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The interconnection between Obesity and Asthma-Obstructive Sleep Apnea Overlap: A Comprehensive Review

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Abstract

English:

Asthma and sleep-related respiratory disorders represent common and well-characterized respiratory pathologies, yet ongoing debates persist regarding their association and potential bidirectional relationship. We performed a literature search encompassed PubMed and MEDLINE, exploring studies and publications on the overlap of sleep apnea and asthma, especially considering their common risk factor, obesity. Observational studies, including prospective and retrospective cohort studies, meta-analyses, and case reports, were analyzed. The available data indicate a bidirectional relationship between asthma and obstructive sleep apnea (OSA), with each condition influencing the other. Asthma is identified as a risk factor for OSA, exacerbating its severity, while OSA has been linked to the development and progression of asthma.
Results: *Obesity plays a critical role as an independent risk factor connecting asthma to OSA, emphasizing the intricate interplay between these conditions. A body mass index (BMI) ≥ 25 kg/m2 is a central risk factor for OSA.*
Conclusion: *This research underscores the need for further exploration into the nuanced mechanisms linking obesity, obstructive sleep apnea, and asthma. Additionally, innovative interventions and treatment modalities tailored to address these interconnected health issues are imperative for personalized and targeted approaches in managing patients with obesity-related complications, ultimately improving overall health outcomes.*

Keywords

asthma • obstructive sleep apnea • obesity

Interconexiunea dintre obezitate și astm-obstructiv Suprapunerea apneei în somn: o revizuire cuprinzătoare

Rezumat

Romanian:

Astmul și tulburările respiratorii asociate somnului reprezintă patologii respiratorii comune și bine caracterizate, însă dezbateri continue persistă cu privire la asocierea și relația potențial bidirecțională dintre acestea. Am efectuat o căutare a literaturii în bazele de date PubMed și MEDLINE, examinând studii și publicații privind suprapunerea dintre apneea de somn și astm, având în vedere în special factorul lor comun de risc, obezitatea. Au fost analizate studii observaționale, inclusiv studii de cohortă prospectivă și retrospectivă, meta-analize și rapoarte de caz. Datele disponibile indică o relație bidirecțională între astm și apneea de somn obstructivă (ASO), fiecare afecțiune influențând celălaltă. Astmul este identificat ca un factor de risc pentru ASO, exacerbându-i severitatea, în timp ce ASO a fost asociată dezvoltării și progresiei astmului. Rezultate: Obezitatea joacă un rol critic ca factor de risc independent care leagă astmul de ASO, evidențiind complexitatea interacțiunii dintre aceste condiții. Un indice de masă corporală (IMC) ≥ 25 kg/m2 reprezintă un factor central de risc pentru ASO. Concluzie: Această cercetare subliniază necesitatea explorării continue a mecanismelor subtile care leagă obezitatea, apneea de somn obstructivă și astmul. În plus, intervențiile inovatoare și modalitățile de tratament adaptate pentru abordarea acestor probleme de sănătate interconectate sunt imperative pentru abordări personalizate și direcționate în gestionarea pacienților cu complicații legate de obezitate, îmbunătățind în final rezultatele generale de sănătate. Cuvinte cheie: astm, apneea de somn obstructivă, obezitate.

Cuvinte-cheie

astm • obezitate • sindrom de apnee in som

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1. Introduction

Asthma and sleep-related respiratory disorders are two of the most commonly encountered and well-characterized respiratory pathologies. However, debates have not yet concluded regarding their association, mutual comorbidity, and potential bidirectional relationship. They are, moreover, considering that a significant common risk factor for both pathologies is obesity, which is in an inversely proportional relationship with them, capable of influencing their deterioration and improvement.

According to the International Classification of Sleep Disorders, the most common sleep disorder is obstructive sleep apnea (OSA), whose incidence is higher than previously believed. Patients with moderate-to-severe OSA account for approximately 20% of adult males and 10% of postmenopausal women not only in Western countries but also in Eastern ones; this increase is due to the obesity epidemic. [1] There are around 2 billion adults currently living with overweight, of which 650 million are considered to be affected by obesity (BMI ≥30 kg/m²). That equates to 39% (39% of men and 40% of women) of adults aged 18 or over living with overweight and 13% living with obesity [2].

