Effects of Continuous Positive Airway Pressure on Nonalcoholic Fatty Liver Disease in Patients with Obstructive Sleep Apnea: A Systematic Review

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ABSTRACT

Background: *Nonalcoholic fatty liver disease (NAFLD) is associated with obstructive sleep apnea (OSA). Continuous positive airway pressure (CPAP) is the first-line therapy for OSA. However, the effect of CPAP on NAFLD in patients with concomitant OSA is still unclear. This study aims to identify the use of CPAP on NAFLD in patients with OSA.*

Method: *A systematic literature search was performed using particular keywords and medical subheadings in three journal databases: Cochrane, PubMed, and EBSCOhost. The results were screened and assessed using inclusion and exclusion criteria by three independent authors. The randomized controlled trial (RCT) quality was evaluated with Jadad scale and the cohort studies quality was assessed with Newcastle-Ottawa quality assessment scale.*

Results: *Two RCTs and three cohort studies were eligible to fulfil the inclusion criteria, consisting of 620 total patients. Two RCTs showed no statistically significant improvement after CPAP treatment in NAFLD based on intrahepatic triglyceride (measured by proton magnetic resonance spectroscopy), liver stiffness measurement, serum cytokeratin-18 fragment, and liver function blood test parameters. Meanwhile, 2 cohort studies in adults and 1 cohort study in children showed significant improvement in ALT, AST, and APRI. However, one cohort study showed no significant improvement in serum fibrosis markers and transient elastography measurement after CPAP treatment.*

Conclusion: *CPAP might be beneficial in some patients with OSA to improve NAFLD, but further research that includes many subjects and longer duration of CPAP therapy is needed to confirm this result.*

Keywords: *nonalcoholic fatty liver disease, obstructive sleep apnea, continuous positive airway pressure*

ABSTRAK

Latar belakang: *Penyakit perlemakan hati nonalkoholik (NAFLD) memiliki hubungan dengan henti napas saat tidur (OSA). Continuous positive airway pressure (CPAP) merupakan terapi lini pertama untuk OSA. Namun, efek CPAP terhadap NAFLD pada pasien yang juga memiliki OSA secara bersamaan masih belum jelas diketahui. Penelitian ini bertujuan untuk mengidentifikasi penggunaan CPAP terhadap NAFLD pada pasien OSA.*

Metode: *Pencarian literatur sistematis dilakukan menggunakan kata kunci dan subjudul medis di tiga database jurnal: Cochrane, PubMed, dan EBSCOhost. Hasil tersebut disaring menggunakan kriteria inklusi dan eksklusi oleh tiga penulis independen. Kualitas uji acak terkontrol (RCT) dievaluasi dengan skala Jadad dan kualitas studi kohort diealuasi dengan Newcastle-Ottawa quality assessment scale (NOS).*

Hasil: *Dua RCT dan tiga studi kohort yang secara total terdiri dari 620 pasien memenuhi kriteria inklusi. Kedua RCT tidak menunjukkan peningkatan yang signifikan secara statistik pada NAFLD setelah terapi CPAP berdasarkan trigliserida intrahepatik (diukur dengan spektroskopi resonansi magnetik proton), pengukuran kekakuan hati, fragmen sitokeratin-18 serum, dan parameter fungsi hati pada darah. Namun, 2 studi kohort pada orang dewasa dan 1 studi kohort pada anak-anak menunjukkan peningkatan signifikan pada ALT, AST, dan APRI. Satu studi kohort lainnya menunjukkan tidak adanya perbaikan yang signifikan pada penanda fibrosis serum dan pengukuran elastografi sementara setelah terapi CPAP.*

Simpulan: *CPAP mungkin bermanfaat pada beberapa pasien OSA untuk perbaikan NAFLD, tetapi penelitian lebih lanjut yang mencakup banyak subjek dan durasi terapi CPAP yang lebih lama diperlukan untuk mengonfirmasi hasil tersebut.*

Kata kunci: *penyakit perlemakan hati nonalkoholik, obstructive sleep apnea, continuous positive airway pressure*

