Asian Journal of Medicine and Health

Volume 21, Issue 12, Page 12-20, 2023; Article no.AJMAH.110531
ISSN: 2456-8414

Updates on Obstructive Sleep Apnea as a Risk Factor for Developing Diabetes: A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJMAH/2023/v21i12956

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/110531

Systematic Review Article

Received: 04/10/2023
Accepted: 08/12/2023
Published: 11/12/2023

ABSTRACT

Background: Examining the relationship between obstructive sleep apnea (OSA), diabetes, and diabetic complications is crucial because OSA and diabetes have become more common in recent years. In particular, we detail the contemporary and longitudinal research and give a thorough evaluation of the classical studies.
Objectives: To assess OSA as a risk factor for developing diabetes, especially type 2 diabetes (T2D), and to compare gender differences.
Methods: PubMed, SCOPUS, Web of Science, and Science Direct were systematically searched for relevant literature. Rayyan QRCI was employed throughout this comprehensive process.
Results and interpretation: We included nine studies with a total of 45530 patients, and 25420

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(55.8%) were males. People with OSA are more prone to develop diabetes. This risk was more prevalent in women and had a stronger correlation with obesity and metabolic syndrome. Although gender may have a major impact on this relationship in women, it is unclear whether the correlation between OSA and diabetes in the elderly is different from that in the young and middle-aged. Therefore, it is recommended that future studies examine possible causative relationships between OSA and diabetic complications, how treating OSA influences the emergence of these problems, and how age influences the association between OSA and diabetes. We think that treating these common comorbidities will improve diabetic patients' prognosis and quality of life.

Keywords: Diabetes mellitus; obstructive sleep apnea; risk.

1. INTRODUCTION

OSA is defined as recurring episodes of upper airway inspiratory collapse during sleep, resulting in hypopnea (breathing reduction) or apnea (breathing cessation) episodes with transient hypoxemia (low levels of oxygen in the blood) and hypercapnia (elevated carbon dioxide levels in the blood). The apneic and hypopneic episodes are terminated when the patient awakens from sleep. For a brief amount of time, the patient hyperventilates due to the hypoxemia. These events are critical in determining the severity of a patient's OSA. An apnea/hypopnea index (AHI) determines the severity by counting the number of apnea/hypopnea events per hour [1].

OSA is a common sleep problem that affects 15% to 24% of all adults, but this figure is thought to be inaccurate because OSA is still widely underdiagnosed [2]. Both OSA and HTN are multifactorial disorders [3]. They share numerous risk factors (obesity, male gender, and increasing age) [2].

OSAS etiology is still not well understood. Upper airway obstruction, hypoventilation, and sleep division are the most common clinical signs; pharyngeal muscle collapse is the primary cause of inadequate breathing and sleep pauses. Despite the body's ongoing forceful breathing to adjust, the obstructed pharyngeal airways continue to interfere with adequate ventilation, resulting in apnea and hypopnea [4].

Over 90% of instances of diabetes are type II diabetes, which is currently the seventh most common cause of mortality in the United States [5,6]. Furthermore, throughout the past ten years, diabetes has been found to either worsen the symptoms or raise the risk for several other top 10 causes of mortality in the US, such as cancer and heart disease [7]. The most common sleep disorder worldwide, OSA is found in between 30 and 80% of diabetics (including type I diabetics) [8].

It has been demonstrated that OSA and insulin resistance are independently associated, with the severity of OSA matching the severity of insulin resistance [9]. Gestational diabetes is also linked to OSA [10]. A disorder known as sleep apnea causes breathing to cease during sleep. This can happen due to two main causes: either the tongue or other soft tissues collapse over the airway, obstructing it, or the brain is not telling the body to breathe (central OSA, or CSA) [11]. Inflammation [9], the metabolic syndrome and diabetes mellitus [12], obesity [13], heart disease [14], stroke [15], and mortality [16] are all linked to OSA. This systematic review assesses OSA as a risk factor for developing diabetes.

2. METHODOLOGY

In carrying out this systematic review, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards were adhered to [17].

2.1 Study Design and Duration

November 2023 marked the start of this systematic review.

2.2 Search Strategy

To discover the pertinent literature, a thorough search was conducted across four main databases: PubMed, SCOPUS, Web of Science, and Science Direct. We limited our search to English and considered each database's specific needs. The following keywords were transformed into PubMed Mesh terms and used to locate the pertinent studies; "Obstructive sleep apnea,"

"hypoxia," "Diabetes," "T2D," and "Risk." The Boolean operators "OR" and "AND" matched the required keywords. Publications with full English text, available free articles, and human trials were among the search results.

