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Smoking control in Brazil: a public health success story

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The Brazilian national football team's defeat by Germany during the 2014 World Cup, by a vexatious score of 7-1, was not the worst misery for Brazilians over the last three years. During this same period, an organized plot among federal officials, politicians and chief executive officers (CEOs) of major companies, involving a complex exchange of overpriced government contracts relating to engineering and construction, engineering and energy, with bribery and illegal money for electoral campaigns, was revealed.

The national TV networks have broadcast every detail of the investigation reports from both the federal police and the Brazilian Attorney-General's office, and also from the court trials. The fallout so far is that the President of the Republic (in her second term) was impeached, and the House Speaker and also the former Governor of Rio de Janeiro, who are also two of the wealthiest men in the country, are in jail. All of this is combined with the worst economic recession since the early 1900s. Moreover, in the field of public health, there is a feeling of going back to the past. The Zika epidemic emerged in Brazil, deaths due to pertussis have risen and yellow fever is marching toward urban settings. Consequently, a feeling of discouragement, bewilderment, anger and disenchantment has beset Brazilians and has blurred the vision of any possible improvement in society.

Nonetheless, one piece of good news in the field of chronic diseases stands out: faster decline in smoking prevalence among the most populous countries in the world. The Global Burden of Diseases 2015 Tobacco Collaborators published an extensive paper addressing the prevalence of smoking and the attributable disease burden in 195 countries from 1990 to 2015. From this major paper published in the Lancet,[1] we can focus on comparison of the 10 countries with most people smoking in 1990, i.e. China, India, Indonesia, Russia, United States, Bangladesh, Japan, Brazil, Germany and the Philippines. **Figure 1** shows that among these countries, in 2015, Brazil had the lowest prevalence for both sexes and the lowest for men. The trends over these 25 years were very remarkable in most of the top 10 countries, but the drop in the prevalence rate was most impressive in Brazil with a 55% reduction, as shown in **Figure 2**.

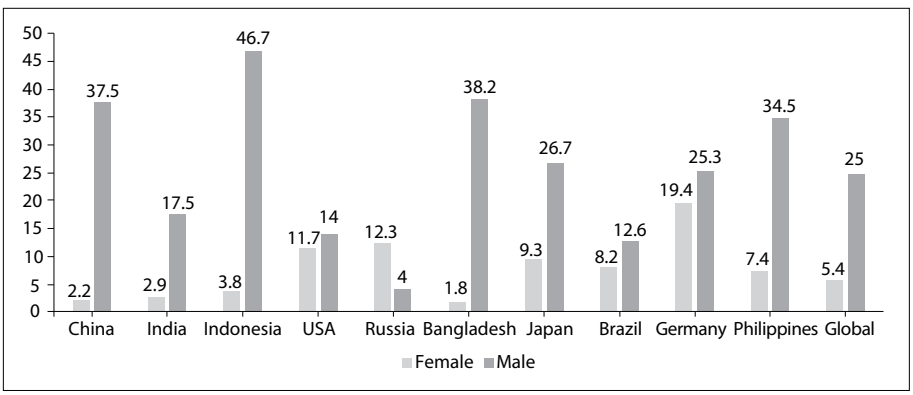

Figure 1. Age-adjusted prevalence rates (in %) for smoking habit among the 10 countries with the highest numbers of smokers, according to the Global Burden of Disease study.[1]

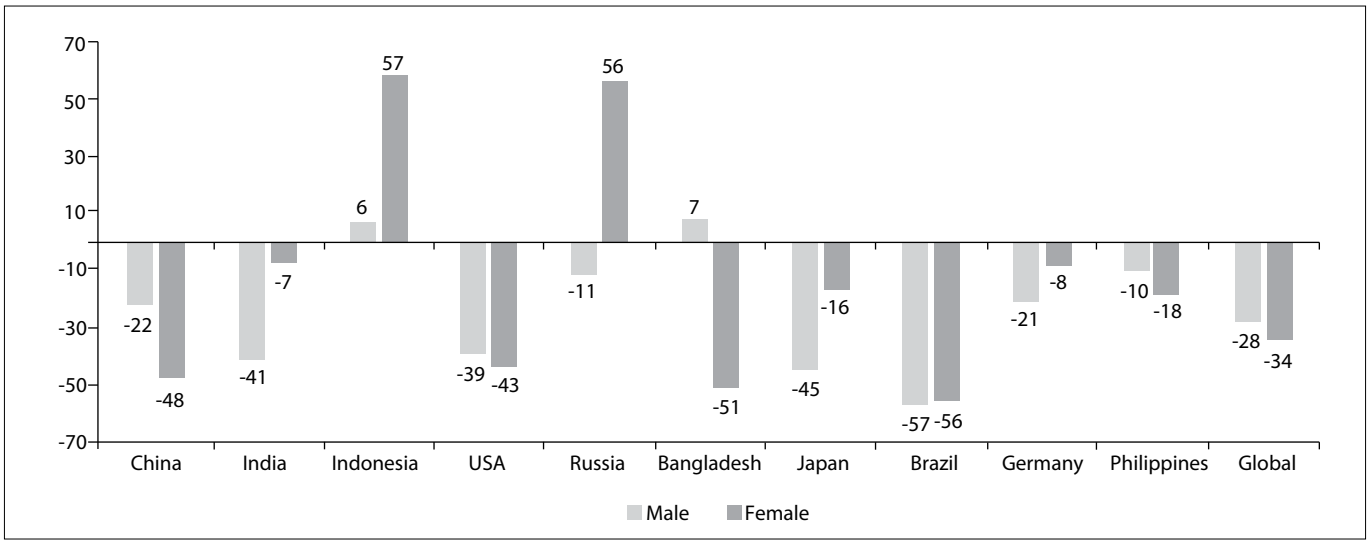

Figure 2. Difference (%) in age-adjusted prevalence rates for smoking habit between 1990 and 2015 among the 10 countries with the highest numbers of smokers, according to the Global Burden of Disease study.[1]

Despite the horrible political situation, some Brazilians believe that this process looks like "creative destruction" of the democratic order, which may lead to reinvigorated institutions in the future. Whether optimistic or not about politics, most Brazilians should be proud of this reduction in the burden of chronic diseases due to diminution of the risk factor of the smoking habit.

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Determinants of outpatient expenditure within primary care in the Brazilian National Health System

Determinantes de gastos ambulatoriais na atenção primária do sistema público de saúde brasileiro

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KEY WORDS:
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Epidemiologia.

ABSTRACT

CONTEXT AND OBJECTIVE: One of the big challenges facing governments worldwide is the financing of healthcare systems. Thus, it is necessary to understand the factors and key components associated with healthcare expenditure. The aim here was to identify demographic, socioeconomic, lifestyle and clinical factors associated with direct healthcare expenditure within primary care, among adults attended through the Brazilian National Health System in the city of Bauru.

DESIGN AND SETTING: Cross-sectional study conducted in five primary care units in Bauru (SP), Brazil.

METHODS: Healthcare expenditure over the last 12 months was assessed through medical records of adults aged 50 years or more. Annual healthcare expenditure was assessed in terms of medication, laboratory tests, medical consultations and the total. Body mass index, waist circumference, hypertension, age, sex, physical activity and smoking were assessed through face-to-face interviews.

RESULTS: The total healthcare expenditure for 963 participants of this survey was US$ 112,849.74 (46.9% consultations, 35.2% medication and 17.9% laboratory tests). Expenditure on medication was associated with overweight (odds ratio, OR = 1.80; 95% confidence interval, CI: 1.07-3.01), hypertension (OR = 3.04; 95% CI: 1.91-4.82) and moderate physical activity (OR = 0.56; 95% CI: 0.38-0.81). Expenditure on consultations was associated with hypertension (OR = 1.67; 95% CI: 1.12-2.47) and female sex (OR = 1.70; 95% CI: 1.14-2.55).

CONCLUSIONS: Our results showed that overweight, lower levels of physical activity and hypertension were independent risk factors associated with higher healthcare expenditure within primary care.

RESUMO

CONTEXTO E OBJETIVO: Um dos grandes desafios dos governos em todo o mundo é o financiamento de sistemas de saúde e, por isso, é necessário compreender fatores e componentes-chave associados a despesas em saúde. O objetivo foi identificar fatores demográficos, socioeconômicos, de estilo de vida e clínicos associados aos gastos diretos com saúde na atenção primária entre adultos do Sistema Único de Saúde da cidade de Bauru.

TIPO DE ESTUDO E LOCAL: Estudo transversal realizado em cinco Unidades Básicas de Saúde em Bauru (SP), Brasil.

MÉTODO: Gastos com saúde nos últimos 12 meses foram avaliados através de prontuários médicos de adultos de 50 anos ou mais. Gastos anuais com saúde foram avaliados com: medicamentos, exames laboratoriais, consultas médicas e total. Índice de massa corporal, circunferência da cintura, hipertensão, idade, sexo, atividade física e tabagismo foram avaliados por meio de entrevista face a face.

RESULTADOS: O gasto total com serviços de saúde para os 963 participantes deste inquérito foi de US$ 112.849.74 (46,9% consultas, 35,2% medicamentos e 17,9% exames). Gastos com medicamentos foram associados com sobrepeso (*odds ratio*, OR = 1,80 [intervalo de confiança, IC 95%: 1,07-3,01]), hipertensão (OR = 3,04 [IC 95%: 1,91-4,82]) e atividade física moderada (OR = 0,56 [95% IC: 0,38-0,81]). Gastos com consultas foram associados com hipertensão (OR = 1,67 [IC 95%: 1,12-2,47]) e sexo feminino (OR = 1,70 [IC 95%: 1,14-2,55]).

CONCLUSÃO: Nossos resultados mostraram que sobrepeso, menor nível de atividade física e hipertensão são fatores de risco independentes associados com maiores gastos com saúde na atenção primária.

INTRODUCTION

One of the big challenges facing governments worldwide is the financing of healthcare systems. The challenge is more difficult in developing nations, not only due to limited budgets, but also because of the increasing prevalence of chronic diseases.[1-3] In 2005, cardiovascular diseases and diabetes mellitus were the leading causes of mortality in developing nations, accounting for 30% of deaths.[1] However, in 2012, among the 56 million deaths that occurred, 67.8% were due to chronic diseases, especially cardiovascular and respiratory diseases and cancer.[4]

In Brazil, treatment of chronic cases relating to overweight/obesity in the adult population alone cost US$ 2.1 billion in 2008, i.e. around 1% of gross domestic product (GDP).[2] The cumulative losses of GDP from 2006 to 2015 due to all chronic diseases were US$ 4.2 billion.[1] In terms of economic impact, the burden of chronic diseases on the Brazilian economy is significant because the Brazilian National Health System grants free access to healthcare services at all levels of complexity to the entire population. In 2011, the costs relating to maintenance of the Brazilian National Health System accounted for 9% of the national GDP.[5]

The growing public healthcare expenditure in Brazil has captured the attention of the Brazilian government. The need for development of preventive strategies to address this issue has been highlighted. However, as far as we know, there is a lack of evidence informing the progress of such policies. Previous studies have examined the association between higher healthcare expenditure and specific determinants, such as physical inactivity, obesity and arterial hypertension.[2,6,7] However, the effects of these variables on healthcare expenditure are usually assessed separately and it is not clear which one is the most relevant as a cause of the rising healthcare expenditure in Brazil. Therefore, identification of correlates of higher healthcare expenditure among the adult population is an important step towards elaborating effective strategies for braking this increasing trend.

To formulate effective policies for addressing the economic burden, not only the drivers of rising costs but also the key components associated with healthcare expenditure need to be understood. These include medication dispensed, laboratory tests and consultations, given that the dynamics of costs may vary according to the type of service.[8] Moreover, even though Brazil is a nation of continental proportions, with huge metropolises like São Paulo and Rio de Janeiro, the largest proportion of the Brazilian population lives in small and medium-sized cities. Recent surveys have shown that these adults living in medium-sized Brazilian cities are widely affected by chronic diseases and other health problems.[9-11] Therefore, in terms of the burden on healthcare costs, small and medium-sized cities are important within the dynamics of healthcare costs in Brazil. However, data on healthcare costs and their correlates in this setting are scarce.

OBJECTIVE

The objective of this study was to identify demographic, socioeconomic, lifestyle and clinical factors associated with direct healthcare expenditure within primary care among adults who were attended through the Brazilian National Health System and who were living in Bauru, a medium-sized city in the state of São Paulo.

METHODS

Study design and population

The data were collected through a cross-sectional study carried out in 2010 (August to December 2010) in the city of Bauru, which has around 360,000 inhabitants and is located in the central region of the state of São Paulo, Brazil. In this study, the minimum sample size required was 882 individuals. The sample size was estimated based on the percentage of adults attended through the Brazilian National Health System who were classified as "high cost" (25%), error of 3.5%, alpha error of 5% (Z = 1.96) and design effect of 50%. The percentage of 25% was arbitrary and came from previous papers,[6,7] in which it had been used because of the absence of previous data about this issue.

Details about the sampling process can be found in previous papers.[6,7,12] Briefly, the Municipal Health Department was contacted, the researchers presented the objectives of the research project and asked for permission to access the patients' medical records. After the Research Ethics Board of São Paulo State University, Bauru campus, had assessed the project and approved it (procedural number 1046/46/01/10), the Health Department authorized access to all medical records within the primary healthcare services of the Brazilian National Health System.

The Brazilian National Health System is divided into primary, secondary and tertiary services. Primary services include preventive actions (e.g. vaccination) and treatment of chronic conditions (e.g. medication for patients with chronic diseases) and clinical consultations. Such services are provided at primary care facilities called primary healthcare units (PHUs), which provide different types of healthcare specialists (e.g. general practitioners, nurses and dentists) and have the capacity to implement low-complexity healthcare procedures for the community. In the city of Bauru, there are 17 PHUs, spread out across all geographical regions of the metropolitan area. In this survey, we only included traditional PHUs (without inclusion in the Family Health Strategy). The survey included five PHUs, i.e. one in each metropolitan area of Bauru (east, west, north, south and downtown). In selecting each PHU, the number of patients served was taken into consideration, i.e. the PHU with the highest number of patients registered was selected in each geographical region.

In each PHU, the participants were randomly selected using the identification number on the medical records. The SPSS software,

version 13.0, was used for random sampling. Among the randomly selected medical records, the inclusion criteria were checked. Firstly, all subjects needed to be aged ≥ 50 years, because this age has been correlated with development of chronic diseases in the Brazilian population[8,11] and is a cutoff point relating to significantly increased healthcare costs among adults.[13] Secondly, all subjects needed to have attended at least one medical consultation during the last six months: this was used as an indicator of current residence in Bauru and usage of the healthcare system.

Patients who fulfilled both of these inclusion criteria were contacted by phone. Those who agreed to take part in the study were invited to come to the PHU for assessment. At the PHU, the participants signed a standard written consent form in which they agreed to participate in this study. They were then interviewed and anthropometric measurements were made.

MEASUREMENTS

Dependent variable

Annual healthcare expenditure

Using participants' medical records (which were stored at the PHU), only the direct annual healthcare expenditure recorded over the last 12 months prior to the survey date were estimated. These estimates were based on the major components: medical consultations, medication dispensed and laboratory tests. At the PHU, in a reserved room, two trained researchers extracted data from the medical records. In the event of any doubts, the head nurse of the PHU was consulted. Public healthcare reimbursement values provided by the PHU office (administrated by the Municipal Finance Department) were used to calculate monetary values for the medication dispensed, laboratory tests done and consultations performed. For the tests and medical consultations, the exact value paid by the municipal administration was calculated using the receipts, while for medicine delivered to the patient, the amount was estimated, because the municipal administration pays for the entire pack of medicine, but in some cases releases less than the entire pack to the patient.

All expenditures were initially calculated in the Brazilian currency (real) and then converted to American dollars (US$) using the mean exchange rate for the period from January 2009 to December 2009. Finally, the monetary values were adjusted according to the annual inflation rate in Brazil observed over the period 2010-2015, so as to express the costs in a manner closer to current values. The inflation index used was IPCA-IBGE (Índice Nacional de Preços ao Consumidor Amplo, from Instituto Brasileiro de Geografia e Estatística).

Four dependent variables indicating different types of expenditure were specified:

1. medication for regular use (sporadic use of medications, such as anti-inflammatory drugs, was not assessed);
2. medical consultations;
3. laboratory tests; and
4. overall (sum of medications, consultations and laboratory tests).

The numbers of medications and consultations were registered and inserted in the multivariate models as a confounder.

Independent variables

The same two trained researchers who were responsible for data collection from the medical records also conducted face-to-face interviews to assess the independent variables (including application of questionnaires and making anthropometric measurements). The independent variables were selected based on variables that had been shown to be correlated with healthcare expenditure in previous studies.[1,2,6,14] Considering that this was the first study of its kind in Brazil, we also included other variables.

Anthropometric measurements and health status

Body mass index (BMI) was calculated using measurements of weight (digital scale with maximum capacity of 150 kilograms) and height (wall-mounted stadiometer with maximum height of 2 meters).[15] Participants with BMI between 25 and 29.9 kg/m^2 were considered overweight and obesity was defined as BMI ≥ 30 kg/m^2.[16] Waist circumference (WC) was used as a screening tool for abdominal obesity and the cutoff points were defined as 1.02 m for men and 0.88 m for women.[17] Hypertension, diabetes mellitus and dyslipidemia were assessed as present based on diagnoses by physicians that were identified through the participants' medical records.

Demographic and socioeconomic variables

Data on chronological age (categorized as < 65 years or ≥ 65 years because of its association with chronic diseases and higher healthcare costs)[6,7,11] and sex were obtained from the medical records and verified through the interviews. Socioeconomic status was measured using a validated Brazilian family income questionnaire,[18] which specifies the following income groups: low (classes C, D and E, i.e. family income of US$ 76.94-966.38 per month) and high (classes A and B, i.e. family income of US$ 1,823.33-2,703.61 per month). This questionnaire estimates income based on data on formal schooling, appliances available in the home and physical characteristics of the home (e.g. number of toilets).

Lifestyle behavior

Information regarding physical activity levels was collected using the questionnaire developed by Baecke et al.[19] Individuals' physical activity levels were expressed as the sum of scores for

all specific domains of physical activity (i.e. occupational, active transportation and sport during leisure time). These scores were then divided into quartiles and the participants were classified into three groups: inactive (≤ P25), moderately active (< P25 and > P75) and sufficiently active (≥ P75).[6,7,14] Smoking status was obtained through the interviews and was specified as "yes" (current smokers regardless of number of cigarettes per day) or "no" (former smokers or never smoked).

Statistical analyses

Binary logistic regression was fitted to analyze the relationship between annual healthcare expenditure and health, demographic, socioeconomic and lifestyle indicators. In the binary logistic regression, all the models were adjusted using all the independent variables with statistical significance (P-value) < 0.05 from the chi-square test, plus the number of consultations, number of medicines and diagnoses of diabetes and dyslipidemia. The dependent variables were specified as binary variables, such that one indicated the highest quartile of expenditures (≥ P75), and zero indicated other levels. Regression models were fitted separately for each of the four dependent variables.

The magnitude of associations was assessed using odds ratios (OR) and their 95% confidence intervals (95% CI). The Hosmer-Lemeshow goodness-of-fit test was used to determine how well the model fitted the data (non-significant results indicated an adequate fit). Bivariate analyses were conducted to identify significant associations between dependent and independent variables. Categorical variables were expressed as rates and were compared using the chi-square test (Yates's correction was applied in 2 x 2 contingency tables).

Due to nonparametric distributions, numerical variables were presented as medians and comparisons were made using the Kruskal-Wallis and Mann-Whitney tests. All statistical analyses were performed using BioEstat (release 5.0) and P-value significance was set at 0.05.

RESULTS

The sample consisted of 963 participants, who were mainly women (73.4% versus 26.6%, P-value = 0.001), with ages ranging from 50 to 96 years. During the data collection, the loss rate was 49.7%, i.e. 1915 calls were made and 952 potential subjects were lost for different reasons (did not pick up the phone, incorrect number in the medical records, did not want to participate in the study, or scheduled for interview but did not show up).

The prevalence of hypertension was 76.8% (95% CI: 74.1 to 79.5), while diabetes mellitus and dyslipidemia were observed in 28.5% and 32.4% of the sample, respectively. We observed that 83.2% (CI: 80.8% to 85.5%) of the individuals had low income.

The total annual healthcare expenditure for the 963 participants of this survey was US$ 112,849.74 and the maximum amount spent on any patient was U$ 941.78 per year. Consultations with healthcare professionals accounted for the highest proportion of total public healthcare expenditure (46.9%; US$ 53,025.05), followed by medication dispensed (35.2%; US$ 39,774.90) and then laboratory tests (17.9%; US$ 20,040.79) (**Table 1**).

The different types of expenditure were found to be associated with different factors. Bivariate analysis showed that female participants were more likely to generate higher healthcare expenditure on laboratory tests (P-value = 0.022) and consultations (P-value = 0.005). Participants with hypertension had higher total healthcare expenditure (P-value = 0.001), especially on medication dispensed (P-value = 0.001) and consultations (P-value = 0.006) (**Table 2**). Smoking was associated with lower healthcare expenditures on consultations (P-value = 0.012). Presence of overweight or obesity was associated with higher healthcare expenditure in all the categories considered. Higher levels of physical activity were associated with lower healthcare expenditure on medication dispensed (P-value = 0.001) (**Table 2**).

After accounting for potential confounders, expenditure on medication was found to be associated with overweight (OR = 1.80; 95% CI: 1.07 to 3.01), hypertension (OR = 3.04; 95% CI: 1.91 to 4.82)

Table 1. Characteristics of the sample in Bauru (SP), Brazil (n = 963)

Characteristics	Mean (95% CI)	Median (IR)
Age (years)	64.7 (64.1 to 65.3)	63.7 (13.6)
BMI (kg/m^2)	29.4 (29.1 to 29.8)	28.6 (7.1)
WC (cm)	99.3 (98.5 to 100.1)	99 (16.4)
SBP (mmHg)	126.5 (125.3 to 127.7)	130 (30)
DBP (mmHg)	76.5 (75.9 to 77.2)	80 (10)
PA score	7.8 (7.6 to 7.9)	8.1 (2.4)
Healthcare expenditure (US$)		
Overall	117.18 (110.81 to 123.56)	92.67 (74.55)
Medication	41.30 (36.22 to 46.38)	15.78 (31.72)
Laboratory tests	20.82 (18.52 to 23.11)	11.63 (30.99)
Consultations	55.06 (53.35 to 56.77)	52.19 (35.04)
	n (%)	**95% CI**
Age		
< 65 years	530 (55)	(51.8% to 58.1%)
≥ 65 years	433 (45)	(41.8% to 48.1%)
Sex		
Male	256 (26.6)	(23.7% to 29.3%)
Female	707 (73.4)	(70.6% to 76.2%)
Economic status		
High income	162 (16.8)	(14.4% to 19.1%)
Low income	801 (83.2)	(80.8% to 85.5%)
Arterial hypertension		
No	223 (23.2)	(20.4% to 25.8%)
Yes	740 (76.8)	(74.1% to 79.5%)

BMI = body mass index; WC = waist circumference; SBP = systolic blood pressure; DBP = diastolic blood pressure; PA = physical activity; IR = interquartile range.

Table 2. Variables associated with high public healthcare expenditure within primary care in Bauru (SP), Brazil (n = 963), from bivariate analysis

Variables	Overall (≥ P75 [US$ 135.08])		Medications (≥ P75 [US$ 36.43])		Laboratory tests (≥ P75 [US$ 30.99])		Consultations (≥ P75 [US$ 71.57])	
	n (%)	P-value	n (%)	P-value	n (%)	P-value	n (%)	P-value
Age								
< 65 years	132 (24.9)	> 0.05	127 (24.1)	> 0.05	125 (23.6)	> 0.05	143 (27.1)	> 0.05
≥ 65 years	109 (25.2)	> 0.05	114 (26.3)	> 0.05	116 (26.8)	> 0.05	99 (22.9)	> 0.05
Sex								
Male	58 (22.7)	> 0.05	67 (26.2)	> 0.05	50 (19.5)	< 0.05	47 (18.4)	< 0.01
Female	183 (25.9)	> 0.05	174 (24.6)	> 0.05	191 (27.1)	> 0.05	195 (27.6)	> 0.05
Economic status								
High	33 (20.4)	> 0.05	32 (19.8)	> 0.05	45 (27.8)	> 0.05	31 (19.1)	> 0.05
Low	208 (26.1)	> 0.05	209 (26.1)	> 0.05	196 (24.5)	> 0.05	211 (26.3)	> 0.05
Smoking								
No	218 (26.1)	> 0.05	217 (26.1)	> 0.05	214 (25.6)	> 0.05	222 (26.6)	< 0.05
Yes	23 (18.1)	> 0.05	24 (18.9)	> 0.05	27 (21.3)	> 0.05	20 (15.7)	> 0.05
Body mass index								
Normal	27 (14.1)	< 0.001	28 (14.5)	< 0.001	38 (19.7)	< 0.05	34 (17.6)	< 0.05
Overweight	92 (24.2)	> 0.05	103 (27.1)	> 0.05	93 (24.5)	> 0.05	99 (26.1)	> 0.05
Obese	122 (31.3)	> 0.05	110 (28.2)	> 0.05	110 (28.2)	> 0.05	109 (27.9)	> 0.05
Waist circumference								
Normal	48 (16.7)	< 0.001	55 (19.1)	< 0.01	60 (20.8)	> 0.05	57 (19.8)	< 0.05
Elevated	193 (28.6)	> 0.05	186 (27.6)	> 0.05	181 (26.8)	> 0.05	185 (27.4)	> 0.05
Arterial hypertension								
No	32 (14.3)	< 0.001	25 (11.2)	< 0.001	52 (23.3)	> 0.05	40 (17.9)	< 0.01
Yes	209 (28.2)	> 0.05	216 (29.2)	> 0.05	189 (25.5)	> 0.05	202 (27.3)	> 0.05
Physical activity								
Inactive	69 (29.1)	> 0.05	77 (32.5)	< 0.05	56 (23.6)	> 0.05	54 (22.8)	> 0.05
Moderately active	119 (24.5)	> 0.05	106 (21.8)	> 0.05	130 (26.7)	> 0.05	121 (24.9)	> 0.05
Active	53 (22.1)	> 0.05	58 (24.2)	> 0.05	55 (22.9)	> 0.05	67 (27.9)	> 0.05

Table 3. Adjusted model for association between high public healthcare expenditure and independent variables in Bauru (SP), Brazil (n = 963)

Variables	Overall* (≥ P75 [US$ 135.08])	Medications* (≥ P75 [US$ 36.43])	Laboratory tests* (≥ P75 [US$ 30.99])	Consultations* (≥ P75 [US$ 71.57])
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age				
< 65 years	-	-	-	-
≥ 65 years	-	-	-	-
Sex				
Male	-	-	1.00	1.00
Female	-	-	1.41 (0.98-2.04)	**1.70 (1.14-2.55)**
Economic status				
High	-	-	-	-
Low	-	-	-	-
Smoking				
No	-	-	-	1.00
Yes	-	-	-	0.57 (0.34-1.00)
Body mass index				
Normal	1.00	1.00	1.00	1.00
Overweight	1.59 (0.93-2.70)	**1.80 (1.07-3.01)**	1.26 (0.81-1.94)	1.50 (0.91-2.47)
Obese	1.78 (0.98-3.22)	1.53 (0.86-2.74)	1.35 (0.88-2.07)	1.37 (0.78-2.41)
Waist circumference				
Normal	1.00	1.00	-	1.00
Elevated	1.17 (0.73-1.86)	1.14 (0.73-1.78)	-	0.93 (0.58-1.49)
Arterial hypertension				
No	1.00	1.00	-	1.00
Yes	**2.17 (1.41-3.35)**	**3.04 (1.91-4.82)**	-	**1.67 11.12-2.47)**
Physical activity				
Inactive	-	1.00	-	-
Moderately active	-	**0.56 (0.38-0.81)**	-	-
Active	-	0.76 (0.49-1.17)	-	-
Hosmer-Lemeshow test	P-value = 0.495	P-value = 0.392	P-value = 0.524	P-value = 0.151
Explanation	75%	75.9%	75%	74.9%

OR = odds ratio; 95% CI = 95% confidence interval; *model simultaneously adjusted for independent variables with P-value < 0.05 from chi-square test plus number of consultations, number of medicines and diagnoses of diabetes and dyslipidemia.

and moderate physical activity (OR = 0.56; 95% CI: 0.38 to 0.81). Expenditure on consultations was found to be associated with hypertension (OR = 1.67; 95% CI: 1.12 to 2.47). Overall healthcare expenditure was associated with female sex and hypertension (**Table 3**). All multivariate models were found to show adequate fit.

Figure 1 presents healthcare expenditure according to lifestyle behavior. Participants who were insufficiently active (**Figure 1, Panel A**), obese (**Figure 1, Panel B**) and hypertensive (**Figure 1, Panel C**) had the highest proportions of expenditure over a 12-month period.

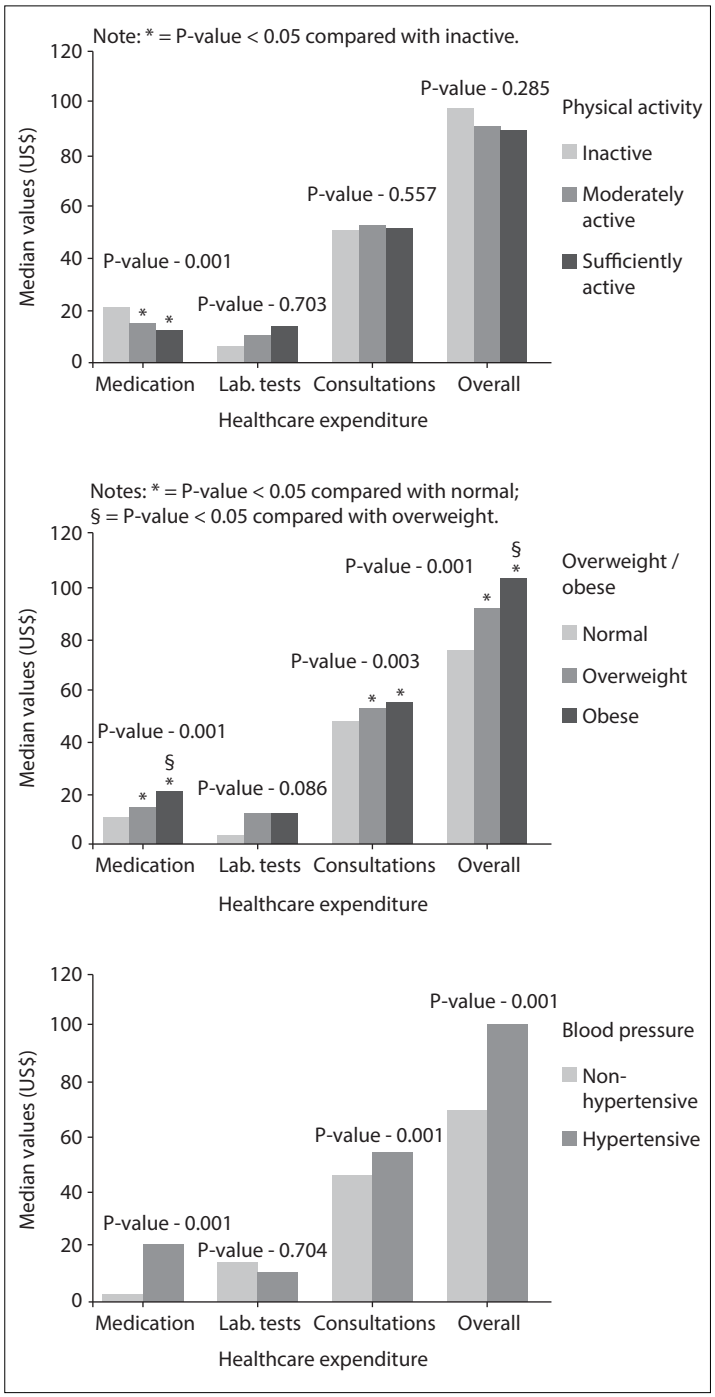

Figure 1. Healthcare expenditure according to physical activity, obesity and blood pressure among adults in Bauru (SP), Brazil (2010).

DISCUSSION

This study involved outpatients attended through the Brazilian National Health System in a medium-sized Brazilian city and investigated the correlates of public expenditure on healthcare services, specifically regarding consultations, laboratory tests and medications. Higher healthcare expenditure was associated with hypertension, overweight, sex and physical inactivity.

The presence of hypertension was associated with higher healthcare expenditure in three different categories (total expenditure, medication dispensed and consultations), thus denoting that this disease gave rise to a significant burden in relation to economic outcomes. This finding corroborates previous evidence that showed that cardiovascular diseases present high economic burdens in developing nations[1]. This result can at least partly be explained by the fact that management of hypertension is expensive, involving regular consultations and laboratory tests, as well as use of antihypertensive drugs.[20]

Additionally, overweight showed an association with increased healthcare expenditure relating to medication dispensed. Higher expenditure on medication among obese subjects might result from the link between obesity and a wide variety of cardiovascular and metabolic diseases.[21] For the period 2008-2010, it has been estimated that the Brazilian Government's expenditure on diseases relating to overweight/obesity was US$ 2.1 billion per year, of which US$ 1.4 billion was due to hospitalizations.[2] In fact, overweight and obesity accounted for 6.8% and 9.3% of all hospitalizations among Brazilian men and women, respectively.[22] Brazilian expenditure on bariatric surgery also increased from US$ 9.4 million in 2008 to US$ 17.4 million in 2011.[23] A similar pattern has been observed in developed nations.[24,25] Our findings also point out that primary care services have strategic relevance regarding preventive actions aimed towards controlling obesity and its future complications.

Physical inactivity is a major public health problem of the 21st century.[26] It is noteworthy that physical activity has a role in reducing the prevalence of obesity and related diseases, such as hypertension.[27-29] Physical inactivity and abdominal obesity can act synergistically towards increasing public healthcare expenditure.[6] Although physical inactivity was found in our study to be associated only with healthcare expenditure relating to medication dispensed, it should be emphasized that 1-4% of the total direct cost of healthcare is attributable to diseases relating to physical inactivity.[6,30] Moreover, considering the role of regular physical activity on blood pressure and weight control, implementation of programs that promote physical activity in the context of the Brazilian National Health System can contribute significantly towards reducing costs.[5,31,32]

The higher expenditure relating to medical consultation that was observed among women is a pattern that has been found worldwide. Especially after the menopause, women use healthcare services more than men do.[13,33,34] Regarding the healthcare services used by women, preventive care and therapeutic treatment are the ones most commonly used,[34] and these services were available in the facilities analyzed in the present survey.

A number of limitations of this study need to be recognized. The cross-sectional design does not support statements of causality between health expenditure and its correlates. Moreover, only direct health care costs were taken into account in this study, while other sources of indirect costs were not considered (e.g. maintenance of the facilities and the size of healthcare professionals' paychecks). It is important to recognize that we only included the biggest healthcare units in a single medium-sized city in Brazil. Thus, our results may not reflect other scenarios and should be extended to other settings only with caution. Other limitations to be considered are that the medical records were usually of poor quality; there was no information about medications obtained from other healthcare units or bought through government subsidy; and no measurements were made regarding adherence to treatments. Although the medical records constitute an important source of information regarding direct costs within primary healthcare, the bias caused through handwritten prescriptions issued by healthcare professionals and whether patients are using their medications correctly need to be considered. Additionally, selection of individuals who had had medical consultations during the previous six months may have biased the results from this study, since not all contacts with the healthcare unit are for medical consultations, and some patients may have less frequent visits. Physical activity was assessed through questionnaires, while other methods might have better accuracy (e.g. accelerometers and pedometers). Lastly, we did not have any information about alcohol consumption, which might have been an important risk factor for consideration as a potential confounder.

CONCLUSIONS

Our findings showed that overweight, physical inactivity and arterial hypertension constituted independent risk factors associated with higher healthcare expenditure in relation to medication use, while arterial hypertension affected not only the overall expenditure, but also the expenditure attributed to medical consultations. Finally, sex seemed to be an important correlate of healthcare expenditure relating to medical consultations.

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Mortality due to noncommunicable diseases in Brazil, 1990 to 2015, according to estimates from the Global Burden of Disease study

Mortalidade por doenças não transmissíveis no Brasil, 1990 a 2015, segundo estimativas do estudo de Carga Global de Doenças

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PALAVRAS-CHAVE:
Doença crônica.
Neoplasias.
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Doenças respiratórias.
Carga global de doenças.

ABSTRACT

CONTEXT AND OBJECTIVE: Noncommunicable diseases (NCDs) are the leading health problem globally and generate high numbers of premature deaths and loss of quality of life. The aim here was to describe the major groups of causes of death due to NCDs and the ranking of the leading causes of premature death between 1990 and 2015, according to the Global Burden of Disease (GBD) 2015 study estimates for Brazil.

DESIGN AND SETTING: Cross-sectional study covering Brazil and its 27 federal states.

METHODS: This was a descriptive study on rates of mortality due to NCDs, with corrections for garbage codes and underreporting of deaths.

RESULTS: This study shows the epidemiological transition in Brazil between 1990 and 2015, with increasing proportional mortality due to NCDs, followed by violence, and decreasing mortality due to communicable, maternal and neonatal causes within the global burden of diseases. NCDs had the highest mortality rates over the whole period, but with reductions in cardiovascular diseases, chronic respiratory diseases and cancer. Diabetes increased over this period. NCDs were the leading causes of premature death (30 to 69 years): ischemic heart diseases and cerebrovascular diseases, followed by interpersonal violence, traffic injuries and HIV/AIDS.

CONCLUSION: The decline in mortality due to NCDs confirms that improvements in disease control have been achieved in Brazil. Nonetheless, the high mortality due to violence is a warning sign. Through maintaining the current decline in NCDs, Brazil should meet the target of 25% reduction proposed by the World Health Organization by 2025.

RESUMO

CONTEXTO E OBJETIVO: As doenças crônicas não transmissíveis (DCNT) são o principal problema de saúde global e geram um elevado número de mortes prematuras e perda de qualidade de vida. O objetivo foi descrever os principais grupos de causas de morte por DCNT e o *ranking* das causas de morte prematura entre 1990 a 2015, segundo estimativas do estudo Global Burden of Disease (GBD) 2015 para o Brasil.

TIPO DE ESTUDO E LOCAL: Estudo transversal do Brasil e 27 Unidades Federadas.

MÉTODOS: Estudo descritivo das taxas de mortalidade por DCNT, com correções para sub-registro e códigos *garbage*.

RESULTADOS: O estudo aponta a transição epidemiológica no Brasil entre 1990 e 2015, com o crescimento da mortalidade proporcional por DCNT, seguida das violências, e com a redução das causas maternas, infecciosas e infantis na carga global de doenças. As DCNT cursaram com as taxas de mortalidade mais elevadas em todo o período, mas com declínio para as doenças cardiovasculares, respiratórias crônicas e câncer. O diabetes aumentou no período. As DCNT lideram entre as causas de morte prematura (30 a 69 anos): doenças isquêmicas do coração e doenças cerebrovasculares, seguidas de violência interpessoal, lesão no trânsito e HIV/aids.

CONCLUSÕES: A queda da mortalidade por DCNT confirma melhora do controle de doenças no país. Entretanto, a alta mortalidade por violência é um sinal de alerta. Mantendo-se a queda atual das DCNT, o Brasil deverá atingir as metas de redução propostas pela Organização Mundial de Saúde de 25% até 2025.

INTRODUCTION

Noncommunicable diseases (NCDs) are the leading health problem globally and generate high numbers of premature deaths and loss of quality of life, thus imposing a high degree of limitation and disability, as well as economic impacts for families and society in general.[1] The World Health Organization (WHO) has estimated that NCDs account for about 70% of all global deaths, i.e. about 38 million deaths annually. Among these deaths, 16 million occur prematurely (under 70 years of age) and almost 28 million are in low and middle-income countries.[2] The NCD burden encompasses individuals in all socioeconomic strata and, more intensely, those belonging to vulnerable groups, such as the elderly and those with low levels of education and income.[3]

In Brazil, NCDs also constitute a major health problem and, according to data from the national mortality information system, they corresponded to 72.6% of the causes of death in 2011. Cardiovascular diseases ranked first among the causes of death, followed by neoplasms, chronic respiratory diseases and diabetes.[4,5]

There is strong evidence correlating social determinants such as education, occupation, income, gender and ethnicity with the prevalence of NCDs and risk factors such as tobacco use, harmful alcohol use, physical inactivity and unhealthy diet.[1] If not properly prevented and managed, these diseases will require medical care with increasing costs due to incorporation of technology, in addition to causing loss of quality of life and premature deaths and having a great impact on the economy, thereby affecting countries' growth and having the capacity to reduce gross domestic product (GDP) by up to 2% a year.[2]

In 2011, the United Nations (UN) recognized the magnitude of NCDs worldwide and established commitments to address this problem (United Nations, 2011) and, in 2013, WHO approved a global action plan for prevention and control of these diseases.[6] This global plan defined a priority goal consisting of a 25% relative reduction in premature mortality due to NCDs (cardiovascular diseases, cancer, diabetes or acute respiratory diseases) among people between ages of 30 and 70 years by 2025.[6] This overarching goal is consonant with the national target defined by the National Plan to Combat Noncommunicable Diseases 2011-2022.[7]

In 2015, the UN Assembly adopted a set of 17 goals as part of a sustainable development agenda, including the goal of "ensuring healthy lives and promoting well-being for all at all ages". One of the targets was to "reduce by one third premature mortality due to non-communicable diseases through prevention and treatment and to promote mental health and wellbeing by 2030", which continued the commitment already made by the World Health Assembly to achieve this by 2025.[8]

It has therefore become a global priority to monitor trends in mortality due to NCDs in order to ascertain whether national and global commitments will be achieved. Since 1990, the concept of the Global Burden of Disease (GBD) has grown in importance for monitoring the burden of disease in various countries. By 2015 all databases had been updated, thus making it possible to analyze information from 1990 to 2015 for most of the world's countries, including Brazil and its 27 federal units (i.e. states), regarding premature death and disability due to more than 290 diseases, injuries and sequelae, along with the attributable burden due to risk factors, for 20 age groups and both sexes.[9]

The methodology used for the GBD consists of major advances and a shift in paradigm in epidemiological analysis on databases. An integrated approach towards diseases and deaths is proposed, with standard methodology for analysis and correction of underrreporting of deaths and garbage code. In this manner, it becomes possible to compare countries, regions and subnational data.[5,9] The GBD study method enables users to assess burden trends, since time series data are adjusted and comparable.[5,9]

Thus, use of GBD estimates provides a great opportunity to move forward in assessing mortality due to NCDs, thereby supporting monitoring efforts and achievement of future global and national NCD reduction targets.[6]

OBJECTIVE

The objective of this study was to describe the major groups of causes of death due to noncommunicable diseases (NCDs) and the ranking of the leading causes of premature death between 1990 and 2015, according to the GBD 2015 study estimates for Brazil.

METHODS

This was a cross-sectional study based on data from the GBD 2015 study and also on the methods that it used, which have already been described in detail in another article.[9]

The GBD 2015 study used data on causes of death available from 195 countries, including Brazil and its 27 states. Information on causes of death was gathered from vital registration systems, mortality surveillance systems, surveys, hospital records, police records and verbal autopsies. The GBD uses methodologies for correcting underreporting of deaths and garbage code. Correction of the codes uses evidence from the medical literature, expert opinions and statistical techniques to designate each item to the most probable causes of death.[9] In Brazil and its 27 federal states, the source of mortality data is the Mortality Information System (Sistema de Informação Sobre Mortalidade, SIM).[5]

After addressing data quality issues, the GBD 2015 study used a variety of statistical models to determine the number of deaths from each cause, through the cause of death ensemble model (CODEm) algorithm. To ensure that the number of deaths per cause did not exceed the total number of estimated deaths, a correction technique called CoCorrect was used. This technique makes certain

that estimates of the number of deaths from each cause do not add up to more than 100% of deaths in a given year.[9-11]

After producing estimates for the number of deaths from each of the 249 fatal outcomes included in the list of causes of the GBD 2015 study, the years of life lost (YLLs) due to premature death were calculated. For every death due to a particular cause, the number of years lost was estimated based on the highest life expectancy in the deceased individual's age group.[9,11]

The GBD study used a cause list that placed 249 causes of death within a four-level hierarchy. The first level divided causes into three groups: communicable, maternal, neonatal and nutritional conditions; NCDs and injuries. The second level consisted of 20 major causes of diseases such as neonatal disorders, cardiovascular diseases and traffic injuries. The third level subdivided level 2 into types such as neonatal preterm birth complications, cerebrovascular disease and traffic injuries; and the fourth level further subdivided those types in some cases, for example: ischemic stroke and hemorrhagic stroke; and pedestrian road injuries, cyclist road injuries, motorcyclist road injuries, motor vehicle road injuries and other road injuries.[9]

In the present study, the following NCDs were selected: cardiovascular diseases (I00-I99), respiratory diseases (J30-J98), neoplasms (C00-C97) and diabetes mellitus (E10-E14). The study used the concept of premature mortality, as previously used by WHO and the UN, respectively in the Global Plan for NCDs (2013) and in the Sustainable Development Goals (SDG) for NCDs (2015), which take premature deaths to be those occurring before the age of 70 years. The 20 leading causes of death were analyzed using the level 3 aggregation of causes of death from the GBD 2016 study, in the age group from 30 to 69 years. The results were compared between the years 1990, 2005 and 2015.

There was no need to submit this study to a research ethics committee, since it was conducted on a public-domain secondary database, without nominal identification, in accordance with Decree No. 7,724 of May 16, 2012, and Resolution No. 510 of April 7, 2016.

RESULTS

Figure 1 shows the relative distribution of deaths according to the three major groups of causes of death in Brazil for both sexes and the whole population. In 1990, proportional mortality due to NCDs corresponded to 59.6% of deaths (95% uncertainty interval, UI: 58.97-60.7); injuries, 14.8% (95% UI: 14.5-15.12); and communicable, maternal, neonatal and nutritional diseases, 25.6% (95% UI: 24.49-26.29). In 2015, proportional mortality due to NCDs had increased to 75.8% (95% UI: 75.05-77.30); injury deaths had decreased to 12.4% (95% UI: 11.97-12.79); and communicable, maternal, neonatal and nutrition diseases had reduced to 11.8% (95% UI: 10.3 to 12.5).

Considering the total numbers of deaths for all ages, there was an increase of 49% in the absolute number over the period, while deaths due to NCDs increased by 89.7% and corresponded to 1.029 million deaths in 2015. As this is proportional mortality, this increase also reflects population growth and changes in age structure.

The age-standardized death rates for all NCDs for the total population displayed a reduction from 818.6/100,000 (1990) (95% UI: 803.9-834.7) to 611.3/100,000 (2015) (95% UI: 589.8-633.9), representing a reduction of 25.3% between 1990 and 2015 (**Table 1**).

Regarding the four groups of NCDs prioritized in the Brazilian and global NCD plans, cardiovascular diseases accounted for 424,058 deaths in 2015, with a rate reduction of 40.5% from 429.5/100,000 inhabitants (1990) (95% UI: 421.1-438.1) to 256/100,000 (2015) (95% UI: 246.3-268.3).

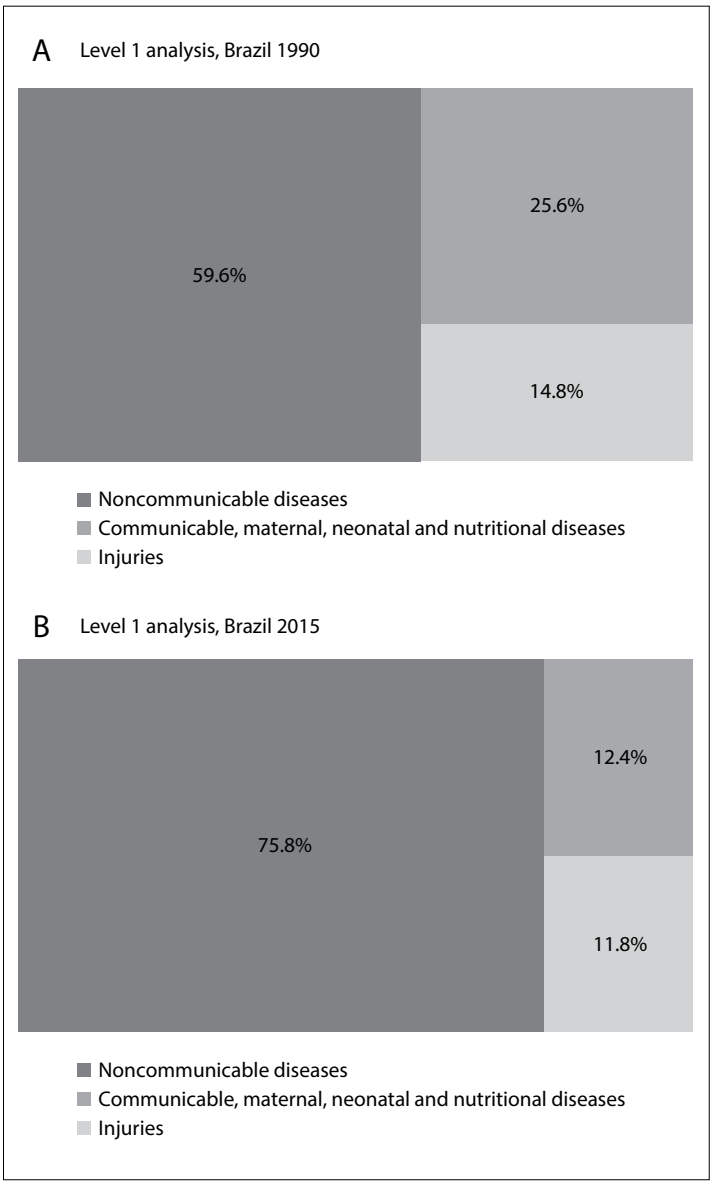

Figure 1. Proportions of numbers of deaths according to causes of death.

Neoplasms accounted for 236,345 deaths in 2015, and the rates went from 142.7/100,000 inhabitants (1990) (95% UI: 139.2-149.1) to 133.5/100,000 (2015) (95% UI: 127.9-140.4), i.e. they remained stable over the period. Chronic respiratory diseases accounted for 79,651 deaths in 2015, with a rate reduction of 28.9% from 69.9/100,000 inhabitants (1990) (95% UI: 67.8-71.9) to 49.7/100,000 (2015) (95% UI: 47.3-52.3). Diabetes mellitus accounted for 62,466 deaths in 2015, and the rates went from 35.9/100,000 inhabitants (1990) (UI: 34.8-37) to 37.5/100,000 (2015) (UI: 35.6-39.3), i.e. they remained stable over the period (**Table 1**).

