Obstructive sleep apnoea and continuous positive airway pressure therapy for patients with non-alcoholic fatty liver disease: abridged secondary publication

DSC Hui *, SSS Ng, GLH Wong, WCW Chu, A Chan, VWS Wong

KEY MESSAGES

1. Of 226 patients with non-alcoholic fatty liver disease (NAFLD) who underwent home sleep test, 222 had evidence of obstructive sleep apnoea (OSA) with respiratory event index (REI) of ≥5/hour.
2. Both therapeutic and subtherapeutic continuous positive airway pressure therapy (CPAP) had similar effects on non-invasive markers of liver fat, steatosis, and fibrosis after 6 months of treatment. Percentage change in weight after 6 months correlated with the change in transient elastography controlled attenuation parameter, which is a marker of liver fat (B=3.249, SE=0.873, 95% Wald CI=1.538-4.960, P<0.001).
3. CPAP alone is unlikely to alter NAFLD activities in patients with concomitant OSA. The additional role of weight reduction through lifestyle modification deserves further investigation.

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[1] DSC Hui, [1] SSS Ng, [1] GLH Wong, [2] WCW Chu, [3] A Chan, [1] VWS Wong

The Chinese University of Hong Kong:
[1] *Department of Medicine and Therapeutics*
[2] *Department of Imaging & Interventional Radiology*
[3] *Department of Pathology*

* Principal applicant and corresponding author: dschui@cuhk.edu.hk

Introduction

Obstructive sleep apnoea (OSA) is associated with metabolic syndrome and non-alcoholic fatty liver disease (NAFLD). OSA may play a role in the progression of hepatic steatosis and the development of steatohepatitis through chronic intermittent hypoxia leading to systemic inflammation, increased oxidative stress, insulin resistance, and dyslipidaemia.[1] This study aimed to screen for OSA in patients with biopsy-proven NAFLD who were followed up at the Hepatology Clinic and assess the effect of auto continuous positive airway pressure therapy (CPAP) versus a control group on subtherapeutic treatment over 6 months with reference to NAFLD activities. We hypothesised that OSA should be common among patients with NAFLD in HK and correction of hypoxemia with nasal CPAP treatment might improve the activities of NAFLD in those with concomitant OSA.

Methods

Patients with biopsy-proven NAFLD were screened for OSA using a home sleep study. The following conditions were excluded as the underlying cause of liver disease in this cohort: a history of excessive alcohol consumption (>30 g/day for men and >20 g/day for women), secondary causes of hepatic steatosis (such as chronic use of systemic corticosteroids), positive hepatitis B surface antigen, anti-hepatitis C virus antibody, or histological evidence of other concomitant chronic liver diseases.[2]

Patients were initially assessed at the respiratory clinic using the Epworth sleepiness score with symptoms evaluated before the home sleep study using the Embletta device.[3] OSA syndrome was defined as a respiratory event index (REI) of ≥5/hour during sleep plus daytime sleepiness or two of the following symptoms: choking or gasping during sleep, recurrent awakenings from sleep, unrefreshed sleep, daytime fatigue, and impaired concentration. REI was defined as the total number of respiratory events scored ×60 divided by monitoring time.

Those with biopsy-proven NAFLD who had REI of ≥5/hour on home sleep test were offered a 30-minute CPAP trial at 4cm$H_2$0 before randomisation into either the auto CPAP group (in auto-adjusting pressure mode ranging 4-20 cm$H_2$0) or subtherapeutic CPAP group (pressure fixed at 4cm$H_2$0).

Baseline measurements included subjective sleepiness based on the Epworth sleepiness score, intrahepatic triglyceride (IHTG) level measured by proton magnetic resonance spectroscopy, liver stiffness assessment measured by fibroscan, routine liver function, and serum cytokeratin-18 fragment. The primary outcome was the difference in changes in IHTG after 6 months of either treatment.

