

Syndrome Z –Relation of Sleep Apnoea, Vascular Risk Factors and Heart Disease

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Abstract: Syndrome Z is defined as the co-occurrence of obstructive sleep apnea (OSA) and metabolic syndrome. There is a paucity of information on the magnitude of syndrome Z in the community and the factors associated with it. Obstructive sleep apnea (OSA) has been linked to increased cardiovascular morbidity and mortality from both coronary heart disease and stroke [1-3] but whether this risk is due to coexistent known cardiovascular risk factors or specific effects of OSA remains to be established. In populations at risk of vascular disease, many patients who experience a cardiovascular event either do not have identifiable risk factors or have disease severity which appears to be out of proportion to their known risk factors. A lot of the variance in the incidence of vascular disease is therefore not explained by known risk factors. It is possible that OSA is a cardiovascular risk factor, previously largely unrecognized, which may account for some of the apparently unexplained variance in vascular risk. Systemic hypertension during daytime measurements of blood pressure is common in patients with OSA [8] but a causal link between these two conditions has been disputed [2, 3]. Sleep apnea has been shown to be common in patients with hypertension [8-11] and, conversely, patients with OSA have a high prevalence of hypertension [1, 5]. The frequency with which risk factors for hypertension such as increasing age and obesity coexist in patients with OSA has confounded identification of a causal relationship between OSA and hypertension.

Keywords: OSA, cardiovascular risk factor, metabolic syndrome, obesity, Systemic hypertension.

INTRODUCTION

Syndrome Z describes the interaction of obstructive sleep apnea (OSA) with vascular risk factors [1]. These include the quartet of hypertension, central obesity, insulin resistance and hyperlipidaemia, also known as the metabolic syndrome or the insulin resistance syndrome. Each component of the metabolic syndrome has an independent and significant impact on the health status of the individual. However, the morbidity and mortality associated with syndrome Z are probably multiplicative rather than additive. Moreover, OSA is an independent risk factor for cardiovascular disease over and above the components of the metabolic syndrome. Therefore, screening for OSA in addition to the metabolic syndrome would provide extra health benefits. The prevalence of OSA is thought to be about 4% [2] and that of the metabolic syndrome about 20% [3]. The prevalence of syndrome Z in the community has not been looked at to date. The aim of this pilot study, therefore, was to determine the prevalence of syndrome Z in our hospital population and extrapolate this information to the community at large. Morbid

obesity is correlated to the syndrome of hypoventilation [4, 5]. The syndrome of obesity hypoventilation may be accompanied by obstructive sleep apnea and may lead to significant clinical problems⁵. The syndrome of obesity and hypoventilation is characterized by findings from the history and physical examination. Patients suffer from sleepiness and they sleep during the day when they are not involved in any specific activity. Patients with coexisting sleep apnea snore so heavily that their snoring is characterized as heroic by their partners. Morbid obesity is the main physical finding. Other findings are the plethoric facies, the short and thick neck, the small oropharynx, rales, cyanosis and symptoms of right cardiac insufficiency, such as increased pressure in the jugular veins, hepatomegaly and pedal edema. Patients with the syndrome of obesity hypoventilation have by definition alveolar hypoventilation, hyperkapnia and hypoxemia when they are awake and breathe room air. Obstructive sleep apnea is frequently observed in these patients [1]. Obstructive sleep apnea may contribute to the development of systemic arterial hypertension in obese

patients⁵ through activation of the sympathetic nervous system, blood leptin increase, insulin resistance, angiotensin II and aldosterone increase, oxidative and inflammatory stress and endothelial dysfunction. If obstructive sleep apnea exists the patients should be treated by different measures such as the application of positive pressure in the airway [8].

