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ORIGINAL CONTRIBUTION

Polyneuropathy in Severely Obese Women Without Diabetes: Prevalence and Associated Factors

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Abstract

Background Obesity and its complications are prevalent in women and increase with age. Polyneuropathy (PNP) is a complication of obesity and bariatric surgery (BS). In subjects with severe (grades II and III) obesity and without DM who are candidates for BS, the prevalence of PNP and associated conditions are not well characterized. The aim of this study was to evaluate the prevalence of PNP in severely obese (SO) women without DM or common nutritional deficiencies in order to determine factors associated with the presence of PNP.

Methods A cross-sectional study was performed on 450 SO women. They were evaluated with the Michigan Neuropathy Screening Instrument, a Sleep Apnea Questionnaire, and the short form of the International Physical Activity Questionnaire. Data on blood pressure, body mass index, waist circumference, serum glucose, glycated hemoglobin, LDL and HDL cholesterol, triglycerides, vitamin B12, and postmenopausal (PM) status were also collected. Patients with DM and other common causes of PNP were excluded. To evaluate which variables were independently associated with PNP (dependent variable), Poisson regression models were used.

Results The prevalence of PNP was 11.6%. In univariate analysis, PNP was associated with age, PM status, and diagnosis of systemic arterial hypertension ($p < 0.001$, $p < 0.001$, and $p = 0.016$, respectively), and there was a trend toward an association with sleep apnea risk ($p = 0.101$). In multivariate analysis, PM status (PR = 2.836, 95% CI 1.735–4.636, $p = 0.001$) and age (PR = 1.0511, 95% CI 1.031–1.071, $p = 0.001$) were independently associated with PNP diagnosis in two different models.

Conclusion Even prior to BS, PNP is highly prevalent and is associated with PM status and age in SO women without diabetes.

Keywords Severe obesity · Aging · Polyneuropathy · Bariatric surgery · Postmenopause

Introduction

Polyneuropathy (PNP) is described as a chronic complication of type 1 and type 2 diabetes mellitus (T2DM), as well as secondary to a deficiency of vitamins, dysproteinemias, alcoholism, leprosy, hypothyroidism, malabsorption, obesity, bariatric surgery (BS), and diseases that occur with inflammation like infectious disease, toxin and medication exposure, cancer, and aging [1–3]. Its evolution is commonly accompanied by pain, loss of sensation, an increase in falling risk, and amputations [1].

In T2DM subjects, after a disease duration of 10 years, the prevalence of PNP is almost 50% [1]. In these subjects, after exclusion of other causes, PNP has been associated with glycemia, weight, height, smoking, blood pressure, and lipid measures [1, 3]. After BS, PNP is associated with vitamin B12, B1, and Cu deficiency, or other causes not yet defined [2].

Emerging evidence indicates that PNP may also be present in 10–30% of subjects with impaired glucose tolerance (ITG), known as pre-diabetes, and in patients with metabolic syndrome (MS) [1, 4] and recent studies show that the prevalence of PNP is increased in obese individuals without diabetes

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[4–6], in whom the causes of PNP are also not well known [7, 8]. Since estrogens are described as having neuroprotective properties [9] and obesity is more prevalent in women with increasing age [10], postmenopausal (PM) status, as well as factors that increase with age like sedentary lifestyle, obstructive sleep apnea (OSA), and dyslipidemia, could be related to PNP in obesity.

The main goal of this study was to evaluate the prevalence of PNP in severely obese (SO) nondiabetic women and to determine whether PNP is independently associated with PM status, age, physical activity (PA), OSA risk, and laboratory and anthropometric measures.

Methods

After approval was obtained from the Research Ethics Committees (approval number 1386978), an observational cross-sectional study was conducted from February 2016 to January 2018 in women undergoing preoperative evaluation for BS in the Obesity Treatment Center (OTC) of our hospital. Subjects aged 18 years and over with a history of obesity grade II and III according to the World Health Organization (WHO) [11] were included sequentially. Laboratory tests were performed to identify any possible metabolic or nutritional abnormalities, as well as any other diseases that could cause PNP: glycemia; glycemia 2 h post ingestion of 75 g glucose; glycosylated hemoglobin (HbA1c); total cholesterol; HDL cholesterol; triglycerides; creatinine; 25-OH-vitamin D; TSH; vitamin B12; hematocrit and hemoglobin; leucogram; globular sedimentation rate; hepatic function tests; serologic evaluations for hepatitis A, B, and C; HIV infection; iron; ferritin; folic acid; albumin; magnesium; and zinc. Those who had a diagnosis of DM or presented with other conditions that could be related to well-defined secondary causes of PNP, such as nutritional deficiencies [1], were excluded.

