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SCIENTIFIC INVESTIGATIONS

Continuous Positive Airway Pressure Therapy on Nonalcoholic Fatty Liver Disease in Patients With Obstructive Sleep Apnea

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Study Objectives: Obstructive sleep apnea (OSA) is associated with nonalcoholic fatty liver disease (NAFLD) and related advanced fibrosis. We studied the treatment of OSA with continuous positive airway pressure (CPAP) in a population with NAFLD.

Methods: Using an institutional database (2010–2014), we identified patients with NAFLD and OSA and studied changes in serum aminotransferases before and after CPAP use. We defined suspected NAFLD (sNAFLD) as serum alanine aminotransferase (ALT) > 30 U/L for men and > 19 U/L for women in the absence of known causes of chronic liver disease. The aspartate aminotransferase (AST) to platelet ratio index (APRI) was used to determine significant fibrosis. Consistent CPAP use for more than 3 months with adequate adherence parameters defined good adherence.

Results: Of 351 patients with OSA on CPAP treatment, majority (mean age 57.6 years, 59.3% male) had abnormal ALT, and 89.4% met the criteria for sNAFLD. The prevalence of sNAFLD was higher among patients with moderate to severe OSA (90.6%) versus mild OSA (86.3%). There was a statistically significant improvement in AST, ALT, and APRI with CPAP therapy (all $P < .01$). There was an apparent dose-response relationship: patients with good adherence to CPAP showed a significantly larger decrease in AST and ALT than did those with poor adherence ($P < .01$). Multivariable logistic regression analysis showed CPAP treatment with adequate adherence (odds ratio = 3.93, 95% confidence interval = 1.29–11.94) was an independent predictor of regression of sNAFLD after adjusting for obesity class and severity of OSA.

Conclusions: OSA treatment with CPAP was associated with significant biochemical improvement and reduction in NAFLD-related fibrosis.

Keywords: chronic intermittent hypoxia, hepatic steatosis, nonalcoholic steatohepatitis, sleep

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Obstructive sleep apnea (OSA) was associated with nonalcoholic fatty live disease (NAFLD) and NAFLD-related advanced fibrosis. However, the effect of continuous positive airway pressure (CPAP) therapy on NAFLD and advanced fibrosis is largely unknown.

Study Impact: CPAP treatment, even for a relatively short term, plays an important role in improving the serum aminotransferase activity in subjects with OSA. In addition, CPAP treatment may play a pivotal role in the improvement of NAFLD-related fibrosis.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in the United States, affecting 20% to 30% of the general population and up to 70% of the diabetic and obese population.[1] In fact, the burden of NAFLD is projected to increase over the next decade in the absence of an effective therapy. With the rising rates of diabetes and obesity, it is expected that the incidence of NAFLD will increase, and as this population ages cirrhosis and end-stage liver disease will develop in a substantial number of them. Currently, NAFLD is the most rapidly rising etiology for liver transplantation in the United States and is on a trajectory to become the leading indication for liver transplant in the next decade or so.[2] The increasing prevalence of NAFLD, particularly NAFLD with advanced fibrosis, is concerning because this subset of patients appears to experience higher mortality from both non-liver-related and liver-related complications than the general population.[3] NAFLD with advanced fibrosis is known to be a significant predictor of mortality, primarily from cardiovascular causes, independent of other factors.[3] Because there is no current established (Food and Drug Administration approved) pharmacologic therapy for NAFLD other than lifestyle modifications, there is an unmet need to develop a viable therapeutic strategy for NAFLD and/or NAFLD-related with advanced fibrosis.

Obstructive sleep apnea (OSA) is a highly prevalent disease, affecting an estimated 24% of middle-aged men and 9% of women, with moderate to severe OSA affecting 9% and 4%, respectively.[4] It is estimated that 50% to 60% of patients with obesity and concomitant metabolic syndrome develop OSA.[5] Several experimental studies have demonstrated that chronic intermittent hypoxia (CIH) in the setting of OSA may be associated with the presence and severity of NAFLD.[6–8] Similarly, a recent meta-analysis showed that OSA was strongly associated

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with NAFLD and that patients with OSA had a 2.6-fold greater risk of advanced fibrosis in those with NAFLD.[9,10] Although no current effective pharmacologic treatment of NAFLD and/or NAFLD-related advanced fibrosis exists, continuous positive airway pressure (CPAP) beyond lifestyle modification is an effective treatment for OSA and may ameliorate metabolic and cardiovascular disease.[11,12] However, it is currently unclear whether CPAP treatment, which is the first-line therapy of OSA, would modify the presence of NAFLD and the severity of advanced fibrosis in patients with both NAFLD in the setting of OSA.