At state level, cardiovascular diseases predominated in all 27 federal states and there were reductions in rates between 1990 and 2015, ranging from 16.4% in Tocantins to 47.9% in Rio de Janeiro. The highest rate in 2015 was 353.2/100,000 inhabitants in Maranhão. Chronic respiratory diseases declined in most states, with the largest reduction in Minas Gerais (41.2%). The highest rate in 2015 was recorded in Acre: 77.5/100,000 inhabitants. In contrast, diabetes mellitus increased in most states, with Piauí showing the highest change (84.9%). Some states presented reductions in rates, and the most significant reductions were in São Paulo (28.5%) and in the Federal District (27.1%). The highest diabetes rate in 2015 was in Maranhão: 69.6/100,000 inhabitants. The level of neoplasms remained stable in most states and the highest rate in 2015 was in Amazonas: 155.1/100,000 inhabitants. There were reductions in total NCDs in most states between 1990 and 2015. The highest rate was in Paraíba: 697.3 per 100,000 inhabitants (**Table 2**).

In the ranking of the 20 leading causes of premature death according to age-standardized rates (at 30 to 69 years of age) for the years 1990 and 2015, NCDs comprised 15 of them in 2015. At the third level of analysis according to the GBD approach, ischemic heart diseases led throughout the period from 1990 to 2015, with a 43.9% reduction in rates over this period. Cerebrovascular diseases were in second place in the ranking and reduced by 54.2% over the period. Road injury was in third place both in 1990 and in 2015, and interpersonal violence rose from fifth to fourth place over the same period. Diabetes went from sixth to fifth place in the ranking of causes of premature death in 2015, and was followed by chronic obstructive lung diseases (COPD), which fell from fourth to sixth place over the same period. Lower respiratory infections remained in seventh place and lung cancer remained in eighth place over the period. HIV/AIDS increased from 24th place in 1990 to ninth in 2015. Also in 2015, chronic kidney disease was in 10th place, cirrhosis and other chronic liver diseases in 11th, breast cancer in 12th, stomach cancer in 13th, colorectal cancer in 14th (showing growth of 20% in its rate), cardiomyopathy 15th, self-harm in 16th, hypertensive heart disease in 17th, alcohol use disorder in 18th, other cardiovascular disease in 19th, esophageal cancer in 20th and cervical cancer in 21st position. Also noteworthy were the considerable reductions in tuberculosis from 17th position in 1990 to 34th in 2015 and Chagas disease from 15th to 36th (**Figure 2**).

DISCUSSION

It is evident that NCDs were addressed as a problem of health surveillance in Brazil between 1990 and 2015. Based on the results from this study, the burden of noncommunicable diseases has continuously gained in importance, followed by violence, while the biggest improvements came from the sharp reductions in the burden of communicable, maternal, neonatal and nutritional diseases. Age-standardized mortality rates for NCDs presented higher rates throughout the period but with declining trends for cardiovascular diseases and chronic respiratory diseases, while cancer and diabetes showed stable rates between 1990 and 2015 in Brazil.

Regarding premature mortality (at 30 to 69 years of age), NCDs accounted for 15 of the top 20 leading causes. Ischemic

Table 1. Age-standardized mortality rates for all causes of death and noncommunicable diseases (NCDs) and percentage changes, for both sexes and all ages; Brazil, from 1990 to 2015

Causes of death	Number of deaths			Age-standardized death rates (per 100,000)		
	1990	2015	% change 1990-2015	1990	2015	% change 1990-2015
All causes	911,317 (896,944-925,847)	1,357,434 (1,312,612-1,400,906)	49.0	1,102.2 (1085.9-1118.6)	786.2 (761.2-810.3)	-28.7
B - Noncommunicable diseases	542,832 (532,149-554,906)	1,029,499 (992,362-1,068,244)	89.7	818.6 (803.9-834.7)	611.3 (589.8-633.9)	-25.3
B.1 - Neoplasms	105,275 (102,761-109,195)	236,345 (226,265-248,290)	124.5	142.7 (139.2-149.1)	133.5 (127.9-140.4)	-6.5
B.2 - Cardiovascular diseases	267,634 (262,150-273,226)	424,058 (407,250-444,686)	58.4	429.5 (421.1-438.1)	256 (246.3-268.3)	-40.4
B.3 - Chronic respiratory diseases	41,272 (40,138-42,445)	79,651 (76,015-83,698)	93.0	69.9 (67.8-71.9)	49.7 (47.3-52.3)	-28.9
B.8.1 - Diabetes mellitus	23,802 (23,109-24,527)	62,466 (59,420-65,474)	162.4	35.9 (34.8-37)	37.5 (35.6-39.3)	4.4

heart diseases presented the highest burden, followed by cerebrovascular diseases, which occupied the second place in the ranking. Road injuries were in third place, followed by interpersonal violence, while HIV/AIDS appeared in ninth position.

The data shown here demonstrate the rapid epidemiological transition that Brazil has been undergoing, which has resulted in a high burden of noncommunicable disease.[12] These changes stem from the underlying demographic transition, with significant decreases in fertility and birth rates, increased life expectancy, an increased proportion of elderly people, rapid urbanization, economic and social growth and unhealthy lifestyles.[7,12]

Noncommunicable diseases are one of the major public health problems because of their contribution towards high numbers of premature deaths and loss of quality of life. They lead to high degrees of limitations and incapacity to conduct activities of daily living, and also have an economic impact on families, communities and society.[3,7,12,13]

The burden of disease in Brazil shows the presence of increasingly pressing problems such as road injuries and interpersonal violence, which are the third and fourth leading causes of premature death.[14,15] Another finding is the dramatic success in reducing the burden of communicable, maternal, neonatal and nutritional diseases. This reduction has been particularly significant in relation to the rapid nutritional transition, which has almost eliminated malnutrition in less than 30 years. However, this transition has also led to a situation in which more than half of the population is overweight and one fifth is obese, consequent to changes in dietary patterns and the sedentary nature of modern life.[12,16,17]

Table 2. Age-standardized mortality rates for noncommunicable diseases (NCDs) and percentage change according to Brazilian states, for both sexes and all ages, Brazil, from 1990 to 2015

Region/states	Cardiovascular diseases			Chronic respiratory diseases			Diabetes mellitus			Neoplasms			Noncommunicable diseases		
	1990	2015	% Change	1990	2015	% Change	1990	2015	% Change	1990	2015	% Change	1990	2015	% Change
Brazil	**429.5**	**256.0**	**-40.4**	**69.9**	**49.7**	**-28.9**	**35.9**	**37.5**	**4.4**	**142.7**	**133.5**	**-6.5**	**818.6**	**611.3**	**-25.3**
North															
Acre	363.0	252.2	-30.5	79.8	77.5	-2.9	29.2	42.6	45.6	121.0	126.3	4.4	740.6	649.7	-12.3
Amapá	313.0	256.3	-18.1	54.5	52.2	-4.2	27.2	39.0	43.6	134.2	144.3	7.5	656.7	636.0	-3.2
Amazonas	363.4	236.9	-34.8	59.2	50.6	-14.5	34.2	43.7	28.0	154.1	155.1	0.7	749.1	629.9	-15.9
Pará	388.8	275.4	-29.2	61.0	56.1	-8.0	26.4	47.0	77.8	123.2	122.2	-0.8	733.0	632.9	-13.7
Rondônia	463.5	269.6	-41.8	83.3	61.6	-26.0	34.7	44.9	29.2	143.0	121.8	-14.8	869.0	630.0	-27.5
Roraima	373.1	234.9	-37.0	56.5	40.3	-28.7	46.6	52.7	13.1	139.3	129.1	-7.4	766.0	600.4	-21.6
Tocantins	389.6	325.8	-16.4	69.3	50.2	-27.6	31.2	49.4	58.2	106.2	119.0	12.1	727.6	685.7	-5.8
Northeast															
Alagoas	459.1	312.4	-32.0	64.5	50.5	-21.8	50.3	68.1	35.3	104.8	103.0	-1.7	836.5	676.4	-19.1
Bahia	394.0	280.9	-28.7	61.6	53.8	-12.7	44.2	55.7	26.0	114.1	127.0	11.3	750.2	662.0	-11.8
Ceará	355.4	286.4	-19.4	51.5	44.0	-14.6	24.0	43.2	80.3	116.1	144.2	24.2	663.5	655.1	-1.3
Maranhão	497.0	353.2	-28.9	59.3	41.5	-30.0	49.6	69.5	40.0	129.3	119.2	-7.8	904.2	729.8	-19.3
Paraíba	386.0	318.0	-17.6	53.6	48.8	-8.9	40.9	64.3	57.3	99.2	124.9	25.9	708.7	697.3	-1.6
Pernambuco	426.1	291.4	-31.6	62.6	63.7	1.7	43.7	57.2	31.0	114.3	122.5	7.1	806.1	676.8	-16.0
Piauí	391.0	320.0	-18.2	53.9	37.3	-30.9	28.6	52.8	84.9	102.1	111.3	8.9	699.9	652.1	-6.8
Rio Grande do Norte	319.4	245.5	-23.1	34.8	32.5	-6.6	38.2	56.0	46.8	109.9	125.6	14.3	620.8	590.1	-4.9
Sergipe	368.2	267.5	-27.4	55.5	43.6	-21.4	50.3	64.6	28.2	112.3	119.2	6.2	728.3	643.9	-11.6
Southeast															
Espírito Santo	443.3	254.9	-42.5	64.2	41.8	-34.9	28.7	33.0	15.2	141.8	128.2	-9.6	809.5	588.8	-27.3
Minas Gerais	436.8	240.9	-44.8	86.1	50.7	-41.2	32.9	29.2	-11.2	142.1	130.0	-8.5	845.1	587.7	-30.5
Rio de Janeiro	491.0	255.9	-47.9	72.0	44.7	-37.9	48.1	40.4	-16.0	156.9	135.3	-13.7	911.6	615.2	-32.5
São Paulo	427.5	229.9	-46.2	62.0	41.8	-32.7	34.1	24.4	-28.5	156.7	132.7	-15.3	825.5	559.2	-32.3
South															
Paraná	486.3	261.8	-46.2	87.7	62.6	-28.6	28.7	37.4	30.3	160.2	147.1	-8.2	898.1	641.4	-28.6
Rio Grande do Sul	435.7	238.9	-45.2	93.5	61.0	-34.8	26.3	28.6	8.6	187.3	160.0	-14.6	873.3	611.6	-30.0
Santa Catarina	445.1	234.3	-47.4	98.9	58.2	-41.1	31.3	31.6	1.1	164.3	144.6	-12.0	872.7	590.2	-32.4
Center-West															
Federal District	350.0	187.0	-46.6	53.0	33.4	-37.1	33.4	24.4	-27.1	142.6	117.9	-17.3	708.1	476.6	-32.7
Goiás	412.6	259.8	-37.0	103.2	68.7	-33.5	25.9	30.7	18.8	136.4	125.2	-8.3	818.0	620.8	-24.1
Mato Grosso	427.1	274.3	-35.8	71.3	60.9	-14.5	29.3	42.2	44.3	135.7	132.3	-2.6	800.7	648.3	-19.0
Mato Grosso do Sul	431.2	278.3	-35.5	66.0	50.9	-22.8	25.5	31.8	24.5	135.5	131.6	-2.9	790.3	629.4	-20.4

The burden of NCDs encompasses individuals in all socioeconomic strata and, more intensely, vulnerable groups such as the elderly and those with low levels of education and income.[1,3] Thus, over the last few decades, Brazil has gone from the typical mortality profile of a young population to a picture of more complex and costly diseases that are typical of the more advanced age groups.[12]

NCDs constitute the largest health problem in Brazil.[7,12] Estimates for this country have indicated that the losses of labor productivity and decreases in family income resulting from just three NCDs combined (diabetes, heart disease and stroke) contributed a loss of US$ 4.18 billion to the economy between 2006 and 2015.[3] The direct costs correspond to the expenses involved in medical assistance, medicines, hospitalizations, examinations, procedures, physiotherapy and rehabilitation. The indirect costs are linked to losses in production and income, productivity, jobs and absenteeism. The intangible costs are difficult to estimate and refer to family income, informal care and other matters.[18]

This increase in the burden of NCDs is directly linked to some negative effects from the globalization process, rapid urbanization, sedentary life and high-calorie diets, along with tobacco and alcohol consumption.[1,7,13,19,20] These behavioral risk factors have an impact on the major metabolic risk factors, such as overweight/obesity, high blood pressure and increased blood glucose, lipid and cholesterol levels, and these may result in diabetes, cardiovascular disease, stroke and cancer, among other diseases.[1,12,19,20]

Also in Brazil, NCDs predominate as the main cause of mortality, especially cardiovascular diseases. However, the incidence of cardiovascular diseases and consequent mortality have been declining over the last few decades.[12] Cardiovascular diseases result from metabolic risk factors, such as high blood pressure, inadequate diet, smoking, physical inactivity and other risk factors.[1,20] Analysis on mortality trends in Brazil between 2000 and 2011 has shown that, despite an increase in the overall number of deaths due to cardiovascular diseases, the age-adjusted mortality rates for these diseases declined by 24%.[20] Healthcare delivered

	1990	Age standardized*		2015	Age standardized*	% change 1990-2005
1	Ischemic heart disease	156.7	1	Ischemic heart disease	87.9	-43.9
2	Cerebrovascular disease	120.7	2	Cerebrovascular disease	55.3	-54.2
3	Road injuries	44.5	3	Road injuries	30.5	-31.6
4	Chronic obstructive pulmonary disease	37.5	4	Interpersonal violence	29.9	-12.4
5	Interpersonal violence	34.1	5	Diabetes mellitus	27.9	-12.9
6	Diabetes mellitus	32.1	6	Chronic obstructive pulmonary disease	22.2	-40.6
7	Lower respiratory infections	27.3	7	Lower respiratory infections	21.7	-20.6
8	Tracheal, bronchial and lung cancer	22.7	8	Tracheal, bronchial and lung cancer	19.9	-12.4
9	Stomach cancer	20.3	9	HIV/AIDS	18.2	137.1
10	Cirrhosis and other chronic liver diseases due to alcohol use	19.4	10	Chronic kidney disease	17.3	-9.1
11	Chronic kidney disease	19.1	11	Cirrhosis and other chronic liver diseases due to alcohol use	15.7	-18.9
12	Hypertensive heart disease	13.8	12	Breast cancer	12.7	-3.0
13	Breast cancer	13.1	13	Stomach cancer	12.1	-40.0
14	Cardiomyopathy and myocarditis	12.4	14	Colon and rectum cancer	11.6	20.2
15	Chagas disease	12.1	15	Cardiomyopathy and myocarditis	9.3	-25.0
16	Cervical cancer	11.4	16	Self-harm	9.1	-18.8
17	Tuberculosis	11.4	17	Hypertensive heart disease	8.7	-37.1
18	Self-harm	11.3	18	Alcohol use disorders	8.0	4.4
19	Other cardiovascular and circulatory diseases	9.7	19	Other cardiovascular and circulatory diseases	7.7	-20.5
20	Colon and rectum cancer	9.6	20	Esophageal cancer	7.6	-17.4
21	Esophageal cancer	9.1	21	Cervical cancer	7.3	-36.1
24	HIV/AIDS	7.7	34	Tuberculosis	4.0	-64.7
25	Alcohol use disorders	7.7	36	Chagas disease	3.6	-70.6

*Age-standardized mortality rate in relation to world population, aged 30 to 69 years.

Figure 2. Leading 20 causes of death: age-standardized mortality rate (30 to 69 years of age), rank and percentage change, for both sexes; Brazil, from 1990 to 2015.

by Brazil's universal public healthcare system, which focuses on primary prevention, has contributed towards this achievement.[20]

Reductions in heart disease mortality rates have varied according to socioeconomic status. A trend analysis on all heart diseases in the city of São Paulo from 1996 to 2010 showed that the decline in the risk of death presented a variable gradient: faster for people living in the wealthiest area and slower for people living in the more deprived neighborhoods.[21] Stroke mortality trends in Brazil (1979-2009) have shown declines for all stroke subtypes.[22] The risk of death due to stroke is decreasing in all regions, but the fastest decline in mortality rates is in the wealthiest area, thus contributing to a situation of increasing inequality.[23]

Cancer is already the second highest leading cause of death in most countries and it has been predicted that it will reach first place over the coming years.[1] In Brazil, over the years studied here, there was stability in the overall rate, but studies have shown distinct trends according to cancer type, age, social status and sex.[15,24-26] Among men, there has been an increase in mortality due to prostate and colorectal cancer, and a reduction in lung cancer. Among women, breast, lung and colorectal cancer mortality rates have increased, while cervical and stomach cancer rates have declined.[12,27]

The incidence of diabetes is growing and it is already among the top ten causes of death worldwide, besides being an important cause of death due to cardiovascular disease. The increase in the death rate due to diabetes has been driven through the growth of the elderly population, the obesity epidemic and unhealthy lifestyles.[28,29] The current study showed that the rate for Brazil was stable between 1990 and 2015, although it increased in several states.

Chronic obstructive pulmonary disease (COPD) is the third highest leading cause of death among adults in Brazil. Previous studies in Brazil have shown reductions of mortality due to chronic respiratory diseases,[12,30] and these have been attributed to advances in access to primary healthcare and access to medications and reduction of smoking.[12]

The national plan to combat NCDs in Brazil,[19,31] WHO's Global Plan and Sustainable Development Goals have established the target of reducing premature mortality rates or mortality among adults under 70 years of age caused by NCDs.[6] The evidence from studies shows that Brazil is on track to meet the goal, since the burden arises from diseases that are sensitive to health promotion interventions and care provision.[12,17] This positive finding is directly related to implementation of highly cost-effective interventions through the National Health System (Sistema Único de Saúde, SUS), such as expansion of primary care and wide distribution of drugs to the population that is at high risk of developing cardiovascular diseases, as well as measures established to control tobacco use.[12,17,20]

This study also draws attention to the importance of external causes of death and the magnitude of such occurrences, caused by interpersonal violence and traffic accidents. These events are particularly frequent among young people and contribute towards premature mortality during the productive phase.[14] Also noteworthy are premature deaths due to HIV, and the rise of HIV in the ranking of causes of premature mortality over the last few decades.

It is important to emphasize the need to ensure quality in mortality estimates in Brazil. Problems regarding the quality of information about deaths have arisen in the past. Thus, analysis based on the GBD study is of great use, particularly for mortality assessment, since it uses methods for correction of underreporting of deaths and for redistribution of garbage codes (deaths attributed to causes that may not be the real causes of death or are not properly described). However, any process of data correction needs to be regarded with caution, since assumptions made in using these methods may lead to overestimation or underestimation of the degree of coverage, thereby generating bias in the estimates of mortality coverage.[32,33]There is still a long way to go to reduce these causes of death and illness. The diseases described here have a long course and require a comprehensive longitudinal approach, with dedicated investment in self-care and bonding.[34] It is therefore essential to reduce inequities within healthcare, so as to ensure access to care for the entire population, especially the most vulnerable groups, given the higher concentration of NCDs and their risk factors in the low-income and low-education population.[1,3]

SUS and universal access to healthcare in Brazil act in a protective manner, especially with regard to care for the great majority of the population. It is important to highlight the role of SUS in achieving the results regarding reduction in mortality due to NCDs that are presented here.[12,17,20]

CONCLUSION

This study shows the epidemiological transition in Brazil between 1990 and 2015, with increasing proportional mortality due to NCDs, followed by violence, and decreasing mortality due to communicable, maternal and neonatal causes within the global burden of diseases. NCDs had the highest mortality rates over the whole period, but with reductions in cardiovascular diseases, chronic respiratory diseases and cancer. Diabetes increased over this period. NCDs were the leading causes of premature deaths (30 to 69 years of age).

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Characterization of the first symptoms of multiple sclerosis in a Brazilian center: cross-sectional study

Caracterização dos primeiros sintomas de esclerose múltipla em um centro brasileiro: estudo transversal

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KEY WORDS:
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Cranial nerves.

PALAVRAS-CHAVE:
Esclerose múltipla.
Centros médicos acadêmicos.
Avaliação de sintomas.
Comportamento de doença.
Nervos cranianos.

ABSTRACT

CONTEXT AND OBJECTIVE: Multiple sclerosis (MS) is a chronic, immune-mediated and degenerative central nervous system (CNS) disease with well-established diagnostic criteria. Treatment can modify the course of the disease. The objective of this study was to describe the initial symptoms of multiple sclerosis in a Brazilian medical center.

DESIGN AND SETTING: Descriptive study, conducted in a Brazilian reference center for multiple sclerosis treatment.

METHODS: Data on 299 patients with confirmed diagnoses of MS were included in the study. Their medical files were evaluated and the data were analyzed.

RESULTS: The most common symptom involved the cranial nerves (50.83%) and unifocal manifestation was presented by the majority of this population (73.91%). The mean time between the first symptom and the diagnosis was 2.84 years. Unifocal symptoms correlated with longer time taken to establish the diagnosis, with an average of 3.20 years, while for multifocal symptoms the average time taken for the diagnosis was 1.85 years. Unifocal onset was related to greater diagnostic difficulty.

CONCLUSIONS: MS is a heterogeneous disease and its initial clinical manifestation is very variable.

RESUMO

CONTEXTO E OBJETIVO: A esclerose múltipla (EM) é uma doença crônica do sistema nervoso central (SNC) imunomediada e degenerativa, com critérios diagnósticos bem estabelecidos. O tratamento pode modificar o curso da doença. O objetivo deste estudo foi descrever os sintomas iniciais da esclerose múltipla em um centro médico brasileiro.

TIPO DE ESTUDO E LOCAL: Estudo descritivo, conduzido em um centro médico de referência no tratamento de EM no Brasil.

MÉTODOS: Foram incluídos no estudo dados de 299 pacientes com diagnóstico confirmado de EM. Seus prontuários foram avaliados e os dados foram analisados.

RESULTADOS: O sintoma mais comum encontrado envolveu nervos cranianos (50,83%) e a manifestação unifocal foi apresentada pela maioria da população estudada (73,91%). O tempo médio entre o primeiro sintoma e o diagnóstico foi de 2,84 anos. O sintoma unifocal foi relacionado com maior tempo para o estabelecimento do diagnóstico, com uma média de 3,20 anos; enquanto para os sintomas multifocais, a média foi de 1,85 anos para o diagnóstico. O início unifocal foi relacionado a maior dificuldade de diagnóstico.

CONCLUSÕES: EM é uma doença heterogênea e sua manifestação clínica inicial é muito variável.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, immune-mediated and degenerative central nervous system (CNS) disease that leads to injury to myelin and axons and results in different neurological signs and symptoms, with dissemination over space and time.[1]

There are no biological markers for MS. Today, the diagnosis is made from clinical findings, lesions identified on magnetic resonance imaging (MRI), presence of oligoclonal bands and/or high levels of immunoglobulin G (IgG) in the cerebrospinal fluid (CSF), as described in the revised McDonald criteria in 2010.[2] The most commonly presented form of MS is relapsing and remitting. In this, neurological symptoms or lesions are followed by periods of clinical improvement or latency. On the other hand, the progressive form can present either at the beginning of the disease (primary progressive), or after years of the relapsing-remitting form (secondary progressive).[3]

Despite these known diagnostic criteria, there is difficulty in establishing the diagnosis of MS and its onset is usually neglected since these initial symptoms may resolve spontaneously. This situation leads to delayed diagnosis, which consequently delays the treatment and has a negative impact regarding the speed of progression of the disease, and its prognosis.[4] Thus, knowledge of the initial manifestations of MS has great epidemiological value, since it can contribute towards decreasing the time between MS onset and treatment, and may slow the progression of the disease.

OBJECTIVE

The aim of this study was to identify the initial symptoms of MS in a group of patients and to identify the symptoms that are related to probable diagnostic difficulty (characterized by longer time between symptoms and diagnosis).

METHODS

This study was previously approved by our institution's Ethics Committee, under protocol no. 075/12. The patients selected for the study were outpatients at Centro de Atendimento e Tratamento da Esclerose Múltipla (Catem), São Paulo, Brazil.

This was a cross-sectional study, in which patients at Catem were selected, in accordance with the inclusion and exclusion criteria specified below.

Data were collected from information contained in medical records and from magnetic resonance imaging (MRI) accessed using IMPAX (Agfa HealthCare NV, Belgium). They were analyzed descriptively using simple statistical ratios consisting of means, standard deviations and percentages.

The symptoms were grouped as follows: motor, sensory, cranial nerve, prodromal, urinary system and balance. The patients were divided between unifocal presentation, when they had one first symptom, and multifocal presentation, when they presented two or more symptoms upon enrollment.

Inclusion criteria:

- Diagnosis of MS (made between 1984 and the present day, fulfilling the diagnostic criteria that were current at the time of diagnosis);
- Presence of information in the medical records regarding: date of symptom onset, symptoms lasting for more than 24 hours and date of diagnosis;
- Initial manifestations dissociated from any other medical condition.

Exclusion criteria:

- Diagnoses of demyelinating diseases other than MS;
- Not meeting the criteria for MS.

RESULTS

Among the 563 patients, 299 met the inclusion criteria and were enrolled in this study. If the patients met the inclusion criteria, they were included as they were attended, sequentially. The population consisted of 214 women (71.57%) and 85 men (28.42%). The average age at the onset of symptoms was 26.99 years (standard deviation, SD ± 9.68), with a minimum of 7 and maximum of 58 years. The median time to diagnosis was 2.74 years and the maximum was 26 years. The minimum was a diagnosis at the time of the initial symptoms. The minimum age at diagnosis was 7 years and the maximum was 63 years.

Of these patients, 221 (73.91%) had unifocal symptoms, 77 (25.75%) had multifocal symptoms and one (0.33%) had no reported symptoms. These 299 patients reported 392 symptoms: 79 (26.42%) had motor symptoms; 96 (32.10%) had sensory symptoms; 152 (50.83%) had symptoms involving the cranial nerves; 23 (7.69%) had prodromal symptoms (like headache, fatigue, asthenia, nausea/vomiting, malaise, low back pain and depression); 40 (13.38%) had symptoms involving their balance; and 2 (0.67%) had urinary system symptoms. The symptoms and their descriptions are presented in **Table 1**.

The mean time between the first symptom and the diagnosis was 2.84 years. Unifocal onset was correlated with longer time to establish the diagnosis, with an average of 3.20 years (minimum of simultaneous diagnosis and maximum of 26 years after the initial symptom). For the patients with multifocal symptoms, the diagnosis was reached on average 1.85 years after symptom onset (minimum time coincident with the clinical manifestation and maximum time to diagnosis of 12 years).

DISCUSSION

Ashtari et al.[5] evaluated 123 MS patients with a mean age of 27.7 years (SD = 8.06) with onset after they reached 16 years of age. Among them, 29.3% initially had optic neuritis, 36.6% paresthesia, 18.7% cerebellar or brainstem symptoms, 14.6% motor symptoms and 0.8% other symptoms. Barkhof et al.[6] found, among

Table 1. Symptoms presented

Symptoms	Patients (n)	Percentage (%)
Sensory		
Hypoesthesia	33	34.375%
Paresthesia	63	65.625%
Balance		
Ataxia	30	75.000%
Coordination	3	7.500%
Vertigo	4	10.000%
Labyrinthitis	3	7.500%
Prodromal		
Headache	11	47.826%
Fatigue/asthenia	4	17.391%
Nausea/vomiting	5	21.739%
Malaise	1	4.348%
Low back pain	1	4.348%
Depression	1	4.348%
Urinary system		
Incontinence	1	50.000%
Retention	1	50.000%
Cranial nerves		
Optic neuritis	69	45.395%
Diplopia	32	21.053%
Decreased visual acuity	15	9.868%
Hypoacusis	4	2.632%
Anosmia	1	0.658%
Hypoesthesia	4	2.632%
Paresthesia	5	3.289%
Spasm	2	1.316%
Paresis	7	4.605%
Facial paralysis	5	3.289%
Dysphagia	1	0.658%
Dysarthria	7	4.605%
Motor		
Paresis	79	100.000%
Total number of symptoms	**392**	

74 MS patients, that 54% had optic neuritis at the onset, 16% cerebellum or brainstem symptoms and 30% spinal symptoms.

In another study, 97 patients with clinically isolated syndrome (CIS) were followed for two years, and 59 were found to fulfill the revised McDonald criteria for MS after 10.1 ± 4.2 months; 37 (38.1%) fulfilled the criteria through radiological parameters and 21.7% from a second clinical event. The initial manifestations of the patients who fulfilled the criteria for MS were related to the optic nerve in 11 (16.18%), cerebellum and brainstem in 15 (22.06%), spinal cord in 19 (27.94%) and supratentorial region in 18 (26.47%), and 5 (7.35%) of them showed multifocal manifestations.[7]

In a study conducted in Denmark, 7,548 patients with diagnoses of MS that were established between 1949 and 1990 were assessed regarding optic neuritis as the initial manifestation of the disease. Among the 6,923 patients whose initial manifestations were known, optic neuritis marked the onset of MS in 1,282 cases (19%). Among the patients for whom optic neuritis was not present at the onset of MS, the mean ages at the time of manifestation and diagnosis were 6.1 years and 4.2 years.[8]

In the present study, the initial manifestations were divided into more categories (motor, sensory, cranial nerve, prodrome, balance and urinary system manifestations), to better describe what was observed clinically. Symptoms like anosmia or dysphagia were presented by small numbers of patients and these manifestations were dissociated from any other medical condition. Therefore, they were also considered to be onset symptoms of MS, thus illustrating the heterogeneity of MS.

The average time to diagnosis was 2.84 years shorter than the time described by Sorensen et al. However, this may be explained by the evolution of MS diagnostic criteria over recent years, through use of neuroimaging and oligoclonal bands, for example.[9] In our study, we used the diagnostic criteria that were current from 1984 to 2015 and we believe that if the inclusion criteria had included the revised McDonald diagnostic criteria, the results would probably have been different.

The importance of early diagnosis lies in early establishment of use of immunomodulatory drugs, given that their use correlates with a decreased rate of progression of the disease.[4] The PRISMS-4 study,[9] for example, demonstrated the benefits of early treatment of MS. Patients diagnosed with MS were divided into two groups: the first received placebo, followed by two years of treatment with 22 mcg or 44 mcg of interferon-β 1a, while in the second group, the patients received treatment for four years in a row. After four years, the first group showed greater development of the disease, as assessed by Expanded Disability Status Scale (EDSS).

CONCLUSION

MS is a heterogeneous disease and its clinical manifestations are quite variable. The average time between the onset of MS symptoms and the diagnosis was 2.84 years, and this time was longer among patients who presented unifocal symptoms (3.20 years) than among those who presented multifocal symptoms (1.85 years). Unifocal onset was correlated with greater diagnostic difficulty. The most common initial symptoms related to cranial nerves (38.77%), followed by sensory symptoms (24.49%) and motor symptoms (20.15%). MS is a heterogeneous disease and its clinical manifestation is quite variable.

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Relationship between periodontal disease and cardiovascular risk factors among young and middle-aged Brazilians. Cross-sectional study

Relação entre doença periodontal e fatores de risco cardiovascular em brasileiros jovens e de meia-idade. Estudo transversal

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Cross-sectional studies.
Risk factors.

PALAVRAS-CHAVE:
Obesidade.
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Doenças periodontais.
Estudos transversais.
Fatores de risco.

ABSTRACT

CONTEXT AND OBJECTIVE: It has been suggested in the literature that periodontal disease (PD) is associated with cardiovascular risk. The objective of this study was to appraise the relationship between periodontal disease (gingivitis and periodontitis) and traditional cardiovascular risk factors (obesity, hypertension, dyslipidemia, diabetes and metabolic syndrome) among young and middle-aged adults attended at a health promotion and check-up center in the city of São Paulo, Brazil.

DESIGN AND SETTING: Cross-sectional study at the Health Promotion and Check-up Center of Hospital Sírio-Libanês, São Paulo, Brazil.

METHODS: We consecutively evaluated 539 subjects without prior cardiovascular disease who were seen within a health promotion program that included cardiovascular and dental evaluation between February and November 2012. Odds ratios (OR) with respective 95% confidence intervals (95% CI) for the association between PD and cardiovascular risk factors were ascertained through multinomial logistic regression.

RESULTS: In this sample of mean age 45 years (standard deviation, SD ± 8.8), which was 82% male, we found PD in 63.2% (gingivitis 50.6% and periodontitis 12.6%). Individuals with PD were older, more obese (without PD 15.2%; versus gingivitis 22.1% and periodontitis 32.4%) and more diabetic (without PD 5.1%; versus gingivitis 4.8% and periodontitis 13.2%), compared with those without PD. Among all cardiovascular risk factors evaluated, obesity was associated with periodontitis (multivariate OR, 2.36; 95% CI, 1.23-4.52). However, after additional adjustment for oral hygiene, this finding was no longer significant (multivariate OR, 1.63; 95% CI, 0.79-3.37).

CONCLUSIONS: We did not find any significant associations between cardiovascular risk factors and periodontal disease in this sample.

RESUMO

CONTEXTO E OBJETIVO: A literatura sugere que doença periodontal (DP) está associada ao risco cardiovascular. O objetivo deste estudo foi avaliar a relação entre doença periodontal (gengivite e periodontite) e fatores de risco cardiovasculares tradicionais (obesidade, hipertensão, dislipidemia, diabetes e síndrome metabólica) em adultos jovens e de meia-idade atendidos em um centro de promoção da saúde e *check-up* na cidade de São Paulo, Brasil.

TIPO DE ESTUDO E LOCAL: Estudo transversal no Centro de Promoção de Saúde e *check-up* do Hospital Sírio-Libanês, São Paulo, Brasil.

MÉTODOS: Avaliamos consecutivamente 539 indivíduos sem doença cardiovascular diagnosticada, observados em um programa de promoção da saúde que incluiu avaliação cardiovascular e odontológica de fevereiro a novembro de 2012. Razões de chances (RC) com respectivos intervalos de confiança de 95% (IC 95%) para a associação entre DP e fatores de risco cardiovascular foram calculadas por regressão logística multinomial.

RESULTADOS: Nesta amostra de pessoas com idade média de 45 anos (desvio padrão, DP ± 8,8), 82% de homens, encontramos 63,2% de casos de DP (50,6% de gengivite e periodontite 12,6%). Indivíduos com DP eram mais velhos, mais obesos (sem DP 15,2%; *versus* gengivite 22,1% e periodontite 32,4%) e mais diabéticos (sem DP 5,1%; *versus* gengivite 4,8% e periodontite 13,2%) comparados com aqueles sem DP. De todos os fatores de risco cardiovascular avaliados, a obesidade foi associada à periodontite (RC multivariada, 2,36; IC 95%, 1,23-4,52). No entanto, após ajuste adicional para higiene bucal, esse achado não foi mais significativo (RC multivariada, 1,63; IC 95%, 0,79-3,37).

CONCLUSÕES: Não encontramos associações significativas entre fatores de risco cardiovascular e doença periodontal nesta amostra.

INTRODUCTION

Recent evidence has suggested that periodontal disease (PD) is an emerging risk factor for fatal and non-fatal cardiovascular outcomes.[1-5] Pooled data from a systematic review found that PD was independently associated with increased risk of coronary heart disease (CHD), with risk estimates ranging from 1.24 (95% confidence interval, CI, 1.01-1.51) to 1.34 (95% CI, 1.10-1.63).[1]

In the Normative Aging and Dental Longitudinal Study, which was conducted on 1,203 men who were followed up for 35 years, chronic periodontitis was also associated with increased incidence of CHD, particularly among individuals younger than 60 years of age, independent of established cardiovascular risk factors (CVRFs) such as dyslipidemia, diabetes and hypertension. In that study, a hazard ratio (HR) of 2.12 (95% CI, 1.26-3.60) from comparing the highest versus the lowest category of radiographic bone loss (which is a measurement of advanced PD) was reported for individuals younger than 60 years, but not for those older than 60 years.[2] Moreover, PD is also associated with all-cause and cardiovascular disease (CVD) mortality.[3,4] In the VA Normative Aging and Dental Longitudinal Study, for each 20% increase in mean whole-mouth radiographic alveolar bone loss (ABL), the risk of death increased by 51%.[3]

In the National Health and Nutrition Examination Survey III (NHANES III), prospective evaluations were performed on 10,849 participants, and 3,105 and 561 individuals were identified as having moderate and severe PD, respectively. The highest HR for all-cause mortality (hazard ratio (HR), 1.64; 95% CI (confidence interval), 1.25-2.15), and particularly for CVD mortality (HR, 2.13; 95% CI, 1.37-3.31), was reported among individuals with severe PD, again only for younger individuals (aged 30-64 years).[4]

In the Women's Health Study, CVD outcomes were found more often among women with PD (incidence and prevalence). The incidence rates for PD were highest for major CVD (adjusted HR, 1.42; 95% CI, 1.14-1.77), for MI (myocardial infarction) (HR, 1.72; 95% CI, 1.25-2.38), for ischemic stroke (HR, 1.41; 95% CI, 1.02-1.95) and for total CVD (HR, 1.27; 95% CI, 1.06-1.52).

Furthermore, recent studies reported positive associations between periodontal disease and subclinical atherosclerosis, mostly reporting alterations in carotid intima-media thickness among individuals with PD.[6-8] The inflammation process of PD may trigger systemic inflammation that could be involved in the progression of atherosclerosis and consequently in CVD outcomes such as myocardial infarction or stroke.[9] However, it is not totally clear what the causal pathway between PD and CVD risk is.[10] Many observational studies have evaluated the association between different levels of periodontal disease and traditional CVRFs, such as obesity or correlated measurements,[11-21] while others have reported some association with diabetes[22] or metabolic disorders.[23,24] Among these studies, most reported an increased odds ratio (OR) for the relationship between obesity and periodontal disease.[13,15,17-21]

Despite the importance of PD as a potential emerging cardiovascular risk,[25,26] there is a paucity of systematic data that might justify inclusion of dental examination as a screening strategy for intermediate to high-risk individuals such as those presenting obesity or diabetes and those with a previous family history of CHD.[1,27]

Moreover, there are no studies that included comprehensive dental examination, including data on oral hygiene and cardiovascular risk factor evaluation at the same time, in a young to middle-aged population. Such populations probably present the greatest susceptibility to CVD risk in the presence of PD.[2,4]

OBJECTIVE

We aimed to appraise the relationship between periodontal disease (gingivitis and periodontitis) and traditional CVRFs (obesity, hypertension, dyslipidemia, diabetes and metabolic syndrome) among young and middle-aged adults who were attended at a health promotion and check-up center in the city of São Paulo, Brazil.

METHODS

Study design and sample

This was a cross-sectional study conducted on a consecutive sample of all consecutive young and middle-aged individuals who were free from CVD (myocardial infarction, coronary revascularization, heart failure and stroke) and who sought attendance through a health promotion program between February and November 2012. All of them underwent standard cardiovascular and dental screening. It should be noted that the normal attendance rate at this check-up center is approximately 300 adults older than 18 years of age per month.

The Health Promotion and Check-up Center forms part of the complex of Hospital Sírio-Libanês (Syrian-Lebanese Hospital), which is a tertiary-level private hospital located in the central zone of the city of São Paulo, one of most populous cities and the most important financial center of Brazil. The population regularly attended at this check-up center is mainly composed of active middle-aged male workers.

The study protocol was approved by the Institutional Review Board that addresses research on human participants, in accordance with the Declaration of Helsinki. All the participants signed an informed consent form.

Data-gathering

All individuals underwent a standard evaluation focusing on cardiological assessment and clinical examinations that were based on screening strategies for the general population recommended by the United States Preventive Services Task Force and the Centre for Health Promotion Canada.[28,29]

Sociodemographic data such as age (mean ± standard deviation) and educational level (up to completed high school or completed undergraduate course), data on CVRFs (hypertension, dyslipidemia, diabetes, obesity and metabolic syndrome) and lifestyle information, which included smoking status (never, former and current) and alcohol consumption (at least once a week), were all evaluated by cardiologists who were specialists in CVD screening. The screening was done in accordance with standardized protocols developed by the check-up center.

Oral health examination

Five dentists at our check-up center, who had been trained by a specialist in periodontal diseases, were responsible for replicating a standardized protocol for oral examinations, in order to maintain the homogeneity of the data gathered.

Information on oral hygiene was obtained using a questionnaire that asked for the following data: frequency of toothbrushing, use of dental floss and presence of halitosis. Oral hygiene was categorized into three levels as follows: poor (0-1 toothbrushing/day + 0-1 dental flossing/day + presence or absence of halitosis; score 0-3); moderate (2 toothbrushings/day + 0-2 dental flossings/day + presence or absence of halitosis; score 4-5); or good (≥ 3 toothbrushings/day + ≥ 3 dental flossings/day + absence of halitosis; score ≥ 6).

All the individuals screened also underwent an oral evaluation using a periodontal probe to measure pocket depths around each tooth, in order to establish the state of health of the periodontium. All teeth were examined at six different sites (mesiobuccal, mediobuccal, distobuccal, mesiolingual, mediolingual and distolingual). All sites were probed and a pocket was considered to be present when the probing depth was 4 mm or greater at at least one site. Periodontal disease outcomes were categorized as follows:

1. Gingivitis: defined as gingival bleeding after 10 seconds of probing;
2. Periodontitis: defined as presence of four or more teeth with one or more sites with probing pocket depth greater than or equal to 4 mm and clinical attachment loss ≥ 3 mm; and
3. Absence of periodontal disease (reference group): no signs of inflammation or pocketing.[30]

Based on this oral examination, each individual was also classified as having poor, fair, good or excellent oral health.

Cardiovascular risk factor definition

Hypertension was defined from the mean of the latest two systolic and diastolic blood pressure (BP) measurements, made using the Omron HEM 705CP oscillometric device. Three measurements were made, at one-minute intervals. Furthermore, the definition of hypertension included previous use of medication to treat hypertension, and systolic BP ≥ 140 mmHg, or diastolic BP ≥ 90 mmHg.

Dyslipidemia was defined as low-density lipoprotein-cholesterol (LDL) ≥ 130 mg/dl or use of cholesterol-lowering medications. The LDL-cholesterol level was calculated using the Friedewald equation, except for cases with elevated triglyceride levels, when an enzymatic colorimetric assay was used (ADVIA 1200, Siemens). Total high-density lipoprotein-cholesterol (HDL) and triglycerides were analyzed by means of the enzymatic colorimetric assay (ADVIA 1200, Siemens). Ultra-sensitive C-reactive protein (us-CRP) was measured using immunochemistry (nephelometry, Siemens).

Diabetes was defined as a medical diagnosis or use of medication to treat diabetes, or was based on fasting plasma glucose level ≥ 126 mg/dl or glycated hemoglobin (HbA1C) ≥ 6.5%.

Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Obesity was defined as BMI ≥ 30 kg/m^2.

Metabolic syndrome was defined in accordance with the NCEP ATP III criteria (Third Report of National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults),[31] as the presence of three of the following items: waist measurement > 88 cm for women or 102 cm for men; HDL-cholesterol < 50 mg/dl for women or < 40 mg/dl for men; systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg; serum triglyceride levels ≥ 150 mg/dl; and fasting plasma glucose ≥ 100 mg/dl (National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol, 2002).

Venous blood samples were obtained after 12 hours of overnight fasting. The serum obtained after centrifugation was used for hormone and biochemical measurements. Analyses were carried out using an automated analyzer.

Statistical analysis

Baseline characteristics and CVRF and laboratory data were analyzed in accordance with periodontal disease status (absence of periodontal disease or presence of gingivitis or periodontitis). Categorical variables were expressed as proportions and compared using the chi-square test. Continuous variables were expressed as means (with standard deviation) and compared using analysis of variance (ANOVA), or as medians (with range) using the Kruskal-Wallis test, according to the distribution of the variables. Multinomial logistic regression models were built using periodontal disease status as the dependent variable to evaluate its relationship with each CVRF (hypertension, diabetes, obesity and metabolic syndrome). From this, the OR with its respective 95% CI was presented in the following models: model 1 (crude); model 2 (adjustment for age and sex); model 3 (adjustment for age, sex, smoking and current alcohol consumption); and model 4 (adjustment for age, sex, smoking and current alcohol consumption and oral hygiene).

The analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22.0. For all analyses, a P-value of < 0.05 was considered significant.

RESULTS

Table 1 shows the baseline characteristics and the distribution of CVRFs among the 539 adults who were screened at the check-up center during the study period, according to their periodontal disease status. In this population, the mean age was 45 years (± SD, 8.8), most of the participants were male (82%) and the educational level was high (97% with college or university degree). It was found that 63.2% presented periodontal disease (50.6% with gingivitis and 12.6% with periodontitis). Individuals with periodontitis were three years older than those without this condition (P < 0.001).

Approximately 70% of our sample had BMI greater than or equal to 25 kg/m^2 and obese individuals accounted for 20.8%. Other frequently observed CVRFs included dyslipidemia (62.5%), hypertension (33.2%), metabolic syndrome (15.4%) and diabetes (5.9%).

We found progressively higher BMI (P < 0.009) and higher frequencies of obesity among individuals with PD (gingivitis: 22.1%; periodontitis: 32.4%), compared with individuals without PD (15.2%), P < 0.05. We also noticed higher frequency of diabetes among adults with periodontitis (13.2%) than among those without PD (5.1%) (P < 0.05). The frequency of PD did not differ among current smokers (3.0%), former smokers (7.2%) and never smokers (89.8%). Other CVRFs, as well as laboratory parameters such us-CRP levels, were not significantly different between individuals with PD and those without this condition (**Table 1**).

Although 88.1% of the adults screened reported having good oral hygiene habits, which included brushing frequency of at least three times a day (84.3%), dental flossing frequency of at least once a day (66.3%) and low frequency of halitosis (1.3%), only 25.9% were considered to have good or excellent oral health. As expected, oral health was progressively worse among individuals with periodontal

Table 1. Baseline characteristics of 539 healthy young and middle-aged adults at a Brazilian health promotion and check-up center, according to periodontal disease

Sociodemographic data	Periodontal disease			
	Without periodontal disease (n = 198)	Gingivitis (n = 273)	Periodontitis (n = 68)	Total (n = 539)
Mean age (± SD)	44 (8.5)	45 (8.9)*	48 (8.5)*	45 (8.8)*
Male (%)	155 (78.3)	230 (84.2)	57 (83.8)	442 (82.0)
Years of education (%)				
Up to completed high school	8 (4.1)	6 (2.2)	2 (2.9)	16 (3.0)
Completed undergraduate course	186 (95.9)	266 (97.8)	66 (97.1)	518 (97.0)
Metabolic parameters				
BMI, kg/m^2 (± SD)	26.8 (4.5)	26.4 (4.3)*	28.3 (4.1)*	25.3 (4.2)*
Total cholesterol, mg/dl (± SD)	199 (37.9)	200 (40.1)	202 (39.9)	200 (39.2)
LDL-cholesterol, mg/dl (± SD)	122 (34.2)	122 (35.3)	126 (37.8)	122 (35.2)
HDL-cholesterol, mg/dl (± SD)	53 (15.5)	51 (15.3)	48 (12.5)	51 (15.1)
Triglycerides, mg/dl (± SD)	122 (61.6)	139 (91.7)	146 (89.9)	134 (81.9)
us-CRP, mg/dl (± SD)	0.27 (0.44)	0.24 (0.34)	0.27 (0.22)	0.25 (0.36)
Fasting glucose, mg/dl (± SD)	90 (17.1)	89 (15.4)	94 (24.7)	90 (17.5)
Pre-clinical comorbidities				
Hypertension (%)†	57 (28.8)	93 (34.1)	29 (42.6)	179 (33.2)
Dyslipidemia (%)‡	124 (61.4)	176 (62.6)	52 (72.2)	352 (63.4)
Diabetes (%)§	10 (5.1)	13 (4.8)‖	9 (13.2)‖	32 (5.9)‖
Obesity (%)¶	30 (15.2)	60 (22.1)‖	22 (32.4)‖	112 (20.8)‖
Metabolic syndrome (%)**	25 (12.4)	49 (17.4)	13 (18.1)	87 (15.7)
Current smoking (%)	4 (2.0)	11 (4.0)	1 (1.5)	16 (3.0)
Current alcohol consumption at least once a week (%)	62 (31.3)	79 (28.9)	14 (20.6)	155 (28.8)

Some proportions might not add up to 100%, due to rounding or missing values (at most 4.7%).

*P-value < 0.001 compared with controls (without gingivitis); †Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, history of hypertension diagnosed by a physician, or current treatment; ‡Diabetes was defined as previous medical history of diabetes, use of medication to treat diabetes, fasting plasma glucose ≥ 126 mg/dl, 2-hour plasma glucose ≥ 200 mg/dl, or HbA1C ≥ 6.5%; §Dyslipidemia was assessed in accordance with the National Cholesterol Program-Adult Treatment Panel III (NCP ATP III) guidelines[31] as follows: LDL-cholesterol ≥ 130 mg/dl or use of lipid-lowering drug; ‖P-value < 0.05 compared with controls; ¶Obesity: BMI ≥ 30 kg/m^2; **Metabolic syndrome was also defined in accordance with NCEP ATP III.[31]

BMI = body mass index; LDL = low-density lipoprotein; HDL = high density lipoprotein; us-CRP = ultra-sensitive C-reactive protein

Reference group: without periodontal disease.

disease, and the frequencies of poor oral health were 25.4%, 11.9% and 1.0% among individuals with periodontitis, with gingivitis and without PD, respectively (P < 0.001). In addition, poor oral hygiene (score 0-3) was more frequent among those with periodontitis (21.2%) than among those with gingivitis (13.5%) or without PD (6.4%) (P < 0.001).

Among all the comorbidities, obesity (yes, 12.5%, versus no, 5.0%; P = 0.001) and dyslipidemia (yes, 7.7%, versus no, 4.5%; P = 0.001) were significantly associated with poor oral health. It should be noted that we found the same trend of poor oral hygiene among obese individuals, mainly due to lack of dental flossing, in comparison with non-obese individuals (frequencies of 43.8% and 31%, respectively; P = 0.06).

In our regression analyses, obesity was the only emerging risk factor that was consistently associated with pre-existing periodontitis (multivariate OR, 2.36; 95% CI, 1.23-4.52), even after adjusting for age, sex, smoking and alcohol intake, but not with gingivitis. However, after additional adjustment for oral hygiene score (brushing and dental flossing and the presence of halitosis), this finding was no longer significant (multivariate OR, 1.63; 95% CI, 0.79-3.37). The associations with periodontitis, hypertension and diabetes presented increased OR in crude analyses, but they lost their significance after progressive adjustments for multiple confounders (**Table 2**). Additional adjustment for oral health instead of oral hygiene did not alter the directions or significance of our findings (data not shown).

DISCUSSION

Overall, we found relatively high frequencies of periodontal disease (more than 60%) in our comprehensive screening program, which comprised dental evaluation in conjunction with cardiovascular assessment among young and middle-aged adults, in relation to other populations of the same age.[15,26,32,33] We did not find any classical cardiovascular risk factors that were independently associated with periodontal disease. Obesity was the risk factor most closely associated with periodontitis, but after multivariate adjustment including oral hygiene and health, this risk was no longer significant.