DISCUSSION

The clustering of cardiovascular disease mechanisms in the metabolic syndrome and OSA are remarkably similar. Patients with OSA have abnormalities in each of the “core” components of the metabolic syndrome – high blood pressure, high fasting glucose, increased waist circumference, low HDL cholesterol, and high triglycerides – as well as in many of its other features, including sympathetic activation, endothelial dysfunction, systemic inflammation, hypercoagulability, and insulin resistance. It has even been suggested that the metabolic syndrome (“Syndrome X”) should encompass OSA (“Syndrome Z”) [3]. However, there is little information about the extent to which the cardinal features of the metabolic syndrome are present simultaneously in patients with OSA. Morbid obesity is correlated to the syndrome of hypoventilation [4, 5]. The syndrome of obesity hypoventilation may be accompanied by obstructive sleep apnea and may lead to significant clinical problems [11]. The syndrome of obesity and hypoventilation is characterized by findings from the history and physical examination. Patients suffer from sleepiness and they sleep during the day when they are not involved in any specific activity. Patients with coexisting sleep apnea snore so heavily that their snoring is characterized as heroic by their partners. Morbid obesity is the main physical finding. Other findings are the plethoric faces, the short and thick neck, the small oropharynx, rales, cyanosis and symptoms of right cardiac insufficiency, such as increased pressure in the jugular veins, hepatomegaly and pedal edema. Patients with the syndrome of obesity hypoventilation have by definition alveolar hypoventilation, hyperkapnia and hypoxemia when they are awake and breathe room air. Obstructive sleep apnea is frequently observed in these patients¹. Obstructive sleep apnea may contribute to the development of systemic arterial hypertension in obese patients⁵ through activation of the sympathetic nervous system, blood leptin increase, insulin resistance, angiotensin II and aldosterone increase, oxidative and inflammatory stress and endothelial dysfunction. If obstructive sleep apnea exists the patients should be treated by different measures such as the application of positive pressure in the airway [7]. Studies have been performed suggesting that sleep apnea may be a manifestation of the metabolic syndrome [8, 9]. It has also been proposed that the metabolic syndrome or “syndrome X” might include obstructive sleep apnea

and then might be called “syndrome Z” [10]. The mechanisms which contribute to the development of cardiovascular disease in the metabolic syndrome and obstructive sleep apnea are similar. Patients with obstructive sleep apnea appear to suffer from the disorders which characterize the metabolic syndrome [3]. Thus, patients with obstructive sleep apnea have hypertension, high fasting blood glucose levels, increased waist circumference, low HDL cholesterol and high triglycerides and many other characteristics, including sympathetic activation, endothelial dysfunction, systemic inflammation, and hypercoagulation and insulin resistance [4]. A positive relationship was observed between the apnea/hyperpnoea index, body weight, body mass index, skinfold thickness, lipid percentage in whole body weight, blood glucose levels, uric acid, fibrinogen levels and leptin levels in men examined for possible apnea hypopnea [5]. The relationship between the apnea/hyperpnoea index and leptin levels disappeared when it was corrected for factors, which are indices of obesity. The exogenous administration of testosterone exacerbates obstructive sleep apnea while hormone replacement therapy with estrogens in postmenopausal women may protect from obstructive sleep apnea [6].

Studies Design

In a recent study it was found that the prevalence of the metabolic syndrome according to the ATP-III criteria is almost 40% greater in patients with obstructive sleep apnea [5, 7]. It is not clear whether the syndrome of obstructive sleep apnea is observed as part of the basic pathophysiology of the metabolic syndrome or whether the syndrome of obstructive sleep apnea through repetitive night hypoxemia and other mechanisms induces the appearance of the characteristics of the metabolic syndrome. The size of the risk for the development of cardiovascular disease that can be attributed to the coexistence of the metabolic syndrome and obstructive sleep apnea may be cumulative, synergic or smaller. It appears that the successful management of obstructive sleep apnea with the application of positive pressure in the airways decreases arterial blood pressure [8] increases insulin sensitivity [6, 9] and improves testicular function in man [6]. Thus, it appears that the successful management of obstructive sleep apnea may decrease morbidity and mortality from cardiovascular diseases. A study that included fifty four patients with CAD and SAS showed that the patients who accepted therapy for the obstructive sleep apnea finally had one third of the risk for the development of a major incident from the cardiovascular system and especially from the coronary arteries compared to patients who did not receive therapy for obstructive sleep apnea [6]. Obese men with sleep apnea had higher plasma leptin levels and higher levels of inflammatory cytokines, such as tumor necrosis factor- α and interleukin-6, which promote the

development of daytime sleepiness and insulin resistance than obese men without apnea and normal weight men⁵. In this study it was found that obese men with sleep apnea had statistically significantly higher amount of abdominal fat than obese men without sleep apnea. It was shown that apnea indices correlated positively with the amount of abdominal fat. In the same study, in the group of men with sleep apnea, a higher degree of insulin resistance was observed compared to obese men without sleep apnea. Higher levels of tumor necrosis factor- α and interleukin-6 have been detected in patients with disorders inducing sleepiness during the day [6, 3]. It has been suggested that these cytokines are responsible for the development of sleepiness during the day. In another study patient with obstructive sleep apnea the successful management of apnea decreased plasma leptin levels^{1, 4} that correlated with the change in the apnea/ hypopnea index. Parish *et al.*, [13] found that the prevalence of metabolic syndrome and hypertension was significantly greater in patients with obstructive sleep apnea compared to those without obstructive sleep apnea. In another study it was observed that obstructive sleep apnea was correlated with hypertension, dyslipidaemia and hyperglycemia [12]. The authors concluded that obstructive sleep apnea may predispose even not obese patients to the development of metabolic syndrome.