On the other hand, an increasing number of asthma cases have been diagnosed, with a prevalence of approximately 300 million people worldwide. It represents a significant public health concern affecting individuals across all age brackets. The prevalence is rising in numerous developing nations, increasing treatment expenses. This places a growing burden on both individuals and society, straining healthcare systems and communities [3].

That being said, through this paper, we aim to review what is currently known about the connection between obesity, whose prevalence is continually rising, and one of the commonly encountered overlaps - sleep apnea syndrome (SAS) and asthma. We also want to debate the most suitable and advanced therapeutic options to help improve these impactful diseases.

2. Materials and Methods

We conducted a literature search of PubMed and MEDLINE for studies and different publications for theoretical information to evaluate and debate the therapeutic opportunities on the overlap of sleep apnea and asthma. The terms used for searching were “asthma,” “sleep apnea,” “obesity,” “positive pressure ventilation,” and “pathophysiology.” Observational studies were included, including prospective and retrospective cohort studies, meta-analyses, and case reports.

3. Result

3.1 Diagnosis and epidemiologic associations

Population surveys and meta-analyses have extensively documented the reciprocal connection between asthma and obstructive sleep apnea (OSA) [4,5,6,7]. Individuals with asthma commonly report issues such as sleep fragmentation, nocturnal asthma symptoms, snoring, and daytime sleepiness [8,9]. Reports indicate a 2-3 times higher prevalence of OSA among asthma patients [8,10,11]. The European Sleep Apnea Database (ESADA) study on a large scale revealed that only 5% of OSA patients had a concurrent diagnosis of asthma, suggesting potential underdiagnosis of asthma in OSA patients or inadequate screening for underlying asthma in those with OSA [12]. Notably, the prevalence of OSA in individuals with asthma may vary depending on the type of sleep studies employed for diagnosis. Polysomnography-diagnosed OSA is more common in patients with uncontrolled asthma, while OSA diagnosed through respiratory polygraphy (a sleep test without an electroencephalogram) is less prevalent in the same individuals [10]. The increasing use of respiratory polygraphy in diagnosis may contribute to underdiagnosing OSA in asthma by potentially missing respiratory events with arousal [13]. The lack of recognition of OSA in individuals with asthma further compounds underdiagnosis.

Available data indicate a bidirectional relationship between asthma and OSA, with each condition influencing the other. Asthma is identified as a risk factor for OSA and can exacerbate its severity [14]. Conversely, OSA has been linked to the development of asthma and its impact on the progression of the condition [10, 15].

Obesity serves as a critical risk factor connecting asthma to obstructive sleep apnea (OSA), being an independent risk factor for various health conditions [16]. Concerning sleep disorders, excess body weight is widely recognized as a significant and independent risk factor for obstructive sleep apnea (OSA) [17,18,19]. Among the numerous risk factors for OSA, a body mass index (BMI) ≥ 25 kg/m2 plays a central role. A prospective cohort study suggests that a 10% increase in weight could result in a 32% rise in the apnea-hypopnea index (AHI). A similar weight loss is associated with a 26% reduction in AHI [20,21]. BMI directly correlates with the severity of OSA syndrome [22]. What sets obesity apart from other OSA risk factors is its modifiability, making excess body weight the most clinically significant risk factor for OSA [23].

Furthermore, OSA itself can contribute to weight gain in obese patients through mechanisms associated with other OSA complications, including sleep fragmentation, sympathetic activation, and insulin resistance [17]. Additionally, obesity is linked to a higher risk of nocturia in OSA patients, a symptom that intensifies with the severity of OSA [24].

Epidemiological and observational studies have consistently demonstrated that obesity plays a substantial role in the onset of asthma and its severity (25, 26). Nevertheless, individuals with asthma may face an increased risk of developing obesity. This is attributed to factors such as reduced physical activity and more frequent oral corticosteroid therapy, which is known to contribute to weight gain (27, 28). Moreover, the daytime fatigue resulting from insufficiently controlled asthma may lead to a sedentary lifestyle, further promoting obesity in individuals with asthma [29].

