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Insulin Resistance, but Not Obstructive Sleep Apnea Is Associated with Hepatic Steatosis in Chinese Patients with Severe Obesity

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Keywords
Hepatic steatosis · Obstructive sleep apnea · Insulin resistance · Obesity

Abstract
Introduction: Severe obesity is often present with non-alcoholic fatty liver disease (NAFLD) and obstructive sleep apnea (OSA). Emerging researches suggest OSA plays an important role in NAFLD development and progression while the relationship between OSA and NAFLD is still conflicting. The interaction of OSA and NAFLD should be further evaluated as obesity surges. The purpose of this study was to assess the prevalence of OSA and NAFLD in patients with obesity undergoing bariatric surgery and evaluate the association between OSA and severity of NAFLD. ***Methods:*** 141 patients with severe obesity undergoing preoperative polysomnography and intraoperative liver biopsy during bariatric surgery were investigated. Clinical, anthropometric variables, liver enzymes, fasting blood glucose, fasting serum insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) were measured. The severity of NAFLD was assessed by degree of steatosis, ballooning, intralobular inflammation, and NAFLD activity score. The diagnosis and severity assessment of OSA was based on an apnea/hypopnea index (AHI). ***Results:*** OSA was diagnosed in 127 (90.07%), NAFLD in 124 (87.94%), and non-alcoholic steatohepatitis in 72 (51.06%) patients. There was a statistical difference in BMI, waist circumstance, neck circumstance, high-density lipoprotein cholesterol, fasting insulin, and HOMA-IR among the three groups divided by the severity of AHI. In addition, the distribution of hepatic steatosis grades among the three groups was statistically different ($p = 0.025$). AHI was significantly associated with HOMA-IR and hepatic steatosis when assessing the association between OSA parameters and liver histology in NAFLD ($p < 0.05$). Patients with steatosis of grades 1–3 had significantly elevated aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, triglycerides, fasting insulin, fasting glucose, HOMA-IR, and AHI compared with the patients with steatosis of grade 0. In a multivariable logistic analysis, the positive association between AHI and hepatic steatosis attenuated after adjusting for HOMA-IR. ***Conclusion:*** Prevalence of OSA and NAFLD was high in patients with obesity eligible for bariatric procedures. HOMA-IR, but not AHI, was an independent risk factor for hepatic steatosis in this population.

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Introduction

In parallel to the rapid transitions of social, economic, and environmental, especially the dramatical changes of lifestyle factors such as dietary habits and physical activity, obesity has become a major public health issue in China. In the most recent national surveys, more than half of Chinese adults are overweight or obese according to the ethnic-specific standards [1]. Global prevalence of non-alcoholic fatty liver disease (NAFLD) has reached 25% with obesity epidemic [2]. NAFLD is a multi-system metabolic disease, which is closely related to obesity, diabetes, atherosclerosis, and cardiovascular disease [3]. Non-alcoholic steatohepatitis (NASH), an inflammatory form of NAFLD, can progress to cirrhosis and even require liver transplantation [4]. Although the mechanisms of pathogenesis for NAFLD remain enigmatic, a multiple-hit hypothesis including lipotoxicity, oxidative stress, insulin resistance, genetic and epigenetic factors, and gut microbiota is the widespread theory for the progression of NAFLD [5].

Like NAFLD, obstructive sleep apnea (OSA), a common sleep-disordered breathing disease characterized by apnea and hypopnea caused by narrowing of the pharynx during sleep, has become a growing health problem worldwide and its prevalence in obese individuals exceeds 40% [6]. The pathogenesis of OSA is a clinical syndrome characterized by chronic intermittent hypoxia and sleep fragmentation, accompanied by a series of physiological changes such as hypoxemia and hypercapnia [7].

OSA can cause multi-system damage and is also associated with metabolic syndrome, such as dyslipidemia, type 2 diabetes mellitus (T2DM), hypertension, and insulin resistance, which influence the progression of NAFLD [8, 9]. A growing number of studies from epidemiological data [10, 11], intermittent hypoxia animal studies [12], and clinical intervention studies [13] suggest that OSA, as an independent risk factor for insulin resistance, may contribute to the progression of hepatic steatosis [14].

Patients with OSA often present with insulin resistance, which is associated with the development and progression of NAFLD [15]. However, the relationship between OSA, NAFLD, and insulin resistance is unclear and requires further research. Furthermore, NAFLD and OSA are both strongly impacted by race [16, 17], while similar study from China is lacking. The primary objective of this study was to investigate the effect of OSA on liver enzymes and NAFLD histological components such as steatosis, hepatocyte ballooning, and lobular inflammation as well as NAFLD activity score (NAS) in Chinese patients with severe obesity.

Materials and Methods

Study Population

This study included 141 consecutive patients who underwent bariatric surgery at Tianjin Medical University General Hospital between January 2020 and January 2022. Severely obese Chinese patients with body mass index (BMI) ≥32.5 kg/m^2 or BMI ≥27.5 kg/m^2 with obesity-related comorbidities were evaluated by a multidisciplinary team. Bariatric surgery is considered for those unable to lose weight with diet, behavior modification, or medication therapy [18]. Electronic medical records were retrospectively reviewed to determine that these patients underwent polysomnography (PSG) prior to surgery and intraoperative wedge liver biopsy. Clinical data were collected including age, sex, BMI, disease duration. A detailed history was obtained including history of alcohol use, T2DM, hypertension, or dyslipidemia. Exclusion criteria included alcohol intake greater than 210 g/week in men and 140 g/week in women, hepatotoxic drug application; concomitant liver disease with other definite etiologies, such as autoimmune hepatitis, Wilson disease, hemochromatosis, or alpha-1 antitrypsin deficiency; and malignant disease. Due to the effect of exogenous insulin on homeostasis model assessment of insulin resistance (HOMA-IR) values, we excluded patients receiving insulin therapy. All patients were tested for hepatitis B and C virus markers, and the results were negative. Figure 1 shows the flowchart of identification of study population.

