Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/19365
DOI URL: http://dx.doi.org/10.21474/IJAR01/19365

RESEARCH ARTICLE

NAVIGATING THE INTERCONNECTIONS OF OBSTRUCTIVE SLEEP APNEA AND DIABETES MELLITUS: A COMPREHENSIVE REVIEW OF PATHOPHYSIOLOGY AND MANAGEMENT STRATEGIES

Shareefah Mohammed Basheri[1], Abdulrahman Mania Alkhalifah[2], Shikah Ibrahim Bin Doukhi[3], Fatmah Yahaya Al Raithy[3], Mohammed Ahmed Asiri[4], Hussein Saleem Hussein Aljuwayed[1], Maha Ali Al Musallam[5] and Fawaz Awad Alharbi[1]

1. Pulmonary Medicine, Prince Sultan Military Medical City, Riyadh, Saudi Arabia.
2. Radiology Department, Prince Sultan Military Medical City, Riyadh, Saudi Arabia.
3. Nursing Services Administration, Prince Sultan Military Medical City, Riyadh, Saudi Arabia.
4. Central Military Laboratory and Blood Bank, Prince Sultan Military Medical City, Riyadh, Saudi Arabia.
5. Department of Endocrinology and Diabetes, Prince Sultan Military Medical City, Riyadh, Saudi Arabia.

Manuscript Info

Manuscript History
Received: 25 June 2024
Final Accepted: 27 July 2024
Published: August 2024

Key words:-
Obstructive Sleep Apnea, Diabetes Mellitus, Insulin Resistance, Continuous Positive Airway Pressure, Interdisciplinary Care

Abstract

The multifaceted bidirectional relationship between Obstructive Sleep Apnea (OSA) and Diabetes Mellitus (DM) represents a critical intersection in chronic disease management, with profound implications for patient outcomes. OSA is highly prevalent among individuals with Type 2 Diabetes Mellitus (T2D), and emerging evidence suggests its significance in Type 1 Diabetes Mellitus (T1D). The underlying pathophysiology involves complex interactions between intermittent hypoxia, systemic inflammation, and insulin resistance, contributing to the development and exacerbation of both conditions. Clinically, the coexistence of OSA and DM accelerates the progression of cardiovascular and microvascular complications, complicating management strategies and increasing patient morbidity and mortality. Early detection and management of OSA in diabetic patients are essential for improving glycemic control and reducing the risk of complications. Current guidelines advocate for routine OSA screening in diabetic patients, particularly those with poor glycemic control or obesity. Treatments like Continuous Positive Airway Pressure (CPAP) have shown promise in improving both sleep quality and metabolic outcomes. However, significant research gaps remain, particularly in understanding the prevalence of OSA in T1D, the molecular pathways linking these conditions, and the long-term benefits of OSA treatment on diabetic outcomes. Future research must focus on large-scale epidemiological studies, mechanistic insights, and personalized medicine approaches to optimize care for patients with coexisting OSA and DM. Addressing these gaps is crucial for advancing clinical practice and improving patient quality of life.

Corresponding Author:- Dr. Shareefah Mohammed Basheri
Address:- Consultant Pulmonary Medicine, Prince Sultan Military Medical City, Riyadh, Saudi Arabia.

Introduction:-

Overview of Diabetes Mellitus

Diabetes mellitus (DM) encompasses metabolic disorders characterized by persistently high blood sugar levels due to insufficient insulin production, ineffective insulin use, or both (1,2). This condition is divided into Type 1 diabetes (T1D) and Type 2 diabetes (T2D). T1D is an autoimmune disorder where the immune system attacks and destroys insulin-producing beta cells in the pancreas, necessitating lifelong insulin therapy (3). T2D involves insulin resistance, where cells fail to respond adequately to insulin, leading to elevated blood sugar levels as the pancreas may not meet increased insulin demands (4,5). Common risk factors for T2D include obesity, poor diet, sedentary lifestyle, and genetic predispositions (6).

Diabetes complications include microvascular damage (e.g., retinopathy, nephropathy, neuropathy) and macrovascular problems (e.g., cardiovascular diseases) (7). Effective management requires lifestyle modifications, medication, and insulin therapy to maintain blood glucose levels and minimize complications (1,2,8). Globally, DM has reached epidemic proportions, challenging public health systems. The International Diabetes Federation (IDF) estimated 537 million adults with diabetes in 2021 (9), with projections of 643 million by 2030 and 783 million by 2045 (10). The rise is attributed to increasing obesity and sedentary lifestyles. In 2019, diabetes caused approximately 4.2 million deaths, with nearly half under 60 years of age (11). The economic impact is profound, with global health expenditure related to diabetes estimated at USD 966 billion in 2021, a 316% increase over 15 years (12).

Overview of Obstructive Sleep Apnea (OSA)

Obstructive Sleep Apnea (OSA) is a sleep-related breathing disorder characterized by repetitive episodes of complete or partial obstruction of the upper airway during sleep, leading to reduced or halted airflow despite respiratory efforts. This results in intermittent hypoxemia, hypercapnia, and fragmented sleep due to frequent arousals (13,14).

