Review Article

Effect of mandibular advancement therapy on inflammatory biomarkers in obstructive sleep apnea: A systematic review

ABSTRACT

To review the literature on the effect of mandibular advancement therapy (MAT) on inflammatory biomarkers in obstructive sleep apnea (OSA). The present systematic review addresses the following focus question: What is the effect of MAT on inflammatory biomarkers in OSA? Electronic and manual literature searches were conducted on databases: PubMed/MEDLINE, Web of Science, and Cochrane Library for studies published until September 2021 to collect information about the effect of mandibular advancement therapy, a non-continuous positive airway pressure alternative measurement of OSA. A systematic literature review was performed following the PRISMA guidelines to identify studies evaluating the effect of MAT in patients suffering from OSA. Randomized clinical trials were included, and case reports, retrospective studies, literature reviews, *in-vitro* studies, observational studies, authors' opinions, letters to the editor, and engineering articles were excluded. Fifty-nine articles published before September 2021 were identified. Fifty-four articles met the inclusion criteria. After assessing inclusion criteria, three clinical trials were included with 148 patients suffering from OSA and treated with mandibular advancement therapy. The follow-up period ranged from two to three months, with the average follow-up being 1.66 months. The mean age of the patients was observed to be 53.11 ± 2.65 years. The mean Epworth Sleepiness Scale observed in patients in all three clinical trials was 9.75 ± 0.89. MAT in patients with moderate or severe OSA reduced apnea-hypopnea index but has less effect on inflammatory and metabolic biomarkers.

Keywords: Inflammatory biomarkers, mandibular advancement therapy, obstructive sleep apnea

INTRODUCTION

Obstructive sleep apnea (OSA) refers to at least five apnea or hypopneas per sleep hour [apnea-hypopnea index (AHI) >5 h], resulting in sleep fragmentation and decreased oxygen saturation. OSA is a condition associated with pathologic sleep deprivation; and respiratory and cardiovascular complications.[1,2] It has been observed that untreated OSA can cause an increase in the risk of cardiovascular diseases (CVD) like ischemic stroke, arterial hypertension, and ischemic heart disease.[3] OSA is a major medical condition, affecting around 4%–13% of the general population, impairing quality of life, and substantially increasing the risk of motor vehicle accidents.[3] In OSA, the recurrent episodes of upper airway collapse are usually characterized by desaturation of oxyhemoglobin and termination by brief arousals, resulting in marked sleep fragmentation and chronic excessive daytime sleepiness. This leads to increased derangement, increased function, sustained activation of the sympathetic nervous system, and expression of systemic inflammatory markers like CRP, TNF-α, ICAM, IL-6, IL-8, VCAM, selectins, etc.[4] The treatment of OSA patients includes weight loss,

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using nasal continuous positive airway pressure (CPAP) therapy, and upper airway reconstructive surgery. It has been observed that adherence to CPAP therapy is very less, with the long-term adherence rate noticed to be as low as 50%. Thus, it is important to look for some alternative treatment options to CPAP and surgery. For patients suffering from mild to moderate OSA, oral appliances (OAs) are proven to be a good alternative.[5] The OAs are the devices that are placed and fitted in the mouth of the patient during sleep, preventing the oropharyngeal tissues and the base of the tongue from collapsing behind and obstructing the upper airway. One of the most commonly used OAs is mandibular advancement devices (MAD).[6] Although MAD is being used with growing evidence, still there lie different barriers to the provision of MAD. These uncertainties usually avert the widespread use of MAD in OSA. Thus, it is important to detail the short and long-term symptomatic and systematic side effects of MAD in relation to mandibular advancement therapy (MAT) in patients of OSA.

We undertook a systematic review of studies to determine the possible correlation between MAT and the effect on inflammatory biomarkers in OSA. (PROSPERO registration number CRD42022299890) We primarily focused on the results of randomized clinical trials.