Obesity is linked to an increased occurrence of asthma, which may be dose-dependent, and a higher likelihood of severe asthma and asthma-related hospitalizations. Alterations in lung mechanics, heightened sensitivity of the airways, a prolonged inflammatory state, and elevated production of adipokines are thought to be the factors responsible for these effects (30). A study by Larsson and Burgess, encompassing over 200,000 individuals from Mendelian randomization studies and de novo analyses within the FinnGenn consortium, concluded that a higher BMI correlates with an elevated risk of various chronic diseases, including asthma [31]. Similar genetic patterns were observed in a study involving African-American patients with both obesity and asthma.[32] In a genetic linkage analysis of Costa Rican family members, PRKCA emerged as a pleiotropic genetic locus associated with a higher BMI and asthma. (33) Moreover, research within a Japanese cohort of 8,000 individuals found that being overweight or obese, along with an increased waist circumference, were significant risk factors for incidents of late-onset asthma, particularly in middle-aged women. This study emphasized the importance of considering regional and demographic factors in understanding the obesity-asthma relationship.

Research has also demonstrated that individuals with asthma face an elevated risk of developing obesity. This could be attributed to corticosteroid exposure from asthma treatment, atherogenic inflammation exacerbated by asthma-induced airway inflammation, or shared upstream factors influencing asthma and weight. In a cohort of 2,171 nonobese children from the Southern California Children's Health Study, those with asthma exhibited a 51% higher risk of developing obesity over ten years compared to those without asthma [34]. Similarly, a study by Stratakis et al. in 2022, involving a US multicohort study of 8,713 children, revealed a 23% higher risk of developing obesity among those with asthma. Noteworthy studies have also been conducted in adults. A European multicohort survey with over 500,000 subjects reported that adult-onset or late-onset asthma patients (comprising >85% of the cohort) had an increased likelihood of being overweight or obese. Another European study by Moitra et al. highlighted that among 7,500 participants, the risk of developing obesity was higher in those with asthma compared to those without.

3.2 Obesity is not the only risk factor related to this overlap

3.2.1 Rhinitis

The nose serves as the primary pathway for breathing during sleep, and nasal factors play a crucial role in determining the patency of the pharyngeal upper airway (UAW). The Starling resistor model of obstructive sleep apnea (OSA) characterizes the collapsible segment of the tube (pUAW) with an intraluminal pressure (critical closing pressure) and surrounding tissue pressures (pharyngeal muscles, pharyngeal and submucosal fat, mucosal edema, etc.). The tube is also influenced by upstream (nose) and downstream (trachea) segments, each with their respective pressures. UAW collapse can occur in various scenarios, such as when the upstream nasal pressure drops below the critical closing pressure, leading to OSA symptoms like snoring and apnea [35].

Rhinitis and asthma commonly coexist. The prevalence of rhinitis (both allergic and nonallergic) in asthma can be as high as 80–90%, and rhinitis is identified as a risk factor for the development of asthma. Rhinitis induces inflammation in the nasal passages, causing nasal obstruction. In the general population, both allergic and nonallergic rhinitis are recognized as risk factors for a high Apnea-Hypopnea Index (AHI). While the degree of nasal obstruction during wakefulness may not directly correlate with OSA severity, peak nasal resistance tends to occur in the early morning (due to circadian effects), potentially contributing to the expression of OSA during that period. Chronic sinusitis and nasal polyposis are closely linked with both asthma and inflammation of the pUAW, leading to reduced patency. Consequently, upper- and lower-airway inflammation in rhinitis and asthma can perpetuate each other, potentially fostering the development of OSA. Notably, a cross-sectional study of asthma patients revealed a significant independent association between diagnosed rhinitis and OSA risk, suggesting that rhinitis may be a risk factor for OSA in individuals with asthma [36].

