The metabolic aspects and hormonal derangements in obstructive sleep apnoea syndrome and the role of CPAP therapy

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Abstract. – Obstructive sleep apnea syndrome (OSAS) is part of a metabolic syndrome, whose main aspects are obesity, hypertension and diabetes, already incriminated for cardiovascular events. The evaluation of the effect of OSAS on the hormonal profile of patients shows a number of complex interactions that preclude the exact role of this syndrome among the numerous derangements on hormone levels as well as the effect of continuous positive airway pressure treatment, since many of the changes are known to occur with obesity as well. The clarification of the exact role and the mechanisms underlying these changes will help to stratify the cardiovascular and other health risks of this syndrome as well as the better application of CPAP therapy.

Key Words: Obstructive sleep apnea syndrome, Hormones, Metabolic syndrome.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a common disorder characterised by frequent episodes of apnoea and hypopnoea during sleep, and excessive daytime sleepiness. Its prevalence is estimated at 2-4% among adult men and 1-2% among adult women\(^1\). Obesity is very common in patients with OSAS\(^3\), who appear to put on weight more easily than equally obese patients without OSAS, with an as yet unknown mechanism\(^4\). Excess weight in adults has been clearly associated with increased incidence of type-2 diabetes and impaired glucose tolerance\(^5\). Insulin resistance, as indicated by an impaired biological response to insulin\(^6\), has been implicated in the pathogenesis of a metabolic syndrome known as “insulin-resistance syndrome”, which is generally accepted to comprise hyperinsulinaemia, glucose intolerance, dyslipidaemia, central obesity and hypertension\(^7\).

This syndrome has an as yet unclear underlying pathophysiology and moreover, the list of risk factors comprising the cluster is not grounded by well-grounded criteria. One recent review\(^7\) studied in detail various papers on the subject and appropriately states that the syndrome conveys no greater information than the sum of its component risk factors. Also, the definition of the syndrome includes risk factors that are only weakly related to insulin resistance or hyperinsulinemia (e.g. blood pressure) and excludes others that are closely related (e.g. CRP, adiponectin). The two existing definitions of the syndrome, namely the WHO and ATP III definitions, do not include some risk factors such as age, sex, family history and physical inactivity that are major cardiovascular risk factors that hamper their usefulness and predictive value\(^8\). Therefore, the metabolic syndrome requires much more study before its designation as a “syndrome” is truly warranted and before its clinical utility is adequately defined.

The investigation of metabolic processes in OSAS during the last years did not only include the study of insulin resistance, but also the measurement of leptin, ghrelin, adiponectin, resistin, thyroid function and cytokines, although the findings in various studies have been conflicting. The interactions between OSAS and metabolic processes may help to clarify and to quantify the effect of this syndrome as an independent factor of insulin resistance, increased cardiovascular risk and decreased survival. Therefore OSAS represents a complication of obesity, but per se does not represent one aspect of metabolic syndrome.
Insulin Resistance and the Obstructive Sleep Apnoea Syndrome

Increased insulin resistance seems to play a key role among the mechanisms responsible for metabolic effects in OSAS. Hyperinsulinaemia raises blood pressure and the main pathophysiology may be a dissociation of intermediate metabolic effects of insulin and its growth-promoting effects especially at the vascular epithelium. Increased insulin resistance has been repeatedly reported in patients with OSAS. However, insulin resistance is not uncommon in the general population and it is also associated with obesity, immobility or with the use of different drugs, like beta-adrenergic blockers used as anti-hypertensives, which is also frequent in the case of OSAS patients. The results of various studies have been conflicting. Some studies reported that the relationship between insulin resistance and disordered breathing is entirely dependent on body mass and failed to show any improvement with CPAP therapy. More recent reports demonstrated that sleep-disordered breathing parameters (the apnoea-hypopnea index or oxygen desaturation) are independent determinants of insulin resistance. Another study unveiled a significant improvement in insulin sensitivity in 40 OSAS patients (AHI > 20) as soon as 2 days after onset of CPAP therapy, which removes any effect of weight change. This effect was maintained after 3 months of CPAP therapy, without any significant changes in body weight having occurred. The leaner group of patients however had better insulin sensitivity and a more rapid improvement during CPAP therapy, suggesting that in obese individuals insulin sensitivity is mainly determined by obesity rather than sleep apnoea. On the other hand, hypoxia has already been shown to be associated with impaired glucose metabolism which could serve as a mechanism of glucose intolerance and insulin resistance in OSAS. Another mechanism is the association of OSAS with an increased sympathetic activity.

