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- Influence of air pollutants on pneumonia hospitalizations among children in a town in the Brazilian Legal Amazon region

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Subclinical thyroid diseases as a non-classical risk factor for cardiovascular diseases

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Cardiovascular diseases are the most common cause of death worldwide and in Brazil.[1-3] Although mortality caused by these diseases has been decreasing over the last few decades, the pace of this decrease has differed according to socioeconomic status. The decrease has been greater among people of high socioeconomic status than among those of low socioeconomic status.[4]

The most common risk factors for cardiovascular diseases, i.e. hypertension, diabetes, dyslipidemia and smoking, do not explain all cases of cardiovascular diseases. As an example, in recent data from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), these classical cardiovascular risk factors explain less than 40% of all of the burden of subclinical atherosclerosis, as measured from the common carotid artery intima-media thickness.[5] However, assessments of these classical risk factors in other cohort studies have explained even less of the burden of atherosclerosis than in ELSA-Brasil. Rundek et al. reported that the classical risk factors explained around 11% of the variance of carotid intima-media thickness, and that addition of less traditional risk factors to the models only increased this proportion to 16%.[6]

Cardiovascular diseases are preventable, but control over the associated risk factors begins with identification of new risk factors beyond the classical ones. Several new risk factors have emerged over the last few years. Changes to thyroid function, such as those due to subclinical thyroid diseases or to alterations in thyrotropin (TSH) and free thyroxine (FT4) levels, are one of these.

Thyroid diseases have worldwide prevalence, and Brazil is one of the countries with the highest prevalence of thyroid diseases.[7] Although thyroid diseases are more common in women, and this is also true for Brazil, data from Brazilian studies have suggested that the female-to-male ratio for these diseases in Brazil is lower than in other countries.[8,9]

In addition to the burden of overt thyroid diseases, subclinical thyroid diseases characterized by low TSH levels with normal FT4 levels (as in the case of subclinical hyperthyroidism) or by high TSH levels with normal FT4 levels (as in the case of subclinical hypothyroidism) have been recognized over recent years as non-classical risk factors for cardiovascular diseases.[10,11] Several studies have shown associations of subclinical hyperthyroidism and subclinical hypothyroidism with coronary heart disease,[12,13] cardiovascular events[13] and all-cause[12] and cardiovascular mortality.[12-14] A Brazilian study has also shown an association of subclinical thyroid diseases with all-cause and cardiovascular mortality, in a sample of Japanese-descendent Brazilians who were followed up for 7.5 years.[15]

Brazil has also contributed to studies on the association of subclinical thyroid diseases with subclinical atherosclerosis. Subclinical hypothyroidism was found to be associated with higher common carotid artery intimal-media thickness values, using euthyroid subjects as the reference (odds ratio, OR 1.30; 95% confidence interval, CI 1.06-1.59), after multivariate adjustment for sociodemographic and cardiovascular risk factors.[16]

In ELSA-Brasil, an association between low TSH levels (first quintile) and coronary artery calcium score was observed in the entire sample of men and women, even after multivariate adjustment for sociodemographic and cardiovascular risk factors (OR 1.57; 95% CI 1.05-2.35), using the third quintile as the reference. In an analysis restricted to men, TSH levels in the first quintile were associated with coronary artery calcium (CAC) scores > 100 Agatston units (OR 1.72; 95% CI 1.07-2.79). However, in women, there was a U-shaped curve such that TSH levels in both the

first quintile (OR 3.31; 95% CI 1.31-8.37) and in the fifth quintile (OR 3.29; 95% CI 1.30-8.31) were associated with CAC > 100 Agatston units. Subjects with TSH levels within the range of subclinical hyperthyroidism and low-normal values (first quintile) had higher odds for CAC > 100, using the third quintile of TSH levels as the reference.[17] Another study conducted in Brazil showed an association between subclinical hypothyroidism and CAC scores > 100 only among men older than 55 years, with a Framingham risk score > 10%.[18]

In this setting, it is essential to be able to diagnose occurrences of thyroid diseases in men. Previous Brazilian data showed that diagnoses of thyroid diseases among older men in low socioeconomic strata are made less often than would be expected.[8] These individuals are also a high-risk group for cardiovascular diseases.[4] Moreover, treatment for thyroid diseases is prescribed more commonly for women than for men, especially among people with low socioeconomic status.[8,9] We can hypothesize that the high burden of thyroid diseases in men, which frequently remains undiagnosed and untreated, may form a non-classical risk factor for coronary heart disease and cardiovascular mortality in Brazil. On the other hand, we can hypothesize that some of the high burden of coronary heart disease in women may also be related to high frequency of thyroid diseases. Although thyroid diseases in women are more frequently treated than those in men, their occurrence is also influenced by low socioeconomic status. Data from ELSA-Brasil showed that women with high mean monthly income were more frequently treated than women with low income.[8,9] Moreover, low socioeconomic status has also been shown to be a risk factor for lower rates of diagnosis and treatment of coronary heart disease, especially among women.[20,21]

This intricate relationship between thyroid and cardiovascular diseases, especially among people of low socioeconomic status in Brazil needs to be investigated more deeply to identify possible strategies for dealing with the problem. Brazil has particular characteristics that may suggest that considerable overlap exists between concomitant occurrences of these two diseases and presence of a high burden from their association in the general Brazilian population. Now is the right time to work on this!

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Comparison of different approaches to small saphenous vein reflux treatment: a retrospective study in two centers

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ABSTRACT

BACKGROUND: Diagnosis and treatment of small saphenous vein (SSV) insufficiency is of utmost importance for relieving chronic venous insufficiency symptoms.

OBJECTIVES: To investigate the efficacy and safety of five different treatment approaches among patients with SSV insufficiency.

DESIGN AND SETTING: Two-center retrospective clinical study, conducted at cardiovascular surgery clinics in a local training and research hospital and a state hospital.

METHODS: A total of 282 extremities of 268 patients with SSV insufficiency alone who were treated for symptomatic varicose veins between January 2012 and January 2017 were included in the study. All extremities included in the study were divided into five groups as follows: high ligation + stripping; radiofrequency ablation (RFA); cyanoacrylate closure (CAC); and endovenous laser ablation (EVLA) at the wavelengths 980 nm and 1,470 nm.

RESULTS: Although the recurrence rate at six months was similar among the treatment groups, we found significant differences in recurrence rates at one year, with lower rates in the CAC, RFA and 1,470 nm EVLA groups, compared with the other treatments (P = 0.005). No sural neuritis was observed in the CAC group. The pigmentation rate was higher in the two EVLA groups (980 nm and 1,470 nm).

CONCLUSIONS: Our study results showed that although CAC, RFA and EVLA at 1,470 nm seemed to be effective methods for treating SSV insufficiency alone, CAC and RFA had better aesthetic results than EVLA at 1,470 nm. We consider that endovenous non-thermal techniques for treating SSV insufficiency may be preferable because of relatively low risk of nerve injury.

INTRODUCTION

The small saphenous vein has been less suspected in the etiology of venous insufficiency than the great saphenous vein, since it is located in the posterior aspect of the leg with a relatively short length and diameter and less reflux. The prevalence of small saphenous vein insufficiency alone has been found to be 3.5%.[1] About 20% of patients with venous insufficiency symptoms are diagnosed with small saphenous vein insufficiency.[2] In particular, a small saphenous vein diameter of ≥ 4 mm has been shown to be associated with venous reflux.[2] The main symptoms of small saphenous vein insufficiency include pain and burning sensation, itching, heaviness, cramps and restless legs. Symptom severity is closely associated with the degree of chronic venous insufficiency.[3] Therefore, diagnosis and treatment of small saphenous vein insufficiency is of utmost importance for relieving the symptoms.

The saphenopopliteal junction is located 2 to 4 cm proximally to the popliteal skin crease, where it is included in the popliteal vein, and it is seen in about 83% of the cases. This junction terminates in a normal fashion in only 62% of the cases, since the medial gastrocnemial vessels and small saphenous vein terminate in a common trunk in one-fourth of patients.[4] In addition, the small saphenous vein is closely connected to the sural nerve from the apex of the calf to the ankle.[4] Because of this close connection with the sural nerve and a high number of anatomical variations in the popliteal fossa, surgical treatment of small saphenous vein insufficiency is more complicated than is treatment of great saphenous vein insufficiency.[5]

Although the basic surgery for treating small saphenous vein insufficiency consists of ligation and/or stripping, inappropriate or improper ligation results in failure in 22% of the cases with one-year and three-year recurrence rates of 31.6% and 51.7%, respectively.[6,7] Over the last decade, endovascular treatment methods have become popular and have been included in the

European guidelines for treatment of small saphenous vein insufficiency.[3] However, no consensus regarding the surgical treatment of small saphenous vein insufficiency has yet been established. Moreover, although the efficacy and safety of different treatments for small saphenous vein insufficiency have already been studied, the number of studies is relatively low, compared with those on great saphenous vein insufficiency. Also, the majority of these studies were limited to head-to-head study designs.

OBJECTIVE

In the present study, we aimed to investigate the efficacy and safety of five different treatment approaches among patients with small saphenous vein insufficiency alone.

METHODS

This retrospective study was conducted at cardiovascular surgery clinics in a local training and research hospital and a state hospital between January 2012 and January 2017. A total of 282 extremities of 268 patients who were diagnosed with small saphenous vein insufficiency and underwent conventional surgery or endovenous therapy for symptomatic varicose veins were included.

The inclusion criteria were as follows: ≥ 18 years of age; a small saphenous vein diameter of ≥ 4 mm; saphenopopliteal junction insufficiency grade ≥ 2; Comprehensive Classification System for Chronic Venous Disorders (CEAP) class ≥ 2 and ≤ 5; and complete follow-up data available at six months and one year postoperatively. The exclusion criteria were as follows: a small saphenous vein diameter of < 4 mm; saphenopopliteal junction insufficiency grade < 2; CEAP class < 2 and > 5; and ligation of the small saphenous vein performed alone.

The study protocol was approved by the local ethics committee (date: August 9, 2017; no. 7/11). The study was conducted in accordance with the principles of the Declaration of Helsinki.

All the extremities included in the study were divided into five groups as follows: high ligation + small saphenous vein stripping (n = 45); endovenous laser ablation at the wavelength 980 nm (n = 39); endovenous laser ablation at the wavelength 1,470 nm (n = 36); radiofrequency ablation (n = 134); and cyanoacrylate closure (n = 28) (Table 1).

The preoperative small saphenous vein diameter, CEAP class, body mass index (BMI), previous history of great saphenous vein surgery, presence of deep venous insufficiency and preoperative and postoperative venous clinical severity scores were recorded. Postoperative procedure-related complications such as bruising, sural neuropathy, thrombophlebitis, pigmentation, skin burns, deep vein thrombosis or pulmonary thromboembolism were also evaluated, along with the severity of postoperative pain and recurrence of venous insufficiency at six months and one year. Data relating to the patients were obtained from the hospital automated record system and from patient files.

The degree of preoperative venous insufficiency was evaluated by the vascular surgeon in accordance with the CEAP classification and venous clinical severity score. The duration of small saphenous vein insufficiency and the vein diameter were assessed using Doppler ultrasonography. Pathological venous reflux was defined as a reverse flow for 0.5 seconds in response to release of calf or thigh compression, with the patient standing, and after a Valsalva maneuver in the supine position.

Preoperative and postoperative (at one year) venous clinical severity scores were calculated for each patient and recorded in the automated system. The severity of postoperative pain was evaluated using a numerical rating scale, i.e. a segmented numerical version of a visual analogue scale, which was found as standard in all patient files.[8]

Sural neuropathy was diagnosed by a neurologist based on clinical examination and electrodiagnostic test results, in patients with typical subjective sensory symptoms such as burning pain, hypesthesia, dysesthesia or paresthesia over the foot or upper calf. Pigmentation was defined as skin color changes during the postoperative period, while persistent pigmentation was defined as the presence of skin pigmentation six months after the operation.[9]

The primary outcome was recurrent varicose veins in treated patients. The postoperative follow-up consisted of clinical examination and Doppler ultrasonography. Recurrence was defined as new-onset varicose veins, subsequent to the procedure.[3] Success in the procedure was defined as the absence of distal small saphenous vein reflux and absence of neovascularization in the saphenopopliteal junction, as shown using Doppler ultrasonography.

Intervention techniques

All the operations were performed under spinal anesthesia in the prone position, except for cyanoacrylate closure, which was performed under local anesthesia. Preoperatively, the location of the saphenopopliteal junction was marked on the skin using color Doppler ultrasonography and the patient was then transferred to the operating room. All patients were placed in the prone position.

The standard conventional technique consisted of high ligation + small saphenous vein stripping, which was carried out as previously described by Hong et al.[8] The endovascular treatment techniques consisted of endovenous laser ablation at the wavelengths 980 nm and 1,470 nm (endovenous laser ablations, FG Group, Ankara, Turkey); radiofrequency ablation (ClosureFast™, Medtronic, USA); and cyanoacrylate closure (VariClose® FG Group, Ankara, Turkey). All of the endovascular catheters were placed from apex of the calf to 2-3 cm distally from the saphenopopliteal junction.

In all thermal techniques, 250-500 ml of tumescent anesthesia (500 ml of normal saline, 15 ml of 2% lidocaine, 20 ml of 8.4% sodium bicarbonate and 0.5 ml of epinephrine [1:1000]) was administered around the small saphenous vein using a 21-gauge needle. The ablation procedure was performed under the guidance of Doppler ultrasonography with application of a local cold pack to the skin. The 980 nm and 1470 nm endovenous laser ablation techniques were performed using 79.6 ± 10.7 (60-100) and 68.2 ± 9.7 (50-90) J/cm, respectively, of laser energy to the vein wall, depending on the diameter of the vein treated.

In the non-thermal procedure, the junction was compressed and collapsed under the guidance of Doppler ultrasonography and glue was continuously injected using a cyanoacrylate system, along the course of the small saphenous vein. Meanwhile, external compression was applied. Once the procedure had been terminated, compression of the small saphenous vein was maintained for an additional 30 seconds. The success rates from the endovascular techniques were evaluated through color Doppler ultrasonography.

Postoperative follow-up

For all patients who underwent conventional surgery or thermal endovascular treatment, an elastic bandage was used. After the elastic bandage was removed, class 2 (25 to 30 mmHg) compression stockings were applied for six weeks, in accordance with the guideline recommendations.[4] On the other hand, neither elastic bandages nor compression stockings were applied to the patients who received cyanoacrylate closure.

The severity of pain was evaluated using a numerical rating scale at six hours postoperatively for the patients who were treated under local anesthesia; or at 24 hours postoperatively for the patients who were treated under spinal anesthesia.

During the postoperative period, a single dose of 0.35 ml of tinzaparin sodium (INNOHEP®, Abdi İbrahim, Istanbul, Turkey) was given for prophylaxis of thromboembolism. The patients were examined by a specialist physician, but not by the surgeon who had performed the treatment, in the outpatient clinic at six and 12 months after the operation.

Statistical analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 17.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed as the mean ± standard deviation (SD) for continuous variables and as numbers and percentages for categorical variables. The chi-square test or Fisher's exact test was used to compare categorical variables between the groups. Analysis of variance (ANOVA) or the Kruskal-Wallis test was used to assess continuous variables in independent groups, for parametric and nonparametric variables, respectively. A P-value of 0.05 was considered statistically significant.

RESULTS

A total of 282 extremities of 268 patients who were treated for small saphenous vein insufficiency were included in this analysis. The right lower extremity was treated in 108 patients (40.3%), the left lower extremity in 146 patients (54.3%) and bilateral lower extremities in 14 patients (5.2%).

Among the patients included, 132 (49.3%) were females and 136 (50.7%) were males. The mean age of all the patients was 44.94 ± 12.44 years (range, 18 to 84). The mean body mass index (BMI) was 27.1 ± 3.1 kg/m^2 (range, 21.2 to 37.3) and 54 patients (20.1%) had a BMI value of ≥ 30 kg/m^2. The mean diameter of the small saphenous vein of all the patients was 6.65 ± 1.99 cm (range, 4 to 14.2). There was no significant difference among the groups in terms of age, gender, CEAP classification, small saphenous vein diameter, BMI and deep venous insufficiency (**Table 1**).

Great saphenous vein surgery had previously been performed in 39 patients (14.6%), and there was no significant difference among the groups (P = 0.073). Microphlebectomy was applied to 118 patients (44%), and the number of patients who underwent microphlebectomy was significantly lower in the cyanoacrylate closure group (P < 0.001).

Although there was no significant difference in the recurrence rate at six months among the treatment groups (P = 0.319), we found a statistically significant difference in the recurrence rate at one year. This indicated lower recurrence rates in the cyanoacrylate closure, endovenous laser ablation at the wavelength 1470 nm and radiofrequency ablation groups, compared with the other treatments (P = 0.005) (**Table 2**).

In addition, there were statistically significant differences in the numerical rating scale scores among the treatment groups. The pain scores were lowest in the cyanoacrylate closure group (P < 0.001). The numerical rating scale scores were similar in the radiofrequency ablation and 1,470 nm endovenous laser ablation groups, with significantly lower scores than among the patients treated with high ligation + small saphenous vein stripping and with endovenous laser ablation at the wavelength 980 nm (**Table 2**).

None of the patients experienced major complications. Among all the patients, 33 (11.7%) developed transient sural neuropathy. Two of these patients (n = 1 in the 980 nm endovenous laser ablation group; and n = 1 in the radiofrequency ablation group) had permanent sensory loss along the path of the sural nerve at the end of six weeks, while all neurological symptoms resolved in the remaining patients. Sural neuropathy was most commonly seen in the patients treated with endovenous laser ablation at the wavelength 980 nm (n = 10; 25.6%). None of the patients in the cyanoacrylate closure group had sural neuropathy (**Table 3**).

The rate of ecchymosis was highest in the open surgery group (n = 8; 17.8%). All ecchymoses disappeared by the end of the second

Table 1. Preoperative patient characteristics of the treatment groups

	HLS		980 nm EVLA		1470 nm EVLA		RFA		CAC		
	n	%	n	%	n	%	n	%	n	%	P
Gender											0.101[a]
Female	17	38.6	16	41.0	15	41.7	66	54.5	18	64.3	
Male	27	61.4	23	59.0	21	58.3	55	45.5	10	35.7	
BMI (kg/m²)											0.07[a]
< 30	38	86.4	33	84.6	33	91.7	88	72.7	22	78.6	
≥ 30	6	13.6	6	15.4	3	8.3	33	27.3	6	21.4	
CEAP classification											0.2[a]
2	23	52.3	26	66.7	24	66.7	57	47.1	15	53.6	
3	13	29.5	11	28.2	5	13.9	37	30.6	8	28.6	
≥ 4	8	18.2	2	5.1	7	19.4	27	22.3	5	17.9	
Deep venous insufficiency											0.279[a]
No	31	70.5	26	66.7	31	86.1	90	74.4	23	82.1	
Yes	13	29.5	13	33.3	5	13.9	31	25.6	5	17.9	
	n	Mean ± SD (Min-Max) (median)		Mean ± SD (Min-Max) (median)		Mean ± SD (Min-Max) (median)		Mean ± SD (Min-Max) (median)		Mean ± SD (Min-Max) (median)	
Age (year)	44	44.98 ± 10.88 (26-71) (44)	39	44.54 ± 13.62 (26-79) (42)	36	44 ± 12.97 (19-73) (41)	121	45.79 ± 12.16 (19-74) (46)	28	42.96 ±14.04 (18-69) (39)	0.827[b]
SSV diameter (mm)	45	7.07 ± 1.99 (4-13) (6.5)	39	6.5 ± 1.68 (4-11) (6)	36	6.98 ± 1.97 (4-14.2) (6.95)	134	6.65 ± 2.13 (4-13) (6)	28	5.83 ± 1.44 (4-9) (5.4)	0.092[b]

HLS = high ligation + stripping; EVLA = endovenous laser ablation; RFA = radiofrequency ablation; CAC = cyanoacrylate closure, BMI = body mass index; CEAP = comprehensive classification system for chronic venous disorders; SD = standard deviation; Min-Max = minimum-maximum; SSV = small saphenous vein.
[a]chi-square test; [b]analysis of variance.

Table 2. Pain scores and recurrence rates of the treatment groups

	HLS		980 nm EVLA		1470 nm EVLA		RFA		CAC		P
	n	Mean ± SD (Min-Max) (median)	n	Mean ± SD (Min-Max) (median)	n	Mean ± SD (Min-Max) (median)	n	Mean ± SD (Min-Max) (median)	n	Mean± SD (Min-Max) (median)	
Pain score (NRS)	44	4.4 ± 1.4 (2-8)	39	3.6 ± 1.9 (0-8)	36	1.9 ± 1.4 (0-6)	121	1.8 ± 1.7 (0-8)	28	0.8 ± 0.9 (0-8)	< 0.001[a]
Recurrence	**n = 45**	**%**	**n = 39**	**%**	**n = 39**	**%**	**n = 134**	**%**	**n = 28**	**%**	**P**
6th month	5	11.4	3	7.7	2	5.6	4	3.3	2	7.1	0.319[b]
1st year	14	31.1	9	23.1	4	11.1	13	9.7	3	10.7	0.005[b]

HLS = high ligation + stripping; EVLA = endovenous laser ablation; RFA = radiofrequency ablation; CAC = cyanoacrylate closure; SD = standard deviation; Min-Max = minimum-maximum; NRS = numerical rating scale.
[a]Kruskal-Wallis test; [b]chi-square test.

Table 3. Complications in the treatment groups

Complications	HLS (n = 45)		980 nm EVLA (n = 39)		1470 nm EVLA (n = 36)		RFA (n = 134)		CAC (n = 28)	
	n	%	n	%	n	%	n	%	n	%
Minor complications										
Ecchymosis	8	17.8	1	2.6	0	0	0	0	0	0
Thrombophlebitis	0	0	0	0	0	0	0	0	2	7.1
Pigmentation	0	0	7	17.9	3	8.3	2	1.5	0	0
Sural neuropathy	6	13.5	10	25.6	5	13.9	12	9	0	0

HLS = high ligation + stripping; EVLA = endovenous laser ablation; RFA = radiofrequency ablation; CAC = cyanoacrylate closure.

week after the operation in all the study groups. Two patients (7.1%) had thrombophlebitis in the cyanoacrylate closure group.

The rate of pigmentation was higher in the endovenous laser ablation groups at the wavelengths 980 nm and 1,470 nm (17.9% and 8.3%, respectively) (Table 3). In the radiofrequency ablation group, there were only two patients (1.5%) with pigmentation. Four patients (10.3%) in the 980 nm endovenous laser ablation group, three patients (7.7%) in the 1,470 nm endovenous laser ablation group and two patients (1.55%) in the radiofrequency ablation group had persistent pigmentation.

There was no significant difference in the preoperative venous clinical severity score scores among the groups (P = 0.493). In addition, there was no significant difference in the postoperative (at one year) venous clinical severity score scores among the groups except for high ligation + small saphenous vein stripping group (P = 0.025). Using each treatment approach, we found a statistically significant clinical improvement in the venous clinical severity score scores, irrespective of the recurrence rate (**Table 4**).

DISCUSSION

Over recent years, endovenous techniques have become popular and have been increasingly used for treating small saphenous vein insufficiency, as an alternative to surgery. Because of the anatomical variations of small saphenous vein and the difficult nature of this surgery, the success rate from conventional surgery is relatively low.[6,7] With increasing use of endothermal ablation techniques and with increasing familiarity with Doppler ultrasonography among vascular surgeons in daily practice, the success rates of the procedure have increased, compared with conventional surgery, for patients with small saphenous vein insufficiency.

In a previous study, the recurrence rates were reported to be 31.6% and 51.7% at one and three years, respectively, among patients undergoing small saphenous vein ligation and/or stripping.[7] In a recent study, however, the recurrence rate was shown to be 4.3% among patients undergoing modified high ligation and segmental stripping, although the sample size was small.[10] In our study, on the other hand, the recurrence rate was 31.1% among patients undergoing high ligation + segmental stripping. This can be attributed to the small sample size and to the fact that endovascular treatment methods were not popular at the beginning of the endovascular era when most patients underwent conventional surgery. Moreover, the small saphenous vein anatomy could not be evaluated accurately, given that vascular surgeons were only rarely familiar with intraoperative Doppler ultrasonography guidance.

Today, endovenous laser ablation and radiofrequency ablation are the most common endothermal ablation techniques. In one study, the obliteration rate of radiofrequency ablation was found to be 93.4%, one year after the procedure.[11] In the literature, there are several studies reporting success rates of 100%, one year after the procedure, among patients treated with endovenous laser ablation at the wavelength 1,470 nm.[12,13] In a systematic meta-analysis that included 49 studies on patients with small saphenous vein insufficiency, the anatomical success rate was 58.0% among 798 patients treated with surgery, 98.5% among 2,950 patients treated with endovenous laser ablation and 97.1% among 386 patients treated with radiofrequency ablation.[14] Most recently, cyanoacrylate closure has been introduced for treating venous disorders. In a meta-analysis on previous studies, the success rate was found to be 96.8%, one year after the procedure, among 53 patients with small saphenous vein insufficiency.[15] In our study, the success rates from the procedures of radiofrequency ablation, cyanoacrylate closure and endovenous laser ablation at the wavelength 1,470 nm (90.3%, 89.3% and 88.9%, respectively) were found to be higher than the rates for the other two treatment groups, one year after the procedure. Our success rate from radiofrequency ablation was consistent with data in the literature, but our rates relating to cyanoacrylate closure and endovenous laser ablation at the wavelength 1,470 nm were somewhat lower than those from previous studies. We consider that the smaller sample size of the groups that underwent cyanoacrylate closure and endovenous laser ablation at the wavelength 1,470 nm, compared with the size of the radiofrequency ablation group, may have affected our results relating to anatomical success rate.

Age, gender and obesity (particularly BMI > 30 kg/m^2) are well-known risk factors for venous insufficiency.[3] In addition, risk factors such as the diameter of the treated vein, deep venous insufficiency, preoperative CEAP classification and type of device used have been shown to be associated with treatment failure from endovascular treatment methods for venous insufficiency.[3,16,17] Casana et al.[18] showed that postoperative vein reduction after the radiofrequency ablation procedure was influenced by preoperative CEAP class. In our study, there was no significant difference

Table 4. Clinical assessment of the treatment groups

	HLS	980 NM EVLA	1470 NM EVLA	RFA	CAC	P
Pretreatment VCSS	4.8 ± 1.4 (2-8)	4.3 ± 1.1 (2-7)	4.5 ± 1.3 (3-8)	4.6 ± 1.4 (2-9)	4.7 ± 1.3 (2-7)	0.493[a]
Post-treatment VCSS	2.2 ± 1.6 (0-5)	1.8 ± 1.3 (0-5)	1.5 ± 1.3 (0-4)	1.4 ± 1.4 (0-7)	1.4 ± 1.2 (0-4)	0.025[a]
P	< 0.001[b]	< 0.001[b]	< 0.001[b]	< 0.001[b]	< 0.001[b]	

VCSS = venous clinical severity score; EVLA = endovenous laser ablation; RFA = radiofrequency ablation; CAC = cyanoacrylate closure.
[a]Kruskal-Wallis test; [b]Wilcoxon signed-rank test.

among the groups in terms of age, gender, CEAP classification, small saphenous vein diameter, BMI or deep venous insufficiency.

In one study, the success rate from the procedure was reported to be 97% at six weeks, among patients with small saphenous vein insufficiency that was treated with laser ablation at the wavelength 980 nm. However, in that study, it was only possible to evaluate 60% of the patients.[19] In another study, Park et al. showed that the success rate from the procedure was 94%, one year after the procedure, among patients with small saphenous vein insufficiency that was treated with endovenous laser ablation at the wavelength 980 nm, although it was only possible to evaluate 40% of the patients.[20] In addition, previous studies revealed that the anatomical success rate was similar between the endovenous laser ablation procedures at the wavelengths 980 nm and 1,470 nm.[14,21] In contrast, we found a significant lower success rate with endovenous laser ablation at 980 nm, compared with the laser at 1,470 nm. In our study, the success rate from the endovenous laser ablation procedure at the wavelength 980 nm was found to be 76.9% at one year, i.e. a lower rate than previous findings. This can be explained by the fact that our sample size was relatively small and nearly half of the patients undergoing endovenous laser ablation at the wavelength 980 nm in studies in the literature could not be evaluated.[19,20]

Postoperative procedure-related complications reported previously have included bruising, sural neuropathy, thrombophlebitis, pigmentation, ecchymosis, skin burns, deep vein thrombosis or pulmonary thromboembolism, among patients with small saphenous vein insufficiency.[3] In our study, no major complications such as skin burns, deep vein thrombosis or pulmonary embolism were seen in any of the patients. Pigmentation resulted in poor esthetic results and reduced the quality-of-life scores of the treated patients.[3]

Along the natural course of the small saphenous vein, it runs just below the skin and shows a wide range of variations. Therefore, thermal injury-related skin changes are more common. Although hyperpigmentation was reported in 5% of the patients after the endovenous laser ablation procedure, hyperpigmentation along the ablated vein after the endovenous laser ablation procedure occurs in up to 12% of the patients.[3,22] On the other hand, hyperpigmentation was reported in 3 to 4% of the patients in the literature, after radiofrequency ablation.[3,18] However, these results were usually given as great saphenous vein treatment results. The hyperpigmentation rate was reported to be 3.3% after endovenous laser ablation surgery to treat small saphenous vein reflux in one randomized clinical trial.[23] The pigmentation rate was higher in the two endovenous laser ablation groups (wavelengths 980 nm and 1,470 nm) in our study (17.9% and 8.3%, respectively). A total of nine patients (n = 4 with 980 nm endovenous laser ablation; n = 3 with 1,470 nm endovenous laser ablation; and n = 2 with radiofrequency ablation) presented persistent pigmentation. These results were higher than what has been reported in the literature and can be attributed to the fact that pigmentation rates were usually not mentioned in previous studies on small saphenous vein surgery. Skin complication rates seem to be higher with endovascular thermal treatment of small saphenous vein insufficiency.

