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Original Research Article

A STUDY ON THE ASSOCIATION BETWEEN NON-ALCOHOLIC FATTY LIVER DISEASE AND OBSTRUCTIVE SLEEP APNEA IN OBESE INDIVIDUALS

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) and Obstructive sleep apnea (OSA) are emerging causes of morbidity and mortality in obese individuals. However, there is a subset of obese individuals without any obesity-related metabolic complications, known as Metabolically Healthy Obese. Studies assessing the risks of acquiring NAFLD or OSA in such individuals are very scarce. Hence this study was done to evaluate the association between NAFLD and OSA in patients with MHO. **Materials and Methods:** This prospective observational study was done in the Department of Bariatric Surgery, Amrita Institute of Medical Science (AIMS), Kochi, from April 2021 to February 2023 which included 50 individuals who fit the criteria for metabolically healthy obesity. **Result:** The majority of study patients belong to 20-30 yrs. The average BMI of the study group is 43.8 ± 6.1, indicating that nearly all people are morbidly obese. all patients were in non diabetic range. 92% had NAFLD on liver biopsy. 66% had OSA on sleep study. The prevalence of NAFLD was high in patients with OSA. **Conclusion:** The study concludes that OSA is an independent risk factor for the development of NAFLD and its progression.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent spectrum of liver conditions ranging from simple fatty infiltration to its progressive form NASH which can lead to cirrhosis and hepatocellular carcinoma.[1] NAFLD has a prevalence of 10% to 24% in the general population and 50% and 85% in obese persons.[2]

Although obesity, age > 45 years, diabetes, hypertriglyceridemia, and hypertension have been identified as risk factors for the progression of NAFLD, the cause remains unknown in up to 25 to 30% of cases.

The common pathogenic mechanism connecting NAFLD and OSA is obesity and associated metabolic syndrome. Obstructive sleep apnea (OSA) is also a very common condition, affecting up to 35% of obese individuals.[3] It is caused by repetitive partial or complete obstruction of the upper airway leading to chronic intermittent hypoxia.[4]

Multiple studies have shown that OSA is associated with impaired glucose metabolism, oxidative stress, systemic inflammation independent of obesity, and liver injury.[5,6] This could be a trigger for early stage of nonalcoholic fatty liver disease (NAFLD) and its progression to NASH, independent of obesity.

A proportion of obese individuals (having BMI > 30) are not at an increased risk for metabolic complications of obesity, and they can be referred to as metabolically healthy obesity or benign obesity - comprise up to 25% - 30% of the adult obese population.[7] However, no universally accepted criteria exist to define metabolically healthy obesity (MHO). The most common definition of MHO used was having a BMI ≥ 30 kg/m2 and no or one Metabolic syndrome criteria (Meigs et al., 2006).[8] Longitudinal studies have confirmed that MHO individuals are at much lower risk for diabetes and

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cardiovascular diseases with well-preserved insulin sensitivity than that of metabolically abnormal obese (MAO) counterparts.[9,10]

Metabolic syndrome is a potential confounder to express the independent association between OSA and NAFLD. This poses a challenge to demonstrate that an independent association exists between these two conditions and not a mere coincidence due to obesity.

Several of the studies that showed an association between OSA and NASH were limited by failure to include histopathological changes and by not applying standard criteria for diagnosing NASH. Moreover, all of the studies done to date included patients with metabolic syndrome. Hence, this study was started to assess the association between OSA and NASH in people with metabolically healthy obesity (MHO) to overcome the effect of a major confounding factor (metabolic syndrome).

MATERIALS AND METHODS

This prospective observational study was done including all patients with obesity coming to the Department of Bariatric Surgery, Amrita Institute of Medical Science (AIMS), Kochi, from April 2021 to February 2023. 50 obese patients aged between 18 – 65 years, who attended the bariatric clinic for bariatric surgery satisfying MHO criteria were included in this study after they gave their consent to participate in the study. We prospectively conducted this study for all patients who have come with obesity without associated metabolic syndrome and undergone Bariatric Surgery (BS) at our academic teaching hospital (AIMS Kochi).

Patients aged <18 years or > 35 years; patients with previously diagnosed liver conditions, patients with positive retroviral disease, or patients with severe cardiopulmonary disease; or with a history of chronic alcohol consumption, or on medications known to cause NAFLD (eg:- steroids, methotrexate, valproate, amiodarone) or patients on treatment for OSA with CPAP were excluded from the study.

