Obstructive sleep apnea syndrome and cardiovascular disease: The influence of C-reactive protein

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Abstract
Obstructive sleep apnea syndrome (OSAS) is a common medical condition, associated with atherosclerosis and cardiovascular disease (CVD). The underlying pathophysiologic mechanisms of this association have not been completely understood and may be multifactorial in origin. A number of studies suggest that inflammatory processes have emerged critical in the pathogenesis of CVD in OSAS. A range of circulating inflammatory molecules has been identified and measured, with a view to assess inflammation and predict vascular damage risk, such as plasma cytokines, adhesion molecules, and C-reactive protein (CRP). CRP is a relevant marker worthy of further study, because not only is elevated in patients with OSAS, but also is rapidly becoming a risk factor for cardiac disease. Furthermore, in selected OSAS patients, aggressive treatment of the disorder may lead to retarding or even improvement of CVD progression. However, still there is a debate on the true correlation between CRP and OSAS, as well as the clinical effect of any reduction after treatment of OSAS. Further research is required to define those OSAS patients who will have a considerable reduction with treatment, as well as to understand the significance of the interaction between cardiovascular risk factor and CRP reduction in patients with OSAS.

Key words: Sleep apnea; Cardiovascular; C-reactive protein

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Core tip: Obstructive sleep apnea syndrome (OSAS) is a common medical condition, associated with atherosclerosis and cardiovascular disease (CVD). A number of studies suggest that inflammatory processes have emerged critical in the pathogenesis of CVD in OSAS. C-reactive protein (CRP) has been the most studied inflammatory protein to date and a frequently used marker to predict the occurrence of CVDs. Unfortunately, the question still remains if CRP is truly related to OSAS, as well as the clinical effect of any reduction after treatment of OSAS.
INTRODUCTION
Obstructive sleep apnea syndrome (OSAS) is a common medical condition, characterized by repetitive episodes of upper airway obstruction that occur during sleep[1]. These intermittent episodes are leading to disruption of normal ventilation and sleep architecture and ultimately through a range of pathophysiological mechanisms in cardiovascular disease (CVD). Indeed OSAS, when not correctly treated, has been associated with higher fatal and nonfatal cardiovascular events[2]. It is worth noting that the cardiovascular consequences of OSAS may develop even in the absence of the traditional cardiovascular risk factors[3]. Therefore, clinicians should be aware that OSAS has emerged as an independent risk factor for CVD[4].

Several mechanisms are involved in the association between OSAS and CVD, such as enhanced sympathetic activity, oxidative stress, systemic inflammation, and endothelial dysfunction which promote atherogenesis. Atherosclerosis could be one of the mechanisms connecting OSAS to CVD. There is growing evidence that the underlying inflammatory process plays a crucial role in all stages of the atherosclerotic disease process, with established CVD seen as the end of a long process of inflammation-mediated atherosclerosis[5,6]. Since inflammation has a key role in the development of CVD it is a common sense to assume that OSAS may contribute to CVD through an inflammatory mechanism. Therefore, evaluation of circulating biomarkers of inflammation could be a useful risk assessment tool for identifying patients with cardiovascular events.

A range of circulating inflammatory molecules has been identified and measured, with a view to assess inflammation and predict vascular damage risk, such as plasma cytokines, adhesion molecules, and C-reactive protein (CRP). Of these markers, CRP, an acute phase reactant synthesized in the liver, is one of the most widely investigated biomarkers of low-grade inflammation in CVD. A number of studies have demonstrated that CRP is a significant risk factor for atherosclerosis and higher CRP levels, even in the high normal range (0.2 to 1.5 mg/dL) are associated with high cardiovascular morbidity and mortality in individuals with and without known CVD[7-10]. In patients with OSAS elevated levels of inflammatory markers, such as CRP, have been found; however there is a debate on the true relationship between CRP and OSAS.

This short review will try to highlight the most clinically relevant updates on the relationship between OSAS and CRP and how this relationship could contribute to CVD. It cannot judge all newly-available information, but information from the literature considered to be of sufficient primary care interest has been summarized.

OSAS AND INFLAMMATORY ACTIVATION
OSAS is characterized by cyclical episodes of hypoxia and reoxygenation that can provoke oxidative stress due to reactive oxygen species production and inflammatory mediators activation[11]. In addition, these alterations can turn on nuclear transcriptional factors, including nuclear factor-B, which induce production of inflammatory mediators, intracellular and vascular cell adhesion molecules[12]. All the above could facilitate vascular endothelial damage and atherogenesis[13-15]. In this way, intermittent hypoxia may lead to atherosclerosis and, ultimately, the cardiovascular consequences of OSAS.