Ecchymosis is an early postoperative complication that is associated with poor pain and quality-of-life scores.[3] In the literature, the rate of ecchymosis has been reported as 3% to 4%, among patients undergoing endovascular treatment of small saphenous vein insufficiency.[3] In our study, the patients who underwent high ligation + small saphenous vein stripping had the highest ecchymosis rate (17.85%), while only one patient (2.6%) in the group with endovenous laser ablation at the wavelength 980 nm developed ecchymosis. The higher rate of ecchymosis in the high ligation + small saphenous vein stripping group can be explained by the high number and variety of small saphenous vein deep venous vascular connections. Because the small saphenous vein is adjacent to the sural nerve, sural nerve injury can be seen during treatment. Sural nerve injury is associated with a burning sensation in the innervation site, numbness and sensory loss, leading to neuroma formation.[3] Although previous studies have demonstrated divergent results, it was found through a meta-analysis that the rates of sural nerve injury from conventional surgery, endovenous laser ablation and radiofrequency ablation were 19.6%, 4.8% and 9.7%, among patients with small saphenous vein insufficiency.[14]

In this context, it is of utmost importance to identify the entry site of the affected saphenous vein. The small saphenous vein is closest to the sural nerve under the mid-calf. In one study, access from the lateral malleolus rather than from the calf was found to be associated with a higher rate of paresthesia, among patients treated with endovenous thermal ablation.[24] In contrast, Sanioglu et al. reported that access from the mid-calf was not safe and suggested that the nerve should be identified under the guidance of ultrasonography.[25] In our study, the rate of neurological sequelae was highest among the patients treated with endovenous laser ablation at the wavelength 980 nm. The rate of neurological sequelae was similar between the other treatment groups, except in the cyanoacrylate closure group, in which no sequelae were seen. The higher rate of neurological complications can be attributed to the fact that endovenous laser ablation at the wavelength 980 nm was previously the most frequently applied treatment within clinical practice.

Our results regarding sural nerve injury seem to be consistent with the findings in the literature regarding endovascular thermal treatment and conventional surgery. Of note, we believe that experience is more important than the access site, in using endothermal techniques, for minimizing neurological complications. In addition, the severity of pain was evaluated on a numerical rating scale among the treatment groups, and the cyanoacrylate closure group presented the lowest pain scores. The radiofrequency ablation and endovenous laser ablation at 1,470 nm showed similar

scores. The lack of microphlebectomy in the cyanoacrylate closure group might have contributed to lower pain scores. According to our study results, although all the treatment techniques were performed under spinal anesthesia except for cyanoacrylate closure, the radiofrequency ablation, endovenous laser ablation at 1,470 nm and cyanoacrylate closure techniques seemed to be associated with less pain.

In our study, the venous clinical severity score was used to assess per-operative clinical improvement. We found that there was a statistically significant improvement in the venous clinical severity score scores postoperatively in all procedures, irrespective of the recurrence rate. Although the high ligation + small saphenous vein stripping group showed a statistically significant postoperative clinical improvement, this group had the highest postoperative venous clinical severity score among the treatment groups, because of the high recurrence rate.

There were some limitations to the present study. It had a small sample size with unequal sizes among the treatment groups. In addition, it was not possible to thoroughly evaluate patient satisfaction due to missing data in the quality-of-life questionnaires. Although the retrospective design can be deemed to be another limitation, we believe that this study will provide additional information for the body of knowledge on this subject, given that no head-to-head studies comparing five different methods for treating small saphenous vein insufficiency alone are available in the literature.

CONCLUSION

Our study showed that although cyanoacrylate closure, radiofrequency ablation and endovenous laser ablation at the wavelength 1,470 nm seemed to be effective methods for treating small saphenous vein insufficiency alone, cyanoacrylate closure and radiofrequency ablation had better esthetic results than those from endovenous laser ablation at 1,470 nm. Although complication rates tend to decrease with increasing experience in endovascular procedures over time, thermal ablation therapies will always imply a risk of neurological complications. Therefore, we consider that endovenous non-thermal techniques for treating small saphenous vein insufficiency may be preferable because of their relatively low risk of nerve injury.

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Chronic low back pain and physical activity among patients within the Brazilian National Health System: a cross-sectional study

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BACKGROUND: This study was based on filling a gap in our knowledge regarding the issue of what the protective effect of physical exercise on patients within the Brazilian National Health System could be, in relation to low back pain.

OBJECTIVES: To determine the prevalence of chronic low back pain (CLBP) and to analyze the protective effect of physical exercise among patients over 50 years old attended at primary healthcare units (PHUs).

DESIGN AND SETTING: Analytical cross-sectional study at Universidade Estadual Paulista (UNESP) that was conducted in two PHUs (Parque Cedral and Vila Real), located in different regions of the city of Presidente Prudente, Brazil.

METHODS: In total, 327 patients were interviewed and evaluated at which retrospective characteristics covering the previous 12 months. The Nordic questionnaire was used to classify CLBP, and the Baecke questionnaire for physical activity level. The body mass index (kg/m^2) was calculated using body mass and height values, both collected at the time of the interview.

RESULTS: High prevalence of low back pain was found; 175 patients (53.5%) reported having had at least one episode of low back pain in the previous year. Of these, 71 (21.7%) answered yes to all four questions on the Nordic questionnaire and were classified as CLBP. Physical exercise remained associated with CLBP, independent of other factors (odds ratio = 0.35; 95% confidence interval = 0.15-0.80).

CONCLUSION: High prevalence of low back pain was identified among PHU users. Physical exercise was associated as an independent protective factor against this pathological condition.

INTRODUCTION

Low back pain has been found to be highly prevalent worldwide, for example in Germany (59%),[1] Turkey (51%),[2] France (55.4%)[3] and the United States (50%).[4] This health impairment can evolve to motor incapacitation, thereby severely compromising the quality of life of the individuals affected. Only 15% of the cases are of known etiology, which makes treatment difficult and reduces the chances of a good prognosis.[4]

Occurrences of low back pain are the second largest cause of medical consultations in the world,[4] and this has a significant impact on public health systems, both through direct expenditure (consultations, medications, physiotherapy and examinations) and through indirect expenditure (reduction in productivity and absenteeism).[5] In the United States, the estimated cost of chronic low back pain is 100 billion dollars per year,[6] while in the United Kingdom the cost of back pain reaches 480 million pounds per year.[7]

A large part of the adult population suffers from this disorder (50.2%), of which 11.3% suffer from chronic low back pain.[8] Consequently, low back pain leads the ranking in disability pensions (29.96 per 100,000 taxpayers).[9] The following determinants of low back pain have been recognized: sex, chronological age, work condition, excess weight and sleep.[8] Physical activity, although not clearly understood, seems to be a great ally in prevention of this pathological condition, especially because this is a non-pharmacological tool with low cost.[10,11]

Primary healthcare units (PHUs) serve the majority of the Brazilian population. They form the main triage locations for primary care, in which the focus is prevention and avoidance of the need for patients to access other levels of healthcare. Public policies need to be based on

scientific evidence, so as to effectively meet the requirements of the community.

OBJECTIVE

The aims of the present study were to determine the prevalence of chronic low back pain and to analyze the possible protective effect of physical exercise in different domains, among patients over 50 years of age who were attended at PHUs in Presidente Prudente, Brazil.

METHODS

Design and setting

This was an analytical cross-sectional study at Universidade Estadual Paulista (UNESP) that was conducted in two PHUs (Parque Cedral and Vila Real), located in different regions of the city of Presidente Prudente, São Paulo, Brazil.

Ethical issues

This study was approved by the local Research Ethics Committee, at the Presidente Prudente campus of UNESP (procedural number: 241291; date: April 5, 2013).

Sample calculation and subject selection process

The sample was composed of adults over 50 years old, of both sexes, who were attended at two PHUs (Parque Cedral and Vila Real), which are located in different regions of the city of Presidente Prudente. This age group was chosen because individuals of this age present greater incidence of chronic low back pain.[8] The PHUs involved in the study were indicated by the Health Department of Presidente Prudente. This city is located in the west of the state of São Paulo and has approximately 208,000 inhabitants and a human development index of 0.806 (which is considered high).

The minimum sample size was calculated using the prevalence of chronic low back pain (14.7%) that was reported by Almeida et al.[12] in an epidemiological study in the city of Salvador, Bahia, and a standard error of 5%. These were inserted into an equation for population parameters. In addition, a population of 208,000 inhabitants was considered, with a 95% confidence interval (95% CI) (z = 1.96). With the configuration described above, the equation indicated that interviews with at least 206 adults of both sexes would be needed. Lastly, 50% was added to allow for possible losses during the 12-month study period. This resulted in a need to interview 310 people, i.e. 155 patients at each BHU.

During the mornings of a 60-day period, all patients attended at these PHUs were invited to take part in the study, if they fulfilled all of the following inclusion criteria: i) registration at that PHU for at least one year, with at least one medical consultation attended over the previous six months; ii) age > 50 years; iii) resident in the city of Presidente Prudente for at least two years; iv) signing of an informed consent statement.

At each of the two PHUs selected, an initial screening of the medical schedules of all patients who had visited the unit over the previous thirty days was performed. At each PHU, all patients seen over the previous 30 days who met the inclusion criteria were invited to participate.

The patients thus selected were invited to attend the PHU for an evaluation and directed interview. The final sample consisted of 327 patients.

Evaluations

Low back pain

The questionnaire developed by Kuorinka et al.[13] and previously validated for the Portuguese language,[14,15] which evaluates occurrences of musculoskeletal symptoms (pain, tingling or numbness), was used in this study but only for the lower back region. For each body region, there are four dichotomous questions (yes or no) regarding:

i. the presence of musculoskeletal disorders over the previous 12 months;
ii. impairment of daily activities over the previous 12 months, due to these disorders;
iii. consulting a healthcare professional because of these disorders; and
iv. feeling the presence of these disorders in the week immediately prior to the interview. Positive responses to these four questions were considered to be indicative of chronic low back pain in the lumbar region.

Economic condition

To determine the participants' economic situation, a questionnaire developed by the Brazilian Association of Market Research Companies (2010) was used. In this, economic situation is subdivided from A (highest) to E (lowest). The sample was subsequently dichotomized into high economic situation (categories A and B) and low economic situation (categories C, D and E), as adopted by Fernandes et al.[16] The present questionnaire was applied through an interview, which was conducted by the research coordinator.

Nutritional status

Body mass index (in kg/m^2) was calculated using body mass and height values, which were both obtained at the time of the interview, in accordance with the protocol of Lohman et al.[17] The presence of overweight/obesity was diagnosed when the body mass index presented values between 25 and 29.9 kg/m^2 for overweight and ≥ 30 kg/m^2 for obesity.[18]

Habitual physical activity

Information regarding habitual physical activity practices was collected by means of an interview using the questionnaire developed by Baecke et al.,[19] which was translated and validated for Brazilian realities by Florindo et al.[20] Through application of the instrument, it was possible to identify the level of habitual physical activity in each domain. The sum of the scores for each section gave the total score, i.e. habitual physical activity. For the purpose of statistical analysis, the sample was subdivided into quartiles according to the total physical activity score from the instrument (which analyzes three domains of physical activity: i- occupational; ii- physical exercise during leisure; iii- leisure and locomotion). Participants in the 75th percentile and above (highest quartile) were considered physically active. Cycling was also computed dichotomously (yes or no).

Confounding factors

The following were considered to be confounding factors: education ([i] 1-4 years; [ii] 5-8 years; [iii] 9-11 years; or [iv] ≥ 12 years); gender (male or female); age (< 65 years or ≥ 65 years); ethnicity (white, black or other color); and current occupational activity (yes or no).

Statistical procedures

Numerical variables were presented as means and standard deviations, and the means were compared using Student's t test. Categorical variables were expressed as absolute and percentage values, and univariate statistical tests were applied to these (χ^2, with the Yates correction applied via 2 x 2 contingency tables). When significant differences were found, the values were inserted in a multivariate model (binary logistic regression) with hierarchical insertion. The magnitude of associations was expressed in terms of odds ratio (OR) values and their respective 95% confidence interval (CI). In our analysis model, associations between the dependent variable (chronic low back pain) and the independent variables were investigated, and the results were corrected for possible confounding variables (sex, economic situation, adiposity and age). The statistical analyses were performed using specific software (BioEstat version 5.0) and, in all procedures, the significance level adopted was 5%.

RESULTS

The sample was composed of 327 patients, i.e. 229 females (70%) and 98 males (30%). The mean body mass index was 29.1 ± 5.4 kg/m², the mean age was 62 ± 8.8 years and 83 patients (25.4%) had a current occupation. Low back pain was found to be present in 175 patients (53.5%), i.e. at least one episode of low back pain in the previous year. Among these patients with low back pain, 71 (21.7%) gave positive responses to the four questions about low back pain and were therefore classified as having chronic low back pain. Females had higher odds of developing chronic low back pain (OR = 2.63; 95% CI = 1.24-1.55). The independent variables are presented in **Table 1**, thus characterizing the sample and the influence of these variables on the outcome of chronic low back pain.

In the whole sample, 78 patients (23.9%) were considered physically active. The variables associated with chronic low back pain were inserted into the binary logistic regression, which resulted in the odds ratios presented in **Table 2**.

Table 1. General characteristics of the sample

	Chronic low back pain*		P-value
	Yes	No	
Numerical variables (μ ± SD)			**t-test**
Age (years)	57.9 ± 6.9	63.1 ± 8.9	**0.003**
Weight (kg)	75.4 ± 15.3	71.5 ± 14.9	0.055
Height (m)	1.57 ± 8	1.57 ± 8.9	0.730
Body mass index (kg/m²)	30.5 ± 6.1	28.7 ± 5.2	0.025
Categorical variables n (%)			**χ^2 test**
Sex			
Female	60 (26.2)	169 (73.8)	**0.004**
Male	11 (11.3)	87 (88.7)	
Ethnicity			0.204
White	44 (20.5)	170 (79.5)	
Black	13 (18.8)	56 (81.2)	
Others	14 (31.8)	30 (68.2)	
Age			**0.001**
< 65 years	61 (28.8)	151 (72.2)	
≥ 65 years	10 (8.8)	105 (91.2)	
Body mass index			0.220
Normal	12 (16.0)	63 (84.0)	
Overweight/obese	59 (23.4)	193 (76.6)	

*Positive responses to the four questions in the questionnaire; μ ± SD = mean and standard deviation.

Table 2. Factors associated with chronic low back pain among Brazilian primary healthcare unit patients

	Chronic low back pain*		χ^2	Crude OR (95% CI)
	Yes n (%)	No n (%)	P-value	
Cycling			0.02	
Yes	4 (8.3)	44 (91.7)		**0.291 (0.101-0.839)**
No	67 (23.8)	212 (76.2)		1.00
Exercise			**0.04**	
Yes	10 (12.8)	68 (87.2)		**0.453 (0.220-0.935)**
No	61 (24.5)	188 (75.5)		1.00
Work			**0.02**	
Yes	26 (31.3)	57 (68.7)		**2.010 (1.146-3.551)**
No	45 (18.4)	199 (81.6)		1.00

*Positive responses to the four questions in the questionnaire; OR = odds ratio; 95% CI = 95% confidence interval.

The variables that were associated with chronic low back pain, as shown in **Table 2**, were inserted hierarchically in multivariate models, as demonstrated in **Table 3**, to test whether these associations were independent of the other factors.

DISCUSSION

The prevalence of low back pain found in the present study (53.5%) is similar to that reported from another survey carried out in the same city (50.2%),[8] and also to reports from other studies around the world.[1-4] However, the prevalence of chronic low back pain, of 21.7%, was higher than what had been found in other studies conducted in Brazil: in the states of Bahia (14.7%)[12] and São Paulo (11.3%)[8]. It is possible this difference is due to the fact that these other studies were population-based studies, thus differing from the characteristics of the population of the present study, which comprised PHU patients. Another important factor that contributed towards higher prevalence of low back pain was the age group evaluated in the present study, i.e. individuals over 50 years old. This differs from population studies, which encompass all adults over the age of 18 years. This important observation reflects the need for prophylactic measures and/or specific treatments to control this pathological condition. This need is not exclusive to the present study.

In the models created, female sex was shown to be a risk factor for the development of chronic low back pain, independently of the other confounding factors (OR = 2.63; 95% CI = 1.24-1.55). This greater occurrence may have been due to anatomical-functional differences, but may also have come from women's double working day.[8] Sex lost statistical significance only when physical and occupational activities were inserted in the model. Culturally, in Brazil, men are more active during leisure time than women,[16] and this would be a protective factor against chronic low back pain. On the other hand, men perform functions with greater physical overloads, which increases the risk of developing chronic low back pain.[3] This factor may be the explanation for the loss of significance when the data were adjusted for these variables.

Table 3. Model adjusted for association between chronic low back pain and independent variables

	Model 1	Model 2*	Model 3**
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Cycling			
Yes	**0.284 (0.094-0.861)**	**0.283 (0.093-0.859)**	0.378 (0.122-1.167)
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Physical exercise			
Yes	**0.390 (0.182-0.836)**	**0.388 (0.181-0.831)**	**0.356 (0.159-0.800)**
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Work			
Yes	1.308 (0.715-2.393)	1.302 (0.711-2.382)	1.181 (0.628-2.220)
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

OR = odds ratio; 95% CI = 95% confidence interval; yes ≥ 75th percentile; no < 75th percentile; Model 1: model adjusted according to socioeconomic variables (sex, age, ethnicity and economic situation); Model 2: model adjusted according to socioeconomic variables and body mass index; *Hosmer and Lemeshow test with P-value = 0.544; Model 3: all variables inserted; **Hosmer and Lemeshow test with P-value = 0.061.

Patients who reported that they were working also presented greater risk of developing chronic low back pain (OR = 2.01; 95% CI = 1.14-3.55). This association lost significance when inserted into the multivariate model together with age and economic situation, perhaps because people in a higher economic situation have better information about healthy life habits and also do not need to work when they have reached this age group.[1]

It is known that workers in several types of occupation perform functions that contribute towards installation of this pathological condition. Moreover, chronic low back pain can cause decreased productivity and quality of life among the individuals affected, and this may lead to susceptibility to absences from work. It is therefore important to stress that management teams in public institutions and other employers need to make efforts to prevent and/or combat this important health problem.[1,22,23]

Encouragement to practice physical activity may be a strategy, through advertisements that incorporate healthy values and increase the level of physical activity. In Brazil, the example of the United States could be adopted, with a national road map to improve the quality of health through a physically active lifestyle, like the one developed by the American College of Sports Medicine, which involves four steps: awareness, education, partnerships and monitoring.[24]

The physical activity practices among PHU users seem to be a relevant problem, since only 24% of the interviewees were classified as sufficiently active. This is a low percentage and is similar to that reported by Turi et al.[25] in the city of Bauru, also among PHU patients (24.9%). In Brazil, promotion of physical activity only began widely in the 1970s.

Promotion of physical activity has greater efficacy among younger individuals. Moreover, if physical activity practices are insufficient during youth, this tends to continue into adulthood, since the characteristics of these practices tend to stabilize over time.[26,27] Given that the population of this study was older than 50 years, the participants had probably not been given as much encouragement as young people currently are, which will have led to higher rates of sedentary behavior among people who are now over 50 years of age.[28]

Lastly, the greatest contribution of the present study was to make a correlation between the level of physical activity and occurrences of chronic low back pain. Physically active people were found to

have 65% less chance of developing chronic low back pain, independently of other factors. This differed from some previous studies, in which physical activity lost its association when inserted in the multivariate model.[8,12] However, the current findings corroborate those of other studies, in which the benefits of being physically active on this disorder were demonstrated.[1,22,23] This validates the practice of physical activity and makes it an important option in relation to prevention and/or treatment of this disorder.

The beneficial effects of regular physical activity on maintenance of good health have been recognized worldwide.[24,28] In relation to chronic low back pain, these effects are no different: physical activity plays a fundamental role, indirectly or directly, in the preventive aspects of reducing the risks of developing this pathological condition.

There is evidence indicating that physically active people are less likely to develop poor sleep quality. Poorer sleep quality has been correlated with chronic low back pain.[8] Another indirect benefit of physical activity to reduce the risks of developing chronic low back pain is in controlling obesity.[8,11,13] Systematized general physical exercise programs of both low and moderate intensities are considered to be directly protective against chronic low back pain, and are applied in treating this disorder.[11]

It is worth highlighting the methodological design of the present study. It used a sample of the population that was of significant size and demonstrated that physical activity was a protection factor in different domains of leisure and locomotion, in relation to chronic low back pain. Thus, public policies aimed towards increasing the level of physical activity should be encouraged, such as inclusion of physical educators and training infrastructure within PHUs.

However, there were some limitations to the present study. The lack of a more sophisticated method for diagnosing low back pain, the reverse causality bias applied in this study and the data collection method used (active charts alone), which led to a large discrepancy in the numbers of men and women in the sample, should be considered to be the main limitations. These form directions for future studies.

CONCLUSION

A high prevalence of low back pain was identified among PHU patients, while the practice of physical exercise during leisure time was a protective factor against this outcome.

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Dyspnea is associated with poor physical performance among community-dwelling older adults: a population-based cross-sectional study

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ABSTRACT

BACKGROUND: Dyspnea and poorer physical performance are conditions that may be related and be present among the elderly. However, few studies have evaluated associations between these variables.

OBJECTIVE: To determine whether there is an association between dyspnea and physical performance among community-dwelling older adults of both sexes (age 60 years and over).

DESIGN AND SETTING: Cross-sectional study conducted in the city of Macapá, state of Amapá, Brazil.

METHODS: Socioeconomic and health data were collected using a structured form. Frailty syndrome was assessed based on the frailty phenotype proposed by Fried et al. Dyspnea was measured using the modified Medical Research Council (mMRC) scale and physical performance was measured using the Short Physical Performance Battery (SPPB). Data were analyzed using a linear regression model.

RESULTS: A total of 411 subjects (70.15 ± 7.25 years) were evaluated, most of them females (66.4%). It was observed from the mMRC scale that 30.9% (n = 127) of the subjects had some dyspnea symptoms: grade 1 was most frequent. The physical performance score from the SPPB was 9.22 ± 2.01. Higher dyspnea scores were associated with poor physical performance, both in the crude analysis (β = -0.233; P = 0.028) and after adjustment for frailty condition (β = -0.148; P = 0.002) and for the socioeconomic and health variables (age, sex, number of diseases, smoking habit and frailty status) (β = -0.111; P = 0.025).

CONCLUSION: Higher dyspnea score was independently associated with poor physical performance among community-dwelling older adults.

INTRODUCTION

Dyspnea is a highly prevalent and common symptom among older adults.[1] Presence of this symptom may be disabling, since it is associated with limited mobility, functional decline and frailty in this population.[2]

According to Mahler,[3] approximately 30% of the population of adults older than 65 years report dyspnea during daily activities such as walks and/or uphill climbing. Among the factors that favor the onset of this symptom, reduced exercise tolerance and a low level of physical activity seem to contribute to a decline in physical performance during activities of daily life.[2,4]

Vaz Fragoso et al.[4] and Larsson et al.[5] reported that poor physical performance assessed on the basis of lower-limb performance in physical tests such as sitting and rising from a chair is associated with an increase in dyspnea among both robust older adults and older adults with frailty and/or chronic obstructive pulmonary disease (COPD).

However, it should be pointed out that few studies evaluating dyspnea and physical performance are available. There is some mention of the health-impairing consequences of dyspnea or poor physical performance in the literature, but only under specific conditions involving populations of older subjects with COPD, postoperative situations, frailty and depressive symptoms.[5-7]

Since dyspnea is a nonspecific symptom associated with adverse outcomes such as exercise intolerance, physical disability and increased mortality among older adults, investigation of dyspnea, allied with evaluation of physical performance, is important. It needs to be borne in mind that a large proportion of older adults who report dyspnea do not have any previously installed cardiopulmonary impairment.[4]

Thus, dyspnea can become a starting point for identifying possible changes that affect older adults under both specific and nonspecific conditions. These conditions include frailty and

situations of age-related increases in multimorbidity. In addition, evaluation of dyspnea is done through a simple measurement that is easy to perform, such that dyspnea is easily identifiable.[8]

OBJECTIVE

The objective of the present study was to determine whether there is any association between dyspnea and physical performance among community-dwelling older adults.

METHODS

Design and sample

This was a cross-sectional study conducted among older adults living in the urban area of Macapá, a city in the Amazon region that is the capital of the state of Amapá, in northern Brazil. Information about the characteristics of the population and the sample size calculation is available in a previous study by Ohara et al.[9]

Inclusion and exclusion criteria

Older adults aged 60 years or over who were living in the urban area of Macapá, and who were able to walk unaided or with a gait-aiding device, were included in the study. Subjects who were not located after three visits and/or subjects who were institutionalized or hospitalized at the time of the interview, or who presented neurological and/or orthopedic conditions that would prevent evaluation, were excluded. Also excluded were subjects with cognitive decline that would prevent them from answering the questions of the interview, as determined using the Mini-Mental State Examination (MMSE), in its version translated and validated for Brazilian Portuguese,[10] which considers cutoff points according to educational level.

The study was approved (protocol no. 1.738.671; dated September 21, 2016) by the local human-research ethics committee. The older adults were recruited and assessed at their respective homes in the year 2017, and interviews were conducted face-to-face by properly trained undergraduate students and monitored by field supervisors (researcher teachers). A total of 443 older adults were recruited and assessed: 27 of these were excluded because they showed cognitive decline and 5 were excluded for other reasons such as incomplete data. After considering the eligibility and loss criteria, the present study was conducted among 411 community-dwelling older adults.

Instruments for data collection

Modified Medical Research Council (mMRC) scale (independent variable)

The sensation of dyspnea was assessed using the modified Medical Research Council (mMRC) scale, which involves a score from 0 to 4. The higher the score is, the worse the sensation of dyspnea is.[11] The older adults of this study graded their onset of dyspnea according to their physical activity, according to the following items: grade 0 (shortness of breath only during intense exercises); grade 1 (shortness of breath when walking fast or climbing uphill); grade 2 (walking more slowly due to shortness of breath or needing to stop during exercise); grade 3 (needing to stop in order to breathe after a 100 m walk); and grade 4 (shortness of breath that prevented the subject from leaving home or that occurred when changing clothes).[11,12]

Short Physical Performance Battery (SPPB) (dependent variable)

Physical performance was assessed using the translated version of the Short Physical Performance Battery (SPPB), which has been adapted to Brazilian realities.[13] This consists of the following components: static standing balance, gait speed at habitual pace and five-time sit-to-stand test without the help of the upper limbs. The total SPPB score is calculated as the sum of the scores for each test and can range from 0 to 12 points. A 0 to 3-point score for the SPPB indicates disability or very poor performance; a score of 4 to 6 indicates poor performance; a score of 7 to 9 indicates moderate performance; and a score of 10 to 12 indicates good performance.[14,15]

Adjustment variables

Socioeconomic and health variables were assessed using a structured questionnaire. Information regarding sex, age and physical health variables such as number of diseases and smoking habit was obtained. Frailty syndrome was determined as described in previous studies[16,17] and was based on the frailty phenotype proposed by Fried et al.,[18] i.e. as follows:

1. Unintentional weight loss measured by means of the following question: "over the last year, did you lose more than 4.5 kg unintentionally (i.e. without diet or exercise)?";
2. Reduced muscle strength, as assessed from handgrip strength using a manual hydraulic dynamometer (Model SH5001, SAEHAN, São Paulo, Brazil) and adopting the cutoff points proposed by Fried et al.;[18]
3. Self-reported exhaustion and/or fatigue, as measured by means of two questions from the Brazilian version of the Center for Epidemiological Studies Depression Scale (CES-D), i.e. item 7 ("Did you feel that you had to make an effort to perform your habitual tasks") and item 20 ("Were you unable to perform your activities?"). The older subjects who obtained a score of 2 or 3 in replying to either question fulfilled the criteria of frailty for this item;
4. Slow gait speed, obtained from the gait time (in seconds) that was needed to cover a distance of 4.6 meters, using the cutoff points proposed by Fried et al.;[18]
5. Low level of physical activity, as determined using the long version of the International Physical Activity Questionnaire

(IPAQ).[19] Subjects who spent 150 minutes or more per week doing physical activity were considered to be sufficiently active, and those who spent 0 to 149 minutes per week doing physical activity were considered to be inactive.

Older subjects with three or more of these items were classified as frail and those with one or two items were classified as pre-frail, while those for whom all the tests were negative were considered to be robust or non-frail.[18]

Statistical analysis

Descriptive statistical analysis was carried out using means, standard deviations, absolute numbers and percentages. For comparisons among groups, the chi-square test and Student's t test were used.

Inferential analysis was performed in order to determine associations between dyspnea and physical performance. For this, crude analyses and analyses adjusted through a linear regression model were carried out, taking a 95% confidence interval (CI) and a 5% significance level ($P < 0.05$). The variables considered for adjustment were age, sex, number of diseases, smoking habit and frailty status. The techniques of residual analysis (normality, linearity and homoscedasticity) and multicollinearity were used to investigate the adequacy of the linear regression model and to detect correlations between its variables and its confidence level.

The data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 21.0.

RESULTS

Table 1 shows the characteristics of the older adults of this study according to occurrences of dyspnea. A total of 411 older adults were evaluated. Most of them were women (66.4%), with a mean age of 70.15 ± 7.25 years. Among these 411 older adults, 28.7% (n = 118) were not frail, 58.4% (n = 240) were prefrail and 12.9% (n = 53) were frail, with a score of 9.22 ± 2.01 for physical performance. Most of the older adults who reported having dyspnea symptoms according to the mMRC scale were female, had a higher mean number of diseases, showed poorer physical performance and were frail.

Table 2 shows the characteristics of these older adults according to their dyspnea symptoms (from the mMRC scale). It was observed that 30.9% (n = 127) of the subjects had some dyspnea symptoms according to the mMRC, and the most frequently mentioned level was grade 1.

Table 3 shows the association of dyspnea (mMRC) with physical performance (SPPB) among these older adults. A higher dyspnea score was associated with poor physical performance in both the crude analysis and the analysis adjusted for frailty condition and for the socioeconomic and health variables of age, sex, number of diseases, smoking habit and frailty status.

