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Obstructive sleep apnea syndrome risk in patients with non-alcoholic fatty liver disease is associated with obesity and presence of NASH

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ABSTRACT – Background – Non-alcoholic fatty liver disease (NAFLD) is the most common form of liver disease and refers to a wide spectrum of histological abnormalities ranging from simple steatosis (HE) to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and hepatocellular carcinoma. **Objective –** To assess the risk of obstructive sleep apnea syndrome (OSAS) and relating it to demographic, biochemical and histological data in patients with non-alcoholic fatty liver disease. **Methods –** Cross-sectional cohort study in individuals with biopsy-proven NAFLD. Anthropometric and biochemical parameters, presence of metabolic syndrome and insulin resistance were evaluated. The Berlin Questionnaire (BQ) was applied to assess the risk of apnea and a food record was requested. Based on the BQ, participants were classified as high or low risk for OSAS. In the correlation of sleep apnea with the severity of NAFLD, presence of nonalcoholic steatohepatitis (NASH) and the degree of liver fibrosis were evaluated. Statistical analysis used the chi-square test, Student's *t* and bivariate logistic regression; values were expressed as mean ± standard deviation. This research project was approved by the Ethics Committee. **Results –** Regarding the parameters evaluated, significant differences were observed between the groups in terms of body mass index (BMI), waist and neck circumference. In the histological evaluation, patients classified as high risk were more likely to have fibrosis and NASH. In bivariate regression, the BMI, presence of fibrosis and steatohepatitis in the biopsy were independently associated with an elevated risk of the syndrome. **Conclusion –** A high prevalence of risk for OSAS was observed in the studied group, with a higher risk being independently associated with BMI and presence of steatohepatitis, suggesting that it is a factor associated with the severity of the disease.

Keywords – Obstructive sleep apnea syndrome; Berlin Questionnaire; non-alcoholic steatohepatitis; liver fibrosis.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common form of liver disease and refers to a wide spectrum of histological abnormalities ranging from simple hepatic steatosis (HE) to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and hepatocellular carcinoma[1]. It is estimated that approximately 30% of adults in industrialized societies have the disease, whereas in obese diabetic individuals, this prevalence can reach 60% to 80%[2].

An association of the disease is observed mainly with visceral obesity, type 2 diabetes mellitus (DM2) and dyslipidemia, factors also related to the presence of the metabolic syndrome (MS)[3]. More than 90% of NAFLD patients have at least one characteristic of MS, and approximately one-third of them have complete syndrome[4].

OSAS is characterized by recurrent episodes of total (apnea) and/or partial (hypopnea) obstruction of the airflow through the upper airways during sleep, generating elevated negative intrathoracic pressure, intermittent hypoxia and severe sleep fragmentation[5]. Its diagnosis is based on the number of episodes of apnea and/or hypopnea and is considered to have the disease if the apnea and hypopnea index (AHI) is ≥5 events/hour of sleep[6].

The prevalence of OSAS classified as moderate (15 to 30 AHI / hour) and severe (>30 AHI / hour) among adults is approximately 15% in males and 5% in females in the general population[7]. In the presence of overweight and MS, these data increase considerably and may affect 50% to 60%, and in patients with obesity with DM2 and those with grade 3 obesity (BMI ≥40 kg/m^2); this percentage can reach 86%[8].

Due to the metabolic changes present in OSAS being common to those observed in patients with NAFLD, it was not surprising that initial studies showed an increase in the frequency of OSAS in patients with NAFLD[9,10], reinforced by more recent research, which suggests the existence of a pathogenic relationship between these two diseases. The chronic intermittent hypoxia observed in OSAS can cause hepatic steatosis (HE) and inflammation even in the absence of obesity by elevating pro-inflammatory cytokines, causing endothelial dysfunction, accentuating oxidative stress, insulin resistance and dyslipidemia, factors that contribute to the worsening of NAFLD and its progression to NASH[11,12].

Although polysomnography is the gold standard for the diagnosis of OSAS, several instruments have been validated in clinical practice to facilitate the screening of patients, the most recognized being the Berlin Questionnaire (BQ), specifically designed to identify risk for development of OSAS, being considered a simple and reliable method to track OSAS[12-15].

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This study aimed to assess the risk of OSAS in patients with NAFLD by applying the BQ and relating this risk to demographic, biochemical and histological characteristics of NASH.

METHODS

This was a cross-sectional cohort study in patients with NAFLD diagnosed by current or previous liver biopsy seen at the liver disease outpatient clinic of the Clinical Gastroenterology Discipline of the Federal University of São Paulo.