OSA is diagnosed when an individual experiences at least five episodes of apnea or hypopnea per hour of sleep, with symptoms such as excessive daytime sleepiness, loud snoring, or observed breathing cessation. The severity of OSA is assessed using the Apnea-Hypopnea Index (AHI), with 5-15 events per hour indicating mild OSA, 15-30 moderate, and more than 30 severe (13,15). OSA affects approximately 9% of middle-aged women and 17% of middle-aged men, with moderate to severe OSA affecting 10-17% of men and 3-9% of women. The prevalence increases with age and is higher in obese individuals, often remaining undiagnosed, particularly in older adults (16,17).

Risk factors for OSA include obesity, male gender, postmenopausal status, age, genetic predisposition, craniofacial abnormalities, smoking, and alcohol consumption (18,19). The pathophysiology of OSA is complex and involves both anatomical and neuromuscular factors that lead to the collapse of the upper airway during sleep (15,20–23).

Significance of the Topic and Rationale

OSA is prevalent among DM patients, particularly those with T2D. Research indicates that about 54.5% of DM patients have OSA, significantly higher than in the general population (24). Studies have shown that 53.9% of diabetic patients have OSA, with a higher prevalence in men (25).

There is a bidirectional relationship between OSA and DM. OSA exacerbates insulin resistance and impaired glucose metabolism, leading to increased sympathetic activity, oxidative stress, and inflammation. Conversely, poorly controlled DM can worsen OSA severity, with research demonstrating a higher risk of DM in OSA patients and vice versa (26,27). The coexistence of OSA and DM challenges management and can lead to poorer clinical outcomes. Patients with both conditions often have higher HbA1c levels, indicating poor glycemic control and an increased risk of cardiovascular mortality (28,29).

Given the high prevalence of OSA in DM patients and the complex relationship between these conditions, routine screening and management of OSA in diabetic patients are critical. This review explores the prevalence of OSA in DM patients, the bidirectional relationship, and the impact of OSA on DM management and outcomes, emphasizing the importance of early detection and comprehensive management.

Bidirectional Relationship Between OSA and DM

DM as a Risk Factor for OSA

DM, particularly T2D, is a significant risk factor for developing OSA. Obesity, common in T2D patients, contributes to OSA by increasing fat deposition around the neck and upper airway, narrowing the airway and increasing its collapsibility during sleep (30,31). Insulin resistance in T2D exacerbates systemic inflammation and oxidative stress, weakening the pharyngeal muscles critical for maintaining airway patency.

Chronic hyperglycemia associated with diabetes can lead to autonomic neuropathy, impairing reflex mechanisms that keep the airway open. This autonomic dysfunction reduces upper airway muscle tone, making it more susceptible to collapse and increasing OSA risk. Elevated blood glucose levels lead to the glycation of upper airway proteins, making them stiffer and more prone to collapse. Hyperglycemia also exacerbates inflammation and oxidative stress, impairing muscle function (27,32).The impact of hyperglycemia on respiratory function is evident in diabetic patients with poor glycemic control, who are more likely to experience severe OSA symptoms. This highlights the importance of managing blood glucose levels to reduce OSA risk and severity (26,33).

OSA as a Risk Factor for the Development of DM

OSA is an independent risk factor for developing T2D. Longitudinal studies show that OSA increases the risk of T2D. For instance, a study revealed that OSA was associated with a 2.21-fold increased risk of developing T2D, adjusted for obesity and age (34).

OSA contributes to T2D through intermittent hypoxia and sleep fragmentation, leading to insulin resistance and impaired glucose metabolism. The chronic activation of the sympathetic nervous system in OSA increases circulating catecholamines, contributing to insulin resistance and the progression from normoglycemia to prediabetes and T2D (35). OSA also accelerates the progression from prediabetes to diabetes, worsening glucose control (36,37). This underscores the need for early detection and treatment of OSA to prevent diabetes progression (38).

Synergistic Effects of Coexisting OSA and DM

The coexistence of OSA and DM amplifies the risk of cardiovascular complications and increases overall mortality. Both conditions contribute to cardiovascular disease (CVD) development independently, but their combined effects lead to a significantly higher risk of myocardial infarction, stroke, and heart failure. OSA exacerbates the pro-inflammatory and pro-thrombotic state induced by DM, accelerating atherosclerosis and increasing cardiovascular event likelihood (39).

Patients with both conditions have a higher incidence of cardiovascular events and mortality compared to those with only one condition. The combined effects of OSA and DM lead to severe hypertension, dyslipidemia, and systemic inflammation, increasing cardiovascular risk and mortality (27,40).

Managing patients with both conditions presents challenges, as OSA worsens glycemic control and increases insulin resistance, complicating diabetes management. Conversely, poorly controlled diabetes exacerbates OSA severity. CPAP therapy for OSA may not fully address diabetes-related metabolic disturbances, necessitating comprehensive treatment. An integrated management strategy should include routine OSA screening in diabetic patients, aggressive cardiovascular risk management, and lifestyle interventions such as weight loss, exercise, and dietary changes (41).