Table 1. Characteristics of the elderly participants according to occurrences of dyspnea. Macapá (AP), Brazil, 2017 (n = 411)

Variables	Dyspnea (mMRC)		P	Total sample (n = 411)
	Yes 127 (30.9%)	No 284 (69.1%)		
Age (years)	70.12 ± 7.43	70.15 ± 7.18	0.970	70.15 ± 7.25
Sex				
Male	32 (25.2%)	106 (37.3%)	0.016	138 (33.6%)
Female	95 (74.8%)	178 (62.7%)		273 (66.4%)
Number of diseases	6.78 ± 3.01	4.82 ± 2.65	< 0.001	5.43 ± 2.90
Number of medications	1.84 ± 1.70	1.52 ± 1.75	0.083	1.62 ± 1.74
Smoking habit				
Yes	11 (8.7%)	28 (9.9%)	0.702	39 (9.5%)
No	116 (91.3%)	256 (90.1%)		372 (90.5%)
SPPB (score)	8.78 ± 1.99	9.41 ± 1.97	0.003	9.22 ± 2.01
Frailty status				
Non-frail	29 (22.8%)	89 (31.3%)	< 0.001	118 (28.7%)
Prefrail	68 (53.5%)	127 (60.6%)		240 (58.4%)
Frail	30 (23.6%)	23 (8.1%)		53 (12.9%)

Data are reported as n = number of subjects; mean ± standard deviation; % = percentage; SPPB = Short Physical Performance Battery; mMRC = modified Medical Research Council scale; χ^2 test; t-test; $P < 0.05$.

Table 2. Characteristics of the older adults according to dyspnea symptoms (from the modified Medical Research Council scale). Macapá (AP), Brazil, 2017 (n = 411)

Dyspnea (mMRC)	n (%)
0	284 (69.1)
1	93 (22.6)
2	10 (2.4)
3	19 (4.6)
4	5 (1.2)

Data are reported as n = number of subjects; % = percentage; mMRC = modified Medical Research Council scale.

Table 3. Association of dyspnea (from the modified Medical Research Council scale) with physical performance (from the Short Physical Performance Battery) among older adults. Macapá (AP), Brazil, 2017 (n = 411)

Variables	SPPB							
	B	SD	β	T	P	95% CI		R^2
						Lower limit	Upper limit	
Dyspnea (mMRC)								
Model 1	-0.549	0.113	-0.233	-4,848	< 0.001	-0.771	-0.326	0.054
Model 2	-0.348	0.109	-0.148	-3,180	0.002	-0.562	-0.133	0.172
Model 3	-0.261	0.107	-0.111	-2,436	0.015	-0.472	-0.050	0.302

SPPB = Short Physical Performance Battery; B = non-standardized coefficients; SD = standard deviation; β = standardized coefficients; T = t test; 95% CI = 95% confidence interval; R^2 = coefficient of determination; mMRC = modified Medical Research Council scale; Model 1 = unadjusted analysis; Model 2 = analysis adjusted for frailty condition; Model 3 = analysis adjusted for socioeconomic and health variables (age, sex, number of diseases and smoking habit) and frailty status; $P < 0.05$.

DISCUSSION

The present study showed that dyspnea was associated with poor physical performance among these community-dwelling older adults, even after adjustment for socioeconomic and health conditions and frailty status.

In a systematic review, Van Mourik et al.[1] identified combined dyspnea prevalences of 36% for scores on the Medical Research Council (MRC) scale ≥ 2; 16% for MRC ≥ 3; and 4% for MRC ≥ 4. The present results revealed that 30.9% (n = 127) of the older adults evaluated reported some dyspnea symptoms according to the mMRC scale, with grade 1 being most frequently mentioned. This indicated that dyspnea was present when the subject was walking fast on a flat terrain or climbing uphill.

In a study on 4,413 subjects older than 65 years conducted by Miner et al.,[20] dyspnea was reported by 17.5% of the participants, irrespective of whether they were in robust health or had cardiorespiratory diseases. Among the healthy older subjects assessed by those authors, presence of dyspnea seemed to be strongly associated with factors such as depression, obesity and poor physical performance in the sit-and-rise test (a test that evaluates lower limb performance). Those findings are in agreement with the results from the present study.

In our evaluation of physical performance, which was assessed using the SPPB, we obtained a score of 9.22 ± 2.01, thus indicating moderate physical performance in the study sample. This finding has clinical implications, since the physical performance evaluated by the SPPB can predict the risk of falls, functional limitations, hospitalization and death among older individuals.[21,22]

In a systematic review, Pavasini et al.[22] observed that SPPB scores of 0-3, 4-6 and 7-9 were associated with progressive increases in the risk of all-cause mortality, regardless of the analysis using adjustment variables, whereas this was not observed for scores of 10-12. In another study, poor SPPB performance with scores of 0 to 4 was also correlated with mortality, hospitalization and functional decline.[23]

In the present study, even after adjustment for frailty and for other possible confounding factors (socioeconomic and health variables and frailty status), dyspnea continued to be associated with physical performance. This suggests that the higher the grade of dyspnea reported by the subject is, the poorer the physical performance also is.

Vaz Fragoso et al.[4] assessed the association between performance in the sit-and-rise test and the presence of moderate to severe dyspnea among older individuals, and also inserted frailty as a covariable in the analyses. Among the results obtained, poor physical performance in the sit-and-rise test increased the likelihood of occurrence of moderate to severe dyspnea by 85% among older individuals when they exerted effort. This result suggests that an association between lower-limb function and the sensation of dyspnea was present even after adjustment for frailty condition.

Similarly, Larsson et al.[5] detected a significant correlation between better physical performance in the sit-and rise test (assessed using the SPPB) and lower dyspnea scores (from the mMRC) among patients of average age with chronic obstructive pulmonary disease (COPD) aged on average 69 ± 6 years. Although the health condition of the population evaluated in their study differed from that of the present sample, their finding is supported by our results. This shows that the greater the sensation of dyspnea reported was, the poorer the physical performance also was, even among older subjects who did not have any respiratory diseases (such as COPD). This finding need to be considered with attention.

We believe that the possible reason for the emergence of the inverse association between dyspnea and poor physical performance in our study related to the ventilatory response of older adults to exercise. Higher levels of ventilation are required in situations of physical exertion, which exposes these individuals to ventilatory stress, as also does the slowing down of respiratory center neuromodulation that occurs during aging.[3] This ventilatory stress gives rise to increased dyspnea upon exertion, which may lead older adults to restrict and/or impair their performance in certain daily activities.

Among the factors that may be related to poor physical performance and dyspnea, correlations between sedentarism and worsening of dyspnea and between frailty and declining muscle function have been highlighted in the recent literature. These correlations have been based on the assumptions that sedentary older individuals have higher dyspnea scores,[6] they present a lack of physical conditioning that impairs their performance in activities requiring effort; and they may have aggravating factors such as poor life habits and associated comorbidities, along with their advanced age per se.

Vaz Fragoso et al.[24] demonstrated an association between sedentarism, dyspnea and poor performance in the gait speed test, in which sedentary older individuals showed impaired ventilatory capacity and/or dyspnea. These variables are associated with physical inactivity and immobility. The same group[25] also reported that, among older individuals with limited mobility, low levels of physical activity were associated with higher likelihood of hospitalization.

In addition, in a study on 565 community-dwelling older adults, Hegendörfer et al.[2] reported that dyspnea was an independent predictor of limitations to cardiorespiratory and physical performance, and that higher dyspnea scores increased the likelihood of mortality, hospitalization and disability.

Thus, both poor physical performance and dyspnea symptoms are factors that influence the health of the older population. Their presence may result in negative outcomes such as disability, hospitalization and even death, as mentioned earlier. Hence, studies investigating these conditions are of fundamental importance for enabling better planning of healthcare for the older population.

Some limitations of the present study should be considered. The evaluations were made in the homes of these older individuals according to their availability, in a place that would be more comfortable for them. Therefore, the times and places for data collection were not controlled. Most of the participants were women; however, we believe that this limitation was minimized due to the adjustment for sex that was incorporated in the analysis. Because of the cross-sectional design of the study, it was not possible to obtain temporality information, as is done in prospective studies. Further investigations are needed in order to obtain more precise results of greater precision regarding the association of these variables, which are still scarce in the literature.

CONCLUSION

Higher dyspnea scores were associated with poor physical performance, both in the crude analysis and in the analyses adjusted for frailty condition and for socioeconomic and health conditions. The results suggest that the higher the degree of dyspnea reported is, the poorer the physical performance among older adults will also be.

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Nutritional status and appetite-regulating hormones in early treatment of acute lymphoblastic leukemia among children and adolescents: a cohort study

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ABSTRACT

BACKGROUND: Children with acute lymphoblastic leukemia are at risk of malnutrition, but few studies have described the changes in nutritional status during the different phases of chemotherapy.

OBJECTIVE: To evaluate changes in nutritional status, food intake and appetite-regulating hormones among children and adolescents with acute lymphoblastic leukemia in the first phase of chemotherapy.

DESIGN AND SETTING: Cohort study developed in the pediatric oncology departments of two hospitals in the city of Natal, Rio Grande do Norte, Brazil.

METHODS: Fourteen children/adolescents (mean age of 7 years; 50% female) with acute lymphoblastic leukemia were monitored over the 28 days of an induction chemotherapy cycle. Anthropometric measurements, 24-hours food weight records and appetite-regulating hormone levels (ghrelin, leptin, insulin and cortisol) were obtained at three different times (before, in the middle and at the end of the induction phase).

RESULTS: Most of the patients (85.7%) had normal weight at the beginning of the treatment, and this did not change significantly during the 28 days. Energy and nutrient intakes improved from the start of the treatment to the midpoint, according to the ghrelin levels (from 511.1 ± 8.3 to 519.3 ± 6.6 pg/ml; P = 0.027). Other appetite-regulating hormones did not present changes.

CONCLUSION: Food consumption improves during the first phase of treatment, without alterations in anthropometric nutritional status.

INTRODUCTION

Pediatric malignancies account for 1% to 3% of cancers diagnosed worldwide, and leukemia is the most common cancer among children, representing about one third of all cancers occurring before the age of 15 years.[1] Approximately 80% of leukemia cases consist of acute lymphoblastic leukemia,[1] which is a primary neoplasia of the bone marrow. This is characterized as a heterogeneous group of diseases in which normal medullary and blood elements are replaced by immature cells (blasts) and these cells accumulate in other tissues.[2] The nutritional status of children with cancer is highly relevant, since good nutritional status enables them to better cope with the intensive cancer treatment regimens.[3] However, few studies have assessed the nutritional status of these patients during treatment.

Children and adolescents with acute lymphoblastic leukemia experience a spectrum of nutrition-related morbidities during and after treatment.[4] Weight gain is either a short or a long-term effect of acute lymphoblastic leukemia therapy. The weight gains and body composition changes that are observed during the first four weeks of treatment are associated with administration sf glucocorticoids such as prednisone and dexamethasone.[5]

It has been recognized that survivors in some pediatric cancer groups, including acute lymphoblastic leukemia, present clinical features of metabolic syndrome. These individuals therefore present increased risk factors for cardiovascular disease, such as visceral obesity, insulin resistance, glucose intolerance, dyslipidemia, hypertension and endothelial dysfunction.[6-8]

Although dietary intake has a direct impact on nutritional status, few studies in homogenous pediatric populations with cancer have assessed this variable.[4,9] The absence of a positive correlation between body composition and food consumption has shown the complexity of the energy balance

during acute lymphoblastic leukemia. Better understanding of the mechanisms involved in appetite control may lead to development of new therapies, in order to prolong survival in association with better quality of life for these patients.[10]

On the other hand, anorexia and cachexia may also occur in cases of acute lymphoblastic leukemia that are diagnosed during childhood. The possible mediators of anorexia-cachexia syndrome include hormones relating to appetite regulation, such as ghrelin, leptin, cortisol and insulin.[11] Over the long term, chemotherapeutic agents can also result in changes to leptin secretion, thereby leading to increased plasma levels. However, very few studies have evaluated alterations in ghrelin and leptin during chemotherapy in different types of cancer, and these discrepant results may be due to the different treatments adopted.[12] Given the risk of malnutrition among children with acute lymphoblastic leukemia,[2] nutritional assessment at diagnosis and throughout treatment has become an important issue. It has now been pointed out that this is a decisive aspect of successful treatment. Few studies have described the changes in nutritional status that occur during the different phases of chemotherapy, and even fewer have evaluated all the parameters together (body composition, food consumption and biochemical parameters), especially during the first phase.

OBJECTIVE

The aim of this study was to evaluate nutritional status in relation to appetite-regulating hormones among children and adolescents who had been newly diagnosed with acute lymphoblastic leukemia, before and during the induction treatment phase. The hypothesis was that the first treatment phase would have a negative impact on the nutritional status of these patients.

METHODS

Participants and ethics

This was a longitudinal study in which children or adolescents (aged less than 19 years) who had been newly diagnosed with acute lymphoblastic leukemia were included. They had received their diagnoses at the pediatric oncology departments of two hospitals in the city of Natal, Rio Grande do Norte, Brazil, between March and December 2015, and were hospitalized there for the beginning of the induction phase of the chemotherapy treatment.

In total, 17 patients were eligible for inclusion, and no patients or their families refused to participate. After inclusion, three patients left the study because their diagnoses were changed to acute myeloid leukemia. Thus, in the end, 14 patients participated in this study.

Ethical approval was obtained from the ethics committee of the Federal University of Rio Grande do Norte (Universidade Federal do Rio Grande do Norte, UFRN), under protocol no. 976,388, approved on March 7, 2015. All parents or legal guardians signed the written informed consent statement, and children older than six years of age were invited to participate in the study and signed a consent agreement. The study was conducted in accordance with the Declaration of Helsinki.

Procedures

Chemotherapy for children with acute lymphoblastic leukemia is divided into induction, consolidation, interim maintenance, delayed intensification and maintenance phases.[13] All the patients in the present study were monitored during the first chemotherapy cycle (induction phase), with nutritional and biochemical measurements that were made at the start (baseline, before chemotherapy), in the middle (after 14 days) and at the end of the induction phase (after 28 days). The goal of induction chemotherapy is to achieve remission. Independent of risk, the children studied here received the following chemotherapy drugs intravenously (IV), intrathecally (IT) and orally: L-asparaginase, methotrexate, prednisone, vincristine and daunorubicin.

Anthropometric assessment

Weight was measured using a digital scale (Filizola, São Paulo, Brazil) and was recorded to the nearest 0.1 kg. Height was measured using a calibrated stadiometer for infants (Filizola, São Paulo, Brazil), and was recorded to the nearest 0.1 cm. Standard deviation scores for weight, height, weight-for-height and body mass index-for-age were calculated as recommended by the World Health Organization (WHO), to adjust for age and gender.[14] The cut-off for the diagnosis of underweight was defined as less than the 5th percentile of body mass index-for-age, while a body mass index greater than or equal to the 85th percentile was classified as being overweight. Lastly, a body mass index greater than or equal to the 95th percentile was defined as obesity. Arm circumference and triceps skinfold thickness were measured using a non-stretchable measuring tape (Sanny, São Paulo, Brazil) and a skinfold caliper (Prime Med, São Paulo, Brazil), respectively, and were classified in accordance with the reference standards.[15] Both measurements were performed in triplicate on the left arm.

Food consumption

Individual food intake during the hospitalization treatment period was determined by the researchers. All foods and beverages consumed during the day were directly weighed at each of the three evaluation times. Each food or preparation was individually weighed before consumption, using the utensils with which the foods were served and zeroing the scale before adding each food. A portable electronic scale with a capacity of 5 kg and accuracy of 1 g was used for weighing solid foods. Liquid foods were measured in 100 ml and 500 ml graduated cylinders with 1 ml and 10 ml increments, respectively. Any food that was not

consumed by each individual was also weighed/measured and was then subtracted from the initial weight.

The food weights were entered into and analyzed using the DietWin Professional software (DietWin Software, Porto Alegre, Brazil) for energy, macronutrients (protein, lipids, cholesterol, carbohydrates and fiber) and micronutrients (vitamin C, vitamin A, vitamin E, vitamin B12, calcium, zinc and iron), primarily taking the Brazilian Table of Food Composition[16] as the reference.

Biochemical analyses

Venous samples were collected (10 ml) in the mornings while fasting, at all three different follow-up times. The concentrations of insulin (IU/ml) and cortisol (µg/dl) were analyzed by means of chemiluminescence (active insulin Enzyme-Linked Immunosorbent Assay [ELISA] and assay design cortisol ELISA kits, Labtest, Lagoa Santa, Minas Gerais, Brazil). Ghrelin levels (pg/ml) were analyzed using a total human ghrelin ELISA kit (Sigma-Aldrich, St Louis, Missouri, USA). Leptin levels (ng/ml) were measured using a human leptin ELISA kit (Sigma-Aldrich, St Louis, Missouri, USA). All analyses were carried out in accordance with the manufacturer's recommended instructions.

Statistical analyses

The data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 22. A normality test was performed using the Shapiro-Wilk test. Descriptive data were presented as the mean and standard error, for variables with normal distribution. In the case of non-normal distribution, the data were summarized as the median and interquartile range.

The anthropometric data were compared between different times using the chi-square test or Fisher's exact test. Dietary variables were adjusted for energy intake in accordance with the residual method,[17] and were analyzed according to the time of data collection using the general estimation equation model. The levels of appetite-regulating hormones were also compared by means of the general estimation equation, with adjustments for age and body weight.

Power estimate analyses regarding the different times (in the middle and at the end of the protocol) were calculated using the WinPepi software, version 11.18. P-values of less than 0.05 were considered statistically significant.

RESULTS

Fourteen participants were included, among whom six (42.9%) were male. One patient died during the last monitoring period after the intermediate evaluation had been done.

Table 1 shows the anthropometric nutritional assessment results from the patients. The patients generally had adequate anthropometric nutritional status, which was maintained during the follow-up. Height was only measured at the first data collection time, and all the patients had adequate height for their age. At the third evaluation, one patient expressed a desire to not undergo the anthropometric assessment, and this wish was respected. Regarding body mass index/

Table 1. Classification of anthropometric nutritional status at different time during the follow-up on chemotherapy

Variables	Start of treatment (day 0) n (%)	In the middle of treatment (day 14) n (%)	At the end of treatment (day 28) n (%)	P
Height/age				
Adequate height for age	14 (100)	-	-	-
Body mass index/age				
Underweight	-	1 (7.1)	-	0.167
Normal	12 (85.7)	12 (85.7)	11 (91.7)	
Overweight or obesity	2 (14.3)	1 (7.1)	1 (8.3)	
Weight/age[1]				
Adequate weight for age	9 (100)	9 (100)	8 (100)	-
Weight/height[2]				
Underweight for height	-	-	1 (25)	1.000
Normal weight for height	3 (75)	4 (100)	3 (75)	
At risk of being overweight or obese	1 (25)	-	-	
Arm circumference (cm)[3]				
Risk of deficit or low fat storage	4 (36.4)	4 (35.4)	4 (40)	0.083
Adequate	7 (63.6)	7 (63.6)	6 (60)	
Arm muscle circumference (cm)[3]				
Risk of deficit or low fat storage	6 (54.5)	6 (60)	5 (55.6)	1.000
Adequate	5 (45.5)	4 (40)	4 (44.4)	
Triceps skinfold (mm)				
Adequate	8 (57.1)	7 (53.8)	5 (45.5)	0.080
Risk of deficit or low fat storage	6 (42.9)	6 (46.2)	6 (54.5)	

[1]For children 0 to < 10 years old; [2]for children 0 to < 5 years old; [3]n = 11 because some assessments were not performed (children with venous access or refusal). P-value with Fisher's exact test before and at the end of the induction phase.

age, it was seen that one patient was underweight at the second data collection time, but had recovered their nutritional status by the time of the third evaluation. The weight-for-age parameter was used for patients under 10 years old, and this did not change during the follow-up. The weight-for-height parameter was used for children under five years of age, and it was noticed that there was a change in one child's nutritional status (from "at risk of being overweight or obese" to "normal weight"). None of the other anthropometric measurements showed any significant alterations during the follow-up.

Table 2 shows the results relating to food consumption during the chemotherapy induction phase. Overall, there were increases in the consumption of all macronutrients, cholesterol, fiber, vitamin B12 and iron, and in energy intake This enhancement of food consumption was in line with the increase in plasma ghrelin concentration between the baseline and the second evaluation (P = 0.027; power analysis 99.3%). At the last evaluation, there was a non-significant difference with a low power analysis value (41.2%) (**Figure 1**). Although a reduction in cortisol concentration had been expected, its levels did not show any significant reduction from the beginning to the end of the induction cycle. Likewise, insulin concentration hardly changed between the evaluations. A similar response was seen in relation to serum leptin, which did not show any significant changes during the treatment.

DISCUSSION

The importance of early identification of nutritional risk and appropriate management of nutrition among hospitalized children at admission is well understood. Numerous screening tools have been developed for this population.

Some cancer patients experience weight loss before diagnosis and during their treatment.[6-7] This problem particularly affects patients with solid tumors and medulloblastoma.[8] However, the majority of the patients in the present study did not present any changes in their anthropometric nutritional status parameters that had been measured at the time of the diagnosis, given that there were no significant changes in these parameters over the 28 days of the chemotherapy induction phase.

Our findings are consistent with those of other studies in the literature.[7-8,11] Those studies showed that the frequency of malnutrition in relation to the hematological system was low at the time of the cancer diagnosis, probably due to the acute nature of the disease. More recently, even with the presence of a catabolic disease like acute lymphoblastic leukemia, many studies have shown increased frequency of overweight and obesity among newly diagnosed patients. Ladas et al.[18] evaluated the nutritional status and food intake of 640 children with acute lymphoblastic leukemia and found that 27% were overweight or obese at the time of the diagnosis. In the study by Tan et al.,[19] the frequency of overweight was 24.5% among 53 children with acute lymphoblastic leukemia and acute myeloid leukemia. In our study, we found a similar frequency (21.4%), which was also in accordance with other studies on patients with hematological cancer.[6-7] It is now known that the presence of obesity affects the prognosis, such that it increases mortality among children and adolescents with acute lymphoblastic leukemia.[20]

The anthropometric nutritional status of our patients was preserved during the induction period, thus differing from previous studies in the literature. According to Brinksma et al.,[8] this weight loss prior to diagnosis may have been due to reduced energy intake, increased energy requirements or altered metabolism. Lindemulder et al.[11] followed up 269 children and adolescents from the time of diagnosis until the maintenance phase of treatment and found that there was a significant increase in body mass index between the time of the diagnosis and the consolidation phase of cancer treatment, but especially during the first month of treatment. In following up patients

Table 2. Food intake of patients at different times during the follow-up on chemotherapy

Variables	Start of treatment (day 0) M ± SE	At the middle of treatment (day 14) M ± SE	At the end of treatment (day 28) M ± SE	P
Energy intake (kcal)	1330.7 ± 176.1[a]	1845.2 ± 191.7[b]	1692.9 ± 244.6[a,b]	0.01
Carbohydrate intake (g)	208.3 ± 7.6[a]	293.9 ± 5.7[b]	214.7 ± 10.4[a,c]	< 0.001
Protein intake (g)	34.7 ± 2.2[a]	58.9 ± 3.0[b,d]	59.9 ± 5.2[c,d]	< 0.001
Lipid intake (g)	24.2 ± 2.1[a]	39.5 ± 2.2[b,d]	45.1 ± 6.8[c,d]	< 0.001
Cholesterol intake (mg)	141.0 ± 25.0[a,b]	273.4 ± 41.7[b,c]	182.4 ± 25.9[a,c]	0.02
Fiber intake (g)	14.8 ± 1.7[a]	19.3 ± 2.11[a,b]	12.0 ± 2.0[a]	0.01
Vitamin A intake (mcg)	1076.9 ± 251.5	1607.7 ± 369.2	1118.9 ± 511.0	0.41
Vitamin C intake (mg)	256.7 ± 147.8	256.7 ± 147.8	203.9 ± 64.9	0.76
Vitamin E intake (mg)	4.4 ± 0.7	4.4 ± 0.8	5.9 ± 1.1	0.45
Vitamin B12 intake (mcg)	0.9 ± 0.2[a]	1.8 ± 0.3[b]	1.8 ± 0.3[b]	0.01
Zinc intake (mg)	5.2 ± 2.2	5.1 ± 0.5	5.2 ± 0.8	0.99
Iron intake (mg)	5.9 ± 0.5[a]	8.9 ± 0.8[b]	7.3 ± 0.7[b]	0.03
Calcium intake (mg)	414.8 ± 66.9	510.4 ± 54.0	604.2 ± 68.3	0.05

M = mean; SE = standard error.

P-value obtained through general estimation equation; [a,b,c,d]Different letters means differences between times according to energy/nutrient intake.

with hematological cancer, Zareifar et al.[9] observed late changes in nutritional status, especially six months after treatment had started. These differences may have been due to the sample sizes in these studies and the different chemotherapy protocols used, with different doses of corticosteroids. They may also have been the result from increased energy intake combined with reduced physical activity.[21]

Epidemiological studies have frequently used body mass index to define obesity and explore its association with cancer risk and mortality.[20] However, associations with other anthropometric markers are also important. Anthropometric measurements of fat reserves may be more sensitive to changes in nutritional status than body mass index.[6,19,22-23]

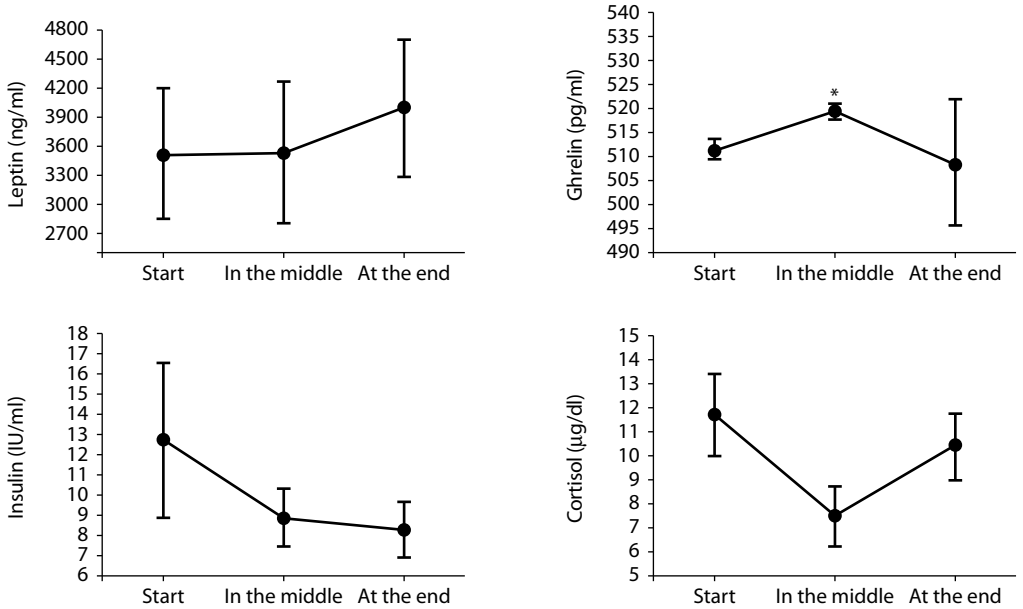
In the present study, it was found that most patients had an adequate body mass index in all the treatment phases, but half of them had low fat reserves, as measured using the triceps skinfold. Similar findings, with high frequency of body fat depletion ascertained through anthropometric techniques, were reported by Dávila et al.[6] and Ani.[7]

Even without significant alterations during the evaluation period, these indicators should not be underestimated, since they contribute towards assessing patients' body composition in the absence of more sophisticated techniques.[24] The short follow-up time of the present study (28 days) was possibly not enough to reverse the changes in fat stores and muscle mass that were measured through anthropometric techniques.

Regarding the food consumption assessment, in which all food and drink consumed during three 24-hour evaluations was weighed and measured, this form of assessment was novel, to the best of our knowledge. It reduced the measurement errors that are usually seen in studies evaluating food intake and increased the accuracy of energy intake measurements, in addition to minimizing underreporting. However, it was difficult to compare the results from our study with other results because the data available have usually come from a 24-hour recall or a dietary diary, which are less accurate and more questionable. Moreover, it was difficult to draw uniform conclusions about the adequacy of dietary intake among childhood cancer patients because intake has been assessed at different time points and because different norms have been used.[25]

Energy intake in some studies has been assessed in relation to recommended daily allowances, whereas in other studies it has been compared with the energy intake of healthy controls. Only one cross-sectional study assessed energy intake against calculated individual requirements,[26] as done in the present study. In that study, the consumption of nutrients among children with hematological malignancies was similar to what was seen in the present study.

We did not use food adequacy data, given the large variation in the ages of the samples in previous studies. Some studies have used 80% of the recommended daily allowances as a cutoff value for determining intake adequacy,[25] but a better strategy would probably consist of comparing the intake of childhood cancer patients



*P = 0.027 for the difference between the start of the treatment and the middle of the treatment, obtained through the general estimation equation with adjustment for the changes in weight and age among the children and adolescents.

Figure 1. Concentrations of appetite-regulating hormones at the different treatment times: start of treatment (day 0), in the middle of treatment (day 14) and at the end of treatment (day 28).

with that of healthy controls. This may also constitute a limitation of the present study, because the food intake that was measured was not consumed in the children's own homes or in places where they were normally fed. Therefore, this does not represent their usual consumption, considering that these children might have had a dietary intake that differed from what was normal for them, given that they were being carefully watched. However, the consumption measurements were always made at the same place in the three evaluations, and the amounts and types of foods were the same, which will have improved the comparison between the evaluation times.