A detailed history was taken using a standard questionnaire for self-reported histories of dyslipidemia, hypertension, or diabetes. Patients were interviewed for their alcohol intake in the last 5 years and were considered drinkers if their mean daily consumption was higher than 20 g of pure alcohol.[11]

Height and weight were measured and Body mass index (BMI) was calculated by dividing body weight by height squared (kg/m2).

Investigations: A fasting venous blood sample was collected in the morning immediately after sleep. Fasting Blood glucose, serum fasting lipid profile, HbA1c, CRP, LFT (Liver Function Tests), RFT (Renal Function Tests), and viral markers were performed. The upper limit normal cutoff values for AST and ALT were > 31 IU/L and > 32 IU/L, respectively. Trans-abdominal ultrasound was done to assess liver morphology.

Criteria for MHO - having a BMI ≥ 30 kg/m2 and none or <1 Metabolic syndrome criteria.

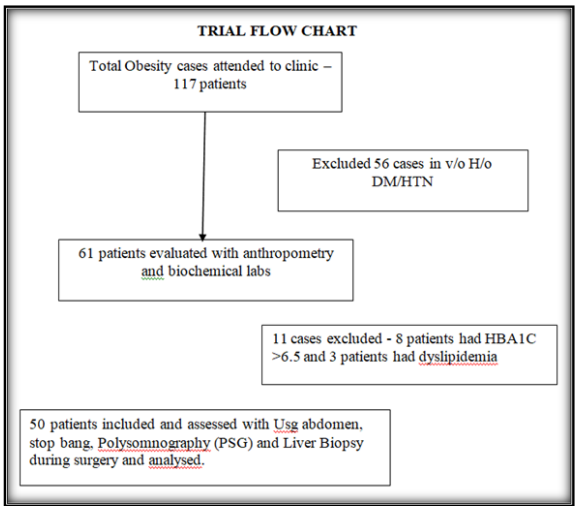
Patients were assessed for OSA by STOP-BANG questionnaire (Annexure1) and Overnight Sleep Study (Polysomnography).

Liver biopsies were performed as a routine part of the operative procedure from both lobes of the liver with a 16 gauge Tru-cut without targeting a specific area in the lobe under direct vision.

Ethical committee approval was taken before the start of the study.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 20.0 software. Categorical variables are expressed using frequency and percentage. Continuous variables are presented by mean and SD. Diagnostic measures such as sensitivity, specificity, and accuracy were computed.



RESULTS

Between April 2021 - Feb 2023, 117 patients attended the bariatric surgery clinic. out of which 50(42.7%) were MHO people and 67(57.3%) were Metabolically unhealthy obese people.

Out of 50 patients studied, 17 (34%) were males and 33(66%) were females. The majority of study patients belonged to the 20 – 30 years age group (n =20; 40%) indicating a relatively younger age of the study population seen with MHO. 12 (24%) patients were in the 31-40 yrs age group, 13(26%) in 41- 50 yrs age group and 5(10%) in 50-60 yrs age group. The mean age of the study group was 36.66 ± 9.8 years.

The majority (n =48; 96%) patients have a BMI > 35. 14 (28%) patients were morbidly obese with a BMI of 40-44.9. The average BMI of the study group is 43.8 ± 6.1, indicating that nearly all people are morbidly obese.

24 patients (48%) had HBA1c in the 5.5 – 5.99 range and 19 patients (38%) had HBA1c of 5 to

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5.49. The mean HBA1c was 5.46±0.39, indicating all patients were in the nondiabetic range.

The most common indication for surgery in obesity and obesity-related complications is snoring in 20 (40%), followed by obesity in 12 (24%), PCOS leading to infertility in 7 (14%), Joint pains in 7 (14%), and restricted mobility. [Table 1]

Out of 50 patients, elevated ALT was seen in 12 (24%) 5 patients (10%) had elevated AST. Both ALT & AST were elevated in 5 patients (10%). Elevated total bilirubin was seen in 1 patient (2%).

A liver biopsy showed that the majority of the study population had NAFLD 92%. NASH was seen in 30%, fibrosis in 32%, and advanced fibrosis in 2%.