It is well known that moderate to severe risk of having chronic morbidities can be associated with BMI levels greater than 30 kg/m^2. Despite the heterogeneity of the studies included in a recent systematic review, a pooled OR of 1.81 (95% CI, 1.42-2.30)

Table 2. Odds ratio (with 95% CI) for the relationship between periodontal disease and cardiovascular risk factors among 539 healthy young and middle-aged adults at a Brazilian health promotion and check-up center, according to periodontal disease

	Gingivitis (n = 273)	P-value	Periodontitis (n = 68)	P-value
Hypertension				
Model 1	1.28 (0.86-1.90)	0.23	1.84 (1.04-3.26)	0.04
Model 2	1.27 (0.81-1.86)	0.34	1.39 (0.76-2.55)	0.28
Model 3	1.21 (0.79-1.83)	0.38	1.39 (0.76-2.55)	0.28
Model 4	1.20 (0.77-1.89)	0.43	1.35 (0.69-2.66)	0.39
Dyslipidemia				
Model 1	1.06 (0.73-1.54)	0.76	11.56 (0.86-2.83)	0.14
Model 2	0.98 (0.66-1.45)	0.92	1.27 (0.68-2.34)	0.46
Model 3	0.97 (0.66-1.44)	0.89	1.23 (0.66-2.28)	0.52
Model 4	0.75 (0.48-1.16)	0.19	0.82 (0.41-1.63)	0.57
Diabetes				
Model 1	0.94 (0.40-2.19)	0.89	2.87 (1.11-7.39)	0.03
Model 2	0.92 (0.39-2.18)	0.85	2.08 (0.78-5.56)	0.14
Model 3	0.92 (0.39-2.20)	0.85	2.00 (0.75-5.35)	0.17
Model 4	0.70 (0.28-1.74)	0.44	1.16 (0.37-3.64)	0.80
Obesity				
Model 1	1.59 (0.98-2.57)	0.06	2.68 (1.41-5.08)	0.003
Model 2	1.55 (0.95-2.52)	0.08	2.40 (1.26-4.59)	0.01
Model 3	1.53 (0.94-2.49)	0.09	2.36 (1.23-4.52)	0.01
Model 4	1.25 (0.74-2.10)	0.41	1.63 (0.79-3.37)	0.18
Metabolic syndrome				
Model 1	1.58 (0.93-2.71)	0.09	1.80 (0.85-3.79)	0.12
Model 2	1.54 (0.89-2.65)	0.12	1.51(0.71-3.21)	0.29
Model 3	1.04 (0.71-1.52)	0.86	1.31 (0.71-2.40)	0.39
Model 4	1.43 (0.79-2.58)	0.24	1.18 (0.50-2.82)	0.71

Model 1 = crude; Model 2 = adjustment for age and sex; Model 3 = additional adjustment for smoking and current alcohol consumption (at least once a week); Model 4 = additional adjustment for oral hygiene. OR = odds ratio; CI = confidence interval.

was reported for the relationship between obesity and periodontitis.[34] Although several studies have reported the relationship between obesity and periodontal disease,[11,13-15,17-21] there is no consensus about which pathophysiological mechanism could explain this relationship. Most findings have come from studies with different methodologies for classifying periodontal disease, or with cross-sectional designs or selected or small samples.[11,13,14,17-20] Some studies were conducted on large and more representative cohorts but still with diverse methodology, particularly relating to the diagnosis of PD, and were restricted to certain sex or age strata.[5,12,15,21]

Very few studies other than ours have considered oral health or hygiene status in their analyses.[12,17] One of these was a Brazilian population-based birth cohort with a representative sample of 720 subjects in which the association between periodontal disease was determined through oral examination (at the age of 24 years) and obesity was evaluated. Waist circumference and the number of episodes of obesity between the ages of 15 and 23 years were taken to be the main exposures. The evaluation of oral hygiene included use of dental flossing and frequency of brushing. In the crude analysis, gingivitis at two or more teeth was found to be associated with obesity (OR, 1.93; 95% CI, 1.08-3.43). However, similarly to our findings, after adjusting for other confounders, including oral hygiene, obesity was found to be no longer associated with gingivitis or periodontal pockets in that cohort.[12] The other study that included oral hygiene in its analysis (tooth brushing) was a cross-sectional study conducted among 372 Japanese adults.[17] In that study, a dose-response relationship with pack-years of smoking, BMI and periodontitis was described, even after adjusting for confounders.[17] The main limitations of that study were: self-reported data and the lack of information about use of dental flossing. Of note, in our study, a poor oral hygiene habit was more associated with periodontitis. In fact, lower frequency of dental flossing was observed among obese than among non-obese individuals in our study.

The explanation for the underlying pathophysiological connection between obesity and PD may be that the adverse effects of obesity on the periodontium are mediated through pro-inflammatory cytokines and various other bioactive substances.[9] In our sample, the total levels of us-CRP were low, with little difference between obese and non-obese adults (0.22 mg/dl versus 0.11 mg/dl, respectively; $P < 0.001$). Other mechanisms that could link these two conditions include the quality of diets that are rich in carbohydrates or saturated fats and/or poor oral hygiene, thereby facilitating the development of local inflammatory processes.[35] Here, we did not evaluate the role of unhealthy diets. However, our findings suggested that poor oral hygiene, mainly due to not using dental flossing, was associated with obesity, which consequently corroborated the increased risk of periodontitis.

Regarding other CVRFs, we found higher frequencies and increased ORs for the relationship between diabetes and hypertension, but these findings were attenuated in our logistic regression analyses after adjustment for multiple confounders, including oral hygiene.

Previous studies found higher incidence or prevalence of PD, particularly in cases of severe forms of diabetes, compared with the healthy population, including in prospective studies.[36-39] High risks for the association between diabetes and periodontitis were described in the Gila River Indian Community in Arizona, where the diabetes rates are considered to be the highest worldwide. According to that study, Indians with diabetes presented increased ORs for destructive forms of periodontitis that were around three times higher than in non-diabetics, even after multivariate adjustment, including for oral hygiene.[39] It is possible that we failed to confirm any high-risk association between PD and diabetes in our logistic analyses because in our sample the frequencies of severe forms of periodontitis and diabetes were much lower and our patients were probably healthier than those included in previous studies.[36-39]

Regarding hypertension, most studies that evaluated the risk of PD also found positive cross-sectional associations[40-42] and some that included oral hygiene habits in their analysis found low ORs (at most 1.5) for the relationship.[41,42] We also found a positive association with hypertension, but after multivariate adjustments this association was no longer significant. Some characteristics, including the distribution of CVRFs and age, may be associated with these disparities among studies.

Our study has some strength. Our findings depict unique data from a young to middle-aged Brazilian population in which both classical CVRFs and periodontal disease were evaluated through an extensive dental evaluation.

Our study has some limitations. We presented data from a cross-sectional assessment, which did not allow us to make causal inferences about the relationship between CVRFs and PD. This was not a population-based study; in fact, our sample was selected from a check-up center and thus we cannot rule out the existence of selection bias that might have compromised generalization of our findings.

CONCLUSIONS

We did not find any significant association between periodontal disease and traditional cardiovascular risk factors in this young to middle-aged sample.

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Comparison of machine-learning algorithms to build a predictive model for detecting undiagnosed diabetes – ELSA-Brasil: accuracy study

Comparação de algoritmos de aprendizagem de máquina para construir um modelo preditivo para detecção de diabetes não diagnosticada – ELSA-Brasil: estudo de acurácia

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ABSTRACT

CONTEXT AND OBJECTIVE: Type 2 diabetes is a chronic disease associated with a wide range of serious health complications that have a major impact on overall health. The aims here were to develop and validate predictive models for detecting undiagnosed diabetes using data from the Longitudinal Study of Adult Health (ELSA-Brasil) and to compare the performance of different machine-learning algorithms in this task.

DESIGN AND SETTING: Comparison of machine-learning algorithms to develop predictive models using data from ELSA-Brasil.

METHODS: After selecting a subset of 27 candidate variables from the literature, models were built and validated in four sequential steps: (i) parameter tuning with tenfold cross-validation, repeated three times; (ii) automatic variable selection using forward selection, a wrapper strategy with four different machine-learning algorithms and tenfold cross-validation (repeated three times), to evaluate each subset of variables; (iii) error estimation of model parameters with tenfold cross-validation, repeated ten times; and (iv) generalization testing on an independent dataset. The models were created with the following machine-learning algorithms: logistic regression, artificial neural network, naïve Bayes, K-nearest neighbor and random forest.

RESULTS: The best models were created using artificial neural networks and logistic regression. These achieved mean areas under the curve of, respectively, 75.24% and 74.98% in the error estimation step and 74.17% and 74.41% in the generalization testing step.

CONCLUSION: Most of the predictive models produced similar results, and demonstrated the feasibility of identifying individuals with highest probability of having undiagnosed diabetes, through easily-obtained clinical data.

RESUMO

CONTEXTO E OBJETIVO: Diabetes tipo 2 é uma doença crônica associada a graves complicações de saúde, causando grande impacto na saúde global. O objetivo foi desenvolver e validar modelos preditivos para detectar diabetes não diagnosticada utilizando dados do Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil) e comparar o desempenho de diferentes algoritmos de aprendizagem de máquina.

TIPO DE ESTUDO E LOCAL: Comparação de algoritmos de aprendizagem de máquina para o desenvolvimento de modelos preditivos utilizando dados do ELSA-Brasil.

MÉTODOS: Após selecionar 27 variáveis candidatas a partir da literatura, modelos foram construídos e validados em 4 etapas sequenciais: (i) afinação de parâmetros com validação cruzada *(10-fold cross-validation)*; (ii) seleção automática de variáveis utilizando seleção progressiva, estratégia *"wrapper"* com quatro algoritmos de aprendizagem de máquina distintos e validação cruzada para avaliar cada subconjunto de variáveis; (iii) estimação de erros dos parâmetros dos modelos com validação cruzada; e (iv) teste de generalização em um conjunto de dados independente. Os modelos foram criados com os seguintes algoritmos de aprendizagem de máquina: regressão logística, redes neurais artificiais, *naïve* Bayes, K vizinhos mais próximos e floresta aleatória.

RESULTADOS: Os melhores modelos foram criados utilizando redes neurais artificiais e regressão logística alcançando, respectivamente, 75,24% e 74,98% de média de área sob a curva na etapa de estimação de erros e 74,17% e 74,41% na etapa de teste de generalização.

CONCLUSÃO: A maioria dos modelos preditivos produziu resultados semelhantes e demonstrou a viabilidade de identificar aqueles com maior probabilidade de ter diabetes não diagnosticada com dados clínicos facilmente obtidos.

INTRODUCTION

Type 2 diabetes is a chronic disease characterized by the body's inability to efficiently metabolize glucose, which increases blood glucose levels and leads to hyperglycemia. This condition is associated with a wide range of serious health complications affecting the renal, neurological, cardiac and vascular systems, and it has a major impact on overall health and healthcare costs.[1]

Recent studies have estimated that around 415 million people have diabetes, and that the number of cases may increase to 642 million by 2040. In addition, approximately half of these individuals are not aware of their condition, which may further intensify the negative consequences of the disease. Diabetes was the main cause of death of nearly five million people in 2015, and it has been estimated that by 2030 it will become the seventh largest cause of death worldwide.[2-4]

It is believed that diabetes, like other noncommunicable chronic diseases, is mainly caused by behavioral factors such as poor diet and physical inactivity. Early interventions aimed towards creating lifestyle changes, with or without associated pharmacological therapies, have been proven effective in delaying or preventing type 2 diabetes and its complications. This has led many countries to invest in national programs to prevent this disease. To reduce costs and amplify the results, population-level interventions need to be combined with interventions that are directed towards individuals who are at high risk of developing or already having diabetes,[5] so as to focus interventions, at the individual patient level, on those for whom they are most appropriate.

To this end, over recent years, a series of clinical prediction rules have been developed to identify individuals with unknown diabetes or those at high risk of developing diabetes.[5-9] However, few of these rules have been drawn up using the most recently developed machine-learning techniques, which potentially have the ability to produce algorithms of greater predictive ability than those developed through the technique most commonly used to date, i.e. multiple logistic regression.

OBJECTIVE

This paper presents the development and comparison of predictive models created from different machine-learning techniques with the aim of detecting undiagnosed type 2 diabetes, using baseline data from the Longitudinal Study of Adult Health (ELSA-Brasil).

METHODS

These analyses were performed on data from the baseline survey (2008-2010) of ELSA-Brasil, a multicenter cohort study that had the main aim of investigating multiple factors relating to adult health conditions, including diabetes and cardiovascular diseases. The study enrolled 15,105 public servants aged between 35 and 74, at six public higher-education and research institutions in different regions of Brazil between 2008 and 2010, as has been previously reported in greater detail.[10,11] The institutional review boards of the six institutions at which the study was conducted gave their approval, and written informed consent was obtained from all participants.

All analyses were performed using R version 3.2.3. The source codes used in the analysis are freely available.

Dataset and preliminary variable selection

Data from the ELSA study baseline were used to create the predictive models. At this baseline, the 15,105 participants were evaluated through interviews, clinical examinations and laboratory tests. The interviews addressed educational achievement; characteristics and composition of home and family; dietary habits; alcohol drinking habits; smoking habits; presence of dyslipidemia or hypertension; physical activity at leisure; sleep quality; medical history; and medication use, among other topics. The examinations involved anthropometric measurements and blood and urine tests, among others. The study generated more than 1500 variables for each participant at baseline, as described previously.[10,11]

A total of 1,473 participants were excluded from the present analyses because they had self-reported diabetes. Another three participants were excluded because some information required for characterizing undiagnosed diabetes was missing. An additional 1,182 participants (8.7%) were excluded from the analyses because data relating to other variables were missing. Among the remaining 12,447 participants, 1,359 (11.0%) had undiagnosed diabetes.

Undiagnosed diabetes was considered present when, in the absence of a self-report of diabetes or use of anti-diabetic medication, participants had fasting glucose levels ≥ 126 mg/dl, glucose levels ≥ 200 mg/dl two hours after a standard 75 g glucose load or had glycated hemoglobin (HbA1c) ≥ 6.5%.

Through procuring variables in the ELSA dataset that were similar to those investigated in previously published predictive models for detecting diabetes or in situations of high risk of developing diabetes, we selected 27 diabetes risk factors for analysis. Any variables that implied additional costs beyond those of filling out a questionnaire and performing basic anthropometry, such as clinical or laboratory tests, were excluded so that the model obtained could be applied using a straightforward survey and simple anthropometric measurements. The final variable subset was validated by experts, and this resulted in the subset of 27 candidate variables described in **Table 1** and **Table 2**. **Table 2** also presents the analysis target variable of prevalent diabetes "a_dm".

The original dataset was randomly divided into two parts in the ratio of 70:30. The first part (training/validation dataset) was used for parameter and cutoff tuning, automatic variable selection and error estimation using cross-validation; the second part (test

Table 1. Numerical variables

Variable identity	Minimum	Median	Mean	Maximum	SD	Variable description
a_cons_est_nacl	0.14	9.67	11.65	3533.00	42.57	Estimated daily salt consumption in grams
a_rcq	0.40	0.89	0.89	1.27	0.09	Waist-hip ratio
a_rendapercapita	27.63	1410.90	1756.34	7884.50	1436.67	Per capita family net income in R$
afia7	0.00	0.00	0.12	7.00	0.68	Bicycle use for transport (days/week)

SD = standard deviation.

Table 2. Categorical variables, including the target variable "a_dm"

Variable identity	Number of levels	Frequency in each level	Description	Possible values
a_ativfisica	3	1: 9523; 2: 1735; 3: 1189	Physical activity during leisure time	1 = weak; 2 = moderate; 3 = strong
a_binge	2	0: 10764; 1: 1683	Sporadic excessive alcohol drinker	0 = no; 1 = yes
a_consdiafrutas	2	0: 5434; 1: 7013	Daily consumption of fruits	0 = no; 1 = yes
a_consdiaverduras	2	0: 6003; 1: 6444	Daily consumption of vegetables	0 = no; 1 = yes
a_dm	2	1: 11088; 0: 1359	Diabetes mellitus	0 = yes; 1 = no
a_escolar	4	1: 619; 2: 773; 3: 4219; 4: 6836	Education	1 = middle school not completed or less; 2 = middle school completed; 3 = high school completed; 4 = university undergraduate course completed
a_fumante	3	0: 7212; 1: 3619; 2: 1616	Smoker	0 = never smoked; 1 = former smoker; 2 = smoker
a_gidade	4	1: 2899; 2: 5077; 3: 3320; 4: 1151	Age group	1 = 35 to 44 years; 2 = 45 to 54 years; 3 = 55 to 64 years; 4 = 65 to 74 years
a_imc2	4	1: 122; 2: 4705; 3: 5011; 4: 2609	Four-level body mass index	1 = underweight; 2 = eutrophic; 3 = overweight; 4 = obese
a_medanthipert	2	0: 9232; 1: 3215	Use of antihypertensive drugs	0 = no; 1 = yes
a_medoutahip	2	0: 12367; 1: 80	Use of other antihypertensive drugs	0 = no; 1 = yes
a_medredlip	4	0: 11122; 1: 1117; 2: 97; 3: 111	Use of lipid-lowering drugs	0 = no use; 1 = use of statins; 2 = use of others; 3 = use of more than one class
a_sfhfprem	2	0: 12371; 1: 76	Self-reported heart failure (< 50 years of age)	0 = no; 1 = yes
a_sfmiprem	2	0: 12386; 1: 61	Self-reported myocardial infarction (< 50 years of age)	0 = no; 1 = yes
a_sfrevprem	2	0: 12402; 1: 45	Self-reported revascularization (< 50 years of age)	0 = no; 1 = yes
a_sfstkprem	2	0: 12373; 1: 74	Self-reported stroke (< 50 years of age	0 = no; 1 = yes
a_sintsono	2	0: 8321; 1: 4126	Sleep quality	0 = no; 1 = yes
a_sitconj	5	1: 8248; 2: 2028; 3: 1283; 4: 474; 5: 414	Marital status	1 = married; 2 = divorced; 3 = single; 4 = widowed; 5 = other
claa2	2	0: 8397; 1: 4050	Pain/discomfort in the legs while walking (Q2)	0 = no; 1 = yes
diea133	3	0: 1038; 1: 11136; 2: 273	Coffee consumption (Q133)	0 = no; 1 = yes, with caffeine; 2 = yes, decaffeinated
hfda07	2	0: 3271; 1: 9176	Hypertension, family history (Q7)	0 = no; 1 = yes
hfda11	2	0: 7879; 1: 4568	Diabetes, family history (Q11)	0 = no; 1 = yes
hmpa08	2	0: 8205; 1: 4242	High cholesterol (Q8)	0 = no; 1 = yes
rcta8	2	1: 5566; 2: 6881	Sex	1 = male; 2 = female

dataset) was used for generalization tests. The models created were evaluated in terms of area under the receiver operating characteristic curve (AUC), sensitivity, specificity and balanced accuracy (arithmetic mean of sensitivity and specificity). The machine-learning algorithm families of logistic regression, artificial neural network (multilayer perceptron/backpropagation), Bayesian network (naïve Bayes classifier), instance-based learning (K-nearest neighbor) and ensemble (random forest) were used.

Machine-learning algorithms

The machine-learning algorithms are briefly described below:

Logistic regression[12] is a well-established classification technique that is widely used in epidemiological studies. It is generally used as a reference, in comparison with other techniques for analyzing medical data.

Multilayer perceptron/backpropagation[13] is the principal artificial neural network algorithm. When there is no hidden layer on the network, this algorithm is equivalent to logistic regression, but it can solve more difficult problems with more complex network architectures. The price of using complex architectures is that it produces models that are more difficult to interpret. Additionally, it can be computationally expensive.

Naïve Bayes classifier[14] is a type of Bayesian network that, despite enormous simplicity, is able to create models with high predictive power. The algorithm works well with heterogeneous data types and also with missing values, because of the independent treatment of each predictor variable for model construction.

K-nearest neighbor (*instance-based learning*)[15] is a classical instance-based learning algorithm in which a new case is classified based on the known class of the nearest neighbor, by means of a majority vote. This type of algorithm is also called lazy learning because there is no model building step and the entire computing procedure (i.e. the search for the nearest neighbor) is performed directly during the prediction. All the cases (training/validation dataset) need to be available during the prediction.

Random forest[16] is a machine-learning algorithm from the "ensemble" family of algorithms,[17] which creates multiple models (called weak learners) and combines them to make a decision, in order to increase the prediction accuracy. The main idea of this technique is to build a "forest" of random decision "trees" and use them to classify a new case. Each tree is generated using a random variable subset from the candidate's predictor variables and a random subset of data, generated by means of bootstrap. This algorithm also can be used to estimate variable relevance.

Data preparation

Standardization of numerical variables

Transformation between different data types (categorical or numerical) was performed by means of binarization or discretization, when necessary. In binarization, a categorical variable with n levels is transformed into n - 1 dummy variables that have values equal to "1" when the case belongs to the level represented by the dummy variable or "0" otherwise.

In discretization, a numerical variable is transformed into a categorical variable by defining a set of cutoff points for that variable, such that the ranges of values between the cutoff points correspond to the levels of the categorical variable. The Ameva algorithm[18] was used to find the best cutoff points for each numerical variable.

General process of model construction and evaluation

The models were built, evaluated and compared using four sequential steps:

1. Parameter tuning;
2. Automatic variable selection;
3. Error estimation; and
4. Generalization testing in an independent dataset.

The complete process is depicted in **Figure 1**. First, manual variable preselection was performed as described above ("Manual Variable Selection" box in the **Figure**). After that, 30% of the dataset ("Test" dataset in the **Figure**), containing 3,709 complete cases, was separated for generalization testing, while the other part ("Training/Validation" dataset in the **Figure**), containing 8,738 complete cases, was used as the dataset for the first three steps of the process.

The first step in model building ("Parameter Tuning" box in **Figure 1**) evaluated each machine-learning algorithm with different sets of configurable parameters of the algorithm by means of tenfold cross-validation, repeated three times. In tenfold cross-validation, the dataset (training/validation) is divided into ten parts, of which nine are used for training (selecting) a model and the tenth for validation of this model. This process is repeated to calculate the validation measurements, such as AUC, while varying the part of the dataset used for validation each time. Finally, the mean of the validation measurements across repeats is calculated. The results from this step ("Best Parameters" item in the Figure), containing the best parameters and cutoffs for classification for each algorithm, were used in the next steps.

The second step ("Automatic Variable Selection" box in **Figure 1**) generated four different variable subsets using different algorithms and cross-validation (using only the best settings found in the preceding step), with the wrapper strategy and a forward selection search for automatic variable selection. The best variable subsets found in this step ("Best Variable Subsets" item in **Figure 1**) were used in the next steps.

The third step ("Error Estimation" box in **Figure 1**) used cross-validation to obtain more reliable estimates of the performance

of different learning schemes, using the best settings and subsets obtained in the preceding steps.

Finally, the last step ("Generalization Testing" box in **Figure 1**) evaluated models using only the learning scheme that obtained the best performance for each algorithm in the test dataset that had not previously been used.

The following sections describe each step in more details.

Parameter tuning

This first step in model building evaluated each algorithm with different parameter configurations to find out which parameter configuration produced the best results for each algorithm and data type conversion used. The parameters tested for each algorithm are listed in **Table 3**.

Because of the wide range of possible values for the parameters, a search strategy was adopted. At first, a limited set of values for each parameter was selected, and each combination of parameters was evaluated by means of tenfold cross-validation, repeated three times, thus generating 30 models. Each instance of machine learning was tested with and without data discretization. The results from

Table 3. Parameters analyzed in parameter tuning

Algorithm	Parameter	Description
Artificial neural network	Size	Number of neurons on hidden layer
	Decay	Weight decay
	Skip	Direct link between input and output neurons
Logistic regression	Epsilon	Convergence tolerance value
Naïve Bayes	Laplace	Real number to control Laplace smoothing
K-nearest neighbor	Minvotes	Minimum votes to define a decision
	k	Number of neighbors considered
Random forest	Ntree	Number of random trees generated

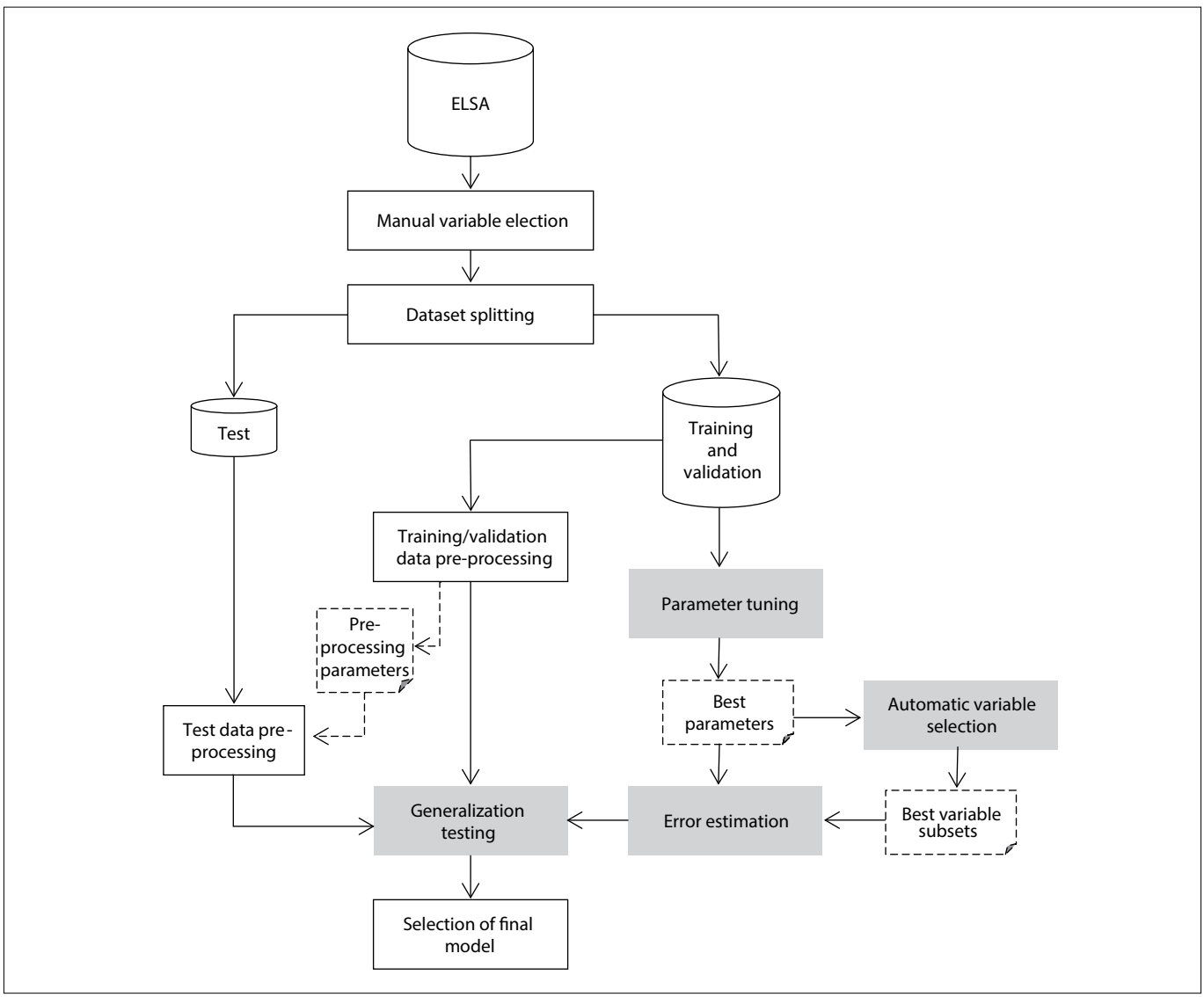

Figure 1. General process of model construction and evaluation.

the 30 models generated in each test were averaged. The parameter configuration that produced the best mean AUC was chosen. Moreover, a set of different cutoffs (predefined by the analyst) to generate the classification was evaluated to find out which produced the best classification on average between the 30 models in terms of balanced accuracy.

After that, the results were analyzed and, when necessary, new parameter values and/or cutoff points were selected for new tests. In this case, the new values were selected around the values from which the best results had been obtained up to that moment. The idea was to start testing a sparse range of values and then decrease the granularity of the values in order to avoid trying values that were very likely to produce poor results. This search stopped when there was no increase in the predictive power of the models that had been created using the specific machine-learning algorithm and data type conversion evaluated.

Automatic variable selection

The automatic variable selection step had the aim of finding subsets from the 27 candidate variables that could increase the performance of the predictive models, compared with other models created using different sets of candidate variables.

These subsets of variables were generated using the wrapper strategy.[19] In this strategy, models are created and evaluated by means of a machine-learning algorithm and a validation method, such as cross-validation, using different subsets of variables. The subset from which the best performance is achieved, in terms of a criterion such as AUC, is chosen as the best subset. Because of the large number of possible subsets, a heuristic search was used to generate the variable subset candidates that were more likely to create better models, thereby optimizing the process. The main advantage of this method compared with other strategies is that it evaluates multiple variables together. The drawback is that, because it depends on a machine-learning algorithm to create/evaluate models, it is possible that the subset of variables that produces the best results using one algorithm can produce bad results when using another algorithm or another parameter setting for the same algorithm.

Four machine-learning algorithms were used: logistic regression, artificial neural network, K-nearest neighbor and naïve Bayes classifier. The random forest algorithm was not included because it already performs an embedded variable selection. The forward selection search strategy was used in modeling because it tends to generate smaller subsets. The same validation technique (tenfold cross-validation repeated three times), decision criterion (mean AUC) and dataset partition that had been used in the parameter tuning step were used again in this step. The best parameter settings obtained in the parameter tuning step were used to configure the parameters of the algorithms for this step. Each machine-learning technique generated a distinct subset of variables. The subsets thus generated were used in the next step.

Error estimation

The error estimation step evaluated each machine-learning algorithm using the parameters obtained in the first step and the subsets generated in the second step, in addition to the original variable subset containing all the candidate variables. This step also served to evaluate the use of discretization. The evaluation was done through tenfold cross-validation, which was repeated ten times to get more reliable prediction performance estimates.

Generalization testing

Finally, one model was generated from the training/validation dataset for each algorithm, using the best results from the preceding step. These best models were then evaluated (hold-out evaluation) in the test set, since this generalization testing has the aim of evaluating model behavior when faced with data that was not used in its creation. The results from this evaluation serve as a quality measurement for these models.

Development of an equation for application of the results

The model with best results from generalization testing was used to create a web tool to apply the questionnaire in practice. The prediction from the logistic regression model for any given individual is calculated by multiplying that individual's value for each variable in the model by the coefficient derived from the model for that variable, and then summing the results and transforming this sum into a probability of undiagnosed diabetes using the logistic function. If this probability is above the predetermined cutoff (here, 11%), the individual is classified as positive (at high risk of undiagnosed diabetes); or otherwise, as negative.

RESULTS

Study sample

Among the 12,447 ELSA participants included in this study, 5,566 (44.67%) were men. The participants were between 35 and 74 years old; the largest proportion (5,077) was in the group between 45 and 54 years old; 6,836 (54.92%) had a complete university education or more; 5,011 (40.26%) were overweight and 2,609 (20.96%) were obese. Using the World Health Organization definition (fasting glucose ≥ 110 mg/dl and/or 2 hour post-load glucose ≥ 140 mg/dl), 5,539 (44.5%) presented intermediate hyperglycemia. Other details about the study sample can be found in **Table 1** and **Table 2**.

Parameter tuning

The best parameter configuration for each data type conversion of each algorithm is depicted in **Table 4**.

The first and second columns of **Table 4** present the name of the algorithm and whether discretization was used, respectively. The third column shows the values of the parameter configuration that provided the best result for the machine-learning algorithm and data type conversion of each row. The next four columns present basic statistics (mean, standard deviation, first and third quartiles and cutoff points, respectively) of the AUC obtained in the cross-validation. The eighth column shows the cutoff that provided the mean best balanced accuracy (BA) and the last two columns shows the mean balanced accuracy and its standard deviation.

Table 4 shows each machine-learning algorithm with its different data type conversions, sorted in descending order in terms of AUC and balanced accuracy for each algorithm and data type conversion.

Although defining which algorithms produce better results was not the objective of this step, it was possible to gain an initial insight into their predictive powers. In this regard, the best results were produced by artificial neural networks and logistic regression with mean AUC of 75.24% (row 1) and 74.98% (row 3), respectively.

Table 4 also shows the impact in terms of performance, when discretization was used in each machine-learning algorithm. For example, performance decreased (around 1% overall and almost 3% in the case of random forest) when the data were discretized in the models generated by all the algorithms except naïve Bayes. In general, the performance behavior of the machine-learning algorithms and conversion remained similar for the next steps.

Another result that can be seen in most cases is the impact on the choice of the parameter settings, caused by the conversion used. For example, the best performance of the artificial neural network algorithm was achieved without data conversion and with size = 175 (i.e. 175 neurons in the hidden layer). However, when discretization was used, the best parameter setting changed to size = 100.

The best parameter setting achieved was used to configure the five algorithms used for the automatic variable selection step, as well as in further steps.

Results from automatic variable selection

The automatic variable selection step generated four distinct subsets of variables as shown in **Table 5** (rows 1 to 4): *lr-fs,* created with logistic regression (*fs* in the name stands for "forward selection"); *ann-fs,* created with an artificial neural network; *knn-fs,* created with K-nearest neighbor; and *nb-fs,* created with a naïve Bayes algorithm.

Table 5. Variable subsets generated in automatic variable selection

Subset	Best mean AUC	Number of variables	Variable names
ann-fs	75.48%	14	a_ativfisica, a_binge, a_escolar, a_gidade, a_imc2, a_medanthipert, a_medredlip, a_rcq, a_rendapercapita, a_sfhfprem, diea133, hfda07, hfda11, rcta8.
lr-fs	75.44%	11	a_ativfisica, a_binge, a_escolar, a_gidade, a_imc2, a_medanthipert, a_rcq, diea133, hfda07, hfda11, rcta8.
knn-fs	74.94%	12	a_binge, a_escolar, a_gidade, a_imc2, a_medanthipert, a_medoutahip, a_rcq, a_sfmiprem, a_sfstkprem, hfda07, hfda11, rcta8.
nb-fs	74.47%	10	a_ativfisica, a_binge, a_escolar, a_gidade, a_imc2, a_medanthipert, a_rcq, afia7, diea133, hfda11.

Table 4. Results from parameter tuning

Algorithm	Data conversion	Parameters	AUC (mean)	AUC (SD)	AUC (1q)	AUC (3q)	Cutoff	BA (mean)	BA (SD)
Artificial neural network	–	Size = 175; decay = 2; skip = false	75.24%	1.87%	73.91%	76.77%	0.12	69.04%	2.36%
Artificial neural network	Discretization	Size = 100; decay = 3; skip = true	74.16%	1.94%	72.71%	74.87%	0.11	67.95%	1.71%
Logistic regression	–	Epsilon = 0.01	74.98%	1.81%	73.83%	76.27%	0.11	68.46%	2.37%
Logistic regression	Discretization	Epsilon = 0.01	74.01%	1.98%	72.61%	74.98%	0.11	67.74%	1.98%
K-nearest neighbor	–	Neighbor = 475	74.45%	2.05%	72.96%	75.56%	0.1	68.59%	1.99%
K-nearest neighbor	Discretization	Neighbor = 275	73.60%	2.11%	72.31%	74.87%	0.09	67.55%	2.30%
Naïve Bayes	Discretization	Laplace = 0.001	73.67%	2.26%	72.21%	75.04%	0.09	68.09%	2.11%
Naïve Bayes	–	Laplace = 1	73.23%	2.58%	71.85%	74.52%	0.31	67.74%	2.57%
Random forest	–	Ntree = 7,000	72.90%	1.94%	71.77%	74.26%	0.13	67.24%	2.06%
Random forest	Discretization	Ntree = 4,300	70.85%	2.12%	69.41%	72.56%	0.12	65.55%	2.11%

AUC = area under the ROC curve; SD = standard deviation; 1q/3q = first and third quartiles; BA = balanced accuracy.

The first column of **Table 5** shows the identifier name of the subset, the second column presents the AUC achieved by the variable subset that was chosen for each algorithm, the third shows the number of variables of each subset and the fourth presents these variable names.

The dataset partitions used for this step were the same as used in the parameter tuning step. Thus, it is possible to gain an insight into the performance improvement in terms of AUC when using a variable subset instead of using all the variables from the original dataset. Furthermore, merely the fact that a smaller subset was used to create the models is already an advantage because this makes the model and its application much simpler.

Because of the nature of the wrapper strategy, it can be expected that each machine-learning algorithm will present better results when using the variable subset created by the algorithm itself. However, in the next step all the subsets were tested with all the algorithms.

Results from error estimation

The aim of this step was to obtain more reliable error estimates regarding algorithm performance. For this reason, 10 repetitions were used instead of 3, for the repeated tenfold cross-validation, thus generating 100 models instead of 30 for each test.

The machine-learning algorithms were tested using the best parameters found in the first step (depicted in **Table 4**), with the variable subsets generated in the second step (described in **Table 5**), as well as with the original set of variables. Performance was tested with and without discretization.

Table 6 describes the best results obtained for each machine-learning algorithm, variable subset and data conversion used. Respectively, the columns represent the name of machine-learning algorithm used; data type conversion; variable subset; AUC mean, standard deviation (SD) and first and third quartiles achieved in cross-validation; and mean and standard deviation of the balanced accuracy (BA).

Like in the results from the parameter tuning step, the artificial neural network algorithm and logistic regression achieved the best results. Without data conversion, these algorithms produced similar models, with AUC of 75.45% (row 1) and 75.44% (row 4), respectively, each using the variable subset generated with its own algorithm, as expected. K-nearest neighbor and naïve Bayes also reached good results, with AUC of close to 75%. The best results with the naïve Bayes classifier were obtained using a subset of variables other than *nb-fs*. This was possible because the variable subset search with this algorithm used discretized data following the best results from parameter tuning, while the best result in the current phase was without variable transformation.

Finally, as in the parameter tuning step, random forest produced the worst results. Independent of the subset of variables, this algorithm showed a worse yield in terms of mean AUC.

Table 6 also shows the impact of using a specific variable subset, compared with the best results obtained from the models generated using the original variable set. This difference is very small: around 0.25% better using the variable subset instead of all the original variables for the artificial neural network models. The results obtained with a subset of variables were slightly better (around 0.5%) than the original with logistic regression and K-nearest neighbor models. The best naïve Bayes classifier model result from using a variable subset was more than 1% better than the best result from using all the variables. Finally, random forest models produced the best results using all of the available variables.

Results from generalization testing

In generalization testing, the best learning scheme (which includes data type conversion used, parameter setting, classification cutoff and variable subset) found for each algorithm in the preceding step was evaluated in the test dataset, which had been separated at the beginning of the process and had not been used until this step.

Table 7 shows the best results obtained in the error estimation phase together with the results obtained in generalization testing.

All the algorithms maintained good performance in generalization testing. The biggest loss of performance in relation to the error estimate step, as assessed from changes in the AUC, was 1.64% for the K-nearest neighbor algorithm. The artificial neural network, logistic regression and naïve Bayes had performance losses of 1.30%, 1.03% and 0.80%, respectively. The least loss in generalization testing was 0.458%, achieved by the random forest algorithm, which produced the worst performance in terms of AUC of all the algorithms. Nevertheless, the worst result was an AUC of 72.35%.

Since the best result from this step in terms of AUC (74.41%) was obtained using logistic regression, and given the easy interpretation and applicability of this model, logistic regression was chosen to be used to create the diabetes risk assessment tool.

Web tool proposed for detecting undiagnosed diabetes

Finally, the model generated using the logistic regression algorithm in the generalization test was selected to build a web tool for detecting undiagnosed diabetes. This model produced sensitivity of 68% and specificity of 67.2%. The prototype interface of the tool is shown in **Figure 2**. Since the model was constructed and probably would be used in Brazil, the tool was created in Portuguese.

The final coefficients of the equation generated are described in **Table 8**.

New cases can be classified using this model, as follows:

1. Standardize the value of the only numerical variable (a_rcq) by subtracting the training mean (0.8889311) from the value

and dividing the result by the training standard deviation (0.08615528).

2. Binarize the categorical variables;
3. Calculate the sum of the variables created in the preceding steps using the coefficients from **Table 8**;
4. Add to this sum the value of the intercept term, described in the first row of **Table 8**;
5. Calculate the probability of undiagnosed diabetes for a given individual = $1/(1+e^{-x})$, where x equals the sum resulting from the preceding steps.

If the probability is greater than 0.11, then classify the individual as presenting high risk of having undiagnosed diabetes; otherwise, classify the individual as presenting low risk.

Table 6. Error estimation results

Algorithm	Transformation	Variable subset	AUC (mean)	AUC (SD)	AUC (1q)	AUC (3q)	BA (mean)	BA (SD)
Artificial neural network	-	ann-fs	75.45%	1.96%	74.18%	76.96%	69.36%	2.17%
Artificial neural network	-	lr-fs	75.42%	1.99%	74.07%	77.04%	69.47%	2.14%
Artificial neural network	-	knn-fs	75.35%	1.98%	74.06%	76.85%	68.90%	2.09%
Artificial neural network	-	nb-fs	75.33%	2.05%	74.01%	76.95%	69.23%	2.30%
Artificial neural network	-	original	75.20%	1.96%	73.93%	76.79%	69.00%	2.20%
Logistic regression	-	lr-fs	75.44%	1.98%	74.00%	77.04%	69.30%	2.12%
Logistic regression	-	nb-fs	75.35%	2.02%	73.97%	76.93%	68.93%	2.07%
Logistic regression	-	ann-fs	75.35%	1.96%	74.09%	76.96%	68.91%	2.07%
Logistic regression	-	knn-fs	75.32%	1.95%	74.02%	77.00%	68.76%	2.10%
Logistic regression	-	original	74.94%	1.97%	73.58%	76.53%	68.41%	2.26%
K-nearest neighbor	-	knn-fs	74.98%	2.13%	73.54%	76.83%	68.52%	2.14%
K-nearest neighbor	-	ann-fs	74.80%	2.23%	73.51%	76.59%	68.74%	2.04%
K-nearest neighbor	-	lr-fs	74.77%	2.20%	73.22%	76.69%	68.63%	2.36%
K-nearest neighbor	-	nb-fs	74.68%	2.17%	73.15%	76.43%	68.64%	2.07%
K-nearest neighbor	-	original	74.44%	2.32%	72.99%	76.34%	68.52%	2.14%
Naïve Bayes	-	lr-fs	74.85%	2.20%	73.30%	76.56%	68.95%	2.17%
Naïve Bayes	-	ann-fs	74.71%	2.23%	73.23%	76.43%	68.79%	2.21%
Naïve Bayes	-	knn-fs	74.66%	2.19%	73.20%	76.39%	68.58%	2.14%
Naïve Bayes	Discretization	nb-fs	74.49%	2.12%	72.97%	76.11%	68.15%	2.06%
Naïve Bayes	Discretization	original	73.75%	2.35%	72.16%	75.53%	68.14%	2.15%
Random forest	-	original	72.81%	2.32%	71.61%	74.35%	67.06%	2.34%
Random forest	-	ann-fs	72.10%	2.24%	70.63%	73.79%	64.59%	2.33%
Random forest	-	knn-fs	71.75%	2.40%	70.05%	73.50%	59.72%	2.43%
Random forest	-	lr-fs	70.62%	2.53%	68.92%	72.33%	61.85%	2.56%
Random forest	-	nb-fs	70.42%	2.47%	68.69%	72.24%	61.19%	2.26%

AUC = area under the ROC curve; SD = standard deviation; 1q/3q = first and third quartiles; BA = balanced accuracy.

Table 7. Generalization testing results compared with those of the error estimation step

Algorithm	Error estimation		Generalization			
	AUC	BA	AUC	BA	Sensitivity	Specificity
Logistic regression	75.44%	69.30%	74.41%	67.62%	67.99%	67.24%
Artificial neural network	75.45%	69.36%	74.17%	67.78%	66.25%	69.30%
Naïve Bayes	74.85%	68.95%	74.06%	68.52%	74.94%	62.1%
K-nearest neighbor	74.98%	68.52%	73.34%	67.76%	70.97%	64.55%
Random forest	72.81%	67.06%	72.35%	67.50%	67.74%	67.24%

AUC = area under the ROC curve; BA = balanced accuracy.

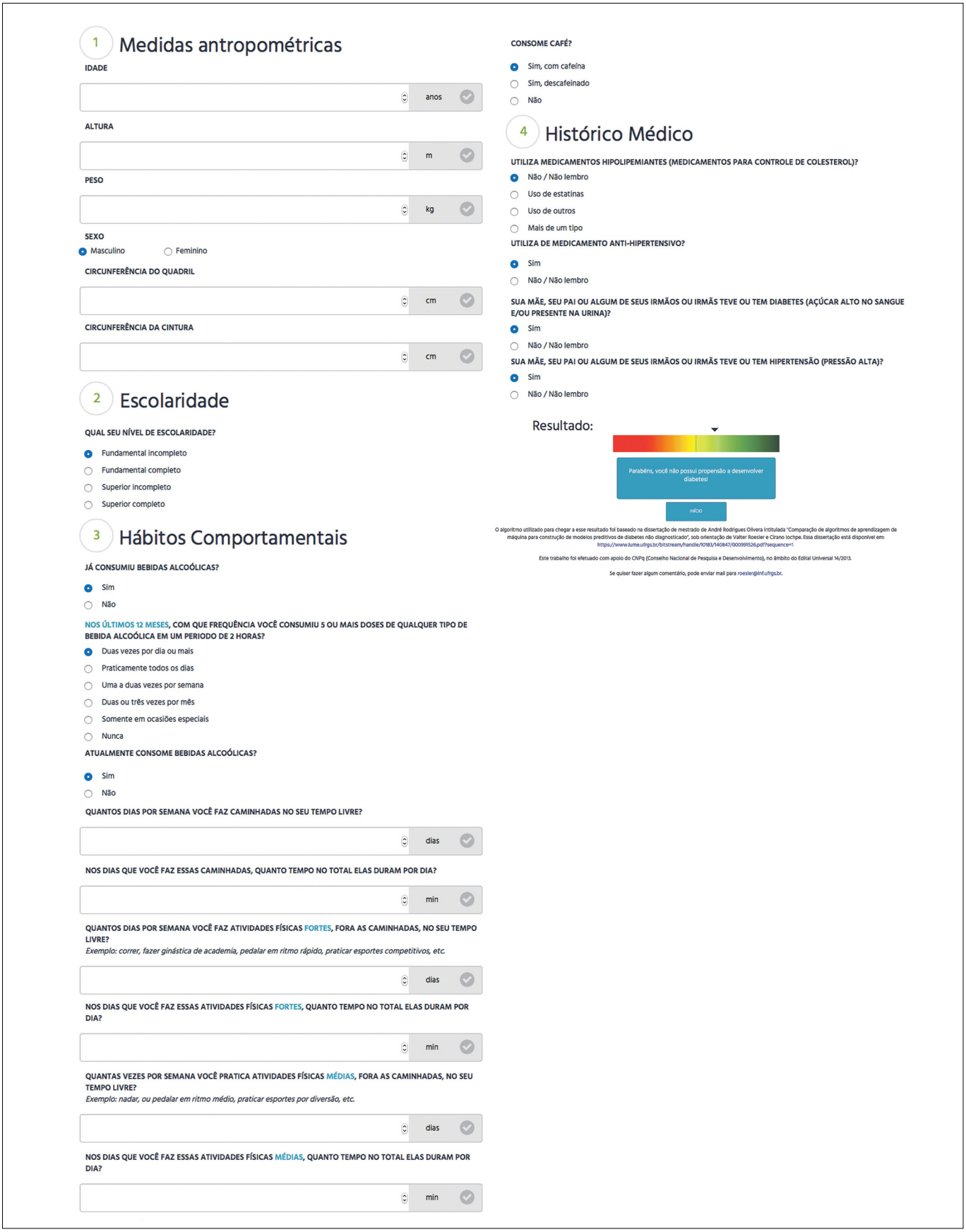

Figure 2. Prototype for a web interface for the risk equation.

Table 8. Coefficients from logistic regression model

Binarized variable	Coefficient
(Intercept)	-1.6929
rcta82	0.1826
a_gidade2	0.6458
a_gidade3	0.9566
a_gidade4	1.0548
a_escolar2	-0.2023
a_escolar3	-0.3556
a_escolar4	-0.6952
diea1331	-0.2811
diea1332	-0.1339
a_binge1	0.2614
a_ativfisica2	-0.1071
a_ativfisica3	-0.3266
a_imc22	-1.0311
a_imc23	-0.8642
a_imc24	-0.3796
a_rcq	0.5417
a_medanthipert1	0.4137
hfda071	-0.1386
hfda111	0.3666

DISCUSSION

We created predictive models for detecting undiagnosed diabetes using data from the ELSA study with different machine-learning algorithms. The best results were achieved through both an artificial neural network and logistic regression, with no relevant difference between them.

Generally, most of the algorithms used achieved mean AUCs greater than 70%. The best algorithm (logistic regression) produced an AUC of 74.4%. Since these test dataset values are superior to the AUCs of several other scores that were previously validated in other populations,[20] this score shows potential for use in practice.

The generalization testing showed the results from asking a population similar to that of ELSA some simple questions. Out of 403 individuals from the testing dataset who had diabetes and did not know about their condition, 274 were identified as positive cases (68.0% sensitivity) using the model generated through the logistic regression algorithm. The web tool prototype for detecting undiagnosed diabetes could be refined for use in Brazil.

The methods and concepts for building predictive models for use in healthcare, as well as the challenges and difficulties faced when analyzing healthcare data, have been well described.[17-23] Many groups have published predictive models for detecting undiagnosed diabetes. Although several groups have reported AUCs above 0.80, these values generally reduce to < 0.70 when tested on independent samples.[20] Differences in predictive power across studies can be ascribed to different characteristics relating to the different datasets, and to different techniques and methods for building and evaluating the models. The characteristics that may vary across studies include the definition of the target variable, model objectives and candidate variables, among others. These models are generally constructed using conventional statistical techniques such as logistic regression and Cox regression. Systematic reviews[5,16,24-26] present several such studies: some, like ours, have focused on predicting undiagnosed diabetes; while others have focused on individuals at high risk of developing incident diabetes.

Use of machine-learning techniques is still new in this field.[27-29] The main studies have compared the results obtained through using a specific technique with the results obtained through logistic regression. One report[30] described creation of pre-diabetes risk models using an artificial neural network and support-vector machines that were applied to data from 4,685 participants in the Korean National Health and Nutrition Examination Survey (KNHANES), collected between 2010 and 2011. In comparison with results[31] from logistic regression on the same dataset, the models created using support-vector machines and an artificial neural network produced slightly better results.

Two other reports[32,33] also compared artificial neural networks with logistic regression for creating predictive diabetes models. In the first, models created using artificial neural networks on data from 8,640 rural Chinese adults (760 of them with diabetes) produced better results (AUC = 89.1% ± 1.5%) than models created using logistic regression (AUC = 74.4% ± 2.1%). In the second, a radial basis function artificial neural network that was applied to data from 200 people (100 cases with diabetes and 100 with pre-diabetes) at 17 rural healthcare centers in the municipality of Kermanshah, Iran, showed better results than logistic regression and discriminant analysis, for identifying those with diabetes. Another study[34] comparing diabetes models created using data from 2,955 women and 2,915 men in the Korean Health and Genome Epidemiology Study (KHGES) showed similar results from logistic regression and naïve Bayes, although naïve Bayes showed better results with unbalanced datasets. Finally, another study[35] used data from 6,647 participants (with 729 positive cases) in the Tehran Lipid and Glucose Study (TLGS) and created models with decision trees reaching 31.1% sensitivity and 97.9% specificity (balanced accuracy was around 64.5%),[36] for detecting increased blood glucose levels.

