THE ASSOCIATION OF THE SEVERITY OF OBSTRUCTIVE SLEEP APNEA AND NON-ALCOHOLIC FATTY LIVER DISEASE

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Significance: 12.2% of 1,102 Filipinos in a local hospital have non-alcoholic fatty liver disease (NAFLD). Evidence suggests that chronic intermittent hypoxia in obstructive sleep apnea (OSA) leads to NAFLD. Apnea-hypopnea index, oxygen desaturation index, lowest desaturation values, and percentage of sleep duration with S_{pO2} <90% are said to predict NAFLD. This study aimed to determine the association of severity of OSA and NAFLD. Apnea-hypopnea index, lowest oxygen saturation and mean nocturnal oxygen saturation were also correlated with the NAFLD.

Methodology: This was a cross-sectional, single-center study involving adults diagnosed with obstructive sleep apnea by overnight polysomnography with records that include body mass index, liver ultrasound, liver function tests, and lipid profile. Subjects with excess alcohol consumption, use of hepatotoxic drugs, viral hepatitis and other chronic liver diseases were excluded. Comparison of the proportion of severity of NAFLD, demographics and clinical parameters with of severity of OSA, and parameters of OSA with NAFLD were analyzed using Chi-square and odds ratio.

Results: 281 subjects were included. The relationship between severity of OSA and severity of NAFLD is insignificant (p-value=0.368). Gender, ALT and BMI were significantly related to severity of OSA. All parameters of OSA had significant p-values, however, a pre-test for homogeneity revealed that only the lowest O_2 saturation was homogenous.

Conclusion: There is no association between OSA and NAFLD which may be due to the inhomogenous sample size, difference in readings by different ultrasonographists using different machines and ultrasonography being used as a substitute for biopsy.

Keywords: Non-alcoholic fatty liver disease, Obstructive Sleep Apnea, Ultrasonography

The Association of the Severity of Obstructive Sleep Apnea and Non-alcoholic Fatty Liver Disease

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a prevalent disease worldwide. The prevalence of NAFLD in the United States is 5% in the general population and 25%-75% in patients with obesity and type 2 diabetes mellitus. In the Philippines, data regarding the epidemiology of NAFLD in the general population is still quite scarce. A study done by De Lusong et al. in 2008 revealed a prevalence of 12.2% among 1,102 patients at the Philippine General Hospital[1]. Of these patients, 71% were female and 29% were male, with a mean age of 42.2 years old. Sixty percent were obese, 56% had hepatomegaly, and 69% had diabetes. AST levels were elevated in 45% of subjects and ALT levels in 64%. NAFLD encompasses a spectrum of liver diseases, including fatty liver, steatohepatitis, and even cirrhosis, in the absence of alcohol intake. Nonalcoholic steatohepatosis (NASH) can lead to cirrhosis, hepatocellular carcinoma and the need for liver transplantation.

Similarly, obstructive sleep apnea (OSA) is a common but under-recognized disorder. Obstructive sleep apnea syndrome (OSAS) is characterized by abnormal apnea-hypopnea index (AHI), which indicates the severity of sleep apnea in terms of the number of apnea and hypopnea events per hour of sleep, and symptoms of excessive daytime sleepiness (EDS). It is present in 2% of women and 4% of men living in Western communities.[2] If these prevalence rates are applied to the local population, the extrapolated prevalence of OSA in the Philippines is approximately 3,804,780.[3] In the Philippines, there is still no prevalence data for OSA. A cross sectional study of 344 Filipino patients with clinical suspicion of OSA and who all underwent nocturnal polysomnography was done in a sleep disorders laboratory of a tertiary medical center in 2003.[4] The within-laboratory prevalence of OSA was 62%. Body mass index, snoring affecting others and daytime sleepiness were found to be significant predictors for OSA.

Increasing evidence has suggested that the pathophysiological alteration in gas exchange, specifically, repetitive hypoxemic and hypercapnic events, called chronic intermittent hypoxia (CIH), can lead to increased proinflammatory cytokine production, endothelial dysfunction, oxidative stress, metabolic dysregulation, and insulin resistance. Subsequently, the association of OSAS to NAFLD is being investigated. Experimental evidence suggests that CIH may trigger liver injury, inflammation, and fibrogenesis.[5] Furthermore, OSAS is also believed to be one of the elements that contribute to the evolution of NAFLD from steatosis to NASH.[6,7,8] A study done by Turkay et al. showed that AHI, oxygen desaturation index, lowest desaturation values, and percentage of sleep duration with S_{pO2} <90% were independent predictors of NAFLD after adjustment for BMI, weight and insulin resistance.[9] Furthermore, the most correlated parameter for the severity of NAFLD was found as the duration of hypoxia during sleep. In addition to this, Cakmak et al. revealed that mean nocturnal S_{pO2} values were significantly lower in mild NAFLD and severe NAFLD compared to a non-NAFLD group.[10] There have also been studies that show that a proportion of NAFLD patients without severe obesity is at risk for OSAS with daytime sleepiness, which is likewise associated with the severity of liver damage, independently of body mass and other cofactors.[11]