Pathophysiology Linking OSA and DM

Intermittent Hypoxia and Oxidative Stress

Intermittent hypoxia (IH), characteristic of OSA, involves repeated oxygen desaturation and reoxygenation during sleep, triggering oxidative stress through increased production of reactive oxygen species (ROS). This oxidative stress impairs glucose metabolism and promotes insulin resistance, contributing to DM development (42,43). Oxidative stress from IH damages pancreatic β-cells, impairs insulin secretion, and disrupts proinsulin processing, leading to a higher proinsulin-to-insulin ratio. It also affects insulin signaling pathways in peripheral tissues, exacerbating insulin resistance and creating a metabolic environment conducive to DM development (44,45).

Sympathetic Nervous System Activation

Sympathetic overactivity influences glucose metabolism through hepatic glucose production and insulin resistance. The sympathetic nervous system (SNS) activation leads to increased hepatic glucose output, promoting

glycogenolysis and gluconeogenesis, raising blood glucose levels (46,47). In OSA patients, intermittent hypoxia triggers chronic sympathetic overactivity, exacerbating glucose metabolism disturbances and insulin resistance. Elevated sympathetic tone increases hepatic glucose production and impairs insulin signaling, leading to further deterioration in glycemic control (48,49). Studies show that blocking sympathetic activity can mitigate the hyperglycemic effects of intermittent hypoxia (50). and OSA is associated with higher catecholamine levels and increased insulin resistance (51).

Inflammatory Pathways

Chronic low-grade inflammation is central to both OSA and DM. Intermittent hypoxia in OSA activates inflammatory pathways, releasing pro-inflammatory cytokines like IL-6 and TNF-α, which contribute to systemic inflammation and exacerbate insulin resistance in DM. This persistent inflammation can lead to endothelial dysfunction, worsening insulin sensitivity and contributing to diabetes-related complications (52,53).

Cytokines and adipokines are crucial in insulin resistance development. Pro-inflammatory cytokines like IL-6 and TNF-α interfere with insulin signaling by activating inhibitory pathways, while adipokines such as leptin and adiponectin regulate insulin sensitivity. The imbalance of these adipokines exacerbates insulin resistance in OSA and DM (54,55).

Sleep Fragmentation and Hormonal Dysregulation

Sleep fragmentation in OSA disrupts sleep architecture, impairing insulin sensitivity and glucose effectiveness. Fragmented sleep increases sympathetic nervous system activity and cortisol levels, contributing to glucose metabolism dysregulation and insulin resistance (56). OSA-induced sleep fragmentation also disrupts cortisol and growth hormone (GH) secretion. Elevated cortisol levels increase hepatic glucose production and reduce peripheral glucose uptake, exacerbating insulin resistance(57). Reduced GH levels, due to decreased slow-wave sleep, further impair insulin resistance and glucose homeostasis (58).

Epidemiology of OSA in Patients with DM

Prevalence of OSA in Diabetic Populations

Although less extensively studied thanT2D, OSA remains a notable concern in T1D. The prevalence of OSA in T1D is lower than in T2D, likely due to the fundamental differences in disease etiology—T1D is an autoimmune disease leading to absolute insulin deficiency, whereas T2D involves insulin resistance. A study focusing on obese children and adolescents, including those with T1D, revealed that around 26% of T1D patients experienced OSA, with many showing associated symptoms such as snoring and daytime fatigue (59). Although the study population was small, and the results are not fully generalizable to the broader T1D population, this underscores the need for further research into the prevalence and impact of OSA in T1D, particularly as obesity—a significant risk factor for OSA—is becoming more common even in younger populations with T1D.

In contrast, the prevalence of OSA in T2D is well-documented and notably high. Obesity, a common factor in T2D, is a major risk factor for OSA. Rates of OSA among T2D patients range from 50% to over 70%. For instance, one study reported a 54.5% prevalence of OSA in T2D patients, with higher rates in men (24). Another significant study by Lam et al. found that 53.9% of T2DM patients had OSA, with 32.7% of these cases being moderate to severe (25). This high prevalence is attributed to overlapping risk factors such as obesity, age, and male gender.

The prevalence of OSA in diabetic populations, especially T2D, is substantially higher than in the general population. OSA prevalence in the general population is estimated at 2-7%, but among diabetic patients, particularly those with T2D, rates can be significantly elevated. A study found that 48.5% of T2D patients were at high risk for OSA (60), underscoring the strong association between T2D and OSA and the importance of early screening and management.

Risk Factors for OSA in Diabetic Patients

The primary risk factors that contribute to the development of OSA in diabetic patients, along with the mechanisms supporting these associations, are shown in **Table 1**.

Central obesity, particularly excess fat around the abdomen, is a significant risk factor for OSA in diabetic patients. This fat accumulation increases the likelihood of airway collapse during sleep. Central obesity is also linked to insulin resistance, which is a crucial factor in T2D. Studies show a strong correlation between higher BMI and waist

circumference with increased OSA risk in diabetic individuals. Effective weight management is crucial in preventing and managing OSA in this population (66).