In summary, use of machine-learning techniques may prove to be a viable alternative for building predictive diabetes models, often with good results, but rarely with notably superior results, compared with the conventional statistical technique of logistic regression.

CONCLUSION

Comparison between different techniques showed that all of them produced quite similar results from the same dataset used, thus demonstrating the feasibility of detecting undiagnosed diabetes through easily-obtained clinical data. The predictive algorithm for identifying individuals at high risk of having

undiagnosed diabetes — based only on self-reported information from participants in ELSA-Brasil, from which the highest AUC (0.74) was obtained when tested on a part of the sample that had not been used for its derivation — was a logistic regression equation. However, the machine-learning techniques of artificial neural network, naïve Bayes, k-nearest neighbor and random forest all produced AUCs that were similar or slightly smaller.

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Randomized clinical study on the analgesic effect of local infiltration versus spinal block for hemorrhoidectomy

Estudo clínico randomizado do efeito analgésico da infiltração local *versus* bloqueio espinal para hemorroidectomia

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KEY WORDS:
Anesthesia, local.
Anesthesia, spinal.
Analgesia.
Postoperative complications.
Hemorrhoidectomy.
Randomized controlled trial.

PALAVRAS CHAVE:
Anestesia local.
Raquianestesia.
Analgesia.
Complicações pós-operatórias.
Hemorroidectomia.
Estudo clínico controlado aleatório.

ABSTRACT

BACKGROUND AND OBJECTIVES: Postoperative analgesia and early recovery are important for hospital discharge. The primary objective of this study was to compare the analgesic effectiveness of perianal infiltration and subarachnoid anesthesia for hemorrhoidectomy. The secondary objective was to compare time to discharge, adverse effects and complications.

DESIGN AND SETTING: Randomized, prospective and comparative study at Dr. Mário Gatti Hospital.

METHODS: Forty patients aged 18-60, in American Society of Anesthesiologists physical status category 1 or 2, were included. The local group (LG) received local infiltration (0.75% ropivacaine) under general anesthesia; the spinal group (SG) received subarachnoid block (2 ml of 0.5% bupivacaine). Analgesic supplementation consisted of fentanyl for LG and lidocaine for SG. Postoperative pain intensity, sphincter relaxation, lower-limb strength, time to discharge, analgesic dose over one week and adverse effects were assessed.

RESULTS: Eleven LG patients (52.4%) required supplementation, but no SG patients. Pain intensity was higher for LG up to 120 min, but there were no differences at 150 or 180 min. There were no differences in the need for paracetamol or tramadol. Times to first analgesic supplementation and hospital discharge were longer for SG. The adverse effects were nausea, dizziness and urinary retention.

CONCLUSIONS: Pain intensity was higher in LG than in SG over the first 2 h, but without differences after 150 and 180 min. Time to first supplementation was shorter in LG. There were no differences in doses of paracetamol and tramadol, or in adverse effects.

REGISTRATION: ClinicalTrials.gov NCT02839538.

RESUMO

CONTEXTO E OBJETIVO: A analgesia pós-operatória e a recuperação precoce são relevantes para a alta hospitalar. O objetivo primário deste estudo foi comparar a eficácia analgésica da infiltração perianal e da anestesia subaracnóidea para hemorroidectomia. O objetivo secundário foi comparar o tempo para alta, efeitos adversos e complicações.

TIPO DE ESTUDO E LOCAL: Estudo randomizado prospectivo e comparativo, no Hospital Dr. Mário Gatti.

MÉTODOS: Foram incluídos 40 pacientes com idades 18-60 anos, na categoria 1 ou 2 de status físico da Sociedade Americana de Anestesiologistas. O grupo local (GL) recebeu infiltração local (ropivacaína a 0,75%) sob anestesia geral; o espinal (GS) recebeu bloqueio subaracnóideo (2 ml de bupivacaína a 0,5%). A suplementação analgésica foi com fentanil para GL e lidocaína para GS. Foram avaliados: intensidade da dor no pós-operatório, relaxamento do esfíncter, força dos membros inferiores, tempo de alta, dose de analgésico em uma semana e efeitos adversos.

RESULTADOS: Onze (52,4%) pacientes em GL necessitaram de complementação, e nenhum em GS. A intensidade da dor foi maior para GL até 120 minutos, sem diferenças em 150 ou 180 minutos. Não houve diferenças na necessidade de paracetamol ou tramadol. O tempo para a primeira complementação analgésica e a alta hospitalar foram maiores para GS. Os efeitos adversos foram náuseas, tonturas e retenção urinária.

CONCLUSÕES: A intensidade da dor foi maior na GL que na GS nas primeiras 2 horas, porém sem diferenças após 150 e 180 minutos. O tempo para a primeira suplementação foi menor na GL; sem diferenças nas doses de paracetamol e tramadol e efeitos adversos.

REGISTRO: ClinicalTrials.gov NCT02839538.

INTRODUCTION

Hemorrhoidectomy is often performed in outpatient settings. This surgical procedure can be conducted by means of local infiltration,[1-5] in association with sedation and/or general anesthesia with pudendal nerve block,[4,6,7] spinal block[5,6,8] or epidural block,[9,10] or with general anesthesia alone.[7] The choice of anesthesia depends on the characteristics of both the disease and the patient, as well as professional experience.

Quick recovery, along with adequate and safe postoperative analgesia, is an important factor in relation to hospital discharge after any surgical procedure. The adverse effects and complications associated with the various techniques might increase the length of stay at the hospital, patient morbidity and healthcare costs.

Spinal anesthesia is widely used because of its simplicity, the quality of the analgesia obtained and the induction of anal sphincter relaxation that it provides, which is required for hemorrhoidectomy.[11] However, this procedure is also associated with complications such as urine retention,[12] with consequent discharge delay.

Perianal infiltration is a simple, easy-to-perform technique that is safer than spinal anesthesia because it does not involve the neuraxis. Long-acting local anesthetics are used to achieve longer analgesic effects. Some studies have shown that local infiltration with ropivacaine was effective for hemorrhoidectomy.[3] However, other authors have used drug volumes that were too large (i.e. 40 ml for a 0.75% solution).[13,14]

No consensus yet exists regarding the efficacy of local infiltration, the duration of its effect or the associated adverse effects and complications. Therefore, studies that assess both the analgesic and adverse effects are necessary.

The primary objective of this study was to compare the analgesic effectiveness of perianal infiltration and subarachnoid anesthesia for hemorrhoidectomy. The secondary objective was to compare the time to discharge, the adverse effects and the complications.

METHODS

Study type and setting

This was a randomized controlled trial. Data were collected at Hospital Dr. Mário Gatti between December 2014 and November 2015.

Ethics

This study was firstly approval by the ethics committee of Universidade Federal de São Paulo (CAAE 3714054.9000.5505). Patients undergoing hemorrhoidectomy were included in the study after they had signed an informed consent form. The study was registered at ClinicalTrials.gov (NCT02839538).

Sample size

The sample size calculation was performed using SPSS for Windows. It was assumed that the response rate to the treatment tested would be a 30% reduction in pain intensity, with 95% power (beta), P = 0.05 (alpha) and an estimated standard deviation of 2.44. Therefore, the sample size would need to be 18 participants per group.[15]

Participants

All patients undergoing hemorrhoidectomy in the same institution between December 2014 and November 2015 were included. The following patients were excluded from the study: those with associated conditions (fistula and fissure), infection of the puncture site, cognitive disorders, psychiatric illnesses, myocardial ischemia, arrhythmia or any other painful syndrome; those using anticoagulants or analgesics (within the last two weeks before the intervention); illicit drug users; and pregnant women.

Randomization

Randomization was performed by an author who did not participate in the anesthesia and assessment, using the Randomizer software. The group assignment of each participant was placed inside an envelope numbered from 1 to 40. Participant allocation was performed via a draw, in which the envelopes were opened before the start of the intervention, at the surgical center. The participants were thus randomly selected to receive one type of anesthesia. It was impossible to read what was inside the envelopes. One surgeon performed all of the infiltration procedures, and one anesthetist performed both the general anesthesia for the local infiltration group (LG) and the spinal anesthesia for the spinal anesthesia group (SG). Another investigator who was not involved in the study evaluated the participants.

Interventions

The participants were allocated to one of two groups. LG received surgery with local infiltration and general anesthesia, and SG received spinal block.

Monitoring during anesthesia was performed via pulse oximetry, cardioscopy, non-invasive blood pressure measurement and (in LG) capnography.

In LG, general anesthesia was administered using propofol (3 mg/kg), atracurium (0.5 mg/kg), propofol infusion (100 μg/kg/min), oxygen and a laryngeal mask. Next, the same surgeon performed local infiltration with 20 ml of 0.75% ropivacaine, which was injected between the internal and external anal sphincters using a 0.8 x 30-mm needle.

In SG, puncture was performed with the patients in a sitting position, using a 27G Quincke needle between L4 and L5 or between L5 and S1, with injection of 2 ml of 0.5% hyperbaric bupivacaine. After 10 min, the anesthesia was tested via the pinprick method, and patients whose score was zero on the pain scale proceeded to surgery.

Analgesic supplementation was performed as needed, using 50 μg of intravenous fentanyl in LG and infiltration of 5 ml of 1% lidocaine in SG.

Postoperative analgesic rescue was initially performed using acetaminophen 500 mg/dose (maximum: 4 g/day). The cases without adequate relief 1 h later were given a tramadol dose of 50 mg.

Outcomes

Upon discharge, the participants received a form, to be returned one week later, to record the following data: time of pain onset, amount of analgesics taken and adverse effects. Pain intensity was assessed on a numerical scale (from zero to 10).

The following outcomes were also assessed: need for intraoperative analgesic supplementation; sphincter relaxation (under conditions appropriate for surgery); postoperative pain intensity on a rating scale ranging from 0 to 10 at the end of surgery (T0) and every 30 min afterwards up to 180 min; dose of postoperative analgesic; time to first supplementation (from anesthesia to first dose); motor function of the lower limbs every 30 min until discharge in accordance with the Bromage scale (where 0 = no motor block; 1 = able to flex knees and move the feet but not lift the legs; 2 = able to move the feet only; and 3 = unable to move knees or feet); and time to hospital discharge (score 9-10 on Chung's scale).[16] The primary outcome was postoperative pain, and the secondary outcomes were adverse effects and time to discharge. Adverse effects and complications were also recorded.

Statistical analyses

Statistical analyses were performed using SPSS for Windows. The following tests were applied: Mann-Whitney test for body mass index, pain intensity and first need for analgesic; chi-square test for gender, physical status and adverse effects; and Student's t test for age, body weight, height, acetaminophen and tramadol dose, duration of surgery and time to discharge. The significance level was set at $P \leq 0.05$.

RESULTS

Forty patients of both genders, aged 18 to 60 years, who presented physical status 1 or 2 of the American Society of Anesthesiologists classification and were scheduled to undergo hemorrhoidectomy, were included in this study. The protocol sequence is shown in a flowchart (**Figure 1**). The groups did not differ significantly, with

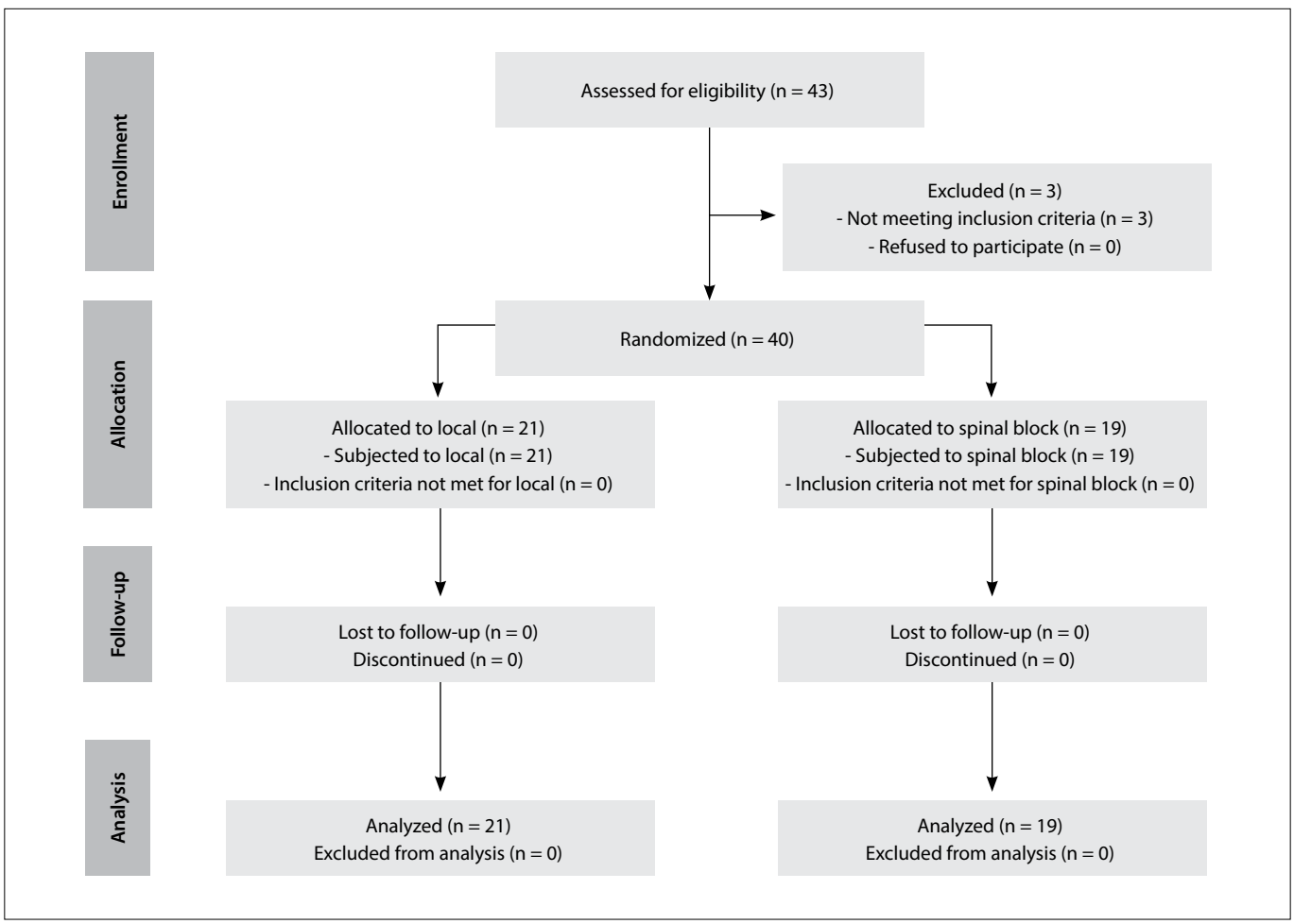

Figure 1. Consort flow diagram.

regard to their demographic data (**Table 1**) or duration of surgery (LG: 48.4 ± 2.9 min; SG: 57.8 ± 4.2; P = 0.07; Student's t test). Sphincter relaxation was satisfactory for all participants.

Eleven participants (52.4%) in LG (local group) (35.7 ± 42.3 μg) but none of the patients in SG required intraoperative analgesic supplementation with fentanyl.

The pain intensity was higher for LG at 0, 30, 60, 90 and 120 min after surgery, but there was no significant difference at 150 or 180 min (**Table 2**). Time to first analgesic supplementation was longer for SG (**Table 3**). The groups did not differ with regard to their use of acetaminophen or tramadol during the first week after surgery (**Table 3**).

All of the participants in SG scored zero on the Bromage scale, 210 min after the end of surgery. The time to discharge, calculated from the onset of anesthesia, was longer for SG (LG: 241.9 ± 8.1 min; SG: 347.5 ± 27.6 min; P = 0.0005; Student's t test).

The participants reported the following adverse effects: nausea (LG: 4; SG = 0; P = 0.14; chi-square test), dizziness (LG: 1; SG: 0; p = 0.340; chi-square test) and urine retention (LG: 0; SG: 4; P = 0.09; chi-square test).

Table 1. Sociodemographic and clinical characteristics of participants, according to age, gender, weight, body mass index and ASA physical status

	Local	Spinal	P
Age (years)	40.1 ± 2.7	40.0 ± 2.3	0.96*
Gender: M/F	8/13	13/6	0.07†
Weight (kg)	71.1 ± 2.9	72.9 ± 3.8	0.71*
Height (cm)	165.0 ± 2.2	159.6 ± 9.1	0.55*
BMI (kg/m²)	24.2	24.9	0.52‡
ASA I/II	12/9	11/8	0.96

BMI = body mass index; ASA = American Society of Anesthesiologists classification; *Student's t test (mean ± standard deviation); †chi-square test; ‡Mann-Whitney test.

Table 2. Intensity of pain at each 30 minutes, according to numerical scale (mean ± standard deviation)

Time	Local	Spinal	P
T0	3.8 ± 3.9	0 ± 0	NC
T30	5.1 ± 2.9	0.1 ± 0.2	< 0.0001
T60	4.3 ± 2.9	0.0 ±0.0	NC
T90	3.9 ± 2.9	0.5 ± 1.3	< 0.0001
T120	3.4 ± 2.8	0.9 ± 1.9	0.003
T150	2.4 ± 2.7	1.3 ± 2.2	0.17
T180	2.0 ± 3.0	1.9 ± 2.9	0.91

Student's t test; NC = not calculated; T0 = end of surgery.

Table 3. Time that elapsed until first postoperative supplementation (after infiltration or spinal block), expressed as mean (minimum-maximum); doses of acetaminophen (mean ± standard deviation, SD); and doses of tramadol (mg) expressed as mean (minimum-maximum)

	Local	Spinal	P
First supplementation (minutes)	84 (68.5-106)	292 (240-343)	< 0.0001*
Acetaminophen (24 hour)	1.605 ± 112.0	1.500 ± 119.5	0.53†
Tramadol (24 hour)	150 (150-200)	150 (100-175)	0.13*
Acetaminophen (1 week)	4.929 ± 606.8	6.426 ± 800	0.14†
Tramadol (1 week)	450 (325-525)	450 (300-600)	0.82*

*Mann-Whitney test, expressed as mean (minimum-maximum); †Student's t test (mean ± SD).

DISCUSSION

The pain intensity was higher for LG than SG over the first 2 h after hemorrhoidectomy. The time to the first analgesic supplementation was significantly shorter, with no difference in the analgesic supplementation or in adverse effects.

This study investigated infiltration because this technique is simple, and recovery is quick; thus, it is appropriate for surgery in outpatient settings. Infiltration alone might promote an adequate level of analgesia for surgery, but patients remain able to perceive the surgical manipulation. This feeling is often uncomfortable; therefore, medication needs to be administered, to sedate the patients. Infiltration can be performed in combination with sedation,[17] or with general anesthesia as in this study. Another study has also combined these methods.[18] Like us, the authors of a previous study[8] used a laryngeal mask to combine general anesthesia with fentanyl, propofol and spinal anesthesia, in order to promote greater patient comfort during local infiltration of anesthetic. In the present study, only fentanyl was used for supplementation, because this was sufficient to maintain postoperative analgesia.

According to the authors of one study, the quality of postoperative analgesia is better when the full posterior perineum is blocked. However, the technique involved is more complex, and higher doses of anesthetics are used.[14] Local anesthetic can be absorbed, causing toxic effects that make it impossible for clinicians to administer large doses, particularly regarding bupivacaine.

As in other studies,[13,14] we administered long-acting 0.75% ropivacaine, which is less toxic than bupivacaine. On the other hand, ropivacaine causes vasoconstriction, which limits its blood absorption.[19] Alternatively, short-acting lidocaine[17] or bupivacaine[12] can also be used.

The volume of anesthetic reported in the literature has varied widely, from 6 ml[9] to 20 ml[10] and 40 ml.[13,14] We used an intermediate dose of 20 ml.

The peak plasma concentration is achieved 15 min after ropivacaine infiltration into the subcutaneous tissue.[20,21] However, no previous study has reported local infiltration for treating hemorrhoidectomy.

In another study, 47% of the patients reported pain and discomfort during surgery. However, the dose used was small (6 ml of 0.25% bupivacaine),[22] compared with what was used in the present study.

Local infiltration with 0.25% bupivacaine has been reported to promote excellent sphincter relaxation.[22] In the present study,

the sphincter relaxation obtained in all of the participants was adequate for surgery.

In one study, there was no difference in pain score after 24 h, after local or spinal anesthesia, except at the 6-h assessment, when the intensity was higher for the group that received spinal anesthesia. Postoperative analgesia was excellent in more than 90% of the participants who received local infiltration, but was excellent in less than 50% of the group that received a spinal block.[5] Another study did not find any differences in pain intensity between the local infiltration and spinal anesthesia groups at 6 and 24 h after surgery; however, the latter group required more analgesic rescue treatment.[12]

In one study in which bupivacaine infiltration was performed in combination with general anesthesia, the analgesic effect lasted for approximately 10 h,[18] i.e. much longer than the effect in the present study (i.e. 84 min).

It should be noted that this study presents the limitation that it was not possible to blind the groups.

In this study, the length of hospital stay was shorter for LG than for SG, which corroborates the results reported in the literature.[5] Longer stays after spinal anesthesia for hemorrhoidectomy have been correlated with urine retention, pain and bleeding.[23]

In this study, urinary retention occurred in 19% of SG. However, the incidence of this complication reported in the literature is higher: between 30%[12] and 36%.[5] Motor block of the lower limbs might prolong the hospital stay.

Following spinal anesthesia, the reported rate of headaches is 24%.[5] In the present study, nausea was reported by 19% of LG, whereas the analgesic rescue dose did not differ between the groups. One study that used perianal infiltration did not detect any complications.[24] Intraoperative arterial hypotension occurred in another study,[12] but did not occur in the present study.

CONCLUSION

In this study, local infiltration showed less postoperative analgesic efficacy, but recovery was faster. In clinical practice, analgesia might be enhanced through preventive multimodal combination of analgesics at the end of surgery. Infiltration might be an alternative option for patients undergoing hemorrhoidectomy.

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Somatic maturation and the relationship between bone mineral variables and types of sports among adolescents: cross-sectional study

Maturação somática e o relacionamento entre variáveis minerais ósseas e modalidades esportivas em adolescentes: estudo transversal

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KEY WORDS:
Adolescent.
Bone density.
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PALAVRAS-CHAVE:
Adolescente.
Densidade óssea.
Crescimento e desenvolvimento.
Esportes.
Puberdade.

ABSTRACT

CONTEXT AND OBJECTIVE: Peak height velocity (PHV) is an important maturational event during adolescence that affects skeleton size. The objective here was to compare bone variables in adolescents who practiced different types of sports, and to identify whether differences in bone variables attributed to sports practice were dependent on somatic maturation status.

DESIGN AND SETTING: Cross-sectional study, São Paulo State University (UNESP).

METHODS: The study was composed of 93 adolescents (12 to 16.5 years old), divided into three groups: no-sport group (n = 42), soccer/basketball group (n = 26) and swimming group (n = 25). Bone mineral density and content were measured using dual-energy x-ray absorptiometry and somatic maturation was estimated through using peak height velocity. Data on training load were provided by the coaches.

RESULTS: Adolescents whose PHV occurred at an older age presented higher bone mineral density in their upper limbs (P = 0.018). After adjustments for confounders, such as somatic maturation, the swimmers presented lower values for bone mineral density in their lower limbs, spine and whole body. Only the bone mineral density in the upper limbs was similar between the groups. There was a negative relationship between whole-body bone mineral content and the weekly training hours (β: -1563.967; 95% confidence interval, CI: -2916.484 to -211.450).

CONCLUSION: The differences in bone variables attributed to sport practice occurred independently of maturation, while high training load in situations of hypogravity seemed to be related to lower bone mass in swimmers.

RESUMO

CONTEXTO E OBJETIVO: O pico de velocidade de crescimento (PVC) constitui importante evento maturacional durante a adolescência, afetando o tamanho do esqueleto. O objetivo do estudo foi comparar variáveis ósseas em adolescentes praticantes de diferentes modalidades esportivas, bem como identificar se diferenças nas variáveis ósseas atribuídas à prática esportiva são dependentes do estado da maturação somática.

DESENHO E LOCAL: Estudo transversal, Universidade Estadual Paulista (UNESP).

MÉTODOS: O estudo foi constituído por 93 adolescentes (12 a 16,5 anos), divididos em três grupos: grupo sem envolvimento esportivo (n = 42), futebol/basquete (n = 26) e natação (n = 25). A densidade e conteúdo mineral ósseo foram mensurados utilizando absortiometria de raio-x de dupla energia e a maturação somática foi estimada através do uso do PVC. Informações sobre volume de treinamento foram fornecidas pelos treinadores.

RESULTADOS: Adolescentes com idade tardia no PVC apresentaram maiores valores de densidade mineral óssea em membros superiores (P = 0,018). Após ajustes por variáveis de confusão, como a maturação somática, os nadadores apresentaram menores valores de densidade mineral óssea em membros inferiores, coluna e corpo inteiro. Apenas a densidade mineral óssea de membros superiores foi similar entre os grupos. Existiu relação negativa entre conteúdo mineral ósseo de corpo inteiro e tempo de treino semanal (β: -1563.967; 95% intervalo de confiança, IC: -2916.484 a -211.450).

CONCLUSÃO: As diferenças em variáveis ósseas atribuídas à prática esportiva ocorrem independentemente da maturação, enquanto elevada quantidade de treinamento em situações de hipogravidade parece estar relacionada com menor massa óssea em nadadores.

INTRODUCTION

Osteoporosis constitutes a widespread disease among the elderly population and it is associated with high economic costs.[1,2] Although less common in pediatric populations, development of osteoporosis has been linked to peak bone mass gained during early life.[3,4] There is a natural decrease in bone mass during later life and, therefore, adolescents who present lower peak bone mass have an increased likelihood of developing osteoporosis during adulthood.[3,4] Consequently, early life has been highlighted as a critical period for development of osteoporosis during adulthood.[5] Hence, variables relating to peak bone mass during childhood and adolescence have been widely investigated and several variables have been pointed out as potential determinants of modifications to peak bone mass, such as: nutritional factors, genetics and practicing physical activity.[3-5]

Regarding physical activity, its practice stimulates release of hormones relating to higher rates of bone formation.[6,7] In addition, the physical load on bone structure that is generated by exercise stimulates its turnover.[7] Several sports cause high training load during practice and thus act positively on bone accrual during growth, such as soccer, tennis and rugby.[8-11] However, the effects on bone mineral variables caused by sports participation performed in hypogravity during adolescence still remain unclear,[10,12] mainly because previous studies failed to control for the burden of important potential confounders in early life, such as training load and biological maturation.[12]

In terms of bone mass gain, the pubertal period is responsible for significant accrual of bone mass in both boys and girls.[13] Peak height velocity (PHV) is an important maturational event that occurs during adolescence, significantly increasing the skeleton size.[13] PHV precedes the peak bone mass accrual, thus denoting a period of potential risk of fractures,[13,14] during which skeletal mass does not accompany the increase in skeleton size. On the other hand, the impact of this dissociation between linear growth and bone mass gain on the recognized osteogenic effect caused by exercise is still unclear.

OBJECTIVE

Therefore, the purposes of this study were:

1. To compare bone mineral variables in adolescents according to different sports; and
2. To identify whether the potential differences in bone mineral variables attributed to sports participation are dependent on somatic maturation status.

METHODS

Design, setting and ethics

This was a cross-sectional study that formed part of a larger cohort study entitled "*Practice of different sports and bone mass gain in adolescents: 9-month cohort study*", which was conducted from October 2013 to July/August 2014. The information presented in this study concerns data collected at the baseline. Adolescents were recruited from three public schools and three sports clubs that specialized in soccer, basketball and swimming. This study was previously approved by our institution's ethics board (CAAE; no. 02891112.6.0000.5402).

Sample

The sample size estimation was made using an equation based on analysis of variance (ANOVA), which took into account a minimum difference for whole-body bone mineral content (BMC) of 89 grams between the control and sports groups,[15] a standard deviation of 37 g for three independent groups (no-sport, swimming and soccer groups), power of 80% and alpha of 5%. The final sample size was estimated as a minimum of 12 adolescents per group and, therefore, a minimum of 36 adolescents was required.

Participants

The following inclusion criteria were adopted:

1. Chronological age between 11 and 17 years old;
2. A minimum of six months of practice (swimming, soccer or basketball) or absence of participation in any organized sports over the previous six months (no-sport group);
3. No use of medication that could affect bone metabolism; and
4. Prior authorization from the coach and parents to take part in the study and presentation of a signed consent form.

Initially, 190 adolescents of ages ranging from 11 to 17 years old were contacted (74 in the no-sport group and 116 athletes).

Adolescents in the no-sport group were excluded in the following situations: [1] practice of organized sport within the previous six months; or [2] engagement in recreational sports activities on more than two days per week. Adolescents involved in organized sports were excluded in the following situations: [1] less than six months of practice in the current sport; or [2] engagement in more than one sport. For statistical analysis, impact sports (soccer and basketball) were combined into one group.

The swimmers and soccer players participated in competitions at national level, while the basketball players participated in regional-level competitions. Their coaches provided data on their weekly training load over the previous six months (minutes/week [min/wk]). The athletes reported their previous engagement time (in months) and the age at which they started practicing their current sport.

Anthropometry

Body mass was measured using an electronic scale (Filizola model PL 150; Filizola Ltda., Brazil). Total height (i.e. height when standing upright) and seated height were measured using a stadiometer (Sanny model; American Medical of Brazil Ltda., Brazil)

and leg length was calculated by subtraction of seated height from total height. A single trained technician made all the measurements on the subjects during a visit that they made to the laboratory.

Bone mineral variables

Bone mineral density (BMD, in g/cm^2), BMC (in grams), body fat (in percentages) and fat-free mass (FFM; in kilograms) were assessed using a dual-energy x-ray absorptiometry scanner (Lunar DPX-NT; General Electric Healthcare, Little Chalfont, Buckinghamshire, UK) with Lunar software (version 4.7) (GE Medical Systems). The scanner quality was tested by a trained researcher prior to each day of measurement, following the manufacturer's recommendations. The participants wore light clothing, without shoes, and remained in the supine position on the machine (approximately 15 minutes). BMD measurements were made for:

1. Head (head and neck);
2. Upper limbs;
3. Lower limbs;
4. Spine; and
5. Whole body.

The proportion of each of these body segments as a percentage of whole-body BMC was calculated for the head, lower limbs, upper limbs and trunk (including rig cage, spine and pelvis), as follows: [BMC-body segment * 100]/overall BMC. The precision of the machine in terms of coefficient of variation was 0.66% (n = 30 subjects not involved in this study) and all scans were carried out in a temperature-controlled laboratory at the university.

Peak height velocity

The measurements of body mass, height, seated height and leg length were used to calculate maturity offset, which denotes the time (years) from/to PHV.[16] The sample was stratified according to PHV as follows: (i) "on time" (boys: 13.4-14.8 years; and girls: 11.8-13.0); and (ii) "late" (boys: > 14.8 years; and girls: > 13.0 years), and "early" (boys: < 13.4 years; and girls: < 11.8 years).[17]

Maturity offset for boys (in years) = -9.236
+ (0.0002708 * (leg length * seated height))
+ (-0.001663 * (age * leg length))
+ (0.007216 * (age * seated height))
+ (0.02292 * (body mass/height *100))

Maturity offset for girls (in years) = -9.376
+ (0.0001882 * (leg length * seated height))
+ (0.0022 * (age * leg length))
+ (0.005841* (age * seated height))
+ (0.002658 * (age * body mass))
+ (0.07693 * (body mass/height *100))

Statistical analysis

The descriptive statistics comprised the mean, standard error of the mean (SEM) and 95% confidence interval (95% CI). Training load (minutes per week) presented nonparametric distribution and was therefore analyzed after logarithmic transformation. Linear regression was used to analyze the relationship between training load and bone mineral variables, adjusted for chronological age, sex, biological maturation, height, FFM and duration of previous engagement in the sport. Analysis of covariance (ANCOVA) was used to compare mean differences according to sports, controlled for potential confounders (chronological age, sex, biological maturation, height, FFM and duration of previous engagement in the sport), and to generate estimated means and SEM. In all the ANCOVA models, homogeneity of variance was assessed using Levene's test. The associated magnitude effect was determined by means of effect size correlations (ES-r). This effect size was estimated using the square root of the ratio between the F-value squared and the difference between the F-value squared and degrees of freedom. Coefficients were interpreted as follows: trivial ($r < 0.1$), small ($0.1 > r < 0.3$), moderate ($0.3 > r < 0.5$), large ($0.5 > r < 0.7$), very large ($0.7 > r < 0.9$), nearly perfect ($r > 0.9$) and perfect ($r = 1$).[18] Statistical significance (P-value) was set at $P < 0.05$ and the statistical software BioEstat (version 5.0) was used to perform analyses.

RESULTS

For this study, after checking for compliance with the inclusion criteria, only 93 eligible adolescents were contacted. They were at six different locations, including public/private schools and sports clubs: no-sport group (n = 42) and sport groups (n = 51; 25 swimmers, 18 soccer players and 8 basketball players). The sample thus selected was composed of adolescents of both sexes equally (58.1% boys and 41.9% girls; $\chi^2 = 2.419$; $P = 0.120$) with ages ranging from 12 to 16.5 years.

Table 1 presents descriptive results according to groups of sport practice. There were significant differences for height, fat mass (%) and fat-free mass (kg) in the no-sport group compared with the soccer/basketball group and swimmers. Regarding bone variables (bone mineral density and bone mineral content), we found significant differences between the groups regarding the upper limbs, lower limbs and whole body. After stratification according to PHV, adolescents with late PHV presented higher BMD in the upper limbs, while the values for fat mass and FFM were similar (**Figure 1**).

After adjustments for confounders, such as somatic maturation, swimmers had lower values for BMD in their lower limbs, spine and whole body, compared with the no-sport group and basketball players. Only BMD in the upper limbs was similar between the groups (**Table 2**). The somatic maturation (PHV) presented a trivial effect size in all BMD variables: upper limbs (ES-r 0.000;

P = 0.840), lower limbs (ES-r 0.030; P = 0.110), spine (ES-r 0.004; P = 0.582) and whole body (ES-r 0.004; P = 0.545). BMD in the lower limbs and whole body were marginally significant in the soccer/basketball group, compared with the swimmers and no-sport group.

In the whole sample, the percentage of BMC accounted for by the individual's head in comparison with the whole-body BMC was 18.5% (range: 12.3% to 27.7%), upper limbs 11.4% (8.8% to 14.7%), lower limbs 38.6% (31.4% to 45.8%) and trunk 31.3% (24.1% to 37.5%). Swimmers' heads represented a higher percentage of

Table 1. Characteristics of adolescents practicing different sports (12 to 16.5 years of age)

Variables	No-sport group (n = 42)	Soccer/basketball (n = 26)	Swimming (n = 25)	ANOVA P-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Chronological age (years)	13.1 (1.1)	13.8 (1.3)	13.4 (1.0)	0.063
Age at peak height velocity (years)	14.9 (0.9)	15.2 (0.6)	15.3 (0.6)	0.118
Maturity offset	-1.64 (0.7)	-1.09 (1.0)[a]	-1.31 (0.8)	0.040
Height (cm)	160.3 (6.5)	170.0 (9.1)[a]	166.7 (8.3)[a]	< 0.001
Body mass (kg)	55.2 (10.8)	60.2 (13.0)	58.7 (10.1)	0.182
Fat mass (%)	32.2 (9.9)	15.4 (8.1)[a]	19.8 (10.2)[a]	< 0.001
Fat-free mass (kg)	33.5 (4.5)	47.0 (8.4)[a]	43.4 (8.0)[a]	< 0.001
Duration of previous training (months)*	–	71 (37)	69 (40)	0.821
Quantity of training (minutes/week)*	–	724 (328)	1065 (211)	< 0.001
Bone mineral density†				
DXA upper limbs (g/cm^2)	0.731 (0.07)	0.811 (0.10)[a]	0.786 (0.07)[a]	< 0.001
DXA lower limbs (g/cm^2)	1.144 (0.10)	1.356 (0.14)[a]	1.142 (0.11)[b]	< 0.001
DXA spine (g/cm^2)	1.013 (0.15)	1.066 (0.16)	0.992 (0.09)	0.152
DXA whole body (g/cm^2)	1.071 (0.08)	1.174 (0.10)[a]	1.072 (0.07)[b]	< 0.001
Bone mineral content†				
DXA upper limbs (g)	238.8 (51.5)	321.8 (87.4)[a]	296.8 (66.3)[a]	< 0.001
DXA lower limbs (g)	821.1 (169.2)	1146.5 (250.0)[a]	889.7 (191.1)[b]	< 0.001
DXA spine (g)	180.9 (49.9)	200.8 (52.0)	183.1 (39.3)	0.227
DXA whole body‡ (g)	1756.3 (378.3)	2331.4 (565.7)[a]	1933.0 (379.0)[b]	< 0.001

*Values presented as median and interquartile range; †Variables without adjustment for sex, age, peak height velocity, duration of previous engagement, height and fat-free mass; ‡without head; SD = standard deviation; DXA = dual energy x-ray absorptiometry; [a]P-value < 0.05 compared with control; [b]P-value < 0.05 compared with soccer/basketball; ANOVA = analysis of variance.

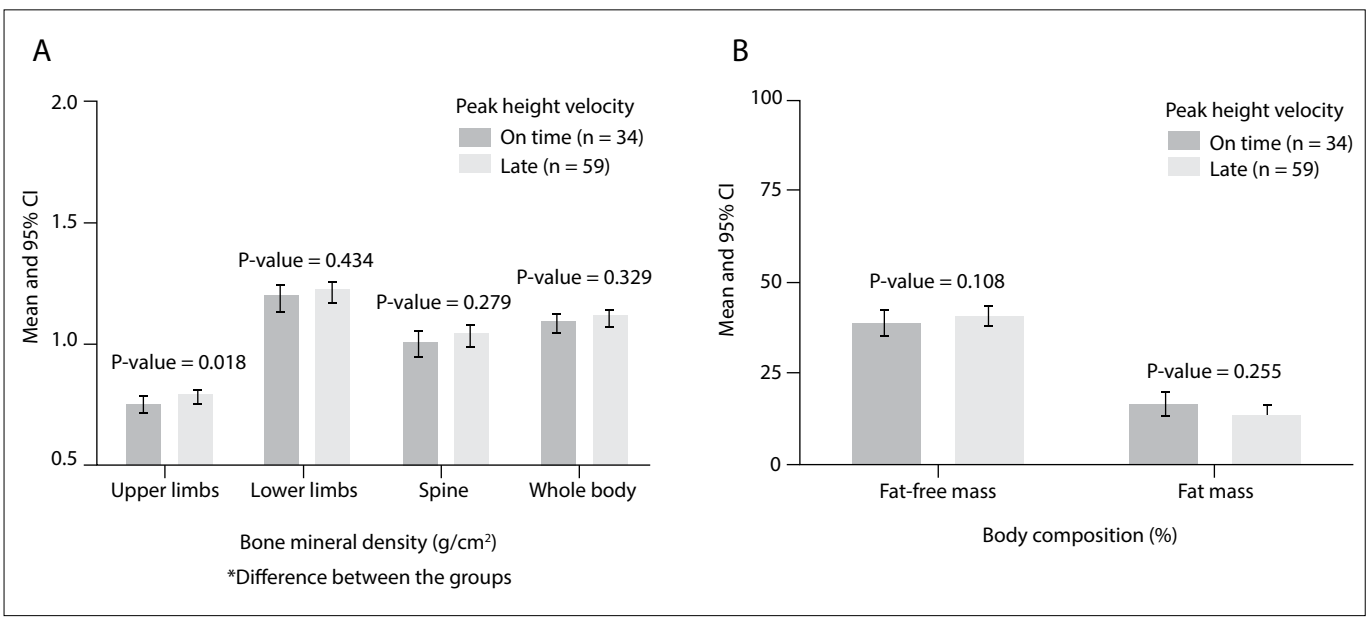

Figure 1. Bone mineral density and body composition in adolescents stratified according to peak height velocity.

whole-body BMC, compared with the soccer/basketball group (P = 0.002). On the other hand, the lower limbs of the soccer/basketball group represented a higher percentage of whole-body BMC, compared with the swimmers (P < 0.001). Swimmers' upper limbs presented a higher percentage of whole-body BMC, compared with the soccer/basketball group (P < 0.001) and the control group (P = 0.010) (**Table 3**). Somatic maturation (PHV) also showed a trivial effect size in all variables (body sites) that constituted overall BMC: head (ES-r 0.000; P = 0.987), upper limbs (ES-r 0.000; P = 0.873), lower limbs (ES-r 0.004; P = 0.568) and trunk (ES-r 0.006; P = 0.475) (**Table 3**).

Finally, there was a negative relationship between whole-body BMC and weekly training time (β: -1563.967; 95% CI: -2916.484 to -211.450) (**Table 4**).

DISCUSSION

This cross-sectional study found that swimmers presented lower bone density than the no-sport group and the group of adolescents engaged in impact sports, independently of somatic maturation.

In the present study, sports participation was related to higher BMD (upper limbs) in adolescents who reached PHV at a late age, but not in adolescents classified as on time. In a systematic review[19] composed of 22 studies, Specker et al. found that exercise protocols targeting bone mass accrual seemed to be more effective in samples composed of pre-pubertal adolescents. The period of maturity offset between -2.0 and +2.0 was characterized by significant linear growth and BMC accrual.[13] Independently of sex, the two years between PHV -1.0 and + 1.0 encompass the peaks of testosterone, estradiol and insulin-like growth factor-1 (IGF-1) levels.[20] Similarly, participation in sports acts towards releasing anabolic hormones, such as IGFBP-3 and testosterone.[21] The anabolic effect promoted by sports participation might be improved through maturational events occurring in the years before and after PHV, and adolescents reaching PHV at a late age are more likely to improve their bone health.

On the other hand, even though significantly boosted by maturation events, the osteogenic effect linked to physical exercise

Table 4. Linear regression (controlled for sex, CA, AHPV, FFM, height and duration of previous training (years) between bone mass and time spent training, among adolescents according to sports

	Soccer/basketball (n = 26)	Swimming (n = 25)
	Exercise training (minutes/week)*	Exercise training (minutes/week)*
	β (β 95% CI)	β (β 95% CI)
DXA BMD (g/cm²)		
Upper limbs	0.015 (-0.093 to 0.122)	-0.130 (-0.499 to 0.240)
Lower limbs	0.020 (-0.099 to 0.132)	-0.364 (-0.913 to 0.185)
Spine	0.115 (-0.080 to 0.310)	-0.290 (-0.722 to 0.141)
Whole body	0.023 (-0.070 to 0.116)	-0.300 (-0.696 to 0.097)
BMC whole body (g)†	19.8 (-375.5 to 415.2)	**-1563.9 (-2916.4 to -211.4)**

*Numerical variable after logarithmic transformation; †without head; 95% CI = 95% confidence interval; DXA = dual energy x-ray absorptiometry; CA = chronological age; APHV = age at peak height velocity; FFM = fat-free mass.

Table 2. Bone mineral density among adolescents, stratified according to sports participation

Overall	No-sport group (n = 42)	Soccer/basketball (n = 26)	Swimming (n = 25)	ANCOVA*			
	Mean (SEM)	Mean (SEM)	Mean (SEM)	F	P-value	ES-r	(qualitative)
Upper limbs	0.788 (0.011)	0.758 (0.013)	0.747 (0.012)	2.348	0.102	0.053	Trivial
Lower limbs	1.217 (0.015)	1.280 (0.018)	1.098 (0.016)[a,b]	38.668	< 0.001	0.479	Moderate
Spine	1.045 (0.020)	1.052 (0.023)	0.954 (0.021)[a,b]	8.002	0.001	0.160	Small
Whole body	1.118 (0.012)	1.134 (0.014)	1.037 (0.013)[a,b]	19.045	< 0.001	0.312	Moderate

*Adjusted for sex, age, peak height velocity, duration of previous engagement, height and fat-free mass; ANCOVA = analysis of covariance; SEM = standard error of the mean; ES-r = Eta-squared correlations (r-Hopkins); [a]P-value < 0.05 compared with control; [b]P-value < 0.05 compared with soccer/basketball.

Table 3. Estimated mean percentage participation (of each body segment) in overall BMC (g), among adolescents according to sports participation.

Overall	No-sport group (n = 42)	Soccer/basketball (n = 26)	Swimming (n = 25)	ANCOVA*			
	Mean (SEM)	Mean (SEM)	Mean (SEM)	F	P-value	ES-r	(qualitative)
Head	18.64 (0.40)	17.45 (0.46)	19.46 (0.42)[b]	6.456	0.002	0.133	Small
Upper limbs	11.32 (0.17)	11.09 (0.20)	12.20 (0.18)[a,b]	11.844	< 0.001	0.220	Small
Lower limbs	38.56 (0.48)	40.06 (0.56)	37.38 (0.50)[b]	8.005	0.001	0.160	Small
Trunk	31.46 (0.43)	31.39 (0.50)	30.95 (0.45)	0.403	0.669	0.010	Trivial

*Adjusted for sex, age, peak height velocity, duration of previous engagement, height and fat-free mass; ANCOVA = analysis of covariance; SEM = standard error of the mean; ES-r = eta-squared correlations (r-Hopkins); BMC = bone mineral content; [a]P-value < 0.05 compared with control; [b]P-value < 0.05 compared with soccer/basketball.

occurs during periods of lower hormonal activity. For instance, Ferry et al.[10] found that 12 months of soccer practice enhanced bone mass and geometry, even in post-pubertal adolescents, while this effect was not observed in swimmers. Therefore, the improvement in bone mass through sports participation seems also to be observed in later adolescence when most other maturational events have been completed.

In our sample, the percentage of participation of the head in the whole-body bone mass was higher in swimmers than in soccer players. Regarding this issue, there have been divergences in the scientific literature. Gómez-Bruton et al.[12] suggested that increased bone mass at other specific sites directly stressed by sports participation, even without a clear biological pathway, is related to lower skull bone mass. In contrast, our findings showed that even after controlling for potential confounders, not only did swimmers have a higher percentage of overall BMC in the skull (no difference between the soccer/basketball and no-sport groups), but also they had a higher percentage of overall BMC in their upper limbs than the soccer/basketball players and the control group. In the soccer/basketball group, there was no apparent decrease in skull bone mass due to sports participation; rather, it presented a lower percentage of whole-body BMC due to the additional bone mass gained at other sites that were directly stimulated by sports participation.

In the present study, the lower values for bone variables in swimmers, compared with soccer players, could be explained by the fact that swimming practice is performed in situations of hypogravity, characterized by lack of mechanical load and lower osteogenic stimulus.[12] Among swimmers, greater weekly quantity of training hours was related to lower BMC in the whole body (excluding the head). Long periods of training performed under conditions of hypogravity and the inflammatory response to exercise might support our findings. Swimmers presented the highest numbers of weekly training hours (17.7 ± 3.5 h/week), which accounted for 15.8% (95% CI: 14.5-17.1) of their wakeful time during the week (assuming 8 hours of sleep per night in a period of 24 hours) and the longest duration of previous practice in the sport (69 ± 40 months). Ferry et al. identified lower numbers of weekly training hours among female swimmers (around 10 hours), but the sample was not composed of swimmers competing at national level (as observed in the present study).[10]

Moreover, swimming practice encompasses periods of training at high-intensity[21] that are related to increased inflammation.[22] Inflammatory marker levels increased by high-intensity exercise have been linked to lower action of growth hormone and IGF-1 in adolescents.[23] Therefore, even without physiological measures relating to intensity, it is feasible to believe that the combination of prolonged inflammatory responses and large quantities of high-intensity training[23] under conditions of hypogravity might explain the negative relationship observed between weekly training hours and BMC among swimmers.

However, in the present study, bone mineral density in the upper limbs was not reduced among swimmers, compared with the other groups. This result can be explained by the fact that swimming movements that generate propulsive forces are concentrated in the upper limbs, especially in the freestyle stroke.[24] However, more studies are needed to corroborate and strengthen this finding.

The limitations of this study need to be recognized. The cross-sectional design constitutes a limitation because it does not allow statements of causality, although this limitation will in the future be overcome through follow-up measurements on this cohort. The lack of female participation in the impact sport group (basketball and soccer) is an important limitation considering that the maturational process and the effect of sports are different between the sexes. Therefore, it is relevant to consider that the differences found in our study according to sports groups may have been overestimated due to the imbalance of sex distribution. The age range in our study also constitutes a limitation, mainly because PHV has higher precision when applied to adolescents with ages ranging from 11 to 15 years old. The absence of nutritional variables also should be considered in future studies (e.g. calcium and vitamin D intake) because of their effect on bone formation. Finally, the effect of some hormones (e.g. testosterone, estradiol and growth hormone) and inflammatory markers need to be taken into account in future studies.

CONCLUSION

In summary, the differences in bone variables attributed to sports participation occurred independently of maturation, while high training loads under conditions of hypogravity appear to be related to lower bone mass in swimmers.

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Postural balance and functional independence of elderly people according to gender and age: cross-sectional study

Equilíbrio postural e independência funcional de idosos de acordo com o sexo e a idade: estudo transversal

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KEY WORDS:
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Accidental falls.
Drug therapy.

PALAVRAS-CHAVE:
Envelhecimento.
Equilíbrio postural.
Atividades cotidianas.
Acidentes por quedas.
Quimioterapia.

ABSTRACT

CONTEXT AND OBJECTIVE: Aging causes changes in men and women. Studies have shown that women have worse postural balance and greater functional dependence than men, but there is no consensus regarding this. The aim of this study was to compare the balance and functional independence of elderly people according to sex and age, and to evaluate the association between postural balance and the number of drugs taken.

DESIGN AND SETTING: Cross-sectional at a state university.

METHODS: 202 elderly people were evaluated regarding balance (Berg Scale), independence (Barthel Index), age, sex, number of medications and physical activity.

RESULTS: The subjects comprised 117 women (70.2 ± 5.6 years old) and 85 men (71.1 ± 6.9 years old). For balance, there was no significant difference regarding sex, but there was a difference regarding age ($P < 0.0001$). For functional independence, there was a difference regarding sex ($P = 0.003$), but not regarding age. The variables of age, medications and physical activity were significant for predicting the Berg score. For the Barthel index, only age and sex were significant. Elderly people who took three or more medications/day showed higher risk of falling than those who took up two drugs/day (odds ratio = 5.53, $P < 0.0001$, 95% confidence interval, 2.3-13.0).

CONCLUSIONS: There was no sexual difference in relation to postural balance. However, people who were more elderly presented a high risk of falling. Functional dependence was worse among females. There was an association between the number of medication drugs and risk of falling.

RESUMO

CONTEXTO E OBJETIVO: O envelhecimento provoca alterações em homens e mulheres. Estudos mostraram que mulheres têm pior equilíbrio postural e maior dependência funcional do que homens, mas isso não é consenso. O objetivo deste estudo foi comparar o equilíbrio e a independência funcional de idosos por sexo e idade, e avaliar a associação de equilíbrio postural com o número de medicamentos ingeridos.

TIPO DE ESTUDO E LOCAL: Estudo transversal em uma universidade estadual.