The exclusion criteria included patients using hepatotoxic drugs; ethanol consumption ≥40 g/day for men and 20 g/day for women; decompensated DM2; untreated hypothyroidism; positive serological markers for the presence of B or C viruses; concomitant liver disease such as autoimmune hepatitis, alpha1-antitrypsin deficiency, Wilson's disease and others and the presence of chronic systemic diseases clinically recognized.

Patients with liver biopsy performed previously, for a period not exceeding 12 months, were included in the study as long as they did not present weight loss equal to or greater than 7% of their body weight at the time of the biopsy in relation to the time of application of the questionnaire[16]. In liver biopsy, the presence or absence of NASH was defined according to Brunt et al.[17], and the staging of the disease was defined according to the criteria of Kleiner et al.[18].

Biochemical tests were performed using the automated kinetic method in Cobas Mira (Roche, Switzerland). The insulin concentration was determined by immunofluorimetry and the assessment of the insulin resistance index (IR) by the homeostatic method (HOMA-IR - Homeostasis Model Assessment Insulin Resistance)[19].

The presence of MS in the population was evaluated according to the criteria of the NCEP-ATP III[20].

The patients included in the study were submitted to anthropometric and food consumption assessments. Weight and height were evaluated to calculate the body mass index (BMI), waist circumference (WC) and neck circumference (NC) according to established criteria[21]. The reference values adopted for WC were those suggested by NCEP-ATP III[20], and for the neck cutoff values determination, the receiver operating characteristic (ROC) curve were utilized for a more specific assessment of the studied population.

Food consumption was assessed by calculating a 3-day food record[22], with quantification of total calories, macronutrients (proteins, carbohydrates and lipids, including saturated, monounsaturated, polyunsaturated and cholesterol) and dietary fibers. The calculations were performed and analyzed by a computerized system using the "NutWin" software[23].

The BQ was used to assess the risk of OSAS[13]. Statistical calculations were obtained using the "Statistical Package for Social Sciences" (SPSS version 16.0), and the descriptive data of the samples were expressed as the mean ± standard deviation (mean ± SD). To compare the categorical variables of the general characteristics between the groups, chi-square or Fisher's exact tests were used. In the others, Student's *t*-test was used for continuous variables. To identify the variables independently associated with a higher risk of obstructive sleep apnea, a stepwise bivariate logistic regression model was designed.

This research project was approved by the Ethics Committee of the Federal University of São Paulo and the participants received detailed information about the research. When they agreed, they signed the Free and Informed Consent Form in accordance with the rules of the Helsinki treaty.

RESULTS

The BQ was applied to 155 individuals of both sexes, aged 18 years or older, with non-alcoholic fatty liver disease diagnosed by liver biopsy. After applying the questionnaire, 74.8% (n=116) of the assessed population was classified as high risk and 25.2% (n=39) as low risk for OSAS.

In the comparative study between the high- and low-risk groups, we found no significant differences in terms of age and sex. The values of BMI and NC however were significantly higher in the group classified as high risk for OSAS (TABLE 1).

TABLE 1. Demographic and anthropometric characteristics of the population studied.

	High risk (n=116)	Low risk (n=39)	*P*
Age (years)	55.2±11.0	55.7±8.9	0.809
Sex feminine n (%)	74 (63.8%)	25 (64.1%)	0.972
BMI (kg/m^2)	31.6±5.0	29.0±3.4	0.003
% NC (cm)	70 (81/116)	51 (20/39)	0.035
% WC (cm)	86 (100/116)	72 (28/39)	0.058

n: number; BMI: body mass index; NC: neck circumference - cutoff values of 40.3 cm for women and 43.6 cm for men; ROC curve. WC: waist circumference. Values expressed as mean ± SD. $P<0.05$.

In the analysis of liver enzyme levels and biochemical markers of carbohydrate metabolism and circulating lipids, as well as albumin values, there were no significant differences between the groups studied (TABLE 2), the same being observed in relation to the food consumption of the analyzed nutrients (TABLE 3).

TABLE 2. Biochemical characteristics of the studied population.