Insulin resistance, common in both T2D and obesity, plays a pivotal role in OSA pathogenesis. It leads to hyperinsulinemia, promoting fat accumulation in the upper airway, which narrows the airway and makes it more prone to collapse. Hyperglycemia associated with insulin resistance increases inflammation and oxidative stress, exacerbating OSA. This creates a vicious cycle where OSA worsens insulin resistance, leading to poorer glycemic control (51,59,67).

Genetic factors also influence susceptibility to OSA among diabetic patients. Certain genetic polymorphisms related to adipokines, like adiponectin, are associated with insulin resistance and central adiposity. Variations in the adiponectin gene are linked to body fat distribution and insulin sensitivity, influencing OSA risk. Ethnic variations are also significant, as some populations, such as African Americans and Hispanics, are more predisposed to central adiposity and insulin resistance due to genetic and environmental factors. Studies like the IRAS Family Study have shown that these populations may have a genetic predisposition to weight gain, increasing their risk of OSA (68,69).

Screening and Diagnosis of OSA in DM

Recommended screening tools

Several screening tools facilitate the early detection of OSA. The STOP-Bang questionnaire and the Epworth Sleepiness Scale (ESS) are widely used due to their simplicity and efficacy. These tools are particularly valuable in primary care and diabetes management settings, where routine screening can help in the early identification of OSA, leading to more targeted diagnostic testing and management strategies.

STOP-Bang Questionnaire

The STOP-Bang questionnaire is a prominent tool for detecting OSA, particularly in high-prevalence populations like diabetes patients. The acronym STOP-Bang stands for Snoring, Tiredness during the day, Observed apnea, high blood pressure, Body mass index (BMI), Age, Neck circumference, and Gender. A score of 3 or more suggests a high risk for OSA. The STOP-Bang questionnaire has high sensitivity, particularly for detecting moderate to severe OSA, with a sensitivity of up to 100% (70). The tool's ease of use and ability to be quickly administered in both clinical and primary care settings contribute to its widespread adoption.

Epworth Sleepiness Scale (ESS)

The ESS assesses daytime sleepiness through eight questions about the likelihood of dozing off in various situations. A total score of 10 or more suggests excessive daytime sleepiness, which may indicate OSA. While less sensitive than STOP-Bang, the ESS is useful for identifying significant daytime impairment due to sleep disturbances and is often used alongside other tools (71).

Berlin Questionnaire

The Berlin Questionnaire categorizes patients into high or low risk based on snoring behavior, daytime sleepiness or fatigue, and hypertension or obesity. It has good sensitivity for moderate to severe OSA but is less commonly used due to its complexity and time requirements (71).

Combined Use of Screening Tools

Combining STOP-Bang and ESS can enhance screening accuracy. STOP-Bang is highly sensitive but may result in false positives, while ESS has higher specificity. Using both tools together can improve the likelihood of accurately identifying patients who need further diagnostic testing (72).

Diagnostic modalities

Once a high risk of OSA is identified using screening tools, formal diagnostic testing is necessary.

Polysomnography (PSG)

PSG is the gold standard for diagnosing OSA and is the most comprehensive method for assessing sleep disorders (73,74). It involves an overnight stay in a sleep laboratory where various physiological parameters are monitored, including brain activity, eye movements, muscle activity, heart rate, respiratory effort, airflow, and blood oxygen levels. PSG provides detailed information about the presence and severity of OSA and can also identify other coexisting sleep disorders. Despite its accuracy, PSG is costly, requires specialized equipment, and may not reflect

the patient's typical sleep environment. It is crucial for complex cases where accurate diagnosis is essential, as evidenced by its role in identifying moderate to severe OSA in cases where Home Sleep Apnea Testing (HSAT) results were inconclusive (73).

Home Sleep Apnea Testing (HSAT)

HSAT is a more convenient and cost-effective alternative to PSG, typically used outside of a sleep lab (75). It involves portable devices measuring a limited set of physiological parameters like airflow, respiratory effort, and blood oxygen levels during sleep at home. While HSAT is effective for diagnosing moderate to severe OSA in patients with a high pretest probability, it does not capture as many data points as PSG, such as brain activity or sleep stages. It may miss other sleep disorders (76,77). The accuracy of HSAT can vary, with sensitivity and diagnostic accuracy dropping for moderate to severe cases compared to PSG (78). The American Academy of Sleep Medicine (AASM) supports HSAT for uncomplicated OSA but emphasizes PSG for complex cases (79). A meta-analysis indicates that while HSAT devices generally have good diagnostic accuracy, effectiveness varies by device and patient population (80).

Comparative Effectiveness and Use in Diabetic Populations

In diabetic populations, where OSA is prevalent and often coexists with comorbidities like obesity and cardiovascular disease, the choice of diagnostic modality is crucial. Both PSG and HSAT are valuable, but their effectiveness varies with clinical context. A combined or sequential approach—using HSAT for initial screening followed by PSG for confirmatory testing—is often effective, particularly when HSAT results are inconclusive or additional risk factors are present (81). This strategy ensures accurate diagnosis and effective management, addressing the high prevalence of OSA in diabetic patients.