METHOD

Search strategy

The present systematic review was conducted using PRISMA guidelines,[7] addressing the following focus question: What is the effect of MAT on inflammatory biomarkers in OSA? Electronic and manual data resources were consulted using databases: PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://mjl.clarivate.com/search-results), and Cochrane Library (https://www.cochrane.org/) for studies published until September 2021. The results were limited to studies written in English. The terms imported in the search strategy on various databases were mandibular advancement therapy, inflammatory biomarkers, OSA, MAD, etc. Literature search on PubMed/MEDLINE was based on terms: (biomarker* AND (((obstructive sleep apnea) OR (OSA) AND ((mandibular advancement appliance OR ((((oral appliance) OR (MAA)) OR (mandibular repositioning appliance)) OR (mandibular repositioning device))). The following terms were used in the search strategy on the Cochrane Library, the database for systematic review: (OSA OR obstructive sleep apnea) AND (biomarker*) AND (mandibular advancement device OR oral appliance) AND (randomized controlled trials OR RCTs). The literature search on the Web of Science was done using ((ALL = (obstructive sleep apnea)) AND (ALL = (biomarker*)) AND (ALL= (mandibular advancement appliance)). On searching at clinicaltrials.gov, we found a single clinical trial, but it was beyond the relevance of our systematic review.

Inclusion and exclusion criteria

Eligibility criteria of analysis have been set according to the PICOS format described:

Participants: Patients of OSA with an AHI of >=10 events/h, without any prior treatment, having an incidence of co-morbidity cardiovascular diseases (CVD), and hypertension were included.

Intervention: Patients with OSA received a mandibular advancement device.

Comparison: Subjects who are using a sham OA.

Outcome: Correlation between MAT and its effect on inflammatory biomarkers in OSA.

Study design: RCTs on humans were included.

Exclusion criteria: The retrospective and prospective studies, case series, case reports, literature reviews, *in-vitro* studies, observational studies, authors' opinions, letters to the editor, and engineering articles were excluded. The studies demonstrating cases of central or predominant mixed sleep apnea, liver and kidney diseases, lung diseases, cancer, acute infection, epilepsy, and severe psychiatric diseases were also not considered.

Study selection

Two reviewers (TP and VS) screened all identified titles and abstracts independently. In addition, the reference lists of the subsequently selected abstracts and the bibliographies of the human RCTs were searched manually. The full text was collected for studies that satisfied the inclusion criteria or for which there was inadequate data in the title and abstract. Disagreements amongst reviewers were resolved through conversation. Finally, the remaining papers were evaluated in full text using the above-mentioned inclusion and exclusion criteria.

Data extraction

Two reviewers (PP and DS) independently extracted data from the included studies. Disagreements were again resolved through discussion. When data were missing or unclear, the corresponding authors were contacted. To answer the issue posed in our systematic review, we looked for data on predictor variables, that is, the use of MAT and its effect on inflammatory biomarkers in cases of OSA. Both reviewers

evaluated the primary outcome, which was the presence or absence of the effect of MAT on inflammatory biomarkers in OSA. Finally, the funding sources of the chosen studies were investigated.

Quality of the studies

The risk of bias of the included randomized clinical controlled trials was evaluated using the Cochrane risk of the bias assessment tool, and a plot was generated using Rob 2.0 Cluster (https://www.riskofbias.info/welcome/rob-2-0-tool).[8] The scale was applied for randomized control trials to judge each included study on the selection of studies, comparability, and the ascertainment of either the exposure or outcome of interest.

RESULTS

The initial electronic database search on PubMed/MEDLINE, the Cochrane Library, and the Web of Science resulted in 59 titles. After screening the abstracts, two independent reviewers selected 54 relevant titles, and 41 were excluded for not being related to the topic. Following examination and discussion by the reviewers, 51 articles were selected for full-text evaluation [Figure 1].

After prescreening, application of the inclusion and exclusion criteria, and handling the question of our systematic review, three studies remained. They were used to extract data and do statistical analysis.

Study characteristics

Characteristics of the included studies are presented in Tables 1 and 2.

All three included studies were RCTs evaluating the effect of MAT on inflammatory blood biomarkers in OSA. In one study, data were evaluated for the last two months (Recoquillon S *et al*.[9]), whereas others were evaluated for the last three months (Niżankowska-Jędrzejczyk A *et al*.[10]; Hedberg P *et al*.[11]). The predictor variables for both studies were the presence or absence of the effect of MAT on inflammatory biomarkers in OSA, except for the study by Recoquillon S *et al*.[9] who also considered the effect of a sham device and compared it with MAD in relation to inflammatory biomarkers of OSA. All three studies determined the effect of MAD on inflammatory blood or serum biomarkers like C-reactive protein, interleukins, and tumor necrosis factors. The assessment of OSA, AHI, and biomarkers was carried out using polysomnography and blood sample collections, respectively.

