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Systemic inflammation and obstructive sleep apnea syndrome (OSA): the role of C–reactive protein (CRP)

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Abstract

English:

The presence of sleep-related disorders, particularly obstructive sleep apnea syndrome (OSA), instigates pathological changes during sleep, giving rise to frequent hypoxic episodes that generate elevated levels of a broad spectrum of inflammatory cytokines. C-reactive protein (CRP), a biomarker signifying the presence and intensity of inflammation, is frequently detected in elevated serum or plasma concentrations, correlating with the number of respiratory events, especially in moderate and severe forms, across both adults and children. Various available therapeutic approaches demonstrate the capacity to diminish serum levels, although the minimum duration of usage typically extends between 2-6 months. In the case of older individuals, OSA commonly coexists with additional conditions, further augmenting the baseline inflammatory level. This accelerated disease progression amplifies mortality rates, incurs heightened costs, and significantly diminishes the overall quality of life.

Keywords

obstructive sleep apnea (OSA) • systemic inflammation • reactive protein (CRP)

Inflamația sistemică și sindromul apneei de somn obstructive (SASO): rolul proteinei C- reactive (CRP)

Rezumat

Romanian:

Tulburările respiratorii în timpul somnului, în special sindromul apneei de somn obstructive (SASO), determină modificări fiziopatologice, cu episoade hipoxice repetitive, ce generează nivele crescute de citokine inflamatorii. Proteina C- reactivă (CRP), un maker al prezenței și severității inflamației, are valori crescute serice și plasmatice, corelate cu numărul moderat sau crescut de evenimente respiratorii nocturne, atât la adulți cât și la copii. După utilizarea minim 2-6 luni a diverselor metode terapeutice, se observă un declin al nivelurilor serice. În cazul persoanelor vârstnice, SASO coexistă frecvent cu afecțiuni cronice, cu efect de sumație al inflamației bazale. Astfel, afecțiunile cronice progresează mai rapid, crește rata mortalității, costurile legate de asistența medicală, și scăde calitatea vieții.

Cuvinte-cheie

apnee obstructivă în timpul somnului (OSA) • inflamație sistemică • proteină reactivă C (CRP)

Introduction

According to the International Classification of Sleep Disorders (ICSD-3), obstructive sleep apnea syndrome (OSA) is part of the spectrum of sleep-related breathing disorders [1]. It represents the most common sleep disorder in adults, with a prevalence in the general population ranging from 6-17%, higher in men (13-33%) compared to women (6-19%), and

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increasing with age [2]. The main risk factors associated with the development of obstructive sleep apnea (OSA) are linked to obesity (BMI >35kg/m^2), which accounts for 41-58% of moderate and severe cases. A 10% increase in weight is associated with a 30% increase in the apnea-hypopnea index (AHI). The diagnosis of obstructive sleep apnea syndrome requires the presence of nocturnal respiratory symptoms (snoring, choking, or breathing pauses), excessive daytime sleepiness, or fatigue despite sufficient sleep duration and in the absence of other conditions. Depending on the apnea-hypopnea index (AHI), it is classified as mild (AHI 5-15/h), moderate (AHI 15-30/h), or severe (AHI >30/h), accompanied by desaturations (>3%). Desaturations below 90% (T90) for more than 20% of sleep time in moderate-severe cases are associated with the presence of hypertension, type 2 diabetes, and increased 5-year mortality [2], [3].

In the pediatric population, the most severe sleep-related breathing disorder is obstructive sleep apnea (OSA), with a prevalence of 1-5%, peaking between 2 and 6 years of age. The detection of a single apneic event is considered pathological. OSA forms are classified based on the apnea-hypopnea index (AHI) as follows: mild (AHI 1-4), moderate (AHI 5-9), and severe (AHI ≥ ten events per hour) associated with desaturations of 4%. The primary risk factor for obstructive sleep apnea (OSA) in children is adenotonsillar hypertrophy (remission rate of 83%-after adenotonsillectomy), followed by obesity in adolescence, craniofacial and dentofacial malformations, neuromuscular disorders, and genetic anomalies (such as Down syndrome with an OSA frequency of 81%) [4].