A comparative table of different screening tools and diagnostic modalities used to detect OSA in diabetic patients is shown in **Table 2**.

Challenges in the Diagnosis of OSA in Diabetic Patients

Symptom Overlap

Symptoms of OSA, such as fatigue, daytime sleepiness, and difficulty concentrating, often overlap with those of diabetes. This overlap can lead to the underrecognition of OSA, as symptoms may be attributed solely to diabetes or poor glycemic control (70). For example, fatigue and sleep disturbances might be misattributed to diabetes rather than an underlying sleep disorder like OSA.

Comorbidities

Diabetic patients frequently have comorbidities like obesity, hypertension, and cardiovascular disease, which also serve as risk factors for OSA. These comorbid conditions can mask or exacerbate OSA symptoms, making diagnosis challenging. Even non-obese diabetic patients can have a high prevalence of OSA, as demonstrated by a study in Japan where 80.5% of non-obese T2D patients showed signs of OSA (85).

Limitations of Screening Tools

Screening tools such as the STOP-Bang questionnaire and the Epworth Sleepiness Scale (ESS) are useful for identifying high-risk patients but may not be sufficiently sensitive or specific in diabetic populations with atypical presentations. While effective for moderate to severe OSA, the STOP-Bang questionnaire may have decreased sensitivity for milder forms or atypical symptoms (86). Additionally, these tools rely on subjective symptom reporting, which can complicate accurate diagnosis.

Complexities of PSG and HSAT

PSG, despite being comprehensive, is expensive and logistically challenging, particularly for patients with additional health issues. HSAT, while more accessible, may miss milder cases of OSA or other sleep-related issues, and its limited scope may not be ideal for patients with multiple comorbidities (87). Diagnostic delays can occur due to the need for specialized testing, patient reluctance, or misattribution of symptoms to other conditions (88).

Ethnic and Genetic Variations

Ethnic and genetic factors can affect the diagnosis of OSA in diabetic populations. Certain ethnic groups may have a higher prevalence of OSA with different symptom profiles or lower BMI thresholds, complicating the use of

standard screening tools. For example, non-obese Japanese patients with T2D have shown a high prevalence of OSA, suggesting that factors other than BMI, possibly genetic predispositions, are involved (85).

Clinical Impact of OSA on Diabetes Management

Effects of OSA on Glycemic Control

OSA significantly affects glycemic control in diabetic patients, particularly those with T2D. OSA's intermittent hypoxia and sleep fragmentation can lead to insulin resistance and impaired glucose tolerance, elevating blood glucose levels. A study of 266 diabetic patients showed a significant association between OSA and poor glycemic control, as evidenced by increased HbA1c and fasting blood sugar (89). This correlation underscores the detrimental impact of OSA on glucose metabolism.

An observational study also found that OSA severity correlates with increased HbA1c levels, suggesting that more severe OSA leads to worse glycemic control (90). Elevated HbA1c levels, reflecting long-term blood glucose control, have been consistently linked with OSA severity, with severe cases showing an adjusted mean increase in HbA1c of up to 3.69% compared to non-OSA patients (91). Additionally, fasting glucose levels are adversely affected by OSA, with studies showing a positive correlation between the severity of nocturnal hypoxia and elevated fasting glucose levels (92).This suggests that addressing OSA in diabetic patients may lead to better glycemic control, reduced risk of diabetes-related complications, and overall improved patient outcomes.

OSA and Diabetic Complications

Cardiovascular Complications

OSA is strongly associated with increased cardiovascular risks in diabetic patients, including hypertension, myocardial infarction, and stroke. The intermittent hypoxia from OSA activates the sympathetic nervous system, leading to elevated blood pressure and a higher risk of cardiovascular events. A cohort study found that T2D patients with OSA had an adjusted hazard ratio (HR) of 1.54 for composite cardiovascular events, compared to those without OSA (93). OSA-induced hypoxia exacerbates vascular damage and atherosclerosis progression.

OSA also contributes to hypertension through intermittent hypoxia and hypercapnia, which activate the renin-angiotensin-aldosterone system (RAAS), resulting in elevated blood pressure. This effect increases cardiovascular risk, highlighting the importance of addressing OSA in diabetic patients to mitigate cardiovascular burden.

Microvascular Complications

OSA exacerbates microvascular complications in diabetic patients, including retinopathy, nephropathy, and neuropathy. Chronic hypoxia from OSA contributes to endothelial dysfunction, which aggravates diabetic microvascular diseases. Diabetic patients with OSA have a higher risk of microvascular complications, including peripheral neuropathy, diabetic foot disease, and chronic kidney disease (93).

OSA-induced hypoxia worsens diabetic retinopathy and nephropathy. For instance, OSA exacerbates retinal ischemia, leading to worsened retinopathy. OSA is also associated with a higher prevalence of diabetic nephropathy, likely due to hypoxia-induced renal injury and exacerbated hypertension (94). Similarly, OSA contributes to severe diabetic neuropathy through nerve ischemia, increasing pain, loss of sensation, and the risk of foot ulcers and amputations.