Results of the individual studies and qualitative synthesis

The three included clinical trials included a total of 148 patients suffering from OSA and treated with mandibular advancement therapy. The follow-up period ranges from two to three months, with the average follow-up being 1.66 months. The mean age of patients was observed to be 53.11 ± 2.65 years. The mean Epworth Sleepiness Scale observed in patients in all three clinical trials was 9.75 ± 0.89. Recoquillon S *et al*.[9] observed no effect on inflammatory and metabolic biomarkers in patients with severe OSA and no overt CVD, despite high objective device adherence and a significant reduction in OSA severity. Niżankowska-Jędrzejczyk A *et al*.[10] in their findings suggested that mandibular advancement splint (MAS) treatment reduced AHI significantly at three months (24 vs. 13.1 h) and further improved it at six months (13.1 vs. 7.05 h). It also significantly improved levels of IL-1β, D-dimer, TAFIa, and CLT.[10] Hedberg *P et al*.[11] compared active and passive OAs for managing OSA. After three months of treatment, they found a significant reduction of the AHI with active OA (effect size 0.258, 95% confidence interval 0.146–0.386, $P < 0.001$). But an insignificant difference was observed between the groups about change inflammatory markers concentration changes during the treatment period (effect sizes between 0.488 and 0.524; all P values ≥ 0.737). Thus, the study observed that OA treatment for three months did not affect circulating concentrations of some common inflammatory markers in patients with OSA and systemic hypertension [Tables 1 and 2].

Quality of the studies

The outcome attributes were improvement in OSA readings and the effect on inflammatory biomarkers. Because of the heterogeneity in study design, intervention, and follow-up period, a quantitative assessment or meta-analysis was not conducted. The risk of bias assessment of Randomized clinical trials[9-11] are summarized in Figure 2. In a study by

Table 1: Characteristics of included studies

Author	Participants	Groups	Follow-up	Biomarkers	Outcome
Niżankowska-Jędrzejczyk A *et al.*,[10] 2014	36 out of 71 managed with active OA	Active versus passive oral appliance	Three and six months	Inflammatory and hemostatic markers	Significant improvement in AHI and levels of markers
Recoquillon S *et al.*,[9] 2019	55 out of 109 were subjected to MAD	MAD versus Sham appliance	Two months	Inflammatory and metabolic markers	Reduced AHI and no significant effect on biomarkers
Hedberg P *et al.*,[11] 2020	22 out of 41 were subjected to MAS	MAS versus control	Three months	Inflammatory biomarkers	Significant improvement in AHI. No significant effect on biomarkers

AHI=apnea-hypopnea index, MAD=mandibular advancement devices, MAS=mandibular advancement splint, OA=oral appliance

