessarily a bad outcome. For instance, although abandoning a course may seem to be an unfavorable event, if the student does this because he has the opportunity to enter another institution that is more aligned with his aspirations, this will indeed be a favorable outcome.

The course completion rate among the assisted postgraduate students was almost equal to that of the control group. Postgraduate courses have more stringent deadlines than undergraduate courses, ranging from 12 to 30 months for a master's degree and 24 to 48 months for a doctorate. Delayed completion of the course results in automatic discharge from the program. The dropout rate among the assisted postgraduate students was similar to that of their colleagues in the control group.

Our study design did not allow us to attribute the positive outcomes that we found solely or directly to the care provided by SAPPE or to any other known factor. Nonetheless, we consider that our results are encouraging with regard to the continuity of efforts towards providing mental health care and other forms of social assistance to university students.

All the limitations of the methods of retrospective medical record reviews need to be taken into consideration in this study. There is no standardization in completing the records, thus offering some room for the researcher's interpretation bias. The academic data could not be directly assessed by the present researchers, but were collected by a professional from the Academic Board. The Academic Board provided data using their own categorization criteria, which were subsequently re-categorized by the researchers.

CONCLUSION

The students who underwent psychiatric treatment were the most severely affected group among the individuals who sought the campus mental health care service. They represented around 15% of the students who were assisted at the service, and included people diagnosed with severe mental disorders. The academic performance indicators found in this group did not differ radically from those of the control group. In the case of the undergraduates, their course completion rates were even somewhat better, which may suggest that there is a positive effect from care with regard to prevention of course abandonment.

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The role of environmental tobacco exposure and *Helicobacter pylori* infection in the risk of chronic tonsillitis in children

O papel da exposição ambiental do tabaco e infecção pelo *Helicobacter pylori* no risco de amigdalite crônica em crianças

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KEY WORDS:
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PALAVRAS-CHAVE:
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Infecção.

ABSTRACT

CONTEXT AND OBJECTIVE: *Helicobacter pylori* (*H. pylori*) is a chronic infectious pathogen with high prevalence. This study investigated the interaction between environmental tobacco exposure and *H. pylori* infection on the incidence of chronic tonsillitis in Chinese children.

DESIGN AND SETTING: Cross-sectional study performed in an outpatient clinic in China.

METHODS: Pediatric patients with chronic tonsillitis were enrolled. *H. pylori* infection was determined according to the presence of H. pylori CagA IgG antibodies. Serum cotinine levels and environmental tobacco smoke (ETS) exposure were determined for all participants.

RESULTS: There was no significant difference in *H. pylori* infection between the children with chronic tonsillitis and children free of disease, but there was a significant difference in ETS between the two groups (P = 0.011). We next studied the association between ETS and chronic tonsillitis based on *H. pylori* infection status. In the patients with *H. pylori* infection, there was a significant difference in ETS distribution between the chronic tonsillitis and control groups (P = 0.022). Taking the participants without ETS as the reference, multivariate logistic regression analysis showed that those with high ETS had higher susceptibility to chronic tonsillitis (adjusted OR = 2.33; 95% CI: 1.67-3.25; adjusted P < 0.001). However, among those without *H. pylori* infection, ETS did not predispose towards chronic tonsillitis.

CONCLUSION: Our findings suggest that tobacco exposure should be a putative mediator risk factor to chronic tonsillitis among children with *H. pylori* infection.

RESUMO

CONTEXTO E OBJETIVO: *Helicobacter pylori* (*H. pylori*) é um patógeno infeccioso crônico com alta prevalência. Este estudo investigou a interação entre exposição à fumaça ambiental do tabaco (FAT) e infecção pelo *H. pylori* sobre a incidência de amigdalite crônica em crianças chinesas.

TIPO DE ESTUDO E LOCAL: Estudo transversal desenvolvido num ambulatório na China.

MÉTODOS: Pacientes pediátricos com amigdalite crônica foram recrutados. A infecção por *H. pylori* foi determinada segundo a presença de anticorpos *H. pylori* CagA IgG. Foi determinado o nível de cotinina sérica e exposição à FAT de todos os participantes.

RESULTADOS: Não houve diferença significativa entre crianças com amigdalite crônica na infecção por *H. pylori* e sem amidalite, mas existia diferença significativa na FAT entre os dois grupos (P = 0,011). Em seguida, estudamos a associação entre FAT e amigdalite crônica com base no *status* de infecção por *H. pylori*. Nos pacientes com infecção por *H. pylori*, houve diferença significativa na distribuição de FAT entre os grupos de amigdalite crônica e controle (P = 0,022). Tomando os participantes sem FAT como referência, a análise de regressão logística multivariada mostrou que aqueles com alta FAT tinha maior susceptibilidade à amigdalite crônica (OR ajustado IC = 2,33, 95%: 1,67-3,25, ajustado P < 0,001). No entanto, naqueles sem infecção por *H. pylori*, a FAT não predispôs a amigdalite crônica.

CONCLUSÃO: Nossos achados sugerem que a exposição ao tabaco é um fator de risco para amigdalite crônica em crianças com infecção por *H. pylori*.

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a chronic infectious pathogen with high prevalence. The *H. pylori* infection rate is as high as 70% in developing countries.[1] It commonly occurs in children before the age of 10 years and even as early as 6 years in some countries.[2] Typically, *H. pylori* infects the stomach, and has been associated with gastritis, peptic ulcer disease, gastric cancer and gastric mucosa-associated lymphoma in humans. *H. pylori* infection may also participate in some non-digestive diseases, such as nutritional iron deficiency anemia, growth retardation, malnutrition, autoimmune idiopathic thrombocytopenic purpura and chronic urticaria in children, as well as the development of adult atherosclerosis-related cardiovascular diseases and some nervous system diseases.[3-7] Recently, several studies reported *H. pylori* colonization in locations outside the gastrointestinal cavity, such as adenotonsillar tissues and nasal and sinus mucosa.[3,8]

Chronic tonsillitis is one of the most frequent otolaryngological diseases in children. It causes symptoms that include poor appetite, sleep disorders, snoring, dysphagia and even growth retardation.[9,10] The role of *H. pylori* infection in chronic tonsillitis remains controversial. Previous studies did not find evidence supporting *H. pylori* colonization of tonsillar tissues in the setting of chronic tonsillitis.[2,11] A systematic review and meta-analysis showed that there was no significant difference in tonsillar *H. pylori* colonization between tissue samples derived from secondary to recurrent tonsillitis and samples from control children. Thus, those analyses did not provide any evidence that *H. pylori* infection might play a role in the pathogenesis or development of chronic tonsillitis.[11] However, a very recent study reported that *H. pylori* was present in the tonsillar tissues of patients with chronic tonsillitis, using the Scorpion real-time polymerase chain reaction (PCR).[12] Using a rapid urease test, another report showed that *H. pylori* was present in 30.5% of the tonsillar tissue of patients with chronic recurrent tonsillitis.[13]

The deleterious effects of environmental tobacco smoke (ETS) exposure on the upper respiratory tract of children are becoming increasingly recognized. A previous study showed that there was a significant association between children's sore throats and maternal smoking. A retrospective case-control study showed that nearly half of children who underwent tonsillectomy to treat recurrent tonsillitis had previous smoke exposure. Further analysis indicated that children with ETS exposure had more than twice the odds of undergoing tonsillectomy for recurrent tonsillitis, compared with those without smoke exposure.[14] Another study revealed the deleterious effects of parental smoking on upper respiratory tract infections in their children. A marked and statistically significant association was found between the incidence of tonsillectomy in children and parental smoking in the home environment. There was a higher frequency of attacks of tonsillitis requiring antibiotic treatment among the children whose parents smoked. If parents stopped smoking, the incidence of tonsillitis and the need for tonsillectomy in their children were diminished.[15]

So far, it remains unknown whether smoke exposure influences the role of *H. pylori* in tonsillitis in children.

OBJECTIVE

We aimed to investigate the interaction between environmental tobacco exposure and *H. pylori* infection regarding the incidence of chronic tonsillitis among Chinese children.

METHODS

This was a cross-sectional study performed in an outpatient clinic in China.

The subjects of this study were child patients (2.5 to 14 years of age) with chronic tonsillitis who were admitted to the hospital affiliated to Binzhou Medical University for tonsillectomy between May 2012 and May 2014. Chronic tonsillitis was defined clinically as chronic infection of the palatine tonsils, on the basis of recurrent tonsillitis. None of the participants were smokers. We obtained information about environmental tobacco smoke exposure through questionnaires applied to each participant's parents, adult household members and regular visitors. We obtained information about the smoking status of each participant's parents, adult household members and regular visitors. We counted the intensity of environmental tobacco exposure in terms of the number of cigarettes consumed daily.

Meanwhile, we also recruited age and sex-matched healthy children who had annual check-ups at our hospital between May 2012 and May 2014. Questionnaires were also answered by the controls' parents, and only individuals without self-reported ETS exposure were enrolled as controls.

This study was conducted in accordance with the principles expressed in the Declaration of Helsinki. All participants or their legal guardian gave their written informed consent, and the study protocol was approved by the Institutional Review Board of Binzhou Medical University (BMU-245).

Blood sampling and serum cotinine analysis

Blood samples were collected from the participants and serum was obtained from them through centrifugation. Serum cotinine levels were quantified by using an enzyme-linked immunosorbent assay (ELISA; Cosmic Corporation, Tokyo, Japan) that had a detection limit of 0.6 ng/ml and an inter-assay variation of < 7%. The mean serum cotinine level in the subjects with ETS was 3.76 ± 0.21 ng/ml.

Detection of H. pylori CagA IgG Antibodies

Blood samples were collected from all participants at enrollment and serum was isolated by means of centrifugation. *H. pyl*ori CagA IgG antibodies were detected in the patients' serum using ELISA kits (MyBioSource, San Diego, CA, USA) in accordance with the manufacturer's instructions. Samples with an antibody index greater than 0.9 were considered positive.[16]

Statistical analysis

Differences in demographic characteristics between patients and controls were compared by using Student's t test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Based on *H. pylori* infection status, all the participants were allocated to subgroups and multiple logistic regression analyses with adjustment for age, sex, body weight, height and education level were performed to determine the risk factors for chronic tonsillitis among the patients. A forward stepwise (likelihood ratio) procedure was used for multivariable analysis. The data were analyzed using the SPSS 13.0 package (SPSS, Inc.) and the results were considered statistically significant at $P < 0.01$ using a two-tailed test. P-values < 0.05 were considered statistically significant.

RESULTS

There were no significant differences in the distribution of age, sex, height, weight, education or place of residence between the patients and the healthy controls (**Table 1**; $P > 0.05$). Regarding the prevalence of *H. pylori* infection among the participants, 81.6% (186 out of the total of 228 patients) were positive for *H. pylori* infection and 83.2% were positive in the control group (199 out of the total of 239 patients). Overall, there was no significant difference in *H. pylori* infection prevalence in the children with chronic tonsillitis, compared with subjects free from this condition. ($P = 0.632$) (**Table 2**).

Table 1. Clinical characteristics of the chronic tonsillitis and control groups

	Chronic tonsillitis (228)	Control (239)	P
Age (years)	10.1 ± 3.8	10.0 ± 3.6	0.454
Male (n)	148	153	0.235
Height (m)	1.39 ± 3.9	1.38 ± 4.5	0.541
Weight (kg)	46.2 ± 4.1	455 ± 4.2	0.443
Education (school grade)			
< grade 3	140	148	0.907
≥ grade 3	88	91	
Living place			
Urban	126	112	0.069
Rural	102	127	
***Helicobacter pylori* infection**			
Presence	186	199	0.632
Absence	42	40	
Environmental tobacco smoke (ETS)			
No	61	87	0.011
Low	77	87	
High	90	65	

ETS = environmental tobacco smoke.

There were 148 participants (61 children with tonsillitis and 87 free of this condition) with no ETS (0 cigarettes/day). The other 319 presented ETS and their mean serum cotinine level was 3.76 ± 0.21 ng/ml. Using this mean serum cotinine value as the cutoff value, these participants were categorized as presenting either low ETS (less than 3.76 ng/ml; n = 77 in the chronic tonsillitis group and n = 87 in the controls) or high ETS (greater than or equal to 3.76 ng/ml; n = 90 in the chronic tonsillitis group and n = 65 participants without tonsillitis). Overall, there was a significant difference in ETS between the children with and without chronic tonsillitis ($P = 0.011$).

We next studied the association between ETS and chronic tonsillitis based on the *H. pylori* infection status. Among the individuals with *H. pylori* infection, there were 51 without ETS, 61 with low-level ETS and 74 with high-level ETS, while among the children without tonsillitis, there were 74 without ETS, 70 with low ETS and 55 with high ETS. There was a significant difference in ETS distribution between the two groups ($P = 0.022$). Taking the participants without ETS as the reference, multivariate logistic regression analysis showed that those with high ETS had higher susceptibility to chronic tonsillitis (adjusted OR = 2.33; 95% CI: 1.67-3.25; adjusted $P < 0.001$), with adjustment for age, sex, body weight, height and education level. However, among those without *H. pylori* infection, the ETS distribution was similar between the two groups ($P = 0.415$).

DISCUSSION

This study provides the first report on an association of *H. pylori* infection and environmental tobacco exposure with the incidence of chronic tonsillitis in Chinese children. Our findings suggest that tobacco exposure is a risk factor for chronic tonsillitis among children with *H. pylori* infection. Therefore, it is important to have a tobacco-free environment for children who are subject to *H. pylori* infection.

H. pylori bacteria can release virulence factors, including the outer inflammatory protein produced by cytotoxin-associated

Table 2. Association between ETS and chronic tonsillitis based on *Helicobacter pylori* infection status

Helicobacter pylori infection		Chronic tonsillitis group	Control group	Adjusted OR*	Adjusted P*
Positive	**No ETS**	51	74	1	
	Low ETS	61	70	0.68 (0.48-1.21)	0.21
	High ETS	74	55	1.91 (1.1-3.2)	0.006
Negative	**No ETS**	10	13	1	
	Low ETS	16	17	0.817 (0.34-2.33)	0.462
	High ETS	16	10	0.48 (0.22-1.6)	0.162

ETS = environmental tobacco smoke; OR = odds ratio. *adjusted for confounding factors, including age, sex distribution, body weight, height and education level.

gene A (CagA), which disrupts cell polarity, promotes apoptosis of epithelial cells and inhibits T cell proliferation in the gastric mucosa and upper respiratory tract.[17] *H. pylori* is detectable in tonsillar tissues and viable *H. pylori* can colonize these tissues. *H. pylori* has been identified in both tonsillar surface and core tissues.[17] A histopathological assessment of tonsillar tissues found that 130 (39.6%) out of 285 children were positive for *H. pylori* and that the rapid urease test was not sensitive enough as a diagnostic tool. A recent review regarding *H. pylori* colonization and chronic tonsillitis showed that *H. pylori* colonization was not more prevalent in tonsillar tissue with chronic or recurrent infections.[11] In our study, we used the PCR method to detect CagA IgG, in order to determine *H. pylori* infection. Consistent with the abovementioned reports, our data showed that the *H. pylori* infection rates were not significantly different between children with and without chronic tonsillitis.

An association between passive smoking and *H. pylori* infection was reported in a study conducted in Germany, which investigated the relationship between parental smoking and *H. pylori* infection in a population-based study among preschool children. After adjustment for confounding factors, a strong positive relation between smoking by the father in the household and *H. pylori* infection (odds ratio = 3.7; 95% confidence interval = 2.3-6.1).[18,19] Cirak et al. demonstrated a relatively high rate of *H. pylori* infection in adenotonsillectomy specimens, through using PCR to detect the CagA gene. They postulated that the tonsil and adenoid tissue may be an ecological niche within the mouth.[20] Likewise, we also detected high rates of *H. pylori*-positive findings using a similar PCR method (81.5% in chronic tonsillitis patients and 83.2% in controls). Di Bonaventura et al. were unable to detect *H. pylori* by means of PCR on tonsil swabs and biopsy materials from their patients, although *H. pylori* was detected in gastric biopsy cultures. They suggested that the tonsils are not an extragastric reservoir for H. pylori infection.[2] Neither of those studies took smoking status into account.

In our study, none of the participants were smokers. Nonetheless, a considerable proportion presented environmental tobacco exposure. A very early study revealed a marked and statistically significant association between the incidence of tonsillectomy among children and parental smoking in the home environment.[15] There was a higher frequency of attacks of tonsillitis requiring antibiotic treatment among the children whose parents smoked.[15] Among children who underwent tonsillectomy due to recurrent tonsillitis, 47.27% had previously been subject to smoke exposure, compared with 67 (27.80%) in the hernia repair group. Logistic regression indicated that children with smoke exposure had more than twice the odds of undergoing tonsillectomy due to recurrent tonsillitis, compared with those with no exposure. In our study, we found that the majority of the participants (73.2% of the chronic tonsillitis patients and 63.6% without this condition) were exposed to environmental smoke (77 with low ETS and 90 with high ETS among the chronic tonsillitis patients; 87 with low ETS and 65 with high ETS among the controls). These high ETS exposure rates suggest that there is an urgent need for a tobacco-free environment for Chinese children. Similarly, our data also show that among those with H. pylori, the risk of chronic tonsillitis was nearly twice the risk among those without it.

Several limitations to this study should be noted. Firstly, we only used the *H. pylori* CagA IgG antibody detection method to detect *H. pylori* infection. Secondly, with 298 participants, the sample size was relatively small. Thirdly, the exact molecular mechanism under which environmental tobacco exposure and *H. pylori* infection predispose towards chronic tonsillitis was not studied.

CONCLUSION

In this study, we reported the interaction between environmental tobacco smoke exposure and *H. pylori* infection for increasing susceptibility towards chronic tonsillitis. This finding suggests that it is important to stop environmental tobacco smoke exposure among children in order to reduce the risk of chronic tonsillitis among children.

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Living near the port area is associated with physical inactivity and sedentary behavior

Morar perto da área portuária está associado à inatividade física e comportamento sedentário

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PALAVRAS-CHAVE:
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Classe social.
Fatores de risco.

ABSTRACT

CONTEXT AND OBJECTIVE: The impact of the port of Santos, Brazil, on the population's health is unknown. We aimed to evaluate the association between living near the port area and physical inactivity and sedentary behavior.

DESIGN AND SETTING: Cross-sectional study developed at a university laboratory and a diagnostic clinic.

METHODS: 553 healthy adults were selected and their level of physical activity in daily life was assessed using accelerometers. Multiple linear and logistic regressions were performed using physical inactivity and sedentary behavior as the outcomes and living near the port area as the main risk factor, with adjustments for the main confounders.

RESULTS: Among all the participants, 15% were resident near the port area. They took 699 steps/day and presented, weekly, 2.4% more sedentary physical activity, 2.0% less time in standing position and 0.9% more time lying down than residents of other regions. Additionally, living near the port area increased the risk of physical inactivity by 2.50 times and the risk of higher amounts of sedentary behavior (≥ 10 hours/day) by 1.32 times.

CONCLUSION: Living near the port of Santos is associated with physical inactivity and higher sedentary behavior among adults, regardless of confounders. The reasons for this association should be investigated in longitudinal studies.

RESUMO

CONTEXTO E OBJETIVOS: O impacto do porto de Santos, no Brasil, sobre a saúde da população é desconhecido. Nosso objetivo foi avaliar a associação entre viver nas proximidades da área portuária e a inatividade física e comportamento sedentário.

TIPO DE ESTUDO E LOCAL: Estudo transversal desenvolvido em laboratório universitário e em uma clínica de diagnósticos.

MÉTODOS: Foram selecionados 553 adultos saudáveis e seu nível de atividade física na vida diária foi avaliado usando acelerômetros. Foi realizada regressão linear múltipla e logística usando a inatividade física e o comportamento sedentário como desfechos e morar perto da área portuária como o fator de risco principal, ajustando para os principais confundidores.

RESULTADOS: Entre todos os participantes, 15% residiam na área portuária. Estes deram 699 passos/dia a menos e apresentaram, por semana, 2,4% da atividade física mais sedentária, 2,0% menos tempo em pé e passaram 0,9% mais tempo deitados do que os residentes das demais regiões. Além disso, morar nas proximidades da área portuária aumentou o risco de inatividade física em 2,5 vezes, assim como o risco de maior comportamento sedentário (≥ 10 horas/dia) em 1,32 vezes.

CONCLUSÃO: Morar perto do porto de Santos tem associação com a inatividade física, assim como o aumento do comportamento sedentário em adultos, independentemente de fatores de confusão. As razões para tal associação devem ser investigadas em estudos longitudinais.

INTRODUCTION

Historically, ports are considered to be engines of economic development for the cities and regions where they are located. The port of Santos in Brazil is one of the most important ports in Latin America due to its size and export capacity.[1] This is the main gateway for incoming and outgoing products in this country. Despite boosting the economy, it is known that ports cause a negative impact on the health of residents of the surrounding areas.[2] Living near the port area is associated with low socioeconomic status,[3] and the pollution of the port increases the risk of developing respiratory[4] and cardiovascular disease.[5]

According to the global recommendations on physical activity for health, "adults aged 18-64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate and vigorous-intensity activity."[6] Thus, physical inactivity is characterized as failure to reach the recommendations mentioned above.[7] Sedentary behavior, in turn, can be defined as "any wakeful behavior characterized by energy expenditure of 1.5 or fewer metabolic equivalent tasks (METs) while in a sitting or reclining posture".[8] It is well known that physical inactivity is related to health impairments, but sedentary behavior has recently emerged as a new independent risk factor for chronic diseases as well as for mortality, regardless of moderate-to-vigorous physical activity.[9-14] Examples of sedentary behavior include watching television, sitting, playing video games and using computers.[15] Current studies have been investigating associations of physical activity and sedentary behaviors separately or combined.

Our previous results showed that the proportion of physically inactive subjects in a sample in the city of Santos was between 14% and 20% and that there was an association between physical inactivity and restrictive lung patterns detected by spirometry.[16,17] The level of physical activity in daily life is influenced by the physical environment in which subjects live, with their social and individual correlates,[18] but may also be related to chronic exposure to air pollutants. The vicinity of the port area in Santos seems to be a violent area with few or no safe public spaces where people can perform physical activities. Moreover, it is a highly polluted area, where the annual average levels of particulate matter grossly exceed what is recommended by the World Health Organization.[19]

Information about the impact of the port of Santos on the population's health is scarce, especially in relation to the level of physical activity within daily life and sedentary behavior directly evaluated by means of triaxial accelerometers. Our hypothesis was that living in neighborhoods close to the port of Santos would be associated with higher prevalence of physical inactivity and increased levels of sedentary behavior, regardless of the main confounders.

OBJECTIVE

We aimed to evaluate the association between living near the port of Santos and physical inactivity and sedentary behaviors among adults.

METHODS

Participants and design

Five hundred and fifty-three adults (≥ 20 years of age) were selected from the Epidemiology and Human Movement Study, i.e. the EPIMOV (Estudo Epidemiológico sobre o Movimento Humano) study. Briefly, the EPIMOV study is an ongoing cohort study with the primary objective of investigating the longitudinal association of sedentary behaviors and physical inactivity with occurrences of hypokinetic diseases, especially cardiorespiratory and musculoskeletal diseases. The present study is a cross-sectional study from the first year of the EPIMOV study. The volunteers who participated in it were recruited through publicity in social networks, folders displayed in the universities of the region, local magazines and newspapers.

We divided the participants into two groups: people residing near the port area and people residing in other surrounding neighborhoods within the metropolitan area of Santos. We used the map of the city to select residents of neighborhoods that are adjacent to the port area. We defined the participants' socioeconomic level according to the mean income of each neighborhood based on official documents held by the city of Santos, which include a map of the city according to the average income of heads of households. The participants were divided into three monthly income levels (i.e. low: R$ 622-1866; moderate: R$ 1866-3732; and high: R$ 3732-6220).

In the early clinical evaluation, personal and demographic data were collected. In addition, the participants answered the physical activity readiness questionnaire[20] in order to evaluate some possible risks relating to performing physical exercises such as cardiopulmonary exercise testing. They also answered questions about any history of respiratory illness, based on the American Thoracic Society questionnaire,[21] to investigate exposure to pollutants, history of asthma and smoking status; and cardiovascular disease risk stratification was performed as specified by the American College of Sports Medicine.[22]

We excluded participants with a self-reported diagnosis of heart disease, lung disease or musculoskeletal disorders. We made objective measurements to evaluate physical activity in daily life through triaxial accelerometry and lung function through spirometry; and conducted cardiopulmonary exercise testing using a ramp protocol on a treadmill. We also investigated the presence of self-reported major risk factors for cardiovascular disease, including age (≥ 45 years for males and ≥ 55 years for females), systemic arterial hypertension, diabetes/hyperglycemia, dyslipidemia/hypercholesterolemia, current cigarette smoking and family history of premature coronary heart disease. A family history of premature

coronary heart disease was defined as myocardial infarction or sudden death of father or other male first-degree relative before 55 years of age, or of mother or other female first-degree relative before 65 years of age. Education level was reported as illiterate or completed primary, secondary or tertiary education.

Smoking was also investigated through self-reporting. The subjects were considered to be smokers if they reported current tobacco use and had smoked 100 or more cigarettes during their lifetime.[23]

The participants were informed about the possible risks and discomforts of this study and signed a consent form. The local Ethics Committee for Human Research approved this study (protocol: 186.796).

Anthropometric measurements

Body weight and height were measured, and the body mass index was calculated in accordance with standardized methods.[24]

Spirometry

Spirometry was performed using a handheld spirometer (Quark PFT/CPET, Cosmed, Pavona di Albano, Italy) in accordance with the criteria established by the American Thoracic Society.[25] The forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio were quantified. The predicted values were calculated using national reference equations.[26]

Cardiorespiratory fitness

The maximum/symptom-limited exercise capacity was assessed during cardiopulmonary exercise testing on a treadmill (ATL, Inbrasport, Curitiba, Brazil), following a ramp protocol. After 3 minutes at rest, the speed and inclination were automatically incremented according to the estimated maximal oxygen consumption ($V'O_2max$), with the aim of completing the test in about 10 minutes.[27,28] Cardiovascular, ventilatory and metabolic variables were analyzed breath by breath, using a gas analyzer (Quark PFT, Cosmed, Pavona di Albano, Italy). Oxygen uptake ($V'O_2$), carbon dioxide production ($V'CO_2$), minute ventilation (V'E), and heart rate were monitored throughout the test. The data were filtered every 15 seconds for further analysis. Peak $V'O_2$ was defined as the arithmetic average of the last 15 seconds at the end of the incremental phase of the cardiopulmonary exercise testing.