Respiratory events during sleep are typically identified through overnight respiratory polysomnography in a specialized sleep laboratory. It is regarded as the gold standard for diagnosis, as it concurrently evaluates various parameters such as brain electrical activity (EEG), cardiac activity (EKG), muscle activity (EMG), eye movement (EOG), respiratory parameters, and snoring. When logistical constraints arise, an alternative approach is using portable devices that only identify respiratory events at night [5].

In terms of treatment options, there are various approaches available. Continuous positive airway pressure ventilation (CPAP) is considered the gold standard for moderate and severe cases. On the other hand, for mild cases associated with anatomical abnormalities in the upper respiratory tract, such as an elevated Mallampati score, septal deviation, adenotonsillar hypertrophy, or macroglossia, corrective surgical methods can be considered as an alternative [6].

Approximately 90% of patients with obstructive sleep apnea (OSA) are not diagnosed and do not receive therapy, thereby presenting an increased risk of hypertension, cardiovascular diseases, heart failure, obesity, diabetes mellitus, strokes, renal dysfunction, and depression [7].

Materials and methods

We conducted a literature review using PUBMED, GOOGLE SCHOLAR, and MEDLINE to search for studies and publications containing information related to the systemic inflammatory effect of obstructive sleep apnea syndrome, with a focus on the role of C-reactive protein. It is important to highlight that the studies that did not involve individuals exhibiting pre-existing conditions (such as cardiovascular disease, hypertension, diabetes mellitus, renal failure, infectious disease, and cancer) were analyzed to assess the OSA influence properly. Secondly, we chose studies that evaluate the impact of elevated CRP levels in patients with OSA on various conditions, such as cardiovascular, metabolic, and chronic obstructive pulmonary diseases. The search critical terms included “sleep apnea and inflammation,” “obstructive sleep apnea and CRP,” “CPAP therapy and CRP,” and “obstructive sleep apnea and inflammation in children.” Included in the review were observational studies, retrospective cohort studies, meta-analyses, clinical trials, and literature reviews.

Results

3.1 The physiopathological pathways of inflammation during an apneic episodes

The pathogenesis of obstructive sleep apnea is intricate, with the primary anomaly being the compromised ability of the dilator muscles, particularly the genioglossus muscle, in the upper airway to counteract the negative pressure created during inspiration. The constriction of the airways, as evidenced by indicators such as the Mallampati score, augmented neck circumference, and the existence of craniofacial anomalies, amplifies the negative pressure encountered during inspiration, ultimately resulting in airway collapse during periods of sleep [8].

Recurrent episodes of breathing cessation give rise to chronic intermittent hypoxia, inducing tissue damage and triggering a diverse array of pathogenic mechanisms. These mechanisms encompass the selective activation of inflammatory molecular pathways, endothelial dysfunction, and oxidative stress, resulting in the production of inflammatory cytokines such as C-reactive protein (CRP), interleukin-6 (IL-6), IL-8, IL-10, TNF-α, and ICAM-1 [7]. CRP, a crucial blood marker of inflammation, is synthesized in the liver and primarily regulated by the proinflammatory cytokine interleukin-6. It plays a significant role in fostering proatherogenic and proinflammatory effects on endothelial cells and vascular smooth muscle cells, thereby instigating cell adhesion and proliferation processes. This, in turn, directly contributes to the initiation and promotion of atherosclerosis [7],[8].