Fatty liver was present in 47(94%) out of a total of 50 patients on ultrasound abdomen, of which mild fatty liver was present in 19(40.4%), moderate fatty liver was present in 24(51%) and severe fatty liver was seen in 4(8.6%). [Table 2]

Ultrasound abdomen was able to correctly diagnose fatty liver in 45(95.75%) and absent fatty liver in 2(66.67%) but missed fatty liver in 1(33.33%). Ultrasound abdomen has a sensitivity of 92% and specificity of 66.7% in detecting fatty liver with an accuracy of 88%.

Grade 1 steatosis was seen in 16 patients (32%), while grade 2 and grade 3 were seen in 24 patients (48%) and 6 patients (12%) respectively.

Histopathological findings:

Ballooning degeneration of hepatocytes was seen in 19(38%) patients, with the majority of them having grade 1 degeneration (17 patients). Lobular Inflammation was present in 23(46%) patients. Fibrosis was seen in 16 (32%) patients. Stage 1, peri sinusoidal fibrosis was seen in 13(81.25%), stage 2, peri portal fibrosis was seen in 2(12.5%) and advanced stage 4 was seen in 1(6.25%) patients.

NAS CRN score indicates the severity of liver pathology. It can be used as another scoring system to diagnose NASH/ Steatohepatitis apart from Brunt criteria and AASLD. Out of 50 patients, NAS scores of 0 to 2 were seen in 29(58%), 3 to 4 were seen in 15(30%), and NAS scores of 5 or >5 were seen in 6(12%) patients. [Table 3]

In our study sensitivity of the NAS CRN score is 40% and the specificity is 100%. The new NAS Fibrosis score is NAS score with an additional component of fibrosis. This new NAS Fibrosis score sensitivity is 86.76% and specificity is 100%.

OSA: The majority of patients (66%) had OSA (AHI >5) indicating a high incidence of OSA associated with the obese population. mild OSA (AHI 5-15 events/hr) was seen in 13 patients (39.39%), moderate (AHI 15 – 30 events/hr) in 14 (42.42%), and severe (AHI >30 events/hr) in 6 (18.18%) indicating majority people have moderate to severe OSA. The mean AHI is 15.43 ±18.33.

15 patients (45.46%) with OSA were males and the rest were females 18(54.54%). Out of 17 males, 15 (88.23%) have OSA compared to out of 33 females only 18(54.54%) have OSA, indicating male gender is associated with a high risk of OSA which is statically significant between with a p-value - < 0.01.

There was no statistical significance in the comparison of AST and ALT levels between the OSA group and the NON-OSA group. On analyzing patients' risk for OSA with pre-op STOP-BANG questionnaire – among the study population of 50, 21(42%) patients had mild risk, 22(44%) patients had moderate risk, and 7(14%) patients had high risk for OSA.

Table 1: Comparison of Mean Anthropometric, Biochemical, and Clinical Characteristics with gender

Variable	GENDER				p-value
	Male (n - 17)		Female (n - 33)		
	Mean	SD	Mean	SD	
Age	37.24	7.12	36.36	11.04	0.77
Height	171.41	8.91	157.36	7.17	0.26
Weight	128.24	21.33	106.7	16.62	0.25
BMI	43.38	5.54	44.02	6.52	0.52
Neck Circumference	42.53	5.3	40.79	5.51	0.72
SBP mmHg	120.70	9.51	124.18	7.72	0.38
DBP mm Hg	77.65	5.25	78.36	4.05	0.06
HBA1C	5.60	0.34	5.39	0.39	0.57
FBS (mg/dl)	91.05	4.55	89.52	4.88	0.69
CRP	10.78	5.42	8.25	7.15	0.26
TG	119.83	20.07	114.84	23.22	0.35
HDL	44.89	5.38	54.18	2.63	0.09
TB	0.49	0.28	0.43	0.17	0.26
ALT	32.37	11.46	24.21	9.52	0.66
AST	24.26	7.39	21.38	6.63	0.47
AHI	26.14	25.48	9.92	9.87	0.01
NAS score	2.76	1.78	2.27	1.42	0.16

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Table 2: Comparison between USG and liver biopsy for fatty liver assessment

USG ABD	NAFLD (LIVER BIOPSY)				Sensitivity (%)	Specificity (%)	Accuracy (%)	p-value
	YES		NO					
	n	%	n	%				
YES	45	95.75	2	4.25	92	66.7	88	1.00
NO	1	33.33	2	66.67				