	High risk (n=116)	Low risk (n=39)	*P*
AST (IU/L)	33.5±19.2	32.6±22.7	0.826
ALT (IU/L)	42.7±28.7	42.7±35.3	0.998
GGT (IU/L)	77.9±93.9	66.6±83.4	0.475
Glucose (mg/dL)	112.9±35.9	118.0±33.8	0.416
Insulin (mU/mL)	12.7±12.1	10.1±6.8	0.098
HOMA – IR*	3.8±4.6	3.1±2.8	0.321
Total Cholesterol (mg/dL)	195.7±42.3	202.8±39.2	0.339
LDL (mg/dL)	114.7±32.4	118.0±36.7	0.507
HDL (mg/dL)	46.1±12.2	50.6±17.3	0.137
Triglycerides (mg/dL)	175.5±95.2	165.7±77.5	0.520
Albumin (g/dL)	4.4±0.4	4.6±0.5	0.128

n:number; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl-transpeptidase; LDL: low density lipoprotein; HDL: high density lipoproteins. *HOMA-IR: Homeostasis Model Assesment insulin resistance, adopting the formula: fasting insulin (mU/mL) x fasting glycemia (nmol/L) / 22.5. Values are expressed as mean ± SD. $P<0.05$.

TABLE 3. Food consumption of OSAS patients in both groups.

	High risk (n=116)	Low risk (n=39)	*P*
TCV (kcal)	1666±566	1567±458	0.270
Carbohydrates (g)	212±91	191±77	0.145
Protein (g)	77.5±38.4	78.0±31.4	0.778
Lipids (g)	60.3±35.2	56.5±31.2	0.335
TC (mg)	201.3±146.3	204.6±255.4	0.919
SFA (mg)	16.3±9.1	15.0±9.1	0.307
MFA (mg)	23.3±29.7	18.1±10.5	0.141
PFA (mg)	16.0±7.4	15.6±8.4	0.707
Dietary fiber (g)	15.8±10.9	13.7±7.60	0.097

OSAS: obstructive sleep apnea syndrome; n: number; TCV: total caloric value; TC: total cholesterol; SFA: saturated fatty acids; MFA: monounsaturated fatty acids; PFA: polyunsaturated fatty acids. Values are expressed as mean ± SD. $P<0.05$.

Regarding the histological findings associated with the progression of liver disease (steatohepatitis and degree of fibrosis), the prevalence of NASH in those classified as high risk was 62.1% versus 35.8% in the low-risk group, a difference that reached statistical significance. The presence of fibrosis and advanced fibrosis was also significantly more frequent among patients at high risk of OSAS when compared to the group at low risk (TABLE 4).

TABLE 4. Presence of steatohepatitis and degree of fibrosis in groups with high and low risk for OSAS according to liver biopsy.

Histological finding*	High risk n (%)	Low risk n (%)	*P*
NASH	72/116 (62.1)	14/39 (35.8)	0.004
Fibrosis (F1–F4)	73/116 (62.9)	15/39 (38.5)	0.008
Significant fibrosis (F2–F4)	33/116 (28.5)	6/39 (15)	0.158
Advanced fibrosis (F3–F4)	19/116 (16.4)	2/39 (5.1)	0.014

n: number. *Degree of fibrosis according to the classification of Kleiner, et al., (2005). NASH: non-alcoholic steatohepatitis according to Brunt et al., (1999). Values are expressed as n (%). $P<0.05$.

To assess which factors are independently associated with the risk of apnea and due to the characteristics of the factors involved, stepwise binary logistic regression analysis was used, and the BMI variable was used as a continuous variable. The TABLE 5 shows that the factors associated with the high risk of apnea with statistical significance were BMI and NASH.

TABLE 5. Binary logistic regression of factors associated with high risk of apnea.

Parameter	RR	CI95%	*P*
BMI (continuous)	1.143	(1.040–1.256)	0.006
NASH (present/ absent)	2.950	(1.355–6.420)	0.006

BMI: body mass index; NASH: non-alcoholic steatohepatitis, RR: risk ratio, CI95%: confidence interval. $P<0.05$. Step 1: BMI; Step 2: BMI + NASH.

DISCUSSION

Although the gold standard for the diagnosis of OSAS is polysomnography, some scales have been validated and used in clinical practice as noninvasive tools to assist in the screening of patients at risk for OSAS[24,25]. Netzer et al.[13] validated the BQ as a screening test, applying it to more than 700 individuals and comparing the result of the questionnaire with the polysomnography test and concluded that it showed high reproducibility (alpha coefficient of Cronbach correlations 0.86–0.92), with a predictive value of 89% for OSAS in patients classified as high risk. The results were confirmed in other studies, such as that by Sharma et al.[26], who found sensitivity and specificity above 85% for the application of BQ[13,26]. These findings have been questioned in other studies, such as that by Chung et al.[27] with a sensitivity of 69% and specificity of 56% for the BQ. Differences in the selection of studied populations and in the cutoff values in the number of AHIs are some of the reasons for these disagreements. In general, the Berlin questionnaire overestimates the diagnosis of OSAS due to its lower specificity[28]. Thus, other tests have appeared in the literature for the diagnosis of patients with apnea/hypopnea syndrome, theoretically presenting greater specificities for this diagnosis[28,29]. However, two comparative meta-analyses concluded that the Berlin questionnaire is the most suitable test for assessing the general population and that it has been shown to be effective in situations that make it difficult to access polysomnography[29,30].