The well-established connection between obstructive sleep apnea syndrome and obesity further complicates this scenario. Excessive adipose tissue, particularly at the visceral level, becomes metabolically active, producing inflammatory cytokines, notably Interleukin-6 (IL-6). The presence of elevated levels of CRP is associated with a predisposition to future cardiovascular events, especially in patients with stable angina, acute coronary disease, and myocardial infarction [8]. Consequently, a continuous and chronic proinflammatory systemic state is induced by apnea, presenting the potential for an underlying mechanism that contributes to the onset of cardiovascular conditions, such as atherosclerosis and metabolic disorders. The presence of obstructive sleep apnea syndrome can be viewed as intricately linked to a low-grade, persistent systemic inflammation. This systemic inflammation can amplify the collapse of the upper airways during sleep, subsequently leading to diminished muscle contractility [8].
In light of these considerations, assessing serum and plasma levels of inflammatory cytokines may assume a specific role in the comprehensive management of OSA, encompassing prognosis, diagnosis, and treatment monitoring. This review aims to highlight and underscore the existing literature data to assess the potential correlation between OSA and CRP levels.

3.2 The level of C-reactive protein in adults and children with obstructive sleep apnea

A comprehensive meta-analysis of the available literature reveals that individuals afflicted with obstructive sleep apnea syndrome (OSA) tend to exhibit elevated values in both serum and plasma CRP when compared to those without this condition [9]. The presence of OSA corresponds to a notable doubling of CRP levels, a phenomenon intricately linked to the frequency of apneic episodes, with particularly noteworthy findings in cases of moderate to severe OSA where AHI exceeds 15 per hour [10]. Furthermore, in instances of severe OSA, there is a discernible trend indicating an increase in C-reactive protein levels when juxtaposed with individuals who do not experience apneic episodes [11].
Extended and profound episodes of oxygen desaturation are postulated to impact physiological stress and adverse health outcomes significantly more than briefer and less severe events. Moreover, individuals experiencing severe hypoxia, despite sharing a similar AHI, may confront more pronounced physiological stress and heightened cardiovascular consequences. Within the spectrum of moderate to severe OSA, there is an observed correlation between the total sleep time spent with saturation levels below 90% and an elevation in CRP levels, ranging from 2.3 to 3.3 mg/L. This association becomes evident when the percentage of total sleep time with oxygen saturation below 90% falls within the range of 1.8% to 10.8% [11]. Notably, in cases of moderate or severe sleep apnea syndrome, average nocturnal peripheral oxygen saturations of 85%, with a range of 79-89%, result in an elevation of serum CRP levels by 0.7-2.0% compared to the baseline [12].
Frequently, individuals under 55 with a body mass index below 25 kg/m^2 have been observed to exhibit double CRP levels. In women, the premenopausal period demonstrates higher values than the postmenopausal period. Consequently, within this demographic, young individuals (age <50, average weight or underweight) exhibit systemic inflammation as a significant pathogenic mechanism in the absence of traditional risk factors like obesity, advanced age, or menopause, contributing to sleep disturbances [13].
The mechanical impact of excess fatty tissue, particularly in the neck and abdominal areas, induces the collapse of the upper respiratory airways and diminishes lung volumes. Obesity is well-established as one of the principal risk factors for obstructive sleep apnea (OSA), with higher degrees of obesity (BMI >30 kg/m^2) associated with increased CRP levels, irrespective of the presence of apneic events. In cases where the body mass index is below 32 kg/m^2, coupled with an average oxygen saturation of 85% and concurrent apnea events, C-reactive protein levels are observed [14].
Elevated levels of interleukin-6 (IL-6) are linked to a higher body mass index and oxygen saturation below 90%, while serum levels are lower in cases with a lower body mass index. Consequently, obesity (BMI >35 kg/m^2) emerges as an independent risk factor for the chronic systemic inflammation observed in OSA, regardless of AHI. In severe apnea cases, elevated body mass values, particularly in the abdominal and central areas, are notably associated with milder or moderate forms [15].
In prospective cohort studies, it has been noted that elevated baseline levels of CRP before diagnosis are correlated with an augmented risk of developing obstructive sleep apnea (OSA), particularly in forms with an AHI exceeding 30 per hour, within the subsequent ten years. In cases where CRP values are doubled, the risk of developing OSA in the next decade spans 7-24% [16].
Concerning symptoms, an elevation in CRP levels has been associated with excessive daytime sleepiness. Additionally, hypomagnesemia, leading to chronic inflammatory effects, is connected to heightened serum CRP levels, particularly in cases where severe OSA is documented [17].
Moreover, ethnic disparities are observable in C-reactive protein levels, with heightened values noted in Caucasian and Asian populations [17].
In pediatric cases diagnosed with obstructive sleep apnea syndrome, notable and significant increases in plasma C-reactive protein levels are consistently observed, particularly