The diagnosis of T2DM was based on the World Health Organization (WHO) criteria, or known diagnosis of diabetes. Hypertension was diagnosed by a blood pressure >130/85 mm Hg or ongoing treatment for hypertension. Hyperlipidemia was defined as a total cholesterol concentration of ≥5.17 mmol/L, a triglyceride (TG) concentration of ≥1.7 mmol/L, a low-density lipoprotein cholesterol (LDL-C) concentration of >3.37 mmol/L, a high-density lipoprotein cholesterol (HDL-C) lipoprotein<1.03 mmol/L in men or 1.29 mmol/L in women, or a history of hyperlipidemia [19].

Anthropometric and Biochemical Measurements

BMI was calculated as weight (in kilograms) divided by height (in meters squared). Neck circumference was measured from the upper edge of the seventh cervical vertebra at the back of the neck (the most protruding part of the back of the neck when looking down) to the front of the pomum adami. Waist circumference was measured at the girth of the midpoint line between the lowest point of the rib and the upper border of the iliac crest.

Blood samples for estimation of biochemical parameters were collected between 08:00 and 10:00 a.m. after a 12-h overnight fasting period. Laboratory tests included serum glucose, serum insulin, aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma glutamyltransferase (GGT), and fasting lipid profile including total cholesterol, TG, HDL-C, and LDL-C. In addition to biochemical indicators, hepatitis B and C serologies were performed concurrently. The HOMA-IR was calculated as fasting insulin (μIU/mL) × fasting glucose (mmol/L)/22.5 [20].

Polysomnography

All patients were referred for overnight PSG before bariatric surgery, and the reports were published according to standard [21]. Apnea/hypopnea index (AHI) was defined as the total number of respiratory events (included apnea plus hypopnea)

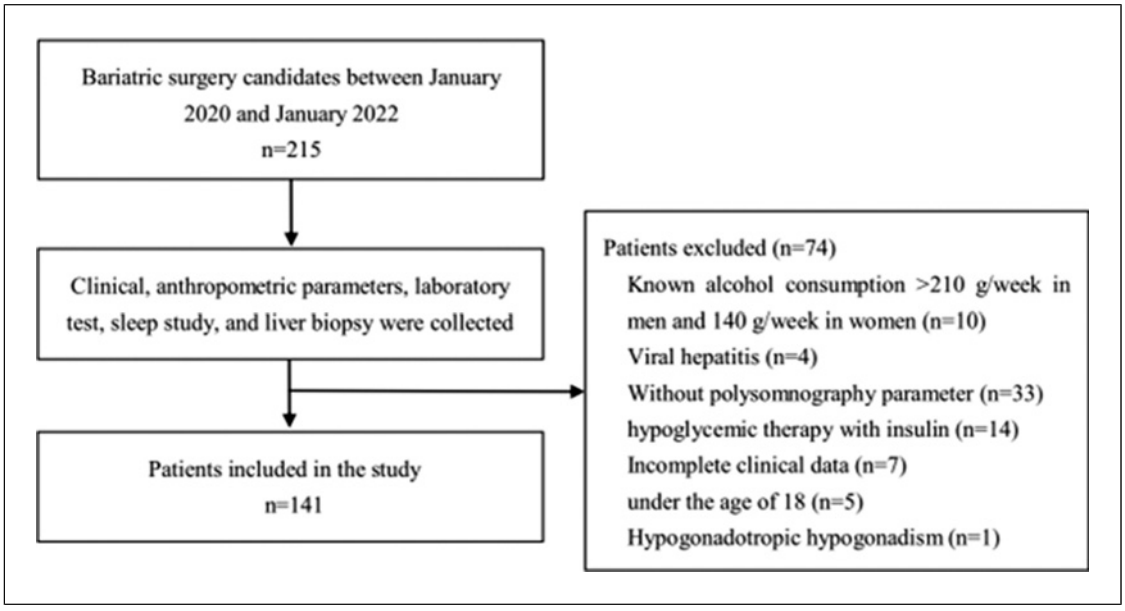

Fig. 1. Flowchart of eligible and available patients in the study.

divided by sleep time (ev/h). Oxygen saturation index (ODI) was defined as the number of times the oxygen saturation decreased by ≥4% per hour of sleep time. Other polysomnographic parameters were also recorded, including the lowest O_2 saturation ($LaSO_2$) and the percentage of total sleep time with oxygen saturation <90% (T90%). The diagnosis of OSA is based on clinical manifestations and AHI ≥5 events/hour. According to AHI thresholds, the severity of OSA was classified as follows: no apnea (AHI <5.0 ev/h); mild apnea (AHI 5.0–14.9 ev/h); moderate apnea (AHI 15.0–30.0 ev/h); and severe apnea (AHI >30.0 ev/h) [22].

Liver Histology

All patients signed consent for liver biopsy and underwent intraoperative liver biopsy during bariatric surgery. Fresh liver biopsy specimens were fixed in 10% neutral buffered formalin and stained with hematoxylin-eosin. Liver biopsy histologic evaluation was interpreted by a single experienced pathologist in a blinded fashion, including grades of steatosis, inflammation, cellular ballooning: (1) steatosis: grade 0 (<5%); grade 1 (5%–33%); grade 2 (34%–66%); grade 3 (>66%); (2) lobular inflammation (necrotic foci counted under ×20 microscope): grade 0, none; grade 1 (<2 foci); grade 2 (2–4 foci); grade 3 (>4 foci); (3) hepatocyte ballooning: grade 0, none; grade 1, rare; grade 2, common. The NAFLD activity score. AS is the sum of scores for steatosis, lobular inflammation, and hepatocyte ballooning, ranging from 0 to 8. NAFLD was defined as the presence of grade 1 or more significant steatosis. NASH was defined as the grade 1 of steatosis plus hepatocyte ballooning and lobular inflammation according to the American Association for the Study of Liver Diseases (AASLD)-recommended liver pathological grade [23].

