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Obesity, obstructive sleep apnoea and metabolic syndrome

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ABSTRACT

OSA is increasingly recognized as a major health problem in developed countries. Obesity is the most common risk factor in OSA and hence, the prevalence of OSA is undoubtedly rising given the epidemic of obesity. Recent data also suggest that OSA is highly associated with the metabolic syndrome, and it is postulated that OSA contributes to cardiometabolic dysfunction, and subsequently vasculopathy.Current evidence regarding the magnitude of impact on ultimate cardiovascular morbidity or mortality attributable to OSA-induced metabolic dysregulation is scarce. Given the known pathophysiological triggers of intermittent hypoxia and sleep fragmentation in OSA, the potential mechanisms of OSA–obesity–metabolic syndrome interaction involve sympathetic activation, oxidative stress, inflammation and neurohumoral changes. There is accumulating evidence from human and animal/cell models of intermittent hypoxia to map out these mechanistic pathways.In spite of support for an independent role of OSA in the contribution towards metabolic dysfunction, a healthy diet and appropriate lifestyle modifications towards better control of metabolic function are equally important as CPAP treatment in the holistic management of OSA.

Key words: mechanistic pathway, metabolic syndrome, obesity, obstructive sleep apnoea.

INTRODUCTION

Obesity has become one of the most important global public health issues, with escalating prevalence in Western countries for several decades, and now also affecting many developing countries, attributable to the modern lifestyle of physical inactivity and unrestricted supply of high-fat diet.[1,2] The epidemic of obesity results in major health related consequences in different ethnic populations. There is increasing awareness of the role of obesity in the development of cardiometabolic disease in recent years.[3] Metabolic syndrome (MS) is strongly linked to obesity, is a clustering of multiple metabolic abnormalities, comprising of hypertension, insulin resistance, central obesity and dyslipidaemia. Current data suggest that there is an increased prevalence of MS in subjects with OSA.[4,5] OSA is a common and increasingly recognized sleep disorder, characterized by recurrent episodes of upper airway collapse that results in oxyhaemoglobin desaturation and periodic arousals from sleep throughout the night.[6] Obesity is a well-known risk factor for OSA;[7] therefore, OSA is possibly an additive pathogenic pathway for the effects of obesity on cardiometabolic dysfunction. There is emerging evidence that obesity and OSA affect similar cascades that contribute to vasculopathy.[8]

OBESITY AND CENTRAL OBESITY

Obesity develops from an imbalance of energy over time, when energy intake exceeds energy expenditure, leading to accumulation of adipose tissue with a corresponding increase in lean body mass.[9] Its severity also depends on a complex interaction of genetic and environmental influences. It is often defined in terms of BMI by body weight relative to height, or evaluated in terms of fat distribution for central obesity with measurements of waist circumference or waist-to-hip ratio. The cut-off value of BMI for obesity in the Caucasian populations is at 30 kg/m^2, but some Asian populations have redefined obesity at a lower BMI of 25 kg/m^2.[10] The World Health Organization taskforce on obesity suggested that Asian populations

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have different associations between BMI, percentage of body fat, and health risks than do Caucasians. The consultation concluded that the proportion of Asian people with a high risk of type 2 diabetes and cardiovascular disease is substantial at BMIs <25 kg/m^2. In 2004, the World Health Organization expert consultation further identified potential public health action points (23, 27.5, 32.5, 37.5 kg/m^2) along the continuum of BMI for Asian populations.[11]

Obesity and central obesity have significant adverse impact on health, yet they are modifiable and thus preventable causes of morbidity and mortality. In a collaborative analysis of 57 prospective studies with nearly 900 000 participants from Western Europe and North America,[3] it was found that, for each 5 kg/m^2 increase in BMI, overall mortality was increased by 30%, with a hazard ratio of 1.29. For each 5 kg/m^2, mortality was increased by 40% for vascular diseases, 60–120% for diabetic, renal and hepatic diseases, 20% for respiratory disease, and 10% for cancer. At BMI 30–35 kg/m^2, median survival is reduced by 2 to 4 years; at 40–45 kg/m^2, it is reduced by 8–10 years.