in severe forms (Apnea-Hypopnea Index, AHI ≥10/h), especially when there is significant adenoid hypertrophy. In adenotonsillar inflammatory processes, activated macrophages and T lymphocytes secrete interleukin-6, establishing a significant correlation between CRP levels and IL-6. Similar to adults, a positive correlation exists between the severity of the apnea-hypopnea index and the serum levels of inflammatory mediators in children. The presence of 20 events per hour, indicative of severe apnea, is directly associated with elevated levels of inflammatory mediators in the serum, including CRP [18],[19],[20].

3.3 Therapeutic approaches employed in managing obstructive sleep apnea syndrome and their impact on CRP levels

The gold standard for managing cases of obstructive sleep apnea syndrome (OSA) is Continuous Positive Airway Pressure (CPAP) therapy. The application of CPAP for a relatively short duration, approximately one month, in cases of moderate or severe OSA, is associated with the preservation of stable serum levels of C-reactive protein (CRP), as opposed to a notable decrease in these levels [21]. Further investigation into the impact of CPAP therapy reveals nuanced gender-specific variations. In men undergoing CPAP therapy over three months, there is a gradual decline in CRP levels, with a significant reduction noted at the 6-month mark compared to baseline. Conversely, for women, a minimum duration of 6 months of CPAP therapy is required to achieve reductions in CRP levels that are comparable to those seen in men at the 3-month mark [22],[23].

When positive airway pressure therapy is not pursued, alternative interventions like oral appliances, specifically mandibular advancement devices, can address mild OSA. These devices are often customized to suit individual needs. Clinical investigations evaluating the impact of these oral appliances have shown promising outcomes. When utilized for a minimum duration of 6 months to treat moderate cases (AHI >15/h) with a nightly usage duration of at least 5 hours, more than half of the users experienced a reduction in serum CRP levels [24].

Various surgical interventions targeting the upper respiratory tract, including correction of septal deviation, uvulopalatopharyngoplasty, reduction of the tongue base, and maxillomandibular advancement, can serve as alternative treatments for severe OSA where AHI exceeds 39 events per hour. Notably, at an interval of 6 months or more postoperatively, a significant reduction of 78.8% in serum C-reactive protein (CRP) levels is observed compared to the time of diagnosis. This reduction also correlates with a notable decrease of 50% in the number of apneic events [25].

The association between morbid obesity (BMI > 40 kg/m^2) and obstructive sleep apnea is well-established, and the coexistence of these two conditions results in a combined inflammatory effect. Bariatric surgeries, such as Roux-en-Y gastric bypass or gastric sleeve, are effective methods for managing morbid obesity. Polysomnography findings at 12 months post-intervention reveal decreased apnea-hypopnea index and total duration (T90), nocturnal oxygen saturation below 90%, and significant declines in serum CRP levels. These changes are associated with a reduction in the body mass index by approximately 16 kg/m^2, transitioning from an average BMI of 45 kg/m^2 to 29 kg/m^2 over the same period. [26].

For children, there is limited data on the levels of CRP after the application of treatment methods. The implementation of CPAP therapy over eight weeks resulted in a decrease in CRP levels, dropping from 1.30 mg/L to 0.40 mg/L. (26) Hypertrophy of the adenoids and tonsils is the most common cause of obstructive sleep apnea in children, as previously mentioned. After adenotonsillectomy, there is a reduction in the frequency of elevated obstructive nocturnal events, coupled with a significant decrease in serum CRP levels, decreasing from 1.87 mg/dL to 0.20 mg/dL.(9). A prospective study assesses the reduction in CRP levels after a 4-6 month period, revealing a decrease of 0.6 mg% [27].