Accelerometer-based sedentary behavior and physical activity in daily life

Sedentary behavior and physical activity in daily life were evaluated using a previously validated triaxial accelerometer (ActiGraph GT3X+, MTI, Pensacola, FL, USA).[29-31] The equipment consisted of a small, lightweight box (4.6 cm x 3.3 cm x 1.5 cm) that was attached to the waist above the dominant hip, by means of a band (total weight = 19 g). It had the capacity to measure human movement along the vertical, sagittal and mediolateral axes. The participants were subjected to seven consecutive days of evaluation during their wakeful hours. To be considered valid, data collection days needed to have at least 10 hours of continuous monitoring, starting when the subject woke up, together with absence of excessive counts (> 20,000). We instructed the participants to remove the accelerometer at bedtime and during showers and aquatic activities.

Periods with fewer than 60 counts per minutes (cpm) on the accelerometer were interpreted as periods when the accelerometer was not worn, with a tolerance of 2 minutes for periods with some movement, i.e. less than 50 cpm. The thresholds for the intensity of the physical activity were as follows:[32] 1. very light (100-759 cpm); 2. light (760-1951 cpm); and 3. moderate-to-vigorous (> 1951 cpm). The minimum quantity and intensity levels for physical activity to be considered as such was 150 minutes of moderate-to-vigorous physical activity per week.[33,34] Individuals who did not reach this level of physical activity were considered to be physically inactive.

The total amount of sedentary behavior was determined based on the number of minutes with counts less than 100. On the other hand, active time was considered to be time spent on activities with ≥ 100 cpm. By means of the inclinometer located inside the accelerometer, the time spent in each body position was measured (i.e. reclining during wakeful hours, sitting or standing). The measurements were calculated as minutes/week and as percentages of the total time. Sedentary behavior was also assessed as a categorical variable in accordance with the threshold recently described.[13,14] Participants who performed ≥ 10 hours/day of sedentary activities were classified in a group with a high amount of sedentary behavior, whereas the group with a low amount was defined as < 10 hours/day of such activities. Only data from the participants who used the accelerometer for at least four valid days were analyzed.

Statistical analysis

The sample size was calculated in accordance with the prevalence of physical inactivity of around 20% that was observed in previous findings from the EPIMOV study in the metropolitan area of the city of Santos.[16] Through taking a 99% confidence interval, it was found that at least 423 participants needed to be enrolled in the present study. We performed the sample size calculation using the free tools available on the website www.openepi.com.

Our first statistical analysis was a descriptive analysis of the data. We then evaluated whether being a resident in the port area was associated with physical inactivity in daily life and sedentary behavior, by means of multiple linear regression, regardless of socioeconomic and educational level. We developed two multiple logistic regression models in which physical inactivity and sedentary behavior were taken to be the outcomes and living near the port area was the main exposure. Adjusted odds ratios and 95% confidence intervals were calculated. Both multiple logistic regressions were adjusted according to the following: age; sex;

race (i.e. categorized as black, white, mixed, Amerindian or East Asian); education level (i.e. classified as tertiary educational attainment or not); self-reported cardiovascular disease risk factors (i.e. hypertension, diabetes, dyslipidemia, smoking, obesity or physical inactivity); cardiorespiratory fitness (peak $V'O_2$ [ml/min/kg])]; and lung function (FEV_1 [liters]). Obesity was categorized as yes or no (body mass index ≥ 30 or < 30 kg/m^2, respectively). The probability of alpha error was set at 5%.

RESULTS

Fifteen percent (n = 83) of our participants were residents in the port area. These were significantly younger and had higher socioeconomic status (**Table 1**). However, the univariate analysis showed that sex, race, anthropometry, lung function, exercise capacity, smoking status, physical inactivity and risk of cardiovascular disease variables were not statistically different between residents and non-residents in the vicinity of the port. The prevalences of diabetes mellitus, hypertension and dyslipidemia in this study were similar to those found in population-based studies in Brazil.

Table 1. General characteristics of the sample

	Residents in port area (n = 83)	People who did not live in port area (n = 470)
Age (years)*	41 ± 12	45 ± 14
Sex (%, male/female)	44/56	36/64
Race (%)		
White	66.2	73.7
Black	6.0	4.6
Mixed	22.2	19.4
East Asian	5.6	1.0
Amerindian	0	1.3
Weight (kg)	75 ± 19	76 ± 16
Height (m)	1.64 ± 0.11	1.63 ± 0.09
Body mass index (kg/m^2)	27 ± 6	28 ± 5
FVC (liters)	3.89 ± 1.16	3.56 ± 1.03
FVC (% pred.)	97 ± 11	94 ± 13
FEV_1 (liters)	3.19 ± 0.97	2.89 ± 0.84
FEV_1 (% pred.)	96 ± 12	93 ± 13
FEV_1/FVC (%)	82 ± 5	81 ± 5
Peak $V'O_2$ (ml/min/kg)	34 ± 11	29 ± 10
Completed secondary educational level (%)	42.3	50.8
Socioeconomic level (%)		
Low income*	13.2	35.6
Moderate income	43.3	34.2
High income*	43.3	18.4
Cardiovascular risk (%)		
Systemic arterial hypertension	12.5	18.2
Diabetes mellitus	8.3	11.2
Dyslipidemia	23.6	28.8
Obesity	29.2	36.3
Smoking	6.9	11.3
Physical inactivity†	20.8	21.9

Data presented as mean ± standard deviation or as count and percentage. *P < 0.05: residents of the port area versus residents of other neighborhoods; †Assessed using triaxial accelerometers.
FVC = forced vital capacity; FEV_1 = forced expiratory volume in the first second; $V'O_2$ = oxygen uptake.

The results from the linear multiple regression analysis showed that there was an association between living near the port area and increased sedentary behavior, as evaluated using triaxial accelerometers. Other variables such as socioeconomic status, education level and smoking were also significant determinants of higher amounts of sedentary behavior (**Table 2**). Living in the port area increased the risk of physical inactivity more than twofold, independently of any other confounder. Age and smoking also increased the risk of physical inactivity, after adjusting the logistic regression model according to age, gender, education level, socioeconomic status, risk factors for cardiovascular disease, cardiorespiratory fitness, lung function and smoking. On the other hand, cardiorespiratory fitness reduced the risk of physical inactivity (**Table 3**).

Regarding sedentary behavior, 51.7% of our participants performed ≥ 10 h/day of sedentary activities. Living near the port increased the risk of high amounts of sedentary behavior by 32%. In this multiple logistic regression model, age, gender, socioeconomic status, education level and smoking were also selected as determinants of high amounts of sedentary behavior. There was a positive association between higher socioeconomic status and higher amounts of sedentary behavior (**Table 4**).

Through multiple regression analysis, the residents of the port area showed higher amounts of sedentary behavior, i.e. less time standing and more time reclining, and also a lower number of steps/day, in comparison with people who did not live in the port area (**Table 5**).

DISCUSSION

This study investigated the association between living near the largest port in Latin America and physical inactivity and sedentary behavior among adults. The associations found indicated that living near the port of Santos increased the risk of physical inactivity and sedentary behavior among adults, regardless of socioeconomic status, education level, cardiovascular risk, lung function or cardiorespiratory fitness.

Unlike what we expected, the residents of the port area were younger and had higher socioeconomic status than people who did not live in the port area. These results contrast with previously published data. Grobar[3] observed that the unemployment and poverty rates are significantly higher in port districts. This disparity is possibly due to a peculiarity of the city of Santos. The neighborhood of Ponta da Praia, one of the neighborhoods with the highest average income of the city, is located very close to one of the main terminals of the port. Nevertheless, living near the port region increased the risk of physical inactivity and sedentary behavior, regardless of the higher socioeconomic status of

the residents of Ponta da Praia. This finding is interesting because studies have shown that low socioeconomic status groups perform an insufficient amount of physical activity to achieve health benefits.[35] Our results suggest that living next to a major port could affect lifestyle, even among people with privileged socioeconomic status in relation to Brazilian patterns. Therefore, whether living in the port area in Santos is different from living in another port area elsewhere in the world remains to be clarified.

Although there was no association between socioeconomic status and physical inactivity, we observed a positive association

Table 2. Results from linear multiple regression analysis on the association between sedentary behavior evaluated using accelerometers and living in the port area

Outcome	Living in port area, beta (95% CI)	P	Other significant exposures	R^2
Sedentary physical activity (hours/week)	13.2 (2.4 – 24.0)	0.045	–	0.024
Sedentary physical activity (%/week)	2.4 (1.1 – 3.7)	0.003	Education level Socioeconomic status Smoking Peak $V'O_2$	0.067
Time standing (hours/week)	-4.4 (-7.0 – -1.8)	0.006	Education level Socioeconomic status Hypertension Obesity	0.157
Time standing (%/week)	-2.0 (-3.3 – -0.7)	0.014	Education level Socioeconomic status Hypertension Obesity	0.180
Time reclining (hours/week)	1.5 (0.2 – 2.8)	0.074	Smoking Peak $V'O_2$	0.068
Time reclining (%)	0.9 (0.3 – 1.2)	0.051	Smoking	0.055
Average number of steps/day	-699.1 (165.5 – 1232.7)	0.031	Smoking Obesity Peak $V'O_2$	0.079

CI = confidence interval. Models adjusted for age, gender, education level, socioeconomic status, hypertension, diabetes mellitus, dyslipidemia, obesity, cardiorespiratory fitness, lung function and smoking.

Table 3. Results from the logistic regression analysis between physical inactivity assessed using accelerometers and factors associated to it (exposures)

Exposures	Odds ratio	95% confidence interval		P
		Lower limit	Upper limit	
Living in port area	2.50	1.40	4.47	0.002
Age (years)	1.03	1.01	1.04	0.000
Sex (male)	0.69	0.48	1.007	0.055
Socioeconomic status				
Low income	1			
Moderate income	1.05	0.67	1.66	0.815
High income	1.12	0.68	1.84	0.648
Completed secondary educational level	1.04	0.70	1.54	0.837
Hypertension	0.78	0.49	1.25	0.313
Diabetes mellitus	1.04	0.60	1.81	0.868
Dyslipidemia	0.85	0.57	1.26	0.423
Obesity	0.97	0.67	1.41	0.979
Smoking	1.87	1.16	3.04	0.010
FEV_1 (liters)	1.07	0.59	1.92	0.814
Peak VO_2 (ml/min/kg)	0.90	0.86	0.95	0.000

Models adjusted for age, gender, education level, socioeconomic status, hypertension, diabetes mellitus, dyslipidemia, obesity, smoking, lung function and cardiorespiratory fitness. FEV_1 = forced expiratory volume in the first second; $V'O_2$ = oxygen uptake.

Table 4. Results from the logistic regression analysis between sedentary behavior assessed by accelerometers and factors associated to it (exposures)

Exposures	Odds ratio	95% confidence interval		P
		Lower limit	Upper limit	
Living in port area	1.32	1.02	1.71	0.034
Age (years)	1.03	1.01	1.15	0.022
Sex (male)	0.73	0.62	0.87	0.000
Socioeconomic status				
Low income	1			
Moderate income	1.24	1.01	1.51	0.032
High income	1.40	1.12	1.75	0.002
Completed secondary educational level	0.67	0.56	0.81	0.000
Hypertension	0.84	0.66	1.17	0.175
Diabetes mellitus	0.86	0.64	1.15	0.310
Dyslipidemia	1.05	0.87	1.36	0.125
Obesity	1.17	0.97	1.41	0.087
Smoking	1.61	1.22	2.11	0.001
FEV_1 (liters)	0.95	0.61	1.47	0.837
Peak VO_2 (ml/min/kg)	1.01	0.97	1.04	0.525

Sedentary behavior: categorized as high (≥ 10 hours/day) or low (< 10 hours/day). Models adjusted for age, gender, education level, socioeconomic status, hypertension, diabetes mellitus, dyslipidemia, obesity, smoking, cardiorespiratory fitness and lung function. FEV_1 = forced expiratory volume in the first second; $V'O_2$ = oxygen uptake.

between higher socioeconomic status and higher amounts of sedentary behavior. It has been suggested that the associations between socioeconomic status and sedentary behavior present different directions in high-income countries, compared with low and middle-income countries, and that this varies according to the domain of sedentary behavior. Overall, the association between socioeconomic level and sedentary behavior is inverse.[36] However, Mielke et al.[36] observed that this relationship varies according to the income level of the country. In high-income countries, socioeconomic status presented an inverse association with sedentary behavior (effect size: 0.67; 95% CI: 0.62-0.73), whereas a positive relationship was observed in low to middle-income countries (effect size: 1.18; 95% CI: 1.04-1.34). Unlike in high-income countries, in which all indicators of socioeconomic level were negatively associated with sedentary behavior, only resources showed a significant positive association in low to middle-income countries. Despite the significant relationship mentioned above, living in the port area remained a significant determinant of higher amounts of sedentary behavior.

Residents near port areas are exposed to increased levels of air pollution due to emissions of particulate matter derived from the exhaust fumes of trucks and ships, and as a result of mechanical processes of milling operations and the ensuing street dust suspensions. Very recent studies have reported on the influence of air pollution on decreased physical activity.[37-39] In one of these studies, particulate matter and O_3 levels were correlated with reduction in physical activity in daily life and the number of steps/day, among patients with chronic obstructive pulmonary disease (COPD).[38] Although air pollution was not assessed in our study, we believe that this in the port of Santos may partly explain the higher proportion of physically inactive people and larger amount of sedentary behavior among residents of the port area. In fact, a recent large study conducted in Brazil showed that the particulate matter monitoring in the city of Santos is poor and started only in 2011. Moreover, Santos only has two air-monitoring stations and is classified as having the sixth highest concentration of particulate matter in the state of São Paulo, Brazil. The average level of particulate matter in the metropolitan area of the city of Santos was 37.23 μg/m^3 (annual mean) in 2011, which was significantly above the levels recommended by the World Health Organization. Despite the lack of assessment of particulate air pollution in the present study, it would be rational to suppose that environmental exposure to particulate matter may play a major role in the results presented here.[19]

Our results also showed that smoking was associated with physical inactivity and with greater amounts of sedentary behavior, independently. Previous results from the EPIMOV study[40] reinforce the findings of the present study. We compared two groups of physically active individuals, one formed by smokers and the other by nonsmokers. Although they performed the same amount of moderate-to-vigorous physical activity, as assessed directly using triaxial accelerometers, and were matched regarding major confounders, the smokers performed higher amounts of sedentary physical activity and spent more time sitting and lying down per week. Like in the present study, other recent studies have reported an association between smoking and physical inactivity.[41,42]

As we expected, cardiorespiratory fitness was inversely associated with physical inactivity and living near the port did not alter the risk of physical inactivity. Ecological models for physical activity and sedentary behavior identified influences from several attributes, including individual components, the social environment, the physical environment and public policy. Some of the main barriers preventing physical activity are lack of motivation, awareness and time, and lack of structure for physical activity.[43] People may have the necessary knowledge, skills, attitudes and motivation to be physically active, but if they do not have access to the necessary opportunities, they may be restricted or prohibited from being active. Building or enhancing facilities for physical activity can require a large amount of time and resources. Public health policies and intervention programs designed with a focus on increasing the level of physical activity and decreasing sedentary behavior are probably necessary for this region of Santos. Regarding the determinants of physical inactivity and sedentary

Table 5. Comparison between residents of the port area and people living in other areas regarding sedentary behaviors and the number of steps/day

Variables	People living in other areas			Residents of port area		
	Median	Percentile 5	Percentile 95	Median	Percentile 5	Percentile 95
Sedentary physical activity (h/week)*	70.73	40.22	152.22	79.50	42.31	160.07
Sedentary physical activity (%/week)*	75.30	61.30	88.70	77.40	64.90	90.87
Time standing (h/week)*	37.87	17.20	65.44	33.68	12.41	57.52
Time standing (%/week)*	21	9	34	20	7	34
Time spent lying down (h/week)*	6.31	1.48	22.93	7.86	2.07	24.35
Time spent lying down (%)*	4	1	13	4	1	17
Number of steps/day*	7,646	3,584	13,249	7,215	3,410	12,569

*P < 0.05: residents of the port area versus residents of other neighborhoods.

behavior, cohort studies are needed to investigate the causes of the associations of physical inactivity and greater amounts of sedentary behavior with living near the port area of Santos.

This study has limitations that need to be described. The cross-sectional design did not allow us to establish any relationship between cause and effect. However, our objective was to evaluate the association between living near the port area of Santos and physical inactivity and sedentary behavior. We found that these associations were consistent. Our findings may guide new research questions towards identifying other determinants of physical inactivity and sedentary behavior relating to major ports.

CONCLUSIONS

Living near the largest port in Latin America, located in the city of Santos, Brazil, is associated with physical inactivity and sedentary behavior among adults, regardless of socioeconomic status, education level, cardiovascular risk, lung function or cardiorespiratory fitness. Whether this association is related to environmental exposure and/or to lack of equipment for physical activity in this region should be investigated in cohort studies.

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The effectiveness of aspirin for migraine prophylaxis: a systematic review

Eficácia da aspirina na profilaxia da enxaqueca: uma revisão sistemática

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ABSTRACT

CONTEXT AND OBJECTIVE: Many researchers have suggested that aspirin prevents migraines. However, the evidence is unclear. The aim of this study was to analyze the available evidence on the effect of aspirin as a migraine prophylactic.

DESIGN AND SETTING: Systematic review, conducted at the Pontifícia Universidade Católica do Paraná, Brazil, and at the University of São Paulo, Brazil.

METHODS: We performed electronic searches in the databases of MEDLINE/PubMed, Embase, WEB OF SCIENCE, the World Health Organization, CENTRAL and OpenGrey, and we also searched manually for interventional studies published before April 2016 that compared the effects of aspirin with a control, in adults. Two authors independently extracted data on the publication, population recruited, intervention (aspirin dosage, follow-up and combined treatment) and main outcomes (frequency, severity and duration of migraine). We evaluated the quality of the studies using the Cochrane risk-of-bias tool.

RESULTS: Our search retrieved 1,098 references, of which 8 met the selection criteria for this systematic review. The total population was 28,326 participants (18-64 years old); most (96%) were men. The dosage varied from 50 to 650 mg/day across the studies. The risk of bias was generally low or unclear. The only outcome for which most of the studies included (6/8) reported a significant reduction was frequency of migraine, which was reduced at an aspirin dosage of at least 325 mg/day.

CONCLUSION: Aspirin can reduce the frequency of migraines. However, the optimal dosage is unclear.

RESUMO

CONTEXTO E OBJETIVO: Muitos pesquisadores têm sugerido que a aspirina previne enxaquecas. No entanto, a evidência não é clara. O objetivo deste estudo foi analisar as evidências disponíveis para os efeitos da aspirina como um profilático da enxaqueca.

DESENHO E LOCAL: Revisão sistemática, realizada na Pontifícia Universidade Católica do Paraná, Brasil, bem como na Universidade de São Paulo, Brasil.

MÉTODOS: Foram realizadas buscas eletrônicas nas bases de dados MEDLINE/PubMed, Embase, WEB OF SCIENCE, Organização Mundial de Saúde, CENTRAL e OpenGrey. Nós buscamos manualmente estudos de intervenção publicados antes de abril de 2016, comparando efeitos da aspirina com um controle em adultos. Dois autores extraíram independentemente os dados de publicação, população recrutada, intervenção (dose de aspirina, acompanhamento e tratamento combinado) e os resultados principais (frequência, gravidade e duração da enxaqueca). Foi avaliada a qualidade dos estudos com a ferramenta da Cochrane para risco de viés.

RESULTADOS: A nossa busca recuperou 1.098 referências, das quais 8 preencheram os critérios de seleção para esta revisão sistemática. A população total foi de 28,326 participantes (18-64 anos); a maioria (96%) de homens. A dosagem variou entre 50 a 650 mg/dia em todos os estudos. O risco de viés foi geralmente baixo ou pouco claro. O único desfecho para o qual a maioria dos estudos incluídos (6/8) relatou redução significativa foi a frequência de enxaqueca, que foi reduzida com uma dose de aspirina de pelo menos 325 mg/dia.

CONCLUSÃO: A aspirina pode reduzir a frequência das enxaquecas; no entanto, a dosagem ideal não é clara.

INTRODUCTION

Migraine is a common and debilitating disorder,[1,2] ranking as the third most prevalent disorder and the seventh highest specific cause of disability worldwide.[3] In the Global Burden of Diseases study, migraine was one of eight conditions that affected more than 10% of the population (11.7%) from 2006 to 2013.[4] In Latin America, a multicenter study conducted in Argentina, Brazil, Colombia, Mexico and Venezuela found that 62% of the participants suffered from headaches, and that the prevalence of migraine among women was 6.1% to 17.4%, while that among men was 2.9% to 7.8%.[5]

Furthermore, several studies have identified a subgroup of patients who experience chronic migraine,[6, 7] in which headache occurs on at least 15 days per month for more than 3 months,[2, 8] with features of migraine headache on at least 8 days per month. Conversely, migraine with a headache burden of less than 15 days per month is defined as episodic migraine.[2, 9] In both forms of migraine, prophylaxis is indicated.[2, 10]

Several medications are used to prevent migraine. Specifically, beta-blockers (metoprolol and propranolol)[11, 12] and anticonvulsants (valproic acid and topiramate) are considered to be level A treatments,[10,12, 13] while antidepressants (amitriptyline)[14,15] are regarded as a level B treatment.[11] Other medications, such as angiotensin-converting-enzyme inhibitors, have not shown the same efficacy. Nonetheless, they have been advocated as second or third-line agents.[16]

Since the 1980s, aspirin has been considered to be a possible migraine prophylactic.[17] Despite some well-known side effects (e.g. gastrointestinal and renal dysfunction),[18] aspirin is a possible means for treating migraine, as it is less costly and safer than some other medications, such as beta-blockers and anticonvulsants.[19, 20] However, few studies have explored the effects of aspirin on migraine. Most investigations involving this drug have primarily been designed to evaluate its impact on cardiovascular outcomes.[17, 21] Nonetheless, several such investigations have reported some benefits on migraine. For instance, in the British Doctors' Trial,[17] 5,000 healthy male doctors received 500 mg of aspirin daily; migraines were reported significantly less often in the intervention group than in the control group. Similarly, the Physicians' Health Study[21] reported that migraine recurrence was 20% lower among men who had received 325 mg of aspirin on alternate days than among those in a placebo group. On the other hand, the Women's Health Study,[22] which was also designed primarily to evaluate the cardiovascular outcomes of aspirin use, reported that low doses of aspirin (100 mg) had a small effect on the frequency, severity and duration of migraine among middle-aged women. However, this effect was not significant, perhaps precisely because the effects on migraine were not the focus of the study.[23]

OBJECTIVE

These conflicting results indicate that the evidence regarding the effects of aspirin on migraines remains inconclusive. For this reason, we conducted a systematic review to analyze the effectiveness of aspirin for migraine prophylaxis.

METHODS

Search strategy

We conducted a systematic review of the current literature (published before April 2016) in the following databases: MEDLINE/PubMed, Embase, WEB OF SCIENCE, WHO, CENTRAL and OpenGrey. We searched for studies that used aspirin as a prophylactic to treat migraine. These computer-based searches combined search terms related to the intervention ("aspirin" OR "aspirin/therapeutic use") and outcomes of interest ("migraine disorders" OR "migraine disorders/prevention and control") without any language restriction. The search terms were investigated both as controlled vocabulary (MeSH terms), and as free text words in the title and/or abstract. In addition to the electronic searches, we searched the reference list of all studies included and we also searched manually for interventional studies published before April 2016 that compared the effects of aspirin with a control in adults (**Table 1**).

Study identification and selection

Two authors independently reviewed the title and abstract of each reference to determine whether the study should be included. They based their decision on the following selection criteria. Studies had to:

1. report interventions in the adult population, as randomized controlled trials (RCT) or clinical trials in which an intervention was compared with a control group in a parallel or crossover design;
2. be crossover studies that tested aspirin as a prophylactic treatment for migraine;
3. report the criteria for migraine; or
4. examine the effect of aspirin (acetylsalicylic acid [ASA] or similar) on migraine prophylaxis, regardless of frequency and dose.

Since most studies were published before the Third Classification of the International Headache Society (IHS) defined migraine,[8] we chose to retrieve all papers that included prophylaxis of migraine as an outcome, regardless of the definition of migraine.

All the studies included reported outcomes within a few hours of the migraine attack. Studies were excluded when:

1. the migraine was described as acute;
2. headache was not differentiated from migraine;
3. the effects of other drugs were compared with those of aspirin;

4. only cost-effectiveness was analyzed;
5. drug therapy was compared with non-pharmacological intervention;
6. pregnant women were included; or
7. animals were used.

Letters, abstracts and conference proceedings were also excluded. Any disagreements regarding article selection were resolved through discussion; a third author was available to resolve disagreements. The papers included were read fully after an initial appraisal. They were then assessed once more by two independent authors to ensure that they met the selection criteria.

Data extraction

We extracted data using a structured database that had been created prior to the literature search. Specifically, we extracted detailed, study-level characteristics; namely, study design (such as sample size and follow-up duration), population characteristics (age, gender and ethnicity), intervention (aspirin only or aspirin combined with other medications and compared with a control group in which only the other medications were used), outcome assessment (ascertainment criteria), analysis (statistical method, measure of association and sensitivity analyses) and variance (standard error and confidence interval [CI]).

Quality scoring

Two reviewers independently evaluated the methodological quality of each study. To do so, they used the Cochrane Collaboration tool for assessing the risk of bias in randomized trials,[24] which categorizes the following domains as "high risk", "unclear" or "low risk":

1. random sequence generation;
2. allocation concealment;
3. blinding of participants, personnel and outcome assessors;
4. incomplete outcome data;
5. selective reporting; and
6. other sources of bias.

Synthesis of results

We had originally intended to perform a meta-analysis that compared migraine frequency between aspirin-treated and placebo-treated patients. However, we were only able to summarize three studies that had reported comparable units of migraine frequency (Benseñor et al.,[19] Buring et al.[21] and Bousser et al.[25]). These studies had high heterogeneity (I^2 = 80.0%; P = 0.007) that could not be explored. Therefore, we chose not to perform a meta-analysis.

RESULTS

Study selection

Overall, we identified 1,098 papers, of which 1,062 were excluded on the basis of the title or abstract. The reasons for this exclusion are shown in **Figure 1**. Most prominently, several studies involved pregnant women or children, some were based on acute migraine and others were designed as reviews, involved a different intervention or evaluated different outcomes. The remaining 23 articles were fully assessed, and eight studies were ultimately selected for data extraction.