The aim of this study is to determine whether the intervention with CPAP treatment for OSA would modify the presence of NAFLD and the severity of advanced fibrosis in NAFLD.

METHODS

Patient Selection

We identified CPAP-treated OSA adult patients age 20 years or older who had available serum alanine aminotransferases (ALT) data before (within 3 months) and after (within 6 months) CPAP treatment using the Stanford Medicine Research Data Repository (STARR) from January 2010 to December 2014. STARR is a research and development project at Stanford University to create a standards-based informatics platform supporting clinical and translational research.[13] This prospective database could track all patients undergoing CPAP treatment. From this database, all adults who had ALT data within 3 months before CPAP treatment and 6 months after CPAP treatment were identified. The inclusion criteria were a clinical diagnosis of OSA by polysomnography, CPAP treatment with a diagnosis of OSA, age 20 years or older, and patients with available ALT data. Subjects who underwent CPAP-based therapy were recommended and prescribed to initiate CPAP following polysomnography by a sleep medicine specialist. None of the patients in our study was treated with CPAP under an investigational protocol; the CPAP use is part of a routine clinical care plan for this indication at our center and considered standard of care.

We excluded the following patients: (1) those with prior OSA treatment with CPAP (n = 15) or bariatric surgery during CPAP (n = 3); (2) evidence of a specific etiology for liver disease such as viral hepatitis B or C, hemochromatosis, autoimmune, cholestatic liver disease, alcoholic liver disease, liver metastasis and/or liver transplantation (n = 34); (3) history of heart and/or lung transplantation (n = 16); (4) insufficient ALT follow-up period (n = 17, < 2 months); and (5) no polysomnography data (n = 15). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of the Stanford University School of Medicine.

Clinical and Laboratory Assessment

Information such as anthropometric, laboratory data, and polysomnography results as well as CPAP adherence results were extracted from the database and reviewed in electronic medical records. From the database and medical records, laboratory data were obtained, including ALT, aspartate aminotransferase (AST), albumin, platelet count, and fasting glucose. Diabetes mellitus was defined as a fasting glucose ≥ 126 mg/dL or treatment with antidiabetic drugs or documented diagnosis and treatments in the medical charts. Height and body weight could be retrieved from polysomnography reports. Body mass index (BMI) was calculated as weight (kg) divided by height-squared (m^2).

Definition of Suspected NAFLD and Fibrosis

Suspected NAFLD (sNAFLD) was diagnosed if serum ALT > 30 U/L for men and > 19 U/L for women[14,15] in the absence of other known causes of chronic liver disease (eg, alcoholic liver disease, chronic hepatitis B or C, etc.). Of the subjects with sNAFLD, we identified those with advanced fibrosis by using the AST to platelet ratio index (APRI) score. The APRI score was calculated using the published formula: APRI score = ([AST / upper limit of normal] / platelet count [10^9/L]) × 100.[16] We used the previously published cutoffs for low and high probability of significant fibrosis, namely 0.5 and 0.7, respectively.[17]

Severity of OSA and CPAP Treatment

All patients underwent overnight standard polysomnography and a CPAP titration study to allow for the individual adjustment of CPAP therapy either after discussion with participants about the polysomnography report or during the same night (split-night sleep study). Apnea was defined as a near-complete cessation of nasal pressure for 10 seconds or longer. Hypopnea was defined as a drop by 30% or greater from preevent baseline for 10 seconds or longer. Oxygen desaturation was defined as any respiratory event during sleep with at least a 3% drop. The apnea-hypopnea index (AHI) was calculated as the sum of all apneic and hypopneic events divided by the hours of total sleep time.[18] OSA was defined as an AHI score of 5 or more events/h. OSA severity was described as mild for an AHI score of 5 to less than 15, moderate for an AHI score of 15 to 30, and severe for an AHI score of more than 30.[19] Adequate CPAP adherence is typically assessed by a cutoff (eg, 4 h/night > 70% of the time). CPAP adherence was defined as "good" for at least 3 months of treatment with adequate CPAP adherence, "partial" for less than 3 months of treatment with adequate CPAP adherence, and "poor" for less than 3 months of treatment without adequate CPAP adherence.