Problem Statement

Obstructive Sleep Apnea may be a causal factor in the development of NAFLD. Furthermore, it may contribute to the progression towards NASH, liver cirrhosis and hepatocellular carcinoma.

Research Question

Are patients with obstructive sleep apnea at risk for developing NAFLD?

Significance

Addressing the problem of obstructive sleep apnea may decrease the risk for developing NAFLD or progression to NASH, cirrhosis, or even hepatocellular carcinoma.

Objectives

The primary objective of this study was to determine the association of the severity of obstructive sleep apnea and non-alcoholic fatty liver disease.

The secondary objective of this study was to determine the association between the degree of NAFLD and severity of OSA. Severity of OSA (mild, moderate, severe), apnea-hypopnea index (AHI), lowest oxygen saturation and mean nocturnal oxygen saturation were correlated with the severity of NAFLD.

Scope and Limitations

This is a study that determined the prevalence of NAFLD in patients diagnosed with OSA by polysomnography at the Sleep Center of St. Luke's Medical Center, Quezon City. It did not tackle the efficiency of treatment regimens for OSA on liver disease. Patients with NAFLD were diagnosed by liver ultrasound as an alternative to liver biopsy[12, 13]

REVIEW OF RELATED LITERATURE

The key feature in the pathophysiology of OSAS is chronic intermittent hypoxia. The mechanism is similar to the ischemia-reperfusion injury. In OSAS, oxidative stress markers are augmented and subsequently instigate inflammation, endothelial dysfunction, and atherosclerosis. Recent studies have focused on the effects of hypoxia on metabolic pathways and on mechanisms of cell injury in NAFLD. CIH is said to induce hyperglycemia and hepatic lipid peroxidation and enhances activity of nuclear factor kappa B (NF-κ B) which is a master regulator of inflammatory response.[14] Histologically, this is characterized by swelling and significant increase in accumulation of glycogen in hepatocytes. In spite of the fact that OSA is usually associated with obesity, CIH may independently contribute to liver injury.

Murine models have demonstrated that CIH leads to a significant rising in hepatic lipid peroxidation, α 1-collagen mRNA and amount of myeloperoxidase, and proinflammatory cytokines (such as IL-1β, IL-6, the chemokine macrophage inflammatory protein-2, and TNF-α).[15] These studies suggest that, in the chronic hypoxic conditions associated with OSAS, a high-fat diet could promote NAFLD. Hypoxia is said to reduce insulin sensitivity in mice and enhance expression of the lipogenic transcription factors sterol regulatory-element binding protein-1c (SREBP-1c), peroxisome proliferator-activated receptor-γ (PPAR-γ), acetyl-CoA carboxylase 1 (ACC1), and acetyl CoAcarboxylase 2 (ACC2). PPAR-γ is necessary for regulation of insulin sensitivity and lipid metabolism, and could therefore, cause lipid accumulation. Moreover, hypoxia also reduces the expression of genes regulating mitochondrial β -oxidation (e.g., PPAR-α and carnitine palmitoyltransferase-1 (CPT-1)), which could decrease fat oxidation and promote lipid accumulation. PPAR-α has anti-inflammatory properties and suppresses the expression of proinflammatory genes, allowing the control and inhibition of inflammation. In summary, hypoxia can upregulate the expression of lipogenic genes and downregulate genes involved in lipid metabolism, promoting hepatic triglyceride accumulation, necroinflammation, and fibrosis that promote the progression of NAFLD.[5] Furthermore, Nobili et al. revealed that in pediatric NAFLD the presence of OSAS was associated with the presence of NASH and of significant fibrosis, and the severity of sleep apnea and nocturnal hypoxemia correlated with NAS score and fibrosis stage, independently of overall/abdominal obesity, metabolic syndrome, and insulin resistance.[16]. Furthermore, CIH directly activates hypoxia-inducible factor- (HIF-) 1a and HIF-2a, two key transcription factors regulating the expression of genes involved in hepatocyte de novo lipogenesis and free fatty acid oxidation and in Kupffer and hepatic stellate cell activation, eventually promoting hepatic steatosis, necroinflammation,and fibrogenesis.[17]

METHODOLOGY

This study was a cross-sectional, single-center study involving adults diagnosed with obstructive sleep apnea by overnight polysomnography test in the sleep laboratory of St. Luke's Medical Center, Quezon City. This study was performed in compliance with Good Clinical Practices, including archiving of essential documents.