Of the OTC outpatients, 80% are women, and since the prevalence of PNP differs between women and men with T2DM [1], and we were interested in looking for the effect of menopause on PNP in obesity, we investigated the prevalence and factors related to PNP only in women.

The sample size was calculated based on the study of Nienov [5] by using the WinPEPI program (Programs for Epidemiologists for Windows) version 11.63. Considering the proportion of nondiabetic SO women who had at least one sign of PNP (Michigan ≥ 2.5 and a symptom ratio of 0.792), a 95% confidence interval, an estimated difference of 5%, and a loss of 10%, the minimal final sample size required was 352 women.

The study protocol and definitions used were the same as those described in a previous study [12], plus the Michigan Neuropathy Screening Instrument (MNSI) [13], a PA level protocol (Brazilian version of the International Physical Activity Questionnaire [IPAQ, WHO—version 6)] [14], and the OSA risk determination (STOP-BANG questionnaire—Snoring, Tiredness, Observed apnea, high blood Pressure, Body mass index, Age, Neck circumference and Gender) [15]. The MNSI questionnaire (Portuguese version) was used as described by Oliveira [16]. This test has a specificity and sensitivity of 79% and 61%, respectively, when compared to the neurological exam plus nerve conduction studies [13]. It has been described in detail in a previous publication by our group [5]. For menopausal status, women were classified according to their menstrual history or laboratory criteria (FSH and estradiol levels) [17].

Data Analysis

We defined the presence of PNP as a score of 2.5 or more points on the MNSI and the presence of at least four neuropathic-positive symptoms. Statistical analysis was performed using the SPSS program for Windows, version 18.0. Initially, continuous variables were tested using the Shapiro-Wilk test to verify normality, and then, according to the distribution found, the appropriate test (Student's t test or Mann–Whitney U test) was applied. Categorical data on the prevalence of neuropathy between groups were compared by Yates Test (Continuity Correction) or Pearson's test when appropriate. Differences were considered statistically significant at $p \leq 0.05$. At the end, we looked for independent associations between individual variables and the occurrence of PNP by using multiple logistic regression analysis (Poisson). Variables that showed a p value lower than 0.2 in the univariate analysis were added to the regression model.

Results

The sample of the present study was composed of 450 SO women with a median age of 36 years (29.9–43.0). The prevalence of grade III obesity was 60.5% ($n = 271$). Of the 546 women recruited, 96 (17.5%) met one or more of the exclusion criteria and were therefore withdrawn from the study. The predominant ethnicity was Caucasian (78.8%) ($n = 373$).The prevalence of PNP [PNP (+) group] in the included women was 11.6%. In premenopausal women, it was 8.4% ($n = 32/379$) and in the postmenopausal group, 28.1% ($n = 20/71$) ($p < 0.001$). Table 1 describes the clinical and anthropometric data and all quantitative variables of the participants according to the occurrence or not of PNP (88.4% without PNP, $n = 398$ and 11.6% with PNP, $n = 52$).

The two groups [PNP (+) and PNP (−) groups] did not differ in body weight, height, BMI, WC, energy expenditure, serum levels of HbA1C, HDL-cholesterol, LDL-cholesterol, triglycerides, creatinine, and vitamin B12 ($p > 0.05$).

Table 1 Univariate associations of quantitative variables analyzed, according to the presence [PNP (+)] or absence [PNP (−)] of polyneuropathy in obese (grades II and III) women