Statistical Analysis

Continuous variables were expressed as the mean ± standard deviation or medians (and interquartile ranges). Categorical variables were represented as proportions and percentages. Comparisons between groups were analyzed by means of independent *t* tests or analysis of variance if the data were normally distributed and a Mann-Whitney *U* test or Kruskal-Wallis test if not. A chi-square test or Fisher exact test was used to compare proportions. The treatment effect of CPAP was compared using a paired *t* test if the data were normally distributed and the Wilcoxon signed-rank test if they were not. Values of $P < .05$ were considered statistically significant. Statistical analysis was carried out using SPSS 23.0 (IBM Corp., Armonk, New York, United States).

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Table 1—Demographic and baseline characteristics of the study population.

	Total Population (n = 351)	Mild OSA (AHI 5–14) (n = 73)	Moderate OSA (AHI 15–29) (n = 102)	Severe OSA (AHI ≥ 30) (n = 176)	*P*
Age (year)	57.6 ± 14.8	54.2 ± 16.5	57.7 ± 15.0	59.0 ± 13.8	.068
Male (%)	208 (59.3)	37 (50.7)	53 (52.0)	118 (67.0)	.012
Body mass index	32.2 ± 8.0	31.6 ± 10.1	29.9 ± 6.4	33.9 ± 9.3	.001
Ethnicity					.295
White	194 (55.3)	37 (50.7)	59 (57.8)	98 (55.7)	
African- Americans	28 (8.0)	10 (13.7)	4 (3.9)	14 (8.0)	
Asians	65 (18.5)	12 (16.4)	23 (22.5)	30 (17.0)	
Hispanics	64 (18.2)	14 (19.2)	16 (15.7)	34 (19.3)	
AHI (n = 351)	37.21 ± 27.02	9.82 ± 3.05	21.30 ± 4.33	57.79 ± 23.64	< .001
ODI (n = 322)	24.48 ± 26.20	4.08 ± 3.25	11.02 ± 6.10	42.21 ± 27.94	< .001
MOS (n = 350)	83.5 ± 7.9	89.1 ± 5.4	85.7 ± 5.0	79.9 ± 8.3	< .001
Diabetes	108 (30.8)	19 (26.0)	21 (20.6)	68 (38.6)	.004
Glucose (n = 318)	117.5 ± 43.9	110.5 ± 31.9	109.7 ± 31.5	124.5 ± 52.0	.013
Albumin (n = 328)	3.78 ± 0.42	3.79 ± 0.43	3.86 ± 0.36	3.74 ± 0.44	.076
AST (n = 337)	28.0 ± 15.8	25.1 ± 9.6	28.7 ± 12.9	28.7 ± 18.9	.243
ALT (n = 351)	44.5 ± 22.3	40.2 ± 14.7	43.8 ± 17.9	46.7 ± 26.7	.103
Platelet (n = 302)	224.7 ± 69.0	226.0 ± 68.1	230.6 ± 62.6	221.0 ± 72.7	.589
APRI (n = 265)	0.35 ± 0.26	0.31 ± 0.19	0.34 ± 0.20	0.38 ± 0.31	.199
sNAFLD	313 (89.4)	63 (86.3)	96 (94.1)	155 (88.1)	.173
Fibrosis (by APRI)					
No fibrosis	225 (84.9)	49 (92.5)	66 (88.0)	110 (80.3)	.123
Intermediate	25 (9.4)	2 (3.8)	4 (5.3)	19 (13.9)	
Advanced	15 (5.7)	2 (3.8)	5 (6.7)	8 (5.8)	
Adherence					.483
Poor	106 (30.2)	24 (32.9)	29 (28.4)	53 (30.1)	
Partial	99 (28.2)	23 (31.5)	33 (32.4)	43 (24.4)	
Good	146 (41.6)	26 (35.6)	40 (39.2)	80 (45.5)	

Data are shown as the mean ± standard deviation and number (proportion). AHI = apnea-hypopnea index, ALT = alanine aminotransferase, APRI = AST to platelet ratio index, AST = aspartate aminotransferase, MOS = minimum oxygen saturation, ODI = oxygen desaturation index (the number of times per hour of sleep that the blood's oxygen level drops by 3 percent or more from baseline), OSA = obstructive sleep apnea, sNAFLD = suspected nonalcoholic fatty liver disease.