The medical records of patients diagnosed with obstructive sleep apnea from September 2012 to September 2016 were reviewed. Inclusion criteria were patients diagnosed with OSA by overnight polysomnography, 18 years old and above with medical records that include Body mass index (BMI), liver ultrasound, laboratory tests such as liver function tests, blood glucose levels, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglyceride values. Exclusion criteria included a history of excess alcohol consumption (identified as >20 g/day for men and >10 g/day for women), current use of hepatotoxic drugs, viral hepatitis and other chronic liver diseases.

The sonographic features of hepatic steatosis were described in terms of echogenicity, hepatorenal index and vascular opacity. The severity of fatty liver is categorized as mild, moderate and severe based on the ultrasound results.

Overnight polysomnography identified apnea as reduction in ventilation by >/= 90% from baseline for more than >/= 10 seconds. Hypopnea, on the other hand, is defined as a reduction in ventilation by >/=50% withnin >/= 10 seconds that resulted in a decrease in oxyhemoglobin saturation of 4%. Apnea-hypopnea index (AHI) was obtained by calculation of the apnea and hypopnea numbers at each hour of sleep. Lowest oxygen saturation and mean nocturnal oxygen saturation parameters were recorded. OSA was categorized in three groups as mild when AHI was 5-14 events/hour, moderate 15-29 events/hour and severe when >/= 30 events/hour.

Sample Size Calculation

The sample size was calculated based on the comparison of the proportion of NAFLD in patients with levels of severity of OSA. Assuming that those with severe OSA have 78% chances of having NAFLD and those with non-severe OSA 58.7%, (Turkey et al, 2012) with an α-error of 5%, power of 90%, and one-tailed alternative hypothesis, the sample size calculated is 95 per group or 285 for 3 groups.

Statistical Analysis

Comparison of the proportion of NAFLD across the different levels of severity of OSA was analyzed during Chi-square test initially in the univariate analysis. Odds ratio at the 95% confidence interval was also calculated. Control of confounders will then be done using a stratified analysis. Multiple logistic regression was then be utilized. Level of significance was set at $\alpha=0.05$. All analyses were performed using SPSS software.

RESULTS

Two hundred eighty one subjects (197 males, 84 females) were included in the study. All patients' data for complete clinical and anthropometric profile findings, ultrasonographic results and laboratory results were available.

Fatty liver disease was diagnosed in 238 subjects according to ultrasound findings. Out of those diagnosed with fatty liver, 56% had mild fatty liver, 20% had moderate fatty liver, and 9% had severe fatty liver. The mean ages were 50.09 for those without fatty liver, 50.66 for those with mild fatty liver, 48.75 with moderate fatty liver, and 46.08 with severe fatty liver (Table 1). Only BMI, HDL and ALT were significantly related to the severity of fatty liver (Table 1).

Table 1. Demographic and Clinical Characteristics of Subjects with Different Severities of Fatty Liver

	Severity of Fatty Liver				
	Severe (n=26)	Moderate (n=55)	Mild (n=157)	None (n=43)	P-value
Age	46.1±11.7	48.8±9.8	50.7±11.6	50.1±14.2	0.268
Gender (M/F)	19/7	38/17	109/48	31/12	0.14
BMI	38.6±12.3	32.9±7.1	30.7±6.0	27.7±5.2	0.000
DM	9	18	48	5	0.667
Total Cholesterol	188.6±45.5	194.1±46.6	191.6±42.5	193.2±43.0	0.944
LDL	124.3±39.5	127.2±43.3	120.74±37.4	117.6±35.2	0.607
HDL	41.9±10.2	43.6±14.2	46.3±14.0	51.7±14.0	0.007
Triglycerides	146.4±68.6	156.4±76.6	152.3±86.9	124.7±68.8	0.204
ALT	58.1±25.4	70.0±36.7	61.4±38.2	44.7±28.4	0.002

Among subjects with diagnosed with fatty liver, 87% had severe OSA, 76% had moderate OSA, and 81% had mild OSA. On the other hand, among those without fatty liver, 13% had severe OSA, 24% had moderate OSA, and 3% had mild OSA (Table 2). The Chi squared testing the indicative power of the severity of OSA on the presence or absence of fatty liver is insignificant (p-value=0.140) (Table 2). Another chi squared test was done, this time testing OSA severity on a 4-tiered diagnosis of fatty liver severity; again, this proved to be insignificant (p-value=0.368) (Table 3). The odds ratios of fatty liver in OSA severity, in particular those comparing severe versus mild, and moderate versus mild cases were computed but are not seen to be significant (Table 4). Among the subjects' demographic and clinical

parameters, only gender, ALT and BMI were noted to be significantly related to the severity of OSA (Table 5). Of the parameters of OSA, although the P-values of all 3 parameters were significant, a pre-test for homogeneity revealed that only the lowest O_2 saturation was noted to be homogenous (Table 7).