Adipocytes produce a number of molecules, adipocytokines, that contribute to the development of the metabolic syndrome. One such molecule is adiponectin, discovered in 1996 as a product of the adipose most abundant gene transcript. It has also been reported that plasma adiponectin levels decrease with obesity, type 2 diabetes, dyslipidaemia and coronary artery disease. The mechanisms of this paradoxical reduction of adiponectin in obesity are not known. Reduced plasma adiponectin concentration is a risk factor for cardiovascular, cerebrovascular and metabolic disorders partly due to reduced antagonism towards the insulin-resistance producing effects of tumour necrosis factor alpha (TNF-α). Again, the results have been conflicting. One study demonstrated the levels of adiponectin to be elevated in 26 otherwise healthy OSAS subjects when compared with 29 BMI-matched controls and suggested that this could be due to an inherent protective mechanism against cardiovascular disease. Other studies showed the levels of adiponectin to be lower in OSAS patients, whereas others failed to show any differences in adiponectin levels between mild, moderate and severe OSAS patient groups and to be largely influenced by obesity. Yet another study showed a significant relation between adiponectin level and the insulin sensitivity index in overweight patients with OSAS. The differences could be due to the circadian levels of plasma adiponectin, and to the different sampling hours between the various studies, at least in some part.

Recently, diurnal variations in circulating levels of adiponectin in diabetic and nondiabetic obese subjects and in healthy normal-weight male human subjects have been investigated. The Hotta et al study did not observe any daily changes in circulating levels of adiponectin in obesity. In normal-weight subjects, Gavrila et al found an ultradian pulsatility as well as a diurnal variation in adiponectin plasma levels with a significant decline at night, reaching a nadir in the early morning. A more recent study however investigated the ultradian rhythm and pulsatility of adiponectin in obese subjects before and after weight loss. This study showed again that adiponectin is secreted in a pulsatile fashion and has a diurnal variation which is blunted in obese individuals. Weight reduction was associated with restoration of the homeostatic control of adiponectin secretion and of its pulsatility parameters. The nocturnal decline was not present however, and this could be due to dysregulation of the hypothalamus-pituitary-adrenal axis or to the fact that severe obese patients maintain an imprinting, likely of genetic or epigenetic nature, of their former obese state, although the adiponectin pulsatility is restored during the daytime.

Leptin and Ghrelin Levels in Patients With Obstructive Sleep Apnea Syndrome

The investigation of metabolic processes in OSAS included the study of two other hormones,
namely leptin and ghrelin. Leptin is the protein product of the ob gene and adipocytes are the main source of this 167-amino acid, 16-kDa hormone. Other sources of it are the skeletal muscle and stomach. It plays an important role in body composition, energy homeostasis and feeding behaviour in human beings. Changes in serum leptin levels or leptin-receptor insensitivity may be involved in the pathogenesis of progressive weight gain in OSAS. More recently, ghrelin, a hormone that also influences appetite and energy has been discovered. There is a growing body of evidence that this 28 amino acid gut-brain peptide and composition in both animals and humans. It stimulates hunger and food intake when administered intravenously in healthy humans. Human obesity is associated with decreased ghrelin levels that increase after weight reduction. Such findings identify ghrelin, to some degree, as an antagonist of leptin. Hints on other functions have been the demonstration of growth hormone (GH) secretagogue-binding sites in peripheral tissues, such as the brain and the lung, and the observation that ghrelin promotes slow-wave sleep in males.