RESULTS

In the STARR database, there were 458 patients who underwent CPAP treatment and had available ALT data for pre- and post-CPAP treatment. **Figure S1** in the supplemental material displays the study flow chart diagram and exclusion criteria. When the study eligibility criteria were applied, 351 patients were suitable subjects for this analysis.

Population characteristics of the 351 patients with OSA who underwent CPAP (mean age 57.6 years, 59.3% male) are shown in **Table 1**, stratified by spectrum of OSA severity. A baseline comparison revealed that age, sex, BMI, and fasting glucose were less favorable in subjects with severe OSA compared to those with mild OSA. The prevalence of diabetes was higher in subjects with severe OSA than in those with mild OSA. No difference was found between groups in albumin, liver enzyme, platelet count, APRI score, and CPAP compliance. Most of the patients who received CPAP had abnormal ALT, and 89.4% met the definition of sNAFLD. The prevalence of sNAFLD was higher (90.6%) among patients with moderate to severe OSA versus among those with mild OSA (86.3%). Similarly, significant fibrosis was correlated with OSA severity (7.6% for mild OSA versus 12.0% moderate OSA versus 19.7% for severe OSA, $P = .079$). As shown in **Table S1** in the supplemental material, AHI and ALT were the only two variables that differed significantly according to adherence status. Patients with more severe OSA and with more advanced liver injury tend to demonstrate a higher level of adherence to CPAP treatment. There were no differences in age, BMI, ethnicity, blood glucose levels, prevalence of diabetes, and prevalence of NAFLD according to adherence status.

As shown in **Table 2**, the results for all variables except serum ALT levels were not available for all patients because of missing values. Therefore, the comparison between pre- and post-CPAP treatment was based on the results of 330 (AST), 255 (platelet), 318 (albumin), 300 (fasting glucose), and 221 (APRI score) patients. There was a statistically significant improvement in ALT, AST, and APRI scores with CPAP therapy in the entire population (all $P < 0.01$). However, CPAP treatment did not improve the fasting glucose, platelet count, or

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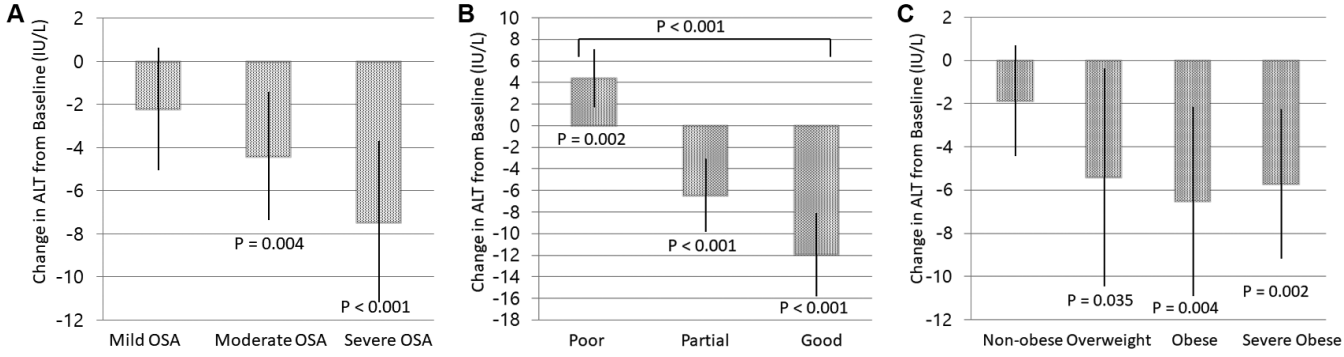
Table 2—Changes in laboratory data and fibrosis index following CPAP treatment.