Table 2. Association between Severity of Obstructive Sleep Apnea and the Presence or Absence of Fatty Liver

		Fatty LIver					
		Present		Absent		Total	
		n	%	n	%	n	%
OSA	Severe	187	87.0%	28	13.0%	215	100.0%
	Moderate	38	76.0%	12	24.0%	50	100.0%
	Mild	13	81.2%	3	18.8%	16	100.0%

Table 3. Association between Severity of Obstructive Sleep Apnea and Severity of Fatty Liver

		Fatty Liver									
		Severe		Moderate		Mild		None		Total	
		n	%	n	%	n	%	n	%	n	%
OSA	Severe	23	10.7%	45	20.9%	119	55.3%	28	13.0%	215	100.0%
	Moderate	2	4.0%	7	14.0%	29	58.0%	12	24.0%	50	100.0%
	Mild	1	6.2%	3	18.8%	9	56.2%	3	18.8%	16	100.0%
	Total	26	9.3%	55	19.6%	157	55.9%	43	15.3%	281	100.0%

Table 4. Odds Ratio of Fatty Liver and Severity of Obstructive Sleep Apnea (Variables in the Equation)

	B	Sig.	Odds Ratio(OR)	95% C.I.for OR	
				Lower	Upper
OSA		.149			
OSA(Se:Mi)	.433	.520	1.541	.413	5.750
OSA(Mo:Mi)	-.314	.664	.731	.178	3.003
Constant	1.466	.022	4.333		

a. Variable(s) entered on step 1: OSA.

Table 5. Demographic and Clinical Characteristics of Subjects with Different Severities of Obstructive Sleep Apnea

	Severity of Obstructive Sleep Apnea			
	Severe (n=215)	Moderate (n=50)	Mild (n=16)	P-value
Age	50±11.8	48.8±12.2	50.1±9.2	0.796
Gender (M/F)	160/55	29/21	8/8	0.014
BMI	32.0±7.6	29.8±.6.6	27.7±4.0	0.017
DM	59	15	6	0.667
Total Cholesterol	193.6±42.9	187.3±40.1	189.0±53.7	0.624
LDL	122.7±39.0	119.2±35.4	118.3±41.5	0.787
HDL	45.9±13.8	47.1±15.3	47.8±11.2	0.755
Triglycerides	154.3±83.4	128.9±69.0	128.4±76.3	0.082
ALT	62.7±38.7	48.6±19.6	63.4±35.0	0.003

Table 6. Association of Parameters of Obstructive Sleep Apnea with Different Severities of Fatty Liver

	Severity of Fatty Liver				
	Severe (n=26)	Moderate (n=55)	Mild (n=157)	None (n=43)	P-value
AHI	60.8±36.0	58.5±28.6	45.3±26.4	40.9±20.6	0.004
Lowest O2 Saturation	80.1±8.6	81.0±10.1	83.4±8.2	85.7±7.3	0.015
Mean Nocturnal O2 Saturation	92.8±4.7	93.0±5.5	94.5±3.2	96.2±1.9	0.000

Table 7. Test of Homogeneity of Variances

	Levene Statistic	df1	df2	Sig.
AHI	3.321	3	277	.020
Lowest O2 sat	1.243	3	277	.294
Mean nocturnal O2 sat	6.274	3	277	.000