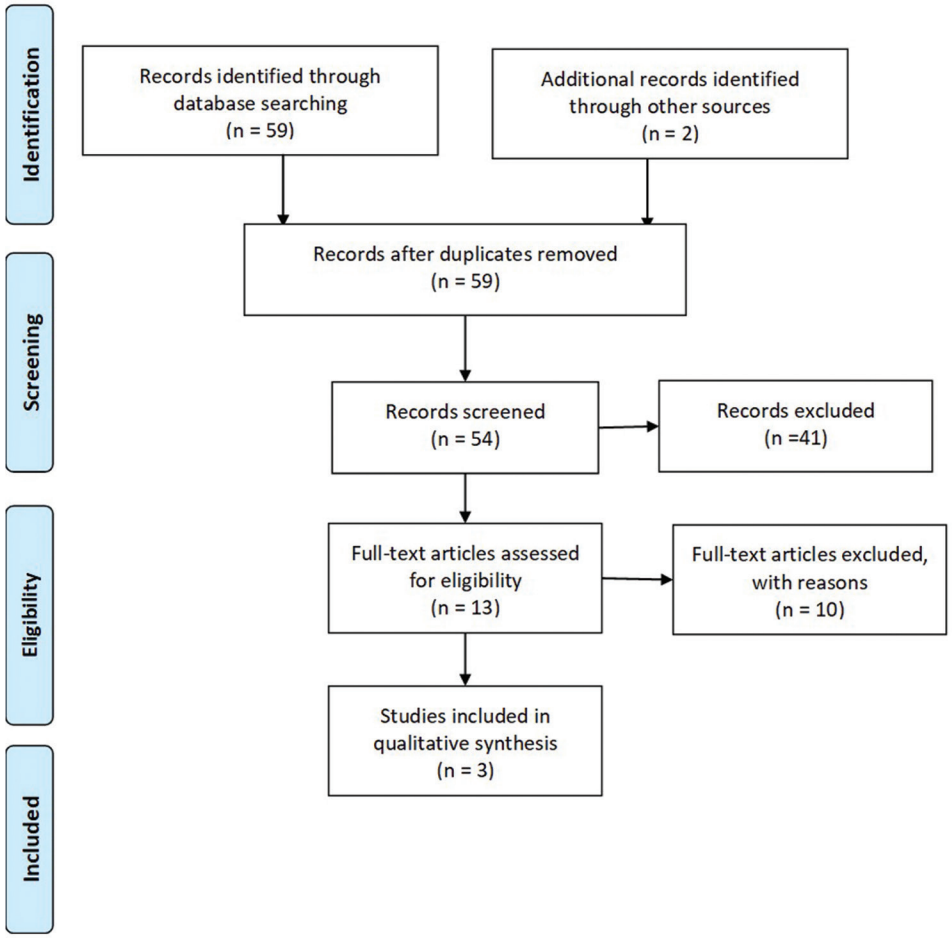

Figure 1: PRISMA flow chart

Table 2: Characteristics of included studies (extended)

Author	Study design	Definition of OSA	Key results	Additional information
Niżankowska-Jędrzejczyk A *et al.*[10], 2014	Randomized clinical trial	Not mentioned	AHI reduced from 24.0 to 13.1 at three months and 7.05 at six months. All biomarkers improved (IL-1β, D-dimer, TAFIa, and CLT)	Priori sample calculation: yes Accuracy of measurements: yes Baseline comparability: yes
Recoquillon S *et al.*,[9] 2019	Randomized clinical trial	Not mentioned	Complete response: AHI reduced by≥50% to less than 5 h in 10% of patients; partial response (AHI reduced by≥50% to but persistent≥5 h in 50% of patients; 40% were poor responders with <50% reduction	Priori sample calculation: yes Accuracy of measurements: yes Baseline comparability: yes
Hedberg P *et al.*,[11] 2020	Randomized clinical trial	Not Mentioned	A large reduction in the AHI in the OAa group compared with the OAp group. Reduction of the AHI by >50% compared with baseline was significantly more common in the OAa group (69% vs. 34%; *P*=0.006).	Priori sample calculation: yes Accuracy of measurements: yes Baseline comparability: yes

AHI=apnea-hypopnea index, OSA=obstructive sleep apnea, OA=oral appliance

Recoquillon S *et al*.,[9] several characteristics were presented that may have contributed to a lower cardiovascular response and/or a floor effect of the intervention, including a small proportion of metabolic disorders, no overt CVD, and moderate daytime sleepiness at baseline. Irrespective of the other two studies, Niżankowska-Jędrzejczyk A *et al*.[10] compared MAS with control for OSA. Hedberg P *et al*.[11] had experienced normal values of inflammatory biomarkers because of the floor effect, leading to an insignificant change in biomarkers after active OA therapy. Considering the results obtained from the clinical trials that were included and compiled as a systematic review, there is a tendency for the mandibular advancement of OAs to produce a better reduction in polysomnographic and AHI measurements and effect on inflammatory biomarkers. However, a statistically significant improvement cannot be calculated due to the inability to perform the meta-analysis. The results from individual studies provide evidence that MAT could

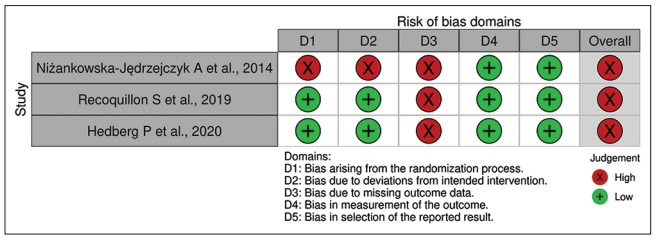

Figure 2: Traffic plot graph

produce favorable results regarding reduction in AHI and polysomnography and inflammatory mediators. None of the research looked at the long-term impact of wearing these items on the TMJ and surrounding muscles and structures. Furthermore, because these studies were only conducted for a short period, the long-term impact of these devices on sleep apnea could not be thoroughly investigated.