An increase in energy and macronutrient intake during the induction phase was observed in the present study, possibly because the children were stressed or lacking in appetite because of the time that elapsed before the chemotherapy started. This increase was also mentioned in another study that evaluated patients with cancer over a one-year period,[25] and also in an evaluation on the intake among children with acute lymphoblastic leukemia during the induction phase, compared with a healthy control group.[21]

In contrast with the amount of data in the literature regarding energy intake, there is a scarcity of data in the literature regarding protein requirements during childhood. Proteins are essential for growth and synthesis of lean body mass.[22] Protein requirements are assumed to increase during illness, so as to compensate for muscle deterioration, which is caused by inflammation and inactivity.[27] Some studies (like the present study) have shown that protein intake among patients exceeds the daily recommendations after chemotherapy is started.[25,28] One possible reason for this increase in energy and protein intake after treatment is started might be the use of anabolic steroids, particularly glucocorticoids, which are characteristically administered to patients with acute lymphoblastic leukemia, given its anabolic nature.[29]

Ghrelin, leptin and insulin are hormones relating to food intake regulation and consequently to body weight control.[30] Cortisol mobilizes energy, increases cerebral perfusion and glucose utilization and enhances cardiovascular function to help individuals adjust to real or perceived threats.[31] In the present study, we evaluated these hormones in addition to the eating behavior response among patients with acute lymphoblastic leukemia. Aside from the ghrelin levels (which significantly increased at the second assessment), no other statistical difference was observed. Changes to the levels of these hormones are associated with chronic exposure to diets with low caloric content,[22] which was not the case in the present study, in which patients were followed up for a relatively short period of time and showed adequate energy intake. For example, in the study by Adam et al.,[32] the fasting insulin levels significantly increased during the first year of chemotherapy. Another possible reason why no changes to the levels of these hormones were seen in the present study may have been the absence of energy restrictions among our population over this period.[33]

According to Mariani et al.,[34] use of chemotherapeutic agents can also result in modified leptin secretion over the long term, thus leading to increased plasma levels. However, the behavior of leptin reported in studies available in the literature has varied considerably. In the study by Park et al.,[35] children with pediatric cancer showed higher plasma leptin concentrations than those of healthy children, but lower plasma ghrelin levels. Acute leukemia-related inflammation and serum hyperlipidemia may suppress ghrelin at the time of diagnosing childhood acute lymphoblastic leukemia if the inflammatory indices are abnormal, i.e. when low-grade inflammation is present. A recent study from our group showed that children with acute lymphoblastic leukemia presented reduced inflammation and oxidative stress during the induction period.[33]

Moschovi et al.[36] followed up nine pediatric acute lymphoblastic leukemia patients from diagnosis to the maintenance phase, and no significant decrease in leptin levels was observed in these patients. These discrepant results may have been due to the body weight changes and food consumption of these patients. The increased ghrelin levels observed in the present study , although small, coincide with the results from the study by Moschovi et al.,[3] in which nine patients with leukemia were evaluated and a notable increase in these hormone levels was observed after the eighth chemotherapy cycle. Increased ghrelin levels coincided with the increased food intake of the patients in the present study, and it can be suggested that a cause-effect mechanism may exist. However, few studies have evaluated ghrelin alterations during chemotherapy among acute lymphoblastic leukemia pediatric patients to help support this hypothesis. The small sample size of our study does not allow us to generalize the data, especially because of the low statistical power.

The strong point of the present study is that it included many variables relating to nutritional status (body composition, food consumption and biochemical parameters). Moreover, this study made it possible to follow up patients over a 24-hour period at three different times during the induction phase. Thus, food consumption could be evaluated through weighted recordings, and potential confounders were controlled for.

On the other hand, the types of patient evaluated in the present study are rare, even in large oncological institutions. Therefore, it is obvious that the patients in our study may have represented heterogeneous groups, and the small sample size reflects this. Hence, this is another limitation of our study: the small sample size had the consequence that it was unclear whether ethnic/racial diversity or cultural factors may have played a role in eating behavior.

Nonetheless, our study is one of the few prospective cohort studies describing the changes in nutritional status among pediatric patients with acute lymphoblastic leukemia. Although the sample size was small, the longitudinal design of the study, its low dropout rate and its results are useful for developing nutritional strategies to improve the outcomes among children with cancer.

CONCLUSION

Increases in food consumption and ghrelin concentration were observed during the induction period for treating acute lymphoblastic leukemia, but without recovering the patients' anthropometric status. Other appetite-regulating hormones did not undergo changes. Our initial hypothesis that the first treatment phase could have a negative impact on the patients' nutritional status was rejected. The relative improvement in dietary consumption may have been related to the hormonal response or to the pharmacological therapy for acute lymphoblastic leukemia. Further studies with a similar design but larger sample size should be conducted to confirm these results among acute lymphoblastic leukemia patients.

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Influence of air pollutants on pneumonia hospitalizations among children in a town in the Brazilian Legal Amazon region: a time series study

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ABSTRACT

BACKGROUND: Exposure to particulate material produced as a result of increased agricultural activity may increase the number of pneumonia hospitalizations among children. We hope to contribute to the knowledge base through highlighting the environmental mechanisms involved in this outcome and optimizing pollutant control policies.

OBJECTIVES: To investigate the association between pneumonia hospitalizations among children and presence of environmental pollutants in a town in the Brazilian Legal Amazon region.

DESIGN AND SETTING: Time series study conducted in the town of Tangará da Serra, Mato Grosso (MT), Brazil.

METHODS: A total of 158 children aged 0 to 10 years participated in the study. Data on environmental variables and pollutants were extracted daily through the Coupled Chemistry-Aerosol-Tracer Transport model coupled to Brazilian Regional Atmospheric Modeling System (CCATT-BRAMS). Meteorological data were provided by the Weather Forecasting and Climate Studies Center (CPTEC).

RESULTS: There was greater frequency of pneumonia hospitalizations in the months of transition between the rainy and dry seasons, with a prevalence ratio 2.4 times higher than in other periods. For environmental pollutants, there was a significant positive correlation between particulate matter ($PM_{2.5}$) and pneumonia hospitalizations (correlation 0.11), with more admissions on the days when $PM_{2.5}$ levels were highest (averages of 6.6 $\mu g/m^3$ when there were no admissions and 13.11 $\mu g/m^3$ on days with two or more admissions).

CONCLUSIONS: The higher the $PM_{2.5}$ level was, the greater the frequency of hospitalizations also was. Children living in peripheral areas had higher prevalence of pneumonia hospitalizations in the dry period than those who were living in the town center.

INTRODUCTION

Air pollution is gaining increasing importance within the environmental scenario because it causes great risks to health, with higher risk of death and respiratory diseases among children.[1,2] In 2016, one out of every nine deaths among children was attributed to the effects of pollution, with a total of 7 million deaths worldwide.[3]

Particulate matter (PM) is a mixture of solid and liquid components formed by a variety of compounds that depend on the emission source. These fine and ultra-fine particles can reach the alveoli, where they are phagocytized by macrophages and neutrophils that release inflammatory mediators and may cause irritation to the eyes, throat and lungs. According to the World Health Organization (WHO), the mean limit of acceptability of exposure for particulate matter of size smaller than 2.5 μm ($PM_{2.5}$) is a concentration of 25 $\mu g/m^3$ for 24 hours.[4] Several mechanisms are involved in the respiratory disease caused by particulate matter, especially induction of pulmonary oxidative stress. This leads to overproduction of oxidative reaction, thus damaging the deoxyribonucleic acid (DNA) and inducing inflammatory lesions and epigenetic disorders, thereby contributing to the development of diseases such pneumonia.[5,6,7,8]

Carbon monoxide (CO) is a systemic asphyxiant that induces depression of the central nervous system that at acute levels can cause death because it has affinity for hemoglobin that is 200 times higher than that of oxygen. In situations of chronic poisoning, slow hypoxia may develop and this may lead to permanent sequelae.[9] National Environmental Council (Conselho Nacional do Meio Ambiente, CONAMA) resolution no. 3 of 1990 sets the parameters for air quality as an average concentration of 10,000 mg/m^3 (9 ppm) over an eight-hour period and an average concentration

of 40,000 mg/m^3 (35 ppm) over a one-hour period that is not to be exceeded more than once a year.[10]

OBJECTIVE

The objective of this study was to investigate the influence of pollutants on pneumonia hospitalizations among children in a town in the Brazilian Legal Amazon region.

METHODS

A time series study was conducted among children living in the town of Tangará da Serra, Mato Grosso (MT), Brazil, from August 1, 2017, to July 31, 2018. It was approved by the local research ethics committee under opinion no. 2.325.965 on October 10, 2017.

Tangará da Serra is located in a region with plenty of agricultural activities and is in the region of the arc of deforestation of the Brazilian Amazon region. It has well-defined seasonal periods, with a rainy season (November to March), a transition period (April and May) and a dry season (June to October). In 2005, this town presented the highest rate of hospitalizations due to respiratory diseases in its state (Mato Grosso, MT), among children younger than 15 years of age, and pneumonia was the leading cause of hospitalization (90.7%).[11] The high rate of hospitalizations, along with the location of the town, are particularly relevant.

Convenience sampling was performed among the children hospitalized at a public hospital who presented a clinical diagnosis of pneumonia that had been confirmed by a pediatrician. This diagnosis was verified by the researcher in loco with the pediatrician, though radiographs, laboratory tests and clinical examination. This sampling was done according to convenience because we investigated all the children hospitalized over a one-year period to confirm the diagnoses, identify geographical data relating to their homes and ascertain their health histories.

The study included children aged 0 to 10 years who were living in the town of Tangará da Serra (MT), in either its urban area or its rural area. Children were excluded from the study if they had pneumonia with associated comorbidities such as chronic diseases of the respiratory system; autoimmune, neurological or immunosuppressive diseases; prolonged use of corticosteroids; oncological treatment; long-term bedridden state; or malnourishment.

Health history and demographic data were collected from the parents/guardians during their children's hospitalization, through a questionnaire that the authors created. Nutritional characteristics were assessed using the body mass index (BMI). Data were collected on a regular basis from the patients' medical records through an instrument that the authors developed.

The cases were grouped according to the neighborhood in which the children lived. These neighborhoods were analyzed regarding their proximity to the downtown region and to the peripheral areas (i.e. the areas closest to the highway and to agricultural activities).

Data on pollutants were collected daily from the Coupled Chemistry Aerosol and Tracer Transport model for the Brazilian developments on the Regional Atmospheric Modelling System (CCATT-BRAMS), which is one of the strategies commonly used in research carried out in regions that do not have monitoring stations, such as the state of Mato Grosso. CCATT-BRAMS is a reliable mathematical model that is used to make emission estimates. These data are made available daily in Grid Analysis and Display System (GRADS) binary format files corresponding to South America. A specific point for these estimates was determined through the geographic coordinates of the municipality (latitude: -14.6279; longitude: -57.507). Estimates for the pollutants CO and particulate matter ($PM_{2.5}$) were selected because of the lack of complete data on other pollutants.

Climate data were provided by the Weather Forecasting and Climate Studies Center of the National Institute for Space Research (Centro de Previsão de Tempo e Estudos Climáticos, CPTEC) through the Brazilian National Institute of Meteorology (Instituto Nacional de Metereologia, INMET) automatic weather station that is installed at the Mato Grosso State University Campus. The data were provided in the form of Excel spreadsheets. The climate variables collected were relative air humidity, environmental temperature, wind speed and precipitation.

To seek a correlation between environmental variables and pneumonia hospitalizations, univariate analysis was performed to obtain central trend and dispersion measurements. Bivariate analysis was carried out through the use of Spearman correlation analysis for nonparametric data. Multiple linear regression was performed to identify which variables were predictors for pneumonia hospitalization. Also, multivariate analysis was performed using the Kruskal-Wallis model to estimate the relationship between frequency of pneumonia hospitalization and exposure to environmental variables. The dependent variables were hospitalizations for pneumonia and CO and $PM_{2.5}$ levels and the independent variables were the climate variables.

Associations were assessed between variables that correlated with the cases of hospitalization due to pneumonia, on the day of hospitalization. We separated the daily hospitalizations into three categories: days without hospitalizations, days with one hospitalization and days with two or more hospitalizations. To these, we applied the Kruskal-Wallis test and one-way analysis of variance (ANOVA). The chi-square test was used to evaluate the number of daily hospitalizations per seasonal period (drought, transition and rain).

For all analyses, the significance level was set at $P = 0.05$, and the Epi-Info 6.04 and SPSS version 20.0 software was used.

RESULTS

A total of 158 children participated in the study; 121 (76.6%) had a diagnosis of bronchopneumonia; 82 (51.9%) were males and

97 (61.4%) had brown skin color. Regarding their health history, 153 (96.8%) of the children were born at term and 109 (69%) had received all vaccines, with three doses of pneumococcal vaccine (Pneumo 10). There were 95 children (60.1%) aged between one and five years old (**Table 1**).

Regarding the distribution of cases in the city, it was observed that most were concentrated on the periphery, especially in neighborhoods near the highway and agricultural activities. Thus, there were 61 cases (38.6%) in peripheral neighborhoods, 16 cases (10.1 %) in the countryside and only 4 cases in the city center (2.5%).

In the analysis on the correlations of environmental variables, air pollutants and hospitalization for pneumonia, there was a significant positive correlation between the number of pneumonia hospitalizations and $PM_{2.5}$ levels, and a negative correlation between the number of hospitalizations and the relative humidity and rainfall. Furthermore, it was found that CO levels showed significant positive correlations with $PM_{2.5}$ levels and temperature, and significant negative correlations with humidity and wind speed. $PM_{2.5}$ levels presented significant negative correlations with humidity and rain. These results are shown in **Table 2**.

Analysis on the behavior of pollutants between different seasonal periods showed that CO levels were higher during the rainy season, despite maintaining an average of 0.1 ppm, although there was a significant negative correlation with humidity. $PM_{2.5}$ levels were higher in the dry season, with an average of 10.7 $\mu g/m^3$.

Table 1. Clinical and demographic characteristics of children aged 0 to 10 years admitted to a public hospital in the town of Tangará da Serra (MT), 2017- 2018

Characteristics	n = 158 (%)
Diagnosis	
Bronchopneumonia	121 (76.6)
Pneumonia	37 (23.4)
Sex	
Male	82 (51.9)
Female	76 (48.1)
Color	
Brown	97 (61.4)
Black	56 (35.5)
White	5 (3.1)
Age	
Younger than 1 year	44 (27.8)
1 to 5 years	95 (60.1)
6 to 10 years	19 (12.1)
Prematurity	
Yes	5 (3.2)
No	153 (96.8)
Vaccination with Pneumo 10	
No vaccine	4 (2.5)
Ongoing vaccination	39 (24.7)
Completed vaccination	109 (69)
Late vaccination	6 (3.8)

Among the climate variables (**Table 3**), temperature (T) was higher in the rainy season with an average of 25 °C. Relative humidity (RH) was higher in the rainy season (80.9%). Wind speed was higher in the rain season and transition period, with a speed of 2.1 m/s in both of these periods. Radiation was greater in the dry season, with an average of 765.6 kJ/m^2.

After multiple linear regression, it was found that $PM_{2.5}$ level, RH and period of the year were predictors for pneumonia hospitalization among these children, as shown in **Table 4**.

Table 2. Analysis of correlations between environmental variables and pneumonia hospitalizations. Tangará da Serra (MT), 2017-2018

	PNMHosp	CO	$PM_{2.5}$	T	RH	Wind	Rain
PNMHosp	1						
CO	-0.51	1					
$PM_{2.5}$	0.11*	0.41*	1				
T	0.07	0.34*	0.03	1			
RH	-0.10*	-0.10*	-0.38*	-0.52*	1		
Wind	-0.26	-0.20*	-0.16*	-0.41*	0.38*	1	
Rain	-0.13*	0.15*	-0.38*	-0.20*	0.64*	0.23*	1

*Significant correlation for $P < 0.05$.
PNMHosp = pneumonia hospitalizations; CO = carbon monoxide; $PM_{2.5}$ = particulate matter; T = temperature; RH = relative air humidity.

Table 3. Means for pollutants and climate variables in the dry, rainy and transition periods. Tangará da Serra (MT), 2017-2018

Variables	Dry season	Rainy season	Transition period
$PM_{2.5}$			
Mean (SD)	10.7 (7.9)	4.2 (5.6)	7.5 (10.4)
Minimum-maximum	1.9-54.5	0.1-32.2	1-66.8
CO			
Mean (SD)	0.1 (0.1)	0.1 (0.1)	0.1 (0.03)
Minimum-maximum	0.1-0.4	0.1-0.5	0.05-0.2
T			
Mean (SD)	24.5 (3.5)	25 (1.2)	24.1 (1.9)
Minimum-maximum	12.7-29.7	20.6-28.4	16.5-26.2
RH			
Mean (SD)	61.3 (16.4)	80.9 (4.7)	79.7 (5.2)
Minimum-maximum	30-96.5	70.4-96.1	67.2-91.8
Wind			
Mean (SD)	1.3 (1.3)	2.1 (0.6)	2.1 (0.6)
Minimum-maximum	0-5.4	0.9-3.8	1.1-3.6
Rain			
Mean (SD)	0.02 (0.1)	10.3 (19)	3.4 (8.2)
Minimum-maximum	0-0.6	0-159	0-48.8
Radiation			
Mean (SD)	765.6 (190.2)	18.3 (4.6)	17 (3.4)
Minimum-maximum	196.4-1286	2.2-27.8	7-22.5

CO: ppm; $PM_{2.5}$: $\mu g/m^3$; T: °C; RH: %; wind: m/s; rain: mm; radiation: kJ/m^3. $PM_{2.5}$ = particulate matter; CO = carbon monoxide; T = temperature; RH = relative air humidity; SD = standard deviation.

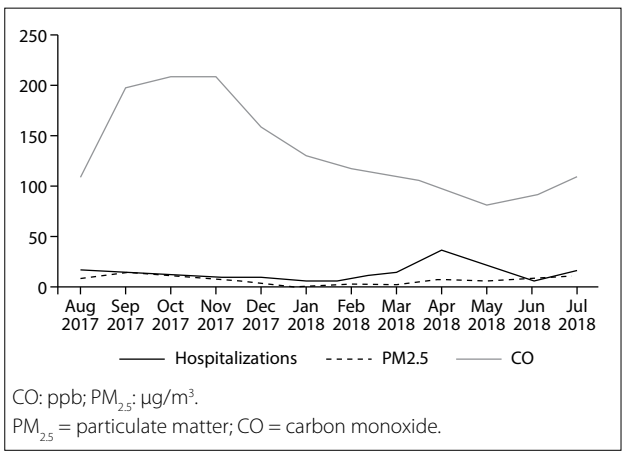
For better understanding of the positive correlation between $PM_{2.5}$ level and pneumonia hospitalizations, the distribution of daily hospitalizations was divided into three categories: no hospitalization, one hospital admission and two or more hospital admissions per day. The Kruskal-Wallis test showed mean values for $PM_{2.5}$ of 6.6 µg/m³ on the days when there was no hospitalization, 7.39 µg/m³ on the days when there was one hospital admission and 13.11 µg/m³ on the days when there were two or more hospital admissions. There were higher numbers of hospitalizations as the $PM_{2.5}$ level increased. Regarding seasonality, there was a significant difference between the groups, with an association between a greater number of hospitalizations per day and the transition period, with a prevalence ratio 2.4 times higher in this period than in other periods.

Comparing the period of the year and the numbers of pneumonia hospitalizations among the children (**Figure 1**), there were higher numbers of hospitalizations due to pneumonia/bronchopneumonia in the months of August and September (dry season), lower numbers between November and February (rainy season) and a peak in the numbers of hospitalizations in the months of April and May (transition period), in 2018.

Table 4. Predictors for pneumonia hospitalization among children that were found to be statistically significant through multiple linear regression

Variables	Coefficients	Standard error	t	P
Period of the year	0.182	0.039	4.634	< 0.001
$PM_{2.5}$ µg/m³	0.009	0.002	3.933	< 0.001
RH (%)	-0.008	0.002	-4.152	< 0.001

CO (carbon monoxide): adjustment variable.
$PM_{2.5}$ = particulate matter; RH = relative air humidity.



CO: ppb; $PM_{2.5}$: µg/m³.
$PM_{2.5}$ = particulate matter; CO = carbon monoxide.

Figure 1. Pneumonia hospitalizations among children aged 0 to 10 years and levels of $PM_{2.5}$ and CO according to the period of the year, in Tangará da Serra (MT), 2017-2018.

DISCUSSION

There was a higher number of pneumonia hospitalizations among children aged 0 to 5 years, with predominance among males. This had previously been seen in other studies, which reported that this difference between males and females was due to anatomical reasons. This was ascribed, for example, to immunological immaturity and reduced airway caliber, along with greater exposure to risk factors among boys at this age.[4,11,12]

The findings showed that there was a significant positive correlation of $PM_{2.5}$ levels with pneumonia hospitalizations. This had also been reported in studies conducted in Brazil by Machin and Nascimento,[13] in the city of Cuiabá, and by Negrisoli and Nascimento,[14] in the city of Sorocaba. These authors reported that hospitalization occurred four days after exposure. This was also shown in a systematic review in the state of São Paulo, in which an association between presence of particulate matter of size 10 µm (PM_{10}) and respiratory tract diseases in children was found.[15]

This association can be explained by several factors, such as presence of oxidative stress, structural damage and immune system disorders associated with carbon compounds and biomass burning. These lead to inflammation and harm to health, especially among children younger than 10 years.[16,17,18] On the other hand, Tuan, Venâncio and Nascimento[19] did not identify any correlation between presence of PM_{10} and pneumonia hospitalization among children under five years of age. The reason for their findings was that there was little emission of PM during the study period and few hospitalizations, which may be indicative of a dose-response effect.

CO levels did not show any significant positive correlation with the number of pneumonia hospitalizations. This finding differed from those of studies that correlated CO levels with car traffic. For example, in a study conducted among schoolchildren in the city of Quito, Ecuador, it was reported that there was a substantial decline in CO levels after a five-year program of vehicle emission control, together with a reduction in the incidence of respiratory diseases.[20] In a retrospective cohort study among children up to two years of age in Atlanta, United States, the $PM_{2.5}$, nitrogen oxide (NO_X) and primary CO levels from vehicle traffic showed an association with the presence of otitis media and bronchiolitis.[21]

In our study, it appears that pollution caused by agricultural activity is higher than pollution resulting from vehicle traffic, since business activity in Tangará da Serra is essentially agricultural and its car fleet is not large, which also explains the low rates of CO emission in the study period.

There are some differences in the literature regarding relative air humidity. In a study by Kim et al.,[4] it was found that there were differences among the geographical regions studied. There was a positive correlation in some regions but a negative one in others, which the authors attributed to local environmental factors. Ho

et al.[22] evaluated climatic effects on the population aged 0 to 16 years living in Ho Chi Minh City, Vietnam. The authors reported that higher incidence of pneumonia hospitalizations was associated with higher humidity and precipitation. In a study by Andrade Filho et al., conducted in Manaus, Brazil, there was a significant positive association (R = 0.126) between greater numbers of hospitalizations due to respiratory diseases among children and higher relative humidity in the Pearson correlation analysis. Moreover, high humidity explained 84% of the hospitalizations.[23]

Regarding the frequency of hospitalization in different seasonal periods, Santos et al.[24] investigated the population aged 0 to 5 years in the city of Rondonópolis, Brazil. They reported that there were greater numbers of hospitalizations due to pneumonia in the months of April and May. They attributed this to the sudden change of temperature that occurs in these months.

Ignotti et al.[25] found that hospitalizations due to respiratory diseases among children aged 0 to 5 years in Tangará da Serra peaked at the end of the rainy season (April). In analyzing pneumonia hospitalizations in the same town, Rosa et al.[11] found a reduction in the frequency of hospitalizations during the rainy months, followed by an increase in the number of cases in March and subsequently a 10% increase in hospitalizations during the months of drought.

There was a higher prevalence rate of pneumonia among children who were living in peripheral areas, during the drought period. Pinto, Maggi and Alves[26] reported that children younger than five years who were living in rural areas of the state of Pernambuco had twice as much risk of pleural involvement in pneumonia as did those who were living in urban areas. This finding correlated with worse conditions of sanitation and lower income. However, in a study on a population aged 2 to 18 years in the state of Georgia, United States, Strikland et al.[27] did not find any association between levels of urbanicity and pneumonia hospitalizations. They attributed their finding to the limitation of their study of not characterizing the composition of $PM_{2.5}$ in each area, since its composition differs between urban and rural areas.

The state of Mato Grosso has strong presence of agribusiness, with intense agricultural activity in the months with peaks of pneumonia hospitalization among children. These activities include controlling of cotton crop pests, herbicide application on sugar cane, preparation and planting and fertilization of soil for corn and soybean crops.[28]

In a study conducted in California, Ganesh and Smith[29] highlighted the strong influence of anthropogenic actions on $PM_{2.5}$ emissions resulting from agricultural pollution, such as cultivation, harvesting and vehicle traffic. Their findings showed that mitigation activities may benefit the health of populations. In a study conducted in China, it was found that a reduction in the number of farms in a region may reduce the regular levels of pollution from agricultural sources.[30] In a study conducted in Turkey, there was harm to the respiratory tract after use of pesticides in agriculture.[31]

Importantly, the effects of $PM_{2.5}$ on human health depend on its composition. In a systematic review in which the aim was to identify the properties of PM in the Amazon biome, its predominant characteristic was found to be high concentrations of biogenic elements during the rainy season and anthropogenic elements during the dry season.[32] In another study in Tangará da Serra, there was predominance of anthropogenic emissions over biogenic emissions.[33] These findings, which correlated with higher prevalence of pneumonia among children living in peripheral areas, may indicate that agricultural activities were having an influence. In the transition months, there was greater wind speed, which may have dispersed the emissions produced by agricultural activities that were closer to the outskirts of the town, which may explain the increase in hospitalizations.

Policies for controlling pollutant emissions are paramount for reducing the damage to the health of vulnerable populations. This was highlighted in a systematic review that was carried out to ascertain whether proximity to pollutants in the environment could cause adverse health outcomes. It was shown that populations living close to environmental risks seemed to be more likely to have adverse health outcomes, although this did not necessarily mean exposure at the individual level.[34]

The limitations of the present study included its use of secondary data to obtain the environmental variables with the CCATT-BRAMS system, even though this is recognized to be a reliable mathematical model for estimates on emissions, along with its use of CPTEC data. In addition, the subjects were recruited through convenience sampling at the only public hospital in the town. The sample was only of small size.

CONCLUSIONS

The higher the levels of PM2.5 were, the greater the frequency of hospitalizations also was. Children living in peripheral areas showed higher prevalence of pneumonia hospitalization during the dry season than did those who were living in the town center. Controlling and monitoring of air pollutant emissions, along with recognition of the type of particulate matter emitted in each region, can significantly help reduce unfavorable outcomes. In particular, this is enabled through recognition of anthropogenic influences and implementation of measures for mitigation of the impact of agricultural activities.

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Association of serum levels of secreted frizzled-related protein 5 and Wnt member 5a with glomerular filtration rate in patients with type 2 diabetes mellitus and chronic renal disease: a cross-sectional study

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ABSTRACT

BACKGROUND: Diabetic nephropathy is a common complication of chronic kidney disease (CKD). Inflammation in the kidneys is crucial for promoting development and progression of this complication. Wnt member 5a (Wnt5a) and secreted frizzled-related protein 5 (Sfrp5) are proinflammatory proteins associated with insulin resistance and chronic low-grade adipose tissue inflammation.

OBJECTIVE: To determine the correlation between serum Sfrp5 and Wnt5a concentrations and glomerular filtration rate in patients with type 2 diabetes mellitus and CKD.

DESIGN AND SETTING: Cross-sectional, comparative and observational study in the Department of Endocrinology, Civil Hospital, Culiacán, Sinaloa, Mexico.

METHODS: Eighty individuals with chronic kidney disease were recruited. Their serum Sfrp5 and Wnt5a concentrations were quantified using the enzyme-linked immunosorbent assay (ELISA) test. The statistical analysis consisted of the Mann-Whitney U test for independent samples and Spearman correlation, with statistical significance of $P < 0.05$.

RESULTS: Serum Sfrp5 concentration continually increased through the stages of CKD progression, whereas serum Wnt5a concentration presented its highest levels in stage 3 CKD. Negative correlations between estimated glomerular filtration rate (eGFR) and serum concentrations of Sfrp5 (r = -0434, P = 0.001) and Wnt5a (r = -0481, P = 0.001) were found.

CONCLUSIONS: There were negative correlations between serum Sfrp5 and Wnt5a concentrations and eGFR at each stage of CKD, with higher levels in female patients. This phenomenon suggests that Sfrp5 and Wnt5a might be involved in development and evolution towards end-stage renal disease.

INTRODUCTION

Diabetes mellitus (DM) has come to be among the chronic degenerative diseases with the most significant increases in morbidity in Mexico over recent years.[1] Within this, type 2 diabetes mellitus (DM2) is caused by a combination of insulin resistance and an inadequate compensatory insulin secretory response. DM2 is the most prevalent form of DM worldwide, and it leads to high rates of complications such as chronic kidney disease (CKD), along with mortality.[2,3]

Diabetic nephropathy is a relatively common complication of DM that, once established (as the diabetic nephropathy phase), is irreversible and progresses to CKD.[4] In Mexico, the prevalences of both type 2 diabetes mellitus and diabetic nephropathy have increased over recent years. A previous study showed that the prevalence of diabetic nephropathy was 24% in an adult population among rural communities.[5]

Previous studies have shown that inflammation in the kidneys is crucial for promoting development and progression of diabetic nephropathy. During the physiopathological development of this condition, macrophages and T cells accumulate in the glomeruli and interstices, even in the early stages of the disease. This interstitial macrophage accumulation is strongly correlated with serum creatinine and inversely with renal function, thus creating a proinflammatory profibrotic stage and angiogenesis. Products that are secreted include tumor necrosis factor-α (TNF-α), interleukin (IL)-1 and IL-6, among others. Likewise, elaborate chemokines further direct migration

of additional macrophages to the kidneys, thereby establishing an inflammatory cycle.[6]

Wnt member 5a (Wnt5a) is a proinflammatory protein belonging to the Wnt family. Presence of this protein has been correlated with macrophage release, insulin resistance and chronic low-grade inflammation within adipose tissue.[7] On the other hand, secreted frizzled-related protein 5 (Sfrp5) is an anti-inflammatory protein that is mainly released by fat cells, which has also been linked with insulin resistance and chronic low-grade inflammation within adipose tissue, and which acts as an endogenous inhibitor of Wnt5a.[8,9] There have been reports indicating that members of this family become altered in kidney diseases and in chronic inflammatory diseases such as fibrosis.[10] However, no studies on the participation of Sfrp5 and Wnt5a in patients with chronic kidney disease have been conducted.

OBJECTIVE

The aim of this study was to determine the correlation between serum Wnt5a and Sfrp5 concentrations and glomerular filtration rate in patients with type 2 diabetes mellitus and chronic kidney disease.

METHODS

Study population

A cross-sectional, comparative and observational study was conducted during the period from August 2014 to November 2015. This study was approved by the Ethics Committee of the Universidad Autónoma de Sinaloa, Mexico (date: October 20, 2014; approval number: 0161).