2.3 Selection Criteria

We considered the following criteria for inclusion in this review:

- Studies that assesses OSA as a risk factor for developing diabetes.
- We included only T2D.
- Studies conducted between 2015 and 2023.
- We did not include studies that investigated diabetic treatments.
- Only human subjects.
- English language.
- Free accessible articles.

2.4 Data Extraction

The search technique's output was double-checked using Rayyan (QCRI) [18]. By modifying the combined search results with inclusion/exclusion criteria, the researchers evaluated the relevance of the titles and abstracts. Each paper that met the requirements for inclusion underwent a careful examination by the reviewers. The authors talked about methods for resolving disputes. The approved study was uploaded using a data extraction form already created. The authors extracted data about the study titles, authors, study year, country, participants, gender, follow-up duration, diabetes type, and main outcomes. A separate sheet was created for the risk of bias assessment.

2.5 Strategy for Data Synthesis

Summary tables were created using data from relevant studies to provide a qualitative assessment of the findings and study components. After the data for the systematic review were gathered, the most efficient approach for utilizing the data from the included study articles was chosen.

2.6 Risk of Bias Assessment

The ROBINS-I risk of bias assessment technique for non-randomized trials of therapies was used to evaluate the caliber of the included studies [19]. The seven themes assessed were confounding, participant selection for the study, classification of interventions, deviations from intended interventions, missing data, assessment of outcomes, and choice of the reported result.

3. RESULTS

3.1 Search Results

A total of 422 study articles resulted from the systematic search, and 113 duplicates were deleted. Title and abstract screening were conducted on 309 studies, and 273 were excluded. 36 reports were sought for retrieval, and 2 articles were retrieved. Finally, 34 studies were screened for full-text assessment; 9 were excluded for wrong study outcomes, 14 for the wrong population type, and 2 articles were letters to the editors. Nine eligible study articles were included in this systematic review. A summary of the study selection process is presented in Fig. 1.

3.2 Characteristics of the Included Studies

Table 1 presents the sociodemographic characteristics of the included study articles. Our results included nine studies with a total of 45530 patients, and 25420 (55.8%) were males. Six studies were cross-sectional [20-25], one was retrospective in nature [19], one was prospective in nature [26], and one was cohort study [27]. Table 2 presents the clinical characteristics. All of the included studies stated that OSA holds an increased risk of developing diabetes. This risk was higher among women and more associated with obesity and metabolic syndrome.

4. DISCUSSION

Experts in the field of sickle cell disease (SDB) have long recognized that OSA is a risk factor for reduced glucose tolerance. With the release of the International Diabetes Federation's "Consensus Statement," this knowledge has spread throughout the medical community and even among many patients [28]. In the present study, we found that all of the included studies stated that OSA holds an increased risk of developing diabetes. According to a Wang et al. meta-analysis, moderate to severe OSA is linked to a higher risk of T2D [29]. However, we also

discovered that mild OSA was linked to a higher risk of T2D. This discrepancy might result from the prior meta-analysis's limited sample size and brief follow-up of the included trials, which overestimated the risk of T2D. Furthermore, the connection was not assessed by the authors using a dose-response methodology. We discovered a linear correlation between OSA and T2D in our investigation.

Studies on animals and healthy volunteers suggest that sleep disturbance and intermittent hypoxia (IH) may be risk factors for impaired glucose metabolism, insulin resistance, and T2D in individuals with OSA, while it is still unclear whether OSA can cause T2D. Lower oxygen blood saturation, inconsistent sleep with increased stress, hormonal imbalance, and systemic inflammation are all brought on by obstruction of the upper airways, hypopnea, and apnea. IH plays a major role in the pathophysiology of metabolic disruption and diabetes in OSA since it is, at the very least, partially to blame for the body's decreased ability to utilize glucose and oxygen, as well as for the loss in insulin sensitivity that has been demonstrated in both human and animal models. Patients with OSA experience impaired glucose homeostasis due to mechanisms other than intermittent hypoxia. Many factors are suggested as a possible link between IH and disturbed glucose metabolism, although the exact cause of OSA patients' diabetes is still unknown. These factors include genetics, oxidative stress and inflammation, disruption of the hypothalamo-pituitary-adrenal (HPA) axis with elevated levels of circulating cortisol and free fatty acids, adipokines, elevated levels of endothelin-1 from damaged vascular endothelium, and increased sympathetic system activity [30].