MÉTODOS: 202 idosos foram avaliados quanto ao equilíbrio (Escala de Berg), independência (Índice de Barthel), além da idade, sexo, número de medicamentos e atividade física.

RESULTADOS: Os sujeitos foram 117 mulheres (70,2 ± 5,6 anos) e 85 homens (71,1 ± 6,9 anos). No equilíbrio, não houve diferença significativa por sexo, mas houve por idade ($P < 0.0001$). Para a independência funcional, houve diferença por sexo ($P = 0,003$), mas não por idade. As variáveis idade, medicação e atividade física foram significativas para predizer o escore de Berg. Para o índice de Barthel, apenas a idade e o sexo foram significativos. Idosos que ingeriram 3 ou mais medicamentos/dia mostraram maior risco de cair do que os que ingeriram até 2 drogas/dia (*odds ratio* = 5,53, $P < 0.0001$, intervalo de confiança de 95%, 2,3-13,0).

CONCLUSÕES: Não houve diferença entre sexos em relação ao equilíbrio postural; idosos mais velhos, contudo, apresentaram grande risco de cair; a dependência funcional foi pior no sexo feminino. Foi encontrada associação entre número de medicamentos utilizados e risco de cair.

INTRODUCTION

The global population is aging at an unprecedented rate. In 2012, 23% of the population in the more developed regions and 9% in the less developed regions were aged 60 years or over.[1] It has been estimated that by 2050, the proportion of older citizens will increase to 32% in developed countries and 19% in developing countries.[1]

Human aging causes physiological changes such as decreased postural balance, thus increasing the risk of falls. Postural control is considered to be a complex motor skill derived from interaction of multiple sensorimotor processes.[2] Age-related changes in the peripheral and central components of the visual, somatosensory and vestibular systems can be expected to affect balance and mobility.

One-third of people aged 65 years and over fall one or more times a year. Among community-dwelling older people, the cumulative incidence of falls ranges from 25 to 40%.[3] Falls have been correlated with a number of different risk factors. Some of these, like age or sex, cannot be altered. In a review, Meschial et al.[4] found contradictory results in several databases concerning the proportion of falls with regard to sex. Four studies reporting that women were mostly affected were identified, while one study indicated that men were more prone to falling.

Prospective cohort studies have indicated that falls seem to be an independent determinant of functional decline and dependency in activities of daily living (ADLs) in a general elderly population.[5,6] Sposito et al. showed that women have higher dependence than men in carrying out activities of daily living.[7]

Aging causes the appearance of chronic diseases, and consequently there is an increase in the quantity of medication drugs ingested.[8] Both specific classes of drugs and the total number of drugs may be associated with imbalance[9] and dependency in activities of daily living.

OBJECTIVE

The objectives of this study were to compare the balance and level of functional independence of older adults according to sex and age, and to evaluate the association between postural balance and number of drugs taken.

METHODS

Design, participants and ethics

A cross-sectional study was conducted between 2009 and 2013 in the city of Marília, São Paulo, Brazil. A convenience sample of 209 community-dwelling elderly individuals was recruited at two basic healthcare public units, four healthcare public centers, five community centers and two geriatric clinics. Of the 209 participants initially recruited, 7 were withdrawn because they did not meet the inclusion criteria. Thus, a total of 202 elderly people were enrolled in the study. The study design can be seen in **Figure 1**. The following inclusion criteria were used: age 60 years or older; living in the community; and independent gait (without gait assistance device). The following exclusion criteria were used: cognitive impairment detectable by means of the mini-mental state examination (MMSE), with the following cutoffs: 20 for illiterates; 25 for schooling level of 1 to 4 years; 26.5 for 5 to 8 years; 28 for 9 to 11 years; and 29 for higher levels of education;[10] and factors that interfere with corporal balance, such as: sequelae of neuromusculoskeletal diseases (stroke or Parkinson's disease), uncorrected visual problems, orthostatic hypotension and continuous use of sedatives, antidepressants and hypnotics. The elderly subjects were classified as sedentary or active according to the criteria of the Brazilian Society of Sports Medicine and the Brazilian Society of Geriatrics and Gerontology.[11]

Written informed consent was obtained from all patients before enrollment. The study was submitted and approved by the Research Ethics Committee of the School of Philosophy and Sciences, Universidade Estadual Paulista (UNESP), Marília, São Paulo, Brazil. It was carried out in accordance with Resolution no. 196/96 of the National Health Council.

Outcome measurements

Data were collected via face-to-face interviews with researchers. Within the scope of the present study, the subjects were asked for demographic information such as age, diseases presented and medications used.

The participants were evaluated regarding their balance using the Berg Balance Scale (BBS) and their functional independence in daily activities was evaluated using the Barthel Index (BI).

Balance

The BBS, which measures "functional balance," has three dimensions: maintenance of a position, postural adjustment to voluntary movements and reaction to external disturbances. The subjects'

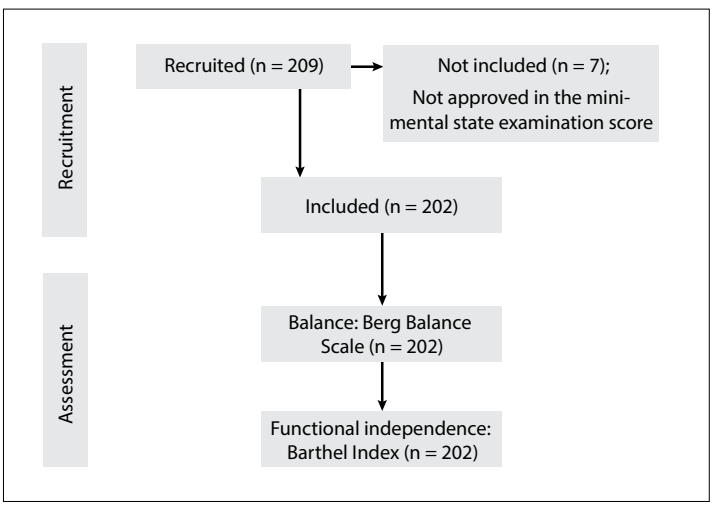

Figure 1. Procedures for data collection.

performance in each of 14 activities is measured on a five-point ordinal scale ranging from 0 to 4 (0 = unable to perform; 4 = independent), such that the aggregate score ranges from 0 to 56. Scores of 48 and less indicate inability to walk independently and safely in daily life and a greater risk of falls.[12]

Functional independence in daily life

The BI is a reliable and valid tool measuring overall disability that represents a subject's ability to perform tasks within activities of daily living. It has been recommended for functional assessments on older people. The version used here evaluated functional independence in relation to 10 activities: feeding, bathing, grooming, dressing, bowel care, bladder care, toilet use, transfers, walking and stair climbing. The overall score is obtained by attributing points to each category, depending on the time taken and assistance needed by each patient. The score ranges from 0 to 100, in 5-point intervals, and the higher the score is, the more independent the patient is.[13]

Data analysis

The Kolmogorov-Smirnov test was used to determine the data distribution. The Mann-Whitney test was used for comparisons between the genders. Correlations between drugs used and the BBS were made using the chi-square test (with Yates correction), with the cutoff point ≤ 48 in BBS for greater risk of falls.[12] Comparisons between the subjects' ages were made using one-way ANOVA with Dunn's post-test. To analyze the effect of independent variables on the dependent variable (Berg or Barthel), a multiple linear regression model was constructed by means of the Enter method (forced input). R2 was analyzed to ascertain the coefficient of determination of the percentage variation explained by the model. ANOVA for repeated measurements was used to compare the Berg and Barthel scales; however, in order to analyze the influence of factors such as age, sex, medication and physical activity, these were included as covariables (ANCOVA). Furthermore, in order to control for the effect of covariables regarding the correlation analysis between Berg and Barthel, a partial correlation analysis was performed. Pearson's correlation test was performed to analyze the correlation without controlling for covariables. The data were analyzed using the SPSS software, version 19.0 for Windows, and P ≤ 0.05 was accepted as significant.

RESULTS

Among the 202 elderly people studied, 117 were women (57.9%) and 85 were men (42.1%). With regard to schooling level, 12 participants (5.94%) were illiterate, 71 (35.14%) had attended school for 1-4 years, 43 (21.32%) for 5-8 years and 76 (37.62%) for more than 8 years. **Table 1** shows the characteristics of the subjects of this study.

The BBS scores showed significant differences between the age groups (60-69 years, 70-79 years and ≥ 80 years), with lower scores in older age groups. For the Barthel index, there was no significant difference (**Table 2**), although in older age groups, the scores were lower, thus indicating greater reliance in the subjects' activities.

The Berg and Barthel scales showed a significant positive correlation. When the variables (age, sex, medication and physical activity) were controlled for, the correlation strength was lower, thus indicating that these variables had an important effect (**Table 3**).

The degree of balance was found to be lower among the women than among the men (51.5 ± 4.3 and 51.8 ± 3.3, respectively; P = 0.08). There was no significant difference in postural balance between the sexes (**Figure 2**).

Figure 3 presents the Barthel scale and shows that the men had a higher average score (99.7 ± 1.7) than the women (98.4 ± 2.9), thus indicating greater dependence among the women than among the men in the tasks evaluated by the scale (P = 0.003). The regression analysis confirmed these data and showed that being a woman contributed towards having a worse Barthel index score (**Table 4**).

Table 1. Subjects' characteristics

	Women	Median (IQR)	Men	Median (IQR)	P
N	117	–	85		–
Age (years) ± SD	70.2 ± 5.6	70.0 (8)	71.1 ± 6.9	71.0 (10.5)	0.17
Drugs/day ± SD	2.6 ± 1.9	2.0 (3)	2.58 ± 2.6	2.0 (3)	0.09
MMSE ± SD	26.4 ± 2.4	27.0 (3)	27.2 ± 2.2	28.0 (3)	0.02
Physically active	72 (61.5%)	–	47 (54%)	–	0.45
Fallers	23 (19.6%)	–	13 (15.3%)	–	0.52

SD = standard deviation, MMSE = mini-mental state examination, IQR = interquartile range.

Table 2. Comparison of scores on Berg Balance Scale (BBS) and Barthel Index (BI), according to age groups

	60-69 years	70-79 years	≥ 80 years	P-trend
BBS	53.1 ± 2.3*,†	51.3 ± 3.9†	44.2 ± 7.4	0.000
BI	99.3 ± 1.9	98.8 ± 2.4	97.3 ± 4.9	0.205

Values are the mean ± standard deviation; *P < 0.01 in relation to age 70-79 years, †P < 0.001 in relation to age ≥ 80 years.

Table 3. Correlation analysis with and without controlling for the variables of age, sex, medications and physical activity

Variable control		Barthel and Berg
Age, sex, medications and physical activity	Correlation coefficient	0.323
	P-value	0.0001
Without control	Correlation coefficient	0.386
	P-value	0.0001

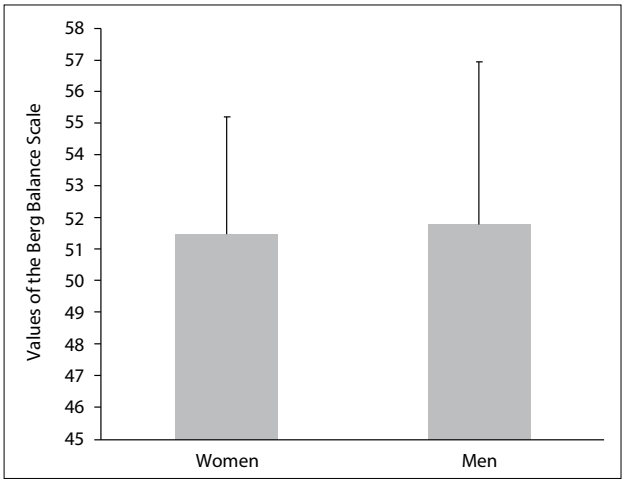

Figure 2. Comparison of scores on Berg Balance Scale (BBS) between women (n = 117; BBS = 51.5 ± 4.3) and men (n = 85; BBS = 51.8 ± 3.3); P = 0.08.

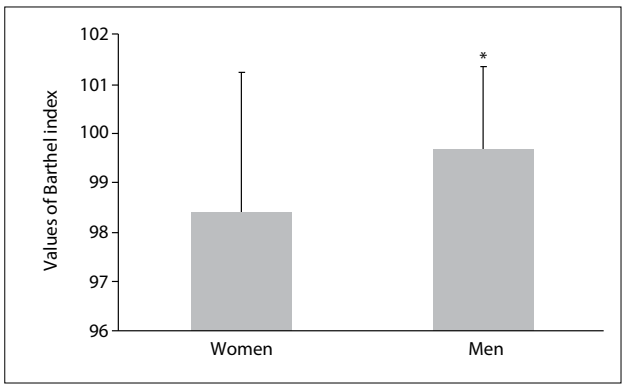

Figure 3. Comparison of scores in Barthel index (BI) between women (n = 117; BI = 98.4 ± 2.9) and men (n = 85; BI = 99.7 ± 1.7); *P = 0.003.

Table 4. Multiple linear regression to analyze the effect of the independent variables on the Berg and Barthel scales

Dependent variable	Parameters	Regression coefficient with 95% CI (lower | upper)	R^2	P-value
Berg	Intercept	76.458 (70.791 | 82.126)	0.369	0.0001
	Age	-0.344 (-0.424 | -0.265)		0.0001*
	Sex	-0.662 (-1.643 | 0.319)		0.185
	Medications	-0.421 (-0.642 | -0.200)		0.000*
	Physical activity	1.693 (0.710 | 2.676)		0.001*
Barthel	Intercept	105.642 (101.690 | 109.594)	0.122	0.0001
	Age	-0.086 (-0.141 | -0.030)		0.003*
	Sex	-1.449 (-2.134 | -0.765)		0.0001*
	Medications	-0.026 (-0.180 | 0.128)		0.743
	Physical activity	0.503 (-0.183 |-0.183)		0.150

*Significant effect of the variable in the regression model for predicting the dependent variable. CI = confidence interval.

There was an association between the number of drugs taken and the risk of falling. Elderly people who reported ingesting three or more medications/day presented higher risk of falling than those who reported taking up to two drugs/day (odds ratio = 5.53; P < 0.0001; 95% confidence interval, CI: 2.3-13.0), considering a cutoff ≤ 48 points for higher risk of falls on the Berg scale.[12]

Through regression analysis, it could be seen that the variables of age, medications and physical activity significantly predicted the Berg score. In addition, the set of variables inserted in the model explained 36.9% (R^2) of the variation in the Berg scores. For the Barthel index, only age and sex were significant, but the regression model indicated that the variables together account for only 12.2% (R^2) of the variation of the scores. This indicates that the Barthel score appears to be less influenced by the covariates of age, sex, medications and physical activity than the Berg scale (**Table 4**).

DISCUSSION

This study examined some important issues regarding elderly people, including the difference between sex and age groups regarding balance and independence, and the relationship between the risk of falling and the number of drugs ingested. There were no differences in postural balance in relation to sex (**Figure 2** and **Table 4**). These results are contrary to data in the literature. Perracini and Ramos[14] and Moreira et al.[15] indicated that women had worse balance than men. The probable reason for our result is that more than 50% of the elderly people in the sample evaluated here practiced regular physical activity (61.5% for women and 54% for men). The literature provides evidence that older adults who maintain regular physical activity have better postural balance and mobility.[16-18] Comparison among age groups, regardless of sex, showed significant differences in BBS scores, thus indicating that deterioration of balance is associated with advancing age and that balance among people aged 80 and over is impaired (mean score 44.2), with high risk of falling (**Table 2** and **Table 4**). The deterioration of postural control with age can be explained by decreased cognitive function, declining sensory inputs and motor responses and deterioration of the integration of systems responsible for postural balance.

The Berg and Barthel scales showed a significant positive correlation, but when the variables of age, sex, medication and physical activity were controlled for, the strength of the correlation became lower, thus indicating that these variables had an important effect (**Table 3**). The variables of age, medications and physical activity significantly predicted the Berg score, thus explaining 36.9% (R^2) of the variation in the Berg scores. For the Barthel index, only age and sex were significant, but the regression model indicated that the variables together were responsible for only 12.2% (R^2) of the variation of the scores. This indicated that the Barthel score appeared to be less influenced by the covariates of age, sex, medications and

physical activity than the Berg scale. This data are in contrast with the study of Dunlop al.,[19] which found a strong relationship between activities of daily living (ADL) and level of physical activities, age and female gender in older adults.

The present study also examined the relationship between the number of drugs taken and balance, and found that older adults who take three or more drugs/day are at higher risk of falls, according to the Berg scale. The number of drugs taken daily has been identified as an independent risk factor for falls: Campbell et al. found that the total number of drugs was an important predictor of falls among women.[20]

The literature indicates that sex is a factor strongly related to occurrences of functional dependency, and that the chance that women will be dependent is twice as high as for men.[21-24] Our results showed that men achieved scores that were higher than those of women on the Barthel Index, thus indicating a greater likelihood that women are more dependent than men in relation to activities of daily living (**Figure 3** and **Table 4**). This difference can be explained through two issues: the predominance of non-lethal incapacitating conditions among women (osteoarthritis, osteoporosis and depression) and the greater capacity of women to report their health status than that of men of the same age.[21] Women have longer life expectancy than men,[1] thus increasing their risk of chronic diseases, which can lead to disability. Furthermore, women tend to report greater functional difficulties than men.[25]

Analysis on the functional capacity of elderly people can be considered an essential mechanism for more detailed clinical evaluation in the field of gerontology and rehabilitation[22] as well as for research relating to postural balance.

One of the limitations found in the present study was the difficulty in finding male elderly individuals who were willing to participate and thus being able to make comparisons with equal numbers of men and women. The strengths of this study were the number of participants and the tests used in evaluations, which are easy to apply in clinical practice.

CONCLUSIONS

The results showed that there was no difference between the two sexes in relation to postural balance in the population studied. However, the older age group presented a great risk of falling. Functional dependence was correlated to sex, such that it was worse among females. Furthermore, there was an association between the number of drugs taken and the risk of falling.

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Age at first childbirth and newly diagnosed diabetes among postmenopausal women: a cross-sectional analysis of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

Idade no primeiro parto e diabetes recentemente diagnosticada em mulheres pós-menopáusicas: uma análise transversal do Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil)

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KEY WORDS:
Diabetes mellitus, type 2.
Pregnancy in adolescence.
Reproductive behavior.
Postmenopause.
Reproducibility of results.

PALAVRAS-CHAVE:
Diabetes mellitus tipo 2.
Gravidez na adolescência.
Comportamento reprodutivo.
Pós-menopausa.
Reprodutibilidade dos testes.

ABSTRACT

CONTEXT AND OBJECTIVE: It has been reported that earlier age at first childbirth may increase the risk of adult-onset diabetes among postmenopausal women, a novel finding with important public health implications. To date, however, no known studies have attempted to replicate this finding. We aimed to test the hypothesis that age at first childbirth is associated with the risk of adult-onset diabetes among postmenopausal women.

DESIGN AND SETTING: Cross-sectional analysis using baseline data from 2919 middle-aged and elderly postmenopausal women in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

METHODS: Age at first childbirth was determined from self-reporting and newly diagnosed diabetes through a 2-hour 75-g oral glucose tolerance test and/or glycated hemoglobin. Logistic regression was performed to examine associations between age at first childbirth and newly diagnosed diabetes among postmenopausal women.

RESULTS: We did not find any association between age at first childbirth and diabetes, either when minimally adjusted for age, race and study center (odds ratio, OR [95% confidence interval, CI]: ≤ 19 years: 1.15 [0.82-1.59], 20-24 years: 0.90 [0.66-1.23] and ≥ 30 years: 0.86 [0.63-1.17] versus 25-29 years; P = 0.36) or when fully adjusted for childhood and adult factors (OR [95% CI]: ≤ 19 years: 0.95 [0.67-1.34], 20-24 years: 0.78 [0.56-1.07] and ≥ 30 years: 0.84 [0.61-1.16] versus 25-29 years; P = 0.40).

CONCLUSION: Our current analysis does not support the existence of an association between age at first childbirth and adult-onset diabetes among postmenopausal women, which had been reported previously.

RESUMO

CONTEXTO E OBJETIVO: Foi relatado que idade mais precoce no primeiro parto pode aumentar o risco do diabetes de início adulto entre mulheres na menopausa, um novo achado com implicações de saúde pública importantes. Até então, no entanto, nenhum estudo conhecido tentou replicar esta descoberta. Objetivou-se testar a hipótese de que a idade no primeiro parto está associada ao risco de diabetes de início na vida adulta em mulheres pós-menopáusicas.

DESENHO DE ESTUDO E LOCAL: Análise transversal utilizando dados de base de 2.919 mulheres pós-menopáusicas de meia-idade e idosas no Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil).

MÉTODOS: A idade no primeiro parto foi determinada por autorrelato e diabetes recentemente diagnosticado por um teste de tolerância à glicose oral de 2 horas com 75 g e/ou hemoglobina glicada. A regressão logística foi realizada para examinar associações entre idade no primeiro parto e diabetes recentemente diagnosticada entre mulheres pós-menopáusicas.

RESULTADOS: Não encontramos associação entre idade no primeiro parto e diabetes, quando ajustados minimamente para idade, raça e centro de estudo (*odds ratio*, OR [intervalo de confiança, IC 95%]: ≤ 19 anos: 1,15 [0,82-1,59], 20-24 anos: 0,90 [0,66-1,23], ≥ 30 anos: 0,86 [0,63-1,17] *versus* 25-29 anos, P = 0,36) ou quando totalmente ajustados para fatores infantis e adultos (OR [IC 95%]: ≤ 19 anos: 0,95 [0,67-1,34], 20-24 anos: 0,78 [0,56-1,07], ≥ 30 anos: 0,84 [0,61-1,16] *versus* 25-29 anos, P = 0,40).

CONCLUSÃO: Nossa análise atual não apoia uma associação entre a idade no primeiro parto e o diabetes de início na vida adulta entre mulheres pós-menopáusicas, como relatado anteriormente.

INTRODUCTION

It has been suggested that reproductive health factors over the course of life may play an important role in the risk of chronic disease in later life.[1] In the context of type 2 diabetes, earlier age at menarche, higher parity and early menopause have all been linked to higher risk in later life.[2-5] It has recently been reported by Kim et al. that postmenopausal Korean women who were ≤ 19 years of age at first childbirth, compared with women who were 25-29 years of age, presented increased odds of having type 2 diabetes (odds ratio, OR 1.492; 95% confidence interval, CI: 1.005-2.215) in analyses adjusted for a comprehensive panel of potential confounding factors.[6] This novel finding, which would imply that the timing of first childbearing and the postmenopausal period would have a combined role in the etiology of diabetes, could have important public health implications and inform screening practices targeting women with adolescent pregnancies. To date, however, no known studies have attempted to replicate this finding.

OBJECTIVE

Given the potential relevance of these findings, we thus aimed to examine the association of age at first childbirth with newly diagnosed adult-onset diabetes in a postmenopausal subset of a large Brazilian cohort of middle-aged and elderly individuals.

METHODS

The Brazilian Longitudinal Study of Adult Health (in Portuguese, Estudo Longitudinal de Saude do Adulto, or ELSA-Brasil) is a prospective cohort study designed to investigate the distribution, determinants and consequences of diabetes and cardiovascular disease. The details of the study, including design, eligibility criteria, sources and recruitment methods, and the measurements obtained, have been described in detail elsewhere.[7,8] The cohort comprises 15,105 civil servants, aged 35 to 74 years at baseline (2008-2010), who were sampled from universities or research institutions located in six cities in three different regions of Brazil. All data for the current cross-sectional analyses were collected at baseline. The study was approved by the local Research Ethics Committees of all the institutions involved. All participants provided written informed consent for their clinical records to be used in this study, prior to enrolment.

Briefly, postmenopausal status was defined as reporting not having experienced a menstrual cycle within the previous 12 months, and included natural or induced menopause. Age at first childbirth was determined from self-reporting. Newly diagnosed diabetes was defined as fasting blood glucose ≥ 7.0 mmol/l, 2-hour postload glucose ≥ 11.1 mmol/l, or HbA_{1c} (glycated hemoglobin) ≥ 6.5%.

Among postmenopausal women with a history of childbirth, we excluded those with missing data (n = 646) and those reporting a previous diagnosis of diabetes or use of diabetes medication (n = 466). Consequently, our sample consisted of 2919 postmenopausal women.

We assessed the association of diabetes with age at first childbirth, with the latter categorized into four groups: ≤ 19, 20-24, 25-29 and ≥ 30 years, taking 25-29 as our reference category. In modeling, we first presented a model that was minimally adjusted for age, race and study center (Model 1), followed by models sequentially adjusted for childhood and adolescent factors that might confound any observed association (Model 2: maternal education and age at menarche), and then for adult socioeconomic and lifestyle factors that might confound or mediate any associations presented (Model 3: education level, family income, smoking, alcohol consumption, number of pregnancies and any use of hormone replacement therapy). Multivariable logistic regression was performed to generate ORs and 95% CIs for the association between age category at first childbirth and newly diagnosed adult-onset diabetes. All statistical tests were two-sided and significance was defined as $P < 0.05$. Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

RESULTS

The participants in our sample were, on average, 57.3 years of age (standard deviation, SD: 6.7) and 9.9 years (SD: 7.1) postmenopausal. Generally, participants who reported earlier age at first childbirth were more likely to be black or mixed-race, have a lower education level and be a current smoker (not shown). At baseline, we found 352 cases (12.1%) of newly diagnosed diabetes.

In logistic regression analyses, we failed to find any association between age at first childbirth and newly diagnosed diabetes in either the model minimally adjusted for age, race and study center (OR [95% CI]: ≤ 19 years: 1.15 [0.82-1.59], 20-24 years: 0.90 [0.66-1.23] and ≥ 30 years: 0.86 [0.63-1.17] versus 25-29 years; P = 0.36) or in models sequentially adjusted for childhood and adolescent factors (OR [95% CI]: ≤ 19 years: 1.14 [0.82-1.59], 20-24 years: 0.90 [0.66-1.22] and ≥ 30 years: 0.86 [0.63-1.17] versus 25-29 years; P = 0.36) and adulthood socioeconomic and lifestyle factors (OR [95% CI]: ≤ 19 years: 0.95 [0.67-1.34], 20-24 years: 0.78 [0.56-1.07] and ≥ 30 years: 0.84 [0.61-1.16] versus 25-29 years, P = 0.40) (**Table 1**).

Nor did we find any association between age at first childbirth and impaired fasting glucose (fasting glucose concentration ≥ 5.5 mmol/l and < 7.0 mmol/l), impaired glucose tolerance (two-hour postload glucose concentration ≥ 7.8 mmol/l and < 11.1 mmol/l) or previously diagnosed diabetes in analyses in all women independent of menopausal status, or in analyses that excluded those who did not experience a natural menopause (not shown).

Table 1. Association of age at first childbirth with newly-diagnosed diabetes in postmenopausal women, Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), 2008-2010; n = 2919

	≤ 19 years	20-24 years	25-29 years (reference)	≥ 30 years	P-value
N	497	759	768	895	
Diabetes cases	75	90	80	107	
	OR (95% CI)	**OR (95% CI)**		**OR (95% CI)**	
Model 1	1.15 (0.82-1.59)	0.90 (0.66-1.23)	1.00	0.86 (0.63-1.17)	0.36
Model 2	1.14 (0.82-1.59)	0.90 (0.66-1.22)	1.00	0.86 (0.63-1.17)	0.36
Model 3	0.95 (0.67-1.34)	0.78 (0.56-1.07)	1.00	0.84 (0.61-1.16)	0.40

Model 1: adjusted for age, race and study center; Model 2: + childhood and adolescent factors (maternal education and age at menarche); Model 3: + adulthood socioeconomic and lifestyle factors (education level, family income, smoking, alcohol consumption, number of pregnancies and any use of hormone replacement therapy). P-value represents the test for an overall association of age at first childbirth with newly-diagnosed diabetes. OR = odds ratio; CI = confidence interval.

DISCUSSION

In this cross-sectional analysis on 2919 middle-aged and elderly postmenopausal women, we did not find any association between age at first childbirth and newly diagnosed adult-onset diabetes, which had been reported previously.

Some important strengths of our study, in relation to the previous analysis, deserve brief comment. Firstly, the extensive laboratory measurements used in ELSA-Brasil to ascertain previously unknown diabetes, including a centrally measured standard 75-g oral glucose tolerance test and measurements of glycated hemoglobin, enabled a broader and more sensitive assessment of adult-onset diabetes than in the previous analysis, which relied solely on fasting plasma glucose. Furthermore, exclusion of postmenopausal women with previously diagnosed diabetes from our analyses allowed us to more accurately test the hypothesis that earlier age at first childbirth was associated with development of diabetes within the postmenopausal period. This is in contrast to the analysis of Kim et al.,[6] who included postmenopausal women with previously diagnosed diabetes in their analysis without knowledge of their duration of diabetes, which masked the age at onset of diabetes among the participants. This inability of their analysis to ascertain whether diabetes was diagnosed pre or postmenopausally makes their suggestion, i.e. that the postmenopausal metabolic milieu might explain their findings, questionable.

Thus, if the null finding in our study, in which diabetes was clearly diagnosed postmenopausally, were to be confirmed in further studies, it would suggest that the findings of Kim et al.[6] could be attributable to residual or unmeasured confounding, ethnic differences in the etiology of diabetes, or chance.

CONCLUSIONS

In conclusion, our analyses failed to replicate any association between age at first childbirth and diabetes among postmenopausal women, which had been reported previously. However, in the light of the increasingly recognized role of women's reproductive health factors operating over the course of life, in shaping the risk of adult-onset diabetes, a putative biological role for adolescent pregnancy in the pathophysiology of diabetes should not be ruled out. Thus, further investigation of a potential link between age at first childbirth and type 2 diabetes in postmenopausal women, particularly in the context of a large-scale prospective study, remains warranted.

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Hospitalizations due to primary care-sensitive conditions among children under five years of age: cross-sectional study

Internações por condições sensíveis à atenção primária em crianças menores de cinco anos: estudo transversal

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KEY WORDS:
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PALAVRAS-CHAVE:
Atenção primária à saúde.
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Saúde da criança.
Hospitalização.
Tempo de internação.

ABSTRACT

CONTEXT AND OBJECTIVE: Hospitalizations due to primary care-sensitive conditions constitute an important indicator for monitoring the quality of primary healthcare. This study aimed to describe hospitalizations due to primary care-sensitive conditions found among children under five years of age (according to their age and sex), in two cities in Paraíba, Brazil.

DESIGN AND SETTING: Cross-sectional study carried out in the municipalities of Cabedelo and Bayeux, in Paraíba, Brazil.

METHODS: Data were collected from four public pediatric hospitals in Paraíba that receive children from these municipalities. Hospital admission authorizations were consulted to gather information on the children's profile and the characteristics of their hospitalizations. Differences in the causes of admissions and the respective lengths of hospital stay length were analyzed according to age group and sex.

RESULTS: The proportion of hospital admissions due to primary care-sensitive conditions was 82.4%. The most frequent causes were: bacterial pneumonia (59.38%), infectious gastroenteritis and its complications (23.59%) and kidney and urinary tract infection (9.67%). Boys had higher frequency of hospitalizations due to primary care-sensitive conditions than girls. The median hospitalization due to primary care-sensitive conditions was found to be four days. The duration of hospital stays due to primary care-sensitive conditions was significantly longer than those due to conditions that were not sensitive to primary care.

CONCLUSIONS: High rates of hospital admissions due to primary care-sensitive conditions were highlighted, especially among children of male sex, with long periods of hospitalization.

RESUMO

CONTEXTO E OBJETIVO: As internações por condições sensíveis à atenção primária constituem importante indicador para o monitoramento da qualidade da atenção primária à saúde. O presente estudo objetivou descrever as internações por condições sensíveis à atenção primária em crianças menores de cinco anos (por idade e sexo) em duas cidades da Paraíba.

TIPO DE ESTUDO E LOCAL: Estudo transversal realizado nos municípios de Cabedelo e Bayeux, Paraíba, Brasil.

MÉTODOS: Coletaram-se os dados nos quatro hospitais públicos pediátricos da Paraíba que internam crianças residentes nos municípios estudados. A partir das autorizações de internação hospitalar, colheram-se informações relativas ao perfil da criança e características das internações. Analisaram-se as diferenças nas causas de internações e respectivos tempos de hospitalização segundo faixa etária e sexo.

RESULTADOS: A proporção de internação por condição sensível à atenção primária foi de 82,4%. As causas mais frequentes foram: pneumonias bacterianas (59,38%), gastroenterites infecciosas e suas complicações (23,59%) e infecção do rim e trato urinário (9,67%). Meninos apresentaram maior frequência de internações por condições sensíveis à atenção primária do que meninas. Verificou-se mediana de quatro dias de hospitalização para as condições sensíveis à atenção primária. O tempo de hospitalização por condição sensível à atenção primária foi significantemente maior do que o tempo da condição não sensível à atenção primária.

CONCLUSÕES: Ressaltam-se altas taxas de internações por condições sensíveis à atenção primária, principalmente em crianças do sexo masculino, com longos períodos de hospitalização.

INTRODUCTION

The indicator "hospitalizations due to primary care-sensitive conditions" was initially proposed in the United States in the 1990s to describe health conditions in which effective primary care provided at the right time can help to reduce or eliminate the need for hospital admissions, because prevention and proper treatment can be applied at early stages of the disease.[1,2] Hospital admissions due to primary care-sensitive conditions have increasingly been used as quality indicators worldwide because of their importance for monitoring and evaluating primary healthcare.[2]

Hospitalizations due to primary care-sensitive conditions have been classified and listed for application in Brazil.[3,4] When used as a performance indicator, hospital admissions due to primary care-sensitive conditions should be applied to age groups separately in order to better analyze primary healthcare quality.[3]

Despite the importance of hospital admissions due to ambulatory care-sensitive conditions, studies targeting children under five years of age in Brazil are few and concentrated in the southeastern region of this country.[2] This indicator has great potential for evaluating the quality of primary healthcare for acute conditions that is provided for this age group. Such conditions lead to an associated high probability of hospital admission among these users.[3,5] Children also present greater vulnerability to social determinants of health and to worsening of diseases than adults, thus making their healthcare a priority.[6]

OBJECTIVE

To describe the hospitalizations due to primary care-sensitive conditions that were identified among children under five years of age (according to age and sex) who were admitted to pediatric hospitals in two cities in Paraíba, Brazil.

METHODS

This was a cross-sectional study on hospital admissions of children under five years of age who were living in the municipalities of Cabedelo and Bayeux, Paraíba. These cities were chosen based on their similarities regarding characteristics such as geographical location (in the metropolitan region of the state capital with access to the network of contracted services), degree of urbanization, sociodemographic indicators, economic resources and tradition within the organization of primary healthcare services (the Family Health Strategy covers nearly 100% of the population). Cabedelo has a healthcare system composed of 28 Family Health Strategy teams and Bayeux, 19 teams.

The field team for the present study was composed of healthcare professionals and students with previous experience of fieldwork. The quality control for the study included training and standardizing the interviewers, preparing an instruction manual, carrying out a pilot study and supervising the data collection process.

Data were collected between March 12 and 21, 2014, from four pediatric public hospitals in Paraíba: one located in Cabedelo and three in João Pessoa. These hospitals are responsible for pediatric hospitalizations for families living in the municipalities studied. The medical and statistical record service of each institution granted permission for use of the hospital records relating to all children born between 2008 and 2013 who were hospitalized in 2013.

Firstly, all children living in the municipalities of interest for whom the difference between their date of birth and date of admission was less than five full years were identified through directly consulting the records. This resulted in the sample size of the study (n = 627).

Next, hospital admission authorizations were analyzed to identify the reasons for hospital admission. Admissions were classified as due to primary care-sensitive conditions or not. For this purpose, the Brazilian list of hospitalizations due to primary care-sensitive conditions was used as a reference.[7] Data on the children's characteristics (sex and birth date) and admissions (length of hospital stay and outcome) were also obtained. Each child's age was calculated as the difference between the consultation date and the birth date, and was then classified into categories (< 25 months or 25-60 months).

The data were doubled-entered and organized in spreadsheets. The "Validate" application of the Epi Info software (version 3.3.2) was used to analyze data consistency, and then the final database that was used in statistical analyses was generated.

The frequency of each cause of hospital admission and its proportional contribution to the total number of admissions and the number of admissions due to primary care-sensitive conditions were assessed. The rates of admissions due to primary care-sensitive conditions in relation to the population living in each municipality in 2013 (for the total population and for children under five) were also analyzed.

The chi-square test was used to analyze differences between causes of admissions according to the children's age group and sex. For children for whom the outcome was discharge, the length of stay (days) was expressed as the median and interquartile range. Differences in length of hospital stay according to age and sex were tested through the Mann-Whitney test. The same test was used for pairwise comparisons of length of hospital stay due to each ambulatory care-sensitive condition.

The normality of the data was checked using the Kolmogorov-Smirnov test and the significance level accepted was 5%, for all statistical analyses. We used the Statistical Package for the Social Sciences (SPSS) software, version 13.0, for the analyses.

This study was approved by the Ethics Committee of the State University of Paraíba, under protocol number 19689613.3.0000.5187.

RESULTS

Among the 627 children under five years of age living in the municipalities of Bayeux and Cabedelo who were admitted to pediatric hospitals in the state of Paraíba in the year 2013, 55.2% were male and 52.6% were aged 25 months or over. The majority of these children were hospitalized for one to five days (73.1%) (**Table 1**).

Table 2 shows that 82.46% of the total number of admissions were due to primary care-sensitive conditions. Bacterial pneumonia (59.38%), infectious gastroenteritis and its complications (23.59%) and kidney and urinary tract infections (9.67%) were the main causes of admissions due to ambulatory care-sensitive conditions. These represented 76.39% of the total admissions and 95.92% of those due to ambulatory care-sensitive conditions. The frequencies of hospitalizations per specific cause ranged from 1.34/1000 (skin and subcutaneous tissue infections) to 24.16/1000 (bacterial pneumonia) in this sample of children under five years.

Regarding age group (**Table 3**), it was observed that infectious gastroenteritis and its complications was more frequent among children between 25 and 60 months of age. Among children younger than 25 months, bacterial pneumonia predominated.

Boys were hospitalized more often (P = 0.017) for primary care-sensitive conditions such as infections gastroenteritis and skin conditions (P < 0.02) than girls. This was observed for infectious

Table 1. Characteristics and hospital admissions among children under five years of age. Cabedelo and Bayeux, Paraíba, 2013

Variables	n	%
Characteristics of children		
Sex		
Female	281	44.8
Male	346	55.2
Age (months)		
< 25	297	47.4
25 |- 60	330	52.6
Characteristics of admissions		
Length of stay (days)*		
1 to 5	453	73.1
6 to 10	128	20.6
> 10	39	6.3
Admission outcomes*		
Transference/death	24	3.8
Discharge from hospital	601	96.2

*Values that differ from the total are due to lack of information on hospital admission orders.

Table 3. Causes of hospital admissions of children under five years of age according to age group. Cabedelo and Bayeux, Paraíba, 2013

Causes of admissions	Age group (months)				P
	< 25		25 |- 60		
	n	%	n	%	
Bacterial pneumonia	163	53.1	144	46.9	**0.005**
Infectious gastroenteritis and complications	42	34.4	80	65.6	**0.001**
Kidney infection and urinary tract	23	46.0	27	54.0	0.840
Infection of skin and subcutaneous tissue	6	35.3	11	64.7	0.312
Other HPCSC*	10	47.6	11	52.4	0.981
Total of HPCSC	244	47.2	273	52.8	0.202
Admissions due to non-sensitive conditions	53	48.2	57	51.8	0.703
Total admissions	297	47.4	330	52.6	0.851

*Causes of admissions that showed low frequencies = asthma; diseases of the lower airways; ear = nose and throat infections; whooping cough; epilepsy; malnutrition; anemia. P = values-P for the chi-square test; P in bold denotes statistical significance; HPCSC = hospitalizations due to primary care-sensitive conditions.

Table 2. Causes of hospital admissions of children under five years of age: frequencies, proportions and hospitalization due to primary care-sensitive conditions (HPCSC) in Cabedelo and Bayeux, Paraíba, 2013

Causes of hospitalizations	Number of admissions	% of admissions	% of HPCSC	Rate to HPCSC (X 1000 population)	Rate to HPCSC (X 1000 children < 5 years)
	Total	Total	Total	Total	Total
Bacterial pneumonia	307	48.96	59.38	2.19	24.16
Infectious gastroenteritis and complications	122	19.46	23.59	0.87	9.60
Infection of the kidney and urinary tract	50	7.97	9.67	0.36	3.94
Infections of skin and skin tissue	17	2.71	3.28	0.12	1.34
Other HPCSC*	21	3.36	4.08	0.15	1.65
Total HPCSC	517	82.46	100.0	3.69	40.69
Admissions due to non-sensitive conditions	110	17.54	-	-	-
Total admissions	627	100.0	-	-	-

*Causes of admissions that presented low frequency: asthma; diseases of the lower airways; ear, nose and throat infections; whooping cough; epilepsy; malnutrition; anemia.

gastroenteritis and its complications, and for skin and subcutaneous tissue infections (**Table 4**).

Children admitted due to primary care-sensitive conditions were hospitalized for longer times than children admitted due to conditions that were not sensitive to primary care. Among the primary care-sensitive causes, the length of hospital stay due to infectious gastroenteritis and its complications was significantly lower than that found for the other groups of causes. Considering all admissions, the length of hospital stay was longer for girls than for boys (**Table 5**).

Table 4. Causes of hospital admissions of children under five years of age according to sex. Cabedelo and Bayeux, Paraíba, 2013

Causes of admissions	Sex				P
	Male		Female		
	n	%	n	%	
Bacterial pneumonia	167	54.4	140	45.6	0.698
Infectious gastroenteritis and complications	70	57.4	52	42.6	**0.000**
Kidney infection and urinary tract	14	28.0	36	72.0	0.423
Infection of skin and subcutaneous tissue	11	64.7	6	35.3	**0.017**
Other HPCSC*	12	57.1	9	42.9	0.854
Total HPCSC	274	53.0	243	47.0	0.173
Admissions due to non-sensitive conditions	72	65.5	38	34.5	**0.001**
Total admissions	346	55.2	281	44.8	**0.017**

*Causes of admissions that showed low frequencies: asthma; diseases of the lower airways; ear, nose and throat infections; whooping cough; epilepsy; malnutrition; anemia. P = P-values for the chi-square test; P in bold denotes statistical significance; HPCSC = hospitalizations due to primary care-sensitive conditions.

DISCUSSION

The present study showed that a high proportion of admissions were due to ambulatory care-sensitive conditions. Bacterial pneumonia, infectious gastroenteritis and its complications, kidney and urinary tract infection and skin and subcutaneous tissue infection presented the highest proportions. In other localities of Brazil, primary care-sensitive conditions were also found to be the main reason for hospitalization among children.[5,6] Thus, the social, economic and cultural complexity of the reality and demands of this population group needs to be considered in healthcare planning.[8,9]

The high number of hospitalizations among the children in the present study was attributed to cases of bacterial pneumonia, infectious gastroenteritis and its complications, kidney and urinary tract infection and skin and subcutaneous tissue infection. This corroborates a previous study that also showed the same clinical conditions as the main causes of primary care-sensitive hospitalizations.[3,10] Similar results have been also systematized recently.[2] These acute conditions are highly prevalent among the sicknesses affecting children, whereas greater diversification and variability of illnesses are observed in the adult population as a consequence of aging and higher levels of poor lifestyle choices.[3,5] The vulnerability to illness among children under five years of age is associated with accelerated physical growth and age-specific frailty.[11]

The two main primary care-sensitive causes observed in the study population, namely bacterial pneumonia and infectious gastroenteritis and its complications, have also been observed in other scenarios in Brazil.[3,9,12] These diseases may be related to environmental and socioeconomic conditions, in particular water purification, waste water treatment and air quality. Thus, prevention needs to be strengthened through guidance for children's

Table 5. Hospital stay length of the causes of admissions of children under five years of age according to the child's sex. Cabedelo and Bayeux, Paraíba, 2013

Causes of admissions	Median number of days of hospital stay (interquartile range)	Median number of days of hospital stay (interquartile range)		P
	Total	Sex		
		Male	Female	
Bacterial pneumonia	4.0 (3.0)[a]	4.0 (3.0)	4.0 (3.0)	0.754
Infectious gastroenteritis and complications	3.0 (3.0)[b]	3.0 (2.0)	3.0 (4.0)	0.078
Kidney infection and urinary tract	4.0 (4.0)[a]	4.0 (2.0)	4.0 (5.0)	0.417
Infection of skin and subcutaneous tissue	4.0 (2.5)[a]	4.0 (3.0)	4.0 (2.3)	0.525
Other HPCSC*	4.0 (4.0)[a]	3.0 (2.8)	5.0 (4.0)	0.516
Total HPCSC	4.0 (3.0)[a]	4.0 (3.0)	4.0 (4.0)	0.079
Admissions due to non-sensitive conditions	3.0 (3.0)[b]	3.0 (2.0)	3.0 (5.0)	0.161
Total admissions	4.0 (4.0)[a]	4.0 (2.0)	4.0 (4.0)	0.013

*Causes of admissions that showed low frequencies: asthma; diseases of the lower airways; ear, nose and throat infections; whooping cough; epilepsy; malnutrition; anemia. P = P-values for the chi-square test; P in bold denotes statistical significance; P > 0.05 for the analysis by age group; [a,b]Different superscript letters denote statistical difference in length of hospital stay among the causes of hospitalizations; HPCSC = hospitalizations due to primary care-sensitive conditions.

caregivers and should cover integration between various sectors of public policy.[3,13,14] Kidney and urinary tract infection ranked as the third largest cause of hospital admission among the children in this study, and this was similar to what was found in Paraná[3] and was recently systematized.[2] Importantly, it is possible to diagnose and treat these conditions at their early stages through urine analyses and pharmacological treatment with antibiotic drugs.[2,15]

The vulnerability of young children to hospitalization due to bacterial pneumonia that was observed in the current study was similar to the findings from a previous study.[3,13] This can be explained by the immaturity of the immune system of younger children, which is associated with smaller-caliber airways that impose difficulty in the process of removing foreign elements.[11] In the context of healthcare, higher numbers of admissions among children under one year of age is mostly associated with inadequate care during the prenatal period, at delivery and during the postpartum period.[3]

In a survey carried out in São José do Rio Preto, state of São Paulo,[9] and in the current study, older children were more frequently hospitalized due to infectious gastroenteritis and its complications. Other studies have reported higher prevalence of admissions due to this cause among younger children than those in the current study.[1,3,16] Considering the peculiarity of the immaturity of the immune system of young children, who have greater vulnerability to hydroelectrolytic disorders and bacterial and protozoan etiological agents,[1,3,16] it is feasible that these rates may be influenced by greater care given to children younger than 25 months of age. Older children who are also in a vulnerable and immature physiological condition are exposed more often to degraded environments and to their own family's socioeconomic situation.[3]

Previous studies carried out in Brazil identified higher prevalence rates of admissions among male children,[14,17] as in the present report. Greater exposure to infectious agents, among Brazilian boys because of their greater freedom to participate in sports, for sociocultural reasons, probably leads to more hospitalizations of boys than girls.[16]

Length of hospital stay is an indicator of quality of care. Likewise, admissions due to primary care-sensitive conditions and length of stay can also be reduced by providing qualified care in primary healthcare services.[4,18] In spite of this, we were unable to find any study addressing this indicator among Brazilian children, from this perspective. The average length of hospital stay found in this study was four days. The same was found in Colombia.[18] A longer length of stay was reported in the city of Montes Claros, Minas Gerais.[5] This amount of time can be considered long, since the causes of admissions can be treated with antibiotics, which are easily available and effective within 72 hours.[15,19] Deficiencies in the pediatric hospital network of the municipalities studied possibly have a role in this result. Other authors have also found longer hospital stays among children who did not live in the state capital.[20] This hypothesis is supported by the fact that infectious gastroenteritis and its complications required shorter hospital stays, most likely because of its low complexity and because of the possibility that this condition can be resolved within the home environment through simple measures such as rehydration, rest and a bland diet.[16]

A study conducted in the United States showed that hospital stays were longer among girls than among boys,[1,2] just like in the present study. The explanations for sex-specific differences in length of hospital stay have been found in the scientific literature to be inconsistent and, thus, further investigation is merited.[21] It is noteworthy that length of hospital stay is a complex variable that depends on factors such as clinical condition, severity of the disease and the possibility of complications.[18,19]

It is important to note that some determinants of admissions among children were not addressed in this study. These included socioeconomic conditions, which have clear associations with access to health services.[1] Furthermore, families also have a role regarding adherence to the guidelines for child healthcare and placing value on the Family Health Strategy service, as a gateway to the healthcare system.[5,8] The quality of healthcare and the profile of the professionals involved are other components of admissions due to primary care-sensitive conditions that were not considered here.[22,23]

The current study has other limitations that need to be discussed. The first relates to use of hospital admission authorizations for obtaining the reason for hospitalization. The purpose of this instrument is primarily to document the financial reimbursement for services rendered. Thus, there may be flaws in data registration in the hospital (which may or may not be intentional) that compromise the accuracy of the information. The second limitation relates to the focus on services financed through the public system alone, even though hospitalizations due to primary care-sensitive conditions may also occur within the private healthcare system. Moreover, the possibility that children may have been hospitalized in other cities cannot be disregarded.

CONCLUSIONS

High rates of admissions due to primary care-sensitive conditions, including admissions caused by acute illnesses, were observed in the present study, especially among male children. It should be noted that hospital admissions that can be prevented within primary care require longer hospital stays than those resulting from conditions that are not sensitive to primary care.

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Nonalcoholic fatty liver disease and bariatric surgery: a comprehensive review

Doença hepática gordurosa não alcoólica e cirurgia bariátrica: uma revisão abrangente

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ABSTRACT

CONTEXT AND OBJECTIVE: Nonalcoholic fatty liver disease (NAFLD) has been increasingly diagnosed worldwide and is now recognized as a source of public health concern. It comprises a wide spectrum of histological features that range from simple steatosis to severe forms of fibrosis, steatohepatitis and even cirrhosis. The impact of bariatric surgery on the course of NAFLD in individuals with obesity has been extensively studied.

DESIGN AND SETTING: Narrative review; public university hospital.

METHODS: A comprehensive review was conducted based on an online search on the electronic databases MEDLINE and LILACS using the MeSH terms "fatty liver" and "bariatric surgery".

RESULTS: The exact mechanisms that lead to improvement in NAFLD following bariatric surgery are not completely understood. Since Roux-en-Y gastric bypass (RYGB) is the bariatric surgical procedure most performed worldwide, it is also the one from which the effects on NAFLD have been most studied, although there is also consistent evidence regarding the effects from gastric banding, sleeve gastrectomy and biliopancreatic diversions.

CONCLUSION: According to the currently available evidence, bariatric surgery leads to significant improvement in NAFLD. Further research, especially by means of randomized controlled trials enrolling larger cohorts of individuals, is needed to determine the optimal procedure for this group of subjects.