We included all the 80 patients who met the inclusion criteria of having previously been diagnosed with DM2 and CKD, in accordance with the Kidney Disease Improving Global Outcomes (KDIGO) criteria. These patients were recruited at the outpatient clinic of the Department of Endocrinology of the Civil Hospital of Culiacán, Sinaloa, Mexico.

The inclusion criteria were that the patients would be recruited during their regular check-up on their type 2 diabetes that had previously been diagnosed at the Department of Endocrinology of the Civil Hospital and needed also to have a diagnosis of chronic kidney disease in accordance with the KDIGO criteria. In addition, they needed to be 18 years of age or older and to have given voluntary written informed consent to their participation in this study. The exclusion criteria comprised situations in which participants had not given their written informed consent; absence of blood samples from the patient; and presentation of cancer, autoimmune diseases or infectious diseases.

Collection of peripheral blood serum

Peripheral blood was obtained by means of venipuncture and was collected in sterile Vacutainer tubes without anticoagulant. These tubes were incubated for 30 minutes at room temperature. Subsequently, they were centrifuged at 2,500 rpm for 10 minutes. The soluble fraction was recovered and divided into aliquots of 0.5 ml, which were then stored at -80 °C until further use.

Classification of the stages of chronic kidney disease

The glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, with the variables of age, gender, race and serum creatinine. CKD was classified in accordance with the Kidney Disease Improving Global Outcomes (KDIGO) criteria, in terms of estimated glomerular filtration rate (eGFR), as follows: stage 1 (S1) = eGFR > 95 ml/min/1.73 m^2; stage 2 (S2) = eGFR 60-89 ml/min/1.73 m^2; stage 3 (S3) = eGFR 30-59 ml/min/1.73 m^2; stage 4 (S4) = eGFR 15-29 ml/min/1.73 m^2; and stage 5 = eGFR < 15 ml/min/1.73 m^2.[11]

Measurement of serum creatinine concentration

The serum samples were analyzed in a clinical chemical analyzer system (Ortho Clinical Vitros 250 Chemistry System, Minnesota, USA), using the creatinine dry reagent chemistry method. Around 500 µl of the serum sample was deposited in a microcuvette in this analyzer system. Previously, it had been calibrated and controlled for the creatinine analysis. The normal reference values were taken to be 0.5-1.5 mg/dl.[12]

Measurement of serum Wnt5a and Sfrp5 concentrations

The serum Sfrp5 levels were determined using a commercial enzyme-linked immunosorbent assay (ELISA) kit (catalogue no. SEC842Hu; USCN Life Science Inc., USA) while the serum Wnt5a levels were determined using another commercial kit (catalogue no. E83549Hu; USCN Life Science Inc., USA). The volume of standard and serum used per well (undiluted) was 100 µl. Absorbance detection and quantification for the ELISA assays was done using a microplate reader (BioTek Synergy HT; BioTek Instruments, Inc., Winooski, USA) at a wavelength of 450 nm, in accordance with the manufacturer's instructions.

Statistical analysis

Descriptive statistical data analysis was used. The Shapiro-Wilk normality test was also used. Differences between pairs of groups were evaluated using the Mann-Whitney U test for independent samples, while comparisons among more than two groups were made using the Kruskal-Wallis test. Correlations between continuous variables were made using Spearman's rank correlation coefficient. This descriptive statistical method was chosen because the data did not present normal distribution. Results were considered to be statistically significant when $P < 0.05$. The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (version 22.0; NY, USA).

RESULTS

The creatinine levels increased during the progression of the disease. The S1 kidney disease creatinine levels were significantly different from the S2, S3 and S4 creatinine levels. There were no significant differences between S2, S3 and S4. On the contrary, the glomerular filtration rate decreased during the progression of the disease. The rate in S2 was observed to be significantly different in relation to S3 and S4.

To determine the serum concentrations of Sfrp5 and Wnt5a in these patients with chronic kidney disease, they were grouped in each of the stages of the disease (**Table 1**).

The Mann-Whitney U test was used to determine whether there were any significant differences in serum Sfrp5 concentrations between any of the CKD stages. There were significant differences between all of them except between stages 2 and 3. We also observed that the serum Sfrp5 concentration tended to increase with increasing stage (**Table 1**).

On the other hand, we observed that CKD stage 3 had the highest serum Wnt5a concentration. A multiple-comparisons test among the serum Wnt5a concentrations in relation to each CKD stage showed that there were significant differences between stages 1 and 3, stages 1 and 4, stages 2 and 3, and stages 3 and 4. The rest of the results did not show any statistically significant difference between the different stages of CKD secondary to DM2. However, it was observed that the Wnt5a concentrations were statistically significantly higher in the more advanced stages than in the earlier stages of chronic renal disease (stages 3 and 4 versus stages 1 and 2) (**Table 1**).

The GFR of each individual was estimated and the serum Sfrp5 and Wnt5a levels were subsequently quantified to determine the correlation of these proteins with the clinical evolution of CKD patients with type 2 diabetes mellitus. Spearman's rank correlation was used to identify the relationship between serum Wnt5a and Sfrp5 concentrations and glomerular filtration rate. From this, we found a statistically significant negative correlation between serum Sfrp5 concentration and eGFR (r = -0434, P = 0.001) (**Figure 1**) and between serum Wnt5a and eGFR (r = -0481, P = 0.001) (**Figure 2**) in these patients with chronic renal disease, i.e. eGFR decreased with increasing serum concentration of these proteins.

We also found that females had significantly higher serum concentrations of Sfrp5 and Wnt5a, in comparison with males (**Figure 3**).

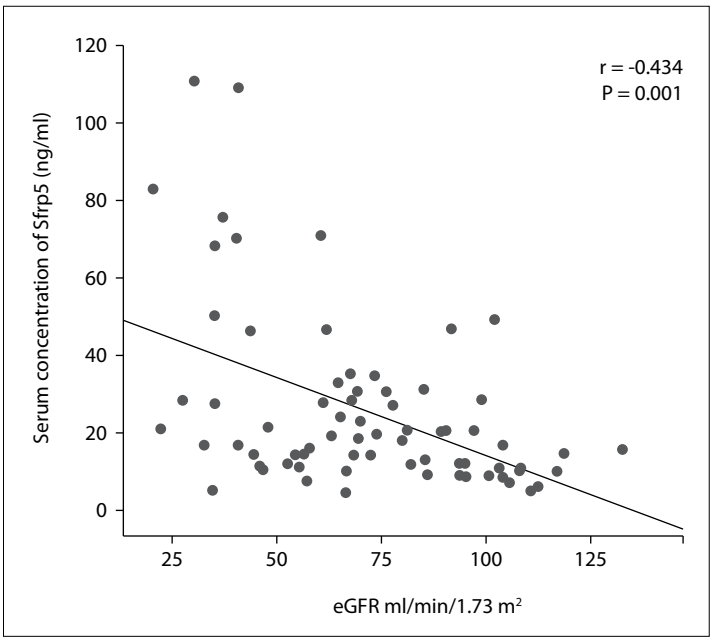

Figure 1. Correlation between serum concentrations of secreted frizzled-related protein 5 (Sfrp5) and estimated glomerular filtration rate (eGFR). Spearman's rank correlation with P < 0.05 was used to determine statistical significance.

Table 1. General parameters of patients according to staging of chronic kidney disease used in this study

Characteristics	Stage 1	Stage 2	Stage 3	Stage 4
Gender				
Female (n = 45)	8	17	14	6
Male (n = 35)	14	9	8	4
Age (years)				
25-39 (n = 5)	4	0	0	1
40-54 (n = 19)	7	7	3	2
55-69 (n = 39)	11	11	14	3
70-85 (n = 17)	0	8	5	4
Creatinine (umol/l)	$0.71 \pm 0.15^{a,b,c}$	1.02 ± 0.15^{a}	1.33 ± 0.25	1.98 ± 1.40^{c}
GFR (ml/min)	$107.06 \pm 8.6^{b,c}$	72.9 ± 7.9^{e}	46.17 ± 16	25.06 ± 7.8^{e}
Wnt5a (ng/ml)	0.19 ± 0.03^{bc}	$0.19 \pm 0.02^{d,e}$	$0.26 \pm 0.08^{b,d}$	$0.22 \pm 0.01^{c,e}$
Sfrp5 (ng/ml)	11.60 ± 4.69^{abc}	$22.18 \pm 9.94^{a,e}$	31.72 ± 32.60^{a}	50.6 ± 223.5^{ae}

GFR = glomerular filtration rate; Wnt5a = Wnt member 5a; Sfrp5 = secreted frizzled-related protein 5.

The data are expressed as the mean ± standard error of the mean (SEM). Results were statistically significant when P ≤ 0.05. [a]stage 1 versus stage 2; [b]stage 1 versus stage 3; [c]stage 1 versus stage 4; [d]stage 2 versus stage 3; [e]stage 2 versus stage 4; [f]stage 3 versus stage 4.

We observed significant differences in serum Sfrp5 concentration, in relation to age, among these patients with chronic kidney disease. In contrast, significant differences in serum Wnt5a concentration were only found in relation to the age ranges of 25-39 and 70-85 years (P = 0.024). There were no statistical differences in serum Wnt5a concentration in relation to the age ranges of 40-54 and 55-69 years (**Figure 4**). Thus, we found that the serum levels of these proteins increased with the evolution of clinical symptoms in chronic kidney disease and with the age of the patients.

DISCUSSION

The present study showed that the serum levels of Sfrp5 increased according to the stages of CKD. It is important to mention that our study was the first to find a correlation between serum Wnt5a levels and glomerular filtration rate in patients with type 2 diabetes mellitus.

Sfrp5 is an anti-inflammatory cytokine that is highly expressed in white adipose tissue.[13] Its presence has been correlated with low-grade chronic inflammation in adipose tissue, obesity, insulin resistance,

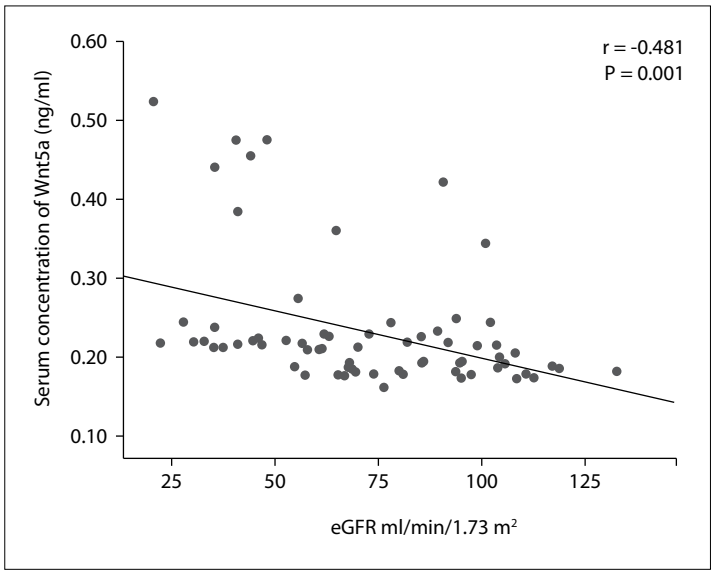

Figure 2. Correlation between serum concentration of Wnt member 5a (Wnt5a) and estimated glomerular filtration rate (eGFR). Spearman's rank correlation with P < 0.05 was used to determine statistical significance.

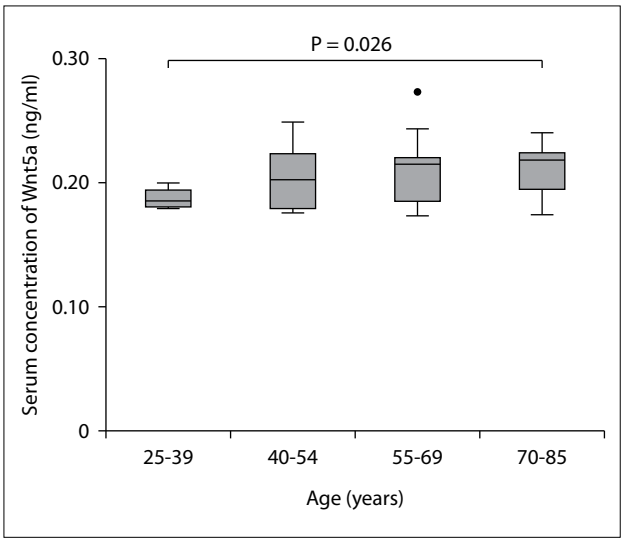

Figure 4. Serum Wnt5a concentration according to age ranges among patients with chronic kidney disease. Differences between groups were obtained using the Mann-Whitney U test and P < 0.05 was used to determine statistical significance.

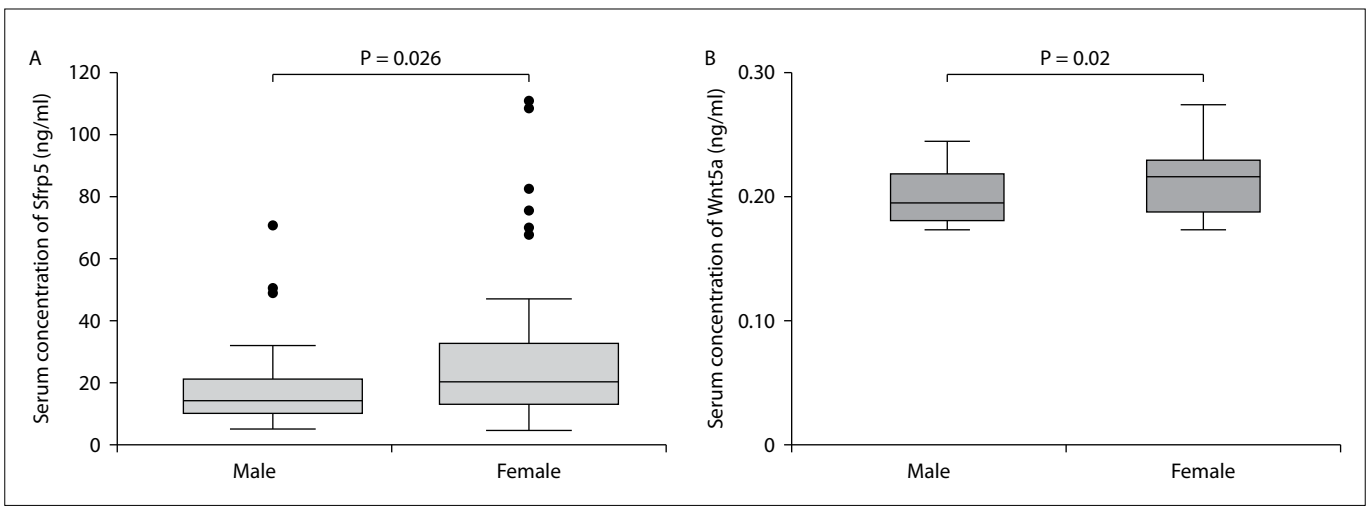

Figure 3. Serum concentrations of secreted frizzled-related protein 5 (Sfrp5) and Wnt member 5a (Wnt5a) according to gender among patients with chronic kidney disease. A) Serum Sfrp5 concentration; and B) serum Wnt5a concentration; differences between groups were ascertained using the Mann-Whitney U test and a P < 0.05 was used to determine statistical significance.

type 2 diabetes mellitus and cardiovascular diseases.[14-16] In addition, presence of Sfrp5 has been correlated with chronic kidney disease, and we also demonstrated that the serum levels of SFRP5 were higher in patients with chronic kidney disease than in healthy patients.[10]

It has been reported that Wnt5a, which is a pro-inflammatory cytokine, promotes insulin resistance.[17,18] Moreover, Wnt5a is secreted by macrophages, which are involved in the production of different pro-inflammatory cytokines and have been associated with chronic low-grade inflammation in adipose tissue and type 2 diabetes mellitus.[18] In comparisons of serum Wnt5a concentration between healthy people and patients with type 2 diabetes mellitus, it has been reported that diabetic patients have higher serum Wnt5a concentration than that of control individuals.[19]

In this study, we observed that serum Wnt5a concentration was higher in the advanced stages of chronic kidney disease, particularly during stage 3. This behavior may have been due to an increase in renal damage and inflammation at this stage.[20] Therefore, infiltration will have become more abundant at this stage, thus leading to release of increased production of different cytokines.[21]

During stage 4, the serum concentration of Wnt5a decreased, but not with any statistically significant difference. This result may have been due to the increased hypoglycemia of end-stage renal disease, which generates thickening of the basement membrane located in Bowman's capsule.[22] This makes the basement membrane more permeable to proteins and other macromolecules that are excreted in urine, which may explain why the serum concentration of Wnt5a is lower in stage 4 than in stage 3. The increases in the serum concentrations of SFRP5 and WNT5A were correlated with decreases in estimated glomerular filtration rate, i.e. there was a negative correlation between these serum concentrations and the glomerular filtration rate. Hence, we observed that increasing serum Sfrp5 concentration was correlated with progression of CKD. This coincided with what was reported in another study about a negative correlation between serum Sfrp5 levels and glomerular filtration rate in patients with chronic kidney disease.[10]

With regard to gender, the serum levels of Sfrp5 and Wnt5a were significantly higher in females than in males. This may have been because hormone levels are greater in females than males. In a study on an anti-inflammatory adipokine similar to Sfrp5, it was reported that there was a negative correlation between testosterone levels and adiponectin concentration in males.[23] Importantly, most of the females included in our study were at or beyond the menopause. These stages give rise to greater inflammation in different cells of the immune system, such as macrophages, with release of pro-inflammatory cytokines like IL-6 and TNF-α.[24] In addition, progesterone (a hormone involved in the menstrual cycle, pregnancy and lactation) induces expression of Wnt5a. Moreover, progesterone is the most commonly used hormone for treating menopausal symptoms.[25, 26]

With regard to the correlation between the ages of these patients with chronic kidney disease and the serum concentration of Sfrp5, no significant differences were observed. However, there was a significant positive correlation with Wnt5a, given that with age progression the concentration of WNT5A also increased. In patients with type 2 diabetes mellitus and chronic kidney disease, their kidneys are the main organ affected because the main function of the kidneys is to filter waste and toxins out of the blood, which gives rise to persistent inflammation with increasing age.[27]

CONCLUSION

This study showed that the glomerular filtration rate gradually decreased through the stages of progression of chronic kidney disease. It also demonstrated that there was a negative correlation between the serum concentrations of Sfrp5 and Wnt5a and the clinical stages of chronic kidney disease. In addition, Sfrp5 was seen to play an important role in the progression to end-stage kidney disease. However, there is a need to carry out complementary studies in order to demonstrate the participation of Sfrp5 and Wnt5a within the pathophysiology of chronic kidney disease.

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Classification of plastic surgery malpractice complaints brought before the São Paulo Medical Board that were treated as professional-misconduct cases: a cross-sectional study

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Surgery, plastic.

AUTHORS' KEY WORDS:
Medical ethics.
Medical board investigations.
Classification of complaints.

ABSTRACT

BACKGROUND: Nowadays, there is an ethical and moral necessity to establish rules that govern professional attitudes and conduct. In the medical field, these rules are multifaceted, given the health consequences inherent to medical procedures. Ethics is an even more delicate subject when it comes to plastic surgery, since one of the aims of this particular medical specialty is esthetic improvement of the body.

OBJECTIVE: To survey and classify São Paulo State Medical Board investigations of plastic-surgery complaints that were treated as professional-misconduct cases between 2007 and 2016.

DESIGN AND SETTING: Cross-sectional study conducted in a medical council.

METHODS: A total of 360 cases were reviewed. Among these, 8 (2.23%) were dismissed, 1 (0.27%) became an administrative lawsuit and 351 (97.50%) were treated as professional-misconduct cases.

RESULTS: A breakdown of the complaints filed over the nine-year period showed that complaints concerning malpractice were the most common (28.43%), followed by those regarding medical advertising (24.19%) and poor doctor-patient relationships (10.39%).

CONCLUSION: Overall, the number of complaints lodged decreased over the last two years reviewed, although complaints regarding malpractice and poor doctor-patient relationships increased by 10% over the same period. In order to further reduce the number of medical board investigations, the medical establishment needs to carefully review the medical training of students and doctors at every stage of their careers.

INTRODUCTION

Regional Medical Councils (Conselhos Regionais de Medicina, CRMs) monitor and ensure proper ethical conduct of doctors throughout Brazil. They are entrusted with encouraging upright practice and championing the professional prestige and regard of the medical profession as a whole and of all who legally practice medicine.[1] CRMs also have the mission of championing the independence of and free legal practice of medicine and defending doctors' rights, while respecting the principles and guidelines contained in the Code of Medical Ethics and the resolutions of the Federal Medical Council (Conselho Federal de Medicina, CFM).

They issue medical documentation and assess working conditions. Furthermore, they review, investigate and decide on the licensing status of doctors who breach professional rules and standards. Board oversight extends from individual activity to both public and private institutional operations, including the entire medical hierarchy of institutions that directly or indirectly provides healthcare services. This means that the CRMs have the power to authorize, order partial suspense of or prohibit the exercising of any activities, along with inspection of services and activities pursued by individuals or institutions in accordance with the law.[2]

Since the CFM is a federally mandated autonomous agency, the CRMs are authorized to discipline medical activity via resolutions that determine medical permissions and prohibitions, and to investigate complaints and determine applicable disciplinary sanctions when the Code of Medical Ethics has been violated. Therefore, the CRMs have the legal prerogative to accept complaints, investigate the facts, judge the doctors involved and weigh up which sanctions are to be applied to each type of violation.

The numbers of formal complaints against doctors' attitudes that have resulted in investigations have been growing both domestically and internationally.[3] This has been seen especially

within the civil courts, which are concerned with damages, and within the administrative courts, which are concerned with medical board investigations and reviews.

In 2017, the Courts of Justice of the State of Pará (Tribunal de Justiça do Pará, TJPA) reviewed criminal cases under the search term "medical malpractice." Cases were assigned to medical specialties as follows: eight cases in obstetrics/gynecology; four in emergency care; two in general surgery; one in anesthesiology/plastic surgery; one in ophthalmology; one in orthopedics; and one in radiology. The courts concluded that surgery and emergency medicine, primarily obstetrics/gynecology, were the medical specialties against which most complaints and lawsuits had been filed.[4]

Once a complaint has been lodged, the full regional medical board or the board's investigation committee opens an investigation to assess the facts of the case.

In the state of São Paulo, by law, the Regional Medical Council of the State of São Paulo (Conselho Regional de Medicina do Estado de São Paulo, CREMESP) must initially accept any complaint lodged by any citizen against doctors who practice within its jurisdiction. Complaints are registered before a notary and are obligatorily subject to review. Upon initial review, the board may solicit clarifications in writing, following which the board will determine either that the case and said explanations and justifications are grounded or that there are insufficient grounds to proceed with an investigation.[5]

Should the board determine that there are sufficient grounds to proceed, the complaint is referred to the disciplinary committee, which then names an investigator. Investigations proceed in accordance with the rules set forth in the Code of Medical Ethics. Once investigations have been instituted and completed, they are debated in plenary sessions and assigned to investigative fora, which may then find for or against the complainant, may order reconciliation between the parties or may order that a behavioral change contract for a given duration be signed.

Investigations judged to have insufficient grounds are dismissed; investigations judged to have sufficient grounds are automatically referred to the Case Disciplinary Committee, which names an evidence-gathering board for hearings involving the parties (complainant, defendant and witnesses) and then one board member as a rapporteur and reviewer for subsequent remittance of the professional-misconduct case to judgment.

Complaints may be lodged by individuals (patients, family members, neighbors or even doctors and other professionals), may be brought by the regional medical board (publicized in the media and originating from government agencies, the courts or medical associations) or may result from anonymous phone calls, written documentation or emails.[6]

According to 2007 data from CREMESP,[7] the number of doctors against whom complaints were lodged in the state jumped from 2,023 in 2000 to 3,569 in 2006, which shows that proceedings brought against doctors in Brazil had reached critical levels over this six-year period, especially in the larger cities.

A review by the Regional Medical Council of the State of Goiás (Conselho Regional de Medicina de Goiás, CRM-GO) of complaints filed between 2000 and 2006[5] showed that 62% of these complaints alleged professional incompetence and poor doctor-patient relationships. Seventy-three complaints corresponded to a mere four plastic surgeons, and one doctor was accused 49 times. The complaint was filed by an individual in 60% of the cases.

Between 2007 and 2009, the Regional Medical Council of the State of Minas Gerais (Conselho Regional de Medicina de Minas Gerais, CRM-MG) reviewed 411 complaints involving 518 doctors. Of these, 330 were absolved of the accusations, and 188 were disciplined with sanctions that ran the gamut from confidential warning, to confidential censure, public censure, 30-day suspension and license revocation.[8]

Silva et al.[9] also showed that the Regional Medical Council of the State of Pará (Conselho Regional de Medicina do Pará, CRM-PA) registered a 15.34% increase in adjudicated medical board investigations but a 13.62% decrease in the number of medical board investigations opened between 2005 and 2007. Furthermore, despite this increase in the number of adjudicated investigations, there was a comparative 16.7% decrease in professional-misconduct cases reviewed between 2005 and 2007.

A further study[10] surveyed the most common medical specialties cited in complaints that were reviewed by the CRM-PA and treated as professional-misconduct cases between 2006 and 2008. Among the 123 professional-misconduct cases that were reviewed over that period, obstetricians/gynecologists were cited most often (an average of 20.33% of the cases per year). In terms of classification, malpractice was the most frequent complaint, averaging 13 cases per year for each of the three years.

A study by Koeche, Cenci, Bortoluzzi and Bonamigo[11] reviewed complaints filed before the Regional Medical Council of the State of Santa Catarina (Conselho Regional de Medicina de Santa Catarina, CREMESC) between January 2005 and December 2009.

They reviewed 468 professional-misconduct cases that were adjudicated due to violation of Article 29 of the 1998 Code of Medical Ethics. A total of 613 doctors were found to be in violation and appropriately judged; out of this number, 122 (19.9%) were found guilty of negligence, recklessness or professional malpractice, and 21 (17%) of these were convicted of medical malpractice. The majority (95.2%) were men; 35% had graduated from medical school 11-20 years earlier; 80.9% had been accused of more than one wrongdoing; and 71.4% were practicing as surgeons in the private healthcare system. General practitioners were the group most convicted (33.2%). The medical specialties with the greatest absolute numbers of convictions were obstetrics/gynecology (14.2%), anesthesiology (9.5%) and general surgery (9.5%).

The social impact of these medical malpractice complaints, which nearly always cause pain and suffering to patients and may involve poor doctor-patient relationships, is of great importance.[12,13] The fact that a doctor is accused does not mean that she or he will be convicted, but medical professionals who are ordered to appear before a medical board for regional board investigations do worry, because they know that there may be irreversible consequences to their actions or errors.[14]

OBJECTIVE

The objective of this paper was to classify CREMESP investigations among plastic surgeons that were reviewed between 2007 and 2016 and were treated as professional-misconduct cases.

METHODS

This was a cross-sectional study in which 360 professional-misconduct cases were surveyed. These cases were reviewed and subjected to medical board investigation between 2007 and 2016. Out of the 360 cases reviewed, 8 (2.23%) were dismissed, 1 (0.27%) became an administrative lawsuit and 351 (97.50%) were treated as professional-misconduct cases per se. The final sample consisted of 351 cases.

This study was conducted via analysis of the cases in the CREMESP database following approval by the Santo Amaro University Research Ethics Committee (no. 2.338.983; on October 19, 2017) and by the president of CREMESP. Only complaints concerning the medical specialty of plastic surgery were reviewed, and the present authors did not have any access to the names of the doctors implicated therein. This study honored the principles of the Declaration of Helsinki and the Nuremberg Code through application of all ethics rules and the subsequent classification of complaints (pursuant to CFM Ruling 1785/2006). The professional-misconduct cases that were dismissed or that were converted into administrative lawsuits (cases that were suspended because the defendant developed a disabling disease that prohibited him/her from practicing medicine) were discarded from the sample.

The study reviewed medical cases pursuant to the protocol established by the present authors. The protocol consisted of questions concerning the nature of the complaints and the year in which the complaints were lodged. Excel 2007 was used to provide a quantitative analysis of the data based on types of variable. A descriptive statistical analysis was used to generate percentages from the data analyzed.

RESULTS

A breakdown of the complaints over the period from 2007 to 2016 showed that complaints concerning malpractice (professional malpractice, recklessness or negligence) were the most common (28.43%), followed by complaints regarding medical advertising (24.19%) and poor doctor-patient relationships (10.39%).

Figure 1 presents the classification of the complaints brought before CREMESP between 2007 and 2016 that were treated as professional-misconduct cases.

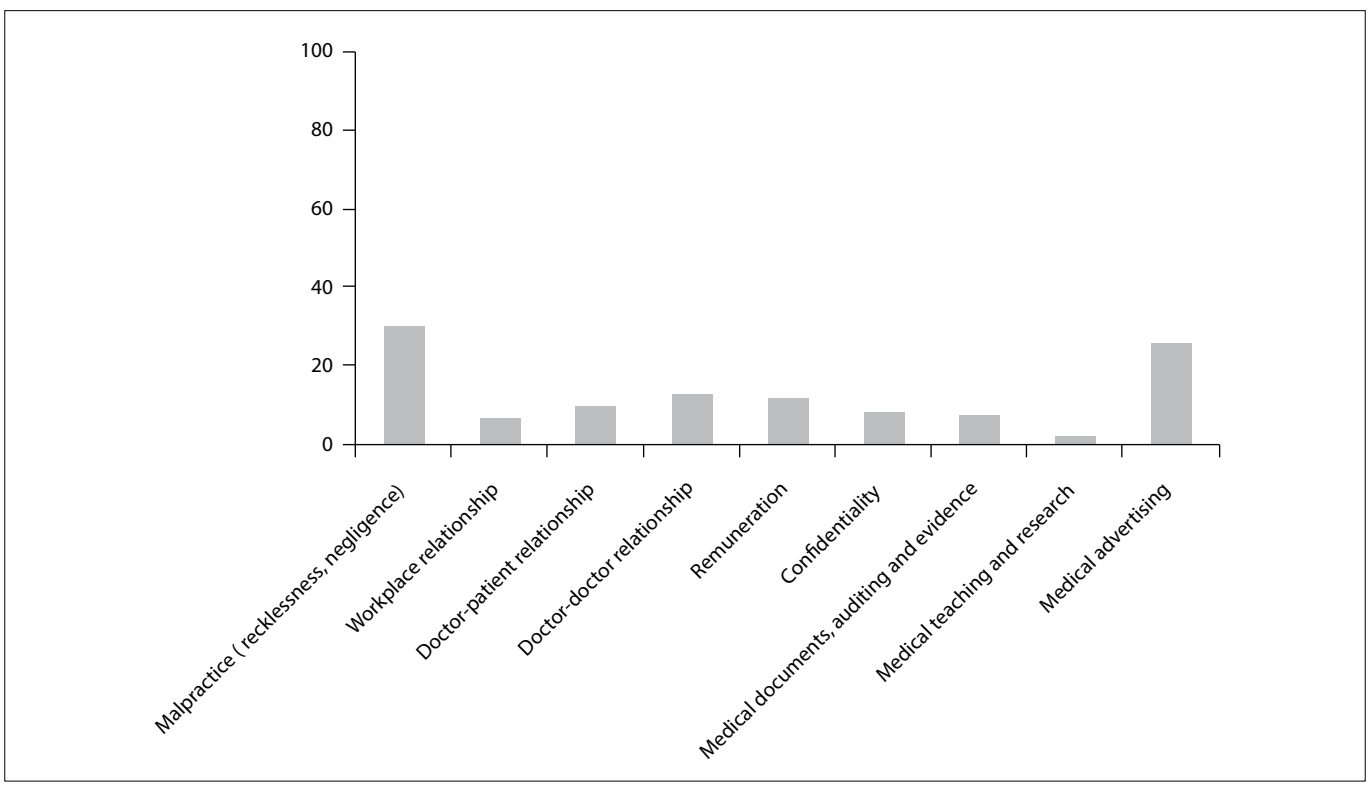

Figure 1. Percentage distribution of classification of complaints brought before CREMESP that were treated as professional-misconduct cases.