	Group (n = 450)			
		PNP (−) (n = 398)	PNP (+) (n = 52)	p value*
Age (years)	36.0 [29.9–43.0]	35.0 [29.0–42.0]	44.0 [35.0–52.7]	< 0.001*(b)
Body weight (kg)	107.0 [98.5–119.0]	107.5 [98.6–119.4]	103.9 [98.3–117.5]	0.498 (b)
Stature (m) MD ± SD	1.61 ± 0.06	1.61 ± 0.06	1.61 ± 0.06	0.506 (a)
BMI (kg/m^2)	40.9 [38.3–44.4]	41.0 [38.1–44.3]	41.0 [37.8–45.9]	0.881(b)
Waist circumference (cm)	108.0 [102.0–115.0]	107.0 [102.0–115.0]	111.0 [103.5–117.5]	0.139 (b)
Neck circumference (cm)	38.0 [36.0–39.5]	37.5 [36.0–39.5]	38.5 [37.0–39.9]	0.049* (b)
Fasting plasma glucose (mg/dL)	91.0 [85.0–99.0]	91.0 [85.0–99.0]	94.0 [86.2–100.7]	0.253 (b)
Plasma glucose after oral glucose (mg/dL)	115.0 [96.0–136.0]	116.0 [96.0–137.0]	108.5 [92.7–134.7]	0.286 (b)
Glycated hemoglobin (%)	5.4 [5.1–5.6]	5.35 [5.1–5.6]	5.4 [5.1–5.6]	0.737 (b)
LDL-cholesterol (mg/dL)	112.4 [92.7–133.8]	112.4 [91.8–133.8]	114.2 [91.9–133.4]	0.547 (b)
HDL-cholesterol (mg/dL)	48.0 [42.0–57.0]	48.0 [42.0–57.0]	48.0 [43.0–57.0]	0.605 (b)
Triglycerides (mg/dL)	124.5 [87.5–171.0]	125.0 [88.0–176.0]	121.0 [74.0–156.0]	0.297 (b)
Vitamin B12 (pg/ml) without supplementation	385.3 [304.4–485.3]	385.0 [301.5–497.7]	434.0 [311.2–498.0]	0.405 (b)
Serum creatinine (mg/dL)	0.69 [0.60–0.77]	0.69 [0.60–0.77]	0.67 [0.60–0.76]	0.698 (b)
Duration of physical activity (minutes/week)	115 [30.0–241.2]	112 [30.0–246.0]	120 [30.0–240.0]	0.976 (b)
METs (min/week)	396.0 [99.0–1034.0]	396.0 [99.0–1059.0]	417.0 [99.0–918.0]	0.987 (b)

Variables were summarized as mean and standard deviation or median and interquartile amplitude (percentiles 25–75). Tests comparing PNP (+) and PNP (−): a t test (a) was used in the case of a symmetrical distribution, and a Mann–Whitney U test (b) was used when the distribution was asymmetric
PNP (+) = MNSI ≥ 2.5 e ≥ 4 symptoms; n = number of subjects. * Statistical significant = $p < 0.05$

Variations in age and neck circumference were highest in the group who had PNP ($p < 0.001$ and $p = 0.049$, respectively).

Table 2 shows the distribution of categorical variables in the PNP (−) and PNP (+) groups. Only an occurrence of menopause and the presence of systemic arterial hypertension (SAH) were associated with the presence of PNP ($p < 0.001$ and $p = 0.016$, respectively). The risk of OSA (STOPBANG score ≥ 3) was also highest in the PNP (+) group ($p = 0.101$).

Table 3 presents the results of a multiple regression model (Poisson) including all variables with $p < 0.2$ (PM status, age, presence of SAH, and risk of OSA). In two different models, only the PM status (2.836, 95% CI 1.735–4.636, $p < 0.001$) and age (PR 1.051, 95% CI 1.031–1.071, $p < 0.001$) were independently associated with the presence of PNP in women with SO ($p < 0.001$).

Discussion

In the present study, in SO nondiabetic women, PNP had a prevalence of 11.6% and was associated with menopause and age in univariate analysis. In order to better understand which variables were independently associated with PNP, we used a multivariate model and looked for factors that had a greater risk of bias (OSA risk, age, PM status, and having a diagnosis of SAH). Our results showed that PNP in SO women was independently and strongly associated with PM status and age.

As in our study, Ziegler et al. showed a high prevalence of age-related PNP when the prevalence of PNP was compared between subjects with T2DM (28.0%), ITG (11.3%), fasting hyperglycemia (13.0%), and normoglycemia (7.4%) [8]. In another publication, the authors showed that for every centimeter increase in WC, there was a 4% increase in the likelihood ratio (LR) of PNP [18]. In this way, WC was considered as independently associated with the presence of PNP in this and other studies [8, 19–22].

In other studies, when subjects with and without diabetes were evaluated for PNP [1], it was reported that height was positively associated with the presence of PNP. A possible explanation for the lack of difference in our study is that height is associated with the PNP of diabetes but not to the PNP of obesity or could also be because the stature variation in our sample is not high: 95% CI of 1.60–1.62 compared to 95% CI of 161.5–181.5 observed by Cheng et al. [18].