Statistical Analysis

Statistical analysis was performed using version 25.0 of IBM SPSS Statistics for Windows. All descriptive data were tested for normal distribution before statistical analysis. Data with normal distribution are expressed as mean ± standard, and data with non-normal distribution are expressed as median (interquartile range). In addition, categorical data are expressed as proportion (percentages). For comparisons between groups of continuous variables following a normal distribution, one-way ANOVA was performed first, followed by post hoc comparisons. For non-normally distributed variables, the Kruskal-Wallis H test (K) was performed to compare multiple groups. Categorical variables were analyzed by χ^2 test or Fisher's exact test. Spearman's correlation test was used to investigate the correlation between variables. Predictor variables that were significant in the univariate analysis at $p < 0.1$ were included in the final multivariate model. Multivariate logistic regression was then used to identify independent predictors of hepatic steatosis. Histological assessments were performed as follows: hepatic steatosis (grade ≥1), ballooning (grade ≥1), lobular inflammation (graded ≥1), which were analyzed as dichotomous variables. A p value of < 0.05 was considered statistically significant.

Study Approval

The study was approved by the Tianjin Medical University General Hospital Institutional Review Board (approval number IRB2020-YX-029-01) with wavier of individual patient consent, and the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. We did not obtain informed consent in the present study because we used an electronic data set compiled from medical records from the Department of Endocrinology and Metabolism, which does not contain personally identifiable information except for the date of birth.

Table 1. General characteristics of the whole cohort and stratified by gender

Variables	Total, n = 141	Male, n = 30	Female, n = 111	p value
Clinical characteristics				
Age, years	30.81±6.83	28.30±6.68	31.49±6.74	0.023*
BMI, kg/m^2	39.77±7.05	43.54±7.03	38.75±6.74	0.001*
Waist circumference, cm	115.00 (106.00–128.50)	131.00 (118.50–143.25)	112.00 (103.00–122.00)	0.000*
Neck circumference, cm	42.00 (39.00–45.00)	46.00 (44.00–48.00)	41.00 (39.00–43.00)	0.000*
Current smoking, n (%)	17 (12.06)	10 (33.33)	7 (6.30)	0.000*
Comorbidity, n (%)				
Diabetes	49 (34.75)	9 (30.00)	40 (36.03)	0.538
Arterial hypertension,	44 (31.21)	14 (46.67)	30 (27.03)	0.039*
Dyslipidemia	124 (87.94)	21 (70.00)	103 (92.79)	0.002*
OSA (AHI ≥5 ev/h)	127 (90.07)	29 (96.67)	98 (88.29)	0.301
Sleep study characteristics				
AHI	19.30 (11.20–48.15)	58.20 (18.93–90.28)	17.40 (10.00–35.70)	0.000*
ODI	16.60 (9.40–41.10)	48.15 (19.08–87.75)	14.90 (9.00–29.30)	0.000*
T90%	0.30 (0.00–6.00)	5.20 (0.23–24.08)	0.10 (0.00–2.90)	0.001*
$LaSO_2$	83.00 (74.00–88.00)	76.50 (69.75–85.25)	85.00 (79.00–88.00)	0.002*
Average SpO_2	95.00 (93.00–96.00)	93.00 (92.00–96.00)	95.00 (94.00–96.00)	0.003*
Biochemical characteristics				
ALT, U/L	41.00 (27.50–78.50)	57.50 (38.50–83.00)	39.00 (24.00–77.00)	0.020*
AST, U/L	26.00 (18.00–45.00)	31.50 (24.00–45.00)	23.00 (17.00–46.00)	0.085
ALKP, U/L	69.00 (60.00–82.00)	74.00 (67.00–83.50)	69.00 (58.00–81.00)	0.122
GGT, U/L	36.00 (24.50–56.50)	52.00 (41.00–75.75)	31.00 (22.00–52.00)	0.000*
TC, mmol/L	4.96 (4.46–5.47)	4.95 (4.27–5.43)	4.96 (4.53–5.58)	0.429
TG, mmol/L	1.81 (1.44–2.50)	1.85 (1.41–2.39)	1.81 (1.44–2.51)	0.761
HDL-C, mmol/L	1.06 (0.96–1.22)	1.00 (0.89–1.14)	1.08 (0.97–1.23)	0.072
LDL-C, mmol/L	3.26±0.74	3.27±0.91	3.25±0.69	0.893
Fasting glucose, mmol/L	5.49 (4.95–6.71)	5.33 (4.86–6.53)	5.50 (4.96–6.74)	0.346
Fasting insulin, μIU/mL	22.60 (16.15–32.25)	23.50 (17.73–33.63)	22.30 (15.80–31.80)	0.636
HOMA-IR	5.93 (4.25–7.64)	5.99 (3.92–7.65)	5.88 (4.27–7.67)	0.936

BMI, body mass index; OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; T90%, the percentage of total sleep time spent with SpO_2 <90; $LaSO_2$, lowest O_2 saturation; average SpO_2, average O_2 saturation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALKP, alkaline phosphatase; GGT, gamma glutamyl transferase; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance. *$p < 0.05$.

Results

Baseline Characteristics

The characteristics of 141 research subjects are presented in Table 1. Of the 141 patients studied, 111 (78.23%) were female. The average age was 30.81 ± 6.83 years with an average BMI of 39.77 ± 7.05 kg/m^2. Age, BMI, and waist circumference were significantly higher in males compared to the females. Diabetes was diagnosed in 49 (34.75%) patients, arterial hypertension in 44 (31.21%) patients, and 124 (87.94%) presented with dyslipidemia. In this study population, there were no differences in the prevalence rates of type 2 diabetes between the men and women, and the prevalence of hypertension in male was significantly higher than that in female (p = 0.039), whereas dyslipidemia was more common in female than in male (p = 0.002). Except for the ALT and GGT, there was no significant difference between male and female subjects for other metabolic parameters.