The most common and most deleterious effects of obesity are on the cardiovascular system, predisposing to hypertension, ischaemic heart disease and cerebrovascular accident, with a putative mechanistic link to increased sympathetic drive on the vasculature.[12] It is apparent that a variety of adaptations or alterations in cardiac structure and function occur as excessive adipose tissue accumulates, even in the absence of systemic hypertension or underlying organic heart disease.[2] Central obesity is an independent risk factor for the development of type 2 diabetes mellitus (DM),[13] which is associated with insulin resistance.

METABOLIC SYNDROME

The metabolic syndrome is also known as insulin resistance syndrome.[14] The constellation of metabolic derangement includes insulin resistance/glucose intolerance, central obesity, hypertension and dyslipidaemia, which are well-known risk factors for cardiometabolic diseases.[15] Several studies have indicated that MS predicts future diabetes,[16,17] as well as an increased risk of cardiovascular disease and all-cause mortality.[18]

There are different criteria (use of different metabolic parameters) for the definitions of MS: World Health Organization 1999; European Group for the Study of Insulin Resistance 1999; National Cholesterol Education Program's Adult Treatment Panel III; and International Diabetes Federation[19] (Table 1).[20] Therefore, comparisons of published prevalence for different populations are difficult despite attempts to reach agreement on the definition of the MS. Nevertheless, a very consistent finding is that the prevalence of MS is increasing with the epidemic of obesity across different ethnic origins.[21] In the United States, the prevalence of MS increased with severity of obesity, and reached 50% in severely obese youngsters with a mean age of 11.3 (10.9–11.8) years.[22] The prevalence of MS was high among obese children and adolescents, increasing with worsening obesity and significantly with insulin resistance after adjustment for ethnic group and degree of obesity.

The underlying pathophysiology of MS is still a subject of debate, and both abdominal/visceral obesity and insulin resistance appear to be the predominant drivers of the syndrome.[23] It has been

Table 1 Different definitions of the metabolic syndrome[20]

WHO (1999)	EGIR (1999)	NCEP ATP III (2001)	IDF (2005)
Diabetes or impaired glucose tolerance or insulin resistance, plus two or more of the following:	Insulin resistance or hyperinsulinaemia (only non-diabetic subjects),plus two or more of the following:	Three or more of the following:	Waist circumference—ethnicity specific,plus two or more of the following:
BMI > 30 kg/m^2 or waist to hip ratio >0.9 in men, >0.85 in women	Waist circumference: ≥94 cm in men, ≥80 cm in women	Waist circumference: >102 cm in men, >88 cm in women	
Triglycerides: ≥1.7 mmol/L	Triglycerides: >2 mmol/L	Triglycerides: ≥1.7 mmol/L	Triglycerides: ≥1.7 mmol/L or medication
HDL C: <0.9 mmol/L in men <1.0 mmol/L in women	HDL C: <1.0 mmol/L	HDL C: <1.03 mmol /L in men <1.29 mmol/L in women	HDL C: <1.03 mmol/L in men <1.29 mmol/L in womenor medication
Blood pressure: ≥140/90 mm Hg or medication	Blood pressure: ≥140/90 mm Hg or medication	Blood pressure: ≥130/85 mm Hg or medication	Blood pressure: ≥130/85 mm Hg or medication
Urine albumin excretion ≥20 mcg/min or albumin : creatinine ratio ≥30 mg/g	Fasting plasma glucose: ≥6.1 mmol/L	Fasting plasma glucose: ≥6.1 mmol/L	Fasting plasma glucose: ≥5.6 mmol/L or type II diabetes

EGIR, European Group for the Study of Insulin Resistance; HDL C, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; NCEP ATP III, National Cholesterol Education Program—Third Adult Treatment Panel; WHO, World Health Organization.

proposed that visceral fat probably plays a role in the hepatic manifestations of central obesity, and systemic free fatty acid concentrations are found to affect muscle, pancreatic β cells, and vascular functions at molecular level.[24] A consensus has emerged that visceral fat is particularly damaging in that it portends greater risk for DM, cardiovascular disease and certain cancers.[25] It is also accepted that insulin resistance is a related characteristic that may be an essential link between central obesity and disease risk. It is possible that hyperinsulinaemia accompanying insulin resistance in non-diabetic but at risk individuals may magnify, or even mediate, some of the detrimental effects of visceral obesity.[26]