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in children and adults.[1] It affects 70% of the diabetic and obese population and 20–30% of the general population.[2] NAFLD is a silent disease, so the exact incidence rates are unknown.[3] The incidence of NAFLD is expected to increase with the increasing rates of obesity and diabetes.[2] This condition encompasses a spectrum of diseases, from uncomplicated hepatic steatosis to non-alcoholic steatohepatitis (NASH), liver fibrosis, and cirrhosis.[1] NAFLD with advanced fibrosis is a significant predictor of mortality from cardiovascular causes.[2]

Emerging evidence suggests that intermittent nocturnal hypoxia and obesity-related obstructive sleep apnea (OSA) are correlated with the progression and severity of NAFLD.[1] A recent meta-analysis showed that OSA was strongly associated with NAFLD. Patients with OSA had a 2.6-fold higher risk of liver fibrosis.[4] The severity of OSA is associated with the severity of advanced fibrosis. In addition, moderate to severe OSA, and hypoxia patients with morbid obesity have more severe hepatic inflammation than those without hypoxia.[1,5]

OSA is a sleep disorder characterized by repetitive complete or partial obstruction of the upper airway, leading to chronic intermittent hypoxia, sleep fragmentation, and increased negative intrathoracic pressure.[6,7] OSA is a highly prevalent disease. It affects approximately 9% of middle-aged women and 24% of men. It is estimated that 50–60% of obese patients with metabolic syndrome develop OSA.[2] The clinical signs and symptoms of OSA and hypoxia are apnea, snoring, daytime sleepiness, and tonsillar hypertrophy.[1] Continuous positive airway pressure (CPAP) is the standard and first-line therapy in the current management of OSA because it treats upper airway collapse. CPAP therapy could decrease daytime sleepiness, hypoxic events, and ameliorate metabolic and cardiovascular diseases.[6,8] With the association of OSA and NAFLD, CPAP may give a potential therapeutic option for patients with NAFLD. However, it is still unclear whether CPAP treatment would modify the presence of NAFLD in patients with both NALFD and OSA. In this systematic review, we aim to identify the use of CPAP on NAFLD in patients with OSA.

METHOD

A systematic literature search was conducted by three independent authors (ST, SA, and DRR) in April 2022. This systematic literature search was performed using particular keywords, such as "obstructive sleep apnea", "nonalcoholic fatty liver disease", and "continuous positive airway pressure" with medical subheadings (MeSH) terms in 3 journal databases, including PubMed, Cochrane, and EBSCOhost (Figure 1). We also manually searched the references from included studies and looked at related articles in Google Scholar. All authors viewed all the studies to determine and affirm the eligibility standards and legitimacy of the study. The results were selected using inclusion criteria, exclusion criteria, and double articles.

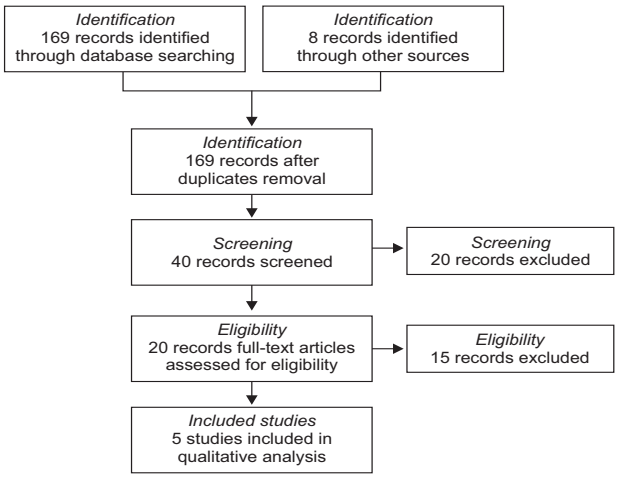

Figure 1. Article selection

The inclusion criteria for this systematic review are a randomized controlled trial, cohort, case-control, or observational studies that reported primary data dealing with CPAP therapy in patients with NAFLD and OSA, written in English, and had the full-text article.