Study characteristics

The characteristics of the eight studies included in this systematic review are shown in **Table 2**. They included a total of 28,326 participants (sample sizes ranged from 12 to 22,071 participants).

Table 1. Search strategies

Database	Search terms	Number of hits
PubMed	((("migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields]) AND (("aspirin"[MeSH Terms] OR "aspirin"[tiab]) OR ("drug therapy, combination"[MeSH Terms] OR "combination drug therapy"[tiab] OR "aspirin/adverse effects"[Mesh Terms]) OR "aspirin/therapeutic use"[Mesh Terms])) AND ((((("primary prevention"[MeSH Terms] OR ("primary"[All Fields] AND "prevention"[All Fields]) OR "primary prevention"[All Fields]) OR "migraine disorders/prevention and control"[Mesh Terms] AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "control"[All Fields])) OR ("secondary prevention"[MeSH Terms] OR ("secondary"[All Fields] AND "prevention"[All Fields]) OR "secondary prevention"[All Fields])) OR ("recurrence"[MeSH Terms] OR "recurrence"[All Fields]))	181
Embase	'migraine disorders'/exp OR ('migraine disorders':de,ab,ti) AND aspirin/exp OR (aspirin) :ab,ti OR 'drug therapy, combination'/exp OR ('combination drug therapy'):ab,ti OR 'aspirin/adverse effects'/exp OR 'aspirin/therapeutic use'/exp AND 'primary prevention'/exp OR (primary :de,ab,ti) AND (prevention):de,ab,ti OR ('primary prevention'):de,ab,ti OR 'migraine disorders/prevention and control'/exp AND ('prevention and control') :de,lnk,ab,ti OR (prevention):de,ab,ti AND (control):de,ab,ti OR ('prevention and control'):de,ab,ti OR (control):de,ab,ti OR 'secondary prevention'/exp OR (secondary):de,ab,ti AND (prevention):de,ab,ti OR ('secondary prevention'):de,ab,ti OR recurrence/exp OR (recurrence):de,ab,ti	121
WEB OF SCIENCE	TS = (migraine OR migraine disorders) AND TS = (aspirin OR drug therapy, combination) AND TS = (prevention OR control) AND (article)	166

Several studies lacked information regarding the number of migraine attacks and the type of migraine. Furthermore, migraine was defined using different criteria across the studies: three studies[25-27] defined migraine using the criteria of the *Ad Hoc* Committee on the Classification of Migraine.[28] Only one study[19] classified migraine according to the IHS criteria.[29] Other studies either used their own definition of migraine[30] or did not mention at all how migraine was defined.[17,21,24] Overall, the studies

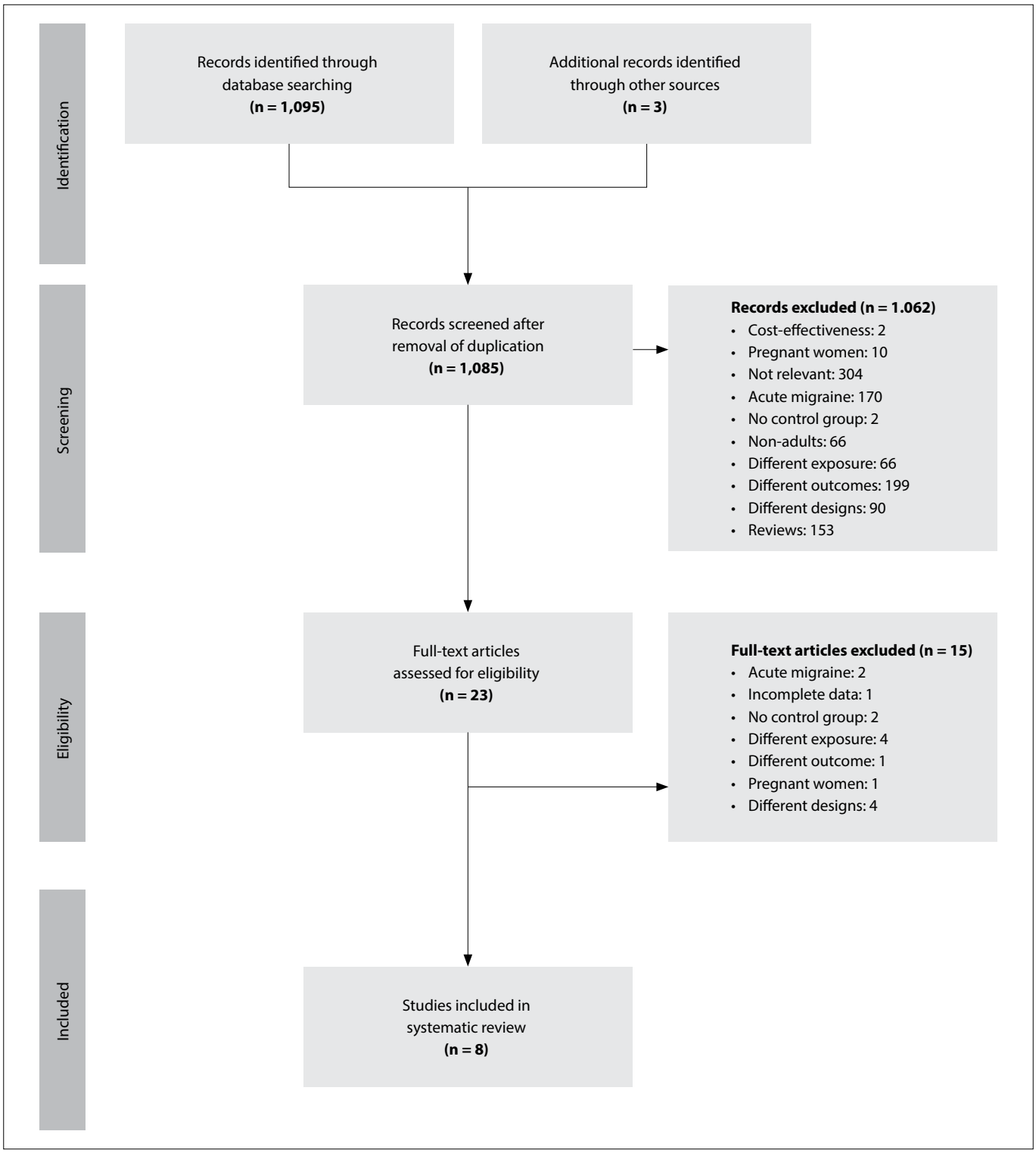

Figure 1. Study flow diagram.

were designed following two different models: parallel randomized clinical trial[17,19,21] and crossover randomized clinical trial.[25-27,30,31] Two studies reported an intervention that combined aspirin with other medication (dipyridamole and dihydroergotamine, respectively) and compared this with a placebo.[26,30] The remaining studies reported interventions that compared the effects of aspirin with those of a placebo. The ASA dosage used in the studies ranged from low (100 mg every other day)[19] to high (650 mg every day).[30,31] Follow-up periods ranged from 2[25] to 72[17] months, with a mean follow-up time of 27.2 months. Five studies included women,[19,24-27] but the two largest studies included in this review only recruited men.[17, 21]

Table 3 shows the main outcomes reported in the studies included. Frequency, for example, was reported as "migraine attacks per month",[19,24,26,27] "migraine index"[26] and "migraine events per 100,000 men in one year".[17] In one study, a migraine index was calculated using the following formula: 1 x (F x D) + 2 x (F x D) + 3 x (F x D), where F is frequency of attacks per month and D is the mean duration of attack in hours.[26] Severity was reported using different subjective scales;[19,27] for instance, 0 = no pain, 100 = severe pain. Two studies that used such scales of measurement also reported the duration of migraine attacks.[19,25]

Characteristics of study populations

Our systematic review included an adult population totaling 28,331 participants. The mean age across the studies ranged from 18 to 64 years, and 96% of the total population (27,218 participants) were men, mainly because two major studies included in the systematic review (the Physician's Health Study and the British Male Doctors' Study) consisted of solely male populations. On the other hand, five of the studies recruited mostly women for the interventions.[19,25,27,28] All the studies reported on otherwise healthy participants.

Quality assessment of the studies included

With regard to random sequence generation, half of the studies showed a low risk of bias. Concerning allocation concealment, only one study had a low risk of bias; most of the remaining studies were determined to have an unclear risk of bias in this regard. In terms of blinding of participants, personnel and outcome assessors, seven studies showed a low risk of bias, and only one had a high risk of bias. Regarding incomplete and selective outcome reporting, most studies showed a low risk of bias. Finally, with regard to the other risks of bias, three studies had a low risk of bias, two showed an unclear risk and three revealed a high risk of bias. The risk of bias in the studies included is presented in **Figure 2**.

Table 2. Characteristics of studies included

Author	Year	Location	Design	N	N women	Women %	Age mean (SD) or range	Population baseline comorbidities	Intervention	Control	Follow-up (months)	Migraine classification at baseline
Benseñor et al.[19]	2001	USA	Parallel	1,001	1,001	100	51.3 (4.9)	Migraine; use of vitamin E	ASA 100 mg every other day	Placebo	36	International Headache Society
Buring et al.[21]	1990	USA	Parallel	22,071	0	0	53.2 (9.5)	Migraine; Regular exercise	ASA 325 mg every other day	Placebo	60	Physician's Health Study
Peto et al.[17]	1988	UK	Parallel	5,139	0	0	No minimum age - 79 years	Migraine	ASA 500 mg daily	Avoid ASA	72	
Masel et al.[30]	1980	USA	Crossover	25	23	92	21 to 64 years	Migraine, BMI < 25	ASA 325 mg plus 25 mg dipyridamole twice a day	Placebo	9	Own classification
O'Neil et al.[31]	1978	USA	Crossover	12	5	41.6	18 to 53 years	Migraine; family history of migraine	ASA 325 mg twice a day	Placebo	6	
Baldrati et al.[26]	1983	Italy	Crossover	18	16	88.8	33.3 (18 to 49 years)	Migraine	ASA 13.5 ± 1.2 mg/kg/day (three times a day)	Propranolol 1.8 ± 0.1 mg/kg/day	6	*Ad hoc* committee
Bousser et al.[25]	1988	France	Crossover	38	26	68.4	39.6 (13.9)	Migraine	ASA 40 mg + DHE 5 mg, twice a day	Placebo	2	*Ad hoc* committee
Hosman-Benjaminse et al.[27]	1986	Netherlands	Crossover	27	21	77.7	35	Migraine	ASA 160 mg daily	Placebo	6	*Ad hoc* committee

The effectiveness of aspirin for prophylaxis of migraine

Benseñor et al.,[19] Buring et al.,[21] Peto et al.,[17] O'Neil et al.,[31] Baldrati et al.[26] and Hosman-Benjaminse et al.[27] reported on aspirin as a single active treatment for migraine. All these studies, except for that of Benseñor et al.,[19] reported that there was an inverse association between aspirin use and migraine frequency.[17, 21, 24, 25] In studies that found a reduction in migraine frequency, the dosage ranged from 1,300 mg[21] to 4,550 mg weekly.[31]

Benseñor et al.,[19] Baldrati et al.[26] and O'Neil et al.[31] analyzed the severity of migraine attacks. Only Baldrati et al.[26] reported that there was an inverse association between severity and aspirin use. Benseñor et al.[19] and Baldrati et al.[26] reported on the duration of migraine episodes as an outcome. Baldrati et al.[26] found an inverse association, while Benseñor et al.[19] found a direct association that was not significant. Benseñor et al.[19] was the only study that described incapacitation as an outcome; after having restricted the analysis to women who fulfilled the modified IHS criteria for migraine, they reported that there was a significant improvement in incapacitation after 12 months (OR = 1.45; 95% CI = 1.04 - 2.02).

Masel et al.[30] reported on an intervention combining dipyridamole and aspirin, while Bousser et al.[25] combined dihydroergotamine with aspirin as an active prophylactic treatment. Each study reported different doses of aspirin, and both compared the outcomes with those of a placebo group. Both studies reported a decrease in the frequency of migraine episodes. However, neither study showed that aspirin had any significant effect on the other outcomes, such

Table 3. Main outcomes reported in the studies included

Author	Year	Main outcome of interest	Outcome frequency	Outcome severity	Outcome duration	Outcome incapacitation
Benseñor et al.[19]	2001	Severity, frequency, duration and level of incapacitation	OR 1.13 (CI 0.86-1.48) RM 0.97 (CI 0.86-1.09)	OR 1.06 (CI 0.81-1.39) RM 0.88 (CI 0.74-1.06)	OR 1.11 (CI 0.85-1.45) RM 1.03 (CI 0.85-1.24)	OR 1.12 (CI 0.86-1.47)
Buring et al.[21]	1990	Frequency	RR 0.80 (CI 0.72-0.88)			
Peto et al.[17]	1988	Migraines events per 10,000 men/year	RR 0.71; P < 0.001			
Masel et al.[30]	1980	Frequency, severity, level of incapacitation	RM 0.57	Severity scale reduction 64.9%		Activity scale improvement 66.6%
O'Neil et al.[31]	1978	Frequency, type of migraine, severity, duration (years) and platelet analysis (aggregation and structure)	75% reported 50% reduction P ≤ 0.0001	33.3% reported less severity No significance		Activity scale improvement 66.6%
Baldrati et al.[26]	1983	Migraine index, frequency, duration, severity, headache days and drug in blood	64.8% reduction of migraine index			
Bousser et al.[25]	1988	Frequency, duration, severity, consumption of acute drugs, treatment and side effects	5.1 (1.6;8.5) fewer attacks; P = 0.003	No significance	No significance	
Hosman-Benjaminse[27]	1986	Frequency and severity	P = 0.21	P = 0.12		

OR = odds ratio; CI = 95% confidence interval; RM = risk of migraine; RR = relative risk.

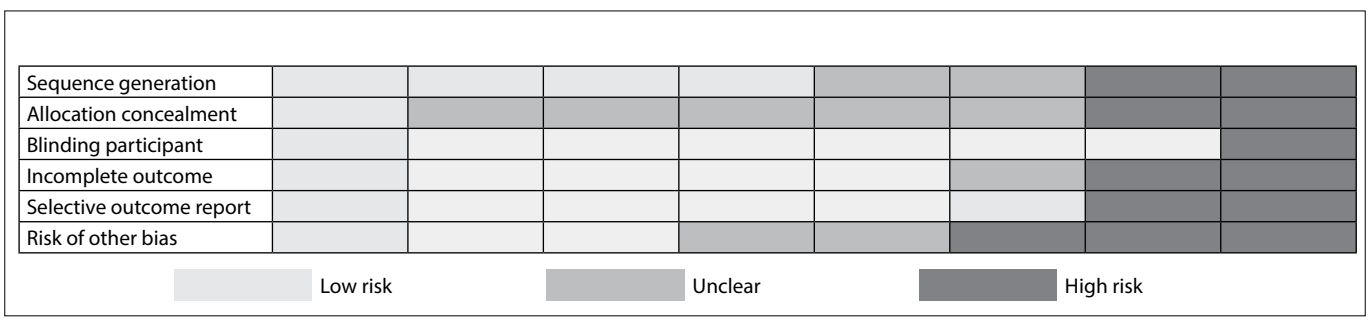

Figure 2. Risk of bias in the studies included.

as severity and duration, and neither of them showed any worsening of any of the outcomes reported. Importantly, because the three studies that reported comparable units regarding frequency of migraine (Benseñor et al.,[19] Buring et al.[21] and Bousser et al.[25]) had high heterogeneity (I^2 = 80.0%; P = 0.007), we chose not to perform a formal meta-analysis. The other studies included presented frequency outcomes as a proportion of the study groups' reported reduction in migraine attacks.

DISCUSSION

The present systematic review included a total of eight articles reporting the effects of aspirin on different migraine-related outcomes, including severity, frequency and duration. In total, we found consistent reports showing that continuous use of aspirin affects the frequency of migraine episodes. Additionally, we found that higher dosages were associated with better results.

The total weekly dose of aspirin (1,300 mg to 4,550 mg) was higher in studies[17,21,24,25] that reported that there was an inverse association between migraine frequency and continuous use of the drug than in studies that reported that there was no significant effect.[19]

Frequency was the only outcome that was analyzed in all the studies included. Nevertheless, it was defined and interpreted differently among the studies, which hindered synthesis of our data.

Severity and duration were defined and registered differently; thus, it was difficult to summarize the data. Disability level, necessity for relief drugs and days with headache were isolated outcomes that were only reported in some studies. Therefore, we could not properly assess these data and include them in this systematic review. Finally, because the outcome measurements were so heterogeneous, we were unable to perform a meta-analysis.

There was no significant association between aspirin and migraine. Neither aspirin dosage nor combination with other medications decreased the severity or duration of migraine attacks in the studies included. Nonetheless, few studies reported severity and duration as outcomes, so it is likely that the data were insufficient to address these questions.

The only study to report an inverse association between aspirin and all three main outcomes[26] also showed high risk of bias. However, the three highest-quality studies showed a significant association[17,21,24] between continuous use of aspirin and reduction in the frequency of migraine attacks, with no significant effect on the duration and severity of outcomes. It is important to note that two of these studies[17,21] were designed to ascertain cardiovascular outcomes and that they used higher dosages of aspirin for this reason. This may explain the significant effect on migraine.

Despite earlier interest in aspirin as a possible prophylactic for migraine,[20] studies comparing aspirin with a placebo in this regard are rare. One strength of the present systematic review is that it gathered individual studies that have tested the prophylactic effect of continuous aspirin use on migraine. Even though most studies had a primary outcome of interest other than migraine, we were able on the basis of the available evidence to identify the direction of association, as well as to ascertain a cutoff dosage for the effect of aspirin on migraine frequency. Furthermore, given that most studies focused on cardiovascular outcomes, we expect that populations using aspirin to prevent cardiovascular events have a lower frequency of migraine.

Our study had some limitations that should be considered. Most importantly, we were unable to classify the migraines that were reported in the studies included according to the recent IHS[8] definition: we only found primary studies that used very different criteria to define migraine. Additionally, the reporting of outcomes and dosage was not standardized across studies, thus preventing us from performing a formal meta-analysis. Furthermore, because migraines were not classified in the studies included, we were unable to categorize the migraines. Therefore, our results should be applied to the general population with caution. Finally, the use of diverse criteria to define migraine across studies may have introduced some misclassifications or misdiagnoses of migraine. However, we cannot be certain of this, and the prophylactic effect of aspirin on migraine may consequently have been underestimated.

Although we could not gather information regarding quantitative effects, it was possible to identify the direction of association in relation to migraine frequency. With regard to severity and duration, no evidence supports prescription of aspirin for this purpose.

Since other combinations of treatments involving aspirin have recently been tested[32] as prophylactic treatment for migraine, we believe that the effect of aspirin in isolation needs to be quantified and made known. For effective prophylaxis, the dosage should be more than 325 mg/day: smaller doses did not show significant effects across all studies included. With regard to side effects in this area, dyspepsia, peptic ulcer, upper gastrointestinal bleeding and renal dysfunction should be assessed.

CONCLUSION

In conclusion, the present systematic review presented the available evidence on the prophylactic effect of aspirin in relation to migraine. The effects on attack frequency were consistent across most of the populations studied, even though the investigations focused on cardiovascular outcomes. Aspirin can reduce the frequency of migraines. However, the optimal dosage is unclear.

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Enlarged waist combined with elevated triglycerides (hypertriglyceridemic waist phenotype) and HDL-cholesterol in patients with heart failure

Cintura aumentada combinada a triglicerídeos elevados (fenótipo da cintura hipertrigliceridêmica) e HDL-colesterol elevado em pacientes com insuficiência cardíaca

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KEY WORDS:
Cholesterol, HDL.
Heart failure.
Hypertriglyceridemia.
Waist circumference.
Cardiovascular diseases.

PALAVRAS-CHAVE:
HDL-colesterol.
Insuficiência cardíaca.
Hipertrigliceridemia.
Circunferência da cintura.
Doenças cardiovasculares.

ABSTRACT

CONTEXT AND OBJECTIVE: The association of serum triglycerides plus waist circumference seems to be a good marker of cardiovascular risk and has been named the "hypertriglyceridemic waist" phenotype. The aim of our study was to investigate the association between the hypertriglyceridemic waist phenotype and HDL-cholesterol among patients with heart failure.

DESIGN AND SETTING: Cross-sectional study in a tertiary-level hospital in southern Brazil.

METHODS: We included patients with heart failure aged > 40 years. Anthropometric assessment (weight, height, waist and hip circumferences) was performed; body mass index (BMI) and waist-hip ratio were calculated and lipid measurements (serum total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides) were collected. In men and women, respectively, waist circumference ≥ 94 cm and ≥ 80 cm, and triglycerides ≥ 150 mg/dl were considered abnormal and were used to identify the hypertriglyceridemic waist phenotype. Analyses of covariance were used to evaluate possible associations between levels of HDL-cholesterol and the hypertriglyceridemic waist phenotype, according to sex.

RESULTS: 112 participants were included, of whom 62.5% were men. The mean age was 61.8 ± 12.3 years and the mean ejection fraction was 40.1 ± 14.7%. Men and woman presented mean HDL-cholesterol of 40.5 ± 14.6 and 40.9 ± 12.7 mg/dl, respectively. The prevalence of the hypertriglyceridemic waist phenotype was 25%. There was a significant difference in mean HDL-cholesterol between men with and without the hypertriglyceridemic waist phenotype (32.8 ± 14.2 versus 42.1 ± 13.7 mg/dl respectively; P = 0.04), even after adjustment for age, body mass index, type 2 diabetes mellitus, use of statins and heart failure etiology.

CONCLUSIONS: The hypertriglyceridemic waist phenotype is significantly associated with lower HDL-cholesterol levels in men with heart failure.

RESUMO

CONTEXTO E OBJETIVO: A associação de triglicerídeos séricos e circunferência da cintura parece ser um bom marcador de risco cardiovascular e é denominada fenótipo da cintura hipertrigliceridêmica. O objetivo do estudo foi avaliar a associação entre o fenótipo da cintura hipertrigliceridêmica e o HDL-colesterol em pacientes portadores de insuficiência cardíaca.

TIPO DE ESTUDO E LOCAL: Estudo transversal em um hospital terciário no sul do Brasil.

MÉTODOS: Foram incluídos indivíduos com insuficiência cardíaca com idade > 40 anos. Foram realizadas as medidas antropométricas (peso, estatura, circunferência da cintura e do quadril) e calculados índice de massa corporal e relação cintura quadril, e foi avaliado o perfil lipídico (colesterol total, LDL-colesterol, HDL-colesterol e triglicerídeos séricos). Em homens e mulheres, respectivamente, circunferência da cintura ≥ 94 cm e ≥ 80 cm e triglicerídeos ≥ 150 mg/dl foram considerados anormais e usados para identificação do fenótipo da cintura hipertrigliceridêmica. Análises de covariância foram usadas para avaliar possíveis associações entre níveis de HDL-colesterol e o fenótipo da cintura hipertrigliceridêmica de acordo com o sexo.

RESULTADOS: Foram incluídos 112 participantes e 62,5% eram homens. A média de idade foi de 61,8 ± 12,3 anos e a fração de ejeção média foi 40,1 ± 14,7%. Homens e mulheres apresentaram médias de HDL-colesterol 40,5 ± 14,6 e 40,9 ± 12,7 mg/dl, respectivamente. A prevalência do fenótipo da cintura hipertrigliceridêmica na amostra foi de 25%. Observou-se diferença significativa entre as médias de HDL-colesterol entre homens com e sem o fenótipo da cintura hipertrigliceridêmica (32,8 ±14,2 *versus* 42,1 ± 13,7 mg/dl, P = 0,04), mesmo após ajuste para idade, índice de massa corporal, diabetes mellitus tipo 2, uso de estatinas e etiologia da insuficiência cardíaca.

CONCLUSÕES: O fenótipo da cintura hipertrigliceridêmica está associado significativamente com menores níveis de HDL-colesterol em homens com insuficiência cardíaca.

INTRODUCTION

Heart failure is a complex systemic clinical syndrome[1] and coronary artery disease is the main cause of heart failure of ischemic origin.[2]

An obesity paradox is commonly reported among patients with heart failure, in which patients with high adiposity have a better prognosis than do individuals who are normal or underweight.[3] The prognostic value of indexes that detect excess abdominal body fat, such as waist circumference (the traditional tool) and the visceral adiposity index (an alternative and emerging tool) have been evaluated among individuals with ischemic heart failure,[4] since abdominal obesity is also associated with coronary heart disease.

In addition to abdominal obesity, there has been increasing interest in the role of the atherogenic lipid triad, i.e. hyperinsulinemia, elevated apolipoprotein B and small, dense low density lipoprotein (LDL) particles, in the genesis of coronary artery disease.[5,6] However, difficulties in obtaining these parameters in routine practice hinder their use in screening for individuals at high cardiovascular risk. The hypertriglyceridemic waist phenotype (enlarged waist and elevated triglycerides, EWET), defined as simultaneous presence of increased waist circumference and elevated triglycerides, seems to more accurately identify individuals who are at risk, compared with isolated measurements of waist circumference or serum triglycerides,[7] and can be applied in clinical practice. In addition to the strong association of the hypertriglyceridemic waist phenotype with the atherogenic triad,[8,9] it is related to increased visceral adipose tissue,[10] worse cardiometabolic profile (both in the general population[11-13] and in individuals who are at risk[14,15] or who present cardiovascular disease[16]), higher incidence of coronary artery disease and cardiovascular mortality.[17]

Low high-density lipoprotein-cholesterol (HDL-c) levels are negatively associated with cardiovascular events in individuals with cardiovascular diseases.[18,19] Individuals with the hypertriglyceridemic waist phenotype have been found to present decreased HDL-c levels[11,12] and smaller HDL particles.[20] Gomez-Huelgas et al.[12] showed that subjects without cardiovascular disease but with the hypertriglyceridemic waist phenotype had lower HDL-c levels independently of sex and age. However, the prevalence of the hypertriglyceridemic waist phenotype was higher in men and it was positively associated with age. In a multiethnic population also without cardiovascular disease,[11] men with the hypertriglyceridemic waist phenotype showed lower HDL-c levels than women, while HDL-c levels were significantly lower in women with hypertriglyceridemic waist than in those without this phenotype.