A range of inflammatory molecules has been localized to the atherosclerotic plaque[16-18]. Among them, CRP and interleukin-6 (IL-6) are the most widely studied in CVD.

OSAS AND CRP
Several authors have studied the relationship between apnea-hypopnea index (AHI) and CRP levels in OSAS patients, but the results are contradictory (Table 1). Factors such as sample size, statistical methodology and study design could be responsible for this disparity. Most of the studies to date[19-22] presented elevated CRP levels in OSAS patients; however the role of obesity and sleep duration in this CRP elevation has been questioned by other studies[20,23]. Therefore, as the role of CRP as a risk factor in OSAS is open to discussion, one could speculate that CRP’s value as a special marker of OSAS-related cardiovascular risk is attenuated. However, a recent meta-analysis has shown that patients with OSAS had a statistically significant higher level of CRP and this effect was positively influenced by OSAS severity[24].

IS CRP PART OF THE LINK BETWEEN CVD AND OSAS?
Cardiovascular complications represent a considerable part of OSAS complications. OSAS is an independent risk factor for CVDs, such as hypertension, arrhythmias, pulmonary hypertension, coronary artery disease, congestive cardiac failure and cerebrovascular events[25,26].

Although a matter of debate, the role of OSAS in the pathogenesis of hypertension is strongly suggested[11,27], involving markers or pathways indicative of systemic inflammation, such as CRP. Furthermore, in animal studies intermittent hypoxia has been shown to produce hypertension[28,29].

Cardiac arrhythmias appear to be a common in OSAS patients; still their true prevalence remains
unknown. The severity of OSAS, as shown in most studies, is independently associated with elevated markers of systemic inflammation, including CRP. CRP is directly associated with an increased atrial fibrillation burden\(^\text{[30]}\) and strongly and independently associated with occurrence of heart failure\(^\text{[31,32]}\). Furthermore, serum levels of CRP were significantly increased in patients with OSAS and an acute cardiovascular event\(^\text{[33]}\). In patients with coronary artery disease on current optimal medications for secondary cardiovascular risk reduction, highly sensitive CRP was significantly correlated with the severity of OSAS, suggesting that OSAS could activate vascular inflammation in these patients despite current best practice medications\(^\text{[34]}\). Moreover, OSAS is independently associated with increased levels of CRP in patients with acute ischemic stroke\(^\text{[35]}\). Therefore, CRP could be a part of the pathophysiological pathway linking OSAS to stroke.

### CONFOUNDING FACTORS

#### Role of obesity

In patients with OSAS, the increased CRP levels are still under criticism, because of the impact of confounding factors such as obesity. Obesity is known to be associated with elevated CRP levels. Furthermore, obesity is a risk factor for OSAS, and the severity of OSAS is associated with obesity. Therefore, it is challenging to disentangle the effects of OSAS and obesity on CRP levels.

### Table 1: Previous studies on the relationship between obstructive sleep apnea syndrome, C-reactive protein and other inflammatory markers