Again, the results have been conflicting regarding the effect of OSAS and CPAP therapy on leptin levels. Some studies showed the levels of leptin to be higher in obese patients with OSAS than in equally obese controls. Serum leptin levels were found to be significantly correlated with the AHI, but failed to reach significance after correction with BMI, except in two studies where the leptin level was significantly correlated with AHI in OSAS patients. A correlation with neck circumference has also been noted. A more recent study showed the following results: (1) leptin levels in nonobese patients with OSAS were higher than in nonobese control subjects; (2) leptin levels in obese patients with OSAS were not different from obese control subjects. A number of studies agree on this point, but others showed different findings. (3) leptin levels in nonobese patients with OSAS were significantly lower than in obese ones; (4) leptin levels decreased only marginally with CPAP therapy. In general, what has been shown is that obesity is the key determinant of leptin levels in OSAS, with apnea contributing to a smaller degree.

Ghrelin has not been investigated in a great degree in the context of OSAS. Ghrelin levels were investigated and were found to be significantly higher in OSA patients than in BMI-matched controls, but decreased to levels similar to those of obese patients without OSA after 2 days of treatment. This decrease occurs within a period of time too short for any significant changes of body fat mass. On the other hand, a more recent study showed no significant difference in serum ghrelin levels between OSAS patients and controls. One question that should be resolved is whether these differences in total ghrelin reflect changes in the biologically active or inactive peptide, since commercially available ghrelin RIA kits detect both octanoylated and nonoctanoylated ghrelin.

**Resistin Levels, OSAS and Subclinical Inflammation**

Resistin was initially identified in mice as a 114-amino-acid peptide, circulating as a homodimer of two peptides joined by a disulfide bridge. It is a member of the family of cysteine-rich secretory protein family, also referred to as “resistin-like molecules (RELM)” or “found in inflammatory zone (FIZZ)” molecules. In rodents, it is predominantly expressed by the white adipose tissue. This suggests a linkage between obesity and subclinical inflammatory activity, which is nowadays regarded as an important reason of atherosclerosis.

In humans, its role is not clear. In lean subjects, resistin mRNA could not be detected within the white adipose tissue. In obese individuals, mRNA of resistin is detectable, but without correlation to body weight or insulin resistance. In a recent study, a moderate correlation between insulin resistance and resistin was demonstrated and while CPAP therapy induced a significant improvement in insulin sensitivity, the resistin levels remained unchanged, showing thus a weak relation between insulin resistance and resistin levels in patients with OSAS. Previous studies also failed to demonstrate a close association between insulin resistance and resistin not only in cell cultures but also in humans. No correlations have been made between the BMI and the body weight with plasma resistin. On the other hand, the same study showed a close relation between resistin and IL-6, a parameter closely associated to the subclinical inflammation known to occur in OSAS and also regarded as one of the most important factors of atherosclerosis. Elevated levels of TNF-α, CRP, ICAM-1 and IL-8 have also been demonstrated. CRP and IL-6 levels in OSAS have been reduced after only one month of CPAP therapy in one study, while another showed a reduction in
ICAM-1 and IL-8 levels. With respect to the recent finding, that resistin promotes endothelial cell activation, the close relation between resistin and ICAM-1 demonstrated in the study by Harsch et al. can be interpreted as a reflection of a close association between resistin not only to subclinical inflammation, but also to endothelial activation.

**Pituitary Reactivity, Androgens, Catecholamines and Thyroid Function in Obstructive Sleep Apnoea Syndrome**

Obstructive sleep apnoea syndrome is characterized by several changes in endocrine functions and it is still unclear whether these changes reflect an overweight status or include peculiar hypoxia-induced hormonal alterations. These include changes in the activity of GH/IGF-I axis as well as alterations in adrenal and thyroid activity. Attempts have been made to clarify the extent of the influence of OSAS to these changes, some of which can be also attributed to obesity.