Lower levels of HDL-c and higher levels of serum triglycerides may lead to a worse prognosis for ischemic heart disease patients.[21] Moreover, adipokines secreted by visceral adipocytes may negatively contribute towards decreased HDL-c levels in individuals with heart failure.[22] Although the hypertriglyceridemic waist phenotype has been investigated in populations in which the obesity paradox is common,[23] it has not yet been evaluated in heart failure patients.

OBJECTIVE

To evaluate a possible association between HDL-cholesterol and hypertriglyceridemic waist in men and women with heart failure.

METHODS

We performed a cross-sectional analysis among patients who had previously been diagnosed with heart failure and who were enrolled at the baseline of a cohort study conducted in a public tertiary hospital. Between 2011 and 2012, these patients were consecutively enrolled if they met the following inclusion criteria: history of New York Heart Association class I-IV heart failure defined by cardiologists in accordance with the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) criteria;[24] age between 40 and 90 years; no history or clinical evidence of severe heart failure comorbidities (coronary artery disease, cerebrovascular disease or severe kidney disease) over the last six months; and residency in the Porto Alegre metropolitan area (southern Brazil). The following were excluded: patients with lower limb amputation, sequelae of stroke, acute coronary syndrome in the last 90 days or valvular heart disease; pregnant women; candidates for myocardial revascularization; patients in the postoperative period of cardiac surgery (myocardial revascularization or heart valve surgery performed less than one year earlier); and individuals with a history of cancer within the last two years.

Dietitians, medical students and nutrition students administered a questionnaire that asked for clinical data (use of medications, history of diseases, hospitalizations, etc.) and sociodemographic data (age, sex, educational attainment and self-reported skin color). A field coordinator (local cardiologist) was responsible for quality control in relation to the interviews. Patients were also asked about alcohol consumption (alcohol abuse was defined as ethanol consumption per day of 30 g or more among men and 15 g or more among women) and smoking habits, in which they were classified as current smokers, ex-smokers or never smokers.

An anthropometric assessment was performed at the first clinical evaluation. Weight and height were measured with the patient wearing lightweight clothing and standing barefoot on a flat surface, in accordance with the method proposed by Lohman.[25] Weight was measured to the nearest 100 g using a calibrated scale with a capacity of 150 kg (Cauduro, Brazil). Height was measured to the nearest 0.1 cm using a stadiometer with a measuring rod of 205 cm (Sanny, Brazil). Body mass index (BMI) was calculated in accordance with the World Health Organization criteria, using a cutoff point of 30 kg/m^2 for the diagnosis of obesity.

Waist and hip circumferences were measured in cm, using an inelastic measuring tape. Waist circumference was measured at the midpoint between the lowest rib and the upper border of iliac crest,[26] and hip circumference was measured at the maximum protuberance of the buttocks. The waist-hip ratio was calculated by dividing the waist circumference by the hip circumference, and an elevated waist-hip ratio was defined as > 0.90 for men and > 0.85 for women.[27]

The ejection fraction (%) was determined during a transthoracic echocardiogram, using color Doppler and tissue Doppler imaging (GE VIVID 3, General Electric, Norway).[2] These data were obtained from patients' medical records. Heart failure etiology was diagnosed by the cardiology staff and was registered in the medical records: ischemic etiology was defined if the individual had a previous diagnosis of ischemic heart disease.

For lipid measurements (serum total cholesterol, LDL-cholesterol, HDL-c and triglycerides), 10 ml of venous blood was collected from each participant. Lipid concentrations were determined using a standard colorimetric enzymatic method. HDL-c levels (dependent variable) were treated as continuous values for statistical analysis. The lipid profile was considered to be altered if the HDL-c level was below 40 mg/dl in men and 50 mg/dl in women, and if serum triglycerides were above 150 mg/dl in men and women,[28] in addition to the medical diagnosis.

Patients were deemed to present hypertriglyceridemic waist (main independent variable) if they had waist circumference ≥ 94 cm (men) or ≥ 80 cm (women) + serum triglycerides ≥ 150 mg/dl.[28,29] Thus, these patients were considered were considered to present the hypertriglyceridemic waist phenotype. Blood pressure was determined using standard techniques, and patients were considered hypertensive if they had previously been diagnosed with hypertension (collected from the medical records), if they had systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or if they were taking antihypertensive drugs.[23] Fasting blood glucose ≥ 126 mg/dl or glycated hemoglobin ≥ 6.5% or a previous medical diagnosis were used to detect patients with type 2 diabetes mellitus.[30]

Sample size was calculated using the WinPepi software, version 11.18. The total sample size required for the study was calculated as 76 individuals, by making the assumptions that the prevalence of hypertriglyceridemic waist phenotype would be at least 20% in the sample, with a difference of at least 7 mg/dl in HDL-c levels between patients with and without the hypertriglyceridemic waist phenotype (standard deviations of 12.3 and 9.4 mg/dl, respectively),[13] a power of 80% and a significance level of 5%.

Analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 17.0 (SPSS, IL, USA). Continuous variables were expressed as means and standard deviations and categorical variables as absolute values and percentages. Student's t test (continuous variables) and Pearson's chi-square or Fisher's exact test (categorical variables) were used for comparisons. Analyses of covariance (ANCOVA) were used to evaluate possible associations between mean HDL-c and hypertriglyceridemic waist after adjustment for potential confounding factors (age, BMI, diagnoses of type 2 diabetes mellitus, statin use and heart failure etiology), separately according to gender. For each analysis, an α-level = 0.05 was considered significant, and 95% confidence intervals (CI) were shown.

The study was approved by the local Research Ethics Committee (CEP-GHC number 10-118), and all patients signed an informed consent statement. There was no external funding for the study.

RESULTS

Between July 2011 and January 2012, 112 patients were included, of whom 70 (62.5%) were men. Eighty-five patients (approximately 76%) were classified as New York Heart Association grade III-IV. The patients had a mean age of 61.8 ± 12.3 years, and a mean of 5 ± 3.3 years of educational attainment. Thirteen patients (12%) were smokers, 55 (49%) ex-smokers, and 44 (39%) never smoked; 10 patients (9%) were identified as alcohol abusers. Thirty-seven patients (33%) were diagnosed with type 2 diabetes mellitus, 86 (77%) had hypertension and 38 (34%) had dyslipidemia. The mean ejection fraction was 40.1 ± 14.7%, and 19 patients (17%) were diagnosed with ischemic heart failure. The prevalence of hypertriglyceridemic waist phenotype was 25% (95% CI: 16.8-35.6).

The mean BMI was 28.4 ± 6.5 kg/m^2, and 36 patients (32%) were considered obese (BMI ≥ 30 kg/m^2). BMI was higher among women (29.7 ± 7.6 kg/m^2) than among men (27.6 ± 5.8 kg/m^2), but with no statistical difference. Elevated waist-hip ratio was identified in 91 patients (81%), and the waist-hip ratio values were higher among men (0.99 ± 0.11) than among women (0.93 ± 0.07), but with no statistical difference. Regarding the prevalence of enlarged waist circumference according to different cutoff points for detecting higher cardiovascular risk, for ≥ 102 cm among men and ≥ 88 cm among women, there were 26 cases (23.2%) and 32 cases (28.6%), respectively; for ≥ 94 among men and ≥ 80 among women, there were 37 cases (33%) and 46 cases (41.1%). Triglyceride levels ≥ 150 mg/dl were detected in 32 individuals (28.6%).

No differences between men and women were observed regarding HDL-c levels (40.5 ± 14.6 mg/dl in men and 40.9 ± 12.7 mg/dl in women), systolic arterial pressure (120.1 ± 17.6 mmHg in men and 124.5 ± 18.7 mmHg in women) or diastolic arterial pressure (74.1 ± 11.8 mmHg in men and 75.1 ± 10.9 mmHg in women).

Regarding patients diagnosed with ischemic heart failure, 17 were using statins, of whom three were classified as New York Heart Association grades I and II, and 14 as New York Heart Association grades III and IV, with no statistical difference (P = 0.3) between them.

Among the patients with nonischemic heart failure, 36 were using these medications, of whom nine were classified as New York Heart Association grades I and II, and 27 as New York Heart Association grades III and IV, also with no statistical difference (P = 0.9).

Table 1 shows the characteristics of the study group according to presence or absence of the hypertriglyceridemic waist phenotype. Patients with the hypertriglyceridemic waist phenotype had higher prevalence of type 2 diabetes mellitus, dyslipidemia and statin use, higher BMI and ejection fraction and lower HDL-c levels, compared with patients without the hypertriglyceridemic waist phenotype. No statistical difference was observed regarding age, self-reported skin color, educational attainment, smoking, hypertension, New York Heart Association functional classification of heart failure or waist-hip ratio. The prevalence of the hypertriglyceridemic waist phenotype was significantly higher among women than among men (P = 0.01). No patient classified as an alcohol abuser had the hypertriglyceridemic waist phenotype.

Mean HDL-c levels in men and women according to presence or absence of the hypertriglyceridemic waist phenotype are shown in **Table 2**. In univariate analysis, men with the hypertriglyceridemic waist phenotype had significantly lower (P = 0.001) HDL-c levels than men without the hypertriglyceridemic waist phenotype, but this was not observed among women (P = 0.2). The significant association between the hypertriglyceridemic waist phenotype and HDL-c (P = 0.04) among men was observed even after adjusting for age, BMI, diagnosis of type 2 diabetes mellitus, statin use and heart failure etiology (ischemic/nonischemic) in the multivariate analysis.

DISCUSSION

To our knowledge, this is the first study to evaluate the presence of the hypertriglyceridemic waist phenotype among individuals with heart failure, and also the association of this phenotype with HDL-c levels. We observed high prevalence of the hypertriglyceridemic waist phenotype in the study group (higher among women than among men), which was associated with HDL-c levels in men after adjusting for age, BMI, diagnosis of type 2 diabetes mellitus, statin use and heart failure etiology. Few studies have investigated the hypertriglyceridemic waist phenotype in Brazil;

Table 1. Participants' characteristics according to presence or absence of hypertriglyceridemic waist (enlarged waist and elevated triglycerides, EWET) [mean ± standard deviation, SD, or n (%)]

	Without EWET	With EWET	P-value
Age (years)	61.4 ± 12.8	63.2 ± 10.5	0.5*
Sex			
Men	58 (82.9)	12 (17.1)	0.01†
Women	26 (61.9)	16 (38.1)	
Ethnicity			
White	62 (75.6)	20 (24.4)	0.8†
Schooling level (years)	5.15 ± 3.3	4.89 ± 3.3	0.7*
Heart failure etiology			
Ischemic	13 (68.4)	6 (31.6)	0.4†
Nonischemic	71 (76.3)	22 (23.7)	
Smoking			
Current	9 (69.2)	4 (30.8)	
Ex-smoker	44 (80)	11 (20)	0.4†
Never smoked	31 (70.5)	13 (29.5)	
Alcohol abuser			
Yes	10 (100)	0 (0)	0.06‡
No	74 (72.5)	28 (27.5)	
Type 2 diabetes mellitus			
Yes	23 (62.2)	14 (37.8)	0.03†
No	60 (81.1)	14 (18.9)	
Hypertension			
Yes	61 (70.9)	25 (29.1)	0.08†
No	22 (88)	3 (12)	
Dyslipidemia			
Yes	24 (63.2)	14 (36.8)	0.04†
No	59 (80.8)	14 (19.2)	
Ejection fraction (%)	38 ± 14.6	45.5 ± 13.7	0.03*
Functional classification (NYHA)			
I and II	20 (74.1)	7 (25.9)	0.9†
III and IV	64 (75.3)	21 (24.7)	
Statin use			
Yes	35 (66)	18 (34)	0.04†
No	49 (83.1)	10 (16.9)	
HDL-cholesterol (mg/dl)	42.3 ± 15	35.4 ± 7.7	0.002*
Body mass index (kg/m²)	27.3 ± 5.6	31.6 ± 8.1	0.002*
Waist-hip ratio	0.97 ± 0.11	0.97 ± 0.69	0.7*

*Student's t test; †Pearson's chi-square test; ‡Fisher's exact test. NYHA = New York Heart Association.

Table 2. Mean high density lipoprotein-cholesterol (HDL-c) levels in men and women according to presence or absence of hypertriglyceridemic waist (enlarged waist and elevated triglycerides, EWET) [mean ± standard deviation, (95% confidence interval)]

	Men			Women		
	Without EWET (n = 58)	With EWET (n = 12)	P-value	Without EWET (n = 26)	With EWET (n = 16)	P-value
HDL-c*	42.1 ± 15.3 (38.4-45.9)	32.3 ± 6.9 (24.1-40.6)	0.001	42.9 ± 14.9 (37.9-47.9)	37.8 ± 7.7 (31.4-44.2)	0.2
HDL-c†	42.1 ± 13.7 (38.4-45.7)	32.8 ± 14.2 (24.6-40.9)	0.04	41.5 ± 12.9 (36.2-46.8)	38.4 ± 13.2 (31.8-45.1)	0.5

*Univariate analysis, Student's t test; †Multivariate analysis, using analysis of covariance (ANCOVA) model: mean adjusted for age, body mass index, medical diagnosis of type 2 diabetes mellitus, statin use (yes/no) and heart failure etiology (ischemic/nonischemic).

prevalence of 4.5% was reported among young adults[31] and 33% among Brazilian women with hypertension.[14]

The prevalence of the hypertriglyceridemic waist phenotype varies according to the population studied. Gasevic et al.[11] compared the prevalence of the hypertriglyceridemic waist phenotype between Aboriginals, Chinese, Europeans and South Asians, and higher prevalence was found among Chinese people, in both genders. The hypertriglyceridemic waist phenotype was reported in 14.5% of the participants in a study conducted in Spain,[12] and in 41.3% of the individuals with diabetes mellitus in a Serbian population.[14] The notable differences in prevalence of the hypertriglyceridemic waist phenotype in previous studies may be due to different cutoff points for defining elevated waist circumference in different ethnic groups, and different serum triglyceride values for calculating the hypertriglyceridemic waist phenotype. In the present study, we used the waist circumference and serum triglyceride values proposed in Brazilian guidelines.

Body fat distribution differs between men and women in the general population,[32] but in our study the frequency of individuals with elevated waist-hip ratio was higher than that of obesity (defined according to BMI), in both genders. Measurement of abdominal adiposity is useful for assessing the risks associated with obesity and excess visceral fat. Visceral adipose tissue, in turn, is metabolically active and associated with insulin resistance, hypertriglyceridemia, small LDL particles and low HDL-c levels.[33]

However, an increased waist-hip ratio may also result from loss of muscle and fat mass from the lower limbs, which is usually associated with the aging process and the pathophysiology of heart failure, particularly the more severe forms. In a study by Fülster et al.[34] on heart failure patients with a mean age of 66 years, muscle wasting was more pronounced in these individuals than what would be expected for subjects of the same age group. These authors suggested that cachexia relating to chronic heart failure prevails over aging-related loss of lean mass. Therefore, an elevated waist-hip ratio may reflect not only excess abdominal fat accumulation, but also a risk of loss of muscle mass or subcutaneous fat. It is worth mentioning that cardiac cachexia is strongly associated with an inflammatory process.[35]

Hypertrophied visceral adipocytes increase the release of fatty acids via lipolysis and may also contribute towards activation of adipokines involved in inflammation.[36] As previously mentioned, visceral adiposity plays a role in the pathophysiology of type 2 diabetes mellitus and dyslipidemia. The hypertriglyceridemic waist phenotype can be considered to be an indicator of visceral adiposity that includes anthropometric and biochemical components that are highly associated with a worse cardiometabolic profile and higher prevalence of diabetes, dyslipidemia and statin use. In addition, the higher ejection fraction values observed in patients with the hypertriglyceridemic waist phenotype could be a reflection of the obesity paradox in cases of heart failure, i.e. higher adiposity levels would be associated with lower mortality and hospitalization rates.[3]

In our study, no patients who were identified as alcohol abusers had the hypertriglyceridemic waist phenotype. HDL-c plays a key role in reverse cholesterol transport and attenuates the levels of serum triglycerides. Additionally, ethanol seems to increase HDL apolipoprotein A-I and A-II transport rates by increasing hepatic production.[37] Therefore, increased HDL-c levels may have contributed towards maintenance of serum triglyceride levels within the normal range (< 150 mg/dl) in the alcohol abusers of our study group. However, we did not evaluate potential associations between other cardiometabolic factors and alcohol consumption.

We found no significant differences in statin use, heart failure functional class and heart failure etiology between patients with and without the hypertriglyceridemic waist phenotype. According to the American Heart Association,[2] statins should not be used as adjunct therapy in cases of heart failure alone, when no other criteria for their use are met (presence of metabolic syndrome and coronary artery disease). Statin therapy in heart failure patients is controversial, because despite its pleiotropic anti-inflammatory effect, the most effective lipoprotein within the context of cardiovascular risk and protection has not yet been identified.[38] Higher levels of serum LDL-cholesterol, HDL-c, ApoA-I, ApoB and triglycerides seem to be associated with a better prognosis.[39]

A significant association between the hypertriglyceridemic waist phenotype and HDL-c levels was found among men but not among women, even after adjusting for some confounding variables. This finding may be explained by several factors: first, the markedly higher visceral fat accumulation in men in comparison with women, which is accompanied by elevated serum triglycerides and reduced HDL-c[40] (although not statistically different, the mean BMI among the women in this study was higher than that of the men, thus suggesting greater subcutaneous fat deposition);[41] second, the effect of abdominal obesity on proinflammatory states and their atherogenic consequences, including reduction in HDL-c levels;[33] and finally, changes in HDL-c levels that are commonly observed in heart failure patients, especially those with ischemic heart failure.[22] The inflammatory process involved in the pathophysiology of heart failure *per se* leads to reduction of HDL-c, which plays a significant anti-inflammatory role in the etiology of the disease. HDL-c inhibits expression of cell adhesion molecules that promote monocyte infiltration through the endothelium, and decreases the inflammatory process that precedes development of heart failure.[42]

Some of the limitations of our study include the facts that this was an exploratory analysis and that the cross-sectional design of the study might point to reverse causality; the small sample size, which may have conferred higher variability and

may have lacked power to detect some associations, especially among women; and the fact that the study was carried out in a public tertiary-level hospital that deals with patients with higher prevalence of more severe forms of heart failure, which may limit the generalization of these results.

CONCLUSION

The prevalence of the hypertriglyceridemic waist phenotype among our patients with heart failure was high. Reduced HDL-c levels were observed in men with the hypertriglyceridemic waist phenotype, even after adjusting for age, general adiposity, statin use and diagnosis of type 2 diabetes mellitus. Further studies are still needed to identify better anthropometric indicators for altered metabolic profiles and better predictors of the risk of cardiovascular events in heart failure patients. Also, further studies on other populations would enable discussion and comparison of our findings.

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Validity of Klotho, CYR61 and YKL-40 as ideal predictive biomarkers for acute kidney injury: review study

Validade de Klotho, CYR61 e YKL-40 como biomarcadores preditivos ideais para lesão renal aguda: estudo de revisão

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PALAVRAS-CHAVE:
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ABSTRACT

CONTEXT AND OBJECTIVE: Acute kidney injury (AKI) is still a headache for clinicians and scientists as a possible reason for increased death among intensive care unit (ICU) patients after invasive cardiac surgery. Furthermore, the diagnostic process for AKI using conventional biomarkers is not sufficient to ensure early warning of this condition because of the morbid influence of non-renal factors that definitively delay the time for the prognosis. These imposed limitations have led to significant amounts of research targeted towards identifying novel biomarkers for AKI with a sustained degree of sensitivity and specificity. Here, we reviewed previous studies conducted on the Klotho, CYR61 and YKL-40 biomarkers in relation to AKI.

DESIGN AND SETTING: Review of the literature conducted in the Institute of Clinical Chemistry & Biochemistry, Ljubljana University Medical Center, Slovenia.

METHODS: The literature was searched in PubMed and the Cochrane Library. From the database of this specialty, we selected 17 references that matched our context for detailed analysis and further investigation.

RESULTS: The studies reviewed showed notable differences in their results relating to the diagnostic impact of Klotho, CYR61 and YKL-40 on early prediction of AKI.

CONCLUSIONS: The results regarding the Klotho, CYR61 and YKL-40 biomarkers showed markedly equivocal performance in the previous studies and did not fulfill the expectations that these factors would form valid possible biomarkers for AKI.

RESUMO

CONTEXTO E OBJETIVO: A lesão renal aguda (LRA) ainda é uma dor de cabeça para os clínicos e cientistas como possível razão para o aumento da mortalidade entre os pacientes de unidade de terapia intensiva (UTI) após cirurgia cardíaca invasiva. Além disso, o processo de diagnóstico para LRA usando biomarcadores convencionais não é suficiente para garantir um alerta precoce desta condição, devido à influência mórbida de fatores não renais que podem retardar o tempo para o prognóstico. Essas limitações geraram quantidades significativas de pesquisas orientadas para identificar novos biomarcadores para LRA com um grau adequado de sensibilidade e especificidade. Revisamos estudos anteriores realizados sobre os biomarcadores Klotho, CYR61, YKL-40 para LRA.

TIPO DE ESTUDO E LOCAL: Revisão da literatura realizada no Instituto de Química Clínica e Bioquímica, Centro Médico da Universidade de Ljubljana, Eslovênia.

MÉTODOS: A literatura foi pesquisada no PubMed e Cochrane Library. A partir da base de dados da especialidade, selecionamos 17 referências que combinavam com o contexto para uma análise detalhada e mais investigação.

RESULTADOS: Os estudos revisados mostraram diferenças notáveis nos resultados sobre o impacto diagnóstico de Klotho, CYR61 e YKL-40 sobre a detecção precoce do LRA.

CONCLUSÃO: Os resultados em relação aos biomarcadores Klotho, CYR61 e YKL-40 mostraram desempenho marcadamente equívoco nos estudos anteriores e não cumpriram as expectativas de que estes fatores constituam possíveis biomarcadores válidos para LRA.

INTRODUCTION

Acute kidney injury (AKI) is a highly progressive critical problem that often occurs after invasive cardiac surgery using cardiopulmonary bypass (CBP).[1,2] It threatens the life of intensive care unit (ICU) hospitalized patients through accompanying irreversible adverse outcomes that ultimately contribute to a 60% increase in mortality rate.[3] Defining AKI is dependent on measurement of baseline serum creatinine, the traditional biomarker of kidney function, which remains unchanged until a sudden 50% of kidney function is lost.[4] Moreover, AKI has been found to be strongly affected by dietary status, exercise, protein supplements, corticosteroids, age, gender and muscle mass.[5,6] Therefore, there is an urgent need for novel biomarkers to predict and diagnose AKI at its earlier stages, so as to prevent complications and potentiate therapeutic approaches.

Classification of AKI

The Acute Dialysis Quality Initiative Group (ADQI) meeting in 2004 gave rise to a new regular criterion for analyzing kidney function, termed Risk Injury Failure Loss of function and End stage (RIFLE).[7,8] RIFLE was dependent on serum creatinine (SCr) or urinary output (UO) measurements to determine the prognostic severity of deterioration of kidney function, classified into three stages.[8] Many studies mentioned that the usefulness of RIFLE was affected by the following substantial limitations: [1] calculation of the SCr baseline using the Modification of Diet in Renal Disease (MDRD) equation showed high specificity for chronic kidney disease (CKD) but not AKI; [2] SCr was directly influenced by nonspecific factors and hence was unreliable; [3] using UO was a good alternative for SCr, but it was affected by diuretics and could only be measured by using a bladder catheter in an ICU and not among long-stay hospitalized patients; and [4] SCr was considered to be a marker for renal function, not kidney injury.[9]

Subsequently, a modified standard was published in 2007 under the name "Acute Kidney Injury Network (AKIN)", with the aim of closing gaps generated by RIFLE. AKIN used two values of SCr within two days instead of baseline SCr, regardless of glomerular filtration rate (GFR) changes. According to AKIN, stage 3 AKI was confirmed when the duration of increased SCr levels did not exceed 48 h and the patient required renal replacement therapy (RRT).[10]

The failure of both RIFLE and AKIN to fulfill precise prognostic stratification of AKI severity and to provide a unified definition of AKI was the reason for establishing the Kidney Disease Improving Global Outcomes (KDIGO) guidelines. These novel criteria suggested that AKI should be defined by SCr levels that reached 26.4 µmol/l within 48 h or increased to a level 1.5 times higher than the baseline level within 7 days, which provides a sufficient timeframe for AKI diagnosis.[11] The differences between all the diagnostic criteria are summarized in **Table 1**.