The exclusion criteria for this systematic review are unpublished articles, duplicate publications, animal or nonhuman studies, case reports, letters, or other studies that did not include primary outcomes or data, such as reviews and editorials. This systematic review did not exclude studies by year.

Data Collection

The primary purpose of this study is to identify the effects of CPAP therapy on NAFLD in patients with OSA concomitant. The basic information about the selected articles included demographic information, study design, CPAP intervention, sample size, and outcome measurements, such as liver enzymes and pathology. Data collection and synthesis were performed by three independent authors and tabulated using Excel (Microsoft, Redmond, Washington, United States).

RESULTS

After performing a systematic literature search in 3 journal databases using particular keywords and MeSH terms, there were 169 articles related to our topics. After screening the full text, we found five articles that fulfill the inclusion and exclusion criteria, comprised 2 RCTs and 3 cohort studies consisting of 620 total patients. A summary of the five studies included in this systematic review is shown in Table 1.

A randomized controlled trial by Ng et al showed no significant differences in intrahepatic triglyceride (IHTG) (p = 0.966), ALT (p = 0.602), liver stiffness measurement (p = 0.544), and serum cytokeratin-18 (p = 0.286) fragment in both groups. However, this study found a significant correlation between hepatic steatosis and markers of severity of OSA.[5] A cohort study by Hirono et al showed a significant decrease in aspartate transaminase (AST) and alanine transaminase (ALT) after six months of CPAP therapy (p = 0.005 and p = 0.021). However, this study found no significant improvement in transient elastography or serum fibrosis markers after CPAP therapy, based on liver stiffness measurement (p = 0.617) and controlled

Table 1. The summary of studies included

Authors (year)	Study design	Number of patients (n)	Intervention and control	Primary endpoint	Follow up
Ng et al[5] (2021)	Randomized controlled trial (RCT)	106 patients	AutoCPAP (4–20 cmH2O) for intervention, and Subtherapeutic CPAP (pressure fixed at 4 cm H2O) for control	IHTG, ALT, liver stiffness, serum cytokeratin-18 fragment	6 months
Hirono et al[6] (2021)	Cohort study	70 patients	AutoCPAP (4–16 hPA) in the NAFLD group for intervention, and AutoCPAP (4–16 hPA) in the non-NAFLD group for control	ALT, AST, serum fibrosis markers, transient elastography	6 months
Kim et al[2] (2018)	Cohort retrospective study	351 patients	Patients > 20 years diagnosed with OSA and underwent CPAP-based therapy with ALT > 30 U/L (men) or > 19 U/L (women)	AST, ALT, APRI	6 months
Sundaram et al[1] (2018)	Cohort study	9 patients	CPAP 5 cm H2O, pressure increase during sleep until snoring & work of breathing were relieved	ALT, AST, metabolic syndrome markers	1–3 months
Julian-Desayes et al[8] (2016)	Randomized controlled trial (RCT)	42 patients	Autotitrating CPAP for intervention and sham CPAP for control	FibroMax (FibroTest, SteatoTest, NashTest)	6–12 weeks

IHTG: intrahepatic triglyceride; ALT: alanine transaminase; AST: aspartate transaminase; APRI: AST to platelet ratio index; NAFLD: nonalcoholic fatty liver disease; OSA: obstructive sleep apnea; CPAP: continuous positive airway pressure

attenuation parameter (CAP) using Fibroscan (p = 0.987).[6]