Effects of OSA on Quality of Life and Cognitive Function in Diabetic Patients

OSA significantly impacts the quality of life (QoL) in diabetic patients by causing excessive daytime sleepiness, fatigue, and cognitive impairments. Studies show that diabetic patients with OSA have lower QoL scores in both physical and mental health domains (95). The presence of cardiovascular and microvascular complications, combined with chronic fatigue and cognitive impairments, further diminishes QoL and contributes to depression, anxiety, and social withdrawal.

OSA is also linked to cognitive decline, affecting memory, attention, and executive function. Diabetic patients with OSA are at increased risk of cognitive disorders, including dementia and mild cognitive impairment (MCI). OSA exacerbates cognitive decline associated with diabetes, particularly in executive function and memory (96). Cognitive impairment complicates diabetes management by affecting adherence to treatment regimens, leading to poor glycemic control and increased risk of complications.

Impact of OSA Treatment on Diabetes Outcomes

Efficacy of CPAP in Improving Glycemic Control

CPAP therapy, the primary treatment for OSA, has been investigated for its potential to improve glycemic control in diabetes (97). CPAP is thought to reduce intermittent hypoxia and sleep fragmentation, thereby mitigating insulin resistance and glucose dysregulation. Martínez-Cerón et al. demonstrated that CPAP significantly reduced HbA1c levels in patients with OSA and poorly controlled T2D, with an average reduction of 0.4% after six months (98). Improvements in insulin sensitivity and reductions in inflammatory markers were also noted.

Lam et al. reported that CPAP therapy led to significant reductions in systolic and diastolic blood pressure, crucial for cardiovascular risk management in diabetes. Although the study did not show a significant change in HbA1c across the entire sample, patients who adhered to CPAP therapy experienced a modest reduction in HbA1c (99). However, other studies have shown mixed results regarding CPAP's impact on glycemic control. For instance, Myhill et al. found that while CPAP improved blood pressure and reduced pulse rate, it did not significantly alter glycemic control or serum lipid levels (100). This indicates that while CPAP has cardiovascular benefits, its effects on glycemic control can vary based on individual factors.

Role of Lifestyle Interventions

Lifestyle interventions, such as weight loss, dietary modifications, and increased physical activity, are crucial in managing both OSA and diabetes. Weight loss, even moderate, can significantly reduce OSA severity. Combining CPAP therapy with a weight loss program led to a 45% reduction in OSA severity and improvements in insulin sensitivity and lipid profiles (101). Dietary changes and regular exercise also support weight loss, improve insulin sensitivity, and reduce OSA severity. Exercise alone enhances sleep quality and reduces OSA severity independent of weight loss (102).

Potential Benefits of Alternative Therapies

For patients unable to tolerate or adhere to CPAP, alternative therapies like oral appliances and surgical interventions offer effective options. Mandibular advancement devices (MADs) can reduce OSA severity and improve symptoms, including daytime sleepiness. A pilot study showed that MAD therapy significantly reduced AHI and improved HbA1c levels in patients with mild to moderate OSA (103).

Surgical options, such as uvulopalatopharyngoplasty (UPPP), maxillomandibular advancement (MMA), and bariatric surgery, can be considered when CPAP and oral appliances are ineffective. Bariatric surgery, in particular, has shown promise by reducing body weight and improving both OSA severity and metabolic outcomes, including HbA1c levels (104).

Addressing OSA through CPAP, lifestyle interventions, and alternative therapies is crucial for improving diabetes management and patient outcomes. The choice of therapy should be individualized based on the severity of OSA, diabetes, and patient preferences.

Current Guidelines and Recommendations

Guidelines for Screening and Diagnosis of OSA in Diabetic Patients

The American Diabetes Association (ADA) and the American Academy of Sleep Medicine (AASM) both recognize the importance of screening for OSA in patients with diabetes, particularly those with T2D, due to the high prevalence and significant impact of OSA on diabetes management and outcomes (17,105,106).

The ADA's Standards of Medical Care in Diabetes emphasize that healthcare providers should be vigilant in assessing sleep disturbances in diabetic patients, particularly in those who are overweight, obese, or have poor glycemic control. The ADA highlights the use of validated questionnaires such as the STOP-Bang or Berlin Questionnaire as initial screening tools in primary care settings to identify individuals at high risk for OSA. The guidelines also recommend that patients identified as high-risk should be referred for further evaluation using PSG or HSAT.

The AASM provides detailed guidance on the management of OSA, including recommendations for screening high-risk populations such as those with T2D. The AASM guidelines suggest routine screening for OSA in all patients with T2D, particularly those who exhibit symptoms such as excessive daytime sleepiness, loud snoring, or witnessed

apneas. The AASM also emphasizes the importance of identifying OSA in patients with comorbid conditions like hypertension or heart failure, which are common in diabetic populations.