OBESITY AND OSA

OSA is the most common sleep disorder whose prevalence is linked to an epidemic of obesity in Western societies. OSA describes the occurrence of recurrent episodes of upper airway obstruction or collapse during sleep. Collapsibility of the upper airway during sleep can be increased by underlying anatomical alteration and/or disturbances in upper airway neuromuscular control, both of which play key roles in the pathogenesis of OSA. Obesity and particularly central adiposity are potent risk factors for sleep apnoea. They can increase pharyngeal collapsibility through mechanical effects on pharyngeal soft tissues and lung volume, and also through the central nervous system—with different interactions of adipokines and adipocyte-binding proteins on binding receptors that may affect the functional aspect, such as airway neuromuscular control.[27]

The impact of changes in body weight on sleep apnoea has been well demonstrated by the Wisconsin Sleep Cohort Study [28]and the Sleep Heart Health Study.[29] The overall incidence of moderate to severe OSA over a 5-year period was 11.1% in men and 4.9% in women, respectively. Men with >10 kg weight gain over the follow-up period had a fivefold risk of increasing their AHI to >15. In contrast, for the same degree of weight gain in women, 2.5-fold risk of a similar increment in the severity of sleep apnoea was seen.[29] Given the impact of obesity on OSA, it is generally accepted that the global rise in obesity has a major impact on the prevalence and severity of sleep apnoea.

The association between OSA and obesity is complex. Newly diagnosed OSA subjects have difficulty losing weight and may be predisposed to excessive weight gain, compared with similarly obese subjects who are free of OSA.[30] Furthermore, fat distribution also appears to be of importance in the relationship between OSA and adiposity. The relationship between OSA and weight gain seems to be particularly strong for visceral fat deposition.[31] Clinically, neck circumference has been reported to be a useful predictor of OSA,[32,33] although the exact role of neck circumference in the development of OSA has not been fully clarified. While neck girth has been reported as a surrogate marker of central obesity,[32] a recent Japanese study reported that neck circumference was associated with the severity of OSA independently of visceral obesity, especially in non-obese patients with OSA.[34] In addition, various phenotypic features may have different contributions towards development of OSA in different races. In an inter-ethnic comparison study of Caucasian ($n = 74$) and Chinese ($n = 76$) patients with OSA, for the same degree of OSA severity, Caucasians were more overweight, whereas Chinese exhibited more craniofacial bony restriction.[35] Therefore, genetics or craniofacial structural factors may also contribute to the natural course of sleep apnoea.

Given that obesity is the only major modifiable risk factor for OSA, weight loss should be recommended for all overweight or obese patients with sleep apnoea, as its beneficial effects embrace other obesity-related health problems, notably cardiometabolic diseases.[36] However, it takes time to achieve the target body weight, and it is difficult to maintain it successfully. In a prospective study of 101 OSA patients who underwent bariatric surgery for weight reduction, OSA was noted in 45% of them.[37] Preoperative BMI correlated with the severity of OSA after adjustment for age and gender. At a median of 11 months after bariatric surgery, mean BMI was significantly reduced from 56 ± 1 to 38 ± 1 kg/m^2 and mean respiratory disturbance index from 51 ± 4 to 15 ± 2. In addition, their minimum oxygen saturation, sleep efficiency and rapid eye movement latency improved.[37] Alternatively, an anti-obesity drug, sibutramine, a serotonin/noradrenalin reuptake inhibitor, was also shown to lead to improvement in OSA severity and daytime sleepiness with weight reduction.[38] In a recent 24-week sibutramine-assisted weight loss trial in 54 middle-aged obese men with moderate to severe OSA, there was a significant reduction in weight (-7.8 ± 4.2 kg) and AHI (-15.9 ± 20.5), leading to increased velopharyngeal airway volume and reduced facial fat, and a reduction in upper airway length was associated with the improvement in AHI.[39] Therefore, both surgically and medically induced significant weight loss can improve obesity-related OSA.