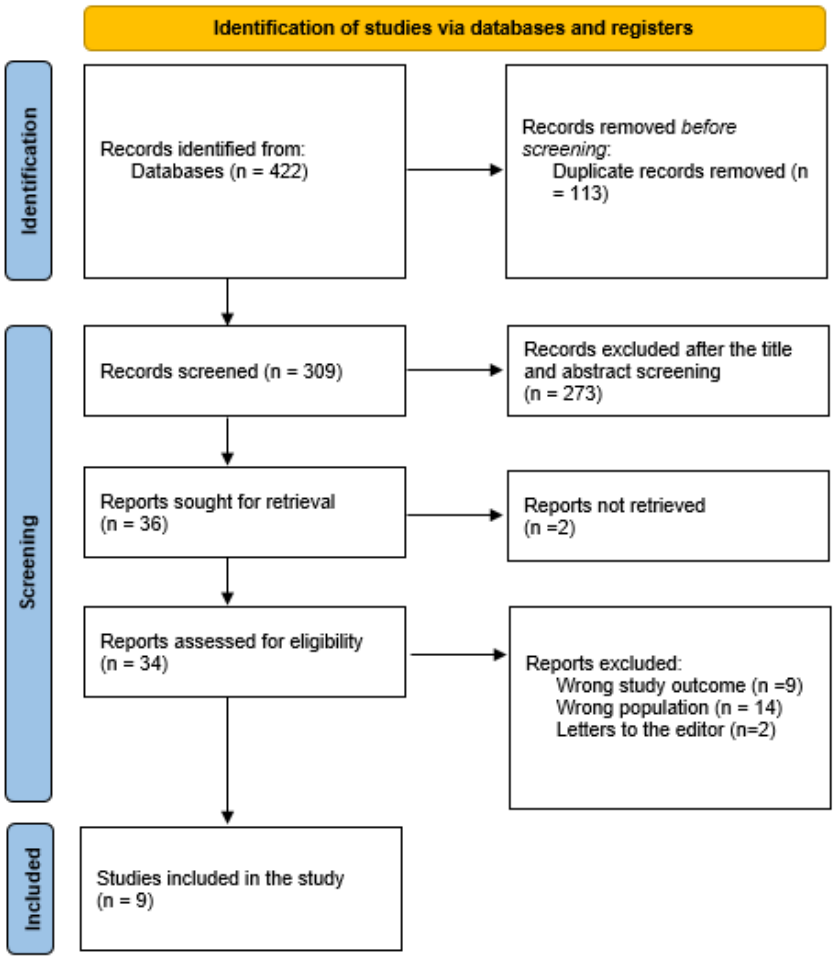

Fig. 1. PRISMA flowchart summarizes the study selection process

Table 1. Sociodemographic characteristics of the included participants

Study	Study design	Country	Participants	Gender (Females)	Age
Andreozzi et al., 2020 [19]	Retrospective cohort	Switzerland	1717	52.8 ± 12.7	1138 (66.3)
Algeffari et al., 2020 [20]	Cross-sectional	Saudi Arabia	201	53.3 ± 9	101 (50.3)
Putra et al., 2023 [21]	Cross-sectional	India	80	NM	50 (62.5)
Bouloukaki et al., 2021 [22]	Cross-sectional	Greece	2279	55	1686 (74)
Haung et al., 2018 [23]	Cross-sectional	USA	2592	25-55	1646 (63.5)
Strausz et al., 2018 [24]	Cross-sectional	Finland	27 161	48.01 ± 13.2	13792 (50.8)
Liu et al., 2017 [25]	Cross-sectional	Taiwan	9174	62.5	5894 (64.2)
Nagayoshi et al., 2016 [26]	Prospective cohort	Australia	1453	60.5	675 (46.5)
Appleton et al., 2015 [27]	Cohort	Australia	873	60.5	438 (50.2)

Table 2. Clinical characteristics and outcomes of the included studies

Study	Diabetes type	Follow-up duration	Main outcomes	ROBIN-I
Andreozzi et al., 2020 [19]	3 months	T2D	African OSA displayed a distinct profile of comorbidities. Compared to Caucasians, some younger patients had less cardiac comorbidities but greater diabetes. Diabetics of African descent should be sent for OSA testing more quickly.	Moderate
Algeffari et al., 2020 [20]	8.6	T2D	There is a chance that over half of Saudi individuals with T2DM have OSA, which may or may not be diagnosed. There was a substantial positive correlation found between the risk of OSA and higher BMI, waist and neck circumferences, and length of diabetes.	High
Putra et al., 2023 [21]	NM	T2D	T2D and OSA have a strong, positively associated association. Patients with T2D had a 3.3-fold increased risk of developing high-risk OSA in comparison to those without the condition.	Moderate
Bouloukaki et al., 2021 [22]	NM	T2D	Significant OSA was linked, in this sizable clinical patient group, to an autonomous three-fold increase in the risk of T2D. These findings imply that routine diabetes screening for severe OSA patients is worthwhile, particularly for younger, drowsier patients.	Moderate
Haung et al., 2018 [23]	10	T2D	While diabetes treated with insulin is independently linked to a higher risk of OSA, especially in women, OSA is independently linked to an increased risk of diabetes. Understanding this reciprocal relationship may help with illness prevention and therapy in the clinical setting. Subsequent investigations targeted at clarifying the mechanisms underlying every association can provide new targets for interventions.	Moderate
Strausz et al., 2018 [24]	22	T2D	Diabetes mellitus, coronary heart disease, and diabetic kidney disease are independent risk factors for OSA. Even among women, who have historically gotten less attention than men in the diagnosis and treatment of OSA, this effect is more noticeable.	Moderate