The integration of routine OSA screening into diabetes care protocols is crucial for improving glycemic control, reducing cardiovascular risk, and enhancing patient outcomes. Early identification and treatment of OSA can lead to better management of diabetes and reduce associated risks.

Management Strategies for Patients with Coexisting OSA and DM

Integrated Care Approaches for Managing OSA and DM

Integrated care approaches are essential for managing patients with both OSA and DM. These approaches involve coordinating care across multiple healthcare providers to ensure a comprehensive management plan.

One key aspect of integrated care is the use of clinical pathways that guide the management of patients with coexisting OSA and DM. These pathways are designed to streamline the process of diagnosis, treatment, and follow-up, ensuring that all healthcare providers involved are on the same page and that the patient receives consistent and coordinated care.

An example of an integrated care model is described in a study where a community-based pathway was introduced for diagnosing and managing OSA. This pathway, which included a multidisciplinary team approach, resulted in more timely diagnosis and treatment, improved patient satisfaction, and reduced healthcare costs compared to traditional hospital-based care (88).

Moreover, the use of electronic health records (EHRs) in integrated care models facilitates the sharing of patient information across different healthcare settings. This allows for real-time access to the patient's medical history, lab results, and treatment plans, which is crucial for coordinating care and making informed decisions (107). The use of EHRs in integrated care has been shown to improve the quality of care and patient satisfaction, particularly in complex cases where multiple conditions need to be managed simultaneously(108).

Role of Multidisciplinary Teams in Optimizing Treatment Outcomes

Multidisciplinary teams (MDTs) are pivotal in optimizing treatment outcomes for patients with OSA and DM (109). These teams, composed of professionals from various fields such as primary care, endocrinology, pulmonology, cardiology, and behavioral health, collaborate to manage the patient's care comprehensively. MDTs improve outcomes by enhancing communication among providers, reducing fragmented care, and integrating diverse expertise to develop effective treatment strategies. For instance, a dietitian might offer guidance on diabetes management through diet, while a sleep specialist addresses OSA treatment (110–112). Furthermore, MDTs help manage the interactions between OSA and DM, such as improving insulin sensitivity through CPAP therapy, and supporting patient adherence through behavioral health interventions (113).

Patient Education and Adherence to Therapy

Patient education and adherence are critical for managing coexisting OSA and DM. Educating patients about their conditions, the importance of adhering to treatments, and the potential consequences of non-adherence is essential for long-term health. Effective education should be individualized and cover the benefits of treatments like CPAP for OSA and medications or lifestyle changes for DM. Ongoing support is necessary to address adherence challenges, particularly with CPAP therapy, which may require regular check-ins and comfort adjustments. For DM, healthcare providers should assist patients in setting realistic goals to enhance adherence to lifestyle changes and medication regimens (114,115).

Future Directions and Research Gaps

Large epidemiological studies are critically needed to better understand the relationship between OSA and DM, particularly across diverse populations. Current research often focuses on specific cohorts, limiting the generalizability of findings. Expanding studies to include a broader range of ethnic and socio-economic groups, especially those with T1D, where OSA prevalence is less well-studied, could provide insights and improve screening and intervention strategies.

Mechanistic studies are also crucial to uncover the molecular mechanisms linking OSA and DM. Research should focus on the roles of intermittent hypoxia, oxidative stress, and their impacts on insulin resistance and β-cell

dysfunction. Additionally, exploring genetic factors that influence susceptibility to both conditions could support the development of personalized medicine strategies, enabling targeted therapies and preventive measures.

Randomized controlled trials (RCTs) are essential to evaluate the efficacy of Continuous Positive Airway Pressure (CPAP) therapy in managing glycemic control in DM patients. While preliminary findings suggest benefits, robust long-term studies are needed to assess the impact of CPAP on glycemic control and the progression of diabetic complications, both microvascular and macrovascular (116).The advancement of personalized medicine is critical for the future management of OSA and DM. Tailoring treatment based on individual risk factors, such as genetic predispositions, OSA severity, and comorbidities, can enhance treatment efficacy and outcomes. Moreover, utilizing biomarkers to predict responses to OSA treatments in diabetic patients could further refine management strategies and improve patient quality of life (116).

Addressing these research gaps will significantly advance our understanding and management of the interplay between OSA and DM, leading to better health outcomes for affected patients.

Conclusion:-

The relationship between OSA and DM is intricate, involving significant epidemiological, pathophysiological, and clinical connections. Epidemiologically, OSA is highly prevalent among patients with T2D, and emerging evidence suggests its relevance in T1D. Pathophysiologically, the interaction between intermittent hypoxia, systemic inflammation, and insulin resistance underscores the bidirectional relationship between OSA and DM. Clinically, the coexistence of OSA and DM increases the risk of cardiovascular and microvascular complications, complicating management strategies.

Understanding these links highlights the need for comprehensive screening, diagnosis, and management approaches for OSA in diabetic patients. Routine screening for OSA should be integral to diabetes care, as early intervention with treatments like CPAP can improve glycemic control, reduce the risk of diabetic complications, and enhance overall quality of life. Integrating OSA screening into diabetes care helps identify at-risk patients and facilitates timely, effective treatment strategies, reducing the overall disease burden.