It appears that obstructive sleep apnea and metabolic syndrome are characterized by the same pathophysiologic environment which increases the risk for the development of cardiovascular diseases [5, 7]. The metabolic syndrome may be the final common pathway connecting sleep apnea with cardiovascular diseases¹⁶. Currently there is an epidemic of obesity resulting in an increase of the prevalence of the metabolic syndrome and obstructive sleep apnea increase [8]. The effect of this increase on the development of cardiovascular diseases may be very significant. An important study by Coughlin and colleagues⁴ in this issue of the Journal addresses this question directly [9]. They performed a cross-sectional study of 61 otherwise healthy subjects with OSA and 29 subjects without OSA. To mitigate confounding due to obesity, they also matched 34 of the OSA patients by body-mass index (BMI) to the 29 controls. Their results suggest that the prevalence of metabolic syndrome (by NCEP) is about 40% greater in patients with OSA [9]. The obesity epidemic and its impact on the prevalence of both metabolic syndrome and OSA make these data especially relevant and timely. Several intriguing questions arise from the Coughlin study. First, does OSA occur as part of the fundamental pathophysiology of metabolic syndrome, or does OSA, via repetitive nocturnal hypoxemia and other mechanisms, promote the components of the metabolic syndrome? In this regard, given what is known about OSA, it is surprising that blood pressure and fasting glucose were not higher

in patients with OSA after controlling for obesity. Second, is the magnitude of cardiovascular risk attributable to coexisting metabolic syndrome and OSA additive, synergistic, or redundant? Here, part of the uncertainty is due to the fact that studies of the metabolic syndrome thus far have not addressed the important question of whether metabolic syndrome *per se* contributes to cardiovascular risk above and beyond the risk attributable to each of its components and/or traditional risk factors. Third, does treatment of OSA attenuate abnormalities in the components of the metabolic syndrome, hence lowering the overall prevalence of the metabolic syndrome in patients with OSA? If so, what consequences does this have for cardiovascular risk? Effective treatment of OSA with continuous positive airway pressure (CPAP) decreases blood pressure⁵ and may increase insulin sensitivity [6]. Reductions in blood pressure lower cardiovascular risk. Therapies that increase insulin sensitivity also improve cardiovascular risk factors and surrogate endpoints, and outcomes trials are currently underway [12]. As such, effective OSA therapy, via these mechanisms alone, might be expected to reduce cardiovascular morbidity and mortality. Further insight into this question is provided by Milleron and colleagues, also in this issue of the Journal [7]. These investigators conducted a prospective cohort study of the effects of OSA therapy on cardiovascular morbidity and mortality. They studied 54 patients who had >70% coronary artery stenosis during elective coronary angiography (>86% underwent revascularization) and subsequently had a polysomnogram that confirmed OSA. Patients were offered therapy and then followed up for an average of 7 years for a composite endpoint of cardiovascular death, acute coronary syndrome, coronary revascularization, or hospitalization for heart failure. Patients who accepted OSA therapy (regardless of noncompliance or later discontinuation) experienced only one third of the risk for the composite endpoint compared to those who refused OSA therapy.

CONCLUSION

When body mass index (BMI) was normal, the increasing median ages of these conditions indicated that the MS may be the first event followed by OSA and eventually syndrome Z develops. With BMI >25 or >30 no clear-cut difference was noted, indicating that the BMI itself could have an independent role in MS, OSA and syndrome Z. Obstructive sleep apnea is closely linked to the cluster of cardiovascular risk factors known as “syndrome X” and the converse is also likely but has not yet been proved (“syndrome Z”). These relationships should lead physicians to consider that patients with OSA may have co-existent modifiable cardiovascular risk factors and, conversely, that OSA should be suspected in patients with hypertension, central obesity, insulin resistant diabetes, or dyslipidaemia. Aside from these co-existent risk factors

there is some evidence that untreated OSA is associated with an additional independent cardiovascular risk which is reduced by effective treatment of OSA. While treatment of OSA eliminates recurrent episodes of hypoxemia, reduces overall blood pressure levels and variability, may reduce insulin resistance and therefore reduce triglycerides, it has little effect on weight or fat distribution. Thus, the relative contributions of improvements in associated risk factors versus elimination of the hemodynamic and respiratory stresses, which occur during sleep in untreated OSA, remain to be fully elucidated. Currently, the majority of patients with OSA are treated because of symptoms such as daytime tiredness or sleepiness. If OSA can be convincingly linked to an increased risk of heart disease or stroke then, in the future, treatment of OSA may be indicated for prognostic reasons.

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