Experimental research has shown that lifestyle changes, including adjustments in diet and increased physical activity, among obese adolescents not only result in weight loss and reduced AHI but also decrease serum CRP levels. This reduction was observed from 10.98 mg/L to 6.78 mg/L after nine months [28].

3.4 The influence of OSA associated with increased levels of CRP on various pathological conditions

Atherosclerosis serves as the primary pathophysiological foundation for cerebrovascular diseases, and the persistent inflammatory response significantly impacts atherosclerosis, exacerbating its occurrence and progression. In OSA, oxidative stress produces a wide range of inflammatory mediators. Atherosclerosis may be viewed as a localized response to systemic inflammation, thereby heightening the risk of stroke. Individuals diagnosed with obstructive sleep apnea (OSA) face an elevated risk of cardiovascular and cerebrovascular disease (CVD). In the case of patients diagnosed with a severe form of OSA, at the initial stage, besides high values of lipid parameters (triglycerides, total cholesterol, low-density lipoprotein-LDL, high-density lipoprotein-HDL) known to be involved in dyslipidemia, high levels of CRP were also recorded. There exists a correlation between carotid intima-media thickness (IMT) and inflammatory factors, including CRP, in patients with varying

degrees of OSA. As the severity of sleep apnea worsens (at AHI >30/h), the thickness of the carotid intima-media layer increases, accompanied by elevated CRP levels, reaching a maximum of 10.4 mg/L. (19). Prospective studies have examined whether elevated CRP levels (mean value of 1.61 mg/L) in individuals with severe obstructive sleep apnea (OSA) are linked to subsequent cardiovascular events. After a 4-year follow-up from the initial assessment, occurrences of myocardial infarctions and unstable angina were observed, being the most frequent, followed by ventricular tachycardia, atrial fibrillation, and stroke. These events were documented in 9.30% of patients with an AHI greater than 30 events per hour [29],[30],[31].

Obstructive sleep apnea (OSA) exhibits a chronic inflammatory state often associated with cardiometabolic disturbances. A noteworthy connection exists between heightened CRP levels, as studies consistently indicate elevated levels in the presence of obesity. This trend is similarly observed in cases of hypertension, where significantly higher CRP levels are noted. Additionally, the presence of metabolic syndrome is linked to increased CRP levels, particularly in women [32].

Overlap syndrome (OVS), which occurs when an individual experiences both obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) simultaneously, is linked to a heightened cardiovascular risk and increased mortality compared to instances where either OSA or COPD is present alone. Elevated levels of C-reactive protein and other cytokines are observed in individuals with overlap syndrome (OVS) or chronic obstructive pulmonary disease (COPD) when contrasted with those having obstructive sleep apnea (OSA) alone. This implies a connection between OVS or COPD and heightened inflammation, as evidenced by increased levels of these biomarkers [33].

The second most prevalent retinal vascular disorder, retinal vein occlusion (RVO), profoundly impacts visual function and the quality of life of affected patients. Chronic hypoxia has been documented as a factor contributing to notable microvascular damage, consequently promoting thrombosis formation in the retinal vein. Furthermore, obstructive sleep apnea has been recognized as a primary condition inducing systemic hypoxia, thereby impacting the occurrence and prognosis of retinal vein occlusion (RVO). Following the assessment of apnea severity, individuals with severe forms exhibited elevated serum levels of oxidative stress and inflammatory biomarkers, including CRP, in cases of retinal vein occlusion (RVO). During the three-month follow-up, a decline in visual acuity and an increased prevalence of macular edema (ME) were observed within the OSA group among all retinal vein occlusion (RVO) instances [34].

Concerning obstructive sleep apnea (OSA), it is estimated that 15–30% of people with OSA concurrently experience type 2 diabetes mellitus (T2DM). Furthermore, there is an association between OSA and insulin resistance and glucose intolerance. The potential association between OSA and the onset of diabetes mellitus could be attributed to the activation of the sympathetic nervous system induced by intermittent hypoxia and sleep fragmentation. Alternatively, increased release of inflammatory cytokines may contribute to insulin resistance in this context. Certain studies have noted cases where individuals diagnosed with diabetes mellitus, undergoing specific treatment, and experiencing moderate to severe obstructive sleep apnea (OSA) along with obesity exhibit elevated levels of C-reactive protein (CRP) at 7.8 mg/L. Moreover, these individuals show increased glycated hemoglobin levels, indicating a value of 5.8%. This suggests poor disease control when associated with apneic events [35].