At the same time, weight reduction also has many beneficial effects on the metabolic profile in OSA subjects. In a case-control longitudinal study of obese subjects in Sweden, the average change of BMI in the 1729 subjects in the bariatric surgical group was -9.7 ± 5 kg/m^2 compared with 0 ± 3 kg/m^2 for the 1748 subjects in the control group.[40] The significant weight reduction in the bariatric surgery group was accompanied by marked improvement in sleep apnoea symptoms and a lower 2-year incidence of type 2 DM and hypertriglyceridaemia. Sibutramine for 6 months was also efficacious in reducing weight in 93 non-diabetic men with moderate to severe OSA, along with reduction of respiratory disturbance index by 30% as well as improvement in insulin resistance and lipid profile.[41] In one of the Australian studies, 25 severely obese patients (mean BMI was 52.7 kg/m^2) with moderate to severe OSA, laparoscopic adjustable gastric banding resulted in an average weight loss of 44.9 ± 22 kg and a significant fall in AHI from 61.6 ± 34 to 13.4 ± 13, when assessed at

17.7 ± 10 months after the surgery.[42] Furthermore, fasting plasma glucose, serum insulin and triglycerides were decreased and high-density lipoprotein cholesterol was significantly increased. At baseline, 20 (80%) of these subjects fulfilled the criteria of the metabolic syndrome, and this was drastically reduced to three subjects (12%) at the postoperative reassessment.

Although it is accepted that adiposity is important in the pathogenesis of OSA, the impact may not be entirely unidirectional, and some mechanisms have been postulated for the influence of OSA on metabolic pathways that influence fat accumulation and deposition. It is possible that hypoxia and sleep interruption in OSA would contribute to changes in body composition over time.[43] It has been hypothesized that a stress reaction activating the hypothalamic–pituitary–adrenal axis leading to release of cortisol and other hormones may trigger mechanisms generating insulin resistance and preferential abdominal fat accumulation.[44] By inducing neurohumeral changes, OSA could promote the development of central obesity directly or indirectly through increasing insulin resistance.[43,45,46] The increased obesity would in turn result in progressive deterioration of sleep apnoea, and thus sleep apnoea and metabolic disturbances may run into a vicious cycle.[47] Nevertheless, this hypothesis remains to be definitively proven despite accumulating data to support some of the individual mechanisms in this complex interplay of clinical manifestations.

Adiposity not only predisposes to metabolic dysfunction in itself, but it may also contribute to the pathogenetic role of OSA in cardiometabolic dysfunction. Adipose tissue is a metabolically active tissue that participates in many systemic metabolic processes.[48] It is recently proposed that adipose tissue hypoxia may be a trigger of inflammation in obesity,[49] and inflammation is a well-known intermediary mechanism in cardiometabolic dysfunction. Adipose tissue is a rich source of various pro-inflammatory adipocytokines and biomolecules, which may promote endothelial dysfunction, insulin resistance and lipid peroxidation.[50–52] A newly recognized consequence of obesity and insulin resistance is non-alcoholic fatty liver disease (NAFLD),[53,54] with identified risk factors of obesity, age >45 years, DM, hypertriglyceridaemia and hypertension, for the progression of NAFLD.[53] Tissue hypoxia in OSA may also contribute to the progression of NAFLD, in a spectrum of disease severity, ranging from steatosis without inflammation to non-alcoholic steatohepatitis and liver cirrhosis.[54,55]

OSA AND METABOLIC SYNDROME

Despite substantial evidence from both epidemiological and clinical studies to suggest an independent link between OSA and MS as a syndromic entity, the issue still remains controversial. The association of the two conditions is very consistent in different ethnic populations, as reported in Caucasian,[4,56–61] Mediterranean[62–68] and Asian[5,69–72] studies (Table 2), and their frequent coexistence has led to the description of 'Syndrome Z'.[73] In a study of subjects with newly diagnosed MS, who were expectedly obese, OSA was present in 68% of them, a figure that was similar to that for other established individual components of metabolic syndrome.[60] OSA also demonstrated associations, independent of obesity, with many of the individual metabolic components in clinical studies.[74,75] Interestingly, in a study of 195 patients with cardiovascular diseases, the metabolic syndrome was found to be a better predictor of nocturnal desaturation than AHI in those with sleep apnoea.[72] A recent study from India suggested sequential development of metabolic syndrome and OSA.[76] Given these closely interwoven relationships between OSA and MS or its defining components, it has been proposed that OSA may well be considered as a manifestation of an expanded MS.[47,58]