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Secondary outcomes included changes in Epworth sleepiness score, transient elastography controlled attenuation parameter (a marker of liver fat), liver stiffness assessment, serum cytokeratin-18 fragment, and objective CPAP usage.[2]

Inclusion criteria were age 20 to 80 years, symptoms of OSA with home embletta REI of ≥5/hour, and NAFLD diagnosed by liver biopsy. Exclusion criteria were (1) unstable cardiovascular diseases (eg recent unstable angina, myocardial infarction, stroke, or transient ischaemic attack within the previous 6 months or severe left ventricular failure), (2) neuromuscular disease affecting or potentially affecting respiratory muscles, (3) moderate-to-severe respiratory disease (ie, breathlessness affecting activities of daily living) or documented hypoxemia or awake SaO_2 <92%, (4) psychiatric disease that limits the ability to give informed consent or complete the study, (5) professional drivers, and (6) gross structural abnormalities (large nasal polyps, gross nasal turbinate hypertrophy or septal deviation, and enlarged 'kissing' tonsils).

Sample size calculation was based on the use of IHTG as the primary endpoint and our previous studies. The mean IHTG in patients with NAFLD was reported to be 12%±6%.[2,4] Patients with NAFLD on usual care had IHTG decreased by 2% in 12 months.[4] An IHTG of 5% was the threshold to define NAFLD; a 7% decrease in IHTG was considered clinically meaningful. Assuming the change in IHTG was -7% in the auto CPAP group and -3% in the subtherapeutic CPAP group, a sample size of 48 patients per arm was expected to achieve 90% power in detecting the difference at a 5% significance level. To allow a dropout rate of 20%, a total of 120 patients were needed.

Data were analysed on an intention-to-treat basis followed by treatment per protocol. For comparisons between the 2 groups at each time point, unpaired t test was used for normally distributed variables and Mann-Whitney U test for non-normally distributed variables. To compare the measurements before and after CPAP treatment, paired t-test was used for normally distributed variables and Wilcoxon's signed rank test for non-normally distributed variables. Two-factor ANOVA (group vs time) with repeated measures on the factor time (baseline minus treatment) was used to test for the effect of CPAP vs conservative treatment. The effect of CPAP treatment and other metabolic parameters including BMI on IHTG was evaluated by multivariable analysis using the linear regression model.

TABLE 1. Baseline demographics of the auto continuous positive airway pressure therapy (CPAP) group and the subtherapeutic CPAP group

Baseline demographic	Auto CPAP group (n=60)*	Subtherapeutic CPAP group (n=60)*	P value
Age, y	54.62±10.37	54.75±9.71	0.943
Weight, kg	77.03±15.52	78.53±14.79	0.408
Body mass index, kg/m^2	28.62±4.47	28.72±4.22	0.783
Neck circumference, cm	39.84±10.64	38.98±3.58	0.288
Waist circumference, cm	98.13±10.97	98.19±11.02	0.815
Hip circumference, cm	103.49±8.79	103.90±8.39	0.631
Epworth sleepiness score	9.18±5.62	9.80±5.24	0.364
Respiratory Event Index	30.38±22.41	33.50±20.58	0.209
Minimum SaO_2 %	77.02±9.59	76.47±8.58	0.423
% of total sleep time with SaO_2 <90%	10.96±17.31	10.64±16.44	0.607
Duration of SaO_2 <90%, min	42.46±65.51	40.51±61.74	0.775
Oxygen desaturation index$_3$	31.48±22.36	33.84±19.88	0.268
Liver stiffness, kPa	6.47±2.46	6.91±3.59	0.789
Transient elastography controlled attenuation parameter, dB/m	319.63±45.53	316.82±41.67	0.717
Fat peak	0.17±0.13	0.16±0.10	0.951
Liver fat, %	13.54±8.99	13.20±7.53	0.951
Total protein, μmol/L	77.08±3.66	76.58±3.99	0.228
Albumin, g/L	39.25±3.00	38.78±3.17	0.419
Total bilirubin, μmol/L	10.63±3.94	11.82±5.96	0.571
Total alkaline phosphatase, IU/L	73.20±23.69	73.40±24.31	0.844
Alanine aminotransferase, IU/L	50.22±41.51	44.28±29.22	0.551
Serum cytokeratin-18 segment	243.58±240.94	229.63±205.32	0.846