Epidemiology of AKI

The AKI incidence rate worldwide has remained imprecise because of the small number of case report studies, gaps in the data collected from patients and differences in definitions of AKI between developed and developing countries.[12-14] Recent studies conducted in the USA and Spain showed incidences of approximately 23.8 cases per 1000 discharges and 209 cases per million, respectively.[15,16] A recent population-based study conducted in the UK reported high incidence of AKI, of 1811 cases per million in 2003.[17] A report from Kuwait indicated an incidence of 4.1 cases per 100,000 population per year.[18] In addition, the annual incidences for AKI in Brazil and northern India were 7.9 and 6.4 cases per 1000 admissions.[19,20] Notably, the mortality

Table 1. Differences between the guidelines "risk injury failure loss of function and end stage" (RIFLE), "acute kidney injury network" (AKIN) and "kidney disease improving global outcomes" (KDIGO) for diagnosing acute kidney injury (AKI)

Staging	RIFLE	AKIN	KDIGO
Stage I	Increase in serum creatinine ≥ 1.5 times from baseline or decrease in estimated glomerular filtration rate ≥ 25% or urinary output < 0.5 ml/kg/h for ≥ 6 h.	Increase in serum creatinine ≥ 26.4 µmol/l or increased 1.5 to 2 fold from baseline or urinary output < 0.5 ml/kg/h for ≥ 6 h.	Increase in serum creatinine ≥ 26.5 µmol/l or increased 1.5 to 1.9 fold from baseline or urinary output < 0.5 ml/kg/h for ≥ 6-12 h.
Stage II	Increase in serum creatinine ≥ 2.0 times from baseline or decrease in estimated glomerular filtration rate ≥ 50% or urinary output < 0.5 ml/kg/h for ≥ 12 h.	Increase in serum creatinine > 2-3 fold from baseline or urinary output < 0.5 ml/kg/h for ≥ 12 h.	Increase in serum creatinine >2.0 to 2.9 fold from baseline or urinary output < 0.5 ml/kg/h for ≥ 12 h.
Stage III	Increase in serum creatinine ≥ 3.0 times from baseline or decrease in estimated glomerular filtration rate ≥ 75% or urinary output < 0.3 ml/kg/h for ≥ 24 h or anuria ≥ 12 h.	Increase in serum creatinine ≥ 3 fold from baseline or serum creatinine ≥ 354 µmol/l or initiation of renal replacement therapy or urinary output < 0.3 ml/kg/h for ≥ 24 h or anuria ≥ 12 h.	Increase in serum creatinine ≥ 3 fold from baseline or serum creatinine ≥ 353.6 µmol/l (> 4 mg/dl) or start of RRT or urinary output < 0.3 ml/kg/h for ≥ 24 h or anuria ≥ 12 h.

rates in developed countries were found to be lower than those in developing countries, where young adults and children were very badly affected.[21]

Prospective biomarkers

Klotho

Klotho (KL) is a novel phosphatonin encoded by the anti-aging KL gene located on chromosome 13q12 as an inactive single-pass transmembrane protein.[22] Upon activation through action by membrane bound-secretases like ADAM10 and ADAM17, driven by insulin, the extracellular domain is cleaved and its serum, urine and cerebrospinal fluid levels become elevated.[23] This ectodomain was termed a soluble Klotho, which would possibly bind directly with FGFR and tend to form an active complex exhibiting high affinity against FGF,[24] thereby alleviating oxidative stress through suppression of growth factors and stimulation of calcium ion channels (TRPV5 and TRPV6)[23] and potassium channels (ROMK)[25] but not sodium-phosphate cotransporters.[26] Meanwhile, the remaining membrane Klotho would function as a coreceptor for bone regulatory hormone FGF23.[27] Normally, Klotho shows greater expression in distal rather than proximal convoluted tubules in the kidneys, and in the choroid plexus of the brain rather than in the heart and parathyroid gland.[28]

The pathological importance of Klotho emerged through studies on animal models for AKI that had previously undergone ischemic reperfusion injury (IRI) or unilateral urethral obstruction (UUO). Thus, a transient reduction in renal Klotho mRNA expression was shown in response to renal tubular injury.[29, 30] Other studies on Klotho applied to humans have demonstrated that the urinary and plasma levels of Klotho in patients with AKI are notably lower than in healthy individuals.[29] From these observations, it has been proposed that Klotho has a role in exacerbating renal damage and has potential as a likely biomarker for AKI.

Cysteine-rich protein 61 (CYR61)

CYR61 is a cysteine-rich matricellular protein encoded by the CYR61 gene located on chromosome 1p22.3. It is intercalated with various integrins and heparin sulfate proteoglycans and is associated with extracellular matrix formation, cell adhesion, proliferation, differentiation, angiogenesis, apoptosis and inflammation due to its biochemical features, which resemble Wnt-1 proto-oncogene, and its number of growth factors.[31] Additionally, renal CYR61 mRNA and protein expression, along with urinary levels, have been found to increase in IRI animal models that suffered from significant hypoxia, despite being indistinguishable at renal levels in normal tissues.[32,33] This result provides encouragement to study CYR61 levels in humans, in order to elucidate its preventive and/or predictive role against AKI.

Chitinase-3-like protein 1 (YKL-40)

Chitinase-3-like protein 1 (CHI3L1) or YKL-40 is a 40 kDa glycoprotein[34] that is expressed from the CHI3L1 gene located on chromosome 1q31-q32.[35] It is considered to be a member of the family of 18 glycoside hydrolases that encompasses chitinases but without any enzymatic activity. It is secreted by various cell types, including macrophages, chondrocytes and some types of cancer cells.[34] Furthermore, Johansen et al. revealed that YKL-40 increased inflammation through activation of the innate immune response and regulation of tissue remolding.[35] In addition, Maddens et al. collected urine samples from mice that presented sepsis two days after intrauterine injection of *E. coli*, and from human patients with sepsis. They showed similar quantitative increases in comparison with controls without AKI.[36] Therefore, studies on YKL-40 remain a prerequisite for understanding the pathophysiology of AKI.

OBJECTIVE

The objective of the current review was to focus on the suitability and validity of Klotho, CYR61 and YKL-40 as ideal predictive biomarkers for acute kidney injury.

METHODS

We conducted a comprehensive systematic search by using the main known databases: PubMed, SCOPUS, SciELO, Lilacs, ScienceDirect and Google Scholar. The MeSH search terms included: ("Klotho and Acute Kidney Injury"), ("CYR61 and Acute Kidney Injury") AND (Chitinase-3-like protein 1 and Acute Kidney Injury"). The search strategy was designed for the PubMed database and was altered as needed for use in other databases. Our last search was finished in January 2016. References were written in the English language. The inclusion criterion was that all research articles, review articles and observational studies included needed to match our context, i.e. "the propensity of CYR61, Klotho and YKL-40 to be novel biomarkers for AKI". Additionally, we excluded papers that investigated these biomarkers in relation to chronic kidney disease (CKD) and other diseases as well as AKI.

RESULTS

Our search revealed a total of 2917 references. From the title and abstract, while omitting review articles, case reports and similar results, the number of papers was reduced to 17, which included seven relating to the biomarker YKL-40, three relating to CYR61 and seven relating to Klotho (**Table 2**). Briefly, we

Table 2. Outlines of the search strategies used for each database

Database used	Search strategy	Number of papers yielded per searchable database	Number of inclusions	Number of exclusions
PubMed	Klotho AND "acute kidney injury"[MeSH Terms]	31	Included in the review article	Excluded because of duplication or lack of match with specialization of proposed description
	Cysteine rich protein 61 and "acute kidney injury"	11		
	Chitinase-3-like protein 1 and "acute kidney injury"	4		
Scopus	Klotho and " acute kidney injury"	45		
	CYR61 and " acute kidney injury"	9		
	Chitinase-3-like protein 1 and "acute kidney injury"	5		
SciELO	Klotho and AKI/"acute kidney injury"	2		
	CYR61	1		
	YKL-40	2		
Cochrane Library	Klotho	21		
	CYR61	4		
	Chitinase-3-like protein 1	6		
LILACS	Klotho	8		
	CYR61	1		
	YKL-40	2		
Science Direct	Klotho biomarker and "acute kidney injury"	256		
	CYR61 and "acute kidney injury"	108		
	YKL-40 and "acute kidney injury"	77		
Google Scholar	Klotho and AKI	909		
	CYR61 biomarker and "acute kidney injury"	663		
	YKL-40 biomarker and acute kidney injury	752		
Total		**2917**	**17**	**2900**

summarized the main results and recommendations for each study in **Table 3**.[29,30,32,36-49] Finally, a synopsis of the biomarkers studied, showing general descriptions, functions and techniques used for measurements, was produced as **Table 4**.

DISCUSSION

In this review article, we discuss the propensity of some novel biomarkers for early detection of AKI. Traditional biomarkers have been proven to be unable to satisfactorily distinguish AKI during the first 24 hours before kidney function is disrupted. This is certain to delay the diagnostic process and gives rise to the possibility that the patient's condition will worsen. Despite the paucity of studies on biomarkers and AKI (for reasons mentioned earlier), we conducted a comprehensive review of the literature encompassing all papers relating to our context, focusing on all the results.

Recent papers have inferred that reduced levels of Klotho correlated with emergence of soft tissue calcifications, cardiovascular diseases, senescence, cancers, chronic hypertension, osteoporosis, renal failure, diabetes mellitus, oxidative stress and uremic parathyroid hyperplasia.[50-52] Furthermore, Hu et al. observed that Klotho levels in both plasma and urine declined immediately in AKI animal models and were detectable within 3 h after injury. This change preceded any changes in serum creatinine by 1 day and plasma NGAL by 5 h, thus suggesting that Klotho may be an early biomarker for renal parenchymal injury.[29,53] In the same manner, Kim et al. demonstrated that there were lower urinary Klotho levels in patients with pre-renal AKI than those with intrinsic AKI, and that this was not accompanied by any change in NGAL at the serum and urinary levels.[45]

Sugiura et al. indicated that renal Klotho levels in rats started to fall on the first day and completely returned to normal within 10 days.[30] On the other hand, Seo et al. studied human subjects and showed that renal Klotho levels were reduced, compared with high serum creatinine levels, according to AKI severity.[49] Likewise, Castellano et al. observed that Klotho levels were significantly increased in renal biopsies on cadaveric donors before transplantation and markedly reduced in patients with delayed graft function (DGF), in comparison with patients with early graft function. Furthermore, serum Klotho levels showed a significant decrease in DGF patients two years after transplantation, thus suggesting that the complement component has a modulatory role through activation of the nuclear factor kappa B (NF-kB) signaling pathway.[47]

A clinical study on urinary Klotho levels found that these were lower in AKI patients than in healthy individuals and recommended that this should be a candidate biomarker for AKI.[29] Surprisingly, Torregrosa et al. concluded that there was no difference in urinary Klotho levels measured by means of the ELISA (enzyme-linked immunosorbent assay) technique between AKI

Table 3. Summary of characteristics and main results of the 17 previous studies included in this review

Serials	Author/ year	Study design	Purpose of the study	Results and recommendations
1	De Loor et al.[37]	Pilot study	To evaluate whether urinary Chitinase 3-like protein 1 (YKL-40) can predict AKI stage ≥ 2 in ICU patients compared with NGAL.	The concentration of UCHI3L1 within 12 hours of AKI stage ≥ 2 was increased with good performance on AUC-ROC curve (0.792, 95% CI), similar to UNGAL AUC-ROC (0.748, 95% CI), and after 24 h, UCHI3L1 showed AUC-ROC twice as high (95% CI: 1.3–3.1) as controls.
2	Huen et al.[38]	Review	Focus on future phenotyping of AKI regarding NGAL and YKL-40.	NGAL and YKL-40 are important novel biomarkers involved in moderate renal tubular protection after AKI.
3	Schmidt et al.[39]	Cohort (comparative) study	To evaluate the role of urinary and blood levels of YKL-40 in allografts after renal transplantation.	Urinary YKL-40 increased early on, within 18 h after surgery (131.3 ± 155.2), with AUC 0.86 ± 0.07; blood YKL-40 retarded to 1 day after surgery (623 ± 285.9), with AUC 0.59 ± 0.08
4	Hall et al.[40]	Observational cohort study	To measure YKL-40 levels in the urine of clinically hospitalized AKI patients.	Urinary YKL-40 levels were detectable (≥ 5 ng/ml) within 1 h and gave better prognostic value (P = 0.04) with NGAL.
5	Tatar et al.[41]	Cohort study	To define relationship between YKL-40 and proteinuria in renal transplant recipients.	Mean serum YKL-40 and proteinuria levels were 66 ± 46 ng/ml and 0.77 ± 1.15 g/day respectively without any apparent correlation.
6	Maddens et al.[36]	Clinical and experimental study	Measurement of urinary and plasma levels of Chitinase 3-like protein 1 and -3 in mice and patients with and without septic AKI.	Urinary CHI3L1 higher in septic-AKI patients than in non-AKI (P < 0.05), but in septic-AKI mice models, CHI3L1 and -3 were found to be high.
7	Malyszko et al.[42]	Review article	Illustration of candidate biomarkers in cases of delayed graft function as a form of acute kidney injury.	Elevated YKL-40 in both urine and serum levels of patients with DGF, 2 days after transplantation.
8	Muramatsu et al.[32]	Experimental study	To test CYR61 in the urinary levels of mice and rats after immediate renal ischemic reperfusion injury.	CYR61 protein increased first within 1 h and appeared in urine 3-6 h after ischemic renal injury.
9	Lai et al.[43]	Experimental study	To investigate the role of CYR61 after unilateral IRI in mice.	CYR61 was significantly induced at renal and urinary levels after IRI.
10	Xu et al.[44]	Experimental study	To indicate CYR61 expression in renal cell lines under hypoxia	Enhanced expression of renal CYR61 in response to hypoxic ischemic injury.
11	Kim et al.[45]	Cohort study	To determine possible influence of AKI on serum and urinary levels of Klotho, S100A8/A9 and NGAL	Urinary Klotho levels were 13.21 ± 17.32 versus 72.97 ± 17.96 pg/ml (P = 0.002) in pre-renal and intrinsic AKI respectively.
12	Torregrosa et al.[46]	Cohort study	Assessment of urinary Klotho levels in patients after cardiac surgery or coronary angiography.	Klotho levels did not behave as a good early biomarker of AKI.
13	Castellano et al.[47]	Experimental study	To investigate whether or not complement components affect Klotho levels after IRI.	Complement activation result in remarkable decline in renal Klotho levels, 24 h after IRI.
14	Liu et al.[48]	Case-control study	To evaluate serum Klotho levels at different time intervals after cardiac surgery.	Serum Klotho levels were 101.97 ± 16.93 versus 121.64 ± 19.87 (P < 0.01) in AKI and non-AKI group respectively at 0 h and continued until 4 h. After 3 days, serum Klotho values were 120.50 ± 13.17 versus 128.67 ± 18.84.
15	Seo et al.[49]	Retrospective cohort study	Assessment of renal Klotho levels in human samples instead of animal models.	Renal Klotho levels were significant reduced with AKI severity.
16	Hu et al.[29]	Experimental and case-control study	To estimate Klotho at urinary and plasma levels, investigating probable protective ability.	Urinary Klotho values (pmoles/l) were 2.52 ± 0.76 in AKI versus 20.66 ± 1.81 in non-AKI, with P < 0.01.
17	Sugiura et al.[30]	Experimental study	To explain the physiological relevance of renal Klotho after IRI in rats.	Renal Klotho levels were significantly reduced in IRI rats, 24 h after ischemia.

Table 4. Description of biomarkers, their functions and measurement methods

Biomarker	Description	Encoded gene	Renal function	Detection sites	Measurement method
Klotho	Type I transmembrane protein	KL gene	Renoprotective and anti-apoptotic	Kidney Blood Urine	PCR ELISA Immunoblotting
CYR61	Matricellular protein (angiogenic factor)	CYR61 gene	Cell proliferative and anti-apoptotic	Kidney Blood Urine	PCR ELISA Immunoblotting
YKL-40	Secreted glycoprotein (anti-apoptotic)	CHI3L1 gene	Inflammatory	Kidney Blood Urine	PCR ELISA Immunoblotting

PCR = polymerase chain reaction; ELISA = enzyme-linked immunosorbent assay.

and non-AKI patients after cardiac surgery or coronary angiography, thus dismissing the possibility that Klotho would be a sensitive AKI biomarker.[46] Recently, Liu et al. showed that there was a notable immediate decline in serum Klotho levels in AKI patients compared with non-AKI (101 ± 16.93 versus 121.64 ± 19.87) after cardiac valve replacement surgery, although the preoperative levels had been steady and close together without any significant difference. Subsequently, 24 hours after the operation, the levels exhibited stepwise recovery towards the preoperative (baseline) levels. This observation indicated that serum Klotho might be a sensitive biomarker limited to a short time after surgery. An emerging suggestion to use the SCr/KL ratio instead of serum creatinine or Klotho alone could improve their diagnostic sensitivity for AKI at later times.[48]

Studies on Klotho were found to exhibit a variety of problematic issues: almost all the studies related to animal models rather than humans, with a narrow scale; there were unexplained variations between comparable studies; the mechanism of Klotho in AKI remains unknown, the behavior of Klotho in animal models differed from its behavior in humans; there was a lack of knowledge of ideal Klotho timing and normal cutoff ranges; and the urinary and plasma levels of Klotho were not indicative for renal Klotho, which might suggest that confounding factors and discrepancies in laboratory methodologies were present.

According to Vaidya and Muramatsu et al., CYR-61 was rapidly stimulated in the proximal renal tubules and was excreted in urine within 3-6 h after bilateral renal ischemic injury in rats. Its peak was within 6-9 h and it declined after 24 h.[32,54] Consequently, urinary CYR61 might act as an acceptable biomarker and screening tool for AKI, with follow-up in both preclinical and clinical studies.[32,55] Moreover, Lai et al. conducted experiments on mice that proved that proinflammatory TGF-β enhanced renal CYR61 in mRNA and protein levels within 10 days after occurrences of unilateral ureteral obstruction (UUO).[56] Subsequently, CYR61 gave rise to inflammatory sequelae through activation of monocyte chemoattractant protein-1 (MCP-1), thereby leading to monocyte chemotaxis and macrophage infiltration.[57] This evidence revealed that inhibition of CYR61 could prevent adverse consequences that would contribute towards irreversible AKI-CKD transition, through postponing inflammation, tubulointerstitial fibrosis and apoptosis.[43] Furthermore, Xu et al. conducted experiments on renal cell lines under conditions of hypoxia and found that CYR61 expression prevented apoptosis through phosphorylation of BAD, which released anti-apoptotic factors (bcl-2, bcl-xl) and enhanced cell proliferation through activation of the Akt and ERK signaling pathways.[44]

Other previous papers investigating CYR61 expression found that it was induced by several growth factors, exposure to UV irradiation,[58] hypoxic conditions, vigorous exercise,[59] bacterial infections[60] and viral infections.[61] Likewise, Pendurthi et al. mentioned that clotting factor VIIa (FVIIa) and thrombin triggered CYR61 redundancy, forced through blood coagulation.[62] This observation matched with Hviid et al., who indicated that CYR61 levels increased at sites of surgical wound closure and that CYR61 was absent from systemic blood, which might explain the mediatory role of platelets in accumulations of CYR61 at sites of tissue injury in AKI patients.[63]

The diagnostic capacity of urinary CYR61 as a biomarker might be blocked through: 1) its poor specificity, since it is normally abundant under both physiological and pathological conditions; 2) its rapid decline over time in spite of AKI progression; 3) the insensitivity of the immunoblotting technique used in quantification in urine; and 4) the fact that most studies were conducted on animal models because of difficulty in obtaining samples from human patients without prolonged routine registry for clinical trials in accordance with the World Health Organization (WHO) requirements and without prior patient approval.

Hall et al. showed that increased levels of urinary YKL-40 of up to 5 ng/ml were moderately correlated with AKI progression and/or mortality among patients. Moreover, apparent increases in YKL-40 levels in urine were observed in cases of kidney transplantation among patients hospitalized within 24 hours of

developing AKI.[40] Further proof was presented by Maddens et al., showing that urinary levels of YKL-40 were elevated in septic AKI patients. Taken together, YKL-40 with the best renal troponins (NGAL) might improve stratification of the risk of AKI among patients without any indications of primary renal damage and strengthen early prediction of sepsis-induced AKI.[36, 38]

Another study by Schmidt and Malyszko et al. reported that urinary YKL-40 was better than serum YKL-40 levels for distinguishing between delayed graft function and slow or immediate graft function, within 3 days after kidney transplantation. Delayed graft function produces greater severity of ischemic kidney injury, while the damage from other types tends to become repaired.[39,42] Synergistically, Hall et al. recommended that urinary YKL-40 could be used as an accurate and reliable biomarker to identify patients at risk of AKI following transplantation, rather than urinary or plasma NGAL.[40] Conversely, a pilot study by De Loor et al. demonstrated that the urinary concentrations of YKL-40 and NGAL in ICU patients with AKI stage ≥ 2 measured within 12 h or 24 h exhibited higher convergent diagnostic performance than did serum YKL-40, which did not show any predictive power against AKI.[37] Moreover, Tatar et al. concluded that high levels of serum YKL-40 was accompanied by increased CRP and proteinuria levels in kidney transplant recipients, thus indicating its inflammatory role.[41] Although YKL-40 showed many important benefits, the pathophysiological mechanism that leads to its expression in cases of AKI remains uncertain and validated cutoffs remain largely absent.

CONCLUSION

The results regarding the Klotho, CYR61 and YKL-40 biomarkers showed markedly equivocal performance in the previous studies and did not fulfill the expectations that these factors would form valid possible biomarkers for AKI.

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Liver failure following biliopancreatic diversions: a narrative review

Falência hepática após derivações biliopancreáticas: uma revisão narrativa

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KEY WORDS:
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PALAVRAS-CHAVE:
Falência hepática.
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Hepatopatias.

ABSTRACT

CONTEXT AND OBJECTIVE: Occurrences of liver failure following jejunoileal bypass were extensively reported in the past and were one of the main factors that led to abandonment of this procedure. The newer predominantly malabsorptive procedures called biliopancreatic diversions (BPDs) have also been implicated in several cases of acute and subacute liver failure. The aim here was to review the current available evidence on occurrences of liver failure following BPDs.

DESIGN AND SETTING: Narrative review; bariatric surgery service of a public university hospital.

METHODS: A review of the literature was conducted through an online search of medical databases.

RESULTS: Associations between BPDs and liver failure have only infrequently been reported in the literature. However, they appear to be more than merely anecdotal. The pathophysiological mechanisms remain obscure, but they seem to be related to rapid weight loss, protein malnutrition, deficits of hepatotrophic factors, high circulating levels of free fatty acids and bacterial overgrowth in the bypassed bowel segments. Reversal of the BPD may ameliorate the liver impairment.

CONCLUSIONS: Although infrequent, liver failure remains a concern following BPDs. Careful follow-up is required in individuals who undergo any BPD.

RESUMO

CONTEXTO E OBJETIVO: A ocorrência de falência hepática após a derivação jejunoileal foi extensivamente descrita no passado e foi um dos principais fatores que levaram ao abandono do procedimento. Os procedimentos predominantemente malabsortivos mais modernos, chamados de derivações biliopancreáticas, também já foram implicados em diversos casos de falência hepática aguda e subaguda. O objetivo foi revisar a atual evidência disponível sobre a ocorrência de insuficiência hepática após derivações biliopancreáticas.

TIPO DE ESTUDO E LOCAL: Revisão narrativa; Serviço de Cirurgia Bariátrica de hospital universitário.

MÉTODOS: Revisão da literatura conduzida por meio de pesquisa *online* de bancos de dados médicos.

RESULTADOS: A associação entre derivações biliopancreáticas e falência hepática na literatura é infrequente. Entretanto, ela aparenta ser mais do que meramente anedótica. Os mecanismos fisiopatológicos continuam pouco compreendidos, mas parecem estar relacionados à rápida perda de peso, desnutrição proteica e déficit de fatores hepatotróficos, altos níveis circulantes de ácidos graxos livres e supercrescimento bacteriano em segmentos intestinais excluídos do trânsito. A reversão da cirurgia pode melhorar o comprometimento hepático.

CONCLUSÕES: Embora infrequente, a falência hepática continua sendo preocupante após as derivações biliopancreáticas. Seguimento cuidadoso é mandatório em indivíduos submetidos a essas cirurgias.

INTRODUCTION

Obesity has become a worldwide public health concern over recent decades. In 2014, according to the World Health Organization (WHO), more than 1.9 billion adults were at least overweight; of these, over 600 million were obese.[1] Recent reports have observed that the prevalence of obesity in Brazil is 17.9%, which corresponds to almost thirty million obese people.[2] Bariatric surgery has become the standard treatment for refractory morbid obesity nowadays. Brazil is currently the country with the second largest number of bariatric surgery procedures performed every year, only behind the United States.[3]

The first bariatric procedures, which were described as early as in the 1950s, were jejunocolic and jejunoileal bypasses. Jejunoileal bypass was characterized as a bypass from the proximal jejunum to the distal ileum, with exclusion of the majority of the small bowel of the digestive tract. Despite its popularity from the 1950s to the 1970s, it was abandoned especially because of high rates of severe protein-calorie malnutrition and acute and subacute liver failure related to the procedure. However, the newer predominantly malabsorptive procedures called biliopancreatic diversions (BPDs) have also been implicated in several cases of acute and subacute liver failure.[4]

BPD mainly encompasses two different bariatric procedures: the Scopinaro operation and the duodenal switch procedure. The Scopinaro operation basically involves distal gastrectomy with a bypass from the remnant stomach to the distal ileum. The duodenal switch consists of resection of the gastric greater curvature and distal bypass from the duodenum to the ileum. The duodenal switch procedure is a modification of the original BPD and uses a longer common channel than the classic BPD. It was designed to improve gastric emptying and to decrease postoperative diarrhea and anastomotic ulceration. Both procedures are associated with high rates of resolution of type 2 diabetes. However, they are also associated with occurrences of protein-calorie malnutrition. Hence, although they are still performed today, they are not routinely the operations of choice in most centers.[5] In the 2003 IFSO report, the Scopinaro operation accounted for 2% and duodenal switch for 2.8%.[6] In the latest report (in 2013) from the International Federation of Surgery of Obesity and Metabolic Disorders (IFSO), duodenal switch accounted for about 1.5% of all bariatric procedures performed throughout the world, while the statistics for the Scopinaro operation did not appear, since it accounted for less than 1%.[7]

Regarding liver disease, BPDs are usually linked to major improvements in metabolic abnormalities relating to nonalcoholic fatty liver disease (NAFLD), especially insulin resistance, but at the same time, there has been a steady rate of occurrence of reports of acute and subacute liver failure following BPDs over the years.

OBJECTIVES

This study aimed to review the current available evidence on occurrences of liver failure following biliopancreatic diversions.

METHODS

A review of the literature was conducted through an online search for the MeSH terms "liver failure", "biliopancreatic diversion" and "bariatric surgery" in Medline (via PubMed); and the MeSH/DeCS terms "liver failure", "biliopancreatic diversion" and "bariatric surgery" in Lilacs (via Bireme) (**Table 1**).

After extensive online research, we identified three case reports and two case series on liver failure subsequent to the classical Scopinaro operation; and one case report and one case series of liver failure subsequent to the duodenal switch procedure. Additionally, we also researched population studies that addressed the evolution of liver disease after biliopancreatic diversions and identified two large cohort studies (one retrospective and other prospective) on liver impairment subsequent to the classical Scopinaro operation; and two retrospective cohorts on liver impairment subsequent to duodenal switch. We also excluded two case reports on liver failure after jejunoileal bypass: one case report on liver failure after biliointestinal bypass and one case series on liver failure after conversion of classical gastric bypass to distal bypass.