In a cross-sectional study of 81 patients with multiple comorbidities recruited from a heart institute, those who suffered from OSA and MS had higher levels of carotid intima media thickness, carotid-femoral pulse wave velocity and carotid diameter compared with those without MS.[77] Therefore, the concurrent presence of MS and OSA may have an additive effect on atherosclerosis. In subjects with MS who were not yet overtly diabetic, presence of OSA was associated with higher fasting glucose level and glycosylated haemoglobin but not with BMI.[60] In two interventional studies of OSA patients with MS, the prevalence of MS was decreased by 45% in parallel with significant weight reduction after 1 year of CPAP treatment[59] and by 20% with no changes in body weight[78] after 6 months of CPAP treatment. These data suggest that early CPAP treatment in otherwise 'healthy' OSA subjects may possibly prevent the development of overt cardiometabolic diseases.

POTENTIAL MECHANISMS UNDERLYING OSA-OBESITY-METABOLIC SYNDROME INTERACTION

Intermittent hypoxia (IH) and oxidative stress

Recurrent obstructive events result in alternating cycles of hypoxia/reoxygenation in OSA, and rapid reoxygenation of transiently ischaemic tissues could lead to tissue injury and release of reactive oxygen species (ROS), the culprit of oxidative stress. These ROS molecules are key activators of inflammatory/adaptive mechanisms.[79] Experimental human or animal /cell models of IH has been frequently used to investigate potential pathogenetic mechanisms in OSA.

Evidence of increased oxidative stress in subjects with OSA was shown in various cells,[80] in plasma,[81] urine[82] and exhaled air.[83] In a study of 10 young healthy men subjected to IH for 6 h per day for four days to simulate the situation in OSA, increased production of ROS without a compensatory increase in anti-oxidant activity was found.[84] There has been a growing body of research using cell/animal models of IH. Nicotinamide adenine dinucleotide phosphate

Table 2 Epidemiological and clinical studies of OSA and metabolic syndrome

Reference	Population	Metabolic parameters	MS (%)	Findings
Coughlin *et al.*[4]	Clinic-based UK, men Obese OSA, $n = 61$ Obese controls = 43	BMI, WC, SBP, DBP, FBS, Insulin, HOMA-IR, TC, TG, HDL C, LDL C, TC/HDL	OSA (87) Non-OSA (35)	OSA was associated with multiple metabolic risk factors MS: OR 9.1 (95% CI: 2.6,31.2)
Lam *et al.*[5]	Community-based Hong Kong, Chinese men and women, $n = 255$ OSA, $n = 95$ Non-OSA, $n = 160$	BMI, WC, SBP, DBP, TC, TG, HDL C, LDL C, TC/HDL C, FBS	OSA(58) Mild OSA (54) Moderate OSA (56) Severe OSA (70) Non-OSA (21)	OSA was associated with all metabolic components in MS. MS: OR 5.3 (95% CI: 3.03–9.26)
Gruber *et al.*[56]	Clinic-based UK, men and women, $n = 79$ Obese OSA, $n = 38$ Obese controls, $n = 41$	BMI, WC, SBP,DBP, TC, TG HDL C, LDL C, FBS, insulin, HOMA-IR	OSA (73) Controls (37)	Insulin resistance was not associated with OSA, independent of obesity. MS: OR 5.9 (95% CI: 2,17.6)
Ambrosetti *et al.*[62]	Clinic-based Italy, men and women, OSA, $n = 89$	WC, HDL C, TG, BP, FBS	OSA (53)	Subjects with OSA and MS were younger, had a higher AHI but did not increase the risk of cardiovascular events after 22 $\pm$ 10 months of CPAP treatment compared with those OSA subjects without MS.
Peled *et al.*[63]	Clinic-based Israel, men $N = 98$ Snorers, $n = 9$ Mild OSA, $n = 9$ Moderate OSA, $n = 27$ Severe OSA, $n = 53$	BMI, WC, FBS, insulin, TC, HDL C, TG, Hs CRP, serum amyloid	Mild OSA (11) Moderate OSA (21) Severe OSA (30)	The prevalence of MS increased with OSA severity.
Sasanabe *et al.*[69]	Clinic-based Japan, men and women, $n = 907$ OSA, $n = 819$ Controls 89	BMI, WC, SBP, DBP, FBS, insulin, HOMA-IR, TC, TG, HDL C, LDL C, β cell function.	OSA (50) Controls (22)	MS was associated with severity of OSA. In severe OSA, MS: in men, OR 5.1 (95%CI: 2.7, 9.7) in women, OR 14 (95% CI: 2.9, 66.8)
Shiina *et al.*[70]	Clinic-based Japan, men and women, $n = 184$ OSA, $n = 94$ Non-OSA, $n = 90$	BMI, SBP, DBP, MBP, TC, HDL C, TG, FBS, brachial-ankle PWV	OSA (43) Non-OSA (16)	MS may constitute an additive cardiovascular risk in OSA.
Kono *et al.*[74]	Clinic-based Case control Japan, men OSA, $n = 42$ Non-OSA, $n = 52$ Matched for age, BMI, VFA	BMI, VFA, SFA, SBP, DBP, TC, HDL C, TG, insulin, FBS, HOMA-IR	OSA (19) Non-OSA (4)	AHI was the predictor of the number of metabolic components in MS.