Studies with skin biopsies evaluating the improvement of cutaneous innervation have demonstrated that the adoption of strategies such as adherence to a PA regimen are effective in the prevention and progression of PNP in pre-diabetic patients [23]. In our study, we evaluated the practice of regular PA in SO women, and it was not different between positive and negative PNP groups ($p = 0.987$).

Table 2 Univariate associations between categorical variables analyzed, according to the presence [PNP (+)] or absence [PNP (−)] of polyneuropathy in obese (grades II and III) women

Categorical variable		Groups				
		PNP (−) ($n = 398$)		PNP (+) ($n = 52$)		
	N (%)	*n*	(%)	*n*	(%)	*p* value*
Post menopause	71 (15.8)	51	(12.8)	20	(38.5)	< 0.001*(a)
Hypertension diagnosis	447 (54.6)	207	(52.4)	37	(71.2)	0.016* (a)
Physical activity ≥ 150 min	446 (42.4)	167	(42.4)	22	(42.3)	1.000 (a)
IPAQ classification	445		(100.0)		(100.0)	0.866 (b)
Sedentary	60 (13.5)	53	(13.5)	07	(13.5)	
Insufficiently active	234 (52.6)	205	(52.2)	29	(55.8)	
Active	151 (33.9)	135	(34.4)	16	(30.8)	
METs (week /minutes)	444	392	(100.0)	52	(100.0)	0.939 (b)
Low	275 (61.9)	242	(61.7)	33	(63.5)	
Moderate	102 (23.0)	90	(23.0)	12	(23.1)	
High	67 (15.1)	60	(15.3)	07	(13.5)	
Sleep Apnea Risk STOPBANG+ ≥ 3	450 (70.0)	273	(68.6)	42	(80.8)	0.101 (a)

*Statistical significance = $p < 0.05$

Numbers presented are the number of patients with percentages between parentheses. Units are also between parentheses

N: absolute frequency; *n*%: relative frequency; (a) Yates continuity correction test. (b) Pearson chi-squared test

PNP (+) = MNSI ≥ 2.5 and ≥ 4 symptoms; *n* = number of patients

OSA is highly prevalent in patients with obesity, and recurrent intermittent hypoxemia in OSA has been identified as an independent risk factor for axonal damage of peripheral nerves, which may lead to PNP [24, 25]. In our study, the risk for OSA assessed by the STOPBANG questionnaire only showed a trend toward an association with PNP ($p = 0.101$), and in the multivariate analysis, there was no association. Given the current data, we cannot, however, rule out the possibility of a higher incidence of OSA among obese neuropathic patients, since an objective measure of the presence of apnea (polysomnography) was not performed in the present study.

Regarding the presence of SAH, studies have found a positive association with the presence of PNP of T2DM [1, 3]. In the women of the present study, the presence of SAH was significantly associated with the presence of PNP in univariate analysis; however, this relationship was not maintained in multivariate analysis.

In summary, our results indicate that PNP in SO subjects is probably occurring as a result of obesity, PM status, and age. In our study, a collinearity was observed between PM status and age (data not shown) and because of that, it is not possible to define which factors associated with aging (e.g., decrease in estrogens or others, like increased body fat) are more important for inducing PNP in obese woman.

Table 3 Regression analyses (Poisson) of variables apparently related to the dependent variable polyneuropathy (PNP)

Variables	PNP (+) (%) ($n = 447$)			
	Model 1 ($p < 0.001$*)		Model 2 ($p < 0.001$*)	
	PR (IC 95%)	*P*-valor	PR (IC 95%)	*P*-valor
Post menopausal status	2.836 (1.735–4.636)	< 0.001*	NA	NA
Age (years)	NA	NA	1.051 (1.031–1.071)	< 0.001*
Diagnosis of hypertension	1.599 (0.898–2.846)	0.111	1.465 (0.843–2.546)	0.176
Risk of positive apnea	1.278 (0.648–2.846)	0.479	1.203 (0.605–2.392)	0.598

*Statistical significance = $p < 0.05$

Conclusion

In nondiabetic SO women, without common nutritional disturbances, dysfunction of the lower limb nerve fibers is high and independently associated with PM status and age. Since we showed a high prevalence of PNP in patients with SO, in addition to some descriptions of increased occurrence of PNP after BS, we suggest that subjects who are candidates for BS should be evaluated for PNP, even if they do not have any measurable nutritional deficits or other diseases that are known to trigger PNP or lead to its progression. This procedure could better define the etiology, evolution, and treatment of PNP in each patient.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval The study was approved by the Ethical Committee of the participating hospital.

Informed Consent Written informed consent was obtained for each participant in the study.

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