Liver Histological Findings

Table 2 shows the histological findings from the hepatic biopsies of the 141 patients studied. NAFLD was diagnosed in 124 (87.94%), and NASH in 72 (51.06%) of the patients studied. The prevalence of NAFLD and NASH was not statistically different between men and women. The patients with steatosis with grade from 0 to 3 were distributed as follows: grade 0: 17 (12.06%), grade 1: 36 (25.53%), grade 2: 49 (34.75%), grade 3: 39 (27.66%);

Table 2. Histological findings of the hepatic biopsies from the 141 obese patients studied

Variables	Total, *n* = 141	Male, *n* = 30	Female, *n* = 111	*p* value
NAFLD, *n* (%)	124 (87.94)	29 (96.67)	95 (85.59)	0.122
NASH, *n* (%)	72 (51.06)	19 (63.33)	53 (47.75)	0.130
Steatosis, *n* (%)				0.057
Grade 0	17 (12.06)	1 (3.33)	16 (14.41)	
Grade 1	36 (25.53)	9 (30.00)	27 (24.32)	
Grade 2	49 (34.75)	7 (23.33)	42 (37.84)	
Grade 3	39 (27.66)	13 (43.33)	26 (23.42)	
Hepatocyte ballooning, *n* (%)				0.778
Grade 0	8 (5.67)	1 (3.33)	7 (6.31)	
Grade 1	95 (67.38)	20 (66.67)	75 (67.57)	
Grade 2	38 (26.95)	9 (30.00)	29 (26.13)	
Lobular inflammation				0.109
Grade 0, *n* (%)	61 (43.26)	9 (30.00)	52 (46.85)	
Grade 1, *n* (%)	35 (24.82)	6 (20.00)	29 (26.13)	
Grade 2, *n* (%)	26 (18.44)	8 (26.67)	18 (16.22)	
Grade 3, *n* (%)	19 (13.48)	7 (23.33)	12 (10.81)	
NAS	4.00 (3.00–5.00)	5.00 (3.00–6.25)	4.00 (3.00–5.00)	0.018*

NAFLD, non-alcoholic fatty liver disease; NAFL, non-alcoholic hepatic steatosis; NASH, non-alcoholic steatohepatitis; NAS, NAFLD activity score. *$p < 0.05$.

hepatocyte ballooning: grade 0: 8 (5.67%), grade 1: 95 (67.38%), grade 2: 38 (26.95%); lobular inflammation: grade 0: 61 (43.26%), grade 1: 35 (24.82%), grade 2: 26 (18.44%), grade 3: 19 (13.48%). NAS was significantly higher in male compared with the female ($p = 0.018$). However, there was no difference between male and female in the distribution of lobular inflammation and hepatocyte ballooning.

PSG Evaluation and Characteristics of Patients Based on AHI Severity

As expected, OSA was diagnosed in 127 (90.07%) research subjects (Table 1). Men had higher AHI, ODI, and T90% than women, whereas the men presented with lower $LaSO_2$ and average SpO_2 than women. The prevalence of OSA did not differ between the men and the women.

Regarding AHI, 50 (35.46%) of the cohort had AHI <15, 37 (26.24%) with AHI 15–30, 54 (38.30%) with AHI >30. The clinical and biochemical characteristics of three groups are shown in Table 3. The three groups did not differ in terms of age, and the prevalence of diabetes, arterial hypertension, dyslipidemia, and smoking. Increasing AHI level was associated with higher BMI, WC, and NC. Except for HDL-C, fasting insulin, and HOMA-IR, there were no significant differences in other biochemical characteristics among the three groups.

The prevalence of NASH was 42.00% in group with AHI <15, 59.46% in group with AHI 15–30, 53.70% in group with AHI >30. However, there was no statistical difference in the prevalence of NASH and NAS among the three groups ($p = 0.242$ and 0.696, respectively). The distribution of patients in different grades of steatosis, hepatocyte ballooning, lobular inflammation, and NAS depending on the severity of AHI is provided in Figure 2. Hepatic histopathology findings demonstrated that no significant differences in hepatocyte ballooning and lobular inflammation ($p = 0.410$ and 0.790, respectively) were detected, while the results showed a significant difference in steatosis among the three groups divided based on AHI severity ($p = 0.025$). The details of proportion in different groups depending on severity of AHI are provided in online supplementary Table 1 (for all online suppl. material, see https//doi.org/10.1159/000528789).

Correlation Analysis of OSA and NAFLD Parameters

To evaluate the relationship of OSA and NAFLD, Spearman correlation analysis was performed on PSG parameters (AHI, ODI, T90%, $LaSO_2$, average SpO_2) with BMI, HOMA-IR, liver enzymes, NAS, steatosis, ballooning, and intralobular inflammation, respectively (online suppl. Table 2), and is displayed via heatmap in Figure 3. The BMI presented a positive statistically significant correlation with AHI ($r_s = 0.425$, $p = 0.000$), ODI ($r_s = 0.492$, $p = 0.000$), and T90% ($r_s = 0.365$, $p = 0.000$), but a negative correlation with $LaSO_2$ ($r_s = -0.412$, $p = 0.000$) and average SpO_2 ($r_s =$