Figure 2 presents the classification of the complaints that were treated as professional-misconduct cases, according to the year in which they were brought before CREMESP. It can be seen the most common complaint for every year reviewed was malpractice, and that complaints of malpractice increased over the last two years reviewed (approximately 10%). Medical advertising complaints were alleged between 2009 and 2011, and complaints regarding medical documents, auditing and evidence between 2012 and 2014. Complaints concerning poor doctor-patient relationships increased by about 10% over the last two years reviewed.

DISCUSSION

This paper analyzed 351 professional-misconduct cases that were reviewed between 2007 and 2016.

In terms of the nature of the complaints, medical malpractice was the most frequent complaint in every one of the nine years reviewed, accounting for a yearly average of 28.24% of the professional-misconduct cases. These complaints showed a 10% increase as a component of all complaints over the last two years reviewed (2015 and 2016). These statistics are in line with previous findings that have been published,[1,8,10] thus corroborating that the most prevalent complaint filed with regional medical boards can be classified as medical malpractice (negligence, recklessness or professional malpractice).

Doctors are prohibited from engaging in medical practice that is harmful to patients and which can be characterized as professional malpractice, recklessness or negligence. This form of culpable practice may be adjudicated by the regional medical board as an ethical violation, or by the civil courts in cases of civil violation and award of damages, or by the criminal courts for prosecution of criminal behavior and application of subsequent penalties.

Negligence is evidenced by a lack of care and precaution when practicing medicine. It is characterized by inaction, indolence, inertia and passivity. It is effectively an act of omission.

Recklessness is the result of a doctor's failure to anticipate the consequences of his/her acts or actions. Reckless doctors make unjustified, precipitated or imprudent decisions.

Lastly, professional malpractice occurs when the doctor demonstrates a lack of or inadequate technical medical knowledge or a lack of preparedness in medical practice. These harmful acts refer to professional conduct such as misdiagnosis, inadequate methods of treatment, improper post-operative care, wrongful drug prescriptions, anesthesia complications, surgical errors, wrongful early discharge and other problems that account for the most common departures from proper medical conduct. According to Cunha,[15] despite technological advances in medical practice, including better diagnosis of a number of diseases and availability of new treatment options, doctors continue to make fundamental mistakes in the practice of medicine.

Complications are also a concern during surgery, considering that surgical procedures are more likely to result in adverse events and severe consequences that are more visible and more easily demonstrable.

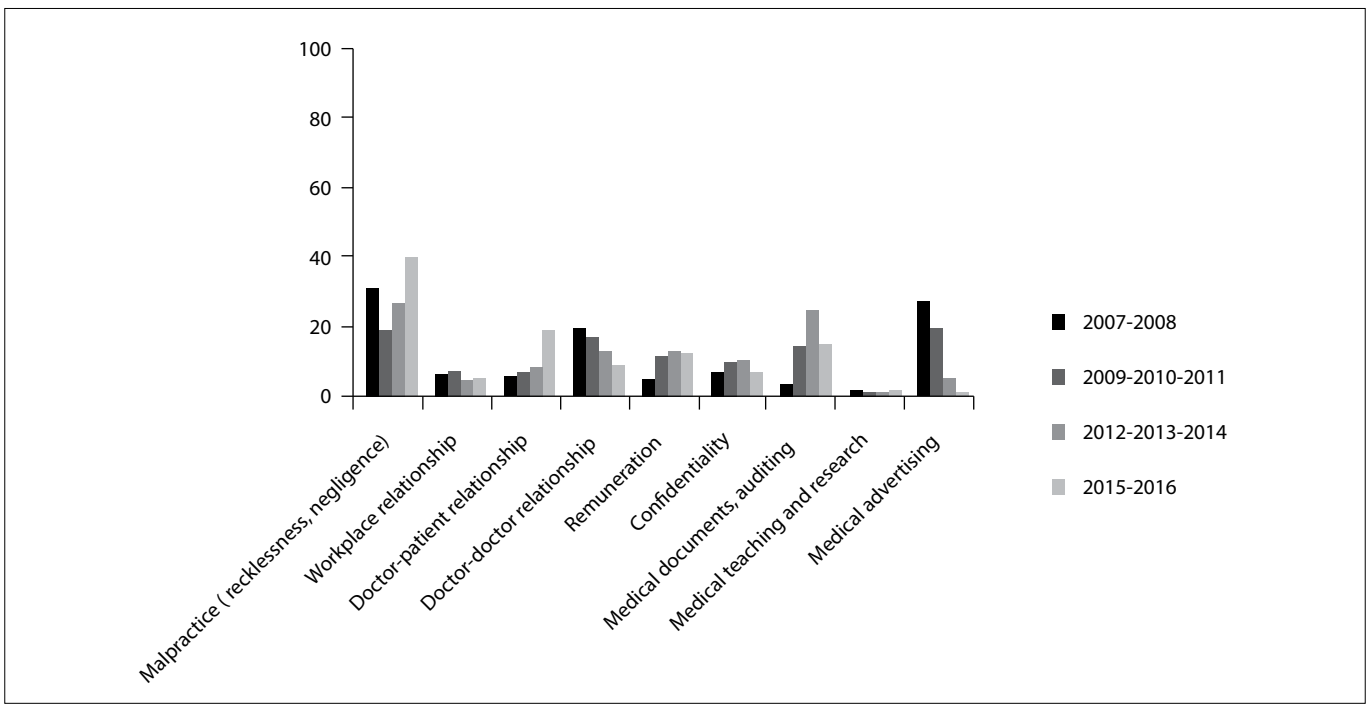

Figure 2. Percentage distribution according to the year, regarding the classification of complaints brought before CREMESP that were treated as professional-misconduct cases.

Medical advertising was the second most common complaint over the nine years reviewed, although there were no complaints in this regard over the final two years studied. The CRMs state that there is no medical specialty officially recognized by the CFM in which the objective is esthetics. This means that the term "esthetic medicine" may not be used in a doctor's or clinic's advertising or marketing materials, since this creates a false sense that there is a discrete medical specialty known as "esthetic medicine." This finding, that medical advertising was a common complaint, is backed by a 2017 study published by Shah et al.[16]

Esthetic procedures are practiced in a number of medical fields. The fact that there is a high demand for such procedures, given the current cultural and social standards of beauty and, consequently, that these procedures are financially lucrative, supports the findings of the present study.

However, doctors must not be influenced by perceived advantage, awards/prizes, increased clientele, financial gains, etc. Profiting from medicine through commercializing medicine constitutes anti-ethical behavior. Similarly, doctors are prohibited from appearing in commercial advertisements of any sort regarding their profession.

Furthermore, no doctor, regardless of medical specialty, may guarantee the result of a given treatment. Doctors must clearly inform the patient of the benefits and risks of any procedures. Publications in which a doctor advertises simple, fast, fully effective treatment are grounds for legal actions that hold him/her liable for the results. The promise of specific results puts doctors in a delicate spot since all procedures are subject to emergencies or unforeseen circumstances. Advertising should disclose information that is scientifically accurate and accepted as good medical practice. Doctors must always act in accordance with the law and ethical standards.

Complaints regarding poor doctor-patient relationships also increased by 10% over the final two years of the study period. The government has recently made a stronger push for greater civic participation, with reinforcement of the consumer protection code (Código de Defesa do Consumidor, CDC) and consumer protection agencies (Proteção ao consumidor, PROCON). It has fostered citizens' awareness of their rights and protections to ensure that their needs as consumers are met, their dignity, health and safety are respected, and their economic interests are respected.

Introduction of the CDC was bold and innovative. It utterly reversed the status quo, meaning that consumers can now cite evidence of damage caused to them by vendors/practitioners. Doctors are considered to be service providers under the scope of the CDC, and the doctor-patient relationship may be referenced within the CDC more on account of inertia that on account of technical and legal grounds. Furthermore, the age-old doctor-patient relationship should not be conflated with the service provider-consumer relationship. It is also clear that unforeseen circumstances and increased workloads lead to a greater likelihood of malpractice suits. Nonetheless, poor relationships between doctors and their patients result in lawsuits that would otherwise be avoidable, were doctors simply to show better bedside manner.

CONCLUSION

Among the professional-misconduct cases reviewed between 2007 and 2016 that were included in this study, those classified as malpractice (negligence, recklessness and professional malpractice) occurred most often (28.43%).

It was clear from the data that CREMESP has dealt with the issue of plastic-surgery complaints effectively and efficiently. Fluctuations and increases in the numbers of complaints over the nine-year period were significant. Advances in case proceedings ensured acceptable resolution rates. The severity of allegations brought before the board was addressed and penalized in a manner that was commensurate with what has been reported from other CRMs throughout Brazil.

It is important for doctors to keep in mind the meaning of the doctor-patient relationship, as essentially a more humanistic way of practicing medicine that respects patients and recognizes their dignity. Better doctor-patient relationships prevent complaints of medical malpractice and avoid a number of inconveniences and problems.

Greater investments in medical training are needed: investments that foster ongoing reflection and review of the ethical and humanistic precepts that shape humankind's attitudes as social beings in familiar, affective, professional and political relationships, of both individual and collective nature. The aim therein should be to better incorporate awareness of biological, social and psychological elements into medical training and awareness of the full extent of the doctor-patient relationship, which is the cornerstone of medical practice.

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Correlation of sleep quality with fatigue and disease activity among patients with primary Sjögren's syndrome: a cross-sectional study

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ABSTRACT

BACKGROUND: Fatigue is a frequent symptom in patients with primary Sjögren's syndrome (pSS) and can be a cause of or be associated with sleep disorders.

OBJECTIVE: To assess the sleep quality of pSS patients and its relationship with fatigue and disease activity.

DESIGN AND SETTING: Analytical observational study conducted at an exercise psychobiology laboratory.

METHODS: Sleep quality was evaluated using the Pittsburg sleep quality index (PSQI) and actigraphy. Fatigue was evaluated through the Profile of Fatigue and Discomfort – Sicca Symptoms Inventory (PROFAD-SSI-SF) and a visual analogue scale for fatigue (VAS-fatigue). Disease activity was evaluated using a visual analogue scale for pain (VAS-pain), EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and Disease Activity Index (ESSDAI). We summarized the data through descriptive statistics.

RESULTS: A total of 50 female patients with pSS, of average age 56.4 years, were included in the study; 80% presented low disease activity. The total PSQI score showed that 74% had poor sleep. The actigraphy showed mean sleep latency of 26.2 minutes and mean nightly awakening of 48.2 minutes (duration of wakings after sleep onset, WASO). There were correlations between PSQI and VAS-pain, VAS-fatigue, PROFAD-SSI and ESSPRI. Actigraphy showed a correlation between the duration of WASO and ESSDAI.

CONCLUSION: The present study provides important information regarding correlations between sleep disorders and disease activity. There is a need for proper control over disease activity and for development of strategies to help patients to sleep better in order to diminish their fatigue.

CLINICAL TRIAL REGISTRATION: NCT03130062.

INTRODUCTION

Sjögren's syndrome (SS) is a systemic autoimmune disease that affects the exocrine glands and, less frequently, internal organs. It is characterized by intense lymphoplasmacytic infiltration, mainly in the epithelium of the tissues affected, and this leads to destruction and loss of their secreting function, and consequent xerostomia and keratoconjunctivitis.[1,2]

This syndrome can be seen alone, in which case it is known as primary Sjögren's syndrome (pSS), or in association with other autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus or scleroderma, in which case it is classified as secondary Sjögren's syndrome (sSS).[1-3] These two variants of the syndrome are different with regard to their clinical, serological and immunogenetic aspects.[3]

Fatigue is a frequent symptom of pSS. It is considered to be a debilitating condition and is the most important cause of dysfunction in these patients.[4-6] It has been described as a lack of physical or mental energy, i.e. a state of exhaustion, which interferes with the person's ability to maintain his/her physical and cognitive activities. It can be persistent and severe.[4-6] Several mechanisms have been proposed to explain occurrences of fatigue among pSS patients, but its underlying physiological basis remains insufficiently defined. It is thus a complex, multi-faceted and poorly understood phenomenon.[4-6]

In population-based studies, approximately 20% of healthy adults report experiencing fatigue and, among patients with autoimmune disorders, this percentage rises to 60%-70%.[1] In pSS, fatigue is the most frequent non-exocrine symptom, and the prevalence of disabling fatigue among patients with pSS has been reported to be approximately 70%. It has been suggested that

fatigue in pSS is mediated by the systemic inflammatory response that characterizes this syndrome. It has also been suggested that fatigue may be related to low blood pressure and abnormalities of the autonomic nervous system, sleep disorders, depression, sedentarism, comorbidities, disease activity, anemia, and decreased physical capacity.[7-12]

Wan-Fai and Simon[13] suggested that fatigue in pSS may be associated with factors such as inflammation, sleep disorders, depression or dysfunction of the neuroendocrine and/or autonomic nervous system. Although the presence of sleep disorders in pSS patients has been previously confirmed in other studies, the relationship with fatigue and disease activity has been insufficiently studied.[7,14]

Insomnia can occur in approximately 33% to 50% of the adult population. Patients with chronic insomnia frequently report more feelings of fatigue (low energy, physical tiredness and weariness) than symptoms of sleepiness (i.e. a real tendency to fall asleep).[15] Assessment of sleepiness among patients with sleep disorders should include use of questionnaires and clinical evaluations and a two-week sleep log to identify sleep patterns, such as through actigraphy.

The Pittsburgh sleep quality index (PSQI) is a self-report questionnaire that measures sleep quality on a Likert scale (0-3), in seven domains (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction over the last month). The sum of the scores for these domains yields one overall score, which ranges from 0 to 21, such that the highest score indicates worst sleep quality. Overall scores of 5 or greater indicate "poor" sleepers.[15]

Actigraphy is a valuable method for determining sleep patterns in normal, healthy adult populations and among patients who are suspected of having certain sleep disorders. Actigraphy enables recording of motor activity through limb movements. In comparison with polysomnography, it provides a reliability coefficient of 0.8-0.9 and is a less expensive method, although it cannot replace polysomnography. Several authors, including the American Academy of Sleep Medicine's standards of practice committee, view actigraphy as a reliable method for assessing awakening patterns in adults.[16,17] Actigraphy can be used easily, with the possibility of recording over many days. The primary baseline measurements obtained from a sleep log include, among others: bedtime, sleep latency (time taken to fall asleep), number of awakenings, duration of wakings after sleep onset (WASO: the sum of lengths of time spent awake between sleep onset and the final awakening), length of time spent in bed and total duration of sleep.[15,18]

OBJECTIVE

The aim of the present study was to assess the sleep quality of patients with primary Sjögren's syndrome (pSS) and its relationship with fatigue, quality of life and disease activity.

METHODS

This was an observational, cross-sectional study in which participants in a clinical trial (NCT03130062) on pSS patients were evaluated. The clinical trial was conducted over a three-year period to evaluate the clinical and psychological aspects and influence of aerobic and resistance exercises among pSS patients. It was approved by the local research ethics committee on October 10, 2012, and it was conducted in the university's exercise psychobiology laboratory (Brazil Platform; CEP: 125.852).

The eligible participants were ambulatory men or women with pSS in accordance with the European-American consensus group criteria of 2002.[19] All participants signed an informed consent statement and were evaluated by a blinded physician. Serum and urine samples were collected and chest x-rays and echocardiograms were performed. Participants with pulmonary disease or heart failure were excluded. Patients taking rituximab or hypnotics were also excluded.

A visual analogue scale for pain (VAS-pain), the European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index (ESSPRI) and the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) were used for assessing disease activity.

VAS-pain scales assess the severity of pain on a physical scale marked out from 0 to 100 millimeters, such that 0 represents "no pain" and 100 represents "the worst possible pain". ESSPRI is a questionnaire in which the aim is to investigate the main symptoms of pSS patients in three domains: fatigue, pain and dryness. The scores are given by the patient by means of visual analogue scales (range from 0 to 10). The total score is the sum of the mean scores in these three domains.[20] ESSDAI is a questionnaire completed by the physician that investigates pSS disease activity. It contains 12 domains relating to clinical and laboratory data (blood, immunological and urinary tests).[21]

To evaluate fatigue, we used the Profile of Fatigue and Discomfort - Sicca Symptoms Inventory (short form) (PROFAD-SSI-SF) and a visual analogue scale for fatigue (VAS-fatigue).

PROFAD-SSI-SF is used to characterize the fatigue pattern associated with Sjögren's syndrome. It consists of nineteen questions that are separated into eight domains. PROFAD has nine questions split into four domains: cutaneous fatigue, mental fatigue, arthralgia and vascular, and SSI has ten questions split into four domains: ocular dryness, oral dryness, vaginal dryness, and cutaneous dryness. The scores can range from zero to seven, such that zero represents "the best" and seven represents "the worst".[22,23] The total score is the mean from summation of PROFAD and SSI and can range from 0 to 28. VAS-fatigue scales assess the severity of fatigue on a physical scale marked out from 0 to 100 millimeters, such that 0 represents "no fatigue" and 100 represents "the worst possible fatigue".[24]

Sleep quality was evaluated using the Pittsburg sleep quality index (PSQI), in its version that has been validated for use in Portuguese, and using actigraphy for 15 days. We also used the Medical Outcomes Survey Short Form 36 (SF-36) for assessing quality of life.

PSQI is a questionnaire that consists of 19 self-rated questions and five questions that should be answered by bedmates or roommates. Each question contains seven components that are scored from 0 to 3 for assessing sleep quality and disturbances during the previous month. The sum of the seven components can range from 0 to 21. Scores ≥ 5 represent poor sleep quality and scores ≤ 4 represent good sleep quality.[25] The PSQI components are as follows: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction.

Actigraphy is a technique used for assessing sleep-awake cycles. It enables recording of motor activities through limb movements.[16,17] The sleep characteristics analyzed through actigraphy are the following: sleep latency, nightly awakenings (WASO) and sleep duration, which are all recorded in minutes; and sleep efficiency (regarding sleep latency), which is recorded as a percentage;

SF-36 is a questionnaire composed of 36 items that assesses functional capacity, pain, general health, vitality, social aspects, emotional aspects and mental health.[26] Its scores range from 0 to 100.

Statistical analysis

The data were summarized through descriptive statistics. For numerical variables, we used means and standard deviations, and minimum, median and maximum values. For categorical data, we used absolute and relative frequencies. The Spearman correlation test was used for analysis of correlations between variables and for comparisons among patients with sleep disorders and Sjögren's syndrome. The correlations were classified as the following ranges: 0.00-0.19 "very weak"; 0.20-0.39 "weak"; 0.40-0.59 "moderate"; 0.60-0.79 "strong"; and 0.80-1.0 "very strong".[27] Student's t test was used to analyze age and the Mann-Whitney test was used for the other variables (VAS-fatigue scale and PSQI). $P < 0.05$ was considered to be statistically significant. The analyses were carried out using the Minitab statistical software, version 13.1.

RESULTS

Descriptive analysis

Sixty-one patients who had previously been diagnosed as presenting pSS were initially assessed from 2015 to 2016. Eleven were excluded because they did not fulfill the inclusion criterion (a diagnosis of pSS in accordance with the 2002 criteria of the European-American consensus group),[19] and one because of a diagnosis of heart disease. A total of 50 female patients with pSS were included in the study, with average age of 56.4 years, age range from 27 to 82 years and duration of syndrome symptoms ranging from 2 to 39 years (mean of 12 years of symptoms).

Regarding ESSDAI, the mean score was 2.3 and ranged from 0 to 12. After categorizing the score, 40 patients (80%) were found to present low disease activity (score < 5), and 10 (20%), moderate activity (scores between 5 and 14). None of them were classified as having high disease activity (score > 14). The ESSPRI and VAS-pain means were 6.31 (standard deviation, SD: 2.31) and 58 mm (SD: 2.8)

The total mean score for PROFAD-SSI-SF was 16.97 (SD: 6.23) and the mean for VAS-fatigue was 66 mm (SD: 2.7). In the fatigue domains, 75% of the participants presented high physical fatigue (PROFAD-physical > 2) and 65% reported having significant mental fatigue (PROFAD-mental > 2).

With regard to SF-36, in which the scores can range from 0 to 100 in each domain, the highest mean score was seen in the domain of functional capacity (mean = 61.5) and the lowest, in the domain of physical aspects (mean = 34.5). In the other domains, the means were as follows: 44.7 for pain, 56.3 for general health, 48.5 for vitality, 59.4 for social aspects, 48.6 for emotional aspects and 60.6 for mental health.

Regarding sleep quality measurement, the PSQI showed a total score of 8.9 (**Table 1**). When categorized, 13 patients (26%) had good sleep quality (score ≤ 5) and 37 patients (74%) had poor sleep quality (score > 5). Actigraphy indicated means of 26.2 minutes for sleep latency, 48.2 minutes for nightly awakening, 89.7% for sleep efficiency and 398.5 minutes (approximately 6.5 hours) for sleep duration (**Table 2**).

Table 3 presents a summary of correlations between PSQI and other variables. There were correlations, albeit weak, with the following: VAS-pain, VAS- fatigue, PROFAD-SSI and ESSPRI.

Table 1. Pittsburg sleep quality index measurement

Domain	Mean	Standard deviation
Sleep duration	1.1	1.2
Sleep disturbances	1.9	0.7
Sleep latency	1.5	1.2
Daytime sleepiness	1.5	0.9
Sleep efficiency	1.0	1.3
General quality of sleep	1.6	0.7
Use of drugs	0.8	1.3
Total score (sum)	8.9	4.7

Table 2. Actigraphy measurement

Domain	Mean	Standard deviation
Latency (minutes)	26.2	16.8
WASO (minutes)	48.2	39.7
Sleep efficiency (%)	89.7	8.4
Sleep duration (minutes)	398.5	80.9

WASO = wakings after sleep onset.

In these cases, a positive correlation indicated that the higher the scale result for these variables was, the higher the total score for the PSQI also was. There were no correlations between PSQI and ESSDAI, between PSQI and duration of the symptoms or between PSQI and SF-36.

Table 4 presents a summary of correlations between nightly awakenings (duration of WASO) and other variables. There was no correlation between the duration of WASO and PROFAD-SSI or between the duration of WASO and ESSPRI, but there was a weak correlation between the duration of WASO and ESSDAI, indicating that the higher the ESSDAI score was, the longer the duration of WASO also was.

DISCUSSION

The present study confirmed that there was high prevalence of fatigue among pSS patients, in line with previous studies: one in which it was demonstrated that 96% of pSS patients suffered from significant physical fatigue (PROFAD-physical = 3.5) and another in which 48% of the patients reported having significant mental fatigue (PROFAD-mental = 2.8).[28,29] Data obtained using multi-dimensional assessment tools showed that physical/somatic fatigue was more severe and more frequent among pSS patients and that, after controlling for depression, pSS patients were more fatigued than healthy controls, regarding general fatigue and physical fatigue, and they presented reduced activity in the MFI (Multifunctional Fatigue Inventory).[29]

It has also been reported that quality of life was worse among pSS patients and that direct healthcare costs in the pSS group were more than double those in the control group.[30-32] A study conducted by Westhoff et al.[33] confirmed this finding and demonstrated that pSS patients presented high levels of healthcare system usage, work disability and early retirement due to psychological and social factors (fatigue was included in those factors), but not glandular manifestations.

If fatigue rather than oral or ocular dryness causes increased healthcare usage and productivity losses, additional studies need to be carried out with the aim of bringing new insights into the mechanisms underlying fatigue, and the strategies that are required for addressing these common problems among pSS patients.

Our study showed significant positive correlations between sleep disorders and disease activity, as demonstrated through the correlation between actigraphy results and ESSDAI. Positive correlations were also found between the PSQI and the following variables: VAS-pain, VAS-fatigue, PROFAD-SSI score and ESSPRI.

A review by Abad et al.[12] found that 75% percent of pSS patients complained of moderate or severe sleep disorders. Moreover, in comparison with rheumatoid arthritis patients, they had significantly higher sleep deficits (the difference between the need for sleep and actual duration of sleep), difficulty in falling sleep, increased muscle tension when trying to fall asleep, increased restless legs sensations, more nocturnal pain and more racing thoughts.[12] The pSS group also complained of significantly more daytime sleepiness and fatigue and of not feeling rested after sleep,[1] as confirmed by Gudbjornsson et al.[34] using polysomnography. In the latter study, most of the patients made an association between daytime fatigue and sleep disorders.[34]

We found similar results, thus confirming the influence of sleep disorders on fatigue. We observed that only 13 patients (26%) indicated that they had good sleep quality in the PSQI, while 37 patients (74%) considered that their sleep was poor, predominantly with complaints regarding sleep quality.

According to Matuzakia et al., who studied sleep patterns in a sample of healthy adults living at the city of São Paulo, the sleep characteristic patterns observed through actigraphy were the following: sleep latency: 12.5 minutes (SD: 11); sleep efficiency: 80.6% (SD: 6.7); total duration of sleep: 365.4 minutes (SD: 57.4); and duration of wakings after sleep onset (WASO): 53.9 minutes (SD: 21.2).[18] In our study, actigraphy showed that the means for sleep latency was 26.2 minutes. This is twice the time for healthy adults that was described by Matuzakia.[18]

Although sleep disorders among pSS patients had previously been demonstrated in other studies, with results similar to those found in our study, there is still a need for further study to clarify the relationship between fatigue and disease activity.[1]

Study limitations

The limitation of the present study was that it had a descriptive design. A more appropriate study design would enable

Table 3. Correlation between total score from Pittsburg sleep quality index (PSQI) and other variables

Variables	rs*	P-value
Duration of symptoms	0.084	0.562
EULAR Sjögren's Syndrome Disease Activity Index	-0.091	0.531
Visual analogue scale for pain	0.329	0.020
Visual analogue scale for fatigue	0.381	0.006
Profile of Fatigue and Discomfort – Sicca Symptoms Inventory	0.308	0.030
EULAR Sjögren's Syndrome Patient Reported Index	0.383	0.006
Short form-36	-0.166	0.248

**Spearman correlation.*

Table 4. Correlation between duration of WASO (wakings after sleep onset) and other variables, shown through actigraphy

Variables	rs*	P-value
Profile of Fatigue and Discomfort – Sicca Symptoms Inventory	0.059	0.682
EULAR Sjögren's Syndrome Patient Reported Index	-0.005	0.974
EULAR Sjögren's Syndrome Disease Activity Index	0.352	0.012

**Spearman correlation.*

better investigation of the association between sleep disorders and fatigue and disease activity. Moreover, a cohort study on patients with high disease activity according to ESSDAI could be conducted in order to confirm our findings.

CONCLUSION

The present study provides important information regarding a possible correlation between sleep disorders and disease activity. The study aimed to describe the characteristics of a group of patients with Sjögren's syndrome, concerning fatigue, pain and sleep disorders. It could be seen that the subjects with the disease presented severe fatigue and sleep disorders. The results also demonstrated that sleep may have an influence on fatigue, and that there is an association between disease activity and sleep. These findings are of great clinical relevance, in view of the limited amount of information on this subject.

Therefore, we conclude that there is a need for proper control over disease activity and for development of strategies to help patients to sleep better in order to diminish their fatigue and improve their quality of life.

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Muscle depletion in cirrhotic patients assessed using computed tomography: a cross-sectional study

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ABSTRACT

BACKGROUND: Sarcopenia is a common complication in patients with cirrhosis and may lead to increased morbidity and mortality.

OBJECTIVE: To investigate the prevalence of sarcopenia and its association with disease severity scores, among patients with cirrhosis.

DESIGN AND SETTING: Observational and retrospective cohort study carried out in a tertiary-care hospital in southern Brazil.

METHODS: This study was conducted among patients with chronic liver disease who were followed up at the gastroenterology and hepatology outpatient clinic of a tertiary-care hospital in southern Brazil and who underwent computed tomography scans of the abdomen through any indication.

RESULTS: We included 83 patients in the study. In the population evaluated, there was a predominance of males (57.80%) and the mean age was 56 years. Hepatitis B or C virus was present in the genesis of the disease in 34.9% of the cases, followed by an etiology of alcohol abuse (30.1%). Sarcopenia was diagnosed in 41 (49.4%) of the patients when the cutoff point for cirrhotic patients was used. There was no significant correlation between the Child-Pugh and MELD severity scores and the occurrence of sarcopenia.

CONCLUSION: Sarcopenia presents high prevalence among patients with chronic liver disease, without any association with predictors of severity.