3.2.2. GER (Gastroesophageal Reflux)

Epidemiological studies have revealed an independent association between GER and OSA, irrespective of other confounding factors. New or persistent nocturnal GER symptoms were linked to increased OSA symptoms and higher Epworth Sleepiness Scale scores, distinguishing them from those without nocturnal GER [37]. GER was found to be a predictive factor for chronic snoring and high OSA risk in an asthma patient cohort. Patients with poorly controlled asthma and obese individuals with asthma may experience GER due to factors like omental fat weight, loss of angulation of the gastroesophageal junction, and changes in the trans diaphragmatic pressure gradient. GER, in turn, can induce

spasms of the pUAW, edema, and neurogenic mucosal inflammation, potentially exacerbating OSA. This could create a vicious cycle, worsening asthma and perpetuating the interplay between the two conditions [36].

3.2.3 Gender

The association between gender and the manifestation of obstructive sleep apnea (OSA) in individuals with asthma remains unclear. In the Wisconsin Sleep Cohort, male gender was linked to an increased occurrence of OSA in individuals with asthma, and menopausal status did not appear to influence the onset of OSA [29]. Conversely, females with fixed airway obstruction (postbronchodilator FEV1/FVC ≤ 0.7) have been identified as having a heightened risk of developing OSA. Additional investigations are required to comprehensively understand the impact of gender on the development of OSA in patients with asthma.

3.3 Advanced therapeutic approaches

3.3.1 The intersection of OSA and asthma

Building upon the preceding discourse, it is reasonable to anticipate that an effective therapy for OSA would positively influence subjective and objective asthma control and vice versa. Early investigations delved into the role of non-invasive ventilation (NIV) in cases of acute respiratory failure secondary to asthma, reporting enhancements in gas exchange and a decrease in mechanical ventilation rates [38]. However, the role of NIV in severe acute asthma remains a topic of controversy.[39] Another recent report suggests the potential utility of CPAP as a controlled oxygen delivery method for acute respiratory failure, including cases involving asthma, in prehospital settings [40].

Nasal CPAP stands as the primary treatment for OSA in adults. A predominantly mechanical impact of CPAP is a sustained augmentation in functional residual capacity (FRC), which can potentially reduce airway smooth muscle contractility. [41,42] CPAP has demonstrated efficacy in lowering GERD and inflammation in OSA patients, potentially leading to a favorable impact on asthma control [43].

It is crucial to underscore that the examination of CPAP's role in asthma is intricate due to various pathways, beyond recurrent upper airway collapse, that contribute to the overlap between OSA and asthma. These pathways include obesity, rhinitis with reduced nasal patency, and GER. Nevertheless, based on promising animal data,[44,45] a limited number of studies have explored the role of CPAP in different asthma and OSA phenotypes, yielding variable results. Selected prospective studies are outlined in Table 2, with additional recent reviews and publications.[46] Notably, CPAP may potentially increase bronchial hyper-responsiveness in non-asthmatics with OSA [47,48] and result in objective degradation of sleep architecture in asthmatics without OSA. [49] Given these conflicting outcomes in diverse clinical populations, more extensive prospective studies focusing on well-defined asthma and OSA phenotypes are essential to elucidate the role and limitations of CPAP in individuals with these prevalent respiratory disorders.

The role of second-line treatments for OSA, such as mandibular advancement devices (MAD), ear, nose, and throat (ENT) interventions, and bariatric surgeries, has not been prospectively assessed for outcomes in populations with overlapping asthma. A substantial prospective series reported a high prevalence of asthma and OSA (approximately one-third each) in a morbidly obese bariatric referral population but without an overlap of the two disorders. This study also observed significant asthma improvement and almost complete OSA resolution two years after surgery [50]. Similarly, medications for controlling asthma (e.g., corticosteroids, leukotriene antagonists) and unconventional treatment options, including immunotherapy, biological drugs like monoclonal antibodies, tumor necrosis factor-a blockers, and oligonucleotides, as well as phosphodiesterase inhibitors, antimicrobials, and bronchial thermoplasty, have not been tested in populations with overlapping OSA and asthma.

Considering the current evidence base, constrained by small sample sizes and the heterogeneity of the clinical populations studied, drawing definitive conclusions or providing guidance for optimal management strategies in patients with overlapping OSA and asthma remains challenging. However, a meticulous evaluation of exacerbating co-morbidities, along with optimizing the treatment of both OSA and asthma, remains crucial in this population [51].