	Post-CPAP	Pre-CPAP	Difference	95% CI of Difference	*P*
ALT (n = 351)	39.1 ± 16.1	44.5 ± 22.3	−5.47	−7.61 to −3.33	< .001
AST (n = 330)	24.9 ± 9.7	27.9 ± 15.9	−3.05	−4.67 to −1.43	< .001
Platelet (n = 255)	225.0 ± 79.4	224.9 ± 70.5	0.12	−6.72 to 6.96	.972
Albumin (n = 318)	3.77 ± 0.42	3.80 ± 0.42	−0.006	−0.047 to 0.035	.764
Glucose (n = 300)	116.2 ± 42.5	117.6 ± 44.7	−1.43	−6.49 to 3.62	.577
APRI (n = 221)	0.31 ± 0.18	0.35 ± 0.27	−0.04	−0.07 to −0.01	.004

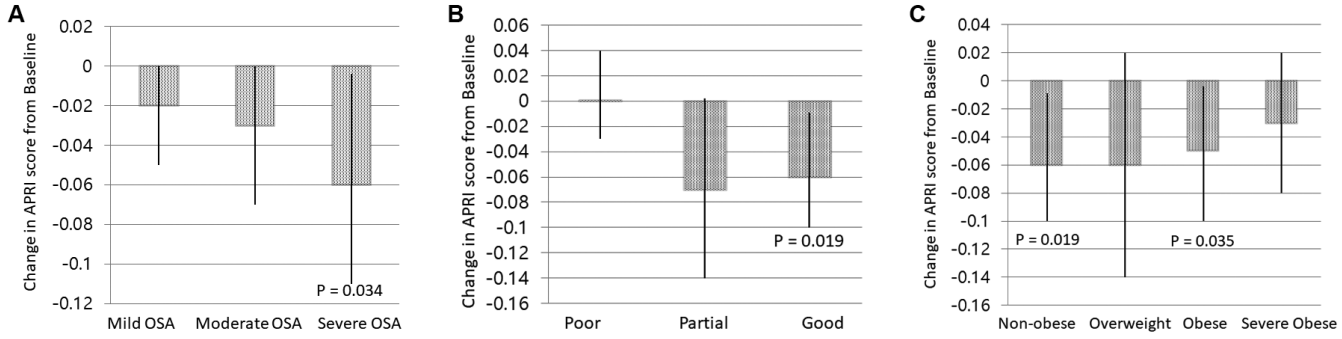
Data are shown as the mean ± standard deviation. Difference was calculated by subtracting the value after CPAP treatment from the value before CPAP treatment. ALT = alanine aminotransferase, APRI = AST to platelet ratio index, AST = aspartate aminotransferase, CI = confidence interval, CPAP = continuous positive airway pressure.

Figure 1—Changes from baseline in ALT levels.



Changes in ALT levels according to severity of OSA **(A)**, adherence status **(B)**, and obesity status **(C)**. Black lines represent 95% confidence intervals. *P* values without brackets represent the change from baseline in each group. *P* values with brackets are for intergroup differences during follow-up. ALT = alanine aminotransferase, OSA = obstructive sleep apnea.

Figure 2—Changes from baseline in APRI score.



Changes in ALT levels according to severity of OSA **(A)**, adherence status **(B)**, and obesity status **(C)**. Black lines represent 95% confidence intervals. *P* values without brackets represent the change from baseline in each group. *P* values with brackets are for intergroup differences during follow-up. ALT = alanine aminotransferase, APRI = aspartate aminotransferase to platelet ratio index, OSA = obstructive sleep apnea.

albumin level. Similarly, there were no significant changes in fasting glucose, platelet count, or albumin level after treatment within or among OSA severity and obesity status levels (**Table S1** in the supplemental material).

There was a dose-response relationship between OSA severity and ALT improvement (**Figure 1A**, **Table S2** in the supplemental material). Among the patients with sNAFLD, the improvements in the APRI score after CPAP treatment showed a dose-response relationship with OSA severity (**Figure 2A**). The serum ALT levels were significantly reduced in patients with severe OSA or moderate OSA but not in patients with mild OSA, and the reduction in the ALT levels was greater in patients with severe OSA than in those with moderate OSA. The trends in results were similar for the serum AST levels. The magnitude of effect associated with CPAP therapy in the three levels of OSA severity was somewhat larger for serum ALT levels than for AST.

As shown in **Figure 1B**, **Table S3** in the supplemental material, there was an apparent dose-response relationship; patients with good CPAP adherence showed a significantly larger

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decrease in ALT and AST than those with poor adherence ($P < .01$). CPAP treatment with good adherence significantly improved liver enzymes compared with those with poor adherence. Although a significant reduction in the liver enzyme levels was noticed in patients who were adherent with CPAP treatment, these levels increased in patients with poor adherence. In terms of hepatic fibrosis, there was a trend for an improving APRI score correlating with adherence status; the trend did not reach statistical significance (**Figure 2B**, **Table S3**). The APRI score was significantly reduced in patients with good adherence ($P = .019$) but not in those with partial or poor adherence.