RESUMO

CONTEXTO E OBJETIVO: A doença hepática gordurosa não alcoólica (DHGNA) tem sido diagnosticada com maior frequência em todo o mundo na atualidade, sendo agora reconhecida como motivo de preocupação em saúde pública. Abrange um amplo espectro de alterações histológicas que variam desde a simples esteatose até formas graves de fibrose, esteato-hepatite e até cirrose. O impacto da cirurgia bariátrica sobre o curso da DHGNA em indivíduos com obesidade tem sido profundamente estudado.

TIPO DE ESTUDO E LOCAL: Revisão narrativa; hospital universitário público.

MÉTODOS: Uma revisão abrangente da literatura foi conduzida baseada na pesquisa *on-line* nas bases de dados eletrônicas MEDLINE e LILACS por meio dos termos MeSH "fígado gorduroso" e "cirurgia bariátrica".

RESULTADOS: Os mecanismos exatos que levam à melhora da DHGNA após a cirurgia bariátrica não são completamente conhecidos. Como o *bypass* gástrico em Y de Roux é a cirurgia bariátrica mais realizada em todo o mundo, é também o procedimento cujos efeitos sobre DHGNA foram mais estudados, embora haja também evidências consistentes sobre os efeitos de banda gástrica, gastrectomia vertical e derivações biliopancreáticas.

CONCLUSÃO: De acordo com as evidências atualmente disponíveis, a cirurgia bariátrica leva à melhora significativa da DHGNA. Mais estudos, especialmente por meio de ensaios clínicos randomizados e controlados, recrutando coortes maiores de indivíduos, são necessários para determinar o melhor procedimento para esse grupo de pacientes.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is defined as accumulation of excessive fat in the liver in the absence of excessive drinking of alcohol and/or any secondary cause.[1-3] Along with obesity epidemics, it has been increasingly diagnosed over the last few decades and is now recognized as a source of public health concern. Today, NAFLD is considered to be the commonest liver disease worldwide. It comprises a wide spectrum of histological features that range from mild steatosis to severe forms of fibrosis, steatohepatitis and even cirrhosis.[3,4]

Epidemiology

Today, the most reliable values for the prevalence of NAFLD and nonalcoholic steatohepatitis (NASH) in the general population in the Western world are 20-30% and 2-3%, respectively.[5-7] In Asia, the prevalence of NAFLD has been found to range from 15% to 30% in the general population.[8] The reported prevalence of NAFLD may vary according to the population studied and the diagnostic method used. The results from population-based studies provide more accurate data than do autopsies, hospital series or studies on high-risk groups, since they avoid higher selection bias. Studies that have detected NAFLD by means of liver enzyme levels have observed prevalences of NAFLD in the general population of between 3% and 23%, i.e. generally lower than those reported from analyses that used imaging methods.[5-11] Studies based on ultrasound scans appear to be more reliable and have shown prevalences of NAFLD among healthy adults of 25-30% in the United States and Italy and 29% in Japan.[5-8]

NAFLD is associated with significantly higher overall mortality, compared with the general population, particularly due to cardiovascular and liver-related complications. The histological stage is nevertheless crucial for the longer-term prognosis. Among patients with NASH, compared with patients with simple steatosis, the prevalence of cirrhosis development within the first 15 years of follow-up is significantly higher (10.8% versus 0.7%, respectively) and liver-related mortality is also significantly higher (7.3% versus 0.9%). The overall and liver-related mortality among patients with NASH is correspondingly higher than would be expected among individuals of the same age and gender with simple NAFLD.[8-11]

Among obese populations with metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM), the prevalence of NAFLD is much higher, ranging from about 50% to 90%. NAFLD has become a challenging public health concern, given that the prevalences of obesity and overweight have increased to epidemic levels over the last few decades. It constitutes an additional risk factor for this group of patients, especially because of the possibility of evolution to severe forms of liver fibrosis (including end-stage liver disease and cirrhosis) and even liver cancer.[5-8,12]

Among cases labelled as "cryptogenic cirrhosis", the prevalence of NAFLD appears to be very high. Nayak et al.[9] carried out a study in which the clinicopathological features of NAFLD were explored through clinical data and by examining the explanted livers of living-donor liver transplant recipients. Among 103 adult liver transplant recipients with different types of chronic liver disease, 30 had a pre-liver transplantation diagnosis of cryptogenic cirrhosis. Out of these 30 cryptogenic cirrhosis cases, 19 (63.3 %) were finally labeled as NAFLD-related cirrhosis and showed histological features that differed in several respects from those reported for the early and established phases of NAFLD.

The risk factors for development of NAFLD have been established. Increasing age presents a direct correlation with the prevalence of NAFLD. This is possibly related to the increasing insulin resistance and incidence of metabolic syndrome that occurs with age.[12] NAFLD generally occurs at a higher rate among men than among premenopausal women. It also differs according to ethnicity, such that it affects 45% of Hispanic people, 33% of Caucasians and 24% of African-Americans in the United States and has been recorded at higher levels among South Asians in the United Kingdom.[7-12] Likewise, among children and adolescents, the prevalence of NAFLD again seems to differ between different ethnic groups, with the highest prevalence in Hispanic people.[5]

Several studies have revealed high rates of NAFLD among obese populations who undergo bariatric surgery.[13-17] Reports on morbidly obese populations have shown that the prevalence of liver fibrosis ranges from 6% to 74.4% and steatohepatitis from 26% to 55%.[16,17]

Pathophysiology

The underlying mechanisms that are present in the development of NAFLD are not completely understood, although much progress has been made over recent years. The classical pathogenetic pathway that leads to NAFLD was described as the "two-hit hypothesis". This theory stated that damage to the liver tissue begins through triglyceride accumulation (the first hit), which functions as a sensitizing factor for secondary damage caused by inflammatory mediators (mainly cytokines or adipokines), mitochondrial dysfunction and oxidative stress (the second hits). These secondary aggressions would lead to steatohepatitis and fibrosis.[18,19] Today, it is widely recognized that free fatty acids (FFAs) also play a direct role in promoting liver injury. One of the consequences of insulin resistance (IR) is greater influx of FFAs to the liver: these undergo β-oxidation or esterification with glycerol to form triglycerides. Additionally, FFAs are able to cause toxicity through directly increasing oxidative stress and activating inflammatory pathways.[20,21] Another "hit" that was recently identified consists of impaired hepatocyte proliferation. In NAFLD, when cell death occurs in the liver tissue, oxidative stress causes disruption to the regenerative process, thus leading to proliferation of

hepatic progenitor (oval) cells. The size of the oval cell population correlates directly with the degree of fibrosis and it is believed that activation of these cells is involved in hepatic carcinogenesis.[18,21-23]

In NAFLD, lipid accumulation within the liver (steatosis) may result from several mechanisms: increased fat synthesis, increased fat delivery, decreased fat export and/or decreased fat oxidation.[23-28]

IR plays an important role in NAFLD development and evolution, and NAFLD also contributes towards worsening of IR. In individuals with IR who present excess visceral fat, the influx of FFAs to the liver is increased, thus leading to both triglyceride accumulation and direct lipotoxicity. On the other hand, several abnormalities intrinsic to NAFLD impair insulin receptor signaling, especially FFAs, tumor necrosis factor-alpha (TNF-α), nuclear factor kappa B (NF-κB), ceramide, Jun N-terminal kinase 1 (JNK1), suppressors of cytokine signaling (SOCS) and cytochrome CYP2E1. The cumulative effect generates a vicious cycle of IR and NAFLD worsening each other.[18,23,29-31]

Steatosis is strongly associated with chronic hepatic inflammation, an effect that is partly mediated by activation of the Iκκ-β/NF-κB signaling pathway. This is associated with elevated hepatic expression of inflammatory cytokines such as TNF-α, interleukin-6 (IL-6) and interleukin 1-beta (IL-1β), and activation of Kupffer cells. Both serum and hepatic levels of TNF-α are elevated in patients with NASH, and these levels are correlated with histological severity.[18,32-35] In addition to the proinflammatory effect, TNF-α promotes IR. Further data suggests that inflammation and NF-κB activation may also promote carcinogenesis and that this chronic inflammatory state may also play a key role in hepatocellular carcinoma (HCC) development.[18,36,37]

Increased leptin levels are observed in cases of obesity and NAFLD. These are usually regarded as states of leptin resistance. It is possible that leptin may have an important role in the pathogenesis of NAFLD. Conversely, the circulating levels of adiponectin are inversely proportional to body fat content and become reduced in patients with NAFLD.[38-41]

Oxidative stress and mitochondrial dysfunction play a well-reported role in NASH, with a direct correlation between the degrees of oxidative stress and the severity of liver disease. Structural mitochondrial abnormalities and impairment of mitochondrial respiratory chain activity have been reported in human studies.[18,42-46]

Endoplasmic reticulum (ER) stress and endotoxemia derived from the gut microbiota are other mechanisms that appear to be implicated in NASH pathogenesis. ER stress is associated with various types of biological stress, such as hyperinsulinemia and hyperlipidemia, and it usually causes IR, inflammation, apoptosis and mitochondrial dysfunction, through several mechanisms. In cases of alcohol-related steatohepatitis, ER stress is a well-established pathophysiological factor, but further study on the possible role that it plays in the development of NASH is needed.[18]

The role of gut bacterial overgrowth in the pathogenesis of NASH is now emerging through recent evidence. Bacterial overgrowth leads to production of ethanol and release of bacterial lipopolysaccharides, both of which can activate TNF-α production in Kupffer cells, thereby inducing inflammation in liver tissue. Individuals with NASH more frequently present bacterial overgrowth in the small intestine and increased gut permeability than do controls. These findings also suggest that this is a possible explanation for the rapid onset of NASH and liver fibrosis following jejunoileal bypass surgery. Furthermore, there is evidence that hepatic inflammation can be reduced by means of changes to the gut microbiota induced by antibiotics and probiotics.[47-56]

Under high levels of oxidative stress, which is a feature usually observed in the presence of injurious factors such as NASH and viral infection, mature hepatocytes may present impairment of their replication process, thus leading to reduction of their proliferative ability. Subsequently, hepatic progenitor cells (HPCs) are recruited; these cells have the capacity to differentiate into either hepatocytes or cholangiocytes and may be involved in carcinogenesis relating both to hepatocellular carcinoma and to cholangiocarcinoma. Initial research has observed that there is a strong association between expansion of HPCs and a ductular reaction in liver biopsy specimens in NASH cases. The extent of ductular reactions in turn strongly correlates with the degree of fibrosis, thus suggesting that HPC expansion/ductular reaction may play an important role in stimulating progressive periportal fibrosis.[57-60]

Histopathology

NAFLD encompasses a wide spectrum of liver histopathological abnormalities that may also have highly variable natural courses. It is grossly divided into two main categories: simple steatosis, in which only hepatocellular steatosis is observed; and NASH, in which necroinflammatory reactions are associated with hepatocellular steatosis. Simple steatosis usually presents a benign course. NASH, on the other hand, is a progressive disease that can evolve into liver cirrhosis and HCC. Steatohepatitis-associated hepatocellular carcinoma (SH-HCC) is a variant of classical HCC in which the onset appears to be strongly linked to NASH.[61,62]

It is important to emphasize that NAFLD/NASH presents a different pattern in pediatric individuals, with lesions that may or may not resemble those observed in adults. It constitutes an area of ongoing investigation within pathology.[61,62] Since pediatric NAFLD is not the focus of this review, it will not be tackled here.

Histopathological features of adult NAFLD

Hepatocellular steatosis is the hallmark of NAFLD; steatosis in more than 5% of the hepatocytes is required for the diagnosis of NAFLD.[61,63,64] Steatosis may be macrovesicular or microvesicular; in NAFLD, the macrovesicular type is usually present, although

about 10% of the cases may also present microvesicular steatosis. It usually begins in zone 3 and may evolve to panacinar steatosis in severe cases.[61,65,66]

Mild intralobular inflammation is present in NASH and consists of an infiltrate of mixed inflammatory cell types (lymphocytes, neutrophils, eosinophils and Kupffer cells). Satellitosis may be sporadically observed in NASH and consists of ballooned hepatocytes surrounded by polymorphs; this feature is more commonly associated with alcoholic hepatitis. Lipogranulomas and lobular microgranulomas are frequently seen in NASH. Portal inflammation in NASH is usually absent or mild; when there is disproportionately severe portal inflammation, the possibility of other concurrent hepatic diseases needs to be considered.[61,67,68]

Hepatocellular ballooning is another feature associated with NAFLD and is characterized by the presence of swollen hepatocytes with rarefied cytoplasm, which may contain fat droplets and Mallory-Denk bodies. It usually reflects hepatocellular injury.[61]

Fibrosis in NASH characteristically follows a perisinusoidal/pericellular pattern and usually begins in zone 3. Typically, an active necroinflammatory reaction is observed, along with fibrosis. Progression of perisinusoidal/pericellular fibrosis may lead to occurrences of portal/periportal fibrosis, bridging fibrosis and liver cirrhosis.[69,70]

Other important features of NAFLD/NASH include glycogenated nuclei, acidophil bodies, Mallory-Denk bodies (MDBs), iron deposition and megamitochondria.[61,62] Glycogenated nuclei are vacuolated nuclei that are usually observed in periportal hepatocytes. They are common in NAFLD, but only rarely observed in alcohol-induced liver disease.[71] Presence of apoptotic hepatocytes (acidophil bodies), usually in the sinusoids, is also commonly observed in NASH.[72] The eosinophilic irregular-shaped aggregates that are usually observed in the cytoplasm of ballooned hepatocytes in zone 3 are known as MDBs. They are not specific to NASH and may be found in alcohol-induced disease, chronic cholestasis and HCC.[73,74] Mild iron deposition within hepatocytes or in the sinusoidal lining cells of the reticuloendothelial system, or in both of these, is common in NAFLD/NASH; its significance is yet to be fully understood.[75] Megamitochondria are massively enlarged round or crystal-shaped eosinophilic structures that are observed in the cytoplasm of hepatocytes, usually with concurrent microvesicular steatosis; they are believed to originate due to lipid peroxidation.[76] Ductular reactions and presence of an arterial branch in zone 3 within perisinusoidal fibrosis are other poorly understood abnormalities observed in NASH.[59]

Diagnosis

According to the current guidelines of the American Association for the Study of Liver Diseases (AASLD), there are four requirements for diagnosing NAFLD:

1. presence of hepatic steatosis detected using imaging methods or biopsy;
2. absence of significant alcohol consumption;
3. absence of possible competing etiologies for hepatic steatosis;
4. absence of concurrent chronic liver disease.[77]

There are several noninvasive methods for assessing and diagnosing NAFLD, although none of them are able to provide the same amount of information that is brought through liver biopsy.[78] Ultrasound scanning is a valuable imaging tool, since it is cheap and highly available and may provide overall accuracy of nearly 80% for detecting NAFLD. On the other hand, it presents limitations that may compromise interpretation of the results, given that it is examiner-dependent and there may be technical difficulties in performing it on obese individuals because of their anatomical features. Thus, although ultrasound provides useful clues towards diagnosing NAFLD, it cannot be taken to be the ultimate method for detecting it. Moreover, it cannot provide nuanced evaluation of the presence of steatohepatitis and the severity of fibrosis.[17,79,80]

Ultrasonography-based transient elastography (FibroScan) is a promising method that can bring reliable results by means of safe examination. However, its cost and low availability compromise its potential impact.[17,81] Furthermore, FibroScan has no value for patients with ascites and presents great limitations relating to examining obese patients, because the probe is calibrated for a specific distance between the liver and the chest wall and the low-frequency vibration induced by the probe and/or the ultrasound wave may be strongly attenuated by the fatty tissue.[82-84]

Development of noninvasive scores for assessing liver disease, including NAFLD, is an important field of study nowadays. The ultimate goal in using these scores is to obtain reliable information from noninvasive laboratory and clinical variables that are available in general practice. The NAFLD fibrosis score is the one most used today and can easily be calculated based on six readily available variables: age, body mass index (BMI), hyperglycemia, platelet count, albumin and aspartate transaminase/alanine transaminase (AST/ALT) ratio. A meta-analysis on 13 studies that enrolled 3,064 patients showed that the NAFLD fibrosis score yielded an area under the receiver operating characteristic curve (AUROC) of 0.85 for predicting advanced fibrosis (bridging fibrosis or cirrhosis). Scores ≤ -1.455 had 90% sensitivity and 60% specificity for ruling out advanced fibrosis, whereas scores > 0.676 had 67% sensitivity and 97% specificity for identifying the presence of advanced fibrosis.[85] However, this score does not replace liver biopsy and cannot in any manner be regarded as a gold standard, given that it does not provide a nuanced evaluation. On the other hand, it does not produce any morbidity and can be easily and readily assessed through routine studies. Thus, this score is quite adequate for population-based studies and for clinical screening and follow-up purposes.[17,84,85]

Despite recent developments in noninvasive methods for assessing NAFLD, liver biopsy remains the gold-standard method for diagnosing and characterizing it, since it may provide a nuanced evaluation that no other method is capable of today. On the other hand, it is expensive and highly invasive, and carries significant risk of morbidity and even mortality.[77] Moreover, the histological features of NAFLD and NASH are unevenly distributed throughout the entire liver parenchyma, and sampling error might result in substantial misdiagnosis and staging inaccuracies.[61,78] The current guidelines state that use of biopsies should be restricted to individuals who would benefit the most from diagnostic and therapeutic guidance, and from prognostic perspectives. Hence, a biopsy should be considered for NAFLD assessment among patients:

1. with NAFLD, who are at increased risk of development of fibrosis and steatohepatitis;
2. with suspected NAFLD, in whom concurrent etiologies for hepatic steatosis and/or coexisting chronic liver diseases cannot otherwise be ruled out.[77]

Current clinical treatment

The current treatment strategies for NAFLD are based on the various aspects of its pathophysiology, especially its relationship with obesity and insulin resistance. The current nonsurgical strategies can be divided in non-pharmacological and pharmacological.

The primary goals of the main nonpharmacological strategies are weight loss and lifestyle changes. Interventions based on low-fat and low-calorie diets have been evaluated in several studies in which it was observed that these diets were associated with reductions in liver enzyme levels and liver fat content and improvement in liver histology.[87-93] Thoma et al. reviewed the efficacy of physical exercise alone versus physical exercise combined with dietary approaches to reduce liver fat content. Energy restriction and weight reduction of 4-14% resulted in significant decreases in hepatic steatosis of 35-81%. Decreases in liver fat correlated most strongly with the degree of weight loss. It was seen that regular exercise might modestly reduce steatosis even without a change in weight.[94] However, the greatest caveat of interventions that use dietary measures for weight loss is their lack of long-term durability. It remains unclear how weight regain affects the natural history of NAFLD/NASH.[94-97]

The primary goal of pharmacological interventions aimed towards NAFLD may either be weight loss or consist of a direct effect on liver disease and its pathophysiological features, especially insulin resistance and inflammation. Evidence regarding the effect of weight loss medications on NAFLD is scarce. The results relating to orlistat were inconclusive in several trials.[87,98] Pentoxifylline, albeit not targeted for weight loss, led to a slight weight reduction and improvement in NASH in one trial.[99]

Regarding insulin resistance, the potential therapeutic effect of insulin sensitizers on NAFLD/NASH has gathered much attention. Rosiglitazone was shown to improve steatosis and aminotransferase levels in patients with NASH in a randomized controlled trial,[100] but its use is prohibited in Europe and very restricted in the United States because it may increase the risk of ischemic heart disease.[101] In randomized controlled trials, pioglitazone induced significant improvements in serum aminotransferase levels and liver histology (steatosis, inflammation, ballooning and Mallory-Denk bodies) in individuals with NASH.[102-104] However, the improvement in the extent of fibrosis was not significant. Use of pioglitazone is also prohibited in Europe, due to the risk of bladder cancer.[101] Use of metformin was not shown to provide any benefits or to have any independent therapeutic role in individuals with NAFLD, in a meta-analysis study. However, there is level III evidence that metformin may have a chemopreventive role in patients with diabetes and chronic liver disease, with reductions in the incidence of HCC and cholangiocarcinoma.[105] Liraglutide, an analogue of glucagon-like peptide 1 (GLP-1), was shown to promote significant improvement in liver histology in individuals with biopsy-proven NASH after 48 hours of therapy. Longer-term research is needed, but the initial results appear promising.[106]

Use of vitamin E, because of its antioxidant effects, has shown benefits regarding liver histology among non-diabetic individuals with NASH. Nonetheless, it is important to emphasize that the safety of long-term usage of vitamin E is questionable, since high-dosage vitamin E supplements are associated with increased incidence of prostate cancer in healthy men, and with all-cause mortality.[101,107-110]

The current usage of lipid-lowering drugs targeted towards NAFLD (mainly statins) is so far unsupported by any substantial results from well-conducted studies. Thus, this practice is not recommended by American guidelines.[77,101] The newer agent ezetimibe, which acts through inhibiting cholesterol absorption, has shown promising effects, especially in association with acarbose, but further results are needed in order to enable its use to be validated as a current recommendation.[111-114]

There is a lack of conclusive evidence supporting the use of ursodeoxycholic acid, N-3 polyunsaturated fatty acids, angiotensin receptor blockers, probiotics and synbiotics as validated treatment options for NAFLD.[77,101]

OBJECTIVE

The aim of this study was to conduct a critical analysis on the evidence available regarding the effect of bariatric surgery on NAFLD.

METHODS

A review of the literature was conducted through an online search for the MeSH terms "fatty liver" and "bariatric surgery" in MEDLINE (via PubMed) and LILACS (via BVS) (**Table 1**). We included original studies that reported on clinical trials on the effects of several types of bariatric surgery on NAFLD. All the papers were checked according to their titles and abstracts

(screening). Full papers were obtained from journals available through the website of the Commission for Improvement of Higher Education Personnel (Comissão de Aperfeiçoamento de Pessoal de Nível Superior, CAPES) (Ministry of Education, Brazil). Unavailable articles were requested from their authors. Articles presenting potentially relevant studies were read and analyzed to assess their inclusion criteria. We excluded articles that consisted of *in vitro* or animal studies, articles in which the participants' characteristics did not match those mentioned above, poster session abstracts, review articles and other types of publications (non-standard bariatric surgical techniques; studies without appropriate follow-up; studies without appropriate NAFLD assessment; or studies with critical methodological issues). Other papers were used for contextualization and discussion.

RESULTS

There was significant overlap between the databases. After careful analysis, we selected three systematic reviews, seven prospective cohort studies and twelve retrospective cohort studies. **Table 2**

Table 1. Database search results for the effects of bariatric surgery among individuals with nonalcoholic fatty liver disease, on November 20, 2016

Electronic databases	Search strategies	Results
MEDLINE (PubMed)	(Fatty liver) AND (Bariatric surgery)	3 systematic reviews 7 prospective cohort studies 12 retrospective cohort studies
LILACS (BVS)	((Fatty liver) OR (Hígado graso) OR (Fígado gorduroso)) AND ((Bariatric surgery) OR (Cirurgia Bariátrica) OR (Cirurgia Bariátrica))	2 systematic reviews 5 prospective cohort studies 9 retrospective cohort studies

Table 2. Main studies on the influence of bariatric surgery on nonalcoholic fatty liver disease

	N	Technique	Methodology	Mean follow-up (months)	Level of evidence	Outcome studied	Rates of improvement
Silverman et al.[115]	91	RYGB	Retrospective	18.4	2b	Biopsy	Steatosis: 74%
Mattar et al.[116]	70	RYGB	Retrospective	15	2b	Biopsy	Steatosis: 90.9% Steatohepatitis: 86.9% Fibrosis: 41.9%
Liu et al.[117]	39	RYGB	Retrospective	18	2b	Biopsy	Steatosis: 96.8% Fibrosis: 50%
Furuya et al.[118]	18	RYGB	Prospective	24	4	Biopsy	Steatosis: 84% Fibrosis: 75%
Moretto et al.[119]	78	RYGB	Retrospective	12	2b	Biopsy	Fibrosis: 31.2%
Vargas et al.[120]	26	RYGB	Retrospective	16	4	Biopsy	Steatohepatitis: 84%
Abdennour et al.[121]	243	RYGB	Prospective	12	2b	Enzymes	Steatosis: 85%
Cazzo et al.[122]	63	RYGB	Prospective	12	2b	Fibrosis score	Fibrosis: 55%
Luyckx et al.[123]	69	VBG	Retrospective	27	2b	Biopsy	Steatosis: 54.2%
Stratopoulos et al.[124]	51	VBG	Retrospective	18	2b	Biopsy	Steatosis: 82% Fibrosis: 6.2%
Dixon et al.[125]	36	GB	Retrospective	25.6	2b	Biopsy	Steatosis: 91.7% Fibrosis: 83.3%
Phillips et al.[126]	29	GB	Prospective	3	2b	MRI	Steatosis: 70.4%
Gastaldelli et al.[127]	159	GB	Prospective	12	2b	Enzymes	Steatosis: 88%
Karcz et al.[128]	236	SG	Prospective	12	2b	Enzymes	Steatosis: 83%
Algooneh et al.[129]	84	SG	Retrospective	39.6	2b	US	Steatosis: 56%
Papadia et al.[130]	99	BPD-S	Retrospective	12	2b	Enzymes	Steatosis: 73%
Ferrer-Marquez et al.[131]	76	BPD-S	Prospective	12	2b	Biopsy	Steatosis: 85.5% Steatohepatitis: 83% Fibrosis: 52.6%
Kral et al.[132]	104	BPD-DS	Retrospective	41	2b	Biopsy	Fibrosis: 52.9%
Keshishian et al.[133]	697	BPD-DS	Retrospective	12	2b	Enzymes	Steatosis: 60%

N = number of individuals; RYGB = Roux-en-Y gastric bypass; VBG = vertical banded gastroplasty; GB = gastric banding; SG = sleeve gastrectomy; BPD-S = biliopancreatic diversion – Scopinaro; BPD-DS = biliopancreatic diversion – duodenal switch; MRI = magnetic resonance imaging US = ultrasound scan. Levels of evidence according to the Oxford classification - 1a: systematic reviews (with homogeneity) of randomized controlled trials; 1b: individual randomized controlled trials (with narrow confidence interval); 1c: all or no randomized controlled trials; 2a: systematic reviews (with homogeneity) of cohort studies; 2b: individual cohort study or low-quality randomized controlled trials (e.g. < 80% follow-up); 2c: "outcomes" research; ecological studies; 3a: systematic review (with homogeneity) of case-control studies; 3b: individual case-control study; 4: case series (and poor quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles".

summarizes the main articles found and their respective characteristics and reported results.[115-133]

A schematic representation of the search in the online databases and the identification, exclusion and selection of the articles is presented in **Figure 1**.

Bariatric surgery and NAFLD

The impact of bariatric surgery on the course of NAFLD in obese individuals has been extensively reported. Surgery plays a significant role in the expected natural history of NAFLD and usually leads to rapid changes in its evolution. Different surgical methods act within this context through a variety of mechanisms, which over the long term may be directly associated with the weight loss achieved, but over the short to medium term appear to be more related to acute structural and endocrine changes that are attributable to the procedures. **Table 1** summarizes the main studies on the influence of bariatric surgery on NAFLD.

Roux-en-Y gastric bypass

A pioneering study conducted by Silverman et al.,[115] which enrolled 91 individuals, revealed that after Roux-en-Y gastric bypass (RYGB), 65 patients presented reduced steatosis, 18 patients had no steatosis, 5 patients with minimal steatosis showed no change and 3 patients presented increased steatosis. Pre-gastric bypass biopsies from 13 patients showed perisinusoidal fibrosis (PSF) that was major with bridging in three patients, moderate in one patient and slight in nine patients. Following RYGB, PSF was found to have been eliminated in 10 patients, was reduced in one patient and was the same in two patients. One patient developed PSF after gastric bypass.

In a study that evaluated 70 individuals who underwent a variety of bariatric procedures by means of intraoperative and postoperative liver biopsies, Mattar et al.[116] observed significant improvement in liver steatosis (from 88% to 8%), inflammation (from 23% to 2%) and fibrosis (from 31% to 13%). Inflammation and fibrosis resolved in 37% and 20% of the patients, respectively, corresponding to significant improvements of 82% in grade and 39% in the stage of liver disease. As expected, purely restrictive procedures produced a significantly less dramatic impact on weight loss than did gastric bypass. Improvement in grade in the purely restrictive group (66% showed improvement in grade) was significantly less than in the gastric bypass group (93%).

In a case series that enrolled 16 individuals, Clark et al.[134] evaluated liver histology at the time of RYGB surgery and at the time of elective incisional hernia repair after weight loss. For all the patients, the initial biopsy showed steatosis, while 94% had inflammation, 88% had ballooning degeneration, 88% had perisinusoidal fibrosis and 81% had portal fibrosis. Steatosis improved in 15 out of the 16 patients, with resolution in 13. Twelve of the 15 patients with inflammation at the baseline showed improvement, and 12 out of 14 showed less ballooning. Six of the 14 patients with perisinusoidal fibrosis and 6 of the 13 patients with portal fibrosis showed improvement. No patient presented worsening of steatosis, inflammation, ballooning or fibrosis.

In a historical cohort that enrolled 90 individuals who underwent liver biopsies during RYGB and one year afterwards, Mottin et al.[135] observed that the prevalence of hepatic steatosis at the

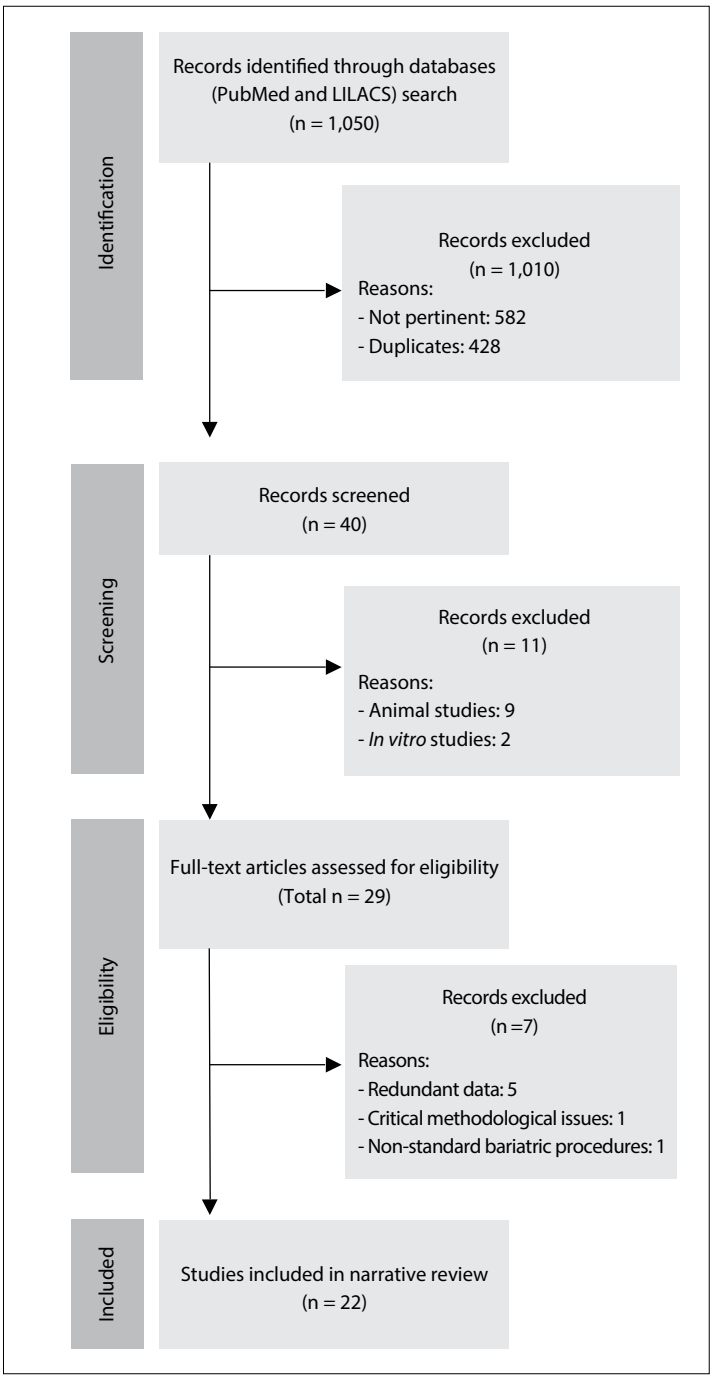

Figure 1. Flow diagram of the narrative review of the literature.

time of the surgery was 87.6%. In the second biopsy, 16 patients (17.8%) out of the total had the same degree of steatosis, 25 (27.8%) presented an improved steatosis pattern and 49 (54.4%) had normal hepatic tissue.

In a study on 19 individuals who underwent liver biopsy during RYGB that confirmed the presence of NASH and were then contacted to undergo a repeat biopsy, Barker et al.[136] observed significant improvements in steatosis, lobular inflammation, portal and lobular fibrosis. Histopathological criteria for NASH were no longer found in 17/19 patients (89%).

In a study that enrolled 16 individuals who underwent liver biopsy during primary RYGB and a new biopsy during repairs on incisional hernias, Csendes et al.[137] observed that 11 out of 15 patients who had had liver abnormalities returned to a normal condition or only had minimal change (73.3%); two patients (13.3%) showed improvements, one patient presented a slight worsening of liver condition and one patient who had presented liver cirrhosis showed no change.

de Almeida et al.[138] studied 16 individuals who underwent a first biopsy during RYGB and another subsequent to the surgery (23.5 ± 8.4 months afterwards). They observed complete regression of NAFLD in 15 patients (93.7%); complete regression of necroinflammatory activity was observed in all patients. Among the four patients presenting fibrosis in the first biopsy, complete remission was observed in one and improvement in one; two continued to show the same degree of fibrosis without evidence of disease activity.

An exploratory study carried out by Klein et al.[139] evaluated whole-body glucose, fatty acid and lipoprotein kinetics, liver histology and hepatic cellular factors involved in inflammation and fibrogenesis in seven severely obese subjects, before and one year after RYGB. A decrease in hepatic steatosis was observed, without changes in standard histological assessments of inflammation and fibrosis. However, there were marked decreases in hepatic factors involved in regulating fibrogenesis (collagen-alpha 1, transforming growth factor-beta 1, alpha-smooth muscle actin and tissue inhibitor of metalloproteinase 1 expression and alpha-smooth muscle actin content) and inflammation (macrophage chemoattractant protein 1 and interleukin 8 expression).

In a retrospective analysis on paired needle liver biopsies taken during and following RYGB in 39 patients, Liu et al.[117] observed that the initial prevalences of hepatic pathological conditions were: steatosis (89.7%), hepatocellular ballooning (58.9%) and centrilobular/perisinusoidal fibrosis (50%). These improved significantly after RYGB: steatosis (2.9%), ballooning (0%) and centrilobular fibrosis (25%); significant decreases in the lobular inflammation score and stage of fibrosis were also noted. Nonetheless, no improvements were seen in portal tract inflammation or fibrosis.

A controlled study conducted by Furuya et al.,[118] which enrolled 18 individuals who underwent a wedge biopsy during RYGB and a percutaneous biopsy two years later, showed that, after a mean excess weight loss of 60%, steatosis disappeared in 84% of the patients, fibrosis in 75% and ballooning in 50%. A slight lobular inflammatory infiltrate remained in 81%, apparently unrelated to fatty degeneration.

Kakizaki et al.[140] conducted a prospective study that enrolled 84 participants, to compare the effects of RYGB on NAFLD in Japanese and non-Japanese individuals. They observed that when the body mass index (BMI) was similar, liver dysfunction among Japanese patients with severe obesity tended to be higher than among non-Japanese patients. Japanese patients with severe obesity would therefore need to reduce their body weight to a greater degree than would non-Japanese patients with the same BMI. The laboratory data and BMI were seen to be significantly improved, one year after laparoscopic RYGB, in both groups.

Tai et al.[141] conducted a prospective study that enrolled 21 patients with morbid obesity who underwent intraoperative liver biopsy and follow-up liver biopsy one year after laparoscopic RYGB. They observed statistically significant histological improvements in the patients' NAFLD activity scores (NAS) and individual components, including steatosis, ballooning degeneration and lobular inflammation. Preoperatively, 4 (19.0%), 11 (52.4%) and 6 (28.6%) patients were found to have NAS ≥ 5, 3 to 4, and ≤ 2, respectively; all patients had NAS ≤ 2 after surgery. The stage of fibrosis also presented significant improvement.

A retrospective study by Moretto et al.[119] that evaluated 78 patients with morbid obesity who underwent RYGB and had liver biopsies taken during surgery and after weight loss, observed that 35 (44.8%) had fibrosis at the time of the first biopsy and 24 (30.8%) had hepatic fibrosis after weight loss, including 19 of the 35 patients (54.3%) with fibrosis at the first biopsy and 5 of the 43 (11.6%) without hepatic fibrosis at the first biopsy. These authors concluded that surgical weight loss among patients with morbid obesity was associated with a significant reduction in the prevalence of hepatic fibrosis.

In a study on 26 paired biopsies collected during RYGB and at an average of 16 months afterwards, Vargas et al.[120] reported that there were significant improvements in steatosis, lobular and portal inflammation and fibrosis in the second biopsy. Twenty-five of the patients (96.1%) presented NASH in their index biopsy, while only four (15.3%) of the repeat biopsies fulfilled the criteria for NASH. Persistence of fibrosis was observed in five patients at the second biopsy. Steatosis and fibrosis at surgery were predictors of significant fibrosis post-surgery.

In a large prospective study that enrolled 1236 participants, Caiazzo et al.[142] compared liver biopsy outcomes following RYGB and gastric banding. All NAFLD parameters improved after surgery. They all improved significantly more after RYGB than after gastric banding (percentage steatosis: one year, 7.9 versus 17.9; five

years, 8.7 versus 14.5; NAS: one year, 0.7 versus 1.1; five years, 0.7 versus 1.0). In multivariate analysis, the superiority of RYGB was primarily but not completely explained by weight loss.

Abdennour et al.[121] conducted a prospective study that enrolled 243 individuals, with the main objective of studying the relationship between white adipose tissue evaluation methods and weight loss. These authors also observed significant improvement in liver enzymes one year after RYGB.

Cazzo et al.[122] conducted a prospective study in which they evaluated changes in NAFLD fibrosis score between the time of surgery and one year after RYGB. They observed that the mean score decreased from 1.142 to 0.066, and that surgery led to a resolution rate for advanced fibrosis of 55%. Resolution was statistically associated with female gender, the percentage of excess weight loss, post-surgical BMI, postsurgical platelet count and diabetes resolution.

In an exploratory study that compared 14 RYGB and 9 sleeve gastrectomy (SG) patients, Froylich et al.[143] observed that all morphological characteristics of NAS improved significantly after RYGB, whereas only steatosis and total NAS improved after SG. The state of fibrosis improved in both groups, but to a greater degree after RYGB. There were no significant differences in the decreases in NAS score after RYGB and SG procedures. These exploratory data support the idea that a randomized trial should be conducted to determine the differential effects of SG and RYGB on NAFLD.

Gastric banding and banded gastroplasty

Luyckx et al.[123] conducted a retrospective clinical analysis on 69 individuals who underwent liver biopsy during gastroplasty and a repeat biopsy later on, during the course of a mandatory surgical procedure. They observed that, after the drastic weight reduction, 45% of the histological observations were considered normal. Abnormal fattiness significantly decreased following surgery (38% versus 83% before). Furthermore, the severity of steatosis was significantly reduced in most cases: mild in 62% versus 21%, moderate in 23% versus 37% and severe in 15% versus 42%, after and before weight loss, respectively. However, a significant increase in hepatitis was observed, in 26% versus 14% before. Nevertheless, 87.5% of the cases were graded as mild and 12.5% as moderate, while no severe hepatitis was observed. The prevalences of fibrosis and cirrhosis remained unchanged.

Busetto et al.[144] examined a case series in which they aimed to evaluate visceral fat content following gastric banding. They enrolled six premenopausal women with morbid obesity with an ultrasonographic diagnosis of liver steatosis and observed that there was a statistically significant reduction in visceral adipose tissue, of 1.0 ± 0.9 liters over the period from 0 to 8 weeks, but only a non-significant further reduction of 0.6 ± 0.7 liters over the period from 8 to 24 weeks. The relative reduction of visceral fat over the period from 0 to 8 weeks was greater than the relative reduction of total fat. The liver volume also showed a statistically significant reduction of 0.24 ± 0.26 liters during the first phase of weight loss, corresponding to a relative reduction of $12.3 \pm 10.6\%$. Hence, during the period from 8 to 24 weeks, liver volume was substantially stable. During the phase of rapid weight loss after gastric surgery, preferential mobilization of visceral fat, compared with total adipose tissue, was observed.

Stratopoulos et al.[124] conducted a study that enrolled 51 individuals who underwent a biopsy during surgery and a second biopsy after an average time of 18 months, and among whom 16 underwent a third biopsy at an average of 17 months after the second one. They reported that, at baseline, steatosis and steatohepatitis (mostly grade 3) were present in 98.0% of the subjects and fibrosis (mostly stage 2) in 94.1%. After an excess weight loss of 66%, steatosis and steatohepatitis improved significantly. Although a significant overall decrease in fibrosis occurred, 21 patients (41.1%) did not present any change, while six patients (11.7%) showed increased fibrosis. None of the patients developed cirrhosis. The third biopsy, performed in 16 of the subjects, showed further significant improvements in liver histology.

Dixon et al.[125] examined a case series of 36 selected obese patients and evaluated paired liver biopsies: the first at the time of laparoscopic adjustable gastric band placement and the second after weight loss. The initial biopsies revealed NASH in 23 patients and steatosis in 12 patients. Follow-up biopsies were taken at 25.6 ± 10 months (range, 9-51 months) after band placement. There were significant major improvements in lobular steatosis, necroinflammatory changes and fibrosis at the second biopsy. Portal abnormalities remained unchanged. Eighteen patients had an initial fibrosis score of 2 or more, while only three patients showed this at the follow-up.

Jaskiewicz et al.[145] conducted a study on 10 individuals who underwent a wedge biopsy during gastroplasty and had a new repeat biopsy eight months later. They observed significant improvements of the degenerative and inflammatory hepatic lesions in the repeat biopsies and liver function readings, eight months after the surgery.

In a prospective study conducted by Phillips et al.,[126] proton magnetic resonance spectroscopy and magnetic resonance imaging were used to estimate the quantities of lipids contained within the liver and abdominal subcutaneous and visceral compartments of 29 obese individuals, before gastric banding and three months afterwards. Significant reductions in body weight, abdominal fat and liver fat were observed three months after surgery. Changes in liver fat content were more closely associated with changes in serum gamma-glutamyl transferase than with changes in waist circumference.

Gastaldelli et al.[127] conducted a prospective study that evaluated 159 subjects with morbid obesity following laparoscopic

adjustable gastric bypass. They observed that one year after gastric bypass, the patients' glucose tolerance, liver function tests and IR had improved; ferritin had not changed significantly but was still correlated with IR. The authors concluded that ferritin might be an additional useful marker for cases of hepatic IR of greater severity.

A prospective study by Moschen et al.,[146] in which 30 individuals who underwent gastric bypass were enrolled, showed that the surgery improved IR, abnormal liver function tests and liver histology. Pronounced weight loss after 6 and 12 months was accompanied by significant increases in serum adiponectin levels, whereas both leptin and visfatin levels decreased. Serum levels of resistin increased after 6 months but fell below baseline values after 12 months. These results suggest that weight loss after gastric bypass surgery improves the adipocytokine milieu towards a more anti-inflammatory direction, both systemically and in the liver.

In a retrospective study that enrolled 16 individuals, Swierczynski et al.[147] observed significant improvements in several laboratory parameters, including serum phenylalanine, ALT, lipid concentrations and IR. A strong positive correlation between serum phenylalanine and serum ALT concentrations might suggest that the deterioration of liver function observed in obese patients contributes towards decreased phenylalanine metabolism and consequently towards increased serum phenylalanine concentration.

A prospective study was conducted by Frige et al.[148] with the aim of comparing the effects of gastric bypass and biliointestinal bypass (BIB) on glucose and lipid metabolism in NAFLD. There were 24 individuals in the gastric bypass group and 12 in the BIB group, and a significantly greater decrease in liver enzymes (ALT) was observed in the gastric bypass patients than in the BIB group.

Sleeve gastrectomy

In an analysis on prospective data gathered from 236 individuals, Karcz et al.[128] observed significant improvements in AST, ALT, triglycerides and high-density lipoprotein (HDL) levels one and three years after SG. NASH patients showed significant losses of body weight and amelioration of NASH status.

A retrospective study was conducted by Algooneh et al.[129] on 84 patients diagnosed with NAFLD prior to undergoing SG. The diagnosis of NAFLD was achieved based on ultrasonographic imaging. A total of 47 patients (56%) showed complete resolution of NAFLD postoperatively. Multivariate analysis showed that there was significant resolution of NAFLD among the patients who achieved > 50% excess weight loss, after controlling for age and sex.

A prospective study conducted by Coupaye et al.,[149] primarily to compare the nutritional effects of SG with those of RYGB, with 30 individuals in each group, also observed that transaminase levels were significantly lower after RYGB than after SG. This suggested that alterations in liver metabolism might affect synthesis or catabolism of some circulating lipids and proteins after RYGB.

Billeter et al.[150] conducted a retrospective matched study on a prospective database, to compare the effects of RYGB and SG on 34 individuals with morbid obesity. Both procedures significantly lowered ALT and aspartate aminotransferase (AST) after 12 months, but SG improved both liver function tests significantly better than RYGB did. In contrast to RYGB, SG normalized elevated ALT levels completely. In a study comparing 30 individuals who underwent paired liver biopsies during surgery and six months afterwards, Praveen-Raj et al.[151] reported that the individuals who underwent SG presented non-significant greater improvement of liver histology than those who underwent RYGB.

Biliopancreatic diversions

Scopinaro operation

In a retrospective analysis on 99 consecutive individuals who underwent surgery, Papadia et al.[130] noticed that AST levels at two months were significantly higher and then were significantly lower at 12 months. Hepatocellular necrosis in this series peaked at two months and decreased thereafter. The weight loss at two months, preoperative body weight, glucose levels and hepatic histology seemed to be of help in identifying patients at increased risk of acute liver damage, thus prompting the need for enhanced surveillance.

Ferrer Márquez et al.[131] conducted a prospective study on 76 obese individuals who underwent biopsy during surgery and 12-24 months afterwards. They observed that there was a significant decrease in overall NAFLD, with decreased inflammation and fibrosis. No cases of liver failure were observed.

Duodenal switch

In an analysis on 104 individuals who underwent the duodenal switch procedure and required further reoperation, Kral et al.[132] observed that severe fibrosis (grade 3-5) decreased in 28 whereas mild fibrosis (grade 1-2) appeared in 42. Increased fibrosis was related to low-normal serum albumin, uncontrolled diarrhea, low intake of alcohol and menopausal status. Fibrosis and inflammation significantly decreased over time. The 11 patients with cirrhosis exhibited decreases in fibrosis, from a mean of grade 5 to grade 3, as well as reduced levels of inflammation, Mallory bodies and glycogenated nuclei. Seven patients presented disappearance of nodules and fibrous bridging, while two showed regression.

Keshishian et al.[133] conducted a retrospective analysis on 697 individuals who underwent laboratory tests 6, 12 and 18 months after surgery. All of them underwent liver biopsies during duodenal switch surgery and 78 individuals underwent a second surgical procedure at least six months after the primary duodenal switch. Transient elevation of liver enzymes at six months was observed; this was seen to have normalized at 12 and 18 months. A three-grade progressive improvement in the severity of NASH and a 60%

improvement in hepatic steatosis were attained three years after the duodenal switch operation.

In a study on different procedures, Weiner[152] analyzed 16 individuals who underwent biopsy during duodenal switch and in a later reoperation. Complete recovery from NAFLD was observed, and it was concluded that obesity surgery improved steatosis, necroinflammatory activity and hepatic fibrosis in patients with morbid obesity and NASH.

Johansson et al.[153] conducted a prospective cohort study on 10 individuals who underwent duodenal switch and 21 cases of RYGB. Patients with morbid obesity treated by means of RYGB or duodenal switch showed sustained reductions in liver enzyme levels.

In a retrospective cohort study evaluating the influence of duodenal switch surgery on liver enzyme levels over a four-year period, among morbidly obese patients with normal aminotransferase and high baseline aminotransferase levels, Aller et al.[154] reported that significant decreases in ALT and AST activity levels occurred. The baseline percentages of high aminotransferase levels and the percentage of ALT/AST ratios that were < 1 were also found to be significantly lower at the one, two, three and four-year follow-ups in both groups.

Systematic reviews and synthesis

A meta-analysis conducted by Mummadi et al.,[157] in which the surgical techniques analyzed were mixed, revealed that steatosis, steatohepatitis and fibrosis appeared to improve or become completely resolved in the majority of patients after bariatric surgery-induced weight loss. These authors emphasized the limitations of their study, regarding mainly the vast heterogeneity of the overall designs and expected outcomes of the studies included. Another meta-analysis, conducted by Bower et al.,[156] revealed that bariatric surgery was associated with a significant reduction in the weighted incidence of a number of histological features of NAFLD, including steatosis (50.2%), fibrosis (11.9%), hepatocyte ballooning (67.7%) and lobular inflammation (50.7%); surgery was also associated with a reduction in liver enzyme levels. These authors emphasized that there was high heterogeneity among the methodologies and results, a factor that may have limited their analysis of these findings. A Cochrane review[157] that specifically addressed the lack of randomized clinical trials and high heterogeneity of the studies available acknowledged that the improvements regarding steatosis and inflammation seemed to be clear. However, it was concluded that the quality of the data available did not allow the authors to draw any unbiased conclusion relating to bariatric surgery for treating NASH. Despite the limitations of these studies, they represent the best level of evidence currently available on this topic.

There are some major concerns regarding research on the effects of bariatric surgery for treating NAFLD that need to be emphasized. Firstly, as is common among surgical studies, there is a lack of randomized controlled studies; in fact, the majority of studies are retrospective and non-controlled, and these aspects may produce data of poor quality. Secondly, and specifically regarding studies on NAFLD, there is no standardized measurement for the outcomes evaluated: some studies have evaluated liver biopsy specimens, while others have compared data from imaging studies or noninvasive methods for assessing liver disease. Thirdly, optimal evaluation of NAFLD is only possible by means of liver biopsies. These can easily and safely be carried out at the time of the primary surgery, but this procedure is not widely available later on, given that it is not risk-free and therefore performing it in individuals who do not require surgical interventions constitutes an ethical concern. This leads to great heterogeneity of outcomes that also cannot be ignored.

Despite the lack of controlled and randomized studies, there is a clear trend towards better results with regard to NAFLD outcomes among obese individuals who undergo surgery. It is also clear that the staging of NAFLD at the time of surgery is an important predictor of success, since it is noticeable that the rates of resolution for simple steatosis are much higher than those observed for steatohepatitis and especially for fibrosis.