Study	Diabetes type	Follow-up duration	Main outcomes	ROBIN-I
Liu et al., 2017 [25]	4.1	T2D	In a cohort of East Asians, they discovered a unidirectional relationship between OSA and incident diabetes. The onset of sleep apnea could not be predicted by baseline diabetes. Nonetheless, there was little prevalence of OSA, and the illness may go undiagnosed.	High
Nagayoshi et al., 2016 [26]	13	T2D	In a community-based sample, severe OSA was linked, independently of obesity, to an increased risk of incident diabetes. The significant frequency of OSA in the general population and its possible connection to incident diabetes should be known to healthcare practitioners.	High
Appleton et al., 2015 [27]	4.7	T2D	Diabetes development was found to be independently correlated with both nocturnal hypoxemia and severe undiagnosed OSA. Patients who report with one illness and are evaluated for the other are likely to have a lower burden of undiagnosed diabetes and undiagnosed OSA.	Moderate

Elevated sympathetic tone exacerbates insulin resistance by impairing beta-pancreatic cells' ability to secrete insulin. One week of CPAP treatment significantly reduced plasma norepinephrine levels throughout the day and at night in patients with OSA who also had hyperglycemia [31,32]. Diabetes-related autonomic neuropathy raises the incidence of OSA in obese patients with T2D by compromising the upper airway mechanoreceptor reflex. The relationship between the autonomic nervous system, hormones, and metabolism that are shared by both diabetes and OSA may exacerbate clinical worsening when present concurrently in a single patient or impair the clinical result of each disease independently. In addition to this relationship, which is being further studied, there has been a rise in interest in recent years about the potential elevated risk of colorectal cancer in those with T2D and OSA [33].

We also found that this risk was higher among women and more associated with obesity and metabolic syndrome. While ageing and obesity are common risk factors for both diabetes and OSA, obesity has little bearing on the link between the two conditions. The main cause of the association between OSA and diabetes is that both sleep fragmentation and intermittent hypoxia independently lower insulin sensitivity. More specifically, it is thought that the activation of sympathetic outflow at the tissue level, elevated oxidative stress, elevated cortisol via activation of the hypothalamic-pituitary-adrenal axis, activation of particular transcription factors like nuclear factor κ B, and downstream synthesis and activity of a variety of inflammatory cytokines, including interleukin-6 and tumour necrosis factor-α, are the mechanisms mediating the decrease in insulin sensitivity [34,35]. Additionally, vasoconstriction and elevated oxidative stress brought on by intermittent hypoxemia cause endothelial dysfunction and microvascular damage [36]. The association between OSA and diabetic nephropathy is mediated by hypertension and modifications in the control of the renin-angiotensin-aldosterone pathway [37]. Furthermore, new research suggests a reciprocal relationship in which hyperglycemia exacerbates SDB by reducing the responsiveness of the pharyngeal dilator or carotid body muscles [38].

A few things are preventing our research. First, the sample size of certain research was small. Marshall et al. [39] examined a mere 303 samples. Lower confidence levels could be brought in by fewer subjects. This could be one possible cause of the heterogeneity. Secondly, we required as much data as possible to construct the linear and spline models. Third, there was irregularity in the OSA measurement. Lastly, the AHI may be influenced by various measurement devices.

Despite the fact that the relationship between OSA and diabetes has been the subject of numerous investigations, the classifications of the two conditions varied significantly in the reports. Depending on the criteria that are applied, both the prevalence of diabetes and OSA can vary [40]. Thus, it is desirable that study criteria be as consistent as feasible for subsequent research.

An intriguing hypothesis was recently put forth, stating that 11.5% of diabetes cases may be avoided if OSA were well treated in the general population [41]. These findings could provide fresh information on the avoidable rate of diabetes for future research.

5. CONCLUSION

Diabetes is more likely to develop in people with OSA. This risk was more common in women and was more closely linked to metabolic syndrome and obesity. It is unclear whether the correlation between OSA and diabetes in the elderly differs from that in the young and middle-aged, despite the fact that gender may have a significant influence on this relationship in women. Future research is therefore encouraged and should look into potential causal links between OSA and diabetic problems, how treating OSA affects the development of these issues, and how ageing affects the relationship between OSA and diabetes. We believe that treating these prevalent comorbidities will enhance the quality of life and prognosis for diabetic patients.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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