* Data are presented as mean ± standard deviation

Results

Of 243 patients with NAFLD who underwent home sleep test, ten failed the test (poor signal [n=8], unable to sleep [n=2]) and seven met exclusion criteria and were withdrawn (hypoventilation [n=2], hepatitis B [n=2], lung cancer [n=1], drivers [n=2]). Of the remaining 226 patients, 222 had REI of ≥5/hour and 198 of them agreed to proceed to a 30-minute CPAP trial at 4 cmH_20. Of the 198 patients, 64 refused further CPAP use and 14 refused randomisation. Finally, 120 patients were equally randomised into either the auto CPAP group or the subtherapeutic CPAP group. The two groups were comparable in terms of baseline demographics, severity of OSA (REI, min SaO_2, % of total sleep time with SaO_2<90%, oxygen desaturation index$_3$ [ODI_3], which is the number of times per hour of sleep that the blood oxygen level dropped by at least 3% from baseline), and NAFLD indices (IHTG, liver stiffness, transient elastography controlled attenuation parameter, serum cytokeratin-18 segment, and liver function blood test parameters (Table 1).

Transient elastography controlled attenuation parameter (a marker of liver fat) correlated with markers of OSA severity including REI (r=0.203,

P=0.026), min SaO_2 (r= -0.167, P=0.068), % of total sleep time with SaO_2 <90% (r=0.265, P=0.003), and ODI_3 (r=0.214, P=0.019). Other fatty liver parameters had no significant correlation with markers of OSA severity (Table 2).

After 6 months of treatment, the objective CPAP usage of the auto CPAP and subtherapeutic CPAP groups was 4.37±2.14 and 3.84±2.29 hours, respectively (P=0.191). The 95th centile pressures were 11.09±1.59 and 4.00±0.00 cmH_20, respectively

TABLE 2. Correlations between obstructive sleep apnoea severity (OSA) markers and non-alcoholic fatty liver disease (NAFLD) markers

OSA marker	Liver stiffness, kPa	Transient elastography controlled attenuation parameter, dB/m	Fat peak	Liver fat, %	Total protein, μmol/L	Albumin, g/L	Total bilirubin, μmol/L	Alkaline phosphatase, IU/L	Alanine amino-transferase, IU/L	Serum cytokeratin-18 segment
Respiratory event index										
Pearson correlation, r	0.057	0.203	0.062	0.069	0.108	0.014	0.094	-0.160	0.027	0.114
P value (2-tailed)	0.538	0.026	0.503	0.453	0.240	0.876	0.309	0.082	0.767	0.214
Minimum SaO_2, %										
Pearson correlation, r	-0.141	-0.167	-0.033	-0.046	0.020	-0.024	-0.096	0.105	-0.034	-0.123
P value (2-tailed)	0.123	0.068	0.724	0.622	0.830	0.793	0.297	0.256	0.713	0.181
% of total sleep time with SaO_2 <90%										
Pearson correlation, r	0.069	0.265	0.176	0.185	0.026	0.117	0.130	-0.152	0.069	0.119
P value (2-tailed)	0.456	0.003	0.062	0.050	0.782	0.214	0.167	0.107	0.466	0.209
Oxygen desaturation $index_3$										
Pearson correlation, r	0.077	0.214	0.099	0.105	0.135	0.041	0.086	-0.136	0.049	0.114
P value (2-tailed)	0.404	0.019	0.298	0.266	0.153	0.664	0.365	0.148	0.608	0.227

TABLE 3. Intention-to-treat analysis of the auto continuous positive airway pressure therapy (CPAP) group and the subtherapeutic CPAP group