Table 3. Characteristics of the participants according to AHI

Variables	AHI <15, *n* = 50	AHI15-30, *n* = 37	AHI >30, *n* = 54	*p* value
Clinical characteristics				
Gender, *n* (%)				
Male	5 (10.00)	6 (16.22)	19 (35.19)	0.005*
Female	45 (90.00)	31 (83.78)	35 (64.81)	
Age, years	29.88±6.17	30.46±7.68	31.91±6.77	0.301
BMI, kg/m^2	36.33±6.46	40.37±7.76	42.53±7.76	0.000*
Waist circumference, cm	107.00 (101.00–115.75)	120.00 (111.50–129.50)	123.50 (110.75–135.25)	0.000*
Neck circumference, cm	40.00 (37.75–43.00)	41.50 (40.00–43.00)	44.00 (41.00–47.00)	0.000*
Smoking, *n* (%)	4 (8.00)	3 (8.11)	10 (18.52)	0.329
Comorbidity, *n* (%)				
Diabetes	17 (34.00)	10 (27.03)	22 (40.74)	0.398
Arterial hypertension	14 (28.00)	9 (24.32)	21 (38.89)	0.281
Dyslipidemia	44 (88.00)	33 (89.19)	47 (87.04)	0.953
Biochemical characteristics				
ALT, U/L	38.50 (26.75–66.50)	44.00 (29.00–90.00)	52.00 (27.75–75.00)	0.432
AST, U/L	23.00 (17.00–35.25)	27.00 (17.00–48.50)	27.50 (18.75–51.00)	0.370
ALKP, U/L	70.00 (57.00–80.25)	69.00 (62.50–82.50)	69.00 (61.00–83.00)	0.853
GGT, U/L	31.00 (22.25–54.00)	41.00 (27.00–50.00)	44.00 (24.50–66.50)	0.362
TC, mmol/L	4.89 (4.42–5.50)	4.96 (4.51–5.33)	5.04 (4.47–5.58)	0.968
TG, mmol/L	1.66 (1.42–2.30)	2.05 (1.55–2.91)	1.81 (1.43–2.47)	0.203
HDL-C, mmol/L	1.09 (0.99–1.26)	1.04 (0.91–1.14)	1.04 (0.92–1.17)	0.029*
LDL-C, mmol/L	3.15±0.63	3.34±0.75	3.30±0.82	0.441
Fasting glucose, mmol/L	5.36 (4.89–6.77)	5.36 (4.90–6.62)	5.79 (5.08–6.75)	0.516
Fasting insulin, μIU/mL	18.50 (14.03–24.48)	27.10 (17.85–33.80)	25.10 (17.90–33.63)	0.006*
HOMA-IR	4.85 (3.10–6.96)	6.39 (4.76–8.34)	6.31 (4.69–9.00)	0.021*

AHI, apnea-hypopnea index; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALKP, alkaline phosphatase; GGT, gamma glutamyl transferase; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance. *$p < 0.05$.

−0.387, $p = 0.000$). The HOMA-IR showed a positive, statistically significant, but weak correlation with AHI ($r_s = 0.225$, $p = 0.007$), ODI ($r_s = 0.246$, $p = 0.003$), and T90% ($r_s = 0.268$, $p = 0.001$), but a negative correlation with $LaSO_2$ ($r_s = -0.294$, $p = 0.000$) and average SpO_2 ($r_s = -0.234$, $p = 0.005$). The weak correlation also occurred between the ALT and average SpO_2 ($r_s = -0.199$, $p = 0.018$), AST and average SpO_2 ($r_s = -0.243$, $p = 0.004$), AST and T90% ($r_s = 0.197$, $p = 0.019$).

In addition, to study the relationship between the OSA parameters and liver histology in NAFLD, correlation tests were also conducted among the polysomnographic parameters and histological findings and NAS. Only AHI presented a positive, statistically significant, but weak correlation with the presence of steatosis ($r_s = 0.209$, $p = 0.013$).

Characteristics of Patients according to the Grade of Steatosis

To clarify the relationship between OSA severity and hepatocyte steatosis, the patients were divided into two groups according to the grade of steatosis: grade 0 and grades 1–3. Table 4 presents the clinical characteristics of the participant, and subjects with steatosis of grades 1–3 had significantly higher AST, ALT, GGT, TG, fasting glucose, fasting insulin, HOMA-IR, and AHI compared with the patients with steatosis of grade 0. Patients with steatosis have lower levels of HDL-C than that without steatosis ($p = 0.045$). There was no significant difference between two groups for demographic, anthropometric, other metabolic, and polysomnographic parameters.

Multivariate Logistic Regression Model of Hepatocyte Steatosis

Hepatic steatosis (grade ≥1) was analyzed as dichotomous variables. In multivariate logistic regression analysis (shown in Table 5), HOMA-IR was significantly associated with steatosis after adjusting for age, sex, neck circumference, BMI, and smoking (model 1) (OR, 1.666; 95% CI, 1.187–2.340; $p = 0.003$). Moreover, adjusting for diabetes, hypertension, and dyslipidemia (model 2) did not alter the association between HOMA-IR and steatosis (OR, 1.625; 95% CI, 1.138–2.321; $p = 0.008$). On the basis