Table 2 *Continued*

Reference	Population	Metabolic parameters	MS (%)	Findings
McArdle *et al.*[75]	Clinic-based Case control Australia, men OSA, $n = 21$ Controls, $n = 21$ Matched for age, BMI, current smoking status	BMI, WC, SBP, DBP, insulin , FBS, TC, LDL C, HDL C, TG, IGF-1, leptin, TNF-α, Adiponectin, urine catecholamines	OSA (23) Controls (4)	OSA was associated with multiple cardiometabolic risk factors.
Parish *et al.*[57]	Clinic-based Retrospective review USA, men and women, $n = 228$ OSA, $n = 146$ Non-OSA, $n = 82$	MS, hypertension, hyperlipidaemia, diabetes.	OSA (60) Non-OSA (40)	MS was associated with OSA severity.
Tkacova *et al.*[64]	Clinic-based Slovakia, men and women, $n = 88$ AHI < 5, $n = 28$ AHI ≥ 5 to <30, $n = 39$ AHI ≥ 30, $n = 31$	BMI, WC, TC, TG, HDL C, LDL C, Apo-AI, Apo-B, FBS, SBP, DBP, MBP	AHI < 5 (46) AHI ≥ 5 to <30 (51) AHI ≥ 30 (77)	MS was associated with OSA severity, In severe OSA, OR 8.4 (95%CI: 2.5, 28) Mild to moderate OSA, OR 1.8 (95% CI: 0.6, 6)
Takama *et al.*[72]	Hospitalized in-patients with cardiovascular diseases, $n = 195$ MS, $n = 56$ Non-MS, $n = 139$	WC, BMI, SBP, DBP, FBS, TC, TG, HDL C, BNP.	OSA (77)	MS was a strong predictor of nocturnal desaturations <90% in patients with cardiovascular diseases.
Oktay *et al.*[59]	Clinic-based Turkey, men and women with OSA + MS, $n = 20$ Longitudinal study of 1 year CPAP treatment	WC, BMI, SBP, DBP, TC, HDL C, LDL C, TG, FBS.		The prevalence of MS was reduced by 45% after 1 year of CPAP treatment.
Drager *et al.*[60]	Clinic-based Brazil, men and women with MS, $n = 81$ OSA, $n = 51$ Non-OSA, $n = 30$	BMI, WC, SBP, DBP, FBS, TC, LDL C, HDL C, TG, IMT, PWV, CD	OSA (63)	OSA increased cardiovascular risk in patients with MS.
Nieto *et al.*[58]	Community-based USA, men and women, $n = 546$ OSA, $n = 253$ Non-OSA, $n = 293$	WC, BMI, SBP, DBP, inuslin, FBS, HOMA, TG, HDL C, urinary cortisol and adrenalin	OSA (32)	OSA is associated with the prevalence of MS, independent of sympathetic and neuroendocrine activation MS in mild OSA: OR 4.0 (95% CI: 2.6–6.3) MS in moderate /severe OSA: OR 5.3 (95% CI: 3.2–8.8)
Papanas *et al.*[65]	Clinic-based Greece, men, $n = 83$ OSA, $n = 53$ Non-OSA, $n = 30$	BMI, WC, SBP, DBP, FBS, TC, LDL C, HDL C, TG,	OSA (59)	OSA is associated with MS, elevated FBS level indicates a higher probability for the presence of OSA.