| Ref. | Study population | Inflammatory markers | Findings |
|------|------------------|----------------------|----------|
| Chami et al\(^\text{[19]}\) | 355 OSAS patients 545 controls | CRP, fibrinogen, IL-6, TNF-α, TNF-R2, CD40-ligand, P-selectin, ICAM1, MCP-1 after PSG | AHI was associated with CRP, IL-6, fibrinogen, ICAM, and P-selectin but not with TNF-α, TNF-R2, CD40-ligand, or MCP-1 levels |
| Kurt et al\(^\text{[20]}\) | 78 OSAS patients 20 controls | CRP, hemoglobin, RDW, MPV, PDW, and white blood cell count | The severity of OSAS was not correlated with CRP, MPV, and RDW |
| Svensson et al\(^\text{[21]}\) | 136 OSAS patients 262 controls | CRP, TNF-α, IL-6, myeloperoxidase and lysozyme | The levels of CRP, IL-6 and lysozyme were significantly higher in subjects with AHI > 15 compared with subjects with lower AHI |
| Lin et al\(^\text{[22]}\) | 109 OSAS patients 35 Controls | Serum glucose, and lipid profile comprising total cholesterol, high density lipoprotein-cholesterol, low density lipoprotein-cholesterol and triglycerides hs-CRP | OSA was independently associated with sum of metabolic components and CRP |
| Guven et al\(^\text{[23]}\) | 47 OSAS patients 29 controls | CRP | The serum CRP levels were significantly higher in the OSA group than in the control group |
| Kokturk et al\(^\text{[24]}\) | 94 OSAS patients 57 controls | CRP and conventional cardiovascular risk factors such as total cholesterol, low-density lipoprotein-cholesterol, low density lipoprotein, high-density lipoprotein, very low density lipoprotein, and triglycerides | CRP levels were significantly elevated in the OSAS group compared to the non-OSAS group |
| Shamsuzzaman et al\(^\text{[25]}\) | 22 OSAS patients 20 controls | CRP | CRP levels were independently associated with OSA severity |
| Punjabi et al\(^\text{[26]}\) | 69 OSAS patients 20 controls | CRP | CRP levels were independently associated with BMI |
| Yokoe et al\(^\text{[27]}\) | 30 OSAS patients 14 controls | CRP and IL-6 | CRP and IL-6 and production of IL-6 were significantly higher in patients with OSAS than in obese control subjects. The severity of OSAS and BMI were independently related to levels of CRP, whereas BMI and apnea-related nocturnal hypoxia were independently related to levels of IL-6 in patients with OSAS |
| Hayashi et al\(^\text{[28]}\) | 60 OSAS patients 30 controls | Hsp-70, TF, MCP-1, hs-CRP, hepatocyte growth factor and plasma vascular endothelial growth factor | Serum CRP, TF, MCP-1 and Hsp-70 levels were significantly higher in OSAS compared with control subjects |
| Schiza et al\(^\text{[29]}\) | 528 OSAS patients | CRP | However, the best correlation with serum CRP levels was BMI and it was the most significant determinant for CRP |

AHI: Apnea hypopnea index; BMI: Body mass index; ODI: Oxygen desaturation index; OSAS: Obstructive sleep apnea syndrome; CRP: C-reactive protein; hs-CRP: Highly sensitive C-reactive protein; IL-6: Interleukin-6; Hsp-70: Heat shock protein-70; TF: Tissue factor; MCP-1: Monocyte chemotactic protein-1.
factors such as obesity, other CVDs and medications. Although, several studies have indicated independent associations between CRP levels and OSAS, others do not demonstrate significant correlations after adjustment for associated confounding variables. It is possible that OSAS alone may not contribute substantially to CVD since multiple factors have been implicated in the occurrence of CVDs in high-risk patients. Among them, metabolic parameters are important factors, since metabolic syndrome is closely related to cardiovascular morbidity and mortality.

One should keep in mind that obesity is prevalent in patients with OSAS, and it has been shown that elevated CRP levels are significantly and independently correlated to high BMI. Similarly, other investigators found that CRP levels in OSAS strongly correlate to obesity and not to OSAS severity. Therefore, based on these studies as nonobese OSAS patients don’t demonstrate statistically increased levels of CRP, any CRP elevation noted in obese OSAS patients may reflect chronic inflammation attributable to obesity and not to chronic hypoxia due to OSAS. Furthermore, it is likely that by interacting with obesity, OSAS further increases systemic inflammation and therefore increases the CRP levels in obese OSAS patients compared to obese without OSAS.

Recent studies, however, have shown a close correlation of CRP level with OSAS severity meaning that the higher the AHI, the higher the levels and CRP elevation seems to be independent from visceral obesity in patients with OSAS, probably due to a greater degree of adiposity in women. Previously we have shown that moderate to severe OSAS females patients had higher although not statistically significant CRP values, compared to matched males, and more recently Yardim-Akaydin et al. showed statistically significant increased values of CRP, in female OSAS patients.

**ROLE OF GENDER**

It is worth noting that gender has been considered as a variable in CRP evaluation. A number of studies have also presented higher CRP levels in women compared to men, probably due to a greater degree of adiposity in women. Previously we have shown that moderate to severe OSAS females patients had higher although not statistically significant CRP values, compared to matched males, and more recently Yardim-Akaydin et al. showed statistically significant increased values of CRP, in female OSAS patients.

**EFFECT OF EXERCISE**

There is no agreement in the scientific literature regarding the correlation between exercise and CRP levels. Cavagnolli et al. evaluated the effects of aerobic exercise on CRP in non-obese patients with OSAS and found that CRP levels were not elevated and did not change after 2 mo of physical exercise.