RESULTS

Scopinaro operation

The reports on liver failure requiring liver transplantation or leading to death following the Scopinaro operation are more than anecdotal. Although the rate of occurrence of liver failure appears to be non-significant in large cohort studies, there is enough evidence to consider that these occurrences in individuals who underwent this procedure are more than mere coincidence.[8]

Table 1. Database search results for liver failure following biliopancreatic diversions, on May 22, 2016

Electronic databases	Search strategies	Results
MEDLINE (PubMed)	(Liver failure) AND (Biliopancreatic Diversion) AND (Bariatric surgery)	3 case series 4 case reports
LILACS (Bireme)	((Liver failure) OR (Fallo hepático) OR (Falência Hepática)) AND ((Biliopancreatic Diversion) OR (Desviación Biliopancreática) OR (Desvio biliopancreático) AND ((Bariatric surgery) OR (Cirurgia Bariátrica) OR (Cirurgia bariátrica))	2 case series 3 case reports

Grimm et al.[9] reported the first case of chronic end-stage cirrhosis after BPD in 1992. The first successful liver transplantation to treat this complication was reported by Castillo et al. in 2001.[10] Greco et al.[11] reported the case of an individual who developed liver failure 16 years after undergoing the Scopinaro operation and presented partial recovery of liver function after the primary procedure had been dismantled. D'Albuquerque et al.[12] reported on three cases of liver failure that occurred between seven and 24 months after the Scopinaro operation: two of the patients underwent liver transplantation and one died. In a survey on liver transplantation centers in Belgium, Geerts et al.[8] detected 10 cases of bariatric surgery-related liver failure, of which nine were caused by the Scopinaro operation and one by jejunoileal bypass; the median time taken to develop liver failure was five years. All of these authors emphasized that, along with transplantation, the intestinal bypass must be revised and the original procedure must be dismantled.[8,10,11] **Table 2** summarizes the main articles on liver failure subsequent to the Scopinaro operation.

Despite the reports of liver failure, large population studies have not identified a significant frequency of occurrence of this complication. Scopinaro et al. conducted a classical retrospective analysis on 2,241 individuals who underwent their procedure and did not identify a single case of liver failure.[15] Papadia et al. did not find any cases of liver failure in a prospective study that enrolled 99 consecutive subjects who underwent the same procedure. However, they observed significant early transient hepatocellular necrosis following the procedure, and noted that individuals with abnormalities seen previously through liver histological analysis were more likely to present postoperative acute liver damage.[16] **Table 3** summarizes the main findings from these population studies.

Duodenal switch

Although the duodenal switch procedure has been more frequently performed than the Scopinaro operation, at least since the 2000s,[6] liver failure appears to be less frequent with this technique than with the classical Scopinaro operation. However, some cases have been reported. Auclair et al.[13] reported the first case of liver failure following duodenal switch, which underwent successful liver transplantation. Baltasar[17] and Baltasar et al.[18] reported on two cases of liver failure following duodenal switch, of whom one underwent transplantation and the other died while on the waiting list. **Table 4** summarizes the main articles on liver failure subsequent to duodenal switch.

The exact mechanisms that lead to liver failure following BPD and its current prevalence remain uncertain. Baltasar et al.[18] observed, in a large population study that enrolled 470 individuals

Table 2. Articles on liver failure subsequent to the Scopinaro operation

Author	n	Treatment	Outcome
Grimm et al.[9]	1	Supportive therapy	Death
Castillo et al.[10]	1	Liver transplantation	Successful
Greco et al.[11]	1	Reversal of intestinal bypass	Successful
D'Albuquerque et al.[12]	3	2: Liver transplantation 1: Supportive therapy	2: Successful (liver transplantation) 1: Death awaiting a graft
Geerts et al.[8]	10 (9: BPD; 1: jejunoileal bypass)	7: Liver transplantation 2: Supportive therapy 1: Awaiting transplantation	4: Successful 1: Successful transplantation followed by death due to *"de novo"* cancer 6 years later 2: Death after transplantation 1: Jejunoileal bypass – reappearance of liver failure 10 months after transplantation; required retransplantation 2: Death while awaiting graft

Table 3. Population-based studies evaluating liver impairment following Scopinaro operation and duodenal switch

Study	Surgical technique	n	Study design	Cases of liver failure - n (%)
Scopinaro et al.[15]	Scopinaro	2,241	Retrospective cohort	0
Papadia et al.[16]	Scopinaro	99	Prospective cohort	0
Baltasar et al.[18]	Duodenal switch	470	Retrospective cohort	1 (0.2%)
Keshishian et al.[19]	Duodenal switch	697	Retrospective cohort	0

Table 4. Articles on liver failure subsequent to duodenal switch

Author	n	Treatment	Outcome
Auclair et al.[13]	1	Liver transplantation	Successful
Baltasar[17]	2	1: Liver transplantation 1: Supportive therapy (while awaiting graft)	1: Liver transplantation – successful 1: Died while awaiting graft

who underwent duodenal switch, that only 10 (2.1%) of them developed liver impairment, ranging from asymptomatic liver enzyme abnormalities to fatal acute liver failure. Conversely, in a study that enrolled 697 individuals, Keshishian et al.[19] found no evidence of liver impairment following duodenal switch. The main findings of these population-based studies are summarized in **Table 3**.

Pathophysiology

The pathophysiological pathways potentially enrolled in development of liver failure following BPD appear to consist of early rapid weight loss, a degree of protein malnutrition, lack of hepatotrophic factors and the effect of high levels of mobilized circulating free fatty acids.[17-19] Exclusion of the long jejunoileal loop can lead to injury to the intestinal mucosal barrier due to nonuse or to functional exclusion of the alimentary bolus. The resulting impaired function of the mucosal barrier may facilitate absorption into the portal venous system of a variety of macromolecules, such as inflammatory cytokines and intestinal toxins arising as a result of changes to the intestinal bacterial flora. After delivery to the liver, these macromolecules may exacerbate hepatic injury.[12]

Even in individuals who do not develop liver failure, BPDs seem to promote a bimodal effect in liver function tests, with early worsening of liver injury, followed by normalization and improvement.[9,17] The reversal of some hepatic features following dismantling of the gut bypass emphasizes the role that this procedure plays in relation to the onset of liver failure. It is possible to propose that the procedure may trigger this change in individuals who are somewhat predisposed towards this. The predisposition factors involved are yet to be identified. In any case, it is reasonable to consider that this surgery is unjustifiable for obese individuals who currently present signs of fibrosis, steatohepatitis and advanced liver disease. Moreover, all individuals undergoing BPD should be carefully followed up, at least by means of serial liver enzyme tests, not just in the early postoperative period, but for their entire lifetime.[8]

CONCLUSIONS

Although very rare, liver failure remains a concern following BPDs. However, since the vast majority of the evidence available is from case reports, there is no evidence level sufficient to provide definite conclusions. Randomized trials comparing the different available bariatric techniques are needed in order to provide data of better quality. Nonetheless, despite the low frequency of occurrences of liver failure, such events are reported nowhere near as often following other, more frequently performed bariatric techniques. The exact mechanism that leads to this ominous complication remains to be determined, but it seems to be characterized by an acute-on-chronic failure that occurs in predisposed individuals who present previous liver impairment. Careful follow-up is required among individuals who undergo any BPD. Reversal of the procedure is warranted when early clinical or laboratory signs of liver failure appear. Despite the lack of specific evidence, it is reasonable to avoid this surgical technique among subjects who present to bariatric surgeons with any degree of significant liver function impairment.

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Boerhaave syndrome – case report

Síndrome de Boerhaave – relato de caso

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KEY WORDS:
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PALAVRAS-CHAVE:
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Ruptura espontânea.
Hematêmese.
Pneumotórax.
Enfisema

ABSTRACT

CONTEXT: Boerhaave syndrome consists of spontaneous longitudinal transmural rupture of the esophagus, usually in its distal part. It generally develops during or after persistent vomiting as a consequence of a sudden increase in intraluminal pressure in the esophagus. It is extremely rare in clinical practice. In 50% of the cases, it is manifested by Mackler's triad: vomiting, lower thoracic pain and subcutaneous emphysema. Hematemesis is an uncommon yet challenging presentation of Boerhaave's syndrome. Compared with ruptures of other parts of the digestive tract, spontaneous rupture is characterized by a higher mortality rate.

CASE REPORT: This paper presents a 64-year-old female patient whose vomit was black four days before examination and became bloody on the day of the examination. Her symptoms included epigastric pain and suffocation. Physical examination showed hypotension, tachycardia, dyspnea and a swollen and painful abdomen. Auscultation showed lateral crackling sounds on inspiration. Ultrasound examination showed a distended stomach filled with fluid. Over 1000 ml of fresh blood was extracted by means of nasogastric suction. Esophagogastroduodenoscopy was discontinued immediately upon entering the proximal esophagus, where a large amount of fresh blood was observed. The patient was sent for emergency abdominal surgery, during which she died. An autopsy established a diagnosis of Boerhaave syndrome and ulceration in the duodenal bulb.

CONCLUSION: Boerhaave syndrome should be considered in all cases with a combination of gastrointestinal symptoms (especially epigastric pain and vomiting) and pulmonary signs and symptoms (especially suffocation).

RESUMO

CONTEXTO: A síndrome de Boerhaave é uma ruptura longitudinal transmural espontânea do esôfago, normalmente da parte distal. Ela geralmente se desenvolve durante ou após vômitos persistentes como consequência do aumento repentino da pressão intraluminal no esôfago. É extremamente rara na prática clínica. Em 50% dos casos, manifesta-se pela tríade de Mackler: vômitos, dor torácica inferior, enfisema subcutâneo. Hematêmese é uma apresentação incomum porém desafiadora da síndrome de Boerhaave. Em comparação com rupturas de outras partes do tubo digestivo, a ruptura espontânea é caracterizada pela taxa de mortalidade mais elevada.

RELATO DO CASO: O artigo apresenta uma paciente do sexo feminino de 64 anos de idade, cujo vômito era preto, quatro dias antes do exame, e continha sangue no dia do exame. Os sintomas incluíam dor epigástrica e sufocação. No exame físico, foi verificada hipotensão, taquicardia, dispneia e abdômen inchado e doloroso. Ausculta revelou estertores laterais na inspiração. A ultrassonografia mostrou estômago dilatado, preenchido com conteúdo líquido. Sucção nasogástrica evacuou mais de 1.000 ml de sangue fresco. Esofagogastroduodenoscopia foi abortada imediatamente ao se entrar no esôfago proximal, onde foi observada grande quantidade de sangue fresco. A paciente foi encaminhada com urgência para cirurgia abdominal, durante a qual faleceu. Autópsia estabeleceu diagnóstico de síndrome de Boerhaave e úlcera no bulbo-duodenal.

CONCLUSÃO: A síndrome Boerhaave deve ser considerada em todos os casos com uma combinação de sintomas gastrointestinais (especialmente dor epigástrica e vômitos) e sintomas e sinais pulmonares (especialmente sufocação).

INTRODUCTION

Boerhaave syndrome consists of spontaneous longitudinal transmural rupture of the esophagus. The syndrome is named after a German doctor, Herman Boerhaave, who first described it in 1724.[1] In comparison with iatrogenic rupture, which may develop during diagnostic or therapeutic endoscopic procedures, traumas or various esophageal diseases, spontaneous rupture most commonly develops during or after persistent vomiting, as a consequence of a sudden increase in intraluminal esophageal pressure. Spontaneous rupture encompasses 15% of all esophageal ruptures.[2] It is extremely rare in clinical practice. The true incidence of Boerhaave syndrome in the general population is unknown. However, it is considered to be more common than once thought, since many cases of Boerhaave syndrome are only diagnosed postmortem, thus resulting in underreporting and underestimation with regard to both incidence and mortality.[1,3] Boerhaave syndrome is seen most frequently among patients aged 50-70 years.[1]

The clinical manifestation of spontaneous rupture of the esophagus depends on the rupture location. In 50% of the cases, it is manifested by Mackler's triad: vomiting, lower thoracic pain and subcutaneous emphysema.[3,4]

If the diagnosis is not established in time and if appropriate therapeutic measures are not undertaken, serious complications can develop and this may lead to a poor outcome. Compared with ruptures of other parts of the digestive tube, spontaneous rupture of the esophagus has the highest mortality rate.[1,5]

CASE REPORT

The patient was a 64-year-old female, with a history of long-term arterial hypertension, who was brought to the Gastroenterology and Hepatology Clinic of the Niš Clinical Center by the emergency medical services. She was admitted presenting with vomiting of fresh blood, black stools, epigastric pain, suffocation and exhaustion.

The problems had first appeared four days before admission in the form of poorly formed black stools and vomiting of small amounts of black substance. She did not see a doctor about these problems. On the day of admission, after vomiting an excessive amount of black substance, she developed a pain in the epigastric region and then began to vomit fresh blood. It was at this stage that she rang the emergency medical services.

Physical examination showed that the patient was alert, adynamic, tachycardiac and easily dyspneic, and her skin was pale. Her blood pressure was 60/40 mmHg. Auscultation of the heart was normal. Auscultation of the lungs showed baseline crackles on inspiration on both sides. The abdomen was tense, especially in the epigastric area and left hypochondrium, with tenderness in the epigastric area. The liver and spleen were of normal size. Appropriate therapy was administered (one ampoule of prantopazole, a total of about 3000 ml of continuous infusion of saline solution and lactated Ringer's solution). The oxygen saturation was 95%. A urinary catheter was placed for monitoring diuresis. An electrocardiogram (ECG) showed sinus tachycardia.

Because of the findings in the abdomen, an ultrasound examination was performed and this showed a distended stomach filled with a large amount of fluid. No free fluid was found in the abdominal cavity. A nasogastric probe was placed in order to extract the contents and perform esophagogastroduodenoscopy (EGD). After inserting the nasogastric probe, about 1,000 ml of fresh blood was extracted. After the hemodynamic status had improved, esophagogastroduodenoscopy was attempted. Immediately upon insertion of the endoscope into the proximal esophagus, reflux of a large amount of fresh blood was observed; further examination was cancelled. The patient was sent for emergency abdominal surgery. However, she died one hour after the first examination.

The laboratory findings and coagulation factors, which were received subsequently, were within normal values. The blood count showed reduced hemoglobin of 70 g/l (reference values: 115-170 g/l) and increased leukocyte count of 12.0 x 10^9/l (reference values: 4.0-10.0 x 10^9/l).

The autopsy showed 650 ml of dark red to black thick fluid content in the right hemithorax and 600 ml in the left hemithorax (**Figure 1**). The heart size measurements were 110 x 105 mm. The heart weighed 380 g. The thickness of the cardiac muscle of the left ventricle was 18 mm and of the right ventricle, 6 mm. A rupture along the longitudinal axis was found in the esophagus, in the posterior left section of the esophageal wall, 15 mm from the cardia.

The rupture was 30 x 20 mm in size. The esophageal mucosa was smooth and almost completely covered in bloody-black content (**Figure 2**). There were no foreign bodies in the abdominal cavity. A small amount of blackish liquid was found in the

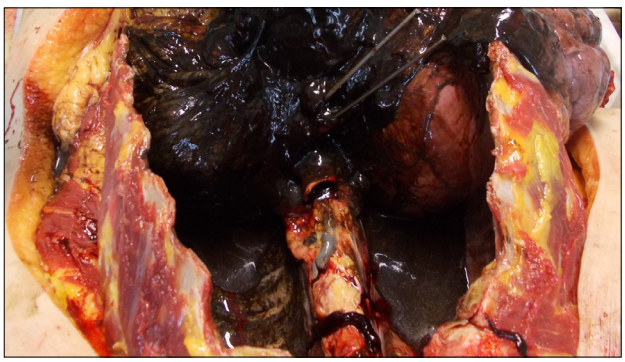

Figure 1. Macroscopic findings from the intrathoracic contents upon opening the thoracic cavity. Note the huge amount of clot.

stomach. Numerous small shallow erosions were found in the fundus and body of the stomach.

A mucosal injury of depth 13 mm, covering an area of 20 mm x 15 mm with firm borders and blackish background, consistent with a duodenal bulb ulcer, was observed (**Figure 3**). The walls were firm and vallum-like and the bottom was partially black. Greenish and black content was present throughout the intestines.

Chemical and toxicological analysis on samples of organ tissues, blood and urine did not reveal the presence of any psychoactive substances or pesticides.

The autopsy report declared that the immediate cause of death was hemopneumothorax due to esophageal injury and a chronic duodenal ulcer.

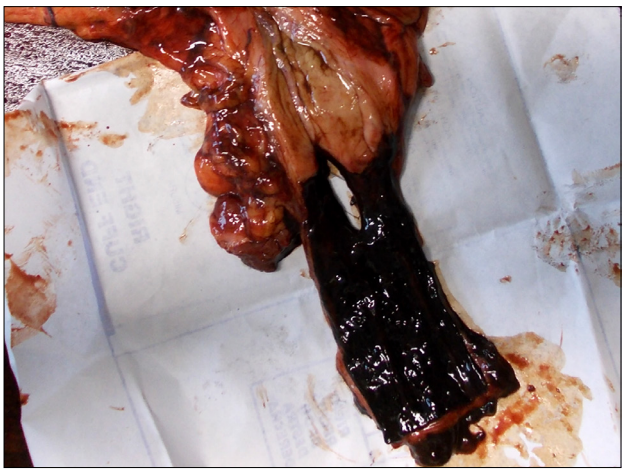

Figure 2. Gross examination of the distal esophagus showing a longitudinal complete rupture 15 mm from the cardia. Note the darkened esophageal mucosa.

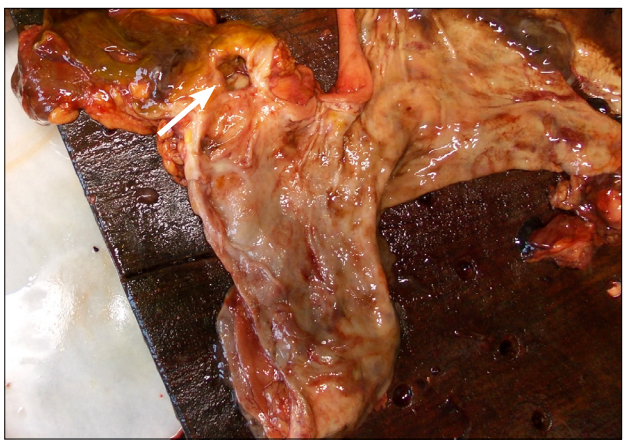

Figure 3. Gross findings from the stomach and duodenum showing deep and wide duodenal ulceration in the duodenal bulb (arrow).

DISCUSSION

Spontaneous rupture of the esophagus is a rare clinical entity with a high mortality rate.[5,6] The pathophysiology of Boerhaave syndrome involves a sudden rise in intraluminal esophageal pressure, thereby forcing the gastric contents against a tight cricopharyngeus muscle.[3,6] It most often develops during or after intense vomiting caused by excessive eating or drinking alcohol.[7] However, spontaneous rupture of the esophagus may occur in the absence of predisposing factors. There are cases of spontaneous esophageal rupture during sleep. In some patients, a muscular layer was missing and this may point to the possibility of anatomical predisposition for the development of rupture.[1,3]

In the literature, there are cases in which the rupture was also associated with gastroesophageal reflux disease (GERD), Barrett's esophagus, peptic stricture of the esophagus, esophageal dysmotility, paraesophageal hernia or bleeding from a duodenal ulcer, which was the case with our patient.[5,8,9] In our patient, the esophageal rupture was a consequence of excessive vomiting due to the bleeding from the duodenal ulcer.

Spontaneous rupture may occur just above the diaphragm in the posterolateral wall of the esophagus. Perforations are usually longitudinal (0.6-8.9 cm long), with the left side more commonly affected than the right (90%). This is probably due to an anatomical weakness of the left posterolateral aspect of the esophagus just above the diaphragm. Spontaneous rupture is rare below the diaphragm or in the thoracic part of the esophagus.[3,7] In our case, the rupture was located in the distal esophagus, 15 mm from the cardia.

The clinical manifestation of Boerhaave syndrome depends on the location of the rupture and the time between its development and examination. Patients with cervical perforation feel pain in the neck and upper half of the thorax. In cases of perforation in the rest of the esophagus, pain is present in the lower part of the thorax and/or upper abdomen. Considering that spontaneous rupture most often happens in the distal esophagus, the majority of patients have Mackler's triad of symptoms and signs: vomiting, lower thoracic pain and subcutaneous emphysema.[3,4] However, this triad is rare, which may delay the diagnosis.[10] In a series of 14 patients with Boerhaave syndrome, only a small percentage had typical signs and symptoms.[3]

The symptoms of Boerhaave syndrome can be nonspecific. Compared with Mallory-Weiss syndrome, Boerhaave syndrome is rarely manifested through hematemesis or other signs of gastrointestinal bleeding, including melena.[1,3,6,10,11] In Boerhaave syndrome, the rupture is transmural, which leads to esophageal perforation. In our patient, hematemesis was the chief complaint. To begin with, she was vomiting an excessive amount of black substance as a result of bleeding from ulcers. Excessive vomiting led to spontaneous rupture of the esophagus, which manifested as vomiting of fresh blood.

During physical examination of patients, subcutaneous emphysema is observed in 28%-66% within the first 24 hours. This finding is significant for the initial diagnosis. More typically, subcutaneous emphysema is found later. Besides typical symptoms, atypical symptoms such as hypotension, tachycardia, tachypnea, feverishness and cyanosis may also be present.[1,7] Atypical symptoms may be prevented through timely diagnosis. Pneumomediastinum is a significant clinical finding.[10] Pneumomediastinum is suspected when, during lung auscultation, crunching sounds that are synchronous with the heartbeat are heard (Hamman's sign). This sign is present in around 20% of the cases.[7]

Esophageal rupture may be followed by serious complications, of which the most important ones are mediastinitis and multiple organ dysfunction. Sepsis may develop within a few hours. In such cases, the clinical picture is dominated by signs and symptoms of sepsis, which additionally prevents timely diagnosis and appropriate therapeutic measures.[6,7,12]

Laboratory findings are not specific for diagnosing spontaneous esophageal rupture. Serum albumin is normal but may be low, while the globulin fraction may be normal or slightly elevated.[7] Radiography of the heart and lungs is valuable for the diagnosis. Radiographs usually show signs of pneumomediastinum or pneumothorax or hydropneumothorax if pleural effusion is concurrent.[3,13] In cases of perforation of the middle third of the esophagus, pleural effusion is present on the right side, while in cases of rupture of the distal esophagus, pleural effusion is present on the left side.[5] Diagnostic thoracentesis shows the presence of food remnants, increased amylase and pH below 6. The presence of pneumomediastinum with data including vomiting and chest pain are almost definite signs of Boerhaave syndrome. Overall, 10% of chest radiographs are normal.[7,14]

Esophagography is an important imaging examination for confirming the diagnosis and the location of perforation because it shows extravasation of contrast into the pleural space. The procedure is performed with water-soluble contrast, such as Gastrografin, since barium may cause severe mediastinitis. Esophagography with Gastrografin is 90% sensitive.[7]

Thoracic computed tomography imaging is indicated for making the diagnosis in patients who do not tolerate esophagography. During the procedure, localized fluid collection is observed, as well as periesophageal air collection.[1,15,16] The role of EGD in the early diagnostic work-up of patients with suspected esophageal perforation has been disputed.[17] EGD is not recommended for diagnosing Boerhaave syndrome, since it may increase the rupture and the amount of air in the mediastinum and pleural space.[13] In cases with hematemesis, such as in our patient, the procedure was attempted in order to ascertain the source of bleeding.

The treatment for Boerhaave syndrome is both conservative and surgical. The goals of pharmacotherapy are to reduce morbidity and to prevent complications. Surgical management is generally required for both spontaneous rupture and traumatic perforation.[14,18] Endoscopic stent insertion offers a promising alternative. The mortality rate varies depending on the time that has elapsed since development of the rupture and its recognition and treatment. If treatment is not started within 24 hours from the onset of symptoms, the mortality rate is 25%; after 24 hours, it is 65%; and after 48 hours, it is 75%-89%.[19]

We reviewed the literature in Medline, PubMed, Embase and Lilacs using the English keywords "Esophagus", "Rupture, spontaneous", "Hematemesis" and "Pneumothorax"; and the Portuguese words "Esôfago", "Ruptura espontânea", "Hematêmese" and "Pneumotórax" (**Table 1**).

CONCLUSION

Boerhaave syndrome should be considered in all patients with a combination of gastrointestinal symptoms (epigastric pain and vomiting) and pulmonary symptoms (suffocation), even when all the signs and symptoms (lower thoracic pain and subcutaneous emphysema) of this disease are absent. Early clinical suspicion will lead to timely diagnosis and maximize the survival chances for the patient.

Table 1. Literature search in medical databases for case reports on Boerhaave syndrome. The literature search was conducted on May 4, 2016

Database	Search strategies	Papers found	Related papers
MEDLINE (via PubMed)	Esophagus AND Rupture, spontaneous AND Hematemesis AND Pneumothorax AND "case reports" [Publication Type]	9	2
Embase (via Elsevier)	Esophagus AND Rupture, spontaneous AND Hematemesis AND Pneumothorax AND "case reports" [Publication Type]	0	0
LILACS (via Bireme)	(Esofago [DeCs]) OR (esophagus [MeSH]) AND (Ruptura espontanea [DeCs]) OR (Rupture, spontaneous [MeSH]) AND (Hematemese [DeCs]) OR (Hematemesis [MeSH]) AND (Pneumotorax [DeCs] OR Pneumothorax [MeSH]) AND " relato de caso"	0	0

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Lichen amyloidosis associated with rheumatoid arthritis: unique presentation in a Bulgarian patient

Amiloidose líquen associada com artrite reumatoide: apresentação única em um paciente búlgaro

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An 80-year-old Caucasian female patient presented with a two-year history of intensively itching skin rash located on her left lower leg and mild swelling of the proximal interphalangeal and metacarpophalangeal joints, accompanied by morning stiffness around these joints, lasting at least one hour before maximal improvement (**Figures 1A** and **1B**). She reported having had a long-lasting medical history of accompanying diseases that had been controlled with medicines. These conditions included arterial hypertension, hypothyroidism, chronic pyelonephritis, angina pectoris and primary glaucoma. There was no family history of cutaneous disorders.

Presence of intensively pruritic erythematous papules located on the left pretibial surface was established clinically (**Figures 1A** and **1B**). Symmetrical soft-tissue swelling around the small joints was also observed, but no rheumatoid nodules were seen. The laboratory blood tests did not reveal any abnormalities in the complete or differentiated blood count. The kidneys and liver showed normal functioning. The rheumatoid factor was 827 u/ml (reference values: less than 40-60 u/ml). Presence of periarticular osteopenia in the interphalangeal and metacarpophalangeal joints was established radiographically. A diagnosis of seropositive rheumatoid arthritis was made, which met most of the criteria postulated by the committee of the American Rheumatism Association.