Table 3: Comparison of variables between people with NASH and those without NASH

Variable	Without NASHn- 35		With NASHn- 15		p-value
	Mean	SD	Mean	SD	
Age	34.86	9.01	40.87	10.6	0.38
BMI	43.99	6.5	43.37	5.46	0.54
CRP	8.76	7.29	10.05	4.8	0.12
NECK	41.31	5.98	41.53	4.13	0.11
SBP mmHg	122.28	8.13	124.67	9.19	0.93
DBP mmHg	78.46	4.42	77.33	4.58	0.51
TB	0.43	0.24	0.49	0.16	0.55
AST	22.52	6.79	21.98	7.56	0.59
ALT	26.34	10.90	28.49	10.90	0.75
TG	116.3	21.93	116.35	23.32	0.86
HDL	50.66	5.66	51.84	6.25	0.62
HBA1c	5.42	0.41	5.56	0.33	0.30
FBS(mg/dl)	89.25	3.66	91.89	6.50	0.06
AHI	10.41	9.44	27.14	27.37	0.006
NAS score	1.63	0.97	4.33	0.81	0.38

Table 4: NAS score and % of patients with NASH

NAS score	No. of patients	% of patients with NASH
0-2	29	0
3-4	15	9
5-8	6	100

Table 5: Comparison between STOP-BANG and OSA grades

STOP BANG	OSA						Accuracy%
	AHI < 5		AHI 5 - 15		AHI >15		
	n- 17	%	n- 13	%	n- 20	%	
Low risk(0-2)	12	57.1	7	33.3	2	9.5	
Medium risk (3-4)	5	22.7	6	27.3	11	50	
High risk(5 - 8)	0	0	0	0	7	100	50

Table 6: Anthropometric and biochemical characteristics comparison with OSA severity

Variables	NO OSA (AHI <5) (n - 17)		Mild OSA (AHI 5- 15) (n - 13)		Severe OSA (AHI > 15) (n - 20)		p-value
	Mean	SD	Mean	SD	Mean	SD	
AGE (yr)	34.94	9.95	34.38	11.63	39.6	8.02	0.22
BMI (kg/m2)	44.41	6.42	40.78	5.55	45.26	5.9	0.10
NECK (cm)	41.12	7.49	39	3.1	43.15	4	0.09
SBP mmHg	124.35	6.75	123.23	8.43	121.70	9.84	0.64
DBP mmHg	78.82	4.36	77.85	4.51	77.70	4.64	0.73
CRP	4.29	3.36	7.91	4.79	14.28	6.44	0.04
TB(mg/dl)	0.37	0.16	0.55	0.29	0.44	0.18	0.06
ALT(IU/L)	24.60	10.87	29.58	11.06	27.33	10.78	0.46
AST(IU/L)	21.67	5.97	24.25	8.30	21.72	6.94	0.53
HBA1c	5.42	0.48	5.39	0.32	5.55	0.35	0.45
FBS(mg/dl)	88.93	4.09	89.68	5.46	91.23	4.85	0.34
TG	118.96	23.48	117.04	22.46	114.16	21.63	0.80
HDL	52.55	4.75	50.12	6.15	50.30	6.39	0.41
NAS score	1.47	1.17	2.46	1.61	3.25	1.37	0.001

Table 7: Association of NAFLD with OSA

NAFLD	OSA				p-value
	Absent (no.17)		Present (no.33)		
	n	%	n	%	
Present (n-46)	13	76.5	33	100	0.01
Absent (n- 4)	4	100	0	0	

NAFLD is present in 33 (100%) patients with OSA compared to 13(76.5%) without OSA. All people with OSA show NAFLD. The association is statistically significant with a p-value of 0.01.

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Table 8: Association of NASH with OSA

NASH	OSA				p-value
	Absent (no.17)		Present (no.33)		
	n	%	n	%	
Present (n-15)	1	5.9	14	42.4	0.02
Absent (n-35)	16	94.1	19	57.6	

NASH is present in 14(42.4%) patients with OSA compared to 1(5.9%) patient without OSA, which is statistically significant with a p-value of 0.02.