Variable	Baseline			Month 6			P value (month 6 vs baseline)		Within-group difference	Between-group difference (95% CI)	P value
	Auto CPAP group (n=60)*	Subtherapeutic CPAP group (n=60)*	P value	Auto CPAP group (n=60)*	Subtherapeutic CPAP group (n=60)*	P value	Auto CPAP group	Subtherapeutic CPAP group			
Epworth sleepiness score	9.18±5.62	9.80±5.24	0.364	6.33±4.66	7.42±4.40	0.087	<0.001	0.001	-2.85±4.88	-0.47 (-2.23 to 1.30)	0.653
Weight, kg	77.03±15.52	78.53±14.79	0.408	77.47±14.91	78.36±14.68	0.567	0.229	0.330	-2.38±4.89	0.99 (-0.43 to 2.41)	0.105
Liver stiffness, kPa	6.47±2.46	6.91±3.59	0.789	6.50±2.25	6.69±3.47	0.787	0.914	0.333	0.84±4.28	0.24 (-0.42 to 0.90)	0.250
Transient elastography controlled attenuation parameter, dB/m	319.64±45.53	316.82±41.67	0.717	316.07±43.15	306.45±43.84	0.283	0.490	0.031	-0.17±3.64	6.80 (-6.97 to 20.57)	0.170
Fat peak	0.17±0.13	0.16±0.10	0.935	0.18±0.12	0.18±0.15	0.585	0.139	0.588	0.03±1.92	-0.01 (-0.04 to 0.02)	0.375
Liver fat, %	13.54±8.99	13.20±7.47	0.944	14.21±8.32	13.83±9.23	0.582	0.149	0.675	-0.22±1.72	0.04 (-1.82 to 1.90)	0.296
Total protein, μmol/L	77.08±3.66	76.58±3.99	0.228	76.37±3.83	76.60±4.28	0.987	0.218	0.993	-3.57±39.84	-0.73 (-1.92 to 0.45)	0.390
Albumin, g/L	39.25±3.00	38.78±3.17	0.419	38.65±2.65	38.33±3.60	0.698	0.160	0.182	-10.37±36.24	-0.15 (-1.02 to 0.72)	0.956
Total bilirubin, μmol/L	10.63±3.94	11.82±5.96	0.571	9.95±3.59	11.47±5.29	0.184	0.074	0.310	0.01±0.08	-0.33 (-1.51 to 0.84)	0.757
Total alkaline phosphatase, IU/L	73.20±23.69	73.40±24.31	0.844	72.80±22.64	74.33±25.37	0.921	0.566	0.762	0.02±0.09	-1.33 (-6.77 to 4.10)	0.823
Alanine amino-transferase, IU/L	50.22±41.51	44.28±29.22	0.551	41.55±28.25	43.53±30.62	0.823	0.027	0.369	0.67±5.45	-7.92 (-17.14 to 1.31)	0.312
Serum cytokeratin-18 segment	243.58±240.94	229.63±205.32	0.846	206.22±193.77	237.50±224.46	0.505	0.208	0.659	0.63±4.79	-45.23 (-110.24 to 19.78)	0.466

(P<0.001) and the residual REI was 3.62±2.3 and 10.88±13.01 per hour, respectively (P<0.001). The two treatment groups were comparable in terms of primary and secondary endpoints based on the intention-to-treat approach (Table 3) and treatment per protocol.

Regression analysis showed that percentage change in weight after 6 months correlated with the change in transient elastography controlled attenuation parameter, which is a marker of liver fat (B=3.249, SE=0.873, 95% Wald CI=1.538-4.960, P<0.001).

Discussion

One study reported that Apnea-Hypopnea Index, ODI, min SaO_2, and % of sleep time with SaO_2 <90% were independent predictors of NAFLD, whereas the most correlated parameter for the severity of NAFLD was the duration of hypoxia during sleep.[6] Our study findings support these correlations of OSA severity with transient elastography controlled attenuation parameter (a marker of liver fat).

Several randomised controlled trials with different treatment duration have showed no significant impact of CPAP in patients with OSA and NAFLD. A meta-analysis concluded that CPAP did not significantly contribute to the improvement in liver histology, liver steatosis, liver fibrosis, and aminotransferase levels,[7] consistent with our findings.

In view of the high (27.3%) prevalence of NAFLD in Hong Kong population[2] and the high frequency of OSA in patients with NAFLD, it is of great interest to examine the role of lifestyle modification[4] on top of CPAP for those with OSA and/or NAFLD using non-invasive assessment of NAFLD activities.

Conclusion

Although transient elastography controlled attenuation parameter correlated with markers of OSA severity, therapeutic and subtherapeutic CPAP had similar effects on non-invasive markers of liver fat, steatosis, and fibrosis. CPAP alone is unlikely to alter NAFLD activities in patients with concomitant OSA. The additional role of weight reduction through lifestyle modification deserves further investigation.

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Disclosure

The results of this research have been previously published in:

1. Ng SSS, Wong VWS, Wong GLH, et al. Continuous positive airway pressure does not improve nonalcoholic fatty liver disease in patients with obstructive sleep apnea. A randomized clinical trial. Am J Respir Crit Care Med 2021;203:493-501.

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