3.3.2 How Asthma Treatments Affect OSA

The use of inhaled corticosteroids (ICS) may pose an increased risk of obstructive sleep apnea (OSA), according to findings presented in Table 2 [52]. Previous studies in canine models have indicated that corticosteroids, while antagonizing smooth muscle bronchoconstriction in the trachea via the p38 MAPK pathway, paradoxically lead to adverse effects on pharyngeal muscles. This includes muscle fiber atrophy and redistribution of central neck fat, ultimately promoting OSA. A survey revealed a dose-dependent correlation between ICS use and the risk of developing OSA, regardless of asthma severity (odds ratio = 4.1). In a study involving high-dose fluticasone over four months for asthma treatment, tongue strength increased during wakefulness, and decreased endurance, as observed in OSA, was noted. The brief duration of this study suggests that individuals on lifelong ICS therapy may be susceptible to pharyngeal myopathy and fat redistribution, heightening their risk of OSA. Long-term use of ICS also influences the release of growth hormone, contributing to metabolic and cardiovascular complications that exacerbate

the effects of OSA in comorbid cases. These findings are significant in light of current GINA guidelines advocating using ICS as both a controller and reliever of asthma.

The particle size of ICS has implications for developing OSA in asthma patients. Inhaling extra-fine particles of ICS (smaller than 2 μm) was associated with a similar risk of developing OSA compared to controls not using ICS. In contrast, inhalers containing standard-sized particles increased the risk of OSA. Larger ICS particles tend to deposit preferentially in the upper airway and posterior pharynx, causing local adverse effects, whereas finer particles reach the terminal lung bronchioles. This distinction may influence the choice of ICS inhalers for asthma patients prone to OSA.

A prospective cohort study investigating continuous or "burst" dose oral corticosteroids in uncontrolled asthma found that 95% of patients had concomitant OSA. This association is believed to be linked to the adverse effects of systemic corticosteroid use, including upper airway remodeling and exacerbated obesity [53].

On the contrary, intranasal corticosteroids have improved the severity of obstructive sleep apnea (OSA) among patients with allergic rhinosinusitis. These corticosteroids effectively reduce airflow resistance and enhance upper airway patency by addressing the inflammation in nasal passages. Santos and colleagues conducted a study to assess the impact of montelukast on sleep disturbances in individuals with perennial allergic rhinitis. This double-masked, placebo-controlled study revealed a significant enhancement in daytime fatigue and sleepiness among patients treated with montelukast [54]. These findings imply that treating rhinitis could offer positive effects for individuals with OSA.

As biological treatments designed to target T2 inflammation in asthma selectively have become available, there are emerging therapeutic targets that warrant further exploration [55]. In a recent case series involving five patients with severe asthma, chronic rhinosinusitis, nasal polyposis, and OSA, a notable reduction in OSA symptoms was observed in all patients following six months of therapy with dupilumab—an IL-4 and IL-13 antagonist [56]. Similarly, in another case, the apnea-hypopnea index (AHI) was halved after six months of asthma treatment with the anti-IgE antibody omalizumab [57].

3.3.3. But what about asthma and obesity?

Asthma associated with obesity tends to be less responsive to conventional asthma medications; managing patients with both obesity and asthma requires a comprehensive approach to addressing obesity and its consequences. In this context, we provide an overview of experiences documented in the literature related to dietary, behavioral, surgical, and pharmacologic interventions for obesity-associated asthma.

Concerning dietary factors, Western diets rich in ultra-processed foods, high-sugar items, and non-plant-based meals have been implicated in poor asthma control and the exacerbation of obesity [58]. Studies suggest associations between asthma and the consumption of sweetened beverages, potentially due to fructose malabsorption leading to pro-inflammatory products [59,60]. Conversely, diets high in fiber, fruits, vegetables, and omega-3 fatty acids have shown positive associations. However, interventions targeting diet in obesity and asthma have yielded mixed results [61,62,63].

Exercise-based interventions have demonstrated benefits in obesity-associated asthma, independent of their impact on weight. Physically inactive asthmatics, characterized by sedentary behavior, obesity, and mood symptoms, showed improved lung function, exercise capacity, asthma control, and reduced inflammation with increased physical activity. Structured programs, including high-intensity pulmonary rehab, have reported short- and long-term benefits [64,65].