Table 9 a): Association of Individual components of NASH with OSA

Variable	OSA				p-value
	Absent (AHI < 5)		Present (AHI > 5)		
	n- 17	%	n- 33	%	
STEATOSIS/NAFLD					
Grade 0 (n-4)	4	23.5	0	0	0.01
Grade 1-3 (n-46)	13	76.5	33	100	
HEPATOCYTE BALLOONING					
Grade 0 (n-31)	13	76.5	18	54.5	0.19
Grade 1 and 2 (n-19)	4	23.5	15	45.5	
LOBULAR INFLAMMATION					
Grade 0 (n-27)	14	82.4	13	39.4	0.008
Grade 1 to 3 (n-23)	3	17.6	20	60.6	
FIBROSIS					
Stage 0 (n-35)	14	82.4	20	60.6	0.01
Stage 1 to 4 (n-15)	3	17.6	13	39.4	
NAS					
0 to 2 (n-29)	14	82.4	15	45.5	0.05
3 to 4 (n-15)	3	17.6	12	36.4	
5 to 8 (n-6)	0	0	6	18.1	

Table 9 b): Association of Individual components of NASH with OSA

	OSA				p-value
	Absent (AHI < 5)		Present (AHI > 5)		
	n- 17	%	n- 33	%	
Grade 0 (n-4)	4	23.5	0	0	NA
Grade 1 (n-16)	8	47	8	24.2	
Grade 2 (n-24)	5	29.4	19	57.6	
Grade 3 (n-6)	0	0	6	18.2	

Table 10: Association of NAFLD with OSA severity

NAFLD/STEATOSIS	No OSA (AHI < 5)		Mild OSA (AHI - 5 to 15)		Moderate OSA (AHI - 15 to 30)		Severe OSA (AHI > 30)	
	n- 17	%	n- 13	%	n- 14	%	n- 6	%
Present (n-46)	13	76.5	13	100	14	100	6	100
Absent (n- 4)	4	23.5	0	0	0	0	0	0

All people with mild to severe OSA showed NAFLD compared to the no OSA group in which 13(76.5%) had NAFLD and 4 (23.5%) didn't show NAFLD. This association is very significant (P value can't be given).

Table 11: Association of NASH with OSA severity

NASH	No OSA AHI < 5		Mild OSA AHI - 5 to 15		Moderate OSA AHI - 15 to 30		Severe OSA AHI > 30	
	n- 17	%	n- 13	%	n- 14	%	n- 6	%
Present (n-15)	1	5.9	5	38.5	5	35.7	4	66.7
Absent (n- 35)	16	94.1	8	61.5	9	64.3	2	33.3

In severe OSA group 4(66.7%) out of 6 showed NASH, and in moderate OSA group 5(35.7%) out of 14 showed NASH, suggesting people with severe OSA will have a higher chance of having NASH and this association is highly significant.

Table 12: Association of Components of NASH with OSA Severity

	No OSA (AHI < 5)		Mild OSA (AHI - 5 to 15)		Moderate OSA (AHI - 15 to 30)		Severe OSA (AHI > 30)	
	n- 17	%	n- 13	%	n- 14	%	n- 6	%
STEATOSIS								
Grade 0 (n-4)	4	23.5	0	0	0	0	0	0
Grade 1 – 3 (n- 46)	13	76.5	13	100	14	100	6	100

ISSN (O): 2687-5365; ISSN (P): 2753-6556

HEPATOCYTE BALLOONING								
Grade 0 (n-31)	13	76.5	8	61.5	9	64.3	1	16.7
Grade 1 and 2 (n-19)	4	23.5	5	38.5	5	35.7	5	83.3
LOBULAR INFLAMMATION								
Grade 0 (n-27)	14	82.3	7	53.8	5	35.7	1	16.7
Grade 1 to 3 (n-23)	3	17.7	6	46.2	9	64.3	5	83.3
FIBROSIS								
Stage 0 (n-34)	14	82.3	7	53.8	11	78.5	2	33.3
Stage1 - 4 (n-16)	3	17.7	6	46.2	3	21.5	4	66.7
NAS SCORE								
0 - 2	14	82.3	7	53.8	7	50	1	16.7
3 - 4	3	17.7	4	30.8	6	42.8	3	50
5 - 8	0	0	2	15.4	1	7.2	2	33.3

Table 13:

	No OSA (AHI < 5)		**Mild OSA (AHI - 5 to 15)**		**Moderate OSA (AHI - 15 to 30)**		**Severe OSA (AHI > 30)**	
	n- 17	**%**	**n- 13**	**%**	**n- 14**	**%**	**n- 6**	**%**
STEATOSIS								
Grade 0 (n-4)	4	23.5	0	0	0	0	0	0
Grade 1 (n-16)	8	47	7	53.8	0	0	1	16.7
Grade 2 (n-24)	5	29.4	5	38.5	13	92.8	1	16.7
Grade 3 (n-6)	0	0	1	7.7	1	7.2	4	66.6

DISCUSSION

The main purpose of this study was to explore the association between OSA and NASH in a cohort of patients with Metabolically Healthy Obesity (MHO). This study demonstrates a high prevalence of OSA (66%) and NAFLD (92%) among patients with severe obesity who underwent bariatric surgery. NAFLD was seen in 92% and NASH seen in 30%, in the present study, a percentage similar to previous studies performed in morbidly obese patients (9.8% to 72.5%).[12]

In the present study, steatosis was present in 92%, and liver fibrosis was found in 32% of the patients, including 2 % with advanced stage 4 fibrosis. These percentages are comparable but on the lower side may be due to the young age of the present study population.

In the present study, OSA was seen in 66% of the patients, similar to the prevalence of OSA in morbidly obese patients waiting for bariatric surgery reported in the literature ranging between 60% to 80% of the patients. 13 Present results showed that the prevalence of NAFLD / NASH was significantly higher in patients with OSA suggesting a role for nocturnal hypoxemia in the pathogenesis of NAFLD/NASH.

Further, the presence of OSA is significantly associated with greater degrees of steatosis and lobular inflammation grade and fibrosis stage but not with ballooning. the NASH lesions (ballooning of hepatocytes, lobular inflammation), NAFLD activity score (NAS), and fibrosis were significantly more severe in patients with severe OSA. In the present study, OSA is strongly associated with higher systemic inflammation (CRP) independent of age, obesity, metabolic syndrome, and NASH.

In the present study, we didn't find any difference in Liver function tests, age, BMI, Neck circumference, Mean BP, HbA1c levels, Blood sugar, and lipid profile.

The present study demonstrated that the OSA per se has a major and independent impact on the severity of NAFLD/NASH. In the present study, we also found that AHI values (OSA severity) are independent predictors of NASH even in the absence of metabolic syndrome and this association is independent of obesity.

The existing literature on the relationship between OSA and NASH is conflicting. Studies by Singh et al,[14] and Jouet et al,[12] failed to show an association between OSA and NASH while Daltro et al,[15] failed to show an OSA with the severity of NASH. Several studies have suggested a relationship between OSA and NASH.[16] All these studies have contributed to the literature on this association but are hampered by several limitations.

To overcome this limitation, NAS CRN members introduced an objective scoring system comprising a combination of 3 main elements of NASH (steatosis, inflammation, and hepatocyte ballooning) with a score > 5 considered as NASH and it is widely used in many trials. The use of the NAS score to define NASH can result in significant misclassification, causing patients with simple steatosis to be misclassified as NASH and is not recommended.[18]

The currently accepted definition of NASH as per AASLD requires a minimum of the presence of each of the following components: (1) >5 % macrovesicular Steatosis, (2) hepatocyte ballooning, and (3) inflammation.

Polotsky et al,[16] studied 90 obese patients, excluding diabetes, and showed that severe OSA was associated with insulin resistance and may predispose to hepatic inflammation, hepatocyte ballooning, and liver fibrosis but it is limited by a small number of subjects from whom liver biopsies were available, restricting the size of subgroups in analysis and limiting the generalization of findings.

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As per Two hit pathogenesis,[18] obesity acts as 'the first hit'' in the progression of NAFLD-inducing hepatic steatosis, and the presence of OSA itself acts as the "second hit", by hypoxia-induced inflammation leading to the progression from early stage of hepatic steatosis to NASH. The present study suggests that apart from a major role in the second hit, OSA can itself induce initiation of steatohepatitis independent of obesity by inducing oxidative stress, systemic inflammation, and ischemic hepatitis.