A cohort retrospective study by Kim et al showed significant improvement in AST from 27.9 ± 15.9 to 24.9 ± 9.7 (p < 0.001; 95% CI: -4.67 to -1.43), ALT from 44.5 ± 22.3 to 39.1 ± 16.1 (p < 0.001; 95% CI: -7.61 to -3.33), and APRI from 0.35 ± 0.27 to 0.31 ± 0.18 (p = 0.004; 95% CI: -0.07 to -0.01).[2] This study also showed adequate adherence to CPAP as an independent predictor of NAFLD regression (OR = 3.93; 95% CI: 1.29-11.94).[2] A cohort study by Sundaram et al showed that CPAP therapy in children improved OSA severity and reduced ALT from 91 ± 29 to 69 ± 19 IU/L (p = 0.02) and metabolic syndrome.[1] This study also found that CPAP increases sleep duration (p = 0.002), improves OSA (measured by AHI, p = 0.03), and hypoxia.[1] A Randomized controlled trial by Jullian-Desayes et al showed no significant reduction in steatosis (p = 0.522), NASH (p = 0.687), or liver fibrosis (p = 0.827) after 12 weeks of effective CPAP.[8]

DISCUSSION

The association between OSA and NAFLD has been reported in several studies. A systematic review by Jin et al involving nine studies and 2,272 patients demonstrated that OSA was independently related to developing NAFLD based on liver enzyme level and histological alterations. Also, OSA was related to ALT levels, steatosis, fibrosis, lobular inflammation, and ballooning degeneration.[9] Hypoxia has a significant role in the development of NAFLD. Chronic intermittent hypoxia (CIH) and sleep fragmentation induce systematic inflammation, oxidative stress, and sympathetic nervous system activation, which is responsible for cardiometabolic consequences. Hypoxia increases lipogenesis and inhibits fat oxidation, leading to fat accumulation and NAFLD development. The repetitive cycle of hypoxia, such as in OSA, is associated with chronic inflammation.[2] Due to the causal correlation between OSA and NAFLD, the efficient treatment of OSA is expected to improve liver injury parameters.[10]

The effects of CPAP therapy on NAFLD in patients with OSA have been reported in several studies. In this systematic review, two RCTs showed no statistically significant improvement after CPAP treatment in NAFLD based on intrahepatic triglyceride (measured by proton magnetic resonance spectroscopy), liver stiffness measurement, serum cytokeratin-18 fragment, and liver function blood test parameters. Meanwhile, 2 cohort studies in adults and 1 cohort study in children showed significant improvement in ALT, AST, and APRI. However, one cohort study showed no significant improvement in serum fibrosis markers and transient elastography measurement after CPAP treatment.

Some factors affect the efficacy of CPAP treatment, such as adherence to CPAP therapy. The CPAP effect is dose-dependent. The adherence levels of more than 4 hours/night are correlated with better outcomes.[11] Previous studies showed that 6–12 months of CPAP therapy might improve metabolic syndrome components, including triglycerides, glycosylated hemoglobin, and blood pressure.[1] CPAP therapy for 1–3 years improved and reversed hepatic steatosis. CPAP therapy for > 6 months showed a significantly larger decrease in AST and ALT.[2] Effective and adequate duration of CPAP therapy was correlated with significant reductions in CIH-related liver fibrosis and biochemical improvement. It suggests that reoxygenation in the long term could reduce liver fibrosis from NAFLD in serum markers.[6] Diverse CPAP response in metabolic disease is also related to the underlying severity of the metabolic disease. Greater CPAP response occurred in patients with a more severe metabolic phenotype at baseline. Patients with NAFLD have a more severe metabolic profile.[2] However, the maximum duration for CPAP therapy obtained by this systematic review is six months.

CPAP may improve NAFLD by ameliorating insulin resistance in OSA patients, which plays an important part in NAFLD development. Down-regulation of leptin and up-regulation of adiponectin may be the possible mechanism of CPAP in ameliorating insulin resistance. In addition, CPAP could significantly reduce oxidative stress and inflammatory serum markers in OSA patients.[10] It is challenging to identify the effect of CPAP therapy on NAFLD progression because the time scale of NAFLD regression/progression needs lengthy CPAP trials, which are costly and difficult; most NAFLD patients do not have liver aminotransferase elevation, and the NAFLD diagnosis in the absence of liver biopsy is increased, which require technical expertise.[12]

CONCLUSION

OSA plays an important role in NAFLD development. CPAP might be beneficial in some patients with OSA to improve NAFLD, but further

research that includes many subjects and a longer duration of CPAP therapy is needed to confirm this result.

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