Akahoshi *et al.*[71]	Clinic-based Japan, men, $n = 416$ Mild OSA, $n = 32$ Moderate OSA, $n = 83$ Severe OSA, $n = 301$	BMI, WC, SBP, DBP, TC, TG, HDL C, FBS, HbA1C	Mild OSA (12.5%) Moderate OSA (39.8%) Severe OSA (60.1%)	MS was associated with OSA severity
Trombetta *et al.*[61]	Clinic-based Brazil, men and women MS + OSA, $n = 18$ MS − OSA, $n = 18$	WC, BMI, FBS, TG, HDL C, SBP, DBP, MBP, MSNA, BRS		Higher BP, increased sympathetic drive and diminished BRS in patients with MS + OSA.
Mota *et al.*[78]	Clinic-based Portugal, men with OSA, $n = 74$	BMI, WC, SBP, DBP, TC, LDL C, HDL C, TG, FBS	OSA (63.5%)	The prevalence of MS was reduced by 20% after 6 months of APAP treatment.
Barcelo *et al.*[66]	Clinic-based Spain, men and women, $n = 238$ OSA, $n = 119$ Non-OSA, $n = 119$	BMI, WC, SBP, DBP, FBS, TC, LDL C, HDL C, TG, uric acid, FFAs, 8-isoprostanes; CRP	OSA (38) Non-OSA (21)	The prevalence of MS was higher in patients with OSA than those without OSA. FFAs were elevated in OSA patients. FFAs were independently associated with OSA severity.
Zito *et al.*[67]	Clinic-based Italy, Spain, Grrece, $n = 336$, men and women with OSA, $n = 336$ Italy, $n = 87$ Greece, $n = 120$ Spain, $n = 129$	BMI, WC, SBP, DBP, TC, TG, FBS	OSA (67.3) Italy (50.6) Greece (76.7) Spain (69.8)	MS was associated with OSA in both Mediterranean and non-Mediterranean countries.
Gasa *et al.*[68]	Clinic-based, Spain, multicentres, $n = 159$ Morbidly obese men and women, BMI ≥ 35 OSA, $n = 115$ Non-OSA, $n = 44$	BMI, WC, SBP, DBP, TC, HDL C, TG, FBS, OGTT, HbA1C	OSA (70) Non-OSA (36)	MS was associated with OSA severity. MS: OR 2.8 (95% CI: 1.3–6.2).

Apo-AI, apolipoprotein AI; Apo-B, apolipoprotein B; BNP, brain natriuretic peptide; BRS, baroreceptor sensitivity; CD, carotid diameter; CI, confidence interval; DBP, diastolic blood pressure; FBS, fasting blood sugar; FFA, free fatty acid; HOMA-IR, homeostatsis model assessment for estimating insulin resistance; HS CRP, high-sensitivity CRP; IGF-1, insulin growth factor-1; IMT, carotid intima media thickness; LDL C, low-density lipoprotein cholesterol; MBP, mean blood pressure; MS, metabolic syndrome; MSNA, muscle sympathetic nerve activity; OR, odds ratio; PWV, pulse wave velocity; RCT, randomized controlled trial; SBP, systolic blood pressure; SFA, subcutaneous fat accumulation; TC, total cholesterol, HDL C, high-density lipoprotein cholesterol; TC/HDL, total cholesterol/ high-density lipoprotein cholesterol; TNF-α, tumour necrosis factor-α; VFA, visceral fat accumulation; WC, waist circumference.

oxidase activity is a major source of cellular ROS,[85] and IH was found to increase expression of several Nicotinamide adenine dinucleotide phosphate oxidase isoforms in cultured PC12 rat pheochromocytoma cells.[86]