INTRODUCTION

Chronic liver disease is a major global public health problem. Liver cirrhosis and hepatocellular carcinoma respectively account for over 1.2 million and 800,000 deaths annually.[1-5] According to a study conducted in Brazil, liver diseases are the eighth leading cause of death among patients treated through the public healthcare system, and cirrhosis is the most prevalent type.[6]

Protein-energy malnutrition is frequently observed in cases of liver cirrhosis. This, in association with low physical activity, may result in sarcopenia. The prevalence of protein-energy malnutrition is around 20%-30% among patients with chronic liver disease and over 60% among patients with advanced cirrhosis.[7-11]

Sarcopenia has been described as a syndrome characterized by progressive and extensive loss of strength and skeletal muscle mass, with a risk of unfavorable outcomes, including patient morbidity and mortality.[7,11-14] It is one of the most common complications in cirrhotic patients, with prevalence ranging from 30% to 70%, and it involves reduced quality of life and increased infection rates. It is an independent mortality factor that implies a worse outcome after liver transplantation.[11,15-18] However, the diagnostic criteria are not uniform.

The European Working Group on Sarcopenia in Older People (EWGSOP) has defined a list of diagnostic criteria. In its latest publication (2018), this group recommended that both low muscle mass and low muscle function (strength or performance) should be used to diagnose sarcopenia.[12,19] The justification for using two criteria is based on the fact that muscle strength does not depend on muscle mass alone.[12,13,19,20] Therefore, when only the 'muscle mass' is evaluated, the term 'muscle depletion' can be used.

On the other hand, the European Association for the Study of the Liver (EASL) recommends that, among cirrhotic patients, sarcopenia should be evaluated by means of abdominal computed tomography (CT). This parameter has been validated using dual-energy x-ray emission densitometry, which is considered to be the gold standard.[11] However, there is divergence in the

literature regarding the best cutoff point for diagnosing sarcopenia in patients with cirrhosis, using CT.[21,22]

OBJECTIVE

The aims of this study were to investigate the prevalence of sarcopenia among cirrhosis patients and to ascertain whether there might be an association between sarcopenia and disease severity.

METHODS

A cross-sectional study was conducted using data obtained through a review of medical records. The patients included were aged 18 years or older, had been diagnosed with cirrhosis of any etiology, had undergone abdominal CT through any indication and were being followed up at the gastroenterology and hepatology outpatient clinic of a tertiary-care hospital in Porto Alegre, southern Brazil. The vast majority of the CT scans were performed to evaluate the presence of liver lesions, but CT was also indicated for evaluating abdominal pain in patients attended at the emergency unit, and also within the routine evaluation for liver transplantation.

The exclusion criteria consisted of occurrences of cases of HIV co-infection, organ transplantation and inadequate records.

Cirrhosis was diagnosed from the clinical findings, laboratory tests, imaging examinations and/or upper digestive endoscopy, and from histopathological examinations.

The review of the medical records was based on data that had been obtained at the time when the abdominal CT scan was performed. The variables analyzed were age, sex, etiology of liver disease, Child-Pugh score,[23] model of end-stage liver disease (MELD) score,[24] ascites at the time of CT, previous history of hepatic encephalopathy, previous history of digestive bleeding, presence of hepatocellular carcinoma (HCC) and patient outcome (death or liver transplantation).

Sarcopenia was diagnosed by means of abdominal CT scans. On these, the third lumbar vertebra (L3) was identified and the transverse area of the abdominal and paraspinal wall muscles involved (psoas, erector spinae, quadratus lumborum, transversus abdominis, internal and external oblique muscles and rectus abdominis) was measured (**Figure 1**). This measurement in square centimeters was divided by the patient's height squared, and is referred to as the L3 skeletal muscle index (L3 SMI). The muscle area in this region is commonly used for diagnostic purposes because it includes central skeletal muscles whose mass is independent of activity and water retention, and it corresponds best to the patient's total muscle mass. All the CT images were analyzed by the same medical physicist using the ImageJ software, which is similar in accuracy to other types of software currently used in diagnosing sarcopenia.[25]

Two pairs of cutoff points for L3 SMI were used for further comparisons. The first was based on Carey et al.,[26] who evaluated a specific cutoff point for patients with cirrhosis, and defined that sarcopenia was present when L3 SMI < 50 cm^2/m^2 in men and < 39 cm^2/m^2 in women. The second was based on Prado et al,[27] who evaluated patients with solid tumors of the respiratory and gastrointestinal tract and took cutoff points for sarcopenia of < 52.4 cm^2/m^2 for men and < 38.5 cm^2/m^2 for women. This second pair of cutoff points are the ones used by the EWGSOP.[12,19]

For the statistical analysis, categorical variables were described according to the frequency and percentage. The sarcopenia prevalence rate was presented with its respective 95% confidence interval (95% CI). Normally-distributed quantitative variables were described in terms of the mean and standard deviation. Categorical variables were compared using the chi-square test or Fisher's exact test. A 5% significance level was used for the comparisons.

The study was approved on November 8, 2011, by the ethics committee of the institution involved, under the protocol number 3675/11.

RESULTS

Among the 570 cirrhotic patients seen at the outpatient clinic, 466 had not undergone abdominal CT, and there was no record of height for 21 patients. Thus, the final sample consisted of 83 patients. These were predominantly male patients (48; 57.80%), with a mean age of 56.68 ± 10.40 years (63.9% were younger than 60 years of age), and a mean body mass index (BMI) of 27.5 ± 4.3 kg/m^2. Regarding etiology, 34.9% of the cases were due to hepatitis B or C, and 30.1% were due to alcohol abuse.

At the time of the evaluation, 40 patients (48.2%) had ascites; 29 (35.4%) had presented upper gastrointestinal bleeding in the past; and 28 (33.7%) had a history of hepatic encephalopathy. The other characteristics of the population are presented in **Table 1**. Eight of the patients (10%) died as a consequence of liver disease.

Sarcopenia was identified in 41 patients (49.4%; 95% CI 38.2%-60.6%) according to the cutoff point specific for cirrhotic patients; and in 40 patients (48.2%; 95% CI 37.1%-59.4%) according to the cutoff point used for oncological patients (P = 0.976).

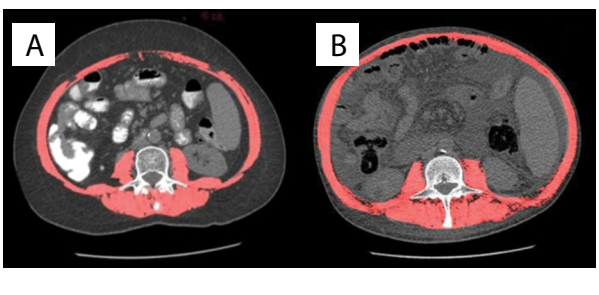

Figure 1. Cross-sectional area of third lumbar vertebra (L3) on abdominal computed tomography in a patient with sarcopenia (32.17 cm^2/m^2) (A) and a patient without sarcopenia (52.3 cm^2/m^2) (B).

Non-obese patients (BMI < 30 kg/m²) presented sarcopenia more frequently than obese patients, regardless of the cutoff point used (P = 0.012 and P = 0.017 respectively).

Among the patients with an etiology of alcohol abuse for cirrhosis, 23 (56.1%) had sarcopenia according to the cutoff point for cirrhotic patients and 23 (57.5%) according to the oncological cutoff point. Among patients with other etiologies, 18 cases (43.9%) of sarcopenia were identified using the cirrhosis cutoff point and 17 (42.5%) were identified using the oncological cutoff point; there was no difference between these etiology groups (P = 0.38 and P = 0.27 respectively).

Evaluation of the patients in terms of compensated cirrhosis (Child-Pugh A) and decompensated cirrhosis (Child-Pugh B and C) showed that among the 41 patients diagnosed with sarcopenia according to the cirrhosis-specific cutoff point, 22 (53.7%) were Child-Pugh A and 19 (46.3%) were Child-Pugh B and C (P = 0.383) (**Table 1**). Among the 40 patients diagnosed with sarcopenia according to the oncological cutoff point, 21 (52.5%) were Child-Pugh A and 19 (47.5%) were Child-Pugh B and C (P = 0.513) (**Table 2**).

Table 1. Clinical characteristics of the patients using the cirrhosis cutoff points (< 50 cm²/m² in men and < 39 cm²/m² in women)

	With sarcopenia	Without sarcopenia	P
	n = 41	n = 42	
ETIOLOGY, n (%)			0.383
Alcohol	23 (56.1)	19 (45.2)	
Other	18 (43.9)	23 (61.1)	
CHILD-PUGH, n (%)			0.383
A	22 (53.7)	18 (49.2)	
B and C	19 (46.3)	24 (57.1)	
MELD, n (%)			
> 15	7 (17.1)	14 (33.3)	0.147
≤ 15	34 (82.9)	28 (66.7)	0.147

MELD = model of end-stage liver disease.

Table 2. Clinical characteristics of the patients using the oncological cutoff points (< 52.4 cm²/m² in men and < 38.5 cm²/m² in women)

	With sarcopenia	Without sarcopenia	P
	n = 40	n = 43	
ETIOLOGY, n (%)			0.275
Alcohol	23 (57.5)	19 (44.2)	
Other	17 (42.5)	24 (55.8)	
CHILD-PUGH, n (%)			0.513
A	21 (52.5)	19 (44.2)	
B and C	19 (47.5)	24 (55.8)	
MELD, n (%)			
> 15	7 (17.5)	14 (32.6)	0.185
≤ 15	33 (82.5)	29 (67.4)	0.185

MELD = model of end-stage liver disease.

There was no significant association between MELD score and sarcopenia (r = -0.035; P = 0.147) using the cutoff of MELD > 15. There was no correlation between sarcopenia and Child-Pugh score according to the cirrhosis-specific cutoff point (P = 0.518) or the oncological cutoff point (P = 0.632) (**Table 2**).

There were no significant differences in the numbers of patients with upper gastrointestinal bleeding (P = 1.00), hepatic encephalopathy (P = 1.00) or ascites (P = 1.00) according to the cutoff point.

Age over 60 years was not significantly associated with either cutoff point. There were 18 patients (21.7%) with type 2 diabetes mellitus, and seven of these (17%) had sarcopenia, which was not significant. Twenty-six patients (31.3%) had HCC and, of these, eight (19.5%) had sarcopenia according to the two cut-off points (P = 0.040).

Among the eight patients who died, two had sarcopenia according to both cutoff points (25%; P = 0.275 for the cirrhosis cutoff point; and 25%; P = 0.269 for the oncological cutoff point).

DISCUSSION

The nutritional status of patients with cirrhosis is increasingly stressed in the literature. In recognition of the impact of muscle loss in these patients, we conducted a study to assess the prevalence of sarcopenia and its relationship with disease severity, with comparisons between different cutoff points used for making the diagnosis. We found that the prevalence of sarcopenia was 49.4% when we used a cutoff point established specifically for cirrhotic patients. Since few studies have evaluated sarcopenia in cirrhotic patients, we also used a cutoff point that had previously been evaluated for an oncological population, which resulted in a prevalence rate of 48%. The results did not differ significantly between the two cutoff points.

The prevalence rate found in the present study is concordant with the findings of Jeong et al., who evaluated a similar outpatient population of 131 cirrhotic patients who underwent CT. Using a cutoff point established by Prado et al.,[27] they found a prevalence of 48.9%.[28]

Tandon et al. also evaluated cirrhotic patients (most of them compensated) in outpatient follow-up with CT or magnetic resonance imaging, and found a prevalence of 43%.[29] Among non-liver transplantation cirrhotic patients evaluated using CT, Hanai et al. found a higher prevalence of sarcopenia (68%).[17]

Interestingly, Montano-Loza et al.[30] and Tandon et al.[31] found lower prevalence of sarcopenia than what was observed in the present study (40% and 41%, respectively). However, they evaluated patients on the liver transplantation waiting list whose condition was more severe. Likewise, Meza-Junco et al. evaluated 116 patients on liver transplantation lists and found a prevalence of sarcopenia of 30%.[32] On the other hand, Giusto et al. found a prevalence of 78% among patients who were eligible for liver transplantation.[18]

In Brazil, Zambrano et al. evaluated cirrhotic patients who were being followed up as outpatients and found a prevalence of 17%.[33]

There are divergences of opinion regarding which cutoff points should be used for diagnosing sarcopenia. Prado et al. evaluated patients with solid tumors of the respiratory and gastrointestinal tract and determined that cutoffs of 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women were associated with increased mortality.[27] Jones et al. used this cut-off point among colorectal cancer patients, and Sheean et al. used it among patients with respiratory failure.[34,35] This is also the cutoff point currently recommended by the EWGSOP.[12,19]

Among patients with liver cirrhosis, there is even greater disagreement about which cutoff point to use, and there have been changes over the years. Tandon et al.,[29,31] Giusto et al.[18] and Montano-Loza et al.[30] evaluated the prevalence of sarcopenia among cirrhotic patients using the cutoffs proposed by Prado et al.[27] However, Montano-Loza et al. subsequently proposed another cutoff point for diagnosing sarcopenia in cirrhotic patients: 50 cm^2/m^2 for men and 42 cm^2/m^2 for women.[36,37] A new study by the same group, this time assessing the inclusion of sarcopenia in MELD, then used cutoffs based on Martin et al. ($\leq$ 53 cm^2/m^2 for men and $\leq$ 41 cm^2/m^2 for women with BMI $\geq$ 25 kg/m^2, and $\leq$ 43 cm^2/m^2 for all patients with BMI < 25 kg/m^2).[38,39] The most recent study on this topic, published by Carey et al. in 2017, was a multicenter study to determine cutoffs for diagnosing sarcopenia in cirrhotic patients. A total of 396 patients were assessed at five liver transplantation centers in the United States, and the cutoff point that was most significant for detecting survival differences between the groups was < 50 cm^2/m^2 for men and < 39 cm^2/m^2 for women.[26]

In view of the controversy regarding the best cutoff point for diagnosing sarcopenia, we chose to evaluate the ones that are most used, i.e. the cutoffs advocated by Carey et al., obtained from cirrhotic patients, and by Prado et al., obtained from patients with solid tumors. These were compared, and no significant difference in the prevalence of sarcopenia was found between them.

Regarding the etiology of cirrhosis, 34.9% of the cases were due to hepatitis B or C, which is a proportion similar to what has been described in the literature.[30] However, there was no statistically significant difference regarding the prevalence of sarcopenia and etiology. Grouping patients according to whether the etiology of their cirrhosis was alcohol abuse did not result in any significant difference.

Regarding sarcopenia and predictors of mortality (Child-Pugh and MELD), some studies did not find any relationship between sarcopenia and the degree of hepatic dysfunction.[17,31,32] However, others found a relationship and suggested that including sarcopenia assessment in Child-Pugh and MELD scores could improve mortality predictions among cirrhotic patients.[31,38,40] In the present study, there was no correlation between sarcopenia and the Child-Pugh and MELD severity scores, although it should be pointed out that sarcopenia was not included in the MELD score as a prognostic tool.

Although it has been shown that sarcopenia increases mortality among cirrhotic patients,[37,41,42] there was no association in the present study between mortality and sarcopenia, which might be explained by the fact that the sample consisted of outpatients, with disease of lower severity.

The main factor that may have contributed towards potential study limitations was the small sample size, which perhaps contributed to the lack of significant differences between severity, mortality and the different cutoff points. Also, the varied indications for CT were potentially a source of bias concerning clinical status. In addition, the retrospective design involved inherent limitations that should be taken into account. On the other hand, the situation depicted in this study represents the real life of outpatients in a reference center.

CONCLUSION

The present study indicated that there was high prevalence of sarcopenia among individuals with cirrhosis, even if this was compensated. In addition, no difference between the cutoff points that were used to diagnose sarcopenia was found, and there was no association between the severity predictor scores (Child-Pugh and MELD) and presence of sarcopenia. Future studies with larger samples could contribute towards better understanding of this topic.

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Theory-based training to promote breast cancer screening among women with breast cancer worries: randomized controlled trial

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ABSTRACT

BACKGROUND: Breast cancer worries are important determinants in relation to behavior favoring breast cancer screening.

OBJECTIVE: To determine the effect of theory-based training to promote breast cancer screening among women with high and low levels of breast cancer worries.

DESIGN AND SETTING: Randomized controlled trial, conducted in two family health centers.

METHODS: In total, 285 women were recruited. Women with low levels of breast cancer worries were included in the first intervention group (112 women) and the first control group (112 women), while women with high levels of breast cancer worries were included in the second intervention group (37 women) and the second control group (43 women). Theory-based training to promote breast cancer screening was given to intervention groups. The women's willingness to undergo breast cancer screening and breast cancer worry scores were evaluated at 1, 3 and 6 months.

RESULTS: The women in the low cancer-worry intervention group performed breast self-examination more in months 1 and 6 following the training, and the women in the high cancer-worry control group performed breast self-examination more in month 3 ($P < 0.05$). No difference between the women who had low or high levels of breast cancer worries were observed in relation to breast self-examination, clinical breast examination or mammography ($P > 0.05$).

CONCLUSION: The level of worry did not affect the success of theory-based training, and the training was partially effective with regard to willingness to undergo breast cancer screening.

CLINICAL TRIAL REGISTRATION: NCT04225741.

INTRODUCTION

Breast cancer is the most frequent type of cancer and the most common cause of cancer death among gynecological cancers. One in every four women with cancer in the world has breast cancer. The International Cancer Agency reported that there were around 2,088,849 new cases and 626,679 deaths due to breast cancer worldwide in 2018.[1] The incidence of breast cancer is higher in developed countries than in developing countries, but the numbers of deaths due to breast cancer are lower in developed countries than in developing countries.[2,3]

It is known that breast self-examination, clinical breast examination and mammography play an important role in making an early diagnosis of breast cancer. The uptake rate for mammography performed on a regular basis is low because this is an expensive method, considering that not all individuals have health insurance and public funding is inadequate, especially in developing countries. Hence, breast self-examination (which has no cost) and clinical breast examination (which only has low cost) remain important diagnostic methods. Moreover, during clinical breast examination, healthcare professionals have the opportunity to advise on breast cancer, risk factors, prevention methods and screening methods.[4-6]

Awareness of the barriers relating to willingness to undergo breast cancer screening is important. Azami-Aghdash et al. found that the biggest barriers impeding willingness to participate in breast cancer screening programs were lack of information, problems regarding transportation to the clinic and fear, in decreasing order.[7] In a study conducted by Tuzcu and Bahar in Turkey, lack of information was found to be the primary factor preventing willingness to undergo breast cancer screening.[8] Several studies in the literature have investigated the effect of

education for overcoming the barrier of lack of information on breast cancer screening.[9-11]

The concept of cancer can cause fear or worry. This fear is the third largest barrier against undergoing breast cancer screening and can direct women's behavior in this regard. Fear or worry about getting cancer can sometimes make women more willing to look for early diagnosis, but sometimes it can be a deterrent.[11] There are results in the literature indicating that negative emotions such as fear and worry about health problems can effectively lead people to avoid seeking early diagnosis relating to cancer.[13-16] Examination of women's worries regarding breast cancer and their behavioral decisions during follow-up should be the focal point of personal education relating to cancer.[12,17,18]

So far, the effects of fear and worries about cancer on women's learning process and behavior regarding breast cancer screening have only been addressed in a limited manner. It is expected that the present study will make a significant contribution towards better understanding of women's attitudes and tendencies towards breast cancer screening.

OBJECTIVE

This study was conducted to determine the effect of theory-based training to promote breast cancer screening among women with breast cancer worries. In addition, behavior regarding breast cancer screening was compared between women with high and low levels of worry about breast cancer.

METHODS

Study design, setting, participants and ethics

A randomized controlled trial was conducted at two family health centers providing primary health care services at locations in eastern Turkey. The population for this study consisted of 3,900 women aged 20-65 years who were registered at these family health centers.

A power analysis was conducted to determine the sample size, through calculations using the publicly available statistical software OpenEpi, version 3 (http://www.openepi.com). This analysis was done using a significance level of 5%, an effect size of 22% and an ability to represent the population of 80% (power). It was shown that the sample size needed to be at least 105 women in each group (i.e. 105 in the intervention group and 105 in the control group).

Regarding randomization and allocation concealment, women for the control groups were selected from Başharık family health center and women for the intervention groups were chosen from Sıtmapınarı family health center. These women were recruited from both family health centers using simple random sampling. A random number table was used at each family health center, which enabled recruitment of 1,530 women.

The Breast Cancer Worry Scale (BCWS) was administered to 420 women who met the inclusion criteria. Women who were found to have low levels of worries about breast cancer were included in the first intervention group and the first control group, while women with high levels of worries about breast cancer were included in the second intervention group and the second control group. Totals of 305 women (intervention 182; control 123) with low levels of worries about breast cancer and 115 women (intervention 55; control 60) with high levels of worries about breast cancer were identified according to their BCWS scores.

After allocation, no blinding for group assignment was possible for either the participants or the researchers. This was because follow-up interviews were conducted between the women and researchers. The study protocol was completed by 173 women in the low breast cancer-worry intervention group and 112 women in the low breast cancer-worry control group (a total of 285); and by 37 women in the high breast cancer-worry intervention group and 43 women in the high breast cancer-worry control group (a total of 80). These smaller numbers were because some women wanted to withdraw from the study (n = 22) and some changed their address (n = 33) during the data collection phase (**Figure 1**).

The inclusion criteria were as follows. The participants included did not have any diagnosis of breast cancer, had not been performing breast self-examination regularly (every month), had not previously had a mammogram, had not previously had a clinical breast examination, were not pregnant or breastfeeding and were literate.

According to the breast cancer screening program of Turkey, women aged 20 years and over should perform breast self-examination every month; women aged 20 years and over should undergo clinical breast examination once every two years; women aged 40 years and over should undergo clinical breast examination once a year; and women aged 40-69 years should undergo mammography every year.[21] Therefore, women who had been doing breast self-examination once a month were accepted as performing breast self-examination. Among women aged 40 years and over, at least one clinical breast examination within the first six months after training and having a mammogram were accepted as having undergone clinical breast examination and mammography. The Sıtmapınarı and Başharık family health centers serve the largest populations around the provincial border of Malatya (Sıtmapınarı family health center serves 2,500 women and Başharık family health center serves 1,400 women), and the populations that they serve present sociodemographic homogeneity.

Ethics

This study was endorsed by the Internal Review Board (Ethics Committee) of Inönü Üniversitesi on April 16, 2014, under the approval number 2014/44. This study was registered in the Clinical Trial Registry (NCT04225741).

Measurements

Data were collected using a personal information form, a breast cancer screening behavior questionnaire (BCSBQ) and the BCWS, between January 2015 and August 2017.

Personal information form: This form, prepared by the researchers, consisted of questions regarding the sociodemographic characteristics of the women.

Breast Cancer Screening Behavior Questionnaire: This questionnaire, prepared by the researchers, comprised questions concerning breast self-examination, clinical breast examination and mammography practices.[19] No validated tool for assessment of breast cancer screening behavior was available in Turkey. The BCSBQ was prepared in line with the national standards that need to be followed during breast cancer screening program studies conducted by the Turkish Ministry of Health.[19]

Breast Cancer Worry Scale: Lerman et al.[20] developed this three-item scale to measure breast cancer worry levels and their effect on daily activities and mood. Lerman subsequently modified the scale, such that it was extended from breast cancer to general cancer and its number of questions was increased to six.[20] Lerman's six-item cancer worry scale was then modified by Timur Taşhan et al. to measure breast cancer worries alone, and a Turkish validity and reliability study on the BCWS was conducted. This Turkish-language validated version of the BCWS uses a five-item Likert-type scale,

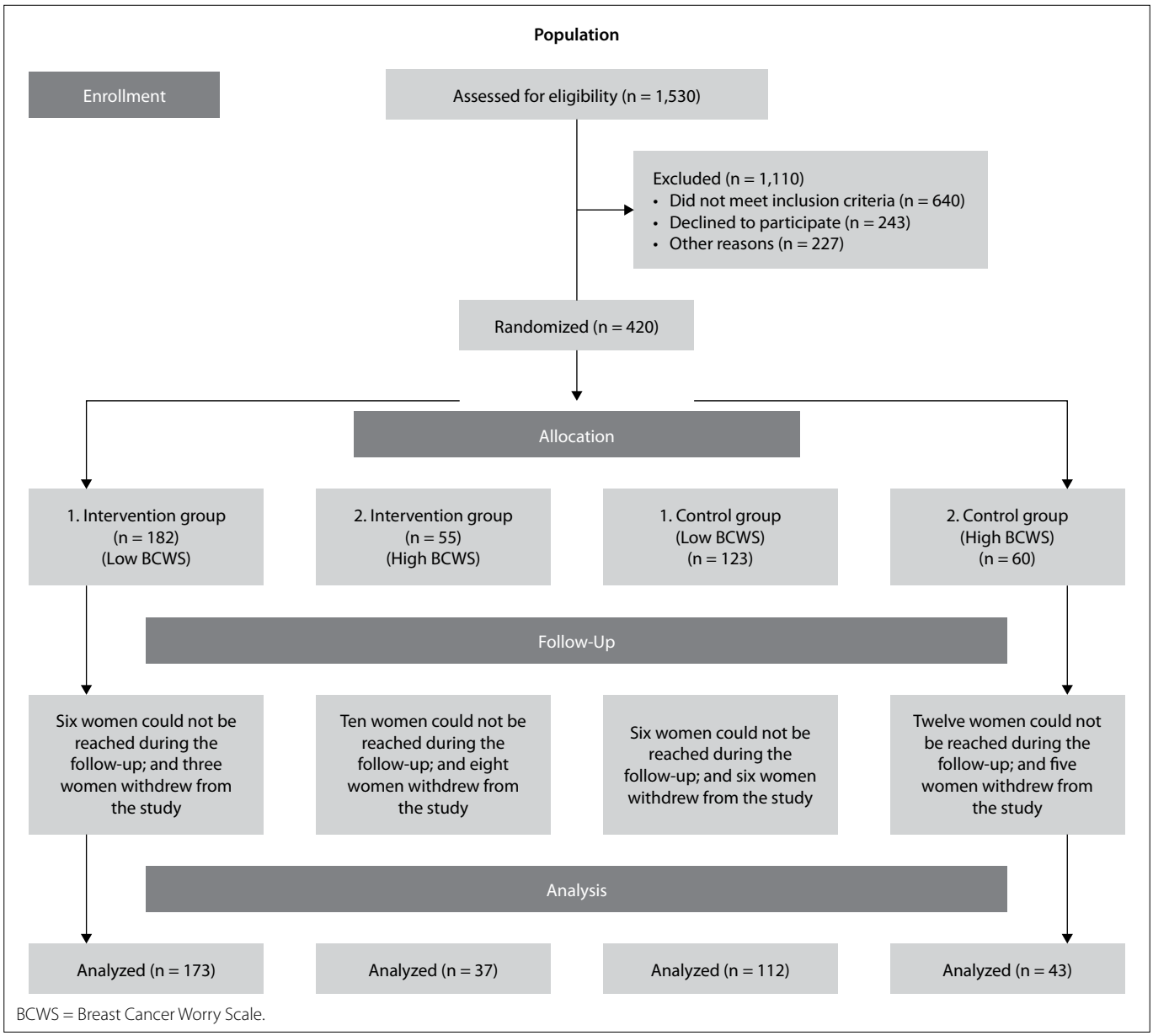

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flowchart for the study.

and for each question on this scale, respondents need to choose one of the following options: never = 0, rarely = 1, sometimes = 2, often = 3, or always = 4. Thus, overall, the lowest score that can be obtained is 0, and the highest is 24. A total score of less than 12 denotes a low level of worry regarding cancer, and a total score ≥ 12 indicates a high level of worry.[21] Cronbach's alpha reliability coefficient for the Turkish-language validated version of the BCWS was 0.78.

Procedure

Written permission to conduct the study was obtained from the Public Health Institution of Turkey and from the Sıtmapınarı and Başharık family health centers. In addition, approval was obtained from Inonu University Health Sciences Scientific Research and Publication Ethics Committee (April 16, 2014, under number 44). Before beginning the study, verbal consent was obtained from all the women who participated. The intervention and control group data were collected simultaneously. After making appointments with the women by phone, the data were collected by the researchers in four stages in the women's own homes, using face-to-face interviews.

The BCWS and the personal information form were administered to the women who had been selected to form the two control groups, during the first interview, in order to determine breast cancer-worry levels. Following this first interview, follow-up interviews were conducted one, three and six months later, and the BCSBQ was administered at each follow-up appointment.

Following administration of the BCWS and the personal information form to the women who had been selected to form the two intervention groups (a low breast cancer-worry group and a high breast cancer-worry group), during the first interview, the researchers gave the breast cancer screening training to both intervention groups under equal conditions in the training room of Sıtmapınarı family health center, in the form of group training (8-12 women). Following this training, the women in the intervention groups received consultations at follow-ups, via home visits in months 1, 3, and 6. At these times, the researchers administered the BCSBQ.

The primary outcome measurement of this study was the efficacy of the theory-based training on breast cancer screening behavior. The secondary outcome measurements were changes to breast cancer screening behavior.

The intervention

The single-session training lasted for approximately 40-45 minutes and was conducted in the training room of Sıtmapınarı family health center, as a suitable environment. The health belief model predicts the determinants of preventive health behaviors and explains inadequate participation in disease prevention and screening programs.[22,23] Furthermore, this model not only explains behavior regarding screening, but also evaluates the cognitive factors that facilitate health-promoting behaviors.[22-24]

Many previous studies have simultaneously examined the health belief model and behavior favoring breast cancer screening.[22,25-28] Therefore, this model was used in the training provided in the present study, with the aim of achieving better comprehension among the participants regarding the importance of screening for breast cancer. Through this training, participants would acquire the ability to correctly perform breast self-examination and would understand the necessity for mammography and clinical breast examination, in accordance with the health belief model. The following notions were addressed:

- Perceived susceptibility: In order to increase the women's perception of susceptibility to breast cancer, explanations of the disease and its epidemiology, the structure of the breast and breast cancer risk factors were provided.
- Perceived severity: In order to increase the women's perception of the severity of breast cancer, the characteristics of breast lumps, as diagnosed in early and late breast cancer, and the differences in the treatment regimens were explained.
- Perceived benefit: In order to improve the women's perception of breast cancer screening, the treatment benefit of early diagnosis of breast cancer, the role of alternative treatment methods, such as lumpectomy instead of radical mastectomy, and the effect of regularly performed examinations on the breast cancer mortality rate were explained.
- Perceived trust: How to correctly conduct breast self-examination, what clinical breast examination consists of, why mammography is performed and how long it takes to perform mammography were explained.
- Perceived barrier: In order to reduce the women's perceived barriers against undergoing breast cancer screening, the factors inhibiting women from conducting breast self-examination and from undergoing clinical breast examination and mammography were explained in detail.