Discussions

This review addresses fundamental questions regarding the inflammatory systemic effect of high CRP levels in obstructive sleep apnea syndrome cases. Do patients with OSAS exhibit elevated CRP levels? Literature findings affirm the existence of heightened CRP levels, with the degree correlating to the form of sleep apnea moderate and severe forms showing at times double values. A direct proportional link is observed between the duration of sleep spent with peripheral oxygen saturation below 90% and high CRP levels (increases by 0.7-2.0% when oxygen saturation is below 90% for at least 10% of total sleep time). Obesity, a risk factor for OSA, enhances CRP levels through the impact of IL-6. Increases in CRP values are noted in both obesity cases (BMI >30 kg/m^2) and its absence (age <55 years, BMI <25 kg/m^2). In the pediatric population, elevated CRP levels are associated with obesity and other classic risk factors for OSAS. Notably, there is a dependency relationship between elevated CRP values and IL-6 in the presence of adenotonsillar hypertrophy. Thus, in OSA detection, there is evidence of a chronic low-grade systemic inflammatory condition with increased CRP values, sometimes doubling, within the context of sleep apnea syndrome.

Does the utilization of therapeutic methods in OSA impact CRP levels? The literature contains data assessing the influence of positive pressure ventilation; regarding the case of males, significant decreases in CRP values are recorded early, at three months of use, with the maintenance of a stable level in females over the same time frame. Similar decreases were recorded in both genders at a 6-month interval. Surgical treatment alternatives and mandibular advancement devices require an equal usage time, with a minimum 6-month interval, to generate an effect. As such, this therapeutic

approach should be employed for at least six months in both genders, aiming to decrease the chronic low-grade systemic inflammation induced by OSA.

There is limited data in the specialized literature concerning the treatment methods applied to children. Reports suggest that the utilization of CPAP over six months resulted in a noteworthy decrease in CRP levels, a pattern similarly observed in individuals undergoing adenotonsillectomy.

The connection between obstructive sleep apnea syndrome and chronic conditions suggests the potential for "systemic" comorbidity. Current data indicates that when obstructive sleep apnea syndrome coexists with elevated levels of inflammatory cytokines, including CRP, it has a widespread multisystemic impact. Presently, most studies correlate atherosclerosis (cardiovascular and cerebrovascular), induced by low-grade chronic systemic inflammation (including CRP) generated by OSA, with the accentuation of the pathophysiological mechanisms involved in its development. As a result, individuals with this combination experience a cumulative inflammatory effect, which is greater than the impact of each condition on its own. Consequently, in the case of this association, the risk of cardiovascular and cerebrovascular events is heightened. There are also other conditions for which the inflammatory effects of CRP have been described, thus indicating a particular potential for "systemic" comorbidity.

One constraint of this review is the limited available data regarding the pediatric population. While systemic inflammation is undoubtedly associated with OSA, the literature on treatment effects is limited. To our knowledge, no data is available regarding the impact of diagnosed systemic inflammation in childhood, its potential influence on children's development, and its association with other pathophysiological changes observed in the context of different diseases. Thus, further investigations are required to either substantiate or challenge the current understanding.

Conclusions

The purpouse of this scientific review was to assess the extent of systemic inflammation observed in obstructive sleep apnea syndrome. Through the evaluation of available data, as documented in numerous publications, and stated above, the findings consistently support the assertion that OSA induces a low-grade chronic systemic inflammation. This inflammatory state is associated with potential ramifications on various aspects, including increased mortality, a heightened incidence of a broad spectrum of complications, and a consequential reduction in the overall quality of life.

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Informed Consent Statement

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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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