A study by Polotsky et al,[16] showed that OSA is associated with increased insulin resistance even in their cohort of non-diabetic population. So we can suggest that in the present population, there may be insulin resistance that can lead to the first hit in steato- hepatitis independent of obesity but as we didn't measure insulin resistance we are not sure about this relation it needs further studies to confirm this association.

Several studies in humans have suggested that OSA leads to liver injury and could be a trigger for early stage of nonalcoholic fatty liver disease (NAFLD) and its progression to NASH, independent of obesity.[15]

The present study postulates that Sleep apnea causes recurrent nocturnal oxygen desaturations with an increase in oxidative stress which leads to consequences like lipid peroxidation, cell degeneration and necrosis, apoptosis, pro-inflammatory cytokine expression, liver stellate cell activation, fibrogenesis.

In the alternative hypothesis of a lipotoxic role of fatty acids hypoxia might induce a decreased ability of free fatty acids flux to enter the oxidative pathway, therefore, increasing their hepatic lipotoxic effect.

Increased oxidative stress and its induced inflammation both seem to play a major role in the development of NASH as suggested by the increase in CYP2E1 and increased expression of iNOS has been observed in the liver of high-fat diet-induced steatohepatitis.[19]

Present data suggest that the hypoxic stress of OSA may induce oxidative stress in the liver which leads to the initiation and progression of NAFLD which culminates into NASH through inflammation and fibrosis but further studies are required to assess exact pathogenesis for such causation.

Demographics of MHO Population

In the present study, the prevalence of MHO is 42.7%. In the literature, prevalence is variable mainly because of the lack of a standard definition for MHO. The present study showed that MHO people are more females and of younger age (< 40 yrs).

In the present study, the major indication of surgery is Snoring followed by restricted mobility and associated joint pains suggesting that being Metabolically healthy is not immune from getting other weight-related complications.

There is no significant difference in gender, age, BMI, mean blood pressure, mean blood sugar, and Lipid profile but they differed significantly in mean AHI score indicating male gender is associated with a high risk of OSA.

In the present study elevated liver enzymes, ALT, and AST are seen in 12(24%) and 5(10%) patients respectively and the prevalence is comparable to previous studies performed on morbidly obese patients.[20]

But the present study also showed OSA people have higher elevated enzyme levels (30% in OSA people) and it was shown that mean AHI is significantly associated with elevated enzymes independent of BMI and it is comparable to the findings in a previous study by Tanne et al.[21]

In the present study, transabdominal ultrasound assessment of fatty liver on comparing liver biopsy has a sensitivity of 92% and specificity of 66.7% which is comparable to previous studies which suggest sensitivity (82 – 94% and specificity (66 – 92%).[22]

When we compare people with NASH and without NASH, the two groups are comparable without much difference in terms of Age, BMI, mean BP, HbA1c levels, LFTs, and Lipid profile except in mean Apnea-Hypopnea Index(AHI) score(OSA) which is significantly different between two groups indicating people with High AHI associated with NASH independent of BMI, HbA1c, Age, mean BP, Lipid profiles. It is similar to the study by Tanne et al,[21] Byrne et al,[20] and Polotsky et al,[16] who showed that OSA is associated with NASH independent of Age, BMI, and Diabetes.

In this study, we also compared the sensitivity and specificity of NAFLD activity score(NAS) with histologically well-defined NASH as recent studies by NASH CRN members advocated the common use in clinical practice of NAS > 5 as a surrogate for histological diagnosis of steatohepatitis and we conclude that a definite diagnosis or absence of steatohepatitis does not always correlate with the threshold value of NAS score.[17]

In the present study, the sensitivity of NAS score to diagnose definite NASH as compared to standard histopathological diagnosis is 40% and it is increased to 80.6% when considered for newly proposed NAS plus fibrosis score and it is comparable to the previous studies.[23]

CONCLUSION

Our study suggests that OSA is associated with NASH and increased NAFLD activity score (NAS score) as well as it is also associated with a greater degree of steatosis, hepatocyte ballooning, and fibrosis in obese patients independent of metabolic syndrome. These findings strongly support the important role of OSA in NASH development and progression and raise the possibility that OSA may be a novel risk factor for NAFLD.

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In our cohort, the metabolic healthy obesity population is in good proportion but being MHO is not making them immune to other obesity-related complications like OSA and Joint pains.
Additional studies are warranted to further evaluate this relationship in people without obesity and the impact of OSA treatment on NASH histology.

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