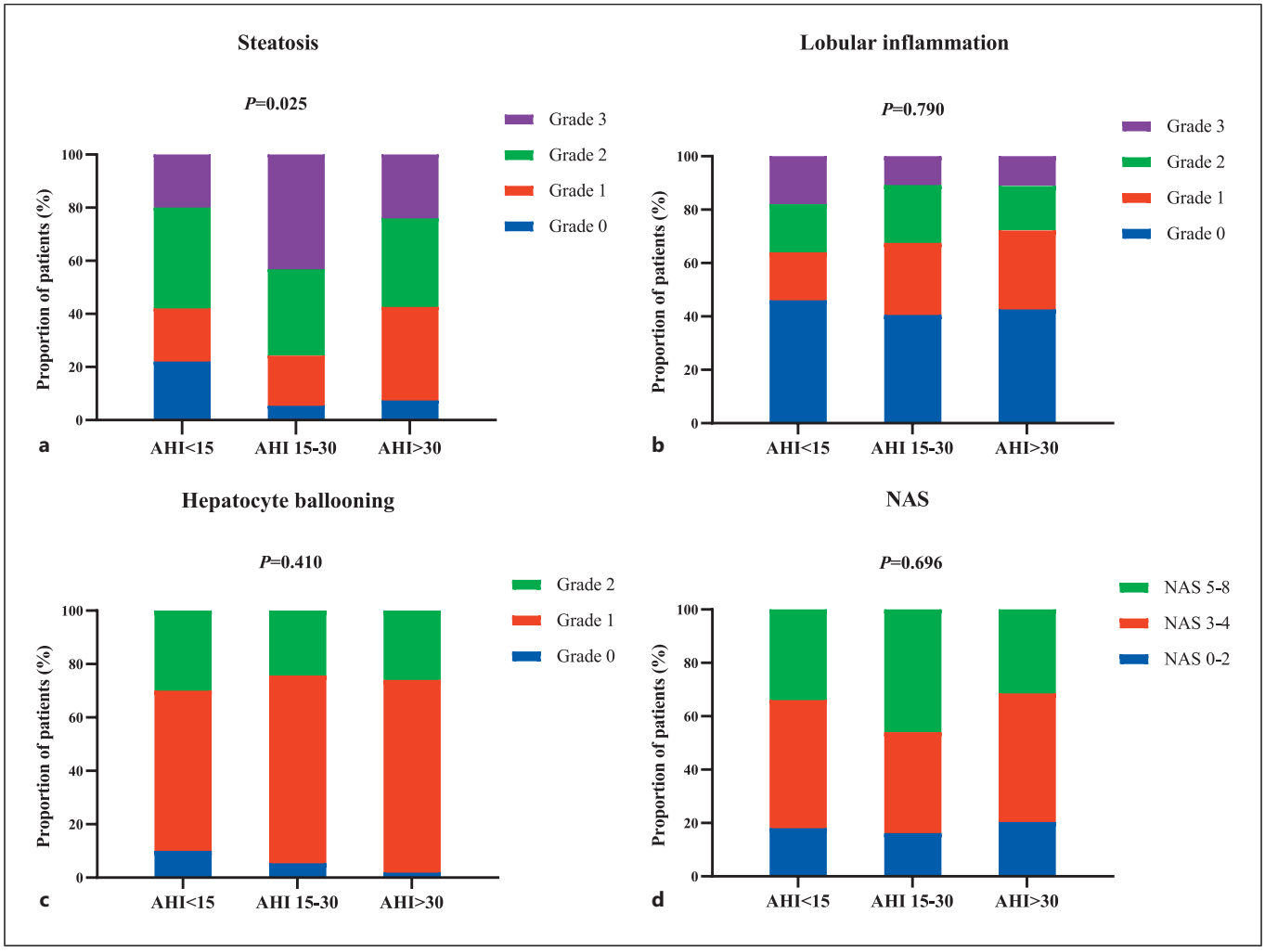

Fig. 2. Proportion of patients in different grades of hepatic histopathology and NAS depending on severity of AHI. **a** Steatosis represented as grade 0, grade 1, grade 2, grade 3. **b** Lobular inflammation represented as grade 0, grade 1, grade 2, grade 3. **c** Hepatocyte ballooning represented as grade 0, grade 1, grade 2. **d** NAS presented as 0–2, 3–4, 5–8. AHI, apnea-hypopnea index; NAS, non-alcoholic fatty liver activity score.

of model 2, hepatocyte ballooning and intralobular inflammation were further adjusted, and the association was still statistically significant (OR, 1.663; 95% CI, 1.146–2.413; p = 0.007). More importantly, the association still existed after adjusting for AHI (OR, 1.671; 95% CI, 1.148–2.434; p = 0.007), suggesting an independent effect of insulin resistance on steatosis.

Discussion

These findings demonstrate a high prevalence of OSA and NAFLD coexistence among patients with severe obesity that underwent bariatric surgery. The relationship between OSA and NAFLD is unclear, we observed an association between AHI and insulin resistance, and insulin resistance was an independent risk factor for hepatic steatosis.

The prevalence of OSA was 90.07% in our study, which was consistent with other studies that have shown a prevalence of more than 70% in the severe obese and bariatric surgery population [24–28]. In addition, the BMI presented a positive statistically significant correlation with AHI, ODI, and T90%, but a negative correlation with $LaSO_2$ and average SpO_2. Our findings support the view of increased prevalence of OSA that is directly related to increased BMI [29]. Furthermore, the prevalence of NAFLD and NASH patients in our study is

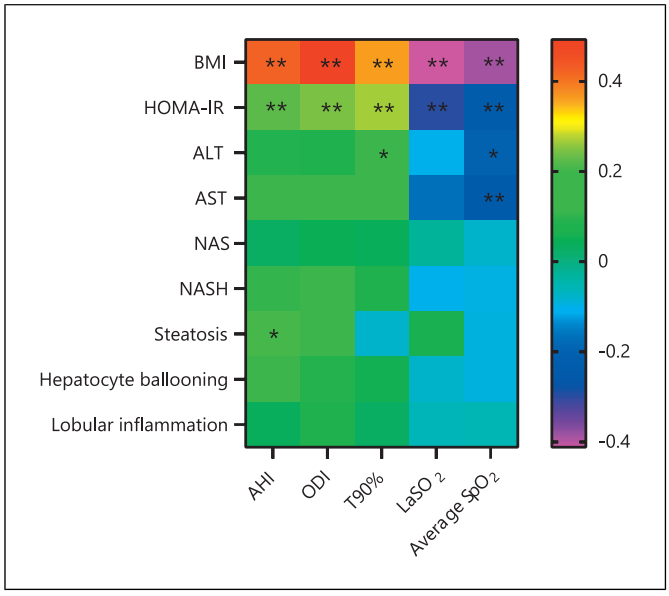

Fig. 3. Relationship between study sleep variables and BMI, HOMA-IR, and NAFLD-related variables. Heat map showing Spearman correlation between study sleep variables (AHI, ODI, T90%, $LaSO_2$, average SpO_2) and BMI, HOMA-IR, ALT, AST, NAS, NASH, steatosis, hepatocyte ballooning, and lobular inflammation. *$p < 0.05$, **$p < 0.01$. NAFLD, non-alcoholic fatty liver disease; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; T90%: the percentage of total sleep time spent with SpO_2 <90; $LaSO_2$, lowest O_2 saturation; average SpO_2, average O_2 saturation; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HOMA-IR, homeostasis model assessment of insulin resistance; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis.

consistent with those found by others in bariatric surgery candidates [24, 30]. This highlighted the importance of screening patients with OSA and NAFLD in patients with severe obesity, especially for the bariatric surgery candidates.