Improvements in the serum aminotransferase and APRI score after CPAP treatment showed consistent results, regardless of the baseline obesity status (**Figure 1C**, **Figure 2C** and **Table S4** in the supplemental material). Analysis of the changes observed in the serum ALT, serum AST, and APRI scores revealed no evidence of significant differences among the four obesity status groups. The decline in ALT and AST was similar in the obesity severity status, and there was no discernible decline in APRI score among the four obesity groups. Even in the nonobese group, serum AST and APRI scores decreased significantly, but the ALT levels also declined but did not reach statistical significance.

The prevalence of sNAFLD decreased after CPAP treatment. After CPAP treatment, 36 of the 314 patients with sNAFLD no longer fulfilled the criteria for sNAFLD (**Table S5** in the supplemental material). Normalized ALT was prominent in patients with moderate-severe OSA compared to patients with mild OSA. In addition, normalized ALT occurred more frequently among patients with good (versus poor) CPAP adherence ($P < .01$). Normalized ALT was significantly higher in patients with good adherence (15.1%) than in patients with poor adherence (3.8%), and was greater in patients with good adherence than in patients with partial adherence (10.1%). On the contrary, normalized ALT after CPAP treatment showed consistent results, regardless of the baseline obesity status.

In the univariate analysis (**Table 3**), normalized ALT was significantly associated with male sex and good CPAP adherence; however, normalized ALT was not associated with age, obesity status, OSA severity, or ethnicity. In the multivariable logistic regression analysis, CPAP treatment with good adherence (odds ratio [OR] 3.89, 95% confidence interval [CI] 1.26–12.06) and male sex (OR 4.79, 95% CI 1.80–12.73) were independent predictors of normalized ALT after adjusting for obesity status and OSA severity at baseline.

Because of the retrospective study design, the ALT levels were variably assessed, with some patients having data for 2 months after CPAP treatment and others having data for more than 6 months after CPAP treatment. There was an apparent dose-response relationship; patients with ALT data more than 6 months after CPAP treatment showed a significantly larger decrease in both ALT and AST than did those with ALT data within 2 to 3 months after CPAP treatment (**Table 4**).

DISCUSSION

In this study, effective CPAP treatment for OSA was associated with improvement in serum aminotransferase activity, a

Table 3—Univariable and multivariable analyses for the factor of normalized alanine aminotransferase.

	Univariable Model		Multivariable Model	
Adherence	OR (95% CI)	*P*	OR (95% CI)	*P*
Poor	1		1	
Partial	2.86 (0.86–9.45)	.085	2.78 (0.81–9.60)	.105
Good	4.29 (1.43–12.87)	.009	3.89 (1.26–12.06)	.019

The multivariable model was adjusted for age, sex, ethnicity, obesity status, diabetes, and severity of obstructive sleep apnea. CI = confidence interval, OR = odds ratio.

Table 4—Changes in serum aminotransferase and fibrosis index after CPAP treatment according to the serum aminotransferase follow-up period.

	Post-CPAP	Pre-CPAP	Difference	95% CI of Difference	*P*
ALT (n = 351)					**.013***
2–3 months (n = 85)	40.8 ± 16.9	42.2 ± 17.7	−1.40	−4.36 to 1.56	.349
4–5 months (n = 107)	39.9 ± 15.2	45.4 ± 26.7	−5.59	−4.75 to 0.62	.028
6 months or longer (n = 159)	37.6 ± 16.1	45.1 ± 21.4	−7.56	−10.52 to −4.60	< .001
AST (n = 330)					**.521***
2–3 months (n = 81)	24.4 ± 10.1	27.0 ± 13.4	−2.59	−5.13 to −0.06	.045
4–5 months (n = 107)	24.5 ± 8.1	26.6 ± 13.3	−2.06	−4.75 to 0.62	.131
6 months or longer (n = 159)	25.3 ± 10.3	29.2 ± 18.3	−3.88	−6.65 to −1.11	.006
APRI (n = 252)					**.168***
2–3 months (n = 63)	0.29 ± 0.19	0.31 ± 0.21	−0.03	−0.06 to 0.01	.148
4–5 months (n = 107)	0.30 ± 0.16	0.32 ± 0.21	−0.02	−0.07 to 0.03	.468
6 months or longer (n = 159)	0.31 ± 0.18	0.36 ± 0.30	−0.05	−0.10 to −0.009	.019

Data are shown as the mean ± standard deviation. Difference was calculated by subtracting the value after CPAP treatment from the value before CPAP treatment. * = *P* value for comparison between three groups. ALT = alanine aminotransferase, APRI = AST to platelet ratio index, AST = aspartate aminotransferase, CI = confidence interval, CPAP = continuous positive airway pressure.