Mechanisms underlying post-surgical improvements in NAFLD

The exact mechanisms that lead to improvement in NAFLD following bariatric surgery are probably strongly related to the metabolic changes that are involved in amelioration of metabolic syndrome (MetS). These changes occur early after the procedures, during a phase when no significant weight loss has yet been achieved. It is clear that while weight loss plays an important role in controlling metabolic abnormalities, this effect appears to be more significant over the long term.[158-160] Furthermore, there is evidence that excess weight is not the main pathophysiological feature relating to NAFLD.[158]

The causes of early improvement of MetS after bariatric surgery are complex and relate to changes on the entero-insular axis mediated by gastrointestinal hormones called incretins.[160-162] The anatomical changes caused by the surgical procedures, particularly duodenal exclusion and overflow of nutrients to the distal small bowel, lead to release of incretins, especially glucagon-like peptide 1 (GLP-1) and gastrointestinal insulinotropic polypeptide (GIP). These increase the production and release of insulin, improve peripheral insulin sensitivity and favor an anorexic state. Moreover, it appears that surgery enhances adipokine metabolism, which probably relates to increasing insulin sensitivity and promotes an anti-inflammatory effect by means of immunomodulation.[160] Recent research has indicated that surgery leads to changes in the gut microbiota and bile acid circulation that may be beneficial regarding MetS and NAFLD.[158-162]

Furthermore, there is a decrease in portal influx of free fatty acids following surgery, which may be related both to feeding restrictions and to metabolic changes in visceral insulin sensitivity.[161,162]

International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) position statement

In the most recent IFSO consensus statement,[163] it is stated that bariatric surgery leads to reversal or significant improvement of NAFLD and NASH. Since the vast majority of the studies that led to this conclusion were non-randomized, non-controlled and observational cohort studies, this postulate constitutes a grade B recommendation, with evidence level 2. The IFSO also concluded that, despite the solid evidence available to date, further research, especially in randomized controlled settings, is necessary in order to reach ultimate conclusions. The high prevalence of NAFLD among the bariatric population also needs to be considered, as a significant factor.[17,164,165] Hence, taking into account the overall impact of bariatric surgery on obesity and obesity-related comorbidities, such as NAFLD, this treatment option should be offered to the group of individuals who fulfill the current criteria of indications, as a potentially effective therapy.

Bariatric surgery in cirrhotic patients

Despite the increasing prevalence of obesity among the population with liver cirrhosis, along with the general epidemic of obesity, the number of studies on this topic is still limited. The main factors that need to be taken into account whenever a candidate for bariatric surgery is cirrhotic are the presence of portal hypertension and abnormalities of hepatocytic function. Regarding obese individuals who are also candidates for liver transplantation, the choice of technique and optimal timing for performing bariatric surgery are also significant issues that are not fully addressed in the current literature.

Among individuals with severe cirrhosis, surgical morbidity and mortality are significantly higher than what is observed in the general obese population. A retrospective study by Mosko et al.[166] that analyzed a national United States database found significantly higher mortality rates among cirrhotic individuals, both in those who were clinically compensated (0.9%) and in those who were not (16.3%), than among non-cirrhotic individuals (0.3%). Moreover, in low-volume centers, mortality reached 41% among non-compensated cirrhotic individuals. Dallal et al.[167] conducted a study that enrolled individuals with an incidental intraoperative diagnosis of liver cirrhosis, determined during bariatric surgery. They found that, among compensated cirrhotic individuals, RYGB presented a mortality rate similar to what was observed in the general population. However, it was also observed that episodes of transient renal failure, longer operation times and greater amounts of intraoperative bleeding and need for transfusion were more common within this group than in the general obese population. In a meta-analysis, Lazzati et al.[168] observed a mean excess weight loss of 66% among morbidly obese cirrhotic individuals over a two-year period, which was comparable to the general population. SG was the surgical procedure most often performed, and the perioperative mortality rate was comparable to what was observed in the general population. However, morbidity (especially due to the need for reoperations) and mortality during the first year following surgery were significantly higher. The heterogeneity of the studies and the small samples analyzed were considered to be major limitations of their review, thus not allowing further conclusions.

Among candidates for liver transplantation, the choice of technique is of major importance, because of two factors: potential impairment of the absorption of immunosuppressive drugs and the possibility of endoscopic access to the biliary tract. Currently, there are no studies analyzing the pharmacokinetics of immunosuppressive drugs in liver-transplanted individuals who underwent bariatric surgery, but among kidney transplantation recipients who underwent RYGB, there are reports of the need for higher dosages of tacrolimus, sirolimus, mycophenolate sodium and cyclosporine.[169] Regarding access to the biliary tract, post-transplantation biliary strictures are common, occurring in up to 17% of the cases.[170] Taking these situations into consideration, SG appears to be the most appropriate technique for this group of individuals, since it does not affect drug absorption and enables endoscopic access to the biliary tract.

The optimal timing for performing bariatric surgery in individuals with cirrhosis who are also candidates for liver transplantation is yet to be determined. This surgery may be performed before, after or even during the transplantation.[171] One significant concern is the potential impact of obesity on the outcomes from liver transplantation. Recently, it was observed that surgical mortality, two-year survival and graft viability were similar in obese and lean individuals. Perioperative morbidity was slightly higher.[172,173] Because of the higher morbidity and mortality observed among non-compensated liver transplantation candidates, the pre-transplantation approach presents clear limitations. Bariatric procedures performed concomitantly with the transplantation have been reported; this approach has the potential to minimize the number of surgical procedures in high-risk individuals. However, it also requires concomitant availability of both surgical teams and generates the risk of combining the complications of both procedures.[174] Based on this latter finding, although there is no consensus yet, the approach that is best accepted is to perform the transplantation first and the bariatric surgery later on, among non-compensated cirrhotic individuals or among those with moderate to severe portal hypertension. According to the current literature, the morbidity is significantly higher, but the mortality is comparable.[175,176]

Current situation and future perspectives

NAFLD is becoming a public health concern worldwide today, and its prevalence is expected to grow even further in the near

future. There is enough evidence to suggest that bariatric surgery should be considered to be the optimal treatment option for NAFLD by choice, and no longer only by chance.[177] It is expected that NAFLD may become the major reason for living-donor transplantation in the United States by 2030.[178]

Although bariatric surgery is currently recognized as the standard treatment option for morbid obesity and its related comorbidities, the number of operations performed is far from sufficient to meet the need for intervention. In fact, less than 500,000 bariatric surgery procedures are performed worldwide every year today. This number represents less than 0.1% of the entire supposedly obese population.[179-181] Moreover, there are large numbers of subjects who do not fulfill the current indications for surgery but present harmful abnormalities relating to fat and glucose metabolism that can lead to and aggravate liver disease.

Hence, the most practical and effective action that can be implemented in relation to this entire disease chain is prevention. Encouragement towards practicing physical activity and following healthy low-fat/low-calorie diets needs to be extensively included in educational and community programs as early in life as possible, since obesity has become a pediatric issue too.[179,180] Continuing education for healthcare professionals regarding liver disease and the methods for detecting, preventing and treating it should be mandatory. Screening of populations at high risk, in order to provide early diagnosis and staging of NAFLD, may also be carried out by means of simple laboratory tests and ultrasound scans. Early detection of MetS and diabetes and prompt management of these illnesses remain significant ways for preventing evolution to liver disease and its ominous severe forms.[180,181]

Regarding the role of bariatric surgery in relation to the clinical course of NAFLD, many questions remain to be answered. Since there is a lack of randomized controlled trials, no ultimate conclusions can yet be provided. It is clear that the overall impact of bariatric surgery on NAFLD is positive, but the optimal surgical technique remains to be determined, as do the longer-term effects and the ways of maintaining the benefits achieved. Since there is also concern regarding the onset of persistent IR or even re-emergence of IR and T2DM[182,183] among individuals who initially presented complete reversal, further research is needed in order to determine the influence of this event on liver histology. Another longer-term concern is the prevalence of weight regain, which may also have a significant effect on NAFLD.

Statement of human and animal rights

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

CONCLUSION

The currently available evidence shows that bariatric surgery may become the treatment of choice for individuals with NAFLD. It is important to emphasize that further research, especially by means of randomized controlled trials enrolling larger cohorts of individuals, is necessary in order to determine the optimal procedure for this group of subjects, as well as whether only individuals with morbid obesity might benefit from the effects of metabolic surgery, since there are vast numbers of lean and overweight individuals who also present NAFLD.

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Simultaneous meningioma and brain metastasis from renal cell carcinoma – a rare presentation. Case report

Meningioma e metástase cerebral de carcinoma de células renais simultâneos – uma apresentação rara. Relato de caso

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KEY WORDS:
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PALAVRAS-CHAVE:
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Carcinoma de células renais.
Meningioma.
Neoplasias do ventrículo cerebral.

ABSTRACT

CONTEXT: Brain metastases are the most common tumors of the central nervous system. Because of their high frequency, they may be associated with rare situations. Among these are tumor-to-tumor metastasis and an even a rarer situation called simultaneous brain tumors, which are more related to primary tumors of the reproductive and endocrine systems.

CASE REPORT: A 56-year-old male patient with a history of renal cell carcinoma (which had previously been resected) presented with a ventricular lesion (suggestive of metastatic origin) and simultaneous olfactory groove lesion (probably a meningioma). First, only the ventricular lesion was dealt with, but after a year, the meningothelial lesion increased and an occipital lesion appeared. Therefore, both of these were resected in a single operation. All the procedures were performed by the same neurosurgeon. The patient evolved without neurological deficits during the postoperative period. After these two interventions, the patient remained well and was referred for adjuvant treatment.

CONCLUSIONS: This study provides the first description of an association between these two tumors. Brain metastases may be associated with several lesions, and rare presentations such as simultaneity with meningioma should alert neurosurgeons to provide the best oncological treatment.

RESUMO

CONTEXTO: As metástases cerebrais são os tumores mais comuns do sistema nervoso central e, devido à sua elevada frequência, podem estar associadas a situações raras. Entre estas estão as *"tumor to tumor metastasis"* e uma situação ainda mais rara chamada de tumores cerebrais simultâneos, mais relacionados a tumores primários dos sistemas endocrinológico e reprodutivo.

RELATO DE CASO: Um homem de 56 anos com histórico de câncer de células renais (extirpado previamente) apresentou-se com lesão ventricular (sugestiva de origem metastática) e simultaneamente com uma lesão em topografia de goteira olfatória (provavelmente meningioma). Primeiramente, apenas a lesão ventricular foi abordada, porém após um ano, a lesão meningotelial aumentou e uma lesão occipital apareceu e então ambas foram ressecadas em uma única cirurgia. Todos os procedimentos foram realizados pelo mesmo neurocirurgião. O paciente evoluiu sem déficits neurológicos no período pós-operatório. Após essas duas intervenções, o paciente permaneceu bem, sendo encaminhado para tratamento adjuvante.

CONCLUSÕES: O presente trabalho é a primeira descrição da associação encontrada entre esses dois tumores. As metástases cerebrais podem associar-se a várias lesões, e manifestações raras, tais como apresentação simultânea com meningioma, devem alertar o neurocirurgião a fornecer o melhor tratamento oncológico.

INTRODUCTION

Brain metastases constitute a common complication of advanced primary tumors. Therefore, they are an important issue that guides the approach taken towards patients with a diagnosis of cancer.[1]

The incidence of brain metastases is about 9 to 17%, based on various studies.[1] However, the exact incidence is thought to be higher, possibly because there are many asymptomatic patients. In several studies, only surgical metastatic disease is included in the statistical analysis.[1]

Brain metastases are observed in 2 to 17% of patients with metastatic renal cell carcinoma (mRCC).[2,3] These patients usually require a neurosurgical approach and adjuvant therapies, especially radiotherapy. However, despite optimal treatment, patients presenting with brain metastasis have a very poor prognosis and probably also have other compromised organs. Another factor associated with increased mortality is that mRCC does not have a good response to radiation.[2-4]

There are two entities that are rarely related to brain metastases but which, when they occur, it is important to be aware of. The first of these is tumor-to-tumor metastasis[5] (collision tumor is used as a synonym by some authors), which was first described in 1902. This is a well-documented phenomenon in which a host tumor that is usually more indolent serves as the source for growth of a more aggressive neoplasm such as a meningioma, thus leading to growth of a high-grade glioma or metastatic lesion.[6-8]

The second of these is an even rarer phenomenon that has been named synchronous or simultaneous tumors, and which forms the topic of the present report. These occur when two histological tumors compromise the central nervous system (CNS) at the same time but there is no histopathological evidence that one tumor served as the source of growth for the other, as occurs in the tumor-to-tumor entity.[9,10]

This report aimed to present a unique case of simultaneous benign meningioma and brain metastasis from renal cell carcinoma in a male adult. We were unable to find any similar cases reported in the literature, through reviewing the MEDLINE database.

CASE REPORT

A 56-year-old male patient came to our neuro-oncology service in 2013, with a history of mild frontal headache, but without neurological symptoms. He had a history of renal cell carcinoma in his right kidney and had undergone nephrectomy in 2011. In the same year, he underwent follow-up examinations but without evidence of brain metastatic disease. He had no other comorbidities.

The headache became progressively worse and was associated with nausea, photophobia and phonophobia. In 2015, on control brain magnetic resonance imaging (MRI), the presence of an intraventricular tumor was noticed (**Figure 1**), along with another lesion in the olfactory groove (on MRI, it was suggestive of a meningioma). A neurosurgical approach was used to treat the ventricular lesion, consisting of transcallosal tumor resection, which was performed in May 2015. The procedure was free from complications, gross total removal was achieved and the patient reported improvement of the headache. He was referred for neuro-oncology outpatient follow-up and for radiotherapy evaluation. Only the larger of the two lesions was resected on this occasion because two different approaches performed at the same time might have increased the morbidity and, moreover, the patient did not have any neurological deficits at this time.

Five months after the first procedure, the patient complained of visual impairment (which upon physical examination was found to

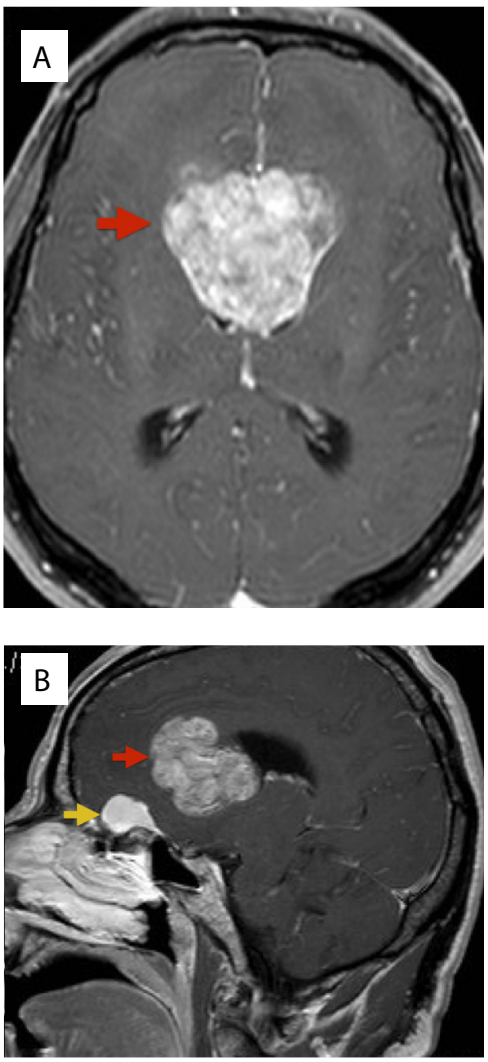

Figure 1. Magnetic resonance imaging of a patient with simultaneous brain tumors: A - axial image showing ventricular tumor; B – sagittal image showing two lesions: olfactory groove meningioma and ventricular tumor.

be due to left hemianopia) and frontotemporal headache. Because of this, MRI was performed again and this revealed another lesion, in the right occipital lobe (**Figure 2**), probably of metastatic origin.

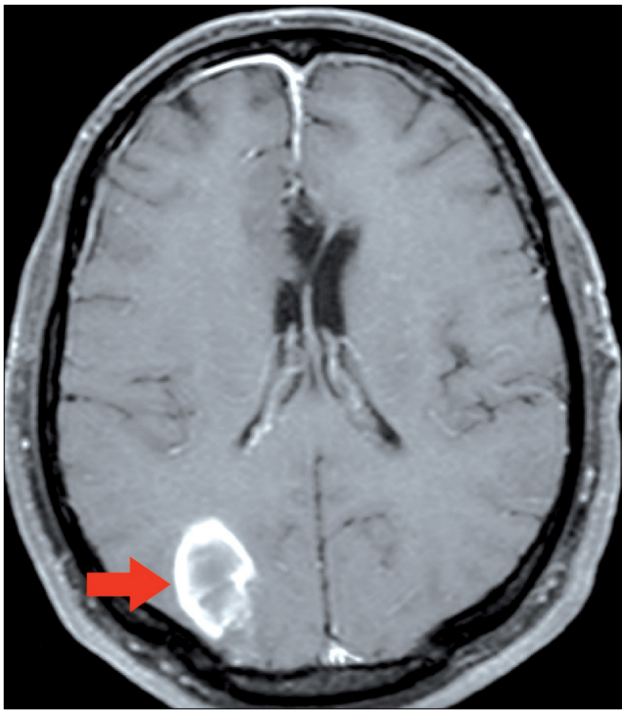

Figure 2. Axial contrasted T1-weighted magnetic resonance imaging exam showing a right occipital lesion after radiation.

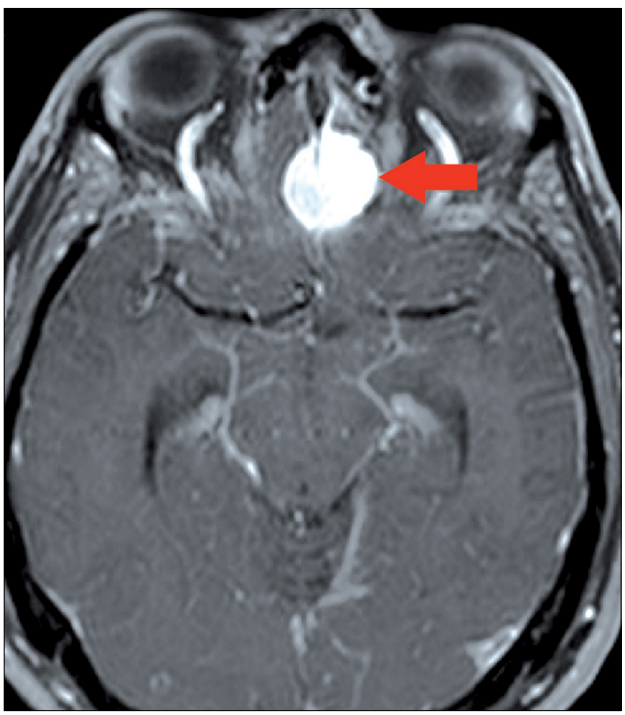

Figure 3. Axial contrasted T1-weighted magnetic resonance imaging exam showing olfactory groove meningioma

The patient underwent whole-brain radiotherapy at this time, without any surgical indication.

The olfactory groove lesion increased after radiation therapy had been completed (**Figure 3**) and the patient reported that his headache had returned. At this time, neurosurgical resection of the two lesions (the olfactory groove meningioma and the occipital lesion) in a single procedure was proposed. Given the possibility of tumor-to-tumor metastasis, it was very important to determine whether the meningioma had served as a basis for the metastatic lesion, in order to better define the complementary treatment.

The surgery was performed without complications and the histopathological and immunohistochemical analyses confirmed that the olfactory groove lesion was a grade I meningioma (**Figure 4**), without evidence of tumors of another origin differing from the meningothelial lineage. The only radionecrosis was observed at histopathological analysis of the occipital lesion. Simpson II resection was performed (**Figure 5**). These two surgical procedures (one to treat the intraventricular metastasis and the other to deal with the olfactory groove meningioma and the occipital lesion) were performed by the same oncological neurosurgeon (JLVA).

The patient reported improvement of his headache and was discharged for outpatient follow-up with the neurosurgical and neuro-oncology team. Complete screening with the aim of revealing any other metastatic lesion that might have been present was performed, consisting of computed tomography (CT) scans on the chest, abdomen and pelvis. There was no evidence of any local or metastatic recurrence.

DISCUSSION

Brain metastases constitute one of the most common neurological complications in oncological patients with advanced disease.[1] In some cases, they may be the initial manifestation, which then

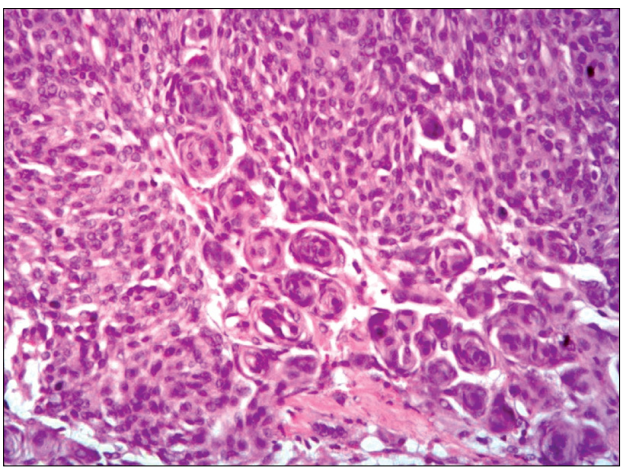

Figure 4. Mature neoplasia of meningothelial origin, characterized by uniform lobed cells. Concentric arrangements are frequent in these tumors. Hematoxylin-eosin staining, 40 x magnification.

leads to diagnosing the primary tumor.[11] The signs and symptoms are nonspecific and may vary according to the site and size. In rare cases, they may manifest as lesions in the scalp and skull.[12,13] The incidence rate is about 9 to 17%, based on various studies, although the exact incidence is thought to be higher.[1,3]

The blood-brain barrier (BBB) and absence of a lymphatic system are factors that make dissemination of cancerous cells more difficult. Thus, patients with brain metastases generally also have extracranial lesions. This shows that when tumor cells invade brain structures, the disease is more advanced and has a worse prognosis.[2,3] Conditions that alter immunological defenses, such as human immunodeficiency virus infection, may be associated with brain metastasis. There are some hypotheses stating that such conditions could favor appearance of some tumors.[14]

Regarding metastatic renal cell carcinoma, brain lesions generally do not occur at the same time as the primary tumor. Some studies have shown that the incidence is highest around 10 to 13 years after the initial nephrectomy.[1] The treatment may be difficult because central nervous system lesions are usually resistant to chemotherapy and radiotherapy.[15] Nonetheless, these lesions may respond to immunotherapy using alpha-interferon[16] or interleukin (IL)-2. After treatment of brain metastases, the median survival is about 4-5 months,[3] but aggressive surgical resection significantly increases this period.

There are some hypotheses explaining why brain metastasis may appear after a long period, in the absence of other metastatic lesions[16] in renal cell carcinoma cases. One hypothesis is that this might be because, in the initial stage, the brain metastasis is microscopic and does not cause any neurological symptoms. Another hypothesis is that adjuvant therapy for renal cell carcinoma decreases host immunopotency and thus leads to faster development of brain lesions.[16] In the present report, the patient evaluated initially did not present central nervous system impairment: it was only after some years that it was found that he had brain metastasis.

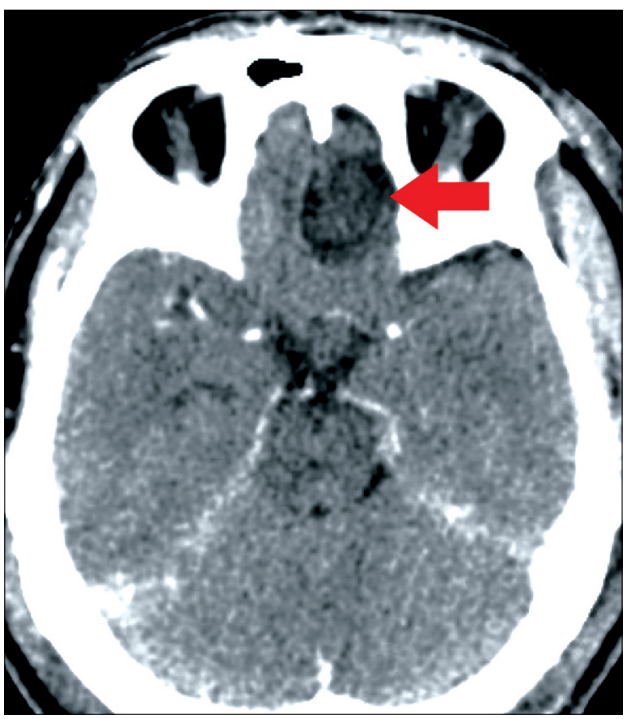

Figure 5. Brain computed tomography showing Simpson II resection of olfactory groove meningioma.

After disruption of the BBB, migration of inflammatory cells, including tumor-associated macrophages (TAMs)[17,18] may contribute towards persistence of increased vascular permeability. TAMs are recruited to tumors through specific chemokine/ chemokine receptor interactions. When neoplastic cells invade the central nervous system and a metastasis develops, the lesion is seen to be well vascularized and is susceptible to spontaneous intracranial hemorrhage,[4] which may include intraventricular bleeding. Metastatic renal cell carcinoma has a unique affinity to the ventricular system, in close association with the choroid plexus, probably due to a chemokine cascade.[11]

Multiple primary intracranial tumors of different histological types are rare, except for cases observed after radiotherapy or in situation of phacomatosis[19] such as Von Recklinghausen syndrome. However, multiple brain tumors in the absence of these conditions constitute an even rarer phenomenon.[10]

When a lesion serves as the source for growth of another neoplasia, this is considered to constitute an entity named tumor-to-tumor metastasis (or collision tumor). A more indolent tumor is generally the substratum for an aggressive lesion.[5] In the present case, however, the histopathological analysis (**Figure 5**) did not reveal that one tumor had served for growth of another but, rather, that two different tumors had simultaneous occurrence at different sites.

Because brain metastases have higher incidence than primary central nervous system tumors, they present greater involvement in cases of multiple brain tumors, such as collision tumors or simultaneous tumors. Systemic cancers rarely metastasize into preexisting intracranial neoplasms; meningiomas are the major recipient of these metastases.[8]

Neuroimaging is unable to predict which entity was present. Only when accurate histopathological and immunohistochemical analysis is performed is it possible to confirm whether one tumor has served as source of growth for another or whether the observed tumor represents two different lesions occurring simultaneously. Brain metastases can sometimes behave on CT and MRI as images of typical meningiomas and thus confuse the diagnosis.[20] In the present case, the appearance of the metastasis was not confused with a meningothelial origin (**Figure 1**).

Simultaneous occurrence of an intracranial meningioma and brain metastases in the same patient at the same time is a rather unusual event. Thus, some thought is needed regarding the pathogenic relationship, pathological diagnosis, surgical indications[10] and imaging patterns. We conducted a search in the MEDLINE

Table 1. Metastatic brain tumors reported in the literature (PubMed database) as simultaneous presentation with meningiomas

Database	Search strategies	Papers found	Type of tumor
MEDLINE (via PubMed)	(Meningioma) and (brain tumors)	Maiuri et al.[10]	15 cases of associations: 6 metastases (breast, ovary and lungs), 3 gliomas, 2 pituitary adenomas, 2 primary cerebral lymphoma, 1 craniopharyngioma and 1 acoustic neuroma
		Seckin et al.[21]	Breast carcinoma metastasis
LILACS (via Bireme)	(Meningioma) and (brain tumors)		None

database (using the terms: simultaneous/synchronous, meningioma and metastasis) and only found two papers (**Table 1**).[10,21] Neither of them reported on simultaneous renal cell carcinoma. There are few reports in the literature describing this condition and the largest review on these simultaneous lesions only brought together fifteen cases. Six of them were metastatic lesions, but none of them was from renal cell carcinoma.[9]

In the case reported here, the patient had a known diagnosis of renal cell carcinoma. Brain MRI showed a ventricular lesion suggestive of metastatic origin. Because the simultaneous olfactory groove meningioma was small at this time, it was preferred to only operate the larger lesion, in order to reduce morbidity that would occur if two different approaches were used. However, after some months, the olfactory groove lesion was found to have increased and a new occipital and symptomatic lesion had appeared.

Neoplasms from the female endocrine and reproductive system are generally more related to meningiomas[10] and, because of this, are usually present in women. In the present report, however, an even rarer situation was discussed: a male patient with meningioma and brain metastasis, for whom the primary form was renal cell carcinoma. We did not find any reports of this association in the literature review that we conducted.

CONCLUSIONS

Brain tumors may present through different patterns and, even if they are benign lesions, as meningiomas generally are, they may be associated with rare situations. An occurrence of two brain tumors is one of these situations, and this constitutes a challenge. Simultaneous lesions are an even rarer phenomenon. Metastases are more often reported as part of this entity, although in most cases endocrine and reproductive system tumors have a closer and larger relationship with meningioma growth and therefore are seen more frequently in females. Renal cell carcinoma had not reported until now as part of this association.

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Pendelluft diagnosed from ventilator weaning indexes obtained through bioelectrical impedance tomography: a case report

Pendelluft diagnosticado através de índices de desmame ventilatório obtidos pela tomografia de bioimpedância elétrica: um relato de caso

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KEY WORDS:
Ventilator weaning.
Respiration, artificial.
Intensive care unit.
Thoracic surgery.
Acute lung injury.

PALAVRAS-CHAVE:
Desmame do respirador.
Respiração artificial.
Unidades de terapia intensiva.
Cirurgia torácica.
Lesão pulmonar aguda.

ABSTRACT

CONTEXT: Today, through major technological advances in diagnostic resources within medicine, evaluation and monitoring of clinical parameters at the patient's bedside in intensive care units (ICUs) has become possible.

CASE REPORT: This case report presents results and interpretations from predictive mechanical ventilation weaning indexes obtained through monitoring using chest electrical bioimpedance tomography. These indexes included maximum inspiratory pressure, maximum expiratory pressure, shallow breathing index and spontaneous breathing test. These were correlated with variations in tidal volume variables, respiratory rate, mean arterial pressure and peripheral oxygen saturation. Regarding the air distribution behavior in the pulmonary parenchyma, the patient showed the pendelluft phenomenon. Pendelluft occurs due to the time constant (product of the airways resistance and compliance) asymmetry between adjacent lung.

CONCLUSION: Bioelectrical impedance tomography can help in weaning from mechanical ventilation, as in the case presented here. Pendelluft was defined as a limitation during the weaning tests.

RESUMO

CONTEXTO: Atualmente, com o grande avanço tecnológico em recursos para diagnósticos em medicina, a avaliação e a monitorização de parâmetros clínicos à beira leito de paciente em unidade de terapia intensiva (UTI) se tornou possível.

RELATO DE CASO: Neste relato de caso, apresentam-se os resultados e a interpretação de índices preditivos de desmame da ventilação mecânica obtidos pela tomografia de bioimpedância elétrica torácica. Esses índices incluíram a pressão inspiratória máxima, pressão expiratória máxima, índice de respiração superficial e teste de respiração espontânea. Estes estavam correlacionados com as variações de volume corrente, frequência respiratória, pressão arterial média e saturação periférica de oxigênio. Quanto ao comportamento da distribuição de ar no parênquima pulmonar, o paciente apresentou o fenômeno *pendelluft*. O *pendelluft* ocorre dado pela constante de tempo (produto da resistência e complacência das vias aéreas) de forma assimétrica entre as unidades pulmonares adjacentes.

CONCLUSÃO: A tomografia de bioimpedância pode auxiliar no desmame da ventilação mecânica, como no caso apresentado. *Pendelluft* foi definido como limitação durante a execução dos testes para desmame.

INTRODUCTION

Today, through major technological advances in diagnostic resources within medicine, evaluation and monitoring of clinical parameters at the patient's bedside in intensive care units (ICUs) has become possible. Bioelectrical impedance tomography on these parameters is one example of these advances. It uses high-frequency electrical signals at low intensity to provide imaging of lung mechanics in real time. These signals are obtained by fixing a strap containing electrodes around the patient's chest, to capture the intensity and frequency of the electric current that is propagated around the chest, between the electrodes. It is a noninvasive technique that does not use any type of radiation. It constitutes an innovation within interpretation of pulmonary mechanics.[1]

The predictive indexes for withdrawing patients from mechanical ventilation include the rapid shallow breathing index (RSBI), maximum inspiratory pressure (PImax) and maximum expiratory pressure (PEmax). The 2013 Brazilian guidelines for mechanical ventilation state that these indexes contribute towards decision-making in cases in which weaning is considered difficult. Thus, the decision-making for referring patients for a spontaneous breathing test (SBT) or for extubation does not rely on a single instrument. Use of these indexes may lead to shorter duration of mechanical ventilation.[2,3]

Use of chest electrical impedance tomography (EIT) at the bedside for patients undergoing a mechanical ventilation weaning process may be an important tool for aiding in this process. EIT takes into account important variables such as tidal volume, the degree of collapse of recruitable alveoli and the degree of alveolar distention. This test is based on differences in electrical properties generated by changes to air content in small regions of the lung, which create impedance between these regions. The pixels generated by the display image represented the percentage change in local impedance, relative to a reference that was obtained at the beginning of the image acquisition. Therefore, the dynamic images shown on the chest EIT monitor represent real-time local air changes during ventilation. At locations where variations in the air within the alveoli occur, the color of the image generated changes on a scale ranging from dark blue (less aeration) to light blue (greater aeration). Grey images represent regions in which there was no change of aeration.[4,5]

Pendelluft is a phenomenon that constitute a new mechanism of lung injury induced by mechanical ventilation. The overstretch that is observed in the dependent lung may cause a hidden injury point, that cannot be detected and thus is overlooked when conventional monitoring is used. Pendelluft can be defined as the air circulation within the lung parenchyma, in non-dependent and dependent areas, when there is no overall change in lung volume. Traditionally, it was believed that contraction of the diaphragm would decrease the pleural pressure uniformly, by the same amount at all points on the lung surface, so as to create a uniform increase in transpulmonary pressure. Pendelluft occurs because, in contrast to the normal lung, the injured lung does not show uniform fluid distribution behavior. Instead, transmission of local changes in pleural pressure is heterogeneous.[6]

Therefore, the objective of this study was to report on lung mechanics behavior, as shown by predictive weaning indexes obtained through bioelectrical impedance and by spontaneous breathing tests, in a patient with mitral valve disease who underwent valve replacement and prolonged weaning.

CASE REPORT

The patient was a 65-year-old female with a history of surgical replacement of the mitral valve by a bioprosthesis 14 years earlier. Her personal history included valvular heart disease, atrial fibrillation, congestive heart failure (functional class IV) and hypertension.

At the time of admission to the clinical hospital of the University of Campinas on July 3, 2015, the patient had had symptoms of progressive dyspnea for the preceding six months. This was also associated with paroxysmal nocturnal dyspnea, orthopnea and lower limb edema. Therefore, the patient had been referred for evaluation of valve dysfunction and surgical assessment.

In the initial clinical evaluation, an echocardiogram was performed on July 6, 2015, which showed increased volume of the left chambers, presence of the biological mitral prosthesis with stenosis and moderate regurgitation, pulmonary hypertension with systolic pulmonary artery depression values of 78 mmHg and left-ventricle ejection fraction of 58% through Simpson's method. Therefore, the patient was admitted to the hospital ward.

On July 7, 2015, her condition evolved with a productive cough and crackling and wheezing observed through auscultation. Pneumonia was diagnosed, which was treated with antibiotic therapy. The patient made continuous use of diuretic and antihypertensive drugs.

After 19 days of hospitalization, the patient underwent surgery for replacement of the bioprosthetic mitral valve with a mechanical prosthesis and also underwent tricuspid valve plasty. The procedure was performed under extracorporeal circulation, with a duration of 124 minutes. There were 46 minutes of myocardial ischemia and 92 minutes of aortic clamping without blood transfusions. No intraoperative events were noted. After surgery, the patient was transferred to the intensive care unit without sedation, with mechanical ventilation using dosages of dopamine diuretic. The patient was extubated in the immediate postoperative period and she started using a Venturi oxygen mask, receiving an inspired oxygen fraction (FiO_2) of 50%.

Two days after the operation, the patient developed worsening of symptoms. This included tachypnea, decreased peripheral

oxygen saturation (SpO_2) and significant radiological worsening, with diffuse infiltrates, signs of pulmonary congestion and opacification of the costophrenic angle of the breasts, as shown in **Figure 1**.

She also presented oliguria and it was necessary to administer furosemide intermittently. Noninvasive mechanical ventilation (NIV) was used for an intermittent period, but with little improvement of the tachypnea.

Since there was no improvement of respiratory symptoms, even through using NIV, it was decided on August 2, 2015, to perform an intubation procedure and start continuous sedation for better respiratory management. After the clinical signs had become stable, the weaning process was started.

At the minimum mechanical ventilation parameters, i.e. spontaneous mode with FiO_2 of 40%, positive end-expiratory pressure (PEEP) of 4 cmH_20 and tidal volume of 5 ml/kg, the patient did not tolerate procedures to produce predictive indexes for withdrawal of mechanical ventilation. She showed signs suggestive of respiratory failure, according to the 2013 Brazilian guidelines for mechanical ventilation. A chest computed tomography (CT) scan was then performed, which revealed the presence of extensive bilateral pleural effusion at the bases of the lungs, and more evidently in the right lung. To relieve this, it was decided to perform thoracentesis, with removal of 1300 ml of citric fluid.

To evaluate the lung mechanics, respiratory monitoring through a scanner by means of bioelectrical impedance analysis was chosen (Timpel Enlight 1800, São Paulo, Brazil). An EIT electrode belt with 16 electrodes was placed around the thorax at the level of the fifth intercostal space, and one reference electrode was also placed on the patient. A tidal image was calculated as the difference between the EIT images at end-inspiration and end-expiration for one tidal breath, which represents the regional distribution of tidal volume (the tidal variation of impedance). Thus, the predictive indexes for success or failure in withdrawing mechanical ventilation and the spontaneous breathing test (SBT) using a T piece were determined and could then be evaluated by means of tomography.

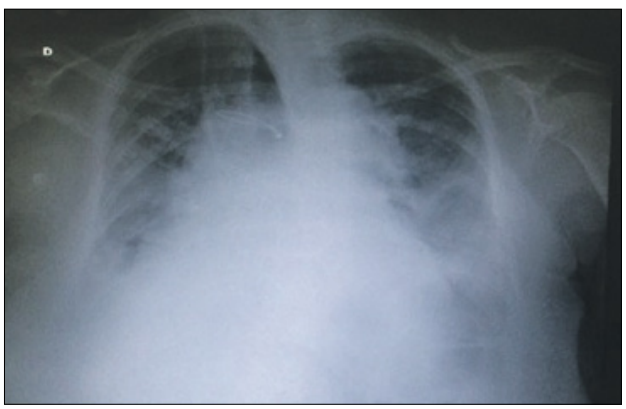


Figure 1. Chest X-ray in posterior-anterior view (April 24, 2015).

The results regarding the variation of heart rate (HR), respiratory frequency (RF), peripheral oxygen saturation (SpO_2) and mean arterial pressure (MAP) are shown in **Table 1**. Any significant variations in tidal volume and in the distribution of lung parenchyma could be checked through determining predictive indexes (RSBI, PImax and PEmax) from electrical bioimpedance tomography images and through determining spontaneous breathing. The behavior of changes in tidal volume at the time of determining the predictive indices and SBT are illustrated in **Graph 1**. The changes in the distribution of air in the lung parenchyma are illustrated in **Figures 2, 3, 4** and **5**. These were obtained from the scanner screen through bioimpedance at the following times: before, during and after determining the predictive indices and before and 5 minutes after completion of the spontaneous breathing test.

Importantly, the patient developed a high response to atrial fibrillation at the time of the spontaneous breathing test, without hemodynamic repercussions. Five minutes after this test was started, the patient showed signs of respiratory failure. This requiring discontinuation of the test and return to mechanical ventilation in spontaneous mode, with the minimum parameters already described above. It was also observed that after the predictive indexes had been determined, there was better distribution of air in the lung parenchyma. This was shown through the positive graphic percentages displayed on the scanner screen (**Figures 2, 3, 4** and **5**).

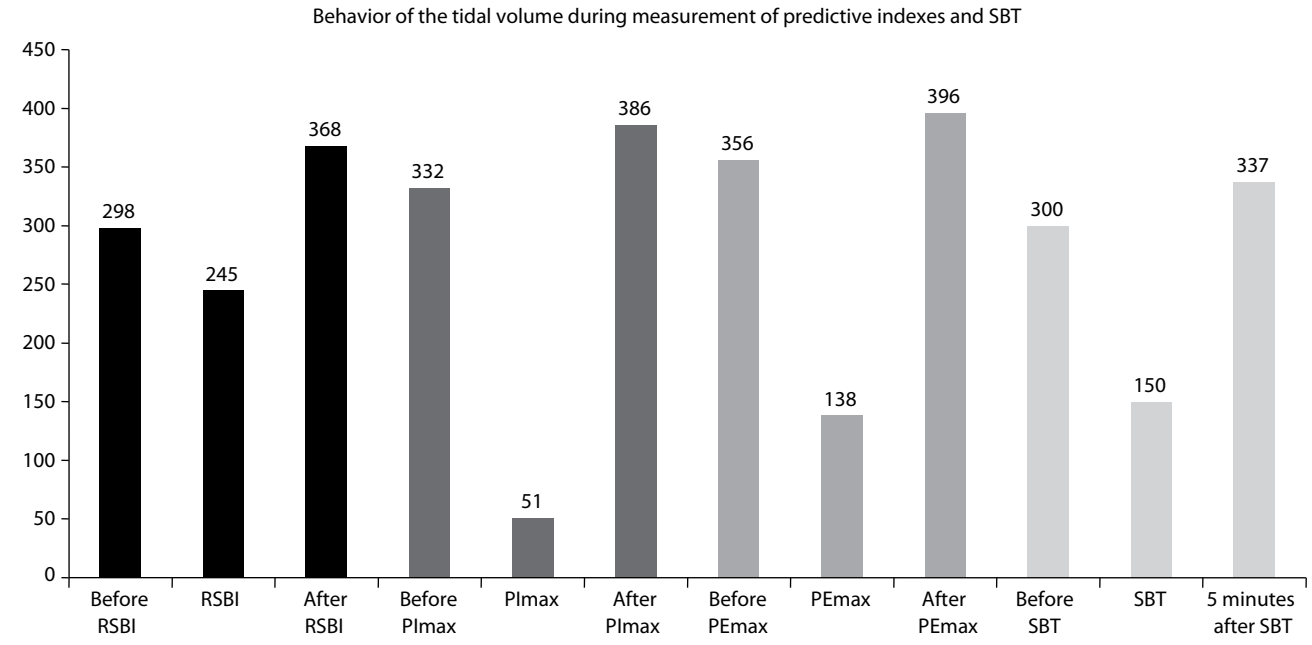
The behavior of the air distribution within the lung parenchyma before, during and after determining the RSBI can be seen in the ventilation map distribution of 64%, 71% and 58% in the right lung and 36%, 28%, 43% in the left lung, as shown in **Figure 2**.

From these findings and because the weaning process failed for a second time, it was decided during a clinical visit and discussion of the case to perform tracheostomy. This was done on

Table 1. Variation of heart rate (HR), respiratory frequency (RF), peripheral oxygen saturation (SpO_2) and mean arterial pressure (MAP), before measuring the predictive indexes, during measurement of the predictive indexes and five minutes after performing the spontaneous breathing test (SBT)

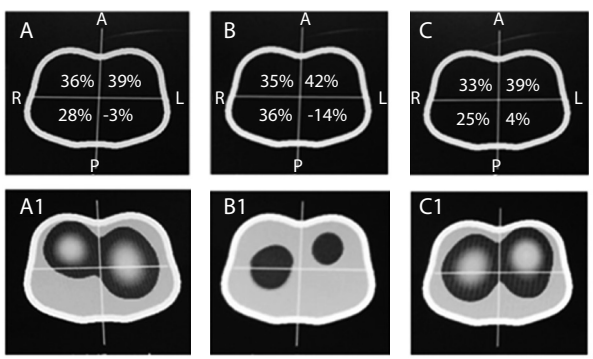
Times	Variables			
	HR (bpm)	RF (rpm)	SpO_2 (%)	MAP (mmHg)
Before tests	81	20	98	57
During RSBI	91	31	94	73
During PImax	82	29	100	65
During PEmax	84	36	100	70
During SBT	89	25	98	70
5 minutes after SBT	78	25	99	56

bpm = beats per minute; rpm = respiration per minute; % = percentage; MAP = mean arterial pressure; mmHg = millimeters of mercury; RSBI = rapid shallow breathing index; PImax = maximum inspiratory pressure; PEmax = maximum expiratory pressure; SBT = spontaneous breathing test.



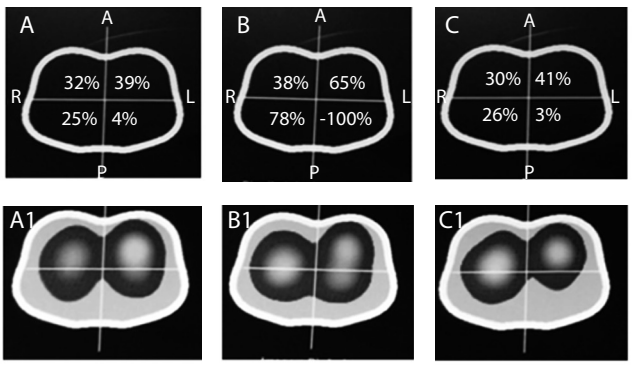
SBT = spontaneous breathing test; RSBI = rapid shallow breathing index; PImax = maximum inspiratory pressure; PEmax = maximum expiratory pressure. Before = before implementing the measurements; After = after the measurements.

Graph 1. Behavior of the variation of tidal volume during measurement of the predictive indexes and spontaneous breathing test (SBT) by means of electrical bioimpedance tomography.



A = air distribution in the lung parenchyma before measurement of RSBI; B = during measurement of RSBI; C = after measurement of RSBI; A1 = dynamic tomography image before RSBI; B1 = during RSBI; and C1 = after RSBI. Images represent a cross-section of the chest (electrode positioning level). Note: there was asymmetrical air distribution in the lung parenchyma, with smaller distribution of ventilation in the left lung and posterior lung fields during measurement of RSBI. There was better air distribution in the lung areas that were previously hypoventilated (left lung and posterior lung fields). R = right; L = left; A = anterior; P = posterior.

Figure 2. Behavior of the air distribution in the lung parenchyma before, during and after measurement of the rapid shallow breathing index (RSBI).



A = air distribution in the lung parenchyma before measurement of PImax; B = during measurement of PImax; C = after measurement of PImax; A1 = dynamic tomography image before PImax; B1 = during PImax; and C1 = after PImax. Images represent a cross-section of the chest (electrode positioning level). R = right; L = left; A = anterior; P = posterior.

Figure 3. Behavior of the air distribution in the lung parenchyma before, during and after measurement of the maximum inspiratory pressure (PImax).

August 11, 2015. On the days following this, progressive reduction of ventilatory parameters was observed and the weaning process was again started, using intermittent mist in a T piece. The patient-progressed satisfactorily and continued to receive continuous

nebulization. After a few days, the plastic tracheostomy tube was exchanged for a metal one.

DISCUSSION

Changes in lung function that occur subsequent to cardiac surgery using extracorporeal circulation are secondary to reactions to use of heparin and comprise protamine complex, edema, congestion, lung injury and microatelectasis. In most cases, mechanical ventilation is absent during extracorporeal circulation. This, together with the inflammatory response due to surgical trauma, leads to changes in respiratory function, consistent with those presented in cases of acute respiratory distress syndrome.[7,8]

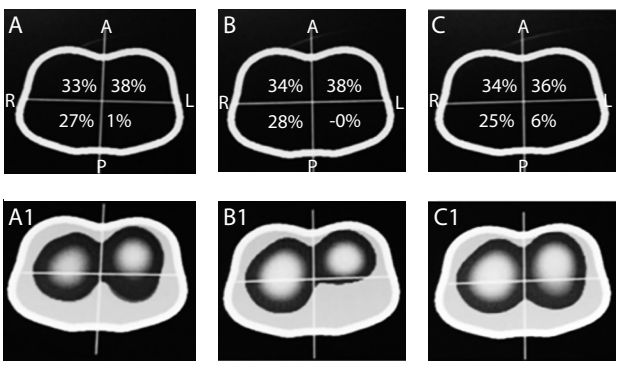
Rodrigues et al. suggested that during and after cardiac surgery, transient dysfunction of gas exchange (TDGE) is evident to varying degrees. Patients with preoperative hypertension and cardiogenic shock presented an association with occurrence of postoperative TDGE. During the postoperative period, presence of pneumonia, need for renal replacement therapy, need for blood therapy and presence of cardiac arrhythmias were correlated with the appearance of a degree of TDGE, thus indicating a risk factor for reintubation.[9]

The case that Rodrigues et al. published consisted of a patient who was reintubated on the second day after cardiac surgery.[9] This patient presented a high response of atrial fibrillation while performing a SBT using a T piece without hemodynamic repercussions. Five minutes after the SBT started, the patient showed signs of respiratory failure and the SBT had to be discontinued. There was a second failure in withdrawing mechanical ventilation and conducting tracheostomy.

The images of **Figures 2, 3, 4** and **5** were obtained in determining rapid shallow breathing index superficial speed breathing index (RSBI), PImax, PEmax and SBT. They show variations in the distribution of air in the lung parenchyma. The behavior exhibited is compatible with the pendelluft effect.

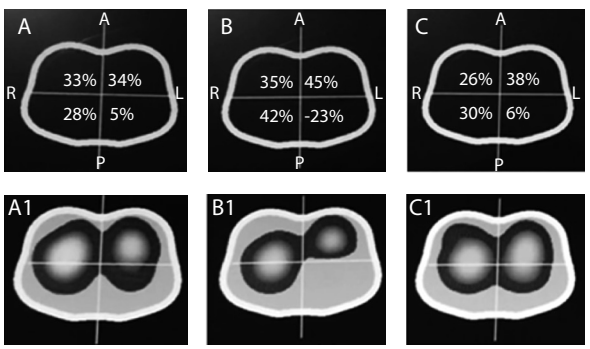
Greenblatt et al. showed that presence of the pendelluft effect may arise due to use of mechanical ventilation in spontaneous mode in cases in which spontaneous breathing efforts are detected, especially when the respiratory rate is high.[10,11]

Yoshida et al. conducted an experimental clinical study in which acute lung injury was induced in seven pigs, with the objective of making comparisons with respiratory monitoring data from a clinical case of a male patient who underwent surgery for coronary revascularization. They observed that when the seven pigs with acute lung injury were under mechanical ventilation without showing spontaneous ventilation effort, there was simultaneous inflation in different areas of their lungs. However, when the pigs showed spontaneous inspiratory efforts during mechanical ventilation, initial inflation of the dependent lung and simultaneous deflation could be observed. Despite these authors' findings, it seems that the pendelluft phenomenon can increase alveolar recruitment in areas of atelectasis that are selectively dependent on inflation, and that the degree of pendelluft is proportional to the intensity of spontaneous effort on mechanical ventilation. These findings corroborate what was found in the present case study.[12]



A = air distribution in the lung parenchyma before measurement of PEmax; B = during measurement of PEmax; C = after measurement of PEmax; A1 = dynamic tomography image before PEmax; B1 = during PEmax; and C1 = after PEmax. Images represent a cross section of the chest (electrode positioning level). Note: there was asymmetrical distribution of air in the lung parenchyma, with smaller distribution of ventilation in the left lung and posterior lung fields during measurement of PEmax. There was better air distribution in the lung areas that were previously hypoventilated (left lung and posterior lung fields). R = right; L = left; A = anterior; P = posterior.