Immunological testing for antinuclear antibody (ANA) and Scl 70 was negative. The cutaneous pathological changes presented required a wide spectrum of differential diagnoses, including pretibial myxedema, necrobiosis lipoidica, the small papular form of cutaneous sarcoidosis, T-cell lymphoma, lichen ruber planus and Arndt-Gottron scleromyxedema. Histopathological evaluations on skin biopsies revealed hyperkeratosis, focal acanthosis, subepithelial structures that stained pink with hematoxylin-eosin and mild to moderate mononuclear infiltrate around single vessels (**Figure 2A**). Subepithelial Congo red-positive deposits were also observed (**Figures 2B** and **2C**), which showed blue-green birefringence under polarized light.

The findings were characteristic of amyloid deposition and a diagnosis of lichen amyloidosis was made. No clinical or laboratory evidence of systemic amyloidosis was presented. Systemic therapy consisting of bilastine (20 mg daily) and acitretin (15 mg daily) was started, with topical application of 0.1% mometasone furoate cream, which produced a satisfactory therapeutic response. The patient was referred to a rheumatological unit for further therapy with biological agents.

Localized cutaneous amyloidosis encompasses several conditions characterized by deposition of amyloid or amyloid-like proteins in the dermis, including macular amyloidosis and lichen amyloidosis.[1] Nodular localized cutaneous amyloidosis is another condition in this group: it is the rarest type and distinct from the other two. In this type, plasma cells produce immunoglobulin light chains that are precursors to the amyloid fibril protein called amyloid L.[1]

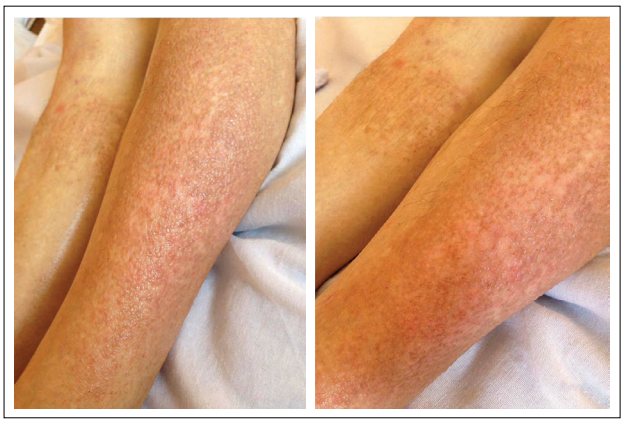

Figure 1. Clinical manifestation of erythematous pruritic papules located on the left pretibial surface of an 80-year-old female patient.

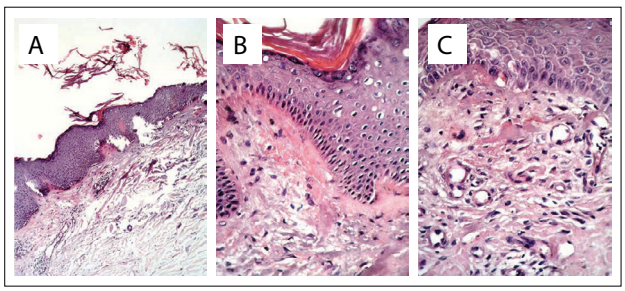

Figure 2. (A) Histopathological findings: focal acanthosis, subepithelial pink-stained structures and mild to moderate mononuclear infiltrate around single vessels (hematoxylin-eosin staining); (B and C) Subepithelial Congo red-positive deposits showing blue-green birefringence under polarized light.

Lichen amyloidosis is a primary form of localized cutaneous amyloidosis that is clinically manifested through hyperkeratotic erythematous to brownish papules, while amyloid deposition can be seen via specific histological staining in previously normal skin without any evidence of visceral involvement.[2] The clinical manifestation of these lesions is practically indistinguishable from that of primary and myeloma-associated systemic amyloidosis, and these lesions result from local plasma cell infiltration.[3]

Although cutaneous lesions may be seen in up to 40% of patients with primary and myeloma-associated systemic amyloidosis, their presence results from tissue deposition of immunoglobulin light chain material derived from a circulating paraprotein.[3] In contrast, amyloid in lichen amyloidosis is not derived from immunoglobulins or serum proteins, but from keratin peptides of necrotic keratinocytes.[4] Familial predisposition also has a pathogenic role.[2]

Although the etiology is not fully understood, chronic irritation to the skin has been proposed as possible etiological factor.[5] Chronic scratching is considered to be a cause of damage to keratinocytes in lichen amyloidosis.[2] The amyloid deposits in patients with lichen amyloidosis are mainly restricted to the upper dermis and arise because of focal epidermal damage with subsequent conversion of necrotic keratinocytes into amyloid in the papillary dermis.[5] The condition persists for many years with intensive pruritus, but an asymptomatic variant has also been reported in the literature.[6,7]

Treatment options include potent topical steroids under occlusion, intralesional steroids, topical dimethylsulfoxide and etretinate.[7,8] Surgical treatment methods include dermabrasion and scalpel scraping of the lesions.[8,9] Given that chronic scratching seems to be the main cause and not the result of the amyloid deposits, treatment should be directed mainly against the pruritus.[4]

We have described a rare association between lichen amyloidosis and rheumatoid arthritis in an 80-year-old female patient, without evidence of systemic amyloid involvement. To the best of our knowledge, this is the first reported case of primary cutaneous amyloidosis in a patient with rheumatoid arthritis, in contrast to the much more frequent association of rheumatoid arthritis with systemic amyloidosis, the pathogenetic relationship remains unclear. It is also unclear whether lichen amyloidosis might be the first clinical manifestation of the initial systemic involvement, in which cutaneous lesions can be seen in up to 40% of the patients,[3] or whether the pathogenetic relationship of the association is more related to an undefined form of autoimmune dysregulation. Because of the rareness of this simultaneous clinical presentation and limited data in the literature on this issue at this stage, the correct answer to these questions will probably only be given at some point in the future.

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What do Cochrane systematic reviews say about diabetic retinopathy?

O que as revisões sistemáticas da Cochrane dizem sobre retinopatia diabética?

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Evidence-based medicine.
Evidence-based practice.

PALAVRAS-CHAVE:
Revisão.
Retinopatia diabética.
Terapêutica.
Medicina baseada em evidências.
Prática clínica baseada em evidências.

ABSTRACT

CONTEXT AND OBJECTIVE: Diabetic retinopathy is a disease caused by increased permeability of retinal vessels. Its incidence and prevalence have been increasing due to urbanization, greater life expectancy and the habits of modern life. Its onset is insidious and it may lead to blindness in 75% of individuals who have been diabetic for more than 20 years. The aim here was to evaluate the evidence from Cochrane systematic reviews on interventions relating to diabetic retinopathy.

DESIGN AND SETTING: Review of systematic reviews, conducted at Cochrane Brazil.

METHODS: We included Cochrane systematic reviews on interventions relating to diabetic retinopathy. Two researchers evaluated the inclusion criteria, summarized the reviews and presented the results narratively.

RESULTS: Ten reviews met the inclusion criteria. They showed some evidence of benefits from: (a) photocoagulation for diabetic retinopathy; (b) strict glucose and pressure control for postponing the onset of retinopathy; (c) antiangiogenic drugs for macular edema (high-quality evidence); (d) anti-vascular endothelial growth factor agents for proliferative diabetic retinopathy (very low to low-quality evidence); and (e) intravitreal injection or surgical implantation for treating persistent or refractory macular edema. However, blood pressure control seems to have no benefit after the onset of retinopathy.

CONCLUSION: Only a few options are likely to be effective for treating diabetic retinopathy. These include photocoagulation and anti-vascular endothelial growth factor agents. Strict glucose and pressure control seem to postpone the onset of retinopathy. For macular edema, antiangiogenic drugs, intravitreal injection and surgical implantation seem to have some benefit.

RESUMO

CONTEXTO: A retinopatia diabética é uma doença causada pelo aumento da permeabilidade dos vasos da retina. Sua incidência e prevalência vêm aumentando devido à urbanização, maior expectativa de vida e hábitos de vida modernos. Seu início é insidioso e pode levar à cegueira em 75% dos pacientes diabéticos com mais de 20 anos de doença. O objetivo foi avaliar a evidência das revisões sistemáticas Cochrane sobre intervenções para retinopatia diabética.

TIPO DE ESTUDO E LOCAL: Revisão de revisões sistemáticas conduzida no Centro Cochrane do Brasil.

MÉTODOS: Nós incluímos revisões sistemáticas Cochrane sobre intervenções para retinopatia diabética. Dois pesquisadores avaliaram os critérios de inclusão, resumiram as revisões e apresentaram os resultados narrativamente.

RESULTADOS: Dez revisões preencheram os critérios de inclusão e mostraram benefícios com: (a) fotocoagulação para retinopatia diabética; (b) controle rigoroso da glicose e da pressão para adiar o início da retinopatia; (c) fármacos antiangiogênicos para edema macular (evidência de alta qualidade); (d) agentes antifator de crescimento do endotélio vascular para retinopatia diabética proliferativa (evidência de qualidade muito baixa a baixa); (e) injeção intravítrea ou implante cirúrgico para o tratamento do edema macular persistente ou refratário. No entanto, o controle da pressão arterial parece não ter benefício após o início da retinopatia.

CONCLUSÃO: Existem poucas opções provavelmente efetivas para o tratamento da retinopatia diabética. Estas incluem fotocoagulação e agentes antifator de crescimento do endotélio vascular. O controle rigoroso da glicose e da pressão parecem adiar o início da retinopatia. Para o edema macular, fármacos antiangiogênicos, injeção intravítrea e implante cirúrgico parecem ter algum benefício.

INTRODUCTION

Diabetic retinopathy is a secondary retinal disease caused by vascular changes due to diabetes. It is a common complication of diabetes and is the leading cause of decreased vision in the economically active population, with large negative impacts both on public health and on the social security system. It has been estimated that, because of increased life expectancy and lifestyle changes associated with urbanization, the worldwide prevalence of diabetes will rise from 126.6 million in 2010 to 191 million in 2030.[1]

According to the World Health Organization, 75% of patients with a 20-year history of type 2 diabetes have some degree of retinopathy.[2] Nonetheless, there is still no intervention capable of preventing the emergence of retinopathy or even of preventing its progression, effectively and safely. Thus, clinical practice is limited to guidance for patients in which they are advised to maintain strict glycemic control because of the risk of disease evolution.

Like other vascular changes in diabetic patients, retinopathy starts in the endothelium. This tissue modulates vascular functions through releasing or inhibiting nitric oxide, endothelin, angiotensin and other substances that act in relation to inflammation, platelet aggregation, permeability, oxidative stress, blood clotting and vascular tone.[3-7]

Diabetic retinopathy is classified based on the degree of involvement of the retinal tissue and may be early non-proliferative, moderate non-proliferative, severe non-proliferative or proliferative.[8] Early non-proliferative retinopathy is characterized by microaneurysms seen via fundoscopy; while in moderate non-proliferative (or exudative) retinopathy, it is possible to observe hard exudates. In severe non-proliferative retinopathy, in addition to the previous changes, there are soft exudates (retinal ischemia), intraretinal abnormalities (intra-microvascular retinal anomalies, IRMA) and vessels "on rosary beads".[8] Finally, in proliferative retinopathy, there is vascular neoformation with blood extravasation, culminating in vitreous hemorrhage. At the most advanced stage, the new vessels can lead to retinal traction with subsequent retinal detachment.[9]

Diabetic retinopathy is diagnosed through observation of the changes described above through direct and indirect fundoscopy, retinography, photographic records of the retina or angiofluoresceinography.[8,9] Early diagnosis is crucial for the best response to treatments, since more advanced degrees of retinopathy have worse prognoses.

Evaluations on diabetic patients without changes seen via fundoscopy or on those with early non-proliferative diabetic retinopathy need to be made annually. Those with moderate non-proliferative diabetic retinopathy need to be evaluated every six months, and those with severe non-proliferative retinopathy, every two to four months.[10] Patients with macular edema also need to be reevaluated within six months, because if this is persistent, treatment with a macular grid is necessary in order to preserve central vision.[10]

Diabetic macular edema is a complication of diabetic retinopathy. It is defined as clinically significant macular edema when it is observed in the presence of hard exudates less than 500 μm from the center of the fovea and/or retinal edema; or if the size of the macular edema is larger than the papillary diameter (1500 μm) of the fovea, with the presence of edema, microaneurysms, soft exudates (areas of retinal ischemia) and hard exudates (lipoprotein buildups).[10,11] The diagnosis of clinically significant macular edema is made by means of posterior pole biomicroscopy using drug-induced mydriasis.[10,11]

The practical approach most used for preventing diabetic retinopathy is strict glucose control and regular eye tracking. The therapeutic options include laser phototherapy, which includes photocoagulation and photostimulation; injection of intravitreal corticosteroids; and use of anti-vascular endothelial growth factor (VEGF) drugs (pegaptanib, ranibizumab, aflibercept and bevacizumab).

It is important to note that once macular disease has become established, treatment for diabetic retinopathy becomes essential and haste is required. On the other hand, although the therapeutic options available seem effective, they are invasive and may be associated with serious adverse events, such as visual field loss, reduced night vision, increased intraocular pressure and endophthalmitis.

Considering the global prevalence of diabetic retinopathy, its comorbidities, the consequences associated with its development and the uncertainties regarding the effectiveness and safety of the preventive and therapeutic interventions available, it is relevant to assess the current literature in order to summarize the best evidence that can guide decision-making processes relating to this important public health problem and direct future research, so as to answer questions that still remain unanswered.

OBJECTIVES

To evaluate the evidence from Cochrane systematic reviews regarding the effectiveness and safety of interventions for prevention and treatment of diabetic retinopathy.

METHODS

Design

This was a review of systematic reviews.

Setting

This review was conducted within the Postgraduate Program on Evidence-Based Health, of the Federal University of São Paulo (Unifesp) and at Cochrane Brazil.

Criteria for including reviews

We only included the last version of completed Cochrane systematic reviews that evaluated the effects of different interventions for preventing or treating diabetic retinopathy. The protocols of systematic reviews in progress and withdrawn reviews were not considered.

Search for reviews

We carried out an electronic search in the Cochrane Library (via Wiley) on August 5, 2016, as presented in **Table 1**.

Selection of reviews

Two researchers independently selected and evaluated all the systematic reviews retrieved, in order to confirm their eligibility, in accordance with the inclusion criteria.

Presentation of results

We presented all the included reviews narratively (qualitative synthesis). We considered that the key points regarding their relevance were the methods used, quality of studies included, results, quality of the body of final evidence for each outcome and applicability.

RESULTS

An initial search resulted in 21 reviews and, after reading the titles and abstracts, ten Cochrane systematic reviews (SRs) were found to be actually related to the topic and fulfilled the inclusion criteria. These were then summarized and are presented below.[12-21]

1. Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy

Vitreous hemorrhage after vitrectomy in patients with diabetic retinopathy is a major complication. In this review,[12] the authors proposed to assess the use of anti-vascular endothelial growth factor (VEGF) after vitrectomy. Their review included randomized clinical trials (RCTs) and "quasi" randomized trials on anti-VEGF, to evaluate the incidence of vitreous hemorrhage post-vitrectomy in patients with proliferative diabetic retinopathy. Twelve RCTs of moderate quality were included, totaling 654 eyes, on patients who received bevacizumab preoperatively or intraoperatively.

Participants who received bevacizumab intravitreally, in association with vitrectomy, developed less early vitreous hemorrhage than did those who underwent vitrectomy alone. However, the effect of administering bevacizumab preoperatively or intraoperatively to prevent late vitreous hemorrhage was uncertain (risk relative, RR 0.72; 95% confidence interval, CI: 0.30 to 1.72; three studies on 196 eyes, with poor quality of evidence). No local or systemic complications were reported. The risk of retinal detachment was low among individuals who received preoperative or intraoperative treatment with bevacizumab (RR 0.46; 95% CI: 0.19 to 1.08; 7 studies on 372 participants, with low quality of evidence). The authors concluded that use of bevacizumab slowed the incidence of early vitreous hemorrhage following vitrectomy. The complications seemed few and it was believed that other ongoing studies would strengthen decision-making regarding use or nonuse of this drug.

Table 1. Search strategy for Cochrane Library

#1	"Diabetic retinopathy" (MeSH term) (search in Title, Abstract, Keywords)
#2	#1 and filter "*in Cochrane reviews*"

2. Topical non-steroidal anti-inflammatory agents for diabetic cystoid macular edema

Cystoid diabetic macular edema, i.e. accumulation of fluid in the inner layers of the retina, is a painless complication leading to reduction or fluctuation of central vision. It may resolve spontaneously, but if it persists, it can lead to permanent loss of vision. It is probably related to inflammatory processes. Therefore, several topical non-steroidal anti-inflammatory drugs (NSAIDs), such as 0.09% bromfenac, 0.1% nepafenac and 0.5% ketorolac have been used to treat chronic diabetics with cystoid macular edema (CMO).

The aim of these authors' review[13] was to select randomized clinical trials and "quasi" randomized trials in order to discover the effects of topical NSAIDs among diabetics with CMO. However, no study was included, since most of the studies were conducted on pseudophakic patients. Presence of pseudophakia can be considered misleading. The authors suggested that there was a need for studies on the use of NSAIDs among diabetic patients with cystoid macular edema.

They concluded that there was a need to conduct properly designed studies in order to clarify the action of this proposed intervention on the clinical condition.

3. Blood pressure control for diabetic retinopathy

These authors'[14] objective was to gather evidence regarding whether hypertension control had protective action relating to prevention and evolution of diabetic retinopathy, thereby preserving visual acuity, through measuring adverse events, quality of life and costs. Secondarily, they aimed to assess the behavior of different classes of antihypertensive drugs regarding the same outcomes. Fifteen clinical trials were included in this review, with varying follow-up times, on a total of 4,157 type 1 diabetic patients and 9,512 type 2 diabetic patients, with or without hypertension. The patients were randomized into groups with intensive pressure control versus less intensive control; standard blood pressure care versus any care; and different classes of antihypertensive drugs versus placebo.

Among type 1 diabetic patients, one out of five studies reported the incidence of diabetic retinopathy and one reported its progression over four to five years of treatment and follow-up; four studies assessed a composite outcome of incidence and progression along over the same period. Among the type II patients, five out of ten trials reported on the incidence and three reported on the progression of retinopathy; one out of these ten trials reported on both the incidence and the progression over the same time interval of four to five years. A test done among type II diabetic patients did not report the outcomes of interest for this review.

The evidence from these clinical trials showed that there was a benefit from treatment with intensive pressure control over a follow-up of four to five years, regarding the incidence of diabetic retinopathy (RR 0.8; 95% CI: 0.71 to 0.92) and the combined outcome of incidence/progression (RR 0.78; 95% CI: 0.63 to 0.97). The evidence showed that there was less benefit regarding progression over the same time interval of four to five years (RR 0.88; 95% CI: 0.73 to 1.05). Pressure control did not have any benefit regarding the progression of proliferative diabetic retinopathy, clinically significant macular edema or moderate to severe loss of visual acuity (RR 0.95; 95% CI: 0.83 to 1.09 for macular edema; and RR 1.06; 95% CI: 0.85 to 1.33 for visual acuity with the best correction), also over the same range of four to five years.

In 7 of the 15 trials, the adverse effect reported most often was death, which led to an estimated RR of 0.86 (95% CI: 0.64 to 1.14); Three trials reported hypotension as an adverse event (RR 2.08; 95% CI: 1.69 to 2.57). Ocular adverse events were described in individual trials.

In this review, the authors concluded that pressure control had a beneficial effect regarding prevention of diabetic retinopathy, but that there was no evidence that the intervention might slow down the progression of retinopathy.

4. Laser photocoagulation for proliferative diabetic retinopathy

Diabetic retinopathy is a complication of diabetes in which high glycemic indexes lead to damage to retinal vessels. Laser is one therapeutic option. The objective of this study[15] was to compare laser photocoagulation with no treatment or other treatments among patients with pre-proliferative diabetic retinopathy.

These authors selected randomized clinical trials on patients with this profile and allocated them into groups of photocoagulation with any type of laser other than xenon or ruby laser. They excluded trials that compared treatments using different laser wavelengths, exposure times and powers of intensity, with absence of treatment or use of other treatments. The primary outcome was considered to be loss of three lines (15 or more letters) from visual acuity with the best correction, over two to five years. Five clinical trials totaling 4,786 people (9,503 eyes) were included in this review.

The authors took all studies with a risk of bias of execution into consideration. Three studies did not show any risk of bias due to attrition. The authors joined the data using a random effects model, except if there were three trials or fewer, in which case they used a fixed-effect model. They found that there was considerable heterogeneity among the trials, with I^2 greater than 50%.

In the 12th month of follow-up, there was no difference between the eyes that had received photocoagulation and the eyes that had no treatment or another treatment, regarding a loss of visual acuity of 15 or more letters (RR 0.99; 95% CI: 0.89 to 1.11; two clinical trials on 8926 eyes, with low quality of evidence). Long-term follow-up did not show any consistency, but one study showed that photocoagulation reduced the risk of loss of accuracy of 15 letters or more over five years by 20%. Laser treatment reduced the risk of severe loss of visual acuity over twelve months by 50% (RR 0.46; 95% CI: 0.24 to 0.86; four clinical trials on 9,276 eyes, with moderate quality of evidence).

There was a beneficial effect on the progression of diabetic retinopathy in eyes that were treated, with a 50% reduction in the risk of progression of diabetic retinopathy (RR 0.49; 95% CI: 0.37 to 0.64; four clinical trials on 8,331 eyes, with low quality of evidence) and similar reductions in the risk of vitreous hemorrhage (RR 0.56; 95% CI: 0.37 to 0.85; two clinical trials on 224 eyes, with low quality of evidence).

The authors concluded that laser photocoagulation remained the treatment of choice for proliferative diabetic retinopathy and suggested that studies combining photocoagulation with anti-angiogenic treatment (VEGFs) should be developed.

5. Anti-vascular endothelial growth factor for proliferative diabetic retinopathy

Given that photocoagulation, the treatment of choice for diabetic retinopathy, has side effects of affecting the field of view and limiting night vision, the authors of this review[16] investigated the efficiency and effectiveness of use of vascular endothelial growth factor (VEGF) as a treatment that might preserve the vision of patients with proliferative diabetic retinopathy. For this, the authors searched for randomized clinical trials comparing VEGF with sham or in combination with other treatments, among patients with proliferative diabetic retinopathy. They found 18 randomized clinical trials on a total of 1,005 patients (1,131 eyes). Eight clinical trials recruited patients referred for photocoagulation, nine for vitrectomy and one for fasciectomy, all with a mean follow-up of six months and ranges from one to twelve months. Seven studies showed a high risk of bias and the others had dubious risk of bias in one or more domains.

A study with a very low level of evidence, on 61 patients, showed that individuals treated with bevacizumab and panretinal photocoagulation were less likely to have lost three or more lines of

visual acuity after 12 months, compared with those treated with panretinal photocoagulation alone (RR 0.19; 95% CI: 0.05 to 0.81). Patients treated with anti-VEGF had a higher chance of gaining three or more lines of vision acuity, but the effect was imprecise and compatible with no effect (RR 0.37; 95% CI: 6.78 to 125.95). No other study noted these two outcomes. On average, people treated with anti-VEGF (bevacizumab, ranibizumab or pegaptanib) had improved visual acuity at 12 months, compared with people who did not receive anti-VEGF (mean difference, MD -0.07; 95% CI of logarithm of the minimum angle of resolution (logMAR): -0.12 to -0.02; five clinical trials on 373 participants, with low quality of evidence). There was evidence suggesting that proliferative diabetic retinopathy regressed through reduction of leakage, seen on angiofluoresceinography, but it was difficult to estimate a result from judging only two studies. People receiving anti-VEGF were less likely to have vitreous bleeding or preretinal bleeding after 12 months (RR 0.32; 95% CI: 0.16 to 0.65; three trials on 342 participants, with low quality of evidence). No study reported health-related quality of life or fluorescein leakage.

People treated with bevacizumab and vitrectomy were less likely to lose three or more lines of vision after 12 months than were those treated with vitrectomy, but the effect was imprecise and compatible with no effect or closer to loss of vision (RR 0.49; 95% CI: 0.08 to 3.14; three trials on 94 participants, with low quality of evidence).

People treated with bevacizumab were more likely to gain three or more lines of vision (RR 1.62; 95% CI: 1.20 to 2.17; three trials on 94 participants, with low quality of evidence). In general, people treated with bevacizumab had better visual acuity after 12 months, compared with people who had not received bevacizumab, but there were doubts regarding the estimates. The confidence interval included zero, i.e. compatible with no effect, and there was considerable inconsistency between the studies (MD -0.24; 95% CI logMAR: -0.50 to 0.01; six clinical trials on 335 people, with I^2 = 67% and low quality of evidence). People who received bevacizumab were less likely to have pre-retinal or vitreous hemorrhage after 12 months (RR 0.30; 95% CI: 0.18 to 0.52; seven clinical trials on 393 participants, with low quality of evidence). No study reported on quality of life. Adverse effects were rarely reported and there was no evidence of any increased risk with anti-VEGF, but there were relatively few studies that reported these effects and the event occurred at a low rate. Thus, the power of analysis to detect any differences was low. The authors considered that the quality of the studies was suspect, with inaccuracy and inconsistency in assessing the risk of bias.

The authors concluded that the evidence from these clinical trials measuring the effectiveness and safety of anti-VEGF, for use in treating proliferative diabetic retinopathy to achieve standard benefits, was of low or very low quality. However, the results suggested that anti-VEGFs can reduce the risk of intraocular hemorrhage in people with proliferative diabetic retinopathy and that new clinical trials to elucidate these questions should be conducted carefully.

6. Anti-vascular endothelial growth factor for diabetic macular oedema

Diabetic macular edema is a common complication of diabetic retinopathy treated with grid or focal laser in order to prevent loss of vision. However, this treatment rarely improves vision. Thus, use of anti-VEGF has been proposed.

These authors[17] investigated the effects of preserving or improving vision, acceptance, security and quality of life with this drug. They included randomized clinical trials comparing anti-VEGF drugs versus sham, other treatments or no treatment, in relation to outcomes of gain or loss of visual acuity of three or more lines, over follow-up periods of up to one year (estimated average of six months).

Eighteen studies were selected. It was concluded that over a one-year period, patients who underwent anti-VEGF treatment gained three or more lines of vision, compared with those treated using a grid (RR 3.6; 95% CI: 2.7 to 4.8; 10 trials on 1,333 cases, with high quality of evidence) and had less chance of losing three or more lines of vision (RR 0.11; 95% CI: 0.05 to 0.24; seven studies on 1,086 cases, with high quality of evidence). It was estimated that eight out of 100 patients with diabetic macular edema were able to gain three or more lines of vision by means of a macular grid, whereas 28 patients would achieve this through antiangiogenic therapy. Thus, 100 patients would need to be treated with antiangiogenic therapy in order to improve the vision of 20 patients (number need to treat, NNT = 20; 95% CI: 13-29).