The results of existing researches on the relationship between OSA and NAFLD are controversial. Jin S et al. [11] conducted a systematic literature review between January 2007 and April 2017, and 9 studies including 2,272 participants were assessed for inclusion. Meta-regression analysis revealed that OSA was remarkably associated with severity of steatosis, hepatocyte ballooning, intralobular inflammation, and fibrosis, but not NAS. In addition, parallel result was implied by Mishra P et al. that OSA is associated not only with NASH, but also with pathological components of NASH such as steatosis, inflammation, and fibrosis. These studies suggest that OSA may play a major role in the occurrence and progression of NAFLD.

Unfortunately, correlation between OSA parameters with NASH and the NAS has not been demonstrated in the present study. The results of two studies conducted by Jouet et al. [31] and Ulitsky et al. [32] failed to confirm an association between OSA and NASH, which support our results. The study by Daltro C et al. [28] evaluated 40 patients with obesity submitted to bariatric surgery and analyzed the association between OSA and the features of NAFLD including severity of steatosis, intralobular inflammation, hepatocyte ballooning, and fibrosis from the intraoperative liver biopsies. Consistent with our findings, they demonstrated that OSA was associated with insulin resistance, not NASH severity.

Although clinical studies have demonstrated a relationship between OSA and NAFLD, the study on the association between OSA parameters and liver histology in NAFLD, including steatosis, hepatocyte ballooning, and lobular inflammation, is limited. Schwenger et al. found the AHI correlated with liver inflammation in a single-center cross-sectional study of 61 patients undergoing bariatric surgery [24], while our study found that AHI is associated with steatosis in correlation analysis.

So far, related studies have reveled conflicting results and further researches are warranted. Liver pathology data for this study were obtained from intraoperative wedge biopsies during bariatric surgery. Liver biopsy methods include needle biopsy and wedge biopsy. Needle biopsy provides a sample of liver parenchyma, while wedge biopsy provides a "wedge" of liver tissue removed from its surface. They are much larger, but are generally not optimal for assessment of liver fibrosis and/or inflammation [33]. Since this study used wedge-shaped liver biopsy, it may have influenced the analysis of the relationship between OSA and lobular inflammation to some extent.

It is relevant to especially emphasize that the definition of NASH has changed over time, and the currently accepted pathological diagnostic criteria require the presence of >5% steatosis, hepatocyte ballooning, and inflammation [34]. However, most studies used NAS ≥5 as the diagnostic criteria for NASH or did not consider hepatocyte ballooning as a necessary condition for the diagnosis of NASH. This histological definition of NASH may lead to severe misclassification, resulting in patients with simple steatosis being misclassified as NASH, and is not recommended [35]. Therefore, we speculate that the conflicting correlation between OSA and NASH may also be affected by the different definition criteria of NASH in related studies. In our study, we defined NASH as the presence of steatosis, hepatocyte ballooning, and

Table 4. Characteristics of the participants according to the grade of steatosis

Variables	Steatosis (grade 0), n = 17	Steatosis (grade 1–3), n = 124	p value
Clinical characteristics			
Gender, n (%)			
Male	1 (5.88)	29 (23.39)	0.122
Female	16 (94.12)	95 (76.61)	
Age, years	29.24±5.96	31.02±6.94	0.313
BMI, kg/m^2	38.47±8.34	39.94±6.88	0.420
Waist circumference, cm	109.00 (101.50–124.50)	117.00 (108.00–128.75)	0.139
Neck circumference, cm	42.00 (38.00–45.00)	42.00 (40.00–45.00)	0.583
Smoking, n (%)	0 (0.00)	17 (13.71)	0.085
Comorbidity, n (%)			
Diabetes	5 (29.41)	44 (35.48)	0.622
Arterial hypertension	7 (41.18)	37 (29.84)	0.344
Dyslipidemia	13 (76.47)	111 (89.52)	0.127
OSA (AHI ≥5 ev/h)	14 (82.35)	113 (91.13)	0.378
Sleep study characteristics			
AHI	8.40 (6.50–28.90)	20.90 (12.75–51.10)	0.014*
ODI	11.00 (4.15–28.45)	17.65 (9.68–42.20)	0.089
T90%, n (%)	0.10 (0.00–2.90)	0.30 (0.00–6.48)	0.366
$LaSO_2$, n (%)	86.00 (73.00–89.00)	83.00 (74.25–88.00)	0.470
Average SpO_2, n (%)	95.00 (94.00–97.00)	95.00 (93.00–96.00)	0.277
Biochemical characteristics			
ALT, U/L	20.00 (12.25–29.50)	49.50 (32.00–83.00)	0.000*
AST, U/L	17.00 (14.00–18.50)	27.50 (19.00–48.50)	0.000*
ALKP, U/L	73.00 (67.50–85.50)	69.00 (60.00–81.75)	0.257
GGT, U/L	19.00 (16.50–38.50)	41.00 (25.25–60.50)	0.001*
TC, mmol/L	4.66 (4.37–5.35)	4.97 (4.48–5.53)	0.317
TG, mmol/L	1.55 (1.08–1.77)	1.86 (1.47–2.72)	0.001*
HDL-C, mmol/L	1.17 (1.04–1.27)	1.05 (0.94–1.19)	0.045*
LDL-C, mmol/L	3.08±0.76	3.28±0.74	0.284
Fasting glucose, mmol/L	5.15 (4.70–5.62)	5.61 (4.98–6.97)	0.011*
Fasting insulin, μIU/mL	16.00 (12.15–25.90)	22.85 (17.53–33.10)	0.016*
HOMA-IR	4.42 (2.49–6.29)	6.07 (4.39–8.36)	0.005*

BMI, body mass index; OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; T90%, the percentage of total sleep time spent with SpO_2 <90; $LaSO_2$, lowest O_2 saturation; average SpO_2, average O_2 saturation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALKP, alkaline phosphatase; GGT, gamma glutamyl transferase; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance. *p < 0.05.

intralobular inflammation, and simultaneously assessed NAFLD activity with NAS rather than defined NASH.