Despite progress in understanding the relationship between OSA and DM, significant research gaps remain. Future research should focus on large-scale epidemiological studies to explore the prevalence and impact of OSA in diverse diabetic populations. Mechanistic studies are needed to elucidate molecular pathways linking OSA and DM, potentially leading to targeted therapies. Additionally, randomized controlled trials are necessary to assess the long-term effects of OSA treatments, such as CPAP, on glycemic control and diabetic complications. Personalized medicine approaches, tailored to individual risk profiles, also hold promise and require further exploration. Addressing these gaps is critical for improving clinical outcomes and advancing patient management. Continued investigation into these areas will enhance care and quality of life for patients with both OSA and DM.

List of abbreviations

Abbreviation	Definition
DM	Diabetes Mellitus
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
OSA	Obstructive Sleep Apnea
AHI	Apnea-Hypopnea Index
PSG	Polysomnography
HSAT	Home Sleep Apnea Testing
SNS	Sympathetic Nervous System
IL-6	Interleukin-6
TNF-α	Tumor Necrosis Factor-alpha
IH	Intermittent Hypoxia
ROS	Reactive Oxygen Species
CPAP	Continuous Positive Airway Pressure
MDT	Multidisciplinary Team
QoL	Quality of Life

CVD	Cardiovascular Disease
RAAS	Renin-Angiotensin-Aldosterone System
AASM	American Academy of Sleep Medicine
ADA	American Diabetes Association
ESS	Epworth Sleepiness Scale
STOP-Bang	Snoring, Tiredness, Observed apnea, high blood pressure, Body mass index, Age, Neck circumference, Gender
MAD	Mandibular Advancement Device
UPPP	Uvulopalatopharyngoplasty
MMA	Maxillomandibular Advancement
MCI	Mild Cognitive Impairment
EHR	Electronic Health Records
RCT	Randomized Controlled Trial

Table 1:- Major risk factors for Obstructive Sleep Apnea (OSA) in diabetic patients.

Risk Factor	Mechanism	References
Obesity (High BMI)	Excess fat deposition around the neck and upper airway increases airway collapsibility during sleep, contributing to OSA.	(61)
Waist Circumference	Increased central fat leads to greater pressure on the airway, exacerbating the risk of airway obstruction.	
Male Sex	Men are more likely to accumulate fat in the upper body, particularly around the neck, which increases the risk of OSA.	(30,62)
Hypertension	Hypertension increases vascular stiffness and contributes to the worsening of OSA symptoms.	(62)
Neck Circumference $\geq$ 40 cm	A larger neck circumference is associated with a higher likelihood of airway collapse during sleep, leading to OSA.	
Physical Inactivity	Lack of physical activity contributes to weight gain and central obesity, which are significant risk factors for OSA.	
Diabetes-Related Foot Disease	Complications of diabetes, such as diabetic foot disease, may be associated with poor circulation and autonomic dysfunction, increasing OSA risk.	(30)
Nocturnal Hypoxemia	Intermittent drops in oxygen saturation during sleep can lead to oxidative stress and contribute to the development and worsening of OSA.	(32)
Insulin Resistance	Insulin resistance contributes to systemic inflammation and increased fat deposition around the airway, exacerbating OSA.	(63)
Genetic Factors	Certain genetic polymorphisms related to adipokines and insulin sensitivity may predispose individuals to OSA, especially in diabetic patients.	(64,65)

Table 2:- Different screening tools and diagnostic modalities used to detect OSA in diabetic patients.

Tool/Modality	Strengths	Weaknesses	References
STOP-Bang Questionnaire	High sensitivity, especially for moderate to severe OSA; easy to administer; widely used in both clinical and non-clinical settings	Lower specificity, particularly for milder forms of OSA; can result in a high number of false positives.	(70,71)
Berlin Questionnaire	Moderate sensitivity and specificity; better performance in predicting severe OSA; suitable for initial screening in primary care	Less effective in identifying mild cases; lower specificity compared to STOP-Bang; can miss a significant percentage of moderate OSA cases.	(82)
Epworth Sleepiness Scale (ESS)	Measures daytime sleepiness, which is a common symptom of OSA; easy to use and widely accepted	Lower sensitivity for OSA detection; primarily identifies excessive daytime sleepiness, which is not specific to OSA; often used in conjunction with other tools	(70,83)
Home Sleep Apnea Testing (HSAT)	High sensitivity and specificity for moderate to severe OSA;	May miss mild cases or other sleep disorders; limited data compared to	(78,79,84)

	convenient and cost-effective alternative to polysomnography; suitable for initial diagnostic assessment	polysomnography; accuracy can vary based on the device used	
Polysomnography (PSG) GOLD STANDARD	A comprehensive diagnostic tool that provides detailed information on sleep stages, respiratory events, and other physiological parameters; essential for complex cases	Expensive and logistically challenging; requires an overnight stay in a sleep lab; may not reflect the patient's typical sleep environment.	(73,78,79)

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