Obesity is connoted with an impairment of somatotroph secretion, reflecting a decrease in GH production rate. Obese patients also show a marked impairment of the somatotroph responsiveness to all provocative stimuli. On the other hand, despite marked GH insufficiency, total IGF-I levels in obesity are generally normal or slightly reduced, whereas free IGF-I levels are even elevated. It has been shown however that OSAS per se impairs GH/IGF-I axis activity, independently of adiposity. Obese OSA patients show a greater reduction in the GH response to a provocative test, such as GHRH plus ARG. Also, nCPAP has been found able to restore IGF-I levels in OSA before any variation in body weight occurred. This could be attributed to hypoxia and recent evidence in animals discloses that acute and prolonged hypoxia reduces GH synthesis and release and reduces IGF-I mRNA expression in endothelial cells in vitro. However, insulin resistance can be proposed to explain the impairment of GH/IGF-I axis, since insulin is able to inhibit GH synthesis and secretion and OSAS patients have insulin resistance. Sex steroids also influence the GH/IGF-I axis, with testosterone having a positive influence on IGF-I synthesis and release and estradiol positively influencing GH secretion but negatively affecting IGF-I synthesis and release. Obesity in males is associated with a relative hypoandrogenic state. The findings in OSA, concerning its effects in sex steroid secretion are somehow discordant, as discussed below. To make the issue more perplexed, GH is also influenced by sleep alterations and sleep stage, which are markedly altered by OSAS. Therefore, the results are open to debate and further research.

Studies on the effect of OSAS on the hypothalamic-pituitary-testicular and hypothalamic-pituitary-thyroid axes as well as on catecholamine and cortisol secretion showed subnormal LH and TSH levels, elevated cortisol and increased plasma epinephrine nocturnal urinary norepinephrine levels and CPAP therapy caused significant reduction in catecholamine levels. Lowest SpO2 has been shown to be the most important factor for increasing 24-h urinary norepinephrine levels, which could also serve as a marker for evaluating the effect of CPAP therapy. Another study has shown that some OSAS patients do not maintain a normal circadian rhythm to whom Holter monitoring showed arterial hypertension. Pituitary provocative tests showed the ACTH response to CRH in OSAS to be markedly higher than in obese controls, which in turn was higher than in normal subjects. The cortisol response to CRH was not significantly different among the three groups. These findings indicate the existence of a peculiarly exaggerated ACTH hyper-responsiveness to CRH that would again reflect hypoxia- and/or sleep-induced alterations of the neural control of corticotroph function. Basal PRL levels and the PRL response to TRH was also normal. Basal FT3 and FT4 levels as well as the TSH response to TRH were not found to be influenced by OSAS and CPAP therapy. Concerning androgen status, total and free testosterone levels have been found to be reduced in obese OSAS patients when compared to obese controls, suggested by the study that hypoxia during sleeping hours may be an additional factor in reducing testosterone levels, regardless of BMI and abdominal fatness. A normal androgen status has been shown by another study.

**Conclusions**

OSAS and its metabolic aspects is a matter of clarifying the complex nature and interactions between various hormones as well as the effect of parameters closely linked with OSAS, like AH and oxygen desaturation. Many of the relations between insulin resistance, adipocyte-de-
rived hormones such as leptin, adiponectin, ghrelin, resistin in OSAS still remain to be elucidated. OSAS, apart from obesity, is also a powerful inducer of subclinical inflammation, which leads to altered endothelial function and an accelerated atherosclerotic process. The clarification and quantification of possible long-term benefits in terms of cardiovascular outcome need studies not only of markers of insulin action and subclinical inflammation mentioned above, but also a clearcut benefit in terms of positive pressure therapy that could serve to normalize the hormonal derangements observed in OSAS, at least in some degree, while also treating the other major culprit which is and always will be, obesity.

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