DISCUSSION

The results showed that there is no significanct association between fatty liver and severity of obstructive sleep apnea, which is contrary to what most studies say. On the other hand, BMI, HDL and ALT, were noted to be significantly related to the severity of fatty liver, which is consistent with previous studies. In addition to this, gender, ALT and BMI were noted to be significantly related to the severity of obstructive sleep apnea. It seems that males have a greater predilection to develop obstructive sleep apnea. It has been proven time immemorial, that obesity is a primary risk factor for obstructive sleep apnea. In spite of this study's finding no association between NAFLD and OSA, the fact that ALT was noted to increase with severity of OSA sheds light on the possibility of an inflammatory process on the liver that is secondary to chronic intermittent hypoxia. The pathogenesis of NAFLD has been described as a two-hit mode. The "first-hit" involves triglyceride accumulation in hepatocytes along with insulin resistance and obesity. There is an increase in the hormone-sensitive lipase activity which leads to an increase in lipolysis and free fatty acids. Subsequently, this results in insulin resistance and an increase in adipocyte tissue. This increase in free fatty acids leads to triglyceride synthesis and accumulation with increase in liver intake. The "second hit" leads to liver inflammation and fibrosis hepatic steatosis progression where oxidative stress and abnormal cytokine production play a primary role. Furthermore, anti-oxidant defense

deficiency, early mitochondrial dysfunction, iron accumulation, gut-derived microbial products and some gene polymorphisms are among the factors playing a role in hepatic steatosis.

This study has several limitations. The fact that no statistical significance was seen between fatty liver and obstructive sleep apnea may be attributed to several factors, one of which is the sample size not being homogenous. The sample size may not have been adequate enough to provide homogeneity among the different parameters used in the study. Secondly, since this study was a cross-sectional study, which involved review of records, the ultrasound machines used may have been of different models. Furthermore, there is the possibility that different ultrasonographist technicians and readers performed and read the ultrasound studies. Finally, there is the issue of using liver ultrasonography instead of the gold standard which is liver biopsy. In a study done by Needleman et al. wherein the accuracy of pattern recognition and sonography of diffuse benign liver disease was investigated, sonography was 88% accurate in assigning the correct pattern to the corresponding pathology (sensitivity 89%, specificity 86%)[13]. The degree of accuracy was dependent on the grade of pathologic severity, with mild disease offering the greatest difficulty; moderate and severe diseases were accurately detected and placed in the correct pattern in all cases. In this study, the fact that most of the patients were diagnosed with mild fatty liver by ultrasound may have contributed to the inaccuracy of the results. In spite of ultrasonography being the most frequently used modality to diagnose hepatosteatosis, biopsy still remains to be the gold standard in diagnosis, staging and prognosis. However, the glaring limitations of liver biopsy such as severe complications, unwillingness of patients, inability to reflect the whole liver tissue and errors in sampling and interpretation remains an issue.

A prospective study involving a homogenous population with NAFLD, subjected to polysomnography would have been a more effective study. In addition to this, a proscpective study that will investigate the length of time that it will take for patients with OSA without fatty liver to develop fatty liver. Also other novel non-invasive diagnostic tools such as the Fibroscan with Controlled Attenuation

Parameter (CAP) can be used instead of the usual liver ultrasound. The CAP is a promising tool for the noninvasive detection of hepatic fibrosis. Advantages include its ease of measurement, operator-independence and simultaneous availability with liver stiffness measurement for fibrosis measurement. Furthermore, prospective and interventional studies are needed to find out whether the treatment of obstructive sleep apnea may delay the development or reduce the severity of NAFLD.

CONCLUSION

This study did not find any association between the presence of fatty liver and the severity of obstructive sleep apnea. Likewise, there was no association between the degree of fatty liver and severity of sleep apnea. Among the parameters of obstructive sleep apnea, the lowest oxygen saturation decreased with increasing severity of obstructive sleep apnea. Among the subjects' demographics and clinical parameters, gender, BMI and ALT were noted to be significantly related to the degree of obstructive sleep apnea. Males were noted to have greater severities of sleep apnea, increasing BMI and ALT was associated with increasing severity of sleep apnea.

In spite of the fact that this study did not show any association between fatty liver and obstructive sleep apnea, there is still a large amount of international studies that showed otherwise. Therefore, the hypothesis that there is indeed an association between the two cannot be completely invalidated. Further studies, ideally prospective studies as aforementioned, will most likely strengthen this hypothesis.

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Appendix

DATA COLLECTION FORM

Hospital number		Case number		Date admitted	
I. PATIENT DEMOGRAPHICS					
AGE					
SEX	☐male ☐female				
BMI					
DIABETES MELLITUS	☐yes ☐no				
II. ANCILLARY TESTS					
ALT					
TOTAL CHOLESTEROL					
LDL					
HDL					
TRIGLYCERIDES					
ULTRASOUND	☐no fatty liver ☐mild fatty liver ☐moderate fatty liver ☐severe fatty liver				
II. POLYSOMNOGRAPHY PARAMETERS					
OBSTRUCTIVE SLEEP APNEA	☐mild OSA ☐moderate OSA ☐severe OSA				
APNEA-HYPOPNEA INDEX					
LOWEST SATURATION					
MEAN NOCTURNAL SPO2%					