OSAS and NAFLD share several similarities with respect to the affected population. Both have an increased prevalence of obesity, MS and DM2[31].

In the city of São Paulo, Brazil, an epidemiologic study where 1042 adult volunteers underwent polysomnography, the diagnosis of OSA was found in 32.8% of the population with increased risk rate for obesity and male sex, as found by others[32].

NAFLD patients also have a high prevalence of OSA, being higher than that of the general population when the risk questionnaires are applied, although with wide variation values, between 33% and 70%[9,33,34]. Even studies with polysomnography confirm high rates of apnea in this group of patients, such as that by Cakmak et al.[35], who found OSAS in 86% of their 137 NAFLD patients. In relation to food consumption, some studies have linked the intake of saturated fatty acids above recommended levels to sleep apnea[35]. Although we observed high consumption of saturated fatty acids in the high-risk group, this difference was not significant, as well as for the other nutrients evaluated in this research.

High BMI values were also observed in this study in patients at high risk for OSAS when compared with the low-risk group, with significant differences. This difference was even more pronounced when the BMI was categorized for the presence of overweight or obesity (data not shown). Expected results since BMI value compatible with obesity is one of the parameters that make up the BQ.

WC and NC were other factors that were associated with a high risk for OSAS in the univariate analysis. The deposition of fat in the neck region favors increased resistance in the upper airways, making the pharynx region more easily collapsible[36,37]. Elevated abdominal fat deposits have a negative impact on the upper airways, as in addition to decreasing their function, they also reduce their diameter[38,39]. Degache et al.[40] observed a significant correlation between BMI, NC and visceral obesity with AHI, corroborating the results found in this study. Liu et al.[41,42] reported similar results, in which the NC, the thickness of the subperitoneal, subcutaneous and

mesenteric fat presented a positive association with the presence of moderate and severe OSAS. In the same sense, Tan et al.[36] found evidence that visceral obesity is related to the severity of OSAS. Glicksman et al.[39] also demonstrated a relationship between the severity of OSAS and BMI and the percentage of neck-abdomen fat in adolescents. Only Turnbull et al.[40] and Kawaguchi et al.[43] found no association between the severity of OSAS and central obesity or BMI. Huang et al.[44], in a study with 4053 participants, showed that increased NC value was associated with a higher prevalence of NAFLD, the same result obtained by Hu et al.[45].

Finally, in our study, we observed a positive association between high risk for OSAS and three parameters of NAFLD severity: NASH, the presence of any degree of fibrosis (F1-F4) and advanced fibrosis (F3-F4). Petta et al.[34], when evaluating 126 Italian NAFLD patients using BQ and a polysomnographic study in part of the participants, reported an increased prevalence of significant fibrosis (F2-F4) in patients with OSAS, although these factors have not been independently associated in the multivariate analysis. Pulixi et al.[33] also reported an independent association between high risk for OSAS and the presence of fibrosis. Bernsmeier et al.[46], in the evaluation of 46 NAFLD patients diagnosed by liver biopsy, found a relationship between fibrosis and mainly advanced fibrosis with somnolence during the day according to the Epworth Sleepiness scale. Contrary to these findings, Minville et al.[47], using noninvasive tests, found only a relationship between the presence of steatosis and severe nocturnal hypoxia but not with the presence of fibrosis.

Importantly, the association with NASH has been more frequently observed. Asfari et al.[10], bringing together almost 1.5 million cases with apnea, demonstrated that, even after adjusting for metabolic risk factors, the presence of OSAS increased three times the chance of the patient presenting non-alcoholic steatohepatitis. This association was also found in the studies by Mishra et al.[11] and Polotsky et al.[12]. Even in the study by Minville et al.[47] previously mentioned, this relationship was observed, although only in the univariate analysis.