**Clinical implications**

As CVDs are detrimental to human health, medical practitioners seek to predict the development of cardiovascular events before they occur. For this reason, the evaluation of CRP as a circulating biomarker of inflammation has become a useful tool for stratifying patients at high risk for future cardiovascular events. CRP is a relevant marker worthy of further study, because not only is elevated in patients with OSAS, but also is rapidly becoming a risk factor for cardiac disease. Furthermore, in selected OSAS patients, aggressive treatment of the disorder may lead to retarding or even improvement of CVD progression.

CRP has also captured researchers attention, because tests measuring their levels are widely available even in general hospitals. High-sensitivity assays to detect low concentrations of the protein have become available, permitting CRP levels measurement as low as 0.007 mg/L. Contrary to other cytokines, CRP levels are quite stable in the same individual over 24 h and may reflect the level of inflammatory response, without concern for time of day. Furthermore, the American Heart Association approves the use of CRP in risk factor estimation in adults without CVD.

**EFFECT OF POSITIVE AIRWAY PRESSURE THERAPY ON LEVELS OF CRP**

Positive airway pressure (PAP), mechanically splints the upper airway, thus preventing soft tissue of upper airway from narrowing and collapsing during sleep, has been considered as the most effective treatment for OSAS. Nevertheless, studies concerning the effects of PAP therapy on CRP levels are also contradictory. Among those, most studies had small sample size, which is prone to a false or spurious conclusion.

Our group and others have shown a gradual decrease of CRP levels with effective PAP therapy, which could subsequently improve cardiovascular morbidity associated with OSAS, whereas others found that PAP therapy did not significant change CRP levels, regardless of PAP therapy duration. Furthermore our study showed that after PAP therapy CRP was decreased more slowly in females compared to matched for OSAS severity males. CRP levels in females remained unaltered for the first 3 mo, irrespective of effective PAP treatment, while on the contrary males presented a significant fall in CRP over that period. At 6-mo, a significant decrease was observed in all patients who used PAP, while CRP values approached those of subjects without OSAS. CRP levels over that period. Furthermore, Xie et al. showed that after PAP therapy CRP was decreased more slowly in females compared to matched for OSAS severity males. CRP levels in females remained unaltered for the first 3 mo, irrespective of effective PAP treatment, while on the contrary males presented a significant fall in CRP over that period. At 6-mo, a significant decrease was observed in all patients who used PAP, while CRP values approached those of subjects without OSAS. A recent meta-analysis on the influence of PAP therapy on CRP levels in OSAS concluded that at least 3 mo of treatment is required to significantly decrease levels indicating that the inflammatory process is still active through this period. CRP levels further declined after 6 mo of PAP treatment. Furthermore, Xie et al. also showed a significant decrease on CRP levels, with better benefits with therapy duration of ≥ 3 mo and more adequate compliance (≥ 4 h/night). A previous meta-analysis showed PAP therapy to significantly reduce CRP.
levels, by 0.11 mg/dL, or 17.8%\(^{(27)}\). In another study\(^{(65)}\) we observed that the division of the patients into a good and a poor PAP compliance group affected CRP evolution, with the good PAP compliance group to show exclusively a statistically significant decrease after 6 mo therapy. Although CRP levels were decreased in the poor compliance group, only a statistically significant trend was observed after 1 year of treatment. Based on that, assuming that PAP use is not adequate according to the generally accepted criteria (use < 4 h per night and < 5 d per week), there is not sufficient influence on OSAS-related cardiovascular sequelae. Once again, as CRP is only a component in the complicated inflammatory process which characterizes OSAS, the evolution of other markers should be considered in order to have final conclusions.

**CONCLUSION**

Since CVDs are detrimental to human health, medical practitioners seek to predict the development of cardiovascular events before they occur. CRP has been the most studied inflammatory protein to date and a frequently used marker to predict the occurrence of CVDs. Unfortunately, the true correlation between CRP and OSAS is open to controversy, as well as the clinical effect of any reduction. CRP is only one element of the underlying noxious inflammatory process in OSAS. However, there is a shortage of simple, standardized, and cost-effective methods for patient follow-up, and CRP presents these features. In this way, CRP might be valuable along with all other parameters used for the follow-up of patients with OSAS in PAP clinics. Further research is required to define those OSAS patients who will have a considerable reduction with treatment, as well as to understand the significance of the interaction between cardiovascular risk factor and CRP reduction in patients with OSAS.

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