None of the interventions described above were applied to the control group.

Statistical analysis

The data were evaluated using the Statistical Package for the Social Sciences software, version 16.0. In the data assessment, percentages, means, independent-sample t tests, chi-square tests, Fisher's exact tests and repeated-measurement analysis of variance (ANOVA) tests were used. To compare the groups regarding categorical variables, the chi-square test and Fisher's exact test were used. An independent t test was used to make comparisons between the intervention and control groups. To test for a significant difference in means over time, repeated-measurement

ANOVA was used. The statistical significance level was taken to be $P < 0.05$.

RESULTS

The age, employment status, marital status, educational level and economic level of the intervention and control groups were similar. No statistically significant difference was found between the intervention and control groups in terms of sociodemographic characteristics (**Table 1**).

The mean BCWS scores of the women in the intervention group with low levels of cancer worries increased gradually from the pre-intervention test to the tests in months 1, 3 and 6, and the differences in the scores were statistically significant ($P = 0.001$). No difference in the mean BCWS scores between the pre-test and the tests in months 1, 3 and 6 was observed among the women in the control group with low levels of cancer worries ($P = 0.096$). There was no difference in the mean BCWS scores between the pre-test and the tests in months 1, 3 and 6 among the women in the intervention group with high levels of cancer worries ($P = 0.263$). The mean BCWS scores of the women in the control group with high levels of cancer worries decreased gradually from the pre-test to the tests in months 1, 3 and 6, and the differences in the scores were statistically significant ($P = 0.001$) (**Table 2**).

With regard to the women with low levels of breast cancer worries, it was found that 41.6% of the women in the intervention group and 20.5% of the women in the corresponding control group performed breast self-examination in the first month after receiving the theory-based training. This difference in use of breast self-examination was statistically significant ($P = 0.001$). In addition, 56.1% of the women in the intervention group and 42% of the women in the control group performed breast self-examination in month 6, which was a statistically significant difference ($P = 0.021$). No differences in the rates of performing breast self-examination in the third month or undergoing clinical breast examination and mammography within the first six months after training were found between the women in the intervention and control groups (**Table 3**).

With regard to the women with high levels of breast cancer worries, it was observed that 45.9% of the women in the intervention group and 79.1% of the women in the control group performed breast self-examination in month 3 after training. This difference in use of breast self-examination was statistically significant ($P = 0.020$). No differences in the rates of performing breast self-examination in months 1 and 6 or having clinical breast examination and mammography within the first six months were found between the women in the intervention and control groups (**Table 4**).

DISCUSSION

Encouraging women to have cancer screening tests on a regular basis is an important requirement in the fight against breast cancer. However, a variety of psychosocial factors affect behaviors such as willingness to undergo cancer screening tests.[3] Cancer-related thoughts can result in various negative reactions, such as anxiety, fear and grief.[11,29] Fear or worry about getting

Table 1. Sociodemographic characteristics of the women in the intervention and control groups

Characteristics	Experimental group (n = 210)		Control group (n = 155)		χ^2	P
	n	%	n	%		
Age (years)						
< 40	90	42.9	53	34.2	2.809	0.094
≥ 40	120	57.1	102	65.8		
Employment status						
Unemployed	159	75.5	114	73.5	0.222	0.638
Employed	51	24.5	41	26.5		
Marital status						
Married	174	82.9	137	88.4	2.163	0.141
Single	36	17.1	18	11.6		
Educational level						
Literate	32	15.3	21	13.5	7.030	0.071
Primary school	75	35.7	76	49.0		
Secondary/high school	58	27.6	30	19.4		
University	45	21.4	28	18.1		
Economic level						
Low	115	54.8	79	51.0	0.516	0.473
Medium	95	45.2	76	49.0		

Table 2. Comparison of breast cancer-worry levels among the women in the intervention and control groups

LBCWS	Low breast cancer-worry intervention group (n = 173)	Low breast cancer-worry control group (n = 112)	t	P
	Mean ± SD	Mean ± SD		
Pre-test	3.70 ± 3.36	4.58 ± 3.61	2.100	**0.037**
Month 1	4.11 ± 3.56	4.75 ± 3.59	1.620	0.106
Month 3	4.25 ± 3.60	4.03 ± 3.42	0.284	0.777
Month 6	4.74 ± 3.41	4.40 ± 3.15	0.657	0.512
F	9.680	2.167		
P	**0.001**	0.096		
HBCWS	**High breast cancer-worry intervention group (n = 37)**	**High breast cancer-worry control group (n = 43)**	**t**	**P**
	Mean ± SD	**Mean ± SD**		
Pre-test	14.72 ± 3.51	14.93 ± 3.01	-0.269	0.788
Month 1	13.51 ± 4.22	12.30 ± 4.25	1.265	0.210
Month 3	13.05 ± 3.12	11.41 ± 5.16	1.622	0.109
Month 6	12.50 ± 3.91	10.6 ± 5.47	1.827	0.071
F	2.668	6.318		
P	0.263	**0.001**		

LBCWS = low breast cancer-worry scale; SD = standard deviation; HBCWS = high breast cancer-worry scale.

cancer is the most prevalent of these psychosocial factors.[11] In this context, studies on the types of differences that psychosocial factors show with regard to willingness to seek early diagnosis, depending on cultural structures, are required.[30] The present study was conducted to determine the effect of theory-based training given to women, on the basis of their breast cancer-worry level, on their behavior towards breast cancer screening.

Table 3. Comparison of breast cancer screening behaviors among the women in the intervention and control groups who presented low levels of cancer worry

Breast cancer screening behaviors	Intervention group (n = 173)		Control group (n = 112)		χ^2	P
	n	%	n	%		
Month 1 BSE						
Yes	72	41.6	23	20.5	13.598	**0.001**
No	101	58.4	89	79.5		
Month 3 BSE						
Yes	91	52.6	50	44.6	1.723	0.189
No	82	47.4	62	55.4		
Month 6 BSE						
Yes	97	56.1	47	42.0	5.411	**0.021**
No	76	43.9	65	58.0		
CBE						
Yes	24	13.9	17	15.2	0.094	0.759
No	149	86.1	95	84.8		
Mammography[a] (n = 170)						
Yes	8	8.2	6	8.2		0.995[b]
No	89	91.8	67	91.8		

[a]Women aged 40 years and over were evaluated; [b]Fisher's exact test was used.
BSE = breast self-examination; CBE = clinical breast examination.

Table 4. Comparison of breast cancer screening behaviors of the women in the intervention and control groups who presented high levels of breast cancer worry

Breast cancer screening behaviors	Intervention group (n = 37)		Control group (n = 43)		P
	n	%	n	%	
Month 1 BSE					
Yes	16	43.2	18	41.9	0.901
No	21	56.8	25	58.1	
Month 3 BSE					
Yes	17	45.9	34	79.1	**0.020**
No	20	54.1	9	20.9	
Month 6 BSE					
Yes	18	48.6	30	69.8	0.054
No	19	51.4	13	30.2	
CBE					
Yes	9	24.3	10	23.3	0.911
No	28	75.7	33	76.7	
Mammography[a] (n = 52)					
Yes	-	-	3	-	
No	23	100.0	26	100.0	

[a]Women aged 40 years and older were evaluated; P: Fisher's exact test was used.
BSE = breast self-examination; CBE = clinical breast examination.

The results from the follow-ups conducted in months 1, 3 and 6 showed that the breast cancer worries of women in the low breast cancer-worry intervention group gradually and significantly increased. In contrast, the breast cancer worries of the women in the high breast cancer-worry control group gradually and significantly decreased ($P < 0.05$).

Janz et al. reported that worry about cancer recurrence led individuals to ask more questions at consultations with their doctors.[23] It has also been stated that there is a high possibility that individuals will follow the recommendations of people in whom they place a high degree of trust, such as doctors and clergymen.[30,31] Çaman et al. observed that the advice of physicians was effective in encouraging women to visit cancer screening centers. These authors also revealed that the actions of healthcare professionals were an important factor with regard to affecting women's levels of worry.[32]

In the present study, breast cancer risk factors, the characteristics of the lump and the differences in the treatment regimens used, depending on whether breast cancer is diagnosed at an early or late stage, were explained under the headings of perceived susceptibility and perceived severity, in accordance with the basic components of the health belief model.[18,25] This information was thought to result in an increase in the level of worry among the women in the low cancer-worry intervention group, but in a decrease in the level of worry among the women in the high breast cancer-worry control group. The increase in the level of worry in this intervention group was attributed to forgetting the information over time.

A difference favoring the low cancer-worry intervention group in months 1 and 6, in terms of breast self-examination, was identified. However, this difference favored the high cancer-worry control group with regard to breast self-examination in month 3. Kim et al.[33] found that women with high levels of cancer worries had unrealistic pessimism. Negative beliefs surrounding cancer treatment or survival may mean that they do not want to know about the cancer in advance, and this can negatively affect their behavior in relation to obtaining early diagnosis of cancer.[11] Gasalberti showed that breast cancer worries were a barrier to carrying out breast self-examination,[34] while Arts-de Jong et al.[35] found a correlation between demoralization and cancer worries. The results from the present study are concordant with the results from these previous studies.

Although some previous studies on the effects of training on women's willingness to undergo breast cancer screening indicated that this training did not have any effect in relation to clinical breast examination[9] or mammography,[8,9] other studies have shown that training has a significant effect on willingness to perform breast self-examination[9,10] and to undergo clinical breast examination and mammography.[10] In a study on cervical cancer conducted by

Ngua et al.,[36] it was found that the training given had no effect in month 6. In the present study, it was shown that the training provided had a short-term effect on the women's behavior, and that this effect was mainly in relation to breast self-examination. It was observed that the training given and the cancer-worry level had no effect on willingness to undergo clinical breast examination and mammography, which are the diagnostic methods that provide the most valuable results. This finding partially supports the hypothesis that "theory-based training does not affect women's acquisition of behavior favoring breast cancer screening". The results from the present study are similar to those of previous studies in this regard.

Numerous studies have found that cancer risk perception and worries about getting cancer are two important variables that have mutual interaction.[3,37-39] In this context, the effects of both breast cancer worries and breast cancer risk perception on willingness to undergo breast cancer screening have been investigated. While some studies showed that behavior favoring breast cancer screening increased as the worry or risk perception increased,[38,40-44] one other study found that there was no difference.[45] Baysal and Gozum[46] found that a higher uptake rate for mammography was associated with low levels of breast cancer risk. There was no difference in the rates of breast self-examination, clinical breast examination and mammography practices between intervention groups with low and high levels of cancer worry. This finding supports the hypothesis that "the level of breast cancer worry among women does not affect the acquisition of behavior favoring breast cancer screening."

Amuta et al.[47] stated that this worry had a short-term effect on health-related behavior and that such behavior also changed when there was no emotion in making decisions regarding health. In addition, these authors found that cancer worries did not affect the frequency of attending cancer screenings. Çaman et al.[32] conducted a study in the Early Diagnosis, Screening and Education Center for Cancer of Turkey and found that there was no statistically significant correlation between cancer risk perception and breast self-examination frequency. In addition, no significant correlation was found between the thought of participating in breast cancer screening programs in the future and cancer risk perception. Seven et al.[39] found that there were no correlations between women's perception of risk with regard to getting breast cancer and their level of knowledge about breast cancer, doing breast self-examination and undergoing mammography. The results from the present study are concordant with the results reported by Amuta et al.,[32] Çaman et al.[39] and Seven et al.[47]

The first limitation of this study was the low number of women included who had high levels of breast cancer worry. The second was that the education given to the women in the experimental group was presented as group-based education. And lastly, the levels of pre- and post-training knowledge and the actual risks of breast cancer among these women were not assessed.

CONCLUSIONS

It was found in the present study that theory-based training had a partial effect on willingness to perform breast self-examination and no effect on willingness to undergo clinical breast examination and mammography. In addition, it was observed that the worry level of the women had no effect on the success of theory-based training to promote breast cancer screening. It is thought that informing these women about the risk factors for acquiring breast cancer screening behaviors caused them to worry, but that their worry did not affect their behavior. Rather, it gave them more positive messages and, therefore, investigation of the effect of this approach on breast cancer screening behavior is required.

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Economic crises, behavioral changes and hospitalization due to affective disorders in Brazil between 2003 and 2017: a nationwide cross-sectional study

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Physical activity.
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ABSTRACT

Our aim was to analyze hospitalization due to affective disorders in Brazil from 2003 to 2017 and the possible association with economic indicators during crises. We used data on hospitalizations due to affective disorders within the Brazilian National Health System, obtained from DATASUS; data on health-related behavior (television-viewing and physical activity) from the VIGITEL database; and economic data from the World Bank database. We found that the numbers of hospitalizations increased one year after the 2009 crisis and one year after the 2016 crisis. Negative changes in health-related behavior also followed changes in the numbers of hospitalizations due to affective disorders.

INTRODUCTION

After the years of economic prosperity in Brazil in the early 2000s, with the success of the "real plan" and the reductions in inflation and unemployment and increases in healthcare investments,[1,2] Brazil experienced two economic crises. The first was the world crisis of 2008-2009 which, although not large in Brazil, was responsible for a 0.1% deflation in the gross domestic product (GDP) in 2009. This was the first deflation in Brazil since 1993.[1] After this, Brazil returned to a period of growth in GDP, with social, educational and public health achievements up to 2015, when the greatest recession in Brazilian history began. The 2016 crisis led to successive years with GDP deflation of more than 3%,[1] along with an important political crisis that included a presidential impeachment.

During these economic and political crises, the percentage of GDP expended on the healthcare system started to reduce, through the impact of several austerity policies.[2] With the economic crises, the levels of unemployment increased. Higher unemployment has the consequences of affecting economic power, social security and job stability (through labor-law deregulation). This may have substantial associations with mental health.[3,4]

OBJECTIVE

Our aim was to analyze occurrences of hospitalizations due to affective disorders in Brazil between 2003 and 2017, along with the economic oscillations and the prevalences of different types of health-related behavior.

METHODS

This ecological study used data on hospitalizations due to affective disorders (International Classification of Diseases 10th edition, ICD 10; codes F30-F39). These data were collected from the morbidity and mortality surveillance system (DATASUS), which records all hospitalizations within the Brazilian National Health System (Sistema Único de Saúde, SUS). DATASUS has national coverage, with registration of approximately 11 million hospital admissions per year.[5]

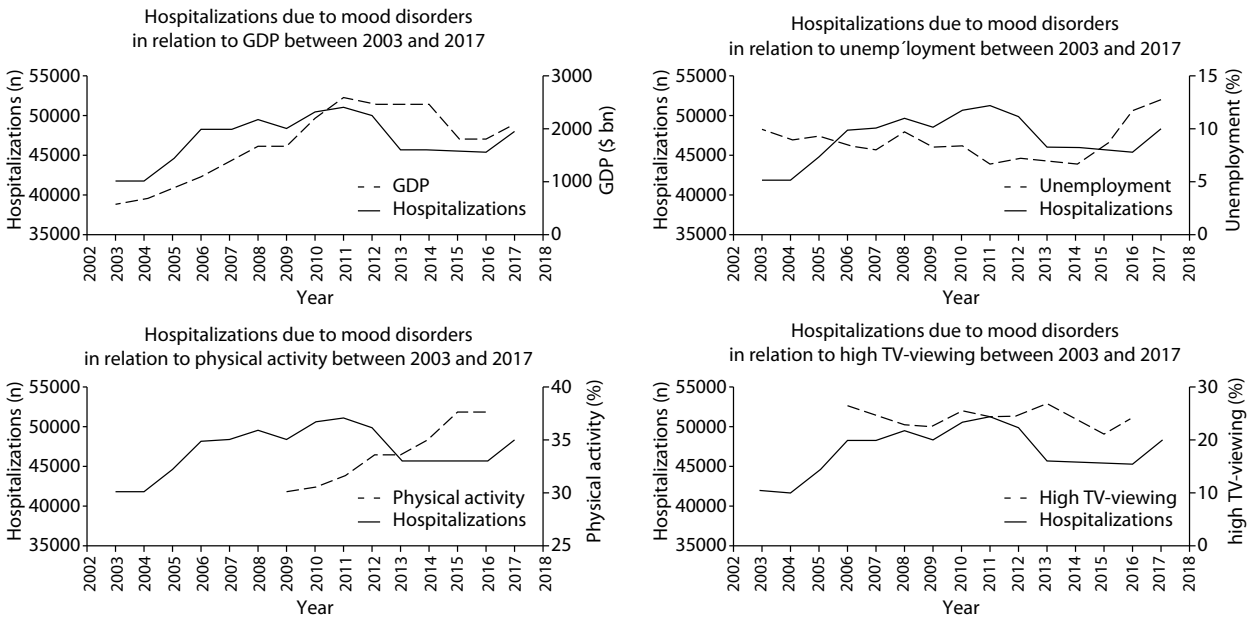
Brazilian data on GDP and unemployment were collected from the World Bank database covering the years 2003-2017.[1] Data on health-related behavior (television-viewing and physical activity) were obtained from the telephone survey-based surveillance system for risk and protective factors for chronic diseases (VIGITEL). VIGITEL is a survey that has been conducted annually since 2006 using a probabilistic sample of adults (≥ 18 years) in 26 Brazilian state capitals and

the Federal District. Here, we used data from 2006 to 2016. More details on VIGITEL are available elsewhere.[6] Data on hospitalizations, economic oscillations and behaviors were cross-referenced to analyze possible interrelationships.

Our statistical approach was to provide crude values for the numbers of hospitalizations due to affective disorders, prevalence of physical activity, prevalence of elevated time spent sitting down, GDP and unemployment rate, in order to obtain an ecological perspective. Moreover, we created an indicator for hospitalization ratio, which comprised the number of hospitalizations due to affective disorders per 1000 all-cause hospitalizations.

RESULTS

Descriptive statistics regarding the prevalence of hospitalizations due to affective disorders, economic oscillations and health-risk behaviors are presented in **Figure 1** and **Table 1**. Greater



GDP = gross domestic product (expressed as billions of United States dollars, $ bn); TV = television.

Figure 1. Association of economic and behavioral factors with hospitalizations due to mood disorders between 2003 and 2017.

Table 1. Frequency of hospitalizations due to mood disorders in relation to economic and behavioral factors

Year	Hospitalizations (n)	Hospitalization ratio (hospitalizations / 1000 all-cause hospitalizations)	GDP ($ bn)	Unemployment (%)	PA (%)	High TV-viewing (%)
2003	41,870	0.36	558.31	9.73	-	-
2004	41,814	3.64	669.32	8.89	-	-
2005	44,509	3.89	891.63	9.31	-	-
2006	48,211	4.25	1,107.64	8.39	-	28.0
2007	48,297	4.26	1,397.08	8.09	-	26.3
2008	49,469	4.60	1,695.82	9.46	-	24.6
2009	48,406	4.35	1,667.02	8.28	30.3	24.0
2010	50,578	4.45	2,208.87	8.36	30.5	27.3
2011	51,216	4.54	2,616.20	6.69	31.6	25.9
2012	49,846	4.49	2,465.19	7.19	33.5	26.4
2013	45,779	4.09	2,472.81	6.99	33.8	28.6
2014	45,879	4.05	2,455.99	6.67	35.3	25.3
2015	45,618	4.01	1,802.21	8.44	37.6	22.5
2016	45,419	4.02	1,793.99	11.61	37.6	25.7
2017	48,202	4.20	2,055.51	12.88	-	-

Note: Hospitalizations refers to hospitalizations due to mood disorders. Hospitalization ratio: hospitalizations due to affective disorders per 1000 all-cause hospitalizations. GDP = gross domestic product (expressed as billions of United States dollars, $ bn); PA = physical activity; TV = television.

numbers of hospitalizations due to affective disorders were found during 2010 and 2011, one year after the economic recession of 2009-2010. Moreover, after the economic recession of 2016, the number of hospitalizations due to affective disorders increased again in 2017. Moreover, when the number of hospitalizations due to affective disorders increased in 2017, the prevalence of high levels of television-viewing also increased, while the levels of physical activity practice remained stagnated. This contrasted with the increase that had been observed over the period between 2006 and 2016.

DISCUSSION

We observed that periods after recessions (with a reduction in GDP and an increase in unemployment) were characterized by an increase in hospitalizations due to mood disorders, especially during 2010 and 2017. Regarding important mental health correlates,[7] television-viewing increased especially during the recession period and followed the kinetics of hospitalizations due to mood disorders. In addition, when the physical activity level of the population stopped increasing, the number of hospitalizations due to mood disorders increased (between 2016 and 2017).

Worldwide, evidence of several negative changes to health outcomes during crisis periods has been found, especially when these have been followed by austerity policies within healthcare systems. Studies on the most recent crisis in European countries found that increases in communicable and non-communicable diseases occurred.[3] One of the main examples comes from Greece, which suffered severe austerity policies in 2010. This was the country that suffered the greatest number of public health consequences.[4]

Although the greatest Brazilian crisis is still recent, the negative impact on public health can already be observed. In times with increased unemployment, labor-law deregulation and social insecurity, mental health seems be affected in different ways.[3,4] One possible explanation for our findings could be the migration of people from private healthcare to the public healthcare system.[2] However, we found similar results when taking into consideration the hospitalization ratio.

Specifically, regarding the impact of economic crises on mental health, previous studies found that economic crises were associated with increases in the prevalences of several negative mental health outcomes, especially stress, anxiety and depressive symptoms. These were correlated with recent economic crises in Italy and Spain.[8,9]

Moreover, employment status seems to be an important mediator of the negative impact of economic crises on mental health. Going beyond unemployment itself, a previous study investigating the impact of an economic crisis in the Netherlands found that working conditions became worse during the crisis and that work insecurity increased. There was also an association with negative health outcomes.[10]

Economic crises can also affect lifestyle behaviors such as physical activity levels, television-viewing and diet.[11,12] Consequently, adoption of unhealthy lifestyles can also be correlated with negative mental health outcomes.[7,13,14]

Given the ecological approach adopted, we do not intend to establish causality between economic crises, health-related behaviors and hospitalizations due to affective disorders. Naturally, many factors could explain changes in the parameters analyzed.

Nevertheless, these data show that a tendency towards changes in the same direction occurs, which may indicate co-occurrence. These findings at least provide empirical evidence regarding the changes at population level that follow periods of economic recess. They also highlight the need for further studies to clarify these interrelationships.

CONCLUSION

These findings confirm the potentially harmful effects of an economic crisis on public health. Similar to the experience of other countries, Brazil will probably feel the negative impacts of the last recession period for some time yet and will take time to recover. Most importantly, this is a period for reflection and decision-making. Brazil could continue to follow examples of strong austerity, with freezing of social spending, as was done in Greece, Spain and Portugal in response to the European crisis; or it could adopt examples such as that of Iceland, which faced up to the financial recession through implementing sustainable measures focusing on social protection.

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INSTRUCTIONS FOR AUTHORS

Scope and indexing

São Paulo Medical Journal (formerly Revista Paulista de Medicina) was founded in 1932 and is published bimonthly by Associação Paulista de Medicina, a regional medical association in Brazil.

The Journal accepts articles in English in the fields of evidence-based health, including internal medicine, epidemiology and public health, specialized medicine (gynecology & obstetrics, mental health, surgery, pediatrics, urology, neurology and many others), and also physical therapy, speech therapy, psychology, nursing and healthcare management/administration.

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

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All studies published in *São Paulo Medical Journal* must be described in accordance with the specific 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] These guidelines ensure that all methodological procedures have been described, and that no result has been omitted. If none of the above reporting guidelines are adequate for the study design, authors are encouraged to visit the EQUATOR Network website (http://www.equator-network.org/) to search for appropriate tools.

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Acknowledgements and funding

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When the general format of the manuscript is deemed acceptable and fully compliant with these Instructions for Authors, and only then, the editorial team will submit the article to the Editor-in-Chief, who will firstly evaluate its scope. If the editor finds that the topic is of interest for publication, he will assign at least two reviewers/referees with expertise in the theme, to evaluate the quality of the study. After a period varying from one to several weeks, the authors will then receive the reviewers' evaluations and will be required to provide all further information requested and the corrections that may be necessary for publication. These reviewers, as well as the Editorial Team and the Editor-in-Chief, may also deem the article to be unsuitable for publication by *São Paulo Medical Journal* at this point.

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Articles will be rejected without peer review if:

- they do not present Ethics Committee approval (or a justification for the absence of this);
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Peer reviewers, associated editors and the Editor-in-Chief may ask for clarifications or changes to be made to the manuscript. The authors should then send their article back to the Journal, with the modifications made as requested. Changes to the text should be highlighted (in a different color or using a text editor tool to track changes). Failure to show the changes clearly might result in the paper being returned to the authors.

The modified article must be accompanied by a letter answering the referees' comments, point by point. The modified article and the response letter are presented to the editorial team and reviewers, who will verify whether the problems have been resolved adequately. The text and the reviewers' final evaluations, along with the response letter, will then be sent to the Editor-in-Chief for a decision.

Manuscripts that are found to be suitable for publication through their scientific merit will be considered "provisionally accepted". However, all articles will subsequently be scrutinized to check for any problems regarding the reporting, i.e. sentence construction, spelling, grammar, numerical/statistical problems, bibliographical references and other matters that may arise, especially in the Methods section. The adherence to reporting guidelines will be checked at this point, and the staff will point out any information regarding methodology or results that the authors should provide. This is done in order to ensure transparency and integrity of publication, and to allow reproducibility.

The editorial team will then provide page proofs for the authors to review and approve. No article is published without this final author approval. All authors should review the proof, although the Journal asks the corresponding author to give final approval.

Submission

Articles should be submitted only after they have been formatted as described below. Texts must be submitted exclusively through the Internet, using the Journal's electronic submission system, which is available at http://mc04.manuscriptcentral.com/spmj-scielo. Submissions sent by e-mail or through the post will not be accepted.

The manuscript should be divided into two files. The first of these, the main document ("blinded"), should contain the article title, article type, keywords and abstract, article text, references and tables, but must omit all information about the authors. The second of these, the "title page", should contain all the information about the authors.

The corresponding author is responsible for the submission. However, all authors should approve the final version of the manuscript that is to be submitted and should be aware of and approve any changes that might be made after peer review.

Covering letter

All manuscripts must be submitted with a covering letter signed at least 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 is not under consideration by any other journal;

2. a statement that the manuscript has been approved by all authors, who agree to cede the copyrights to the Journal, disclose all sources of funding and declare all potential conflicts of interest;
3. a statement that the study protocol was endorsed by an Internal Review Board (Ethics Committee), including the date and number of the approval (in the case of original articles). This is required for absolutely all studies involving human subjects or patient data (such as medical records), in accordance with the Committee on Publication Ethics (COPE) guidelines, and even for case reports;
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5. a list of a minimum of five potential referees outside of the authors' institutions, who could be invited, at the Editor-in-Chief's discretion, to evaluate the manuscript.

General guidelines for original articles

The following are considered to be full-text 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. These types of article should be written with a maximum of 3,500 words (from the introduction to the end of the conclusion).

Typical main headings in the text include Introduction, Methods, Results, Discussion and Conclusion. The authors can and should use short subheadings too, especially those concerning the reporting guideline items.

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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 are accepted for publication if they have received an identification number from one of the public clinical trial registration database (such as ClinicalTrials.gov and/or REBEC and/or the World Health Organization; the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Articles describing systematic reviews must provide the protocol registration number in the PROSPERO database. Articles presenting clinical trials or systematic reviews without registration protocols will be promptly rejected without peer review.

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.

Sample size

All studies published in SPMJ must present a description of how the sample size was arrived at. If it was a convenience or purposive sample, the authors must declare so and explain the characteristics of this sample and recruitment method. For clinical trials, for instance, it is mandatory to inform each of the three main values used to calculate sample size:

- power (usually 80% or more);
- level of significance (usually 0.05 or lower);
- clinically meaningful difference (effect size targeted), according to the main outcome measurement.

Regardless of study results (if "positive" or "negative"), the journal will probably reject articles of trials using underpowered samples, when sample size has not been properly calculated or the calculation has not been fully described as indicated above.

Abbreviations, acronyms and products

Abbreviations and acronyms must not be used, even those in everyday use, unless they are defined when first used in the text. However, authors should avoid them for clarity whenever possible. Drugs or medications must be referred to using their generic names (without capital letters), with avoidance of casual mention of commercial or brand names.

Interventions

All drugs, including anesthetics, 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. The version of the software used should be mentioned.

Any other interventions, such as exercises, psychological assessments or educational sessions, should be described in enough details to allow reproducibility. The Journal recommends that the TIDieR reporting guidelines should be used to describe interventions, both in clinical trials and in observational studies.[13]

Short communications

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. The authors of this kind of communication should explain, in the covering letter, why they believe that publication is urgent. Short communications and case reports must be limited to 1,000 words (from the introduction to the end of the conclusion).

Case reports, case series, narrative reviews and letters to the editor

Starting in June 2018, only individual case reports dealing with situations of public health emergencies will be accepted by *São Paulo Medical Journal*. Case reports that had already been accepted for publication up to May 2018 will still be published in a timely manner.

After initial evaluation of scope by the editor-in-chief, case reports, case series and narrative reviews will be considered for peer-review evaluation only when accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[12] The search strategy for each database and the number of articles obtained from each database should be shown in a table. This is mandatory for all case reports, case series and narrative reviews submitted for publication. Failure to provide the search description will lead to rejection before peer review.

The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms must be used 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.

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FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

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 should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
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, without using abbreviations;
4. Each author should present his/her ORCID identification number (as obtained from www.orcid.org);
5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;
6. Each author should indicate a valid, up-to-date email address for contact;
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The second page must include the title and a structured abstract in English with a maximum of 250 words. References must not be cited in the abstract.

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
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References

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 are only available electronically.

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.

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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Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent at a resolution of 300 DPI and minimum size of 2,500 pixels (width) and be recorded in ".jpg" or ".tif" format. Images submitted in inadequate formats will not be accepted.

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Flowcharts are an exception: these must be drawn in an editable document (such as Microsoft Word or PowerPoint), and should not be sent as an image that can't be changed.

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For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded in the image to indicate the magnification used (just like in a map scale). The staining agents (in histology or immunohistochemistry evaluations) should be specified in the figure legend.

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NOVA DATA

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