Musso et al.[48], in a meta-analysis with 18 studies, found an important association between OSAS, the presence of NASH, fibrosis of any degree and advanced fibrosis in 10 studies where the participants underwent liver biopsy, in agreement with our univariate analysis. In this meta-analysis, the presence of OSAS increased the risk of NASH and fibrosis by more than 2 times. In another meta-analysis where these same findings mentioned above were confirmed, there was also an increase in the levels of liver enzymes (ALT and AST) that we were unable to observe in our patients[49]. Finally, Corey et al.[50] carried out a study in 213 individuals with indications for bariatric surgery, where polysomnography was performed for the diagnosis of OSAS and liver biopsy for NAFLD staging, and concluded that patients with OSAS had a higher prevalence of NASH and liver fibrosis.

Although our study is a cross-sectional study, in most cases, the BQ was applied after a liver biopsy was taken, that is, in patients with clinical and biochemical indications of a more serious disease, which can be a factor of error in population selection. Additionally, due to this fact, we avoided evaluating individual histological parameters by choosing to evaluate only the diagnosis of NASH and the staging of fibrosis, excluding patients with weight loss >7% of the study, as this value has been identified as a cutoff for regression of NASH in patients with NAFLD[18]. Finally, the inclusion of BMI in the analysis of binary regression should be discussed, since BMI ≥30 kg/m^2 is one of the items for counting points in the BQ. However, the relevant prevalence of obesity in OSAS cases assessed by direct methods, such as polysomnography, leaves no doubt about the importance of this parameter in the incidence of the syndrome[12, 39-41], which makes it impossible to assess the association of any other factor on the risk of OSAS, without a correction for the presence of obesity. In addition, we chose to use BMI as a continuous variable in the regression analysis, avoiding the categorization used in the BQ.

CONCLUSION

In summary, the prevalence of OSAS, according to the BQ, was high in the patients with NAFLD (74.8% of cases) studied. A higher risk for OSAS was independently associated with BMI and the presence of steatohepatitis in liver biopsy, suggesting that OSAS is a factor associated with the severity of the disease.

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Authors' contribution

Grillo PM: Conceptualization; data curation; funding acquisition; methodology; project administration; writing, original draft; writing, review and editing. Punaro GR: writing, review and editing. Elias MC: data curation; formal analysis; investigation; methodology; writing, review and editing. Parise ER: conceptualization; data curation; formal analysis; funding acquisition; supervision; writing, review and editing.

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Grillo PM, Punaro GR, Elias MC, Parise ER. O risco de síndrome de apneia obstrutiva do sono em pacientes com doença hepática gordurosa não alcoólica está associado à obesidade e à presença de NASH. Arq Gastroenterol. 2022;59(2):251-6.

RESUMO – Contexto – A doença hepática gordurosa não alcoólica (DHGNA) é a forma mais comum de doença hepática e se refere a um amplo espectro de anormalidades histológicas que variam de esteatose simples a esteato-hepatite não alcoólica (EHNA), fibrose, cirrose e carcinoma hepatocelular. **Objetivo –** Avaliar o risco de síndrome da apneia obstrutiva do sono (SAOS) e relacioná-lo com dados demográficos, bioquímicos e histológicos em pacientes com doença hepática gordurosa não alcoólica. **Métodos –** Estudo de coorte transversal em indivíduos com DHGNA comprovada por biópsia. Foram avaliados parâmetros antropométricos e bioquímicos, presença de síndrome metabólica e resistência à insulina. O Questionário de Berlim (QB) foi aplicado para avaliar o risco de apneia e um registro alimentar foi solicitado. Com base no QB, os participantes foram classificados como de alto ou baixo risco para SAOS. Na correlação da apneia do sono com a gravidade da DHGNA, avaliou-se a presença de EHNA e o grau de fibrose hepática. Na análise estatística foram utilizados: o teste qui-quadrado, *t* de *Student* e regressão logística bivariada; os valores foram expressos como média ± desvio padrão. Este projeto de pesquisa foi aprovado pelo Comitê de Ética. **Resultados –** Em relação aos parâmetros avaliados, foram observadas diferenças significativas entre os grupos em relação ao índice de massa corporal (IMC), cintura e circunferência do pescoço. Na avaliação histológica, os pacientes classificados como de alto risco tiveram maior chance de apresentar fibrose e EHNA. Na regressão bivariada, o IMC, a presença de fibrose e esteato-hepatite na biópsia foram independentemente associados a um risco elevado da síndrome. **Conclusão –** Observou-se alta prevalência de risco para SAOS no grupo estudado, sendo o maior risco associado de forma independente ao IMC e à presença de esteato-hepatite, sugerindo que seja um fator associado à gravidade da doença.

Palavras-chave – Síndrome da apneia obstrutiva do sono; Questionário de Berlim; esteato-hepatite não alcoólica; fibrose hepática.

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