DISCUSSION

Sleep disruption caused by breathing disorders is potentially life-threatening and, therefore, an important global health issue. Repeated arousals engage the hypothalamic pituitary adrenal (HPA) axis, and intermittent hypoxia and sleep fragmentation are linked to sympathetic activation and catecholamine production.[4] The activation of the HPA axis will, in turn, promote associated sympathetic adrenomedullary (SAM) system perturbations, which further exacerbates nocturnal blood pressure fluctuation and induces left ventricular hypertrophy and early left ventricular diastolic dysfunction.[5] Thus, activation of the HPA axis and SAM system may increase the risk for cardiovascular disease in patients with OSA.[12] All three studies showed an increased level of biomarkers. So, the risk of cardiovascular events in OSA can be determined by the serum levels of various representative inflammatory biomarkers (CRP, TNF-α, IL-6, IL-8, ICAM, VCAM, selectins, etc.).[13-15]

MADs have emerged as an effective therapeutic alternative to CPAP for OSA. They work by increasing the upper airway size and thus reducing the risk of sleep apnea and snoring in patients with OSA.[16]

The current systematic review studied the literature on the effect of MADs on inflammatory biomarkers in obstructive sleep apnea patients. The three included papers were randomized clinical trial studies. All the studies were analyzed separately. As demonstrated by the equality of the risk ratios and on account of the limited number of included studies, the relevance of obtained information needs to be verified further. Bias exists in the publications considered, and this might have a significant impact on our findings.

As study by Recoquillon S *et al*.[9] observed no effect on inflammatory (C reactive protein, interleukin-6, tumor necrosis factor-α, and its receptors, adiponectin, leptin, and P-selectin) and metabolic (glucose and lipid metabolism, and N-terminal pro-brain natriuretic peptide) biomarkers in patients with severe OSA. They compared MAD with a sham device. They found that MAD reduces the AHI ($P < 0.001$) but has no effect on circulating biomarkers compared with the sham device, despite high treatment adherence (6.6 h/night). The mean reduction in AHI obtained in the effective MAD group (about 53%) was lower than that usually obtained with CPAP, as stated by Sharples LD *et al*.[17] in their meta-analysis and systematic review. This clinical trial observed the effect of MAD for two months, in contrast to the other two studies[10,11] that had a follow-up of three months.

In contrast to the other two studies,[9-11] Niżankowska-Jędrzejczyk A *et al*.[10] also studied hemostatic markers of OSA along with inflammatory biomarkers. They found that MAS treatment significantly improved levels of IL-1β, D-dimer, TAFIa, and CLT. Oh Jae-Tak *et al*.[18] concluded that MAD treatment modality for a patient with sleep apnea can decrease plasma cytokine levels. After treatment for three months, they concluded that there were significant decreases in TNF- α after mandibular advancement therapy. But have no significant change in the level of CRP, IL-6, IL-10, or IL-1β between baseline and after treatment. The study expands our knowledge of the hemostatic abnormalities observed in OSA and their modulation by MAS treatment.

Hedberg P *et al*.[11] compared active and passive mandible protruded device treatment. Like Recoquillon S *et al*.,[9] they also assessed serum concentrations of the inflammatory biomarkers white blood cells, high-sensitivity C-reactive protein, interleukin 6, interleukin 10, and tumor necrosis factor-α. After three months of treatment. There was a significant reduction of the AHI in the OAa group (active group) compared with the OAp group (passive group) (effect size 0.258, 95% confidence interval 0.146–0.386, $P < .001$). But the study observed that OA treatment for three months did not affect circulating concentrations of some common inflammatory markers in patients with OSA and systemic hypertension. An extended treatment period might be required to achieve an impact on circulating biomarkers.

All the studies have various merits that included: 1) the use of sleep evaluation standards (Epworth Sleepiness Score and AHI) which were specific to evaluate OSA, thus increasing the validity of the study; 2) the selection of a sample consisting of uniform age group; 3) selecting all common inflammatory biomarkers involved in OSA.

Limitations

Due to heterogeneity and variability in study parameters and a smaller number of reported clinical trials, definitive conclusions of the effect of MAT on inflammatory biomarkers of OSA need to be verified with more literature and well-designed long-term RCTs.

CONCLUSION

With all the literature research within the scope of our systematic review, the conclusion drawn is that individuals subjected to MAT have a specific impact on inflammatory biomarkers in OSA subjects having CVD co-morbidity.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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