Weight loss, often a consequence of regular exercise, has been linked to improved airway inflammation and asthma control. Even minimal weight loss (≥5.0 percent) has significantly increased lung function. Combined interventions, such as weight loss plus exercise programs, have reported higher asthma control scores, more significant weight loss, improved lung function, and higher anti-inflammatory biomarkers. Virtual weight loss programs have also demonstrated positive outcomes [66,67].

For suitable candidates, weight reduction surgery, including procedures like gastric bypass and sleeve gastrectomy, is a viable option. Studies have reported better asthma control, lung function, and reduced inflammation post-bariatric surgery. However, benefits may take weeks, and long-term success depends on sustained weight loss and lifestyle changes [68,69].

3.3.4. Pharmacological Treatment

Although there are no medications specifically approved by the FDA for the treatment of obesity-associated asthma due to its increased likelihood of demonstrating T2-low inflammation, there is a rationale for considering azithromycin and tezepelumab as supplementary therapies in the appropriate clinical context, as indicated by findings from specific randomized trials [70]. The pharmacological intervention in obesity-associated asthma is a field of ongoing research, and we present a review of recent and ongoing studies in this regard.

Therapies targeting diabetes and cholesterol have been suggested for obesity-associated asthma, particularly in individuals with underlying insulin resistance or dyslipidemia. Glucagon-like peptide 1 (GLP-1) agonists, known for improving insulin sensitivity and increasing nitric oxide (NO) bioavailability by inhibiting ADMA, have been observed to be associated with improved asthma outcomes. A clinical trial is currently underway to investigate the efficacy of GLP-1 agonists in obesity-associated asthma [71]. Encouraging

data on weight loss has been reported for tirzepatide, a dual GLP-1, and glucose-dependent insulinotropic polypeptide (GIP) agonist, in a recent randomized trial involving 2,539 patients.[72] Pre-clinical studies in mice have also suggested a potential impact of metformin on allergic airway inflammation and airway hyperresponsiveness. Statin therapy has shown significant improvements in healthcare-related quality of life, with modest benefits on disease control, although not specifically on lung function, as indicated by recent meta-analyses [73,74].

Attempts have been made in nutrient supplementation, with an open-label pilot study of L-citrulline, a precursor to L-arginine and a modulator of nitric oxide metabolism, demonstrating positive effects on asthma control, fractional exhaled nitric oxide (FeNO), and forced expiratory volume in one second (FEV1) among individuals with obese asthma [75]. Conversely, a randomized, multi-center trial of fish oil supplementation in overweight or obese individuals aged 12 to 25 did not reveal any significant effects on asthma control, exacerbations, or lung function [76].

Recently, there has been attention on fecal microbiome transplantation, although studies are limited to pre-clinical data. In one study involving mice, administering a specific bacteria, Akkermansia muciniphila reduced hyperreactivity and airway inflammation in obese mice [77]. While these studies are still in the experimental stages, targeting inflammation holds promise as a potential avenue for further advancements in treatments.

4 Discussion

In conclusion, this medical article underscores the intricate connection between obesity, obstructive sleep apnea, and asthma. The evidence presented strongly suggests that obesity serves as a significant risk factor for both obstructive sleep apnea and asthma, creating a complex interplay between these conditions. Understanding these relationships is crucial for developing effective prevention and management strategies.

Moving forward, there is a pressing need for further research to delve into the nuanced mechanisms linking obesity, obstructive sleep apnea, and asthma. Additionally, exploring innovative interventions and treatment modalities tailored to address these interconnected health issues is imperative. This research could pave the way for more personalized and targeted approaches in managing patients with obesity-related complications, ultimately improving overall health outcomes.

As we look to the future, a comprehensive understanding of the links between obesity, obstructive sleep apnea, and asthma will inform clinical practice and guide public health initiatives. By addressing these interconnected health challenges, we can work towards developing holistic and practical strategies to mitigate the impact of these conditions on individuals and populations.

5 Compliance with Ethical Standards

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Institutional Review Board Statement

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Informed Consent Statement

No informed consent was necessary.

Data Availability Statement

Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflict of interest.

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