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surrogate marker of underlying NAFLD. In addition, a potentially favorable effect of CPAP treatment was noted on the regression of hepatic fibrosis using a noninvasive fibrosis marker in patients with OSA and NAFLD. Our study demonstrated that adequate adherence with CPAP treatment in patients with severe OSA optimizes the management of NAFLD and NAFLD-related hepatic fibrosis.

A recent meta-analysis demonstrated that OSA was strongly associated with the serum ALT and AST levels, showing that patients with OSA had an increase of 13.3% compared to an increase of 4.4% in those without OSA.[10] In this analysis, patients with OSA had a 2.6-fold greater risk of hepatic fibrosis.[10] Another meta-analysis reported that OSA was associated with an increased prevalence of nonalcoholic steatohepatitis (NASH) and of fibrosis, independent of age, sex, overall obesity, and abdominal obesity.[9] In this meta-analysis, a dose-response relationship was observed between the severity of OSA and NAFLD.[9] Polotsky et al. showed that patients with moderate to severe OSA exhibited more severe lobular inflammation than did those with mild OSA.[20] In addition, severe OSA was associated with hepatocyte ballooning and liver fibrosis.[20] Currently, the relationship between OSA and NAFLD progression or NAFLD disease activity remains unclear and limited to cross-sectional studies.

Sleep fragmentation and CIH induce intermediate mechanisms such as sympathetic nervous system activation,[21] oxidative stress, and systemic inflammation, which are responsible for cardiometabolic consequences.[22,23] Hypoxia may play a significant role in the development of NAFLD. Several animal studies have shown that hypoxia increases lipogenesis and inhibits fat oxidation, thereby promoting fat accumulation and the development of elevated liver enzymes and NAFLD.[7,8] Moreover, multiple cycles of hypoxia/reoxygenation, such as in OSA, are associated with chronic inflammation.[24] In adipose tissue, CIH, which is the hallmark of OSA, exacerbates adipose tissue inflammation and leads to the dysregulated production of adipocytokines, which may contribute to NAFLD. In an animal model of NAFLD using mice with a hepatocellular deficiency in the *PTEN* gene, 7 days of exposure to 10% inspired oxygen aggravated and accelerated the progression of NASH, with an increased expression of lipogenic genes and downregulation of genes involved in lipid metabolism.[25] Therefore, hypoxia appears to promote the histologic progression of NAFLD to NASH in susceptible mice.[25] Oxidative stress induced by OSA drives the progression of nonalcoholic fatty liver (NAFL) to NASH by a "second hit". This theory is supported by animal experiments showing that CIH results in minor hepatic injury without significant inflammation in mouse without fatty liver. This is in contrast to a setting with NAFL induced by a high-fat diet, in which CIH can lead to NASH.[6,7] Aron-Wisnewsky et al. demonstrated that CIH is strongly associated with higher systemic inflammation (interleukin 6) and more severe fibrotic or inflammatory liver injuries.[26]