In addition, different populations included in clinical studies may also affect the association between OSA and NAFLD. The impact of the metabolic syndrome on the severity of NAFLD is beyond doubt [36]. Peter Benotti et al. [37] found that the association between OSA and NAFLD depended on the presence of metabolic syndrome. They demonstrated that the association of OSA with lobular inflammation and fibrosis was only present in the absence of metabolic syndrome. However, in the metabolic syndrome cohort, the effect of hypoxia appeared to be overwhelmed by the strong effect of metabolic syndrome on NAFLD severity. The majority of bariatric surgery candidates included in this study had metabolic syndrome, affecting the relationship between OSA and NAFLD.

However, the underlying mechanism of the relationship between OSA and NAFLD remains a mystery. Although the pathogenesis of NAFLD remains unclear, the "two-hit" hypothesis is a prevalent theory for the progression of NAFLD [38]. Insulin resistance promotes the accumulation of massive intrahepatic lipids in the liver, leading to the "first-hit." In contrast to the previous "two-

Table 5. Multivariate logistics regression analyses of the association between steatosis and HOMA-IR

	OR	95% CI	*p* value
Model 1	1.666	1.187–2.340	0.003*
Model 2	1.625	1.138–2.321	0.008*
Model 3	1.663	1.146–2.413	0.007*
Model 4	1.671	1.148–2.434	0.007*

Model 1: adjusted for age, gender, neck circumference, BMI, smoking. Model 2: adjusted for variables in model 1 and also adjusted for diabetes, hypertension, and dyslipidemia. Model 3: adjusted for variables in model 2 and also adjusted for hepatocyte ballooning and lobular inflammation. Model 4: adjusted for variables in model 3 and also adjusted for AHI. *$p < 0.05$.

hit" theory, increasing evidence favors the importance of the "multiple-hit" theory in the pathogenesis of NAFLD: including lipotoxicity, oxidative stress, insulin resistance, gut microbiota, dysfunctional mitochondria, and genetic and epigenetic factors [5]. Both the "two-hit" theory and the "multiple-hit" theory affirm the importance of insulin resistance in the progression of NAFLD. Our data demonstrate strong correlations between insulin resistance and steatosis in patients with severe obesity. At multivariable analysis, we demonstrated that insulin resistance was an independent risk factor for hepatic steatosis. The present results support the idea that insulin resistance plays a crucial role in the pathogenesis of NAFLD.

Coincidentally, recent studies have shown an association between insulin resistance and OSA [39–41]. The mechanisms involved are the release of catecholamines due to microarousal, followed by activation of the hypothalamic-pituitary-adrenal axis to increase the production of cortisol, both of which are antagonists of insulin [42]. In addition, epidemiologic data [10, 43] and an interventional study [13] both indicate that OSA as an independent factor of insulin resistance predisposes patients to progression of hepatic steatosis [14]. But this may not actually be the case, in our study, the HOMA-IR showed a statistically significant, but weak correlation with the markers of the severity of OSA, such as AHI, ODI, and T90%. Besides, OSA not only causes insulin resistance, but also exacerbates NAFLD through chronic intermittent hypoxia [44]. OSA disrupts the balance of oxidants and antioxidants, resulting in dyslipidemia, elevated circulating free fatty acid levels, and lipid peroxidation, which are involved in the NAFLD [8].

It is generally known that insulin resistance and fatty acid metabolism disorders can lead to hepatic steatosis, and insulin resistance is also an independent risk factor for OSA [25]. Previous studies of OSA and NAFLD interactions had emphasized potential importance of insulin resistance, which is worth exploring when studying this association. Therefore, it is speculated that OSA may contribute to increased insulin resistance, which in turn increases hepatic steatosis and then leads to the progression of NAFLD [44]. The above hypothesis was confirmed by Daltro C et al. [28], and a positive correlation between HOMA-IR and steatosis severity was observed in their study, suggesting that OSA-induced hepatic steatosis may be mediated by exacerbating insulin resistance. This finding is consistent with our results.

In our study, we investigated the association between OSA and NAFLD in Chinese patients with severe obesity. Moreover, intraoperative liver biopsy was conducted in all study subjects and the severity of steatosis, intralobular inflammation, and ballooning were analyzed. In addition, this study selected Chinese obese people as the study population and provided evidence of different races for OSA and NAFLD. It is undeniable that there are still some limitations in this study. First, this study used a cross-sectional design and cause-and-effect conclusions could not be made. Second, sample size was limited due to the invasive nature of liver biopsies and the availability of PSG. Third, the results of this study were obtained in severe obese population, who may not be representative of the entire NAFLD patient population. Furthermore, obesity itself is a cause of NAFLD, leading to a strong confounding variable. Another major limitation of the present study was the lack of histological data on hepatic fibrosis, thus making it impossible to assess the effect of OSA on fibrosis.

Conclusion

In conclusion, the present study suggests that NAFLD was associated with the insulin resistance but not the severity of OSA in severe obese populations. All studies were observational and prospective studies were lacking to better assess this association. To better explore the potential therapeutic implications and disease prevention progress, future research should focus on the specific mechanisms of insulin resistance in the progression of OSA and NAFLD.

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Statement of Ethics

The study was approved by the Tianjin Medical University General Hospital Institutional Review Board (approval number IRB2020-YX-029-01) with wavier of individual patient consent and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Conflict of Interest Statement

The authors declared no conflict of interest.

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Author Contributions

C.Z., S.T., and J.X. designed research, collected clinical data, and wrote the manuscript. Y.Z. was involved in clinical data collection and revision of the paper. L.S., J.Z., and M.L. designed the study, and revised and edited the manuscript paper. L.D. was accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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