Figure 4. Behavior of the air distribution in the lung parenchyma before, during and after measurement of the maximum expiratory pressure (PEmax).



A = air distribution in the lung parenchyma before measurement of SBT; B = during measurement of SBT; C = five minutes after measurement of SBT; A1 = dynamic tomography image before SBT; B1 = during SBT; and C1 = five minutes after SBT. Images represent a cross-section of the chest (electrode positioning level). Note: there was asymmetrical distribution of air in the lung parenchyma, with smaller distribution of ventilation in the left lung and posterior lung fields during measurement of SBT. R = right; L = left; A = anterior; P = posterior.

Figure 5. Behavior of the air distribution in the lung parenchyma before, during and five minutes after measurement of the spontaneous breathing test (SBT).

Greenblatt et al. considered that pendelluft may be more evident in diseases with a heterogeneous pattern of injury and major changes in respiratory mechanics, with changes in strength and in lung compliance. In the present case study, the chest X-ray suggested that the heterogeneous behavior described by these authors also occurred here.[10]

Recently, Yoshida et al. recommend that it would be important to balance muscle paralysis in relation to maintenance of spontaneous breathing during mechanical ventilation for patients with acute respiratory distress syndrome network (ARDSnet). This would depend on the severity of ARDSnet, its evolution phase and its respiratory demands. In the early phase of severe ARDSnet, partial ventilatory support to promote spontaneous breathing should be avoided. Paralysis of the diaphragm muscle may be effective for preventing pendelluft. In situations of less severity of ARDSnet, and after a short period of diaphragm muscle paralysis in cases of severe ARDSnet, spontaneous breathing should be facilitated by means of partial mechanical ventilatory support. This would prevent large spontaneous respiratory efforts.[13]

The finding of pendelluft can be determined through noninvasive monitoring conducted by means of electrical bioimpedance tomography, without exposing the patient to the invasive measures of other forms of monitoring. Furthermore, this monitoring can make a substantial contribution to research, thus facilitating implementation of a series of studies that together can assist in understanding abnormal physiology. This would include investigating the regional heterogeneity of ventilation and factors associated with pendelluft. A few studies have been conducted on pendelluft diagnosed during weaning. The results from a systematic search in the main databases in the literature are presented in **Table 2**. Electrical bioimpedance tomography is simple to be performed at the bedside and has the potential to provide better understanding of the pathophysiology of a variety of lung disorders resulting from mechanical ventilation.[14,15]

Table 2. Search of the literature in medical databases on October 17, 2016, for cases of pendelluft that have been diagnosed

Database	Search strategies	References retrieved	Related studies
MEDLINE (via PubMed)	Pendelluft during mechanical ventilation Pendelluft during cardiac surgery Pendelluft during intensive care Pendelluft during ventilator weaning ("Respiration, Artificial"[Mesh]) OR (Respiration Artificial) OR (Artificial Respiration) OR (Artificial Respirations) OR (Respirations, Artificial) OR (Ventilation, Mechanical) OR (Mechanical Ventilations) OR (Ventilations, Mechanical) OR (Mechanical Ventilation) OR (Bioelectrical impedance tomography) AND Pendelluft	30	5

CONCLUSION

Electrical bioimpedance tomography can contribute towards interpreting failures of withdrawal of ventilatory support and towards monitoring the side effects caused by mechanical ventilation, especially in patients with heterogeneous patterns of changes to respiratory mechanics. The findings from predictive indexes relating to withdrawal of mechanical ventilation might enable better distribution of air in the lung parenchyma and increased lung homogenization.

It should also be noted that after the predictive indexes had been determined, the tidal volume did not return to its initial value. This effect was caused by alveolar recruitment through the increased respiratory effort during testing.

Electrical bioimpedance tomography can help in weaning patients off mechanical ventilation, as in the case presented here. The limitation of pendelluft while tests on weaning were being performed was defined.

Further studies should be conducted to investigate whether the alveolar recruitment achieved after conducting spontaneous effort, at the time of determining the predictive indices, was maintained after long reconnection to mechanical ventilation.

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What do Cochrane systematic reviews say about non-pharmacological interventions for treating cognitive decline and dementia?

O que as revisões sistemáticas Cochrane falam sobre intervenções não farmacológicas para o tratamento de declínio cognitivo e demência?

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ABSTRACT

BACKGROUND: Dementia is a highly prevalent condition worldwide. Its chronic and progressive presentation has an impact on physical and psychosocial characteristics and on public healthcare. Our aim was to summarize evidence from Cochrane reviews on non-pharmacological treatments for cognitive disorders and dementia.

DESIGN AND SETTING: Review of systematic reviews, conducted in the Discipline of Evidence-Based Medicine, Escola Paulista de Medicina, Universidade Federal de São Paulo.

METHODS: Cochrane reviews on non-pharmacological interventions for cognitive dysfunctions and/or type of dementia were included. For this, independent assessments were made by two authors.

RESULTS: Twenty-four reviews were included. These showed that carbohydrate intake and validation therapy may be beneficial for cognitive disorders. For dementia, there is a potential benefit from physical activity programs, cognitive training, psychological treatments, aromatherapy, light therapy, cognitive rehabilitation, cognitive stimulation, hyperbaric oxygen therapy in association with donepezil, functional analysis, reminiscence therapy, transcutaneous electrical stimulation, structured decision-making on feeding options, case management approaches, interventions by non-specialist healthcare workers and specialized care units. No benefits were found in relation to enteral tube feeding, acupuncture, Snoezelen stimulation, respite care, palliative care team and interventions to prevent wandering behavior.

CONCLUSION: Many non-pharmacological interventions for patients with cognitive impairment and dementia have been studied and potential benefits have been shown. However, the strength of evidence derived from these studies was considered low overall, due to the methodological limitations of the primary studies.

RESUMO

INTRODUÇÃO: Demência é uma condição com alta prevalência e incidência global. Sua característica crônica e progressiva tem impacto em aspectos físicos, psicossociais e na saúde pública. Nosso objetivo foi resumir evidências de revisões Cochrane sobre intervenções não farmacológicas para distúrbios cognitivos e demências.

TIPO DE ESTUDO E LOCAL: Revisão de revisões sistemáticas conduzida na Disciplina de Medicina Baseada em Evidências da Escola Paulista de Medicina, Universidade Federal de São Paulo.

MÉTODOS: Foram incluídas revisões Cochrane sobre intervenções não farmacológicas para disfunções cognitivas e/ou qualquer tipo de demência, após a avaliação realizada de forma independente por dois autores.

RESULTADOS: Vinte e quatro revisões foram incluídas. As revisões mostraram que ingestão de carboidratos e a terapia de validação podem ser benéficas para distúrbios cognitivos. Para demência, existe benefício potencial de programas de atividade física, treino cognitivo, tratamentos psicológicos, aromaterapia, terapia com luz, reabilitação cognitiva, estimulação cognitiva, oxigenoterapia hiperbárica associada a donepezila, análise funcional, terapia de reminiscência, estimulação elétrica transcutânea, decisão estruturada em opções de alimentação, abordagem de gestão de casos e intervenções aplicadas por trabalhadores na área de saúde não especialistas e por unidades de cuidado especializado. Não foram encontrados benefícios para alimentação por sonda entérica, acupuntura, estimulação de Snoezelen, cuidados de repouso, equipe de cuidados paliativos e intervenções para prevenir comportamento de perambulação.

CONCLUSÃO: Várias intervenções não farmacológicas para pacientes com comprometimento cognitivo e demência têm sido estudadas, mostrando benefícios potenciais. Entretanto, a força de evidência derivada desses estudos é em geral considerada baixa, devido às limitações metodológicas dos estudos primários.

INTRODUCTION

Dementia has been considered by the World Health Organization to be a public health priority since 2012,[1] because of its high estimated prevalence and incidence. A report published in 2016 estimated that 47.5 million people have dementia worldwide and this number is expected to almost triple by 2050, to reach 135.5 million.[2] Because of the chronic and progressive nature of this condition, the socioeconomic impact of dementia is extremely important. As a consequence of the estimated increase in prevalence, increases in the familial and societal burden and an even more significant impact on healthcare costs can be expected.[3,4]

Treatment and management of dementia are challenging because of the patients' diminished ability to adhere to therapeutics and to report adverse effects.[5] Also, dementia is not a single condition: rather, it comprises distinct diseases with different pathophysiological mechanisms. The therapeutic and preventive strategies depend particularly on understanding the etiology and other factors such as clinical features, stage of dementia and family support. Some of the most common pharmacological agents are cholinesterase inhibitors,[6] memantine,[7] memantine combined with cholinesterase inhibitors[8,9] and antioxidants.[10,11] There are many non-pharmacological therapies and some of them show little, if any, evidence of benefit regarding dementia.

A quick search on MEDLINE (via PubMed), using the MeSH term "dementia" and applying a filter to identify clinical trials, retrieved an average of 268 (153-334) published papers per year over the last 10 years. The high number of studies published over recent years and the clinical importance of this issue have provided the impulse for comprehensive research syntheses such as this review of reviews.

OBJECTIVES

To identify and summarize Cochrane systematic reviews focusing on non-pharmacological interventions to treat cognitive impairment and dementia, regardless of etiology, and to present their findings in accordance with the quality of the evidence.

METHODS

Design

Review of Cochrane systematic reviews on interventions to treat cognitive impairment and dementia.

Setting

Discipline of Evidence-Based Medicine of Escola Paulista de Medicina, Universidade Federal de São Paulo (UNIFESP).

Criteria for including reviews

- Types of studies

We included the latest version of completed Cochrane systematic reviews, without imposing any restriction on publication date. Protocols relating to systematic reviews and reviews that were coded as "withdrawn" in the Cochrane Database of Systematic Reviews (CDSR) were not included.

- Types of participants

Patients diagnosed with cognitive impairment or dementia, regardless of etiology, including (but not limited to) mild cognitive impairment, vascular dementia, Alzheimer, mixed dementia and dementia secondary to other neurodegenerative diseases.

- Types of intervention

Non-pharmacological interventions including (but not limited to) psychological, social and educational interventions, acupuncture, physical exercise and physical therapy.

- Types of outcomes

Clinical, social and laboratory outcomes, as reported in the systematic reviews.

Search for reviews

We conducted a systematic search in the Cochrane Database of Systematic Reviews (CDSR) (via Wiley) on December 19, 2016, using a sensitive search strategy (**Table 1**).

Selection of systematic reviews

Two reviewers independently evaluated titles and abstracts of records initially retrieved on the basis of the inclusion criteria. Disagreements were solved by reaching a consensus.

Presentation of the results

We presented the results from the systematic reviews included through a narrative structure (qualitative synthesis).

RESULTS

Search results

The initial search retrieved 183 reviews. However, only 24 fulfilled our inclusion criteria.[12-35]

Table 1. Search strategy (December 19, 2016)

#1: "Dementia" in Title, Abstract, Keywords
#2: "Alzheimer Disease" in Title, Abstract, Keywords
#3: Alzheimer in Title, Abstract, Keywords
#4: "Cognitive Dysfunction" in Title, Abstract, Keywords
#5: #1 OR #2 OR #3 OR #4
#6: #5 in Cochrane Reviews

Results from systematic reviews

Among the 24 systematic reviews included, two (~8%) focused on vascular dementia, two (~8%) focused on dementia secondary to other diseases and 16 (~66.6%) focused on all types of dementia. Additionally, one study (~4%) focused on cognition as a broader topic, two (~8%) focused on both dementia and mild cognitive impairment and one (~4%) on mental disorders as a broader topic. Three reviews (12.5%) assessed caregivers' outcomes, and six (25%) focused on interventions relating to healthcare systems.

A brief summary of the systematic reviews included is presented below. The issues addressed, the main findings from each intervention and the quality of the evidence (based on the GRADE approach) are presented in **Tables 2**, **3** and **4**.[12-36]

Table 2. Characteristics, main findings and quality of evidence from systematic reviews focusing on patient-directed interventions

Intervention	Population/comparison	Benefits, harms and safety	Evidence quality (GRADE approach*)
Physical exercise programs[13]	Dementia/usual care; social group activity.	Benefit: activities of daily living. No effect: cognition; neuropsychiatric symptoms; depression.	Very low to moderate
Cognitive training[15]	Multiple sclerosis/any type of care.	Benefit: memory span; working memory. No effect: emotional functions; attention; information processing speed; immediate verbal memory; executive functions; depression.	Very low to low
Cognitive training plus other neuropsychological rehabilitation methods[15]	Multiple sclerosis/any type of care.	Benefit: attention; immediate verbal memory; delayed memory. No effect: emotional functions; attention; information processing speed; everyday cognitive performance; depression; fatigue.	Very low to moderate
Psychological treatments[16]	Dementia/treatment as usual.	Benefit: depression; clinician rated-anxiety. No effect: self-rated anxiety; caregiver-rated anxiety.	Low to moderate
Aromatherapy[17]	Dementia/placebo.	Benefit: agitation; behavioral symptoms. No effect: quality of life; activities of daily living. Adverse effects: not found.	Very low
Light therapy[18]	Dementia/placebo.	Benefit: activities of daily living. No effect: cognition; sleep; challenging behavior; psychiatric symptoms.	Not assessed
Cognitive training[20]	Alzheimer's disease; vascular dementia/ control in the short term.	No effect: overall measurement of cognition, participant's capacity for activities of daily living, participant's mood, immediate verbal memory scores, self-reported burden of care.	Low to moderate
Cognitive rehabilitation[20]	Alzheimer's disease; vascular dementia/ control in the short term.	Benefit: participant's self-reported performance in relation to individual goals; participant's mood; self-reported mood.	High
Cognitive stimulation[22]	Dementia/control.	Benefit: cognition; self-reported quality of life and well-being; staff ratings of communication and social interaction. No effect: mood; activities of daily living; general behavioral function; behavioral problem.	Not assessed
Hyperbaric oxygen therapy plus donepezil[23]	Vascular dementia/ donepezil alone.	Benefit: cognition.	Not assessed
Functional analysis[24]	Dementia/usual care.	Benefit: frequency of challenging behavior; caregiver reaction.	Not assessed
Carbohydrates (glucose drink)[25]	Normal cognition; mild cognitive impairment/placebo.	Benefit: switch condition of the modified Stroop test; computerized test of divided attention.	Not assessed
Enteral tube feeding[27]	Advanced dementia with problems in eating and swallowing and/or poor nutritional intake/no feeding tube.	No effect: survival; nutritional status; prevalence of pressure ulcers.	Not assessed
Adjunctive therapies[28]	AIDS dementia complex/placebo.	No effect: neuropsychological test scores; number of patients who completed the assigned dosage of experimental medication; all-cause mortality. Adverse effects: not found.	Not assessed
Acupuncture[29]	Vascular dementia.	No results.	No results
Reminiscence therapy[31]	Dementia/no treatment/ social contact.	Benefit: cognition; mood; general behavior function; staff knowledge of group members' backgrounds. Adverse effects: not found.	Not assessed

Continue...

Table 2. Continuation.

Intervention	Population/comparison	Benefits, harms and safety	Evidence quality (GRADE approach*)
Transcutaneous electrical nerve stimulation[32]	Dementia/placebo.	Benefit: delayed 8-word recall right after treatment; face recognition right after treatment; motivation right after treatment. No effect: neuropsychological measurements after 6 weeks; behavioral measurements after 6 weeks.	Not assessed
Validation therapy[33]	Cognitive impairment; dementia/usual care.	Benefit: behavior.	Not assessed
Validation therapy[33]	Cognitive impairment; dementia/social contact.	Benefit: depression.	Not assessed
Snoezelen[34]	Dementia/control.	No effect: behavior; mood; communication/interaction; cognition.	Not assessed

*GRADE = Grading of Recommendations Assessment, Development and Evaluation. Tool used for assessing the quality of the body of the current evidence. High quality: low probability that further studies might change the confidence regarding the existing evidence. Moderate quality: probability that further studies will change the confidence regarding the existing evidence. Low quality: high probability that further studies will change the confidence regarding the existing evidence. Very low quality: there is much uncertainty about the information, precluding any valid interpretation.[36]

1. Palliative care interventions

The review[12] (2016) had the purpose of assessing the effectiveness of palliative care interventions in cases of advanced dementia, with inclusion of two randomized controlled trials (RCTs). Because of the heterogeneity of the data, no meta-analysis could be done. The results listed below were found:

- Palliative care team for people with advanced dementia hospitalized for an acute illness (99 participants): no evidence of in-hospital mortality [risk ratio (RR) 1.06, 95% confidence interval (CI) 0.53 to 2.13], cardiopulmonary resuscitation, or clinical care provided during hospital admission;
- Structured decision-making aid for feeding options among surrogate decision-makers of nursing-home residents with advanced dementia (total of 90 participants included): lower scores for decisional conflict [mean difference (MD) -0.30, 95% CI -0.61 to 0.01] in the group of intervention surrogates and more likelihood of discuss feeding options with a clinician, in comparison with the control group (RR 1.57, 95% CI 0.93 to 2.64).

There was insufficient evidence to assess the effect of palliative care interventions on advanced dementia. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011513.pub2/abstract.

2. Physical exercise programs

The objective of the review[13] (2015) was to analyze physical exercise programs for dementia on different outcomes, such as cognition, activities of daily living, neuropsychiatric symptoms, depression and mortality, and the secondary outcomes from the intervention (on family caregivers and on use of healthcare services). A meta-analysis on 17 trials (1067 participants) showed the following results (exercise versus usual care/social group activity):

- Activities of daily living: benefit from exercise programs [six trials, 289 participants; standardized mean difference (SMD) 0.68; 95% CI 0.08 to 1.27, P = 0.02);
- Cognitive functioning: no clear evidence (nine studies, 409 participants; SMD 0.43; 95% CI -0.05 to 0.92, P = 0.08);
- Neuropsychiatric symptoms and depression: no clear evidence. For neuropsychiatric symptoms: one trial, 110 participants; MD -0.60; 95% CI -4.22 to 3.02; P = 0.75; for depression: five trials, 341 participants; SMD 0.14; 95% CI -0.07 to 0.36; P = 0.16;
- Caregiver burden: may be reduced when the caregiver supervises the patient in an exercise program (one trial, 40 participants; MD -15.30; 95% CI -24.73 to -5.87; P = 0.001);
- Other secondary outcomes could not be assessed.

There was promising evidence that exercise programs might improve the ability of people with dementia to perform activities of daily living, but no evidence of benefit regarding cognition, neuropsychiatric symptoms, or depression. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006489.pub4/abstract.

3. Case management approaches to home support

Case management is an intervention for organizing and coordinating care at the level of the individual, providing long-term care for people with dementia in the community. The aim of the review[14] (2015) was to evaluate the effect of case management approaches to home support for dementia, from the perspectives of the different parties involved (patients, caregivers and staff). It included 13 RCTs (9615 participants). The following results were found (comparison of case management versus other treatments):

- Total cost of services: reduction in the case management group at 12 months (two RCTs, n = 5,276; SMD -0.07, 95% CI -0.12 to -0.02, P = 0.01);

- Dollar expenditure: reduction for the total of three years (one RCT, n = 5170; MD -705.00, 95% CI -1170.31 to -239.69, P = 0.003);
- Number of days per month in a residential home or hospital unit: reduction in the case management group at six months (one RCT, n = 88; MD -5.80, 95% CI -7.93 to -3.67, P < 0.0001) and at 12 months (one RCT, n = 88; MD -7.70, 95% CI -9.38 to -6.02, P < 0.0001);
- Number of people admitted to hospital: no differences at six months (four RCTs, 439 participants), 12 months (five RCTs, 585 participants) and 18 months (five RCTs, 613 participants);

Table 3. Characteristics, main findings and quality of evidence from systematic reviews focusing on caregiver-directed interventions

Intervention	Population/comparison	Benefits, harms and safety	Evidence quality (GRADE approach*)
Exercise programs[13]	Dementia/usual care; social group activity.	Benefit: caregiver burden.	Very low to moderate
Respite care[19]	Dementia; caregivers/not respite care.	No effect: caregiver burden; caregiver psychological stress and health.	Very low
Respite care[19]	Caregivers/polarity therapy.	Harm: caregiver perceived stress. No effect: other psychological health measures; other caregiver outcomes.	Very low
Reminiscence therapy[31]	Dementia/no treatment; social contact.	Benefit: caregiver strain. Adverse effects: not found.	Not assessed

*GRADE = Grading of Recommendations Assessment, Development and Evaluation. Tool used for assessing the quality of the body of the current evidence. High quality: low probability that further studies might change the confidence regarding the existing evidence. Moderate quality: probability that further studies will change the confidence regarding the existing evidence. Low quality: high probability that further studies will change the confidence regarding the existing evidence. Very low quality: there is much uncertainty about the information, precluding any valid interpretation.[36]

Table 4. Characteristics, main findings and quality of evidence from systematic reviews focusing on healthcare system interventions

Intervention	Population and comparison	Benefits, harms and safety	Evidence quality (GRADE approach*)
Palliative care team[12]	Advanced dementia hospitalized for acute illness/usual care.	No effect: modification on clinical care provided during hospital admission; mortality in hospital; decisions to forgo cardiopulmonary resuscitation	Very low
Structured aid for decision-making on feeding options[12]	Advanced dementia in nursing homes/usual care.	Benefit: conflict on decisions; likelihood of discussing feeding options with a clinician.	Very low
Case management approaches[14]	Dementia; home setting/ other treatments.	Benefit: number of days/month in a residential home/hospital unit; total cost of servicers; dollar expenditure (3 years); institutionalization (6 months); behavior disturbance (18 months); caregiver burden (6 months); caregiver depression; caregiver wellbeing (6 months). No effect: number of people admitted to hospital; length of time until participants were institutionalized; institutionalization (10-12 and 24 months); mortality; participants' quality of life; behavior disturbance (4, 6 and 12 months); caregivers' quality of life; caregiver burden (12 and 18 months); caregiver well-being (12 and 18 months).	Low to high
Non-specialist healthcare worker interventions[21]	Dementia; caregivers/ usual healthcare services.	Benefit: behavioral symptoms; caregiver mental wellbeing; caregiver burden; caregiver distress.	Moderate
Special care units[26]	Dementia/traditional nursing homes.	Benefit: use of restraints; mood; Neuropsychiatric inventory score. Harm: use of psychotropic medication.	Not assessed
Non-pharmacological interventions for preventing wandering[30]	Dementia in the domestic setting.	No results.	No results
Subjective barriers for preventing wandering[35]	Cognitively-impaired individuals.	No results.	No results

*GRADE = Grading of Recommendations Assessment, Development and Evaluation. Tool used for assessing the quality of the body of the current evidence. High quality: low probability that further studies might change the confidence regarding the existing evidence. Moderate quality: probability that further studies will change the confidence regarding the existing evidence. Low quality: high probability that further studies will change the confidence regarding the existing evidence. Very low quality: there is much uncertainty about the information, precluding any valid interpretation.[36]

- Length of time until participants were institutionalized: uncertain effects at 12 months (one trial; hazard ratio (HR): 0.66, 95% CI 0.38 to 1.14, P = 0.14);
- Institutionalization (admission to residential or nursing homes): significantly less likely for case management group at six months (six RCTs, n = 5741; OR 0.82, 95% CI 0.69 to 0.98, I^2 = 0%, P = 0.02) and at 18 months (four RCTs, n = 363; OR 0.25, 95% CI 0.10 to 0.61, I^2 = 0%, P = 0.003). The effects were uncertain at 10 to 12 months (nine RCTs, n = 5990; OR 0.95, 95% CI 0.83 to 1.08, I^2 = 48%, P = 0.39) and at 24 months (two RCTs, n = 201; OR 1.03, 95% CI 0.52 to 2.03, I^2 = 0%, P = 0.94);
- Mortality and participants' or caregivers' quality of life: no significant events (mortality: at four, six, 12, 18, 24 and 36 months; quality of life: at four, six, 12 and 18 months);
- Behavioral disorder: reduction in case management group at 18 months (2 RCTs, n = 206; SMD -0.35, 95% CI -0.63 to -0.07, I^2 = 0%, P = 0.01) but uncertain effects at four months (two RCTs), six months (four RCTs) and 12 months (five RCTs);
- Caregiver burden: benefits at six months (four RCTs, n = 4601; SMD -0.07, 95% CI -0.12 to -0.01, I^2 = 26%, P = 0.03) but uncertain effects at 12 or 18 months;
- Caregiver depression: small significant improvement in case management group at 18 months (three RCTs, n = 2,888; SMD -0.08, 95% CI -0.16 to -0.01, I^2 = 0%, P = 0.03);
- Caregiver wellbeing: greater improvement in the case management group at six months (one RCT, n = 65; MD -2.20 CI -4.14 to -0.26, P = 0.03) but uncertain effects at 12 or 18 months.

There was evidence that case management was beneficial for improving some outcomes relating to patients and caregivers and for lowering admissions to care homes and overall healthcare costs. There was not enough evidence regarding whether case management might delay institutionalization in care homes, and there were uncertain results regarding patient depression, functional abilities and cognition. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008345.pub2/abstract.

4. Neuropsychological rehabilitation on multiple sclerosis

Cognitive deficits are a common manifestation of multiple sclerosis (MS). The review[15] (2014) aimed to assess the effects of neuropsychological/cognitive rehabilitation on health-related factors (cognitive performance and emotional well-being) among patients with MS, and included 20 studies (986 participants, mean age of 44.6 years and 70% women). The results are listed below (comparison: intervention versus control):

- Cognitive training: improvement of memory span (SMD 0.54, 95% CI 0.20 to 0.88, P = 0.002) and of working memory (SMD 0.33, 95% CI 0.09 to 0.57, P = 0.006). No evidence of effect on emotional functions, attention, information processing speed, immediate verbal memory, executive functions or depression;
- Cognitive training combined with other neuropsychological rehabilitation methods: improvement of attention (SMD 0.15, 95% CI 0.01 to 0.28, P = 0.03), of immediate verbal memory (SMD 0.31, 95% CI 0.08 to 0.54, P = 0.008) and of delayed memory (SMD 0.22, 95% CI 0.02 to 0.42, P = 0.03). No evidence of effect on emotional function, attention, information processing speed, everyday cognitive performance, depression or fatigue.

The review found low-level evidence of positive effects from neuropsychological rehabilitation in relation to MS. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009131.pub3/abstract.

5. Psychological treatments

Anxiety and depressive symptoms are very common in cases of dementia and mild cognitive impairment. The purpose of the review[16] (2014) was to assess the effectiveness of psychological interventions (cognitive behavioral therapy, interpersonal therapy, counselling and others) on anxiety and depression in cases of dementia and mild cognitive impairment. It included six RCTs on dementia (439 participants, six to 12 months of intervention). No studies focusing on mild cognitive impairment were included. The results listed below were found (comparison: psychological treatment versus treatment as usual):

- Depression: positive effect from psychological treatments (six trials, 439 participants; SMD -0.22, 95% CI -0.41 to -0.03);
- Clinician-rated anxiety: positive effect from psychological treatments (two trials, 65 participants; MD -4.57, 95% CI -7.81 to -1.32);
- Self-rated and caregiver-rated anxiety: no difference (for self-rated: two trials, SMD 0.05, 95% CI -0.44 to 0.54; for caregiver-rated: one trial, MD -2.40, 95% CI -4.96 to 0.16).

There was evidence that psychological interventions combined with usual care could reduce the symptoms of depression and clinician-rated anxiety among people with dementia. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009125.pub2/abstract.

6. Aromatherapy

The objective of the review[17] (2014) was to assess the effectiveness of aromatherapy for treating dementia. Seven RCTs (428 participants, three to 12 weeks of intervention) were included in this review, but only two were combined in a meta-analysis. The results listed below were found (comparison: aromatherapy versus placebo):

- Agitation and behavioral symptoms: significant treatment effect from aromatherapy (one study; for agitation: n = 71, MD -11.1, 95% CI -19.9 to -2.2; for behavioral symptoms: n = 71, MD -15.8, 95% CI -24.4 to -7.2) versus no difference (one study; for agitation: n = 63, MD 0.00, 95% CI -1.36 to 1.36; for behavioral symptoms: n = 63, MD 2.80, 95% CI -5.84 to 11.44);
- Quality of life and activities of daily living: no difference in the comparison (one study; for quality of life: n = 63, MD 19.00, 95% CI -23.12 to 61.12; for activities of daily living: n = 63, MD -0.50, 95% CI -1.79 to 0.79);
- Adverse effects: no difference (two studies, n = 124; RR 0.97, 95% CI 0.15 to 6.46).

The benefits of aromatherapy for people with dementia were equivocal according to this review. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003150.pub2/abstract.

7. Light therapy

Stimulation of suprachiasmatic nuclei using light might have the potential to reverse circadian disturbances in cases of dementia. The review[18] (2014) examined the effect of light therapy on cognition, activities of daily living, sleep, challenging behavior and psychiatric symptoms associated with dementia, and included 11 trials (499 participants), among which only 8 could be combined in a meta-analysis. The following results were found (comparison: light therapy versus placebo):

- Activities of daily living: reduction in the development of limitations (one study);
- Cognitive function, sleep, challenging behavior or psychiatric symptoms associated with dementia: no effect.

There was insufficient evidence to justify the use of bright-light therapy in cases of dementia. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003946.pub4/abstract.

8. Respite care

Respite care is any intervention designed to give rest or relief to caregivers. The review[19] (2014) aimed to assess the effect of respite care on dementia patients and their caregivers, particularly regarding institutionalization rates. Four trials (753 participants) were included, but no meta-analysis could be done. The following results were found:

- Respite care versus no respite care: no significant effects on caregiver variables (burden and psychological stress and health);
- Respite care versus polarity therapy: significant effect found in favor of polarity therapy for caregiver-perceived stress (n = 38, MD 5.80, 95% CI 1.43 to 10.17), but not for other psychological health measures and other caregiver outcomes;
- Outcomes for people with dementia: not reported in the studies.

The current evidence did not demonstrate any benefits or adverse effects from the use of respite care, for people with dementia or their caregivers. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004396.pub3/abstract.

9. Cognitive training and cognitive rehabilitation

Cognitive training and cognitive rehabilitation are interventions for improving memory and other aspects of cognitive functioning. The review[20] (2013) aimed to evaluate the effectiveness of these two types of interventions for Alzheimer's disease or vascular dementia, including 11 trials (383 participants receiving interventions from four to 24 weeks) on cognitive training and one on rehabilitation. The following results were found (comparison: intervention versus control over the short term):

- Cognitive training: no effect on any outcomes (overall measurement of cognition, participant's capacity for activities of daily living, participant's mood, immediate verbal memory scores and self-reported burden of care);
- Cognitive rehabilitation: no meta-analysis could be conducted. However, promising results were found for other outcomes (participant's self-reported performance in relation to individual goals, participant's mood and self-reported mood).

This review did not provide evidence to confirm that cognitive training is effective. Although the results regarding cognitive rehabilitation were positive, they were considered preliminary in nature. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003260.pub2/abstract.

10. Interventions to care for mental disorders, conducted by non-specialist healthcare workers

A significant number of people suffering from mental, neurological and substance-use disorders do not receive adequate healthcare. Use of non-specialist healthcare workers and other professionals involved in healthcare is a key strategy for closing the treatment gap. The objective of the review[21] (2013) was to assess the effectiveness of non-specialist healthcare workers and other professionals involved in healthcare in delivering interventions relating to mental, neurological and substance-use disorders within primary and community healthcare, in low and middle-income countries. Thirty-eight studies were included, among which 22 involved use of lay healthcare workers. For the purposes of our study, results from populations other than dementia

patients are not shown (comparison: non-specialist healthcare workers versus usual healthcare services):

- Behavioral symptoms of dementia: improvement for the intervention group (severity of behavioral symptoms: SMD -0.26, 95% CI -0.60 to 0.08);
- Mental wellbeing, burden and distress of caregivers of people with dementia: improvement for the intervention group (caregiver burden: SMD -0.50, 95% CI -0.84 to -0.15).

Use of non-specialist healthcare workers and teachers provided some promising benefits in relation to improving patient and caregiver outcomes in cases of dementia. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009149.pub2/abstract.

11. Cognitive stimulation

Cognitive stimulation (CS) includes implementation of enjoyable activities that provide general stimulation for thinking, concentration and memory. The purpose of the review[22] (2012) was to evaluate the effects of CS on cognition in cases of dementia, and included 15 RCTs (718 patients). The following results were found (comparison: CS versus control):

- Cognitive function: benefit from CS even three months after the treatment (SMD 0.41, 95% CI 0.25 to 0.57);
- Self-reported quality of life and well-being: benefit from CS (SMD 0.38, 95% CI: 0.11, 0.65);
- Staff ratings of communication and social interaction: benefit from CS (SMD 0.44, 95% CI 0.17 to 0.71);
- Mood, activities of daily living, general behavioral function and behavioral problems: no effect.

There was consistent evidence that cognitive stimulation benefited cognition in cases of dementia. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005562.pub2/abstract.

12. Hyperbaric oxygen therapy for treating vascular dementia

Hyperbaric oxygen therapy (HBOT) has shown possible efficacy for treating vascular dementia. The aim of the review[23] (2012) was to assess the effectiveness and safety of HBOT in treating vascular dementia, alone or as an adjuvant treatment. One study (64 patients) was included, showing the results below (comparison: HBOT plus donepezil versus donepezil alone):

- Cognitive function: benefits for the group receiving HBOT plus donepezil, which showed improvements after 12 weeks of treatment (Mini-Mental State Examination: weighted mean difference (WMD) 3.50; 95% CI 0.91 to 6.09; Hasegawa's Dementia Rating Scale: WMD 3.10; 95% CI 1.16 to 5.04);
- Other outcomes and adverse effects: not measured in this study.

There was insufficient evidence to support HBOT as an effective treatment for patients with vascular disease. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009425.pub2/abstract.

13. Functional analysis

Functional analysis (FA) is a promising behavioral intervention that involves exploring the meaning or purpose of an individual's behavior. The review[24] (2012) had the objective of assessing the effects of FA-based interventions relating to people with dementia and their caregivers. It included 18 trials, of which 14 included FA embedded in a broad multicomponent care program, which made it impossible to establish the effect of FA itself. The results showed (comparison: care program with FA versus usual care) that, for the frequency of challenging behavior and caregiver reaction, positive effects after the intervention were not assessed at the follow-up phase. The findings suggested that FA embedded in multicomponent interventions potentially had beneficial effects, but that it was precipitous to draw conclusions about its effectiveness. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006929.pub2/abstract.

14. Carbohydrates for cognition

Carbohydrates are essential and easily accessible macronutrients that influence cognitive performance. The aim of the review[25] (2011) was to assess the effect of carbohydrates on cognitive function in situations of normal cognition and mild cognitive impairment. One study (44 adults, aged 60 to 80 years) was included and the following results were found (comparison: glucose drink versus placebo, drunk on a single occasion):

- Switch condition of the modified Stroop test: glucose drinkers were significantly faster ($F\ 1, 41 = 10.47$; $P < 0.01$);
- Computerized test on divided attention: participants in the glucose group showed significantly lower dual-task cost ($F\ 1, 38 = 8.49$; $P < 0.01$, $^2 = 0.18$).

There was insufficient evidence to base any recommendations regarding use of any form of carbohydrate for enhancing cognitive performance. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007220.pub2/abstract.

15. Special care units for behavioral problems

The purpose of special care units (SCUs) is to optimize care for dementia patients, particularly those with behavioral disorders. The review[26] (2009) aimed to evaluate the effect of SCUs on behavioral problems, mood, need for use of restraints and use of psychotropics in treating dementia. Since no RCTs met the inclusion

criteria, eight non-RCTs were selected, among which only four could be combined in a meta-analysis. The following results were found (comparison: SCUs versus traditional nursing home):

- Need for use of restraints: less need for use of restraints in SCUs after six months (two studies, OR 0.46, 95% CI 0.27 to 0.80, P = 0.006) and 12 months (one study, OR 0.49, 95% CI 0.27 to 0.88, P = 0.02);
- Mood: reduction of depressive symptoms among patients at SCUs after three months (one study, WMD -6.30 (-7.88 to -4.72) Cornell points, P < 0.00001);
- Neuropsychiatric inventory score: limited improvements for patients at SCUs (one study lasting six, 12 and 18 months);
- Use of psychotropic medication: reduced use in traditional nursing home after six months (one study, WMD 0.20, CI 0.00 to 0.40, z = 1.96, P = 0.05);
- Behavioral symptoms: no studies found.

There was no strong evidence of benefit, considering the results from non-RCTs. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006470.pub2/abstract.

16. Enteral tube feeding

Use of enteral tube feeding for patients with advanced dementia with poor nutritional intake is a frequent practice. The review[27] (2009) aimed to evaluate enteral tube nutrition for patients with advanced dementia with eating and swallowing difficulties and/or poor nutritional intake. Seven observational controlled studies were identified. In the comparison of feeding tube versus no feeding tube, survival, nutritional status and prevalence of pressure ulcers, there was no evidence of benefit among patients receiving enteral tube feeding.

There was insufficient evidence to suggest that enteral tube feeding was beneficial among patients with advanced dementia. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007209.pub2/abstract.

17. Adjunctive therapies for treating AIDS dementia complex

AIDS dementia complex is a complication from human immunodeficiency virus type 1. The review[28] (2008) had the aim of determining the efficacy and safety of adjunctive therapies for treating AIDS dementia complex. Ten trials were included (711 participants). The results are shown below (comparison: 10 different treatments versus placebo):

- Neuropsychological test scores, number of patients who completed the assigned dosage of experimental medication and all-cause mortality: no significant differences between groups;
- Adverse effects: no difference between groups.

This study confirmed that there was no evidence that adjunctive therapies improved cognitive performance or quality of life among patients with AIDS dementia complex. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006496.pub2/abstract.

18. Acupuncture for treating vascular dementia

Use of different acupuncture techniques for treating vascular dementia is an accepted practice in China. The aim of the review[29] (2007) was to assess the effects of acupuncture therapy for treating vascular dementia. In the absence of any suitable RCTs in this field, the authors were unable to perform a meta-analysis. Therefore, the effectiveness of acupuncture for treating vascular dementia is highly uncertain. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004987.pub2/abstract.

19. Non-pharmacological interventions for preventing wandering

Although there seems to be a consensus in the literature that, in the majority of cases, non-pharmacological approaches for preventing wandering may work as well as drug treatment and with fewer side effects, clinicians often resort to drugs as the first-line treatment for this condition. The aim of the review[30] (2007) was to evaluate the effect and safety of non-pharmacological interventions to prevent wandering among people with dementia (domestic setting). No suitable trials on this subject were found, and therefore no results could be reported. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005994.pub2/abstract.

20. Reminiscence therapy

Reminiscence therapy (RT) involves discussion of past activities, events and experiences, with another person or group of people and usually with the aid of representative elements, such as photos and music. The objective of the review[31] (2005) was to assess the effects of this therapy on patients with dementia and their caregivers. It included five trials, among which only four (144 participants) presented extractable data. The results are listed below (comparison: intervention versus no treatment/social contact):

- Cognition (at follow-up), mood (at follow-up) and general behavioral function (at the end of the intervention period): statistically significant benefit;
- Caregiver strain: significant decrease for caregivers participating in groups with their relative affected by dementia;
- Staff knowledge of group members' backgrounds: significantly improvement;
- Harmful effects: not identified.

In view of the limited number and low quality of studies, the variation in types of reminiscence work reported and the variation in results between studies, no robust conclusions could be drawn. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001120.pub2/abstract.

21. Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS), which consists of application of electrical current through electrodes to the skin, may improve cognition and behavior in cases of dementia. The purpose of the review[32] (2003) was to determine the effect and safety of TENS for treating dementia, and also the variation in treatment parameters. Nine RCTs were selected, among which only three could be included in the meta-analysis. The following results were found (comparison: TENS versus placebo):

- Delayed eight-word recall, face recognition and motivation: improvement in measurements (four trials) right after treatment;
- Other neuropsychological and behavioral measures: no difference between groups immediately after treatment or after six weeks.

The limited data presented in this study did not allow any definite conclusions on the possible benefits of this intervention. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004032/abstract.

22. Validation therapy

Validation therapy is a form of therapy using specific techniques based on acceptance of the reality and personal truth of another person's experience. The objective of the review[33] (2003) was to evaluate the effect of this intervention for people with cognitive impairment or dementia. Three RCTs (116 participants), showed the following results:

- Validation therapy versus usual care: validation therapy was favored in relation to behavior (one study, six weeks of treatment; MD -5.97, 95% CI -9.43 to -2.51, P = 0.0007);
- Validation therapy versus social contact: validation therapy was favored in relation to depression (one study, 12 months of intervention; MD -4.01, 95% CI -7.74 to - 0.28, P = 0.04).

There were no other statistically significant differences between validation and social contact or between validation and usual therapy. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001394/abstract.

23. Snoezelen stimulation

Snoezelen consists of multi-sensory stimulation of the primary senses of sight, hearing, touch, taste and smell through use of lighting effects, tactile surfaces, meditative music and the odor of relaxing essential oils. The review[34] (2002) aimed to examine the effect of Snoezelen on dementia patients and their caregivers. Two trials (246 subjects) were included, but they could not compound a meta-analysis. The results are shown below (comparison: Snoezelen versus control):

- Behavior, mood and communication/interaction: no effects from session-based Snoezelen program or 24-hour integrated Snoezelen care over the short or long term;
- Cognition: no effects from session-based Snoezelen program over the short or long term.

There was no evidence to show that Snoezelen was efficacious for treating dementia. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003152/abstract.

24. Subjective barriers for preventing wandering

Wandering is a frequent behavioral trait among people with dementia, and it may put them at risk. The review[35] (2000) aimed to assess the effect of subjective exit modifications (visual and other selective barriers, such as mirrors, camouflage and grids/strips of tape) on the wandering behavior of cognitively impaired people. No RCTs or controlled trials were found and, in addition, other studies were considered unsatisfactory. Therefore, there was no evidence that subjective barriers prevented wandering among cognitively impaired people. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001932/abstract.

DISCUSSION

This review of systematic reviews compiled through the Cochrane library focused on non-pharmacological interventions for treating cognitive impairment or dementia, regardless of etiology. It was not our primary objective to assess specific interventions for a given type of dementia but, rather, to present the evidence from up-to-date Cochrane reviews on dementia in general. Despite the major importance of this condition, there was almost no high-quality evidence for any of the outcomes proposed by the systematic reviews included. The primary studies presented limited methodological quality and other limitations, such as small sample sizes, lack of reporting of adverse effects and short-term measurement of outcomes. Consequently, the authors of these systematic reviews were unable to put forward any strong recommendations for clinical practice.

Three other previous reviews of systematic reviews[37-39] aimed to evaluate interventions for treating dementia. The most recent of these[37] compiled any systematic reviews that evaluated the effectiveness of non-pharmacological interventions on behavioral

disturbances in cases of dementia. The authors' conclusions were similar to ours. The other review[38] focused on any kind of intervention to delay functional decline in cases of dementia. Regarding non-pharmacological interventions, the authors found only low-quality evidence relating to physical exercise and dyadic interventions. The earliest review[39] found evidence suggesting that hand massage/gentle touch, music or music therapy and physical exercise were effective.

Differently from the others, our review only included Cochrane systematic reviews: these are developed based on rigorous explicit methods. Another important point is that we included all the outcomes proposed in the systematic reviews that were included, which was not the case for other recent reviews[37,38] that addressed specific outcomes (behavioral disturbances and functional decline).

The limitations of the present study relate to the poor quality of the primary studies included in the systematic reviews, which lowered the strength of evidence.

Given the low quality of the primary studies, no solid recommendations for practice could be made. Some interventions seem to bring potential benefits in relation to limited outcomes, but controlled studies with high methodological quality and adequate sample sizes are needed in order to generate sound practical conclusions. The need for well-designed studies focusing on non-pharmacological interventions is particularly important, considering the personal, familial and societal burden of dementia and considering that many pharmacological interventions might not be safe in this particular population.

CONCLUSION

A wide range of non-pharmacological interventions has been studied in the context of cognitive impairment and dementia, and some have shown potential benefits. However, the strength of evidence derived from these studies was considered low overall, because of the methodological limitations of the primary studies.

The 24 Cochrane systematic reviews included in this study showed that carbohydrates (glucose drink) and validation therapy may be beneficial for treating cognitive impairment. For dementia, there are potential benefits from physical exercise programs, cognitive training (alone or in association with other neuropsychological rehabilitation methods), psychological treatments, aromatherapy, light therapy, cognitive rehabilitation, cognitive stimulation, hyperbaric oxygen therapy associated with donepezil, functional analysis, reminiscence therapy, transcutaneous electrical nerve stimulation, structured aid for decision-making regarding feeding options, case management approaches, interventions from non-specialist healthcare workers and use of special care units. No benefits were found from enteral tube feeding, adjunctive therapies, acupuncture, Snoezelen, respite care, palliative care team, non-pharmacological interventions for preventing wandering or subjective barriers for preventing wandering.

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AIM AND EDITORIAL POLICY

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

All authors should create an ORCID ID record (in www.orcid.org) before submitting their article and link the submission to their existing ORCID ID in the electronic submission system. ORCID identifications help to distinguish researchers with similar names.

During submission, the authors will be asked to indicate the names of three to five referees. All of them should be from outside the institution where they work and at least two should preferably be from outside Brazil.

FORMAT

Title page (cover page)

The title page must contain:

1. Type of paper (original article, review or updating article, short communication or letter to the editor).
2. Title of the paper in English, which must be brief but informative.
3. Full name of each author (the editorial policy of the São Paulo Medical Journal is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full or omitted, without using abbreviations); his/her background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or undergraduate student); and his/her position currently held (for example, Master or Doctoral Student, Assistant Professor, Associate Professor or Professor, but not Head of Department, Dean, Provost or Rector), in the department and institution where he/she works, and the city and country (affiliations).
4. Place where the work was developed.
5. Date and venue of the event at which the paper was presented, if applicable, such as congresses or dissertation or thesis presentations.
6. Sources of support in the forms of finance for the project, study bursaries or funding for purchasing equipment or drugs. The protocol number for the funding must be presented.
7. For Brazilian authors, all grants that can be considered to be related to production of the manuscript must be declared, such as fellowships for undergraduate, master and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors, such as awards for established investigators (*Produtividade* - CNPq), accompanied by the respective grant numbers.
8. Description of any conflicts of interest held by the authors. We recommend that the item "Conflicts of interest" at http://www.icmje.org should be read to obtain clarifications regarding what may or may not be considered to be a conflict of interest.
9. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). The author should also indicate a postal address, e-mail address and telephone number that can be published together with the article.

Main document

Second page: abstract and keywords

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

Use the following headings:

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

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

Text

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

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

References

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

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

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

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent a resolution of 300 DPI and/or minimum size of 2500 pixels (width) and be recorded in ".jpg" or ".tif" format. Do not attach images inside Microsoft PowerPoint or Microsoft Word documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Graphs prepared in Microsoft Excel (do not send them in image formats) spreadsheets must be accompanied by the tables of data from which they have been generated.

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

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

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

Original articles

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

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

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

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

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

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

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

Short communications, case reports, case series and narrative reviews

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

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

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

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

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

Letters to the editor

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

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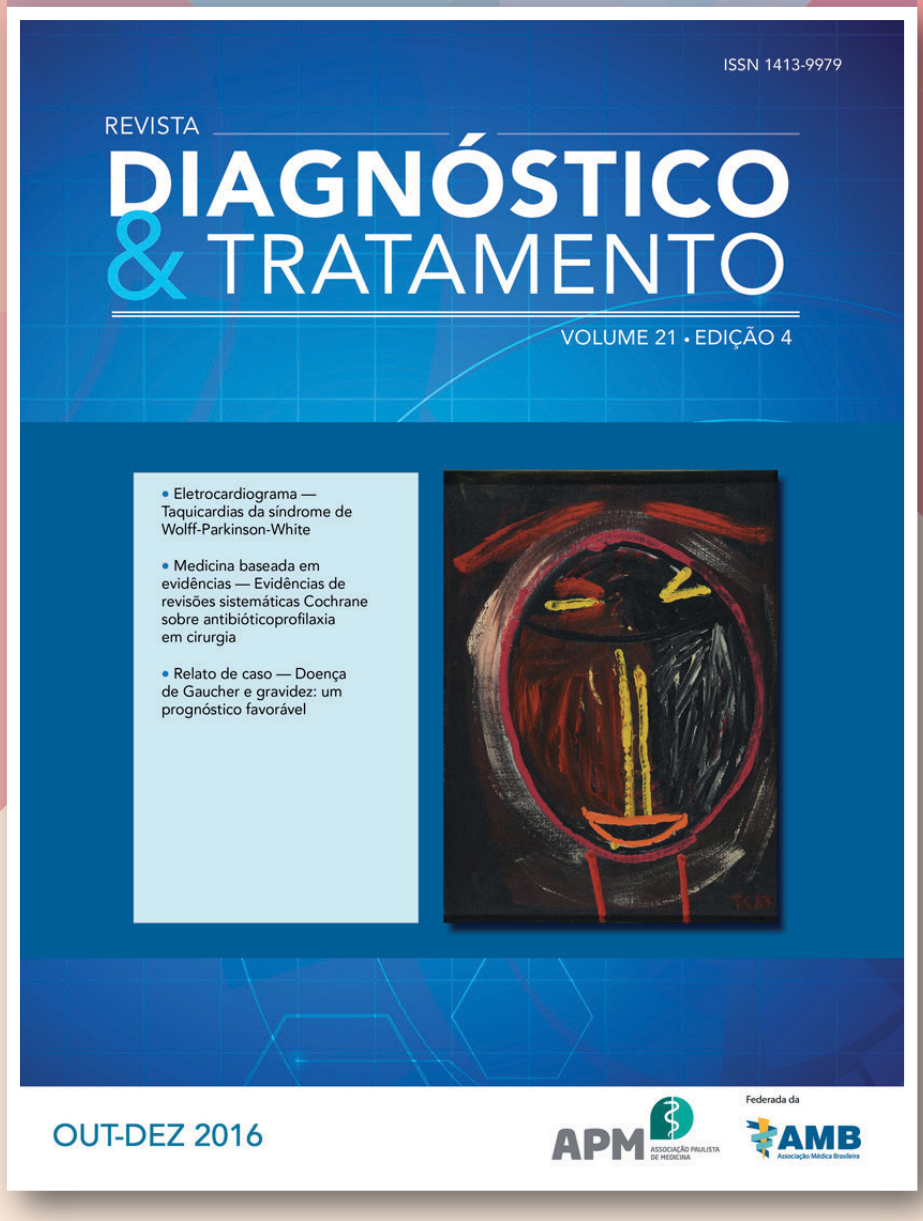

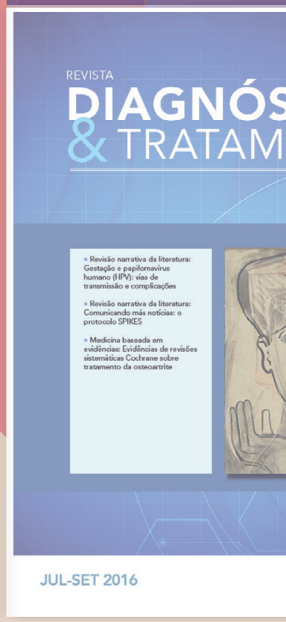

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