People treated with anti-VEGF had an improvement of 1.6 sight lines on average (95% CI: 1.4 to 1.8) after one year, compared with those who received pan-laser photocoagulation (nine studies on 1,292 cases, with high quality of evidence). For this, seven to nine injections were applied during the first year and three or four in the second year, in larger studies, with monthly or fixed follow-up. Compared with sham treatment, the antiangiogenic was more effective (three studies on 919 participants, with high-quality evidence). Ocular adverse effects such as endophthalmitis were rare in the studies included.

A meta-analysis conducted on all the antiangiogenic drugs, compared with sham or photocoagulation, showed that there was no significant difference in relation to adverse systemic effects (15 studies with 441 events among 2985 participants; RR 0.98; 95% CI: 0.83 to 1.17), arterial thromboembolic events (14 studies with 129 events among 3034 participants; RR 0.89; 95% CI: 0.63 to 1.25) and overall mortality (63 events among 3562 participants; RR 0.88; 95% CI: 0.52 to 1.47). The authors judged that the quality of evidence regarding side effects was moderate because the safety

scores were only modest and because participants with prior cardiovascular events had been excluded in some studies.

The authors concluded that there was high-quality evidence favoring use of antiangiogenic drugs, compared with photocoagulation, over a period of one to two years. They suggested that future studies should examine the real-world differences in effectiveness between the drugs used in studies monitoring patients at high cardiovascular risk.

7. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus

In this review,[18] the authors analyzed the effects of strict glucose control versus conventional control, and evaluated whether blood glucose at below normal or at normal levels brought benefits. A search for randomized trials on type I diabetics with follow-ups of at least one year that had been published up to 2012 was conducted. Twelve clinical trials were found, with a total of 2,230 patients with a broad-spectrum population, with follow-ups varying from one to six and a half years. Because of the nature of the intervention, these studies could not be "blinded" to hypoglycemia. Moreover, 50% of these studies were judged to present high risk of bias in at least one other category.

In the group with strict glucose control, the risk of developing microvascular complications was lower than in the group with conventional treatment: 23/371 (6.2%) versus 92/397 (23.2%); RR 0.27; 95% CI: 0.18 to 0.42; $P < 0.00001$; two clinical trials on 768 participants, with high quality of evidence. Regarding the progression of the disease manifested in cases of retinopathy, the effect was weaker. For retinopathy, intensive glucose control reduced the risk of progression in studies with a duration of follow-up of at least two years: 85/366 (23.2%) versus 154/398 (38.7%); RR 0.61; 95% CI: 0.49 to 0.76; $P < 0.0001$; two trials on 764 participants, with moderate quality of evidence. On the other hand, there was evidence for an initial worsening of retinopathy after only one year of intensive glucose control: 17/49 (34.7%) versus 7/47 (14.9%); RR 2.32; 95% CI: 1.16 to 4.63; $P = 0.02$; two trials on 96 participants, with low quality of evidence).

Strict control increased the risk of hypoglycemia. However, the studies were heterogeneous, and only one study, the "Diabetes Complications Clinical Trial (DCCT)", clearly showed any increase in episodes of severe hypoglycemia. Mortality was very low in all the studies.

8. Pentoxifylline for diabetic retinopathy

Vascular occlusion is a leading cause of diabetic retinopathy, since chronic high glucose levels leads to changes in the vascular endothelium that culminate in arteriolar occlusion and poor retinal tissue perfusion, rather than nourishment of these ischemic areas though stimulation from vascular proliferation factors. Pentoxifylline is a drug used in treating occlusive peripheral arterial diseases. Thus, there are clinical trials in the literature that address this subject. However, the authors of this systematic review[19] failed to include any study in their review because none of them met the inclusion criteria proposed in their protocol.

These authors concluded that photocoagulation remained the first choice for treating diabetic retinopathy. However, there was evidence that pentoxifylline would induce decreased proteinuria and albumin excretion, and would also normalize some blood patterns. Diabetic patients treated with pentoxifylline had early absorption of retinal hemorrhage and had less neovascularization. In some cases, there was a reduction of ischemic areas. These results suggested that pentoxifylline might be effective in preventing retinal neovascularization and improving this condition. The authors suggested that further randomized clinical trials should be conducted to assess the treatment. These would be needed in order to prove the efficacy and effectiveness of pentoxifylline in relation to the evolution of diabetic retinopathy.

9. Vitamin C and superoxide dismutase (SOD) for diabetic retinopathy

This Cochrane review aimed to study the effects of vitamin C and superoxide dismutase (SOD), as antioxidants for treating diabetic retinopathy, given the growing evidence of the oxidizing action of this disease. The authors[20] only took clinical trials with one or both drugs into consideration. No studies that assessed treatment of diabetic retinopathy with vitamin C and SOD to indicate whether these substances had any impact on the evolution of the disease were found.

The authors stated that photocoagulation remained the treatment of choice for diabetic retinopathy, although there was evidence that free radicals had a role in the pathogenesis of the disease. They considered that antioxidant therapy could be helpful in preventing the progression of retinopathy, and that a combination of drugs could be needed in order to prevent visual loss among diabetic patients.

10. Intravitreal steroids for macular edema in diabetes

In this study,[21] the authors evaluated the safety and effectiveness of any form of steroids applied intravitreally to treat diabetic macular edema up to 2007. Seven studies on 632 eyes were included. Four studies reported on intravitreal injection of triamcinolone (IVTA), compared with other treatments, by assessing visual acuity after three, six, nine and 24 months. They showed that intravitreal steroids were more beneficial. Three studies examined intravitreal application of fluocinolone acetate implants (FAI) or systemic administration of dexamethasone (DDS). Two studies presented low risk of bias, one had medium risk, two had high risk and two had unclear risk. The results suggested that IVTA had a major

beneficial effect regarding both visual acuity and retinal thickness. Two trials reported that clinical improvements were achieved through FAI, in comparison with the standard treatment, although severely decreased visual acuity was not unusual. Beneficial effects were also observed in a study using DDS, although endophthalmitis was observed and two patients presented ptosis: one with a conjunctival ulcer and one with retinal detachment. Increased intraocular pressure and cataract formation are side effects that require monitoring.

These authors concluded that intravitreal injectable steroids or implantable steroids improved visual acuity in cases of diabetic macular edema that were persistent or recurrent. However, they stated that the question of whether the same beneficial behavior in the early stages of the disease would be obtained, both with their use alone and in association with photocoagulation, remained open.

Treatment with DDS can have positive effects in cases of refractory persistent edema or in cases in which the standard treatment was insufficient. However, because of the variety of protocols, it has not been possible to identify an algorithm for its use in practice. Given that the half-life of DDS is short, patients need to be subjected to repeated injections, which increases the risk of complications relating to the procedure, such as endophthalmitis, retinal detachment and vitreous hemorrhage. FAI can solve the problem of complications due to injections, through having a more sustained effect, but it has higher risk of increased intraocular pressure, which would require medical or surgical intervention, in addition to greater risk of development of cataracts. No studies have addressed the effects of treatment according to diabetic macular edema stage, either as single or as combined therapy.

DISCUSSION

Among the ten SRs found in the Cochrane Library that discuss interventions relating to diabetic retinopathy, four present systemic strategies that might have a preventive nature, such that they might prevent progression of the disease. These strategies would have the capacity to act throughout the microcirculation. The other six SRs analyzed local treatments for disease that had already become established.

It can be noted that among the four SRs presenting systemic interventions, "Blood pressure control for diabetic retinopathy" and "Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus" were the ones that addressed prevention and progression of diabetic retinopathy. In the other two, "Vitamin C and superoxide dismutase (SOD) for diabetic retinopathy" and "Pentoxifylline for diabetic retinopathy", the authors were unable to find relevant clinical trials and, in accordance with their predefined inclusion criteria, they left the topic open for future clinical trials, thereby revealing the need to study these issues.

The SR on the systemic intervention "Blood Pressure control for diabetic retinopathy" showed that there was a benefit from lowering blood pressure in relation to prevention of diabetic retinopathy that lasted for four or five years. However, it lacked evidence to show that this would slow the progression of diabetic retinopathy. This, together with the modest beneficial effect on disease incidence, weakened the conclusion that there was a benefit from intervening in blood pressure only to prevent diabetic retinopathy. In the review "Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus", there was high-quality evidence showing that strict glycemic control decreased the development of retinopathy complications, compared with standard control among young patients. However, the evidence relating to disease progression was weaker. These authors suggested that studies addressing the same outcomes among elderly patients with this disease and macrovascular complications should be conducted.

Systemic interventions, by their very nature, may be the most appropriate form of prevention for retinopathy. It is clear that there is a need for more studies with higher levels of evidence on prophylactic action through the microcirculation, and even on prevention relating to diabetic macrocirculation. These studies should be conducted not only on different populations, as suggested by the authors of several of the abovementioned reviews, but also on other pharmacological classes that act preventively. For example, lipid-lowering drugs are known to protect the macrocirculation, but their behavior in relation to the microcirculation remains a mystery.

Among the six SRs that investigated local therapy, three addressed anti-VEGFs: two of these reviews analyzed studies on proliferative diabetic retinopathy and one, macular edema. One review examined clinical trials involving topical corticosteroid therapy for diabetic macular edema, and another assessed the use of non-steroidal anti-inflammatory drugs to treat cystoid macular edema. The last of these reviews examined clinical trials on photocoagulation.

In the SR "Topical non-steroidal anti-inflammatory agents for diabetic cystoid macular oedema", the authors did not include any clinical trials that might address the use of non-steroidal anti-inflammatory drugs for treating cystoid macular edema. This was because all the studies eventually fell within the exclusion criteria due to the large number of confounding factors relating to the different etiologies of this pathological condition.

The SR "Laser photocoagulation for proliferative diabetic retinopathy" included five trials that did not address near vision or quality of life among the patients who received this treatment. It found that there was little difference in visual acuity between the control group and intervention group after a twelve-month period, with low quality of evidence. There was moderate quality of evidence regarding reduction of the risk of severe loss of visual

acuity. There was a benefit regarding progression of diabetic retinopathy in the intervention group, with low quality of evidence, and also a benefit regarding vitreous hemorrhage.

In the SR "Anti-vascular endothelial growth factor for proliferative diabetic retinopathy", the authors concluded that there was low or very low quality of evidence regarding the safety and efficacy of the use of anti-VEGFs in relation to proliferative diabetic retinopathy. However, they suggested that an improvement was obtained regarding vitreous hemorrhage. This went against the conclusion from the review "Anti-endothelial vascular growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy", which was a review with high-quality evidence.

Among these six SRs, many concluded that the procedure investigated was advantageous. On the other hand, they suggested that further studies should be conducted on patients presenting different profiles or at earlier stages of the disease, or using associations between the therapies to enhance their effectiveness and reduce the side effects foreseen in the procedures.

Regarding visual acuity, the use of anti-VEGF in treating proliferative retinopathy was found to improve visual acuity, with low quality of evidence. There was high-quality evidence regarding its use in macular treatment, compared with use of a macular grid.

As stated earlier, diabetic retinopathy is a disease that causes a negative impact on both health and social security through affecting the economically active population. It also affects patients' self-esteem, because of its deleterious and mutilating nature.

The treatment of choice for proliferative diabetic retinopathy continues to be peripheral retinal photocoagulation. However for treating macular disease, the use of injectable corticosteroids and anti-VEGFs is of great interest with regard to preserving and improving patients' vision. These methods are promising alternatives for treating diabetic macular edema, but further studies on the early phase of this pathological condition are required.

Regarding the implications of the present review for further research, the need for a prophylactic treatment or an option capable of at least reducing the progression of diabetic retinopathy persists even today. The aim of such treatment would be to avoid local treatments, thereby preserving the retinal tissue. Thus, the search for systemic medication that can produce effects on the entire vascular endothelium continues, with the aim of safeguarding diabetic patients' macro and microcirculation and acting as prophylaxis to avoid all the sequelae that diabetes causes to the vascular tree.

CONCLUSION

Only a few options are likely to be effective for treating diabetic retinopathy. These include photocoagulation and anti-vascular endothelial growth factor agents. Strict glucose and pressure control seem to postpone the onset of retinopathy. For macular edema, antiangiogenic drugs, intravitreal injection and surgical implantation seem to have some benefit. However, these findings came from evidence ranging from low to high quality. Low-quality evidence needs to be used with caution in clinical practice until further studies can corroborate it.

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AIM AND EDITORIAL POLICY

Indexing and scope

São Paulo Medical Journal (formerly Revista Paulista de Medicina) was founded in 1932 and is now published bimonthly by the Associação Paulista de Medicina. It accepts articles in the fields of clinical health science (internal medicine, gynecology & obstetrics, mental health, surgery, pediatrics, epidemiology and public health). Articles will be accepted in the form of original articles, narrative reviews, case reports, short communications and letters to the editor. Papers with a commercial objective will not be accepted.

The journal's articles are indexed in MEDLINE, LILACS, SciELO, Science Citation Index Expanded, Journal Citation Reports/Science Edition (ISI) and EBSCO Publishing.

The Journal's peer review policy and procedures

After receipt of the article through the electronic submission system, it will be read by the Editorial Team, who will check whether the text complies with the journal's Instructions for Authors. The Journal has adopted the Viper system for identifying plagiarism and any text that has been plagiarized, in whole or in part, will be rejected.

When the format of the manuscript is deemed acceptable, the Editorial Team will submit the article to the Editor-in-Chief who will assign at least two reviewers/referees with expertise in the theme, to assess it. The authors will then receive the reviewers' evaluation and will be required to provide all further information requested and the corrections that may be necessary. Changes to the text should be highlighted, accompanied by a letter answering the referees' comments, point by point.

Once the Editorial Team has received the revised manuscript, the text will be sent to the Editor-in-Chief for a decision. Manuscripts that are suitable for publication according to their scientific merit will be considered "accepted." However, all of them will subsequently be scrutinized to check for any problems regarding sentence construction, spelling, grammar, bibliographical references and other matters that may arise. The authors should contribute towards improving the manuscript by making it as readable as possible. Lastly, the Editorial Team will provide page proofs for the authors to approve. No article is published without this final procedure.

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THE MANUSCRIPT AND TYPES OF ARTICLES

General guidelines: for all types of articles

All manuscripts must be submitted in English with a covering letter signed by the corresponding author. The letter must contain the following five essential items relating to the manuscript:

1. a declaration that the manuscript is original and that the text has not been nor will be submitted for publication in any other journal.
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4. a brief description of contributorship.
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The Journal recommends that all articles submitted must comply with the editorial quality standards established in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (available at www.icmje.org).[1] This means that each type of study must be described in accordance with the specific quality guidelines for papers reporting on clinical trials (CONSORT),[2] systematic reviews and meta-analyses (PRISMA),[3,4] observational studies (STROBE),[5,6] case reports (CARE)[7] and accuracy studies on diagnostic tests (STARD).[8,9]

Abbreviations must not be used, even those in everyday use. Drugs or medications must be referred to using their generic names, avoiding casual mention of commercial or brand names. All drugs should be followed by the dosage and posology used. Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses.

Grants, bursaries and any other financial support for studies must be mentioned separately, after the references, in a section named "Acknowledgements." This section should also be used to acknowledge any other contributions from individuals or professionals who have helped in producing the study. The Journal supports the position taken by the International Committee of Medical Journal Editors (http://www.icmje.org) regarding authorship. This body's recommendations should be read to obtain clarifications regarding the criteria for authorship.

For any manuscript, all statements in the text that do not result from the study presented for publication in the São Paulo Medical Journal but from other studies must be accompanied by a quotation of the source of the data. All statements regarding health statistics and epidemiological data should generally be followed by references to the sources that generated this information, even if the data is only available electronically.

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Authors of articles published in São Paulo Medical Journal should all have contributed actively to the discussion of the study results and should review and approve the final version to be released. The corresponding author is the primary guarantor of all ethical issues relating to the manuscript, before, during and after its publication. However, São Paulo Medical Journal considers that all authors are held fully responsible for the study, regarding the accuracy or integrity of data and data interpretation in the text.

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FORMAT

Title page (cover page)

The title page must contain:

1. Type of paper (original article, review or updating article, short communication or letter to the editor).
2. Title of the paper in English, which must be brief but informative.
3. Full name of each author (the editorial policy of the São Paulo Medical Journal is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full or omitted, without using abbreviations); his/her background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or undergraduate student); and his/her position currently held (for example, Master or Doctoral Student, Assistant Professor, Associate Professor or Professor, but not Head of Department, Dean, Provost or Rector), in the department and institution where he/she works, and the city and country (affiliations).
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7. For Brazilian authors, all grants that can be considered to be related to production of the manuscript must be declared, such as fellowships for undergraduate, master and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors, such as awards for established investigators (*Produtividade* - CNPq), accompanied by the respective grant numbers.
8. Description of any conflicts of interest held by the authors. We recommend that the item "Conflicts of interest" at http://www.icmje.org should be read to obtain clarifications regarding what may or may not be considered to be a conflict of interest.
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Main document

Second page: abstract and keywords

The second page must include the title and a 250-word abstract in English (case reports with 100 words). Do not cite references in the abstract.

Use the following headings:

1. Background: Describe the rationale for the study including the research question or the scientific hypothesis.
2. Design and setting: Declare study design correctly,[11] and the setting.
3. Methods: Describe methods briefly.
4. Results: Describe primary results with quantitative results describing the sampling strategy.
5. Conclusions: Make a succinct statement of data interpretation answering the research question presented previously.
6. Clinical Trial Registration. Mandatory for clinical trials, optional for observational studies. List the URL, as well as the Unique Identifier, on the publicly accessible website on which the trial is registered.

Insert 3 to 5 key words after the abstract, with terms differing from the title. The words must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which is available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh.

Text

- Typical main headings include Introduction, Methods, Results, Discussion and Conclusion. The authors can use short subheadings too.
- Number the pages.

- Abbreviations must be avoided.
- A maximum of 3000 words in the main text, from the Introduction to the Conclusions; 1000 words for short communications.
- Maximum number of figures and/or tables is 5
- Maximum number of references is 35 (except for systematic reviews).

References

São Paulo Medical Journal uses the reference style known as the "Vancouver style," as recommended by the International Committee of Medical Journal Editors (ICMJE). Follow the instructions and examples at www.icmje.org, item "References", for the format.

In the text, the references must be numbered in the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences, and in superscript (without parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references mentioned in the text.

The reference list should be inserted after the conclusions and before the tables and figures. In the list of references, all the authors must be listed if there are up to and including five authors; if there are six or more, the first three should be cited, followed by the expression "et al." For books, the city of publication and the name of the publishing house are mandatory. For texts published on the internet, the complete uniform resource locator (URL) or address is necessary (not only the main home page of a website or link), so that by copying the complete address into a computer internet browser, the journal's readers will be taken to the exact document cited, and not to a general website.

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All the figures and tables should be cited in the text.

All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded to indicate the magnification used. The staining agent should be specified in the figure legend.

Original articles

Clinical trials; cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies; case series (i.e. case reports on more than three patients analyzed together); and systematic reviews with or without meta-analysis, are considered to be full-text original articles, with a maximum of 3000 words.

Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles.

Short communications and case reports must be limited to 1000 words (from the introduction to the end of the conclusion). The abstracts in short communications should not be structured and have a maximum of 100 words.

Authors will be required to comply with the guidelines for writing each type of original article, as follows:

1. Observational articles: STROBE Statement[5,6]
2. Clinical trials: CONSORT Statement[2]
3. Accuracy studies on diagnostic tests: STARD Statement[8,9]
4. Systematic reviews of the literature and meta-analyses: PRISMA[4]
5. Case reports: CARE[7]

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials have only been accepted for publication if they have received an identification number from one of the clinical trial registers (the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Authors of randomized clinical trials must thus register their studies before submitting them for publication in the São Paulo Medical Journal.

Results from cases with DNA sequences must be deposited in appropriate public databases. The protocol number or URL can be requested at any time during the editorial review. Publication of other research data in public repositories is also recommended, since it contributes towards replicability of research, increases article visibility and possibly improves access to health information.

Short communications, case reports, case series and narrative reviews

Short communications and case reports must be limited to 1000 words (from the introduction to the end of the conclusion), a maximum of five references and one figure or table. They should be structured in the same way as original articles. Individual case reports should contain the following sections: Introduction, Case Report, Discussion and Conclusion. Reports on case series constitute observational studies and these should be structured in accordance with the norms of the STROBE Statement.[5]

Both short communications and case reports must be submitted with abstracts and keywords. The abstracts in short communications should not be structured and have a maximum of 100 words.

The São Paulo Medical Journal is interested in publishing rare or instructive case reports, accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[11] The search strategy for each database and the number of articles obtained from each database must be shown in a table. The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms are appropriate to be utilized for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT) the search dates should be indicated in the text or in the table.

Narrative reviews may be accepted by the São Paulo Medical Journal provided that a systematic search is made, and they should be structured as Original Articles. The search strategy and results should be presented as described above for case reports. By invitation from the Editor-in-Chief, narrative reviews addressing historical personal or collective experiences relating to clinical health sciences, epidemiology and public health may be accepted, but with no more than two authors.

Individual case reports should contain Introduction, Case Report, Discussion and Conclusion. Case reports should be structured in accordance with the norms of the CARE Statements.[7] Case reports published in São Paulo Medical Journal must be submitted with abstracts and keywords.

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Letters to the editor may address articles published in the São Paulo Medical Journal publication or may deal with health issues of interest. Case reports must not be submitted as letters. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

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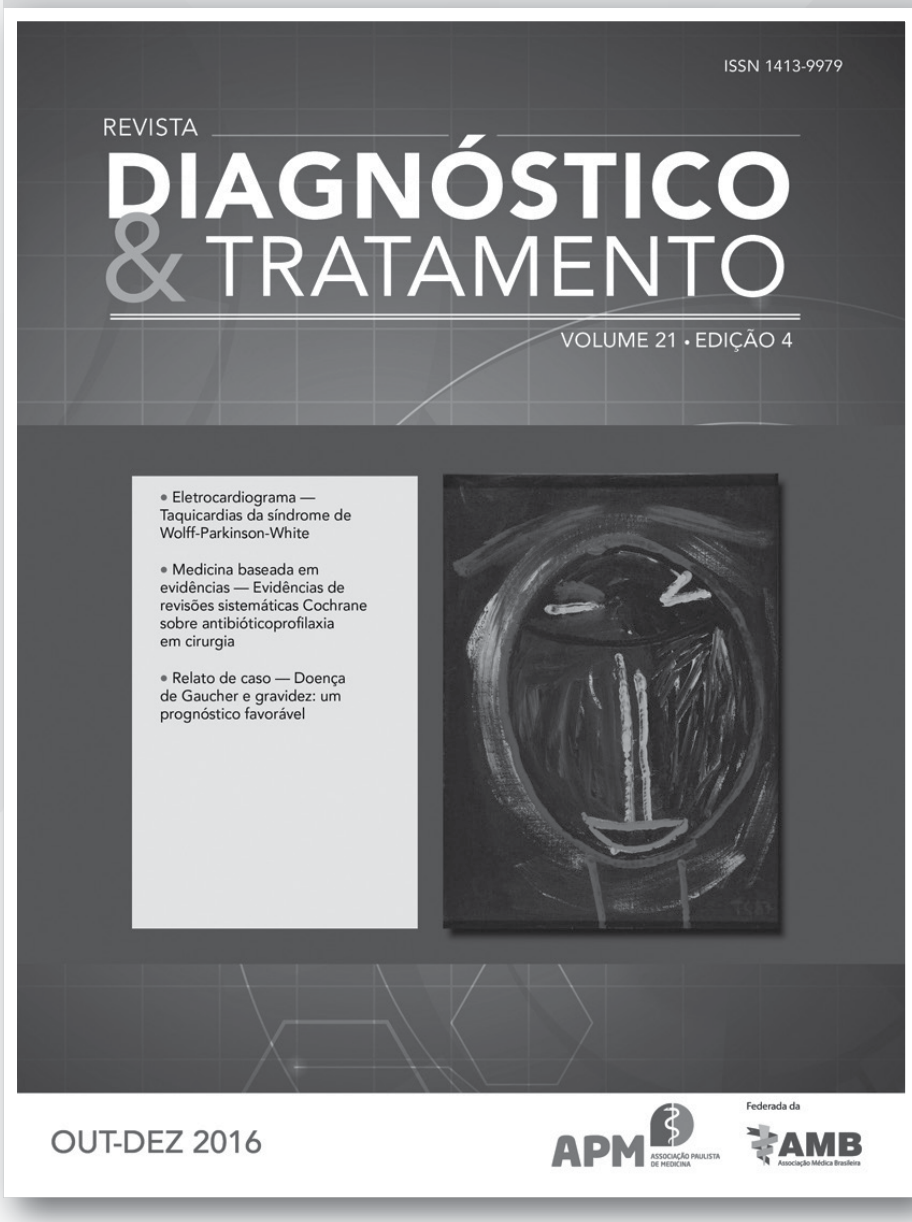

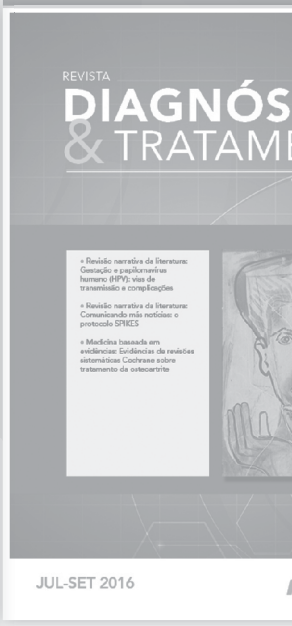

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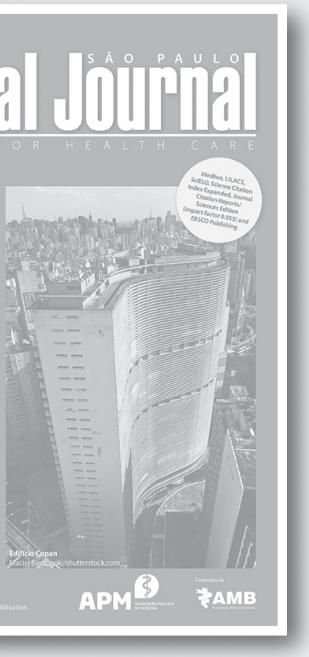

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