The long-term treatment of CPAP decreases mortality risk[11]; however, whether this is the result of CPAP-induced improvements in insulin resistance or body fat distribution has not been established. The effective treatment of OSA may thus represent an important target for reducing metabolic risk. However, the effect of CPAP on metabolic or inflammatory markers needs further evaluation. In obese patients with OSA, CPAP did not affect the prevalence of insulin resistance and metabolic syndrome or levels of lipids and blood glucose.[27,28] In obese patients with OSA, insulin resistance is likely to be determined mostly by obesity and, to a lesser extent, by OSA.[29] According to OSA severity, insulin resistance improved in those with severe OSA, suggesting beneficial metabolic effects from CPAP in severe OSA.[30] Although obesity represents an important predisposing factor for both NAFLD and OSA, the severity of OSA is a stronger predictor of elevated liver enzymes than is elevated BMI.[31] Another study showed that the liver enzyme level was associated with markers of oxygen desaturation and not to BMI.[32] Some studies have shown that OSA-related liver injury and fatty liver also present in nonobese patients.[6,7,33] In addition, the heterogeneous CPAP response in metabolic disease is related to the underlying severity of the metabolic disease. A recent randomized controlled study showed that patients with a more severe metabolic phenotype at baseline had a greater response to CPAP.[12] It is well known that patients with NAFLD have a more severe metabolic profile than do those without NAFLD. A major issue is also the optimal duration of CPAP use as shown in our study. Studies are lacking to help establish the correct duration of CPAP use for reducing cardiometabolic risks. A meta-analysis suggested that there is a dose-response relationship between the reduction in blood pressure and CPAP adherence.[34] Our study showed that patients with severe OSA and without morbid obesity who had a high level of CPAP adherence for a longer duration are likely to benefit.

A recent meta-analysis demonstrated that CPAP treatment was associated with a statistically significant decrease on ALT levels and was more effective in OSA patients with treatment duration longer than 3 months.[35] However, there were no changes in aminotransferase levels after CPAP treatment in randomized controlled trials.[36,37] In these studies, 50% to 77% of patients had ALT levels within the normal range at baseline and the duration of CPAP treatment is limited from 4 weeks to 2 months.[36,37] In our study, only 12% of subjects had ALT levels within normal limits at baseline. Regarding hepatic steatosis, meta-analysis including five randomized controlled trials reported that there are no changes in hepatic steatosis after CPAP treatment.[38] However, the duration of CPAP treatment was relatively short, and it was difficult to draw a definite conclusion. Longitudinal studies showed that CPAP therapy over 1 to 3 years improved and reversed hepatic steatosis.[39–41] The duration of CPAP treatment may need to be long enough, perhaps 6 months or greater, to achieve this goal.[42] Our study also showed CPAP treatment was associated with an improvement in serum aminotransferase activity in a dose-response fashion (> 6 months of CPAP treatment showed a significantly larger decrease in both ALT and AST).

The strengths of our study are the utilization of high-quality in-laboratory sleep data collected by trained personnel with a systematic protocol and a large number of subjects. However, there are some limitations in this study. First, this retrospective study was conducted at a tertiary care center, which introduces the possibility of selection bias. This may prevent a definite inference between OSA and hepatic injury. Second, we did not have imaging data to corroborate the diagnosis of

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NAFLD because of the retrospective design of our study. We used unexplained elevated serum ALT (in the absence of any other known cause of chronic liver disease) to classify NAFLD, which may underestimate and misclassify NAFLD. It may be reiterated that patients with NAFLD in the setting of normal liver enzymes may have been excluded in our study. However, multiple studies have demonstrated that the presence of an elevated ALT level was associated with increased liver-related mortality.[14,43,44] Additionally, patients with advanced fibrosis by APRI had an increased risk of overall mortality compared with patients without advanced fibrosis.[3] Future prospective studies using imaging data are needed to confirm this association. Finally, because of the retrospective design of our study, we were unable to randomize (control group versus intervention group) and standardize the length of CPAP treatment.

In conclusion, CPAP treatment, even for a relatively short term, plays an important role in improving the serum aminotransferase activity in subjects with OSA. In addition, CPAP treatment may play a pivotal role in the improvement of NAFLD-related fibrosis. Thus, CPAP treatment, which is the first-line therapy for OSA, can also help optimize the management of NAFLD in this population. Additional prospective studies are needed to assess the implication of CPAP treatment in patients with concomitant OSA and NAFLD.

ABBREVIATIONS

AHI, apnea-hypoxia index
ALT, alanine aminotransferase
APRI, aspartate aminotransferase to platelet ratio index
AST, aspartate aminotransferase
BMI, body mass index
CI, confidence interval
CIH, chronic intermittent hypoxia
CPAP, continuous positive airway pressure
NAFL, nonalcoholic fatty liver
NAFLD, nonalcoholic fatty liver disease
NASH, nonalcoholic steatohepatitis
OR, odds ratio
OSA, obstructive sleep apnea
sNAFLD, suspected nonalcoholic fatty liver disease

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DISCLOSURE STATEMENT

The authors report no conflicts of interest.

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