IH and resultant oxidative stress have been proposed to be a pathogenetic pathway between OSA and disturbance of glucose homesostasis.[87] A study of 4398 community-dwelling Japanese followed up for a median of 3 years showed that those with moderate-severe nocturnal IH (3% oxygen saturation dips $\geq$ 15/h) on pulse oximetry at baseline had a 1.7-fold risk of incident DM compared with those without significant hypoxia, with a discernible dose-response relationship of incident DM with the desaturation index, after thorough adjustment for multiple confounders.[88] In the Cleveland Family study, measures of hypoxic stress (time spent with <90% O_2 saturation) was the strongest polysomnographic index associated with glucose intolerance.[89] On the other hand, several epidemiological studies have not supported an independent causal role of OSA in the development of glucose intolerance.[90,91]

In a human study, 13 healthy volunteers were subjected to 5 h of IH or normoxia during wakefulness in a randomized manner on two separate days. It demonstrated that glucose disposal was altered by decreasing insulin sensitivity and glucose effectiveness, based on the analysed data from intravenous glucose tolerance test. The decrease in insulin action was not accompanied by a commensurate increase in insulin secretion, and IH was associated with a shift in sympathovagal balance toward an increase in sympathetic nervous system activity. Thus, it can be speculated that IH is a central mechanism responsible for metabolic dysfunction in patients with OSA and that the sympathetic nervous system is a mediator.[92]

In leptin-deficient obese mice, repeated exposure to IH (30-s hypoxia alternating with 30-s normoxia for 12 h/day) for 12 weeks led to a time dependent increase in fasting insulin level and deterioration in glucose tolerance and insulin resistance.[93] In lean mice, exposure to IH with or without inhibiting the autonomic nervous system with hexamethonium, demonstrated that IH decreased whole-body insulin sensitivity and reduced glucose utilization in oxidative muscle fibres, with no change in the hepatic glucose output, suggesting that IH-induced insulin resistance was independent of autonomic activity.[94] In another study, using a chronically catheterized, unhandled mouse model, IH reversed the diurnal glucose rhythm and caused pancreatic β-cell replication.[95] These authors also found that simultaneous hypoxic stress and hyperglycaemia increased the apoptosis rate in pancreatic β-cells, which implied that decompensation may occur in the face of co-factors. Furthermore, a recent study found that plasma levels of nitrite/nitrate and thiobarbituric acid-reactive substances (a marker of oxidative stress) were significantly elevated in the IH-exposed hamsters with a decrease in insulin sensitivity compared with the control animals.[96] Another *in vitro* study of the effect of IH on beta cells showed that it led to increased beta-cell proliferation and cell death, and the cell death response appeared to be due to oxidative stress.[97]

In a mouse model of sleep apnoea, IH caused liver damage due to oxidative stress.[98] In addition, chronic IH induced hyperlipidaemia and lipid peroxidation in lean mice with elevated fasting serum levels of total cholesterol and low-density lipoprotein cholesterol,[99] resulting in liver injury characterized by NAFLD. The mechanism of IH-induced hypercholesterolaemia was due to the sterol regulatory element-binding protein 1 pathway.[100] Animal models of IH showed that IH could induce vascular inflammation, particularly in combination with a high cholesterol diet when it promoted pre-atherosclerotic remodelling or atherosclerotic plaque formation.[101–103]

Role of inflammation and cytokines

Inflammation has been proposed as a putative mechanism of cardiovascular disease in patients with OSA, and it may also impair insulin action in peripheral tissues. This might explain the associated increase in insulin resistance, dyslipidaemia and hypertension in OSA.[104] IH and sleep fragmentation in OSA are postulated to be triggers of the cascade of inflammation in adipose tissue and vascular compartment, and thus an array of inflammatory products may be released.[105] Many of these markers have documented inhibitory effects on insulin sensitivity in the liver and peripheral tissues and, in addition, pose deleterious effects on the cardiovascular system.[106]

Inflammatory cytokines, such as tumour necrosis factor-α and IL-6 were found to be elevated in subjects with OSA,[43] and these markers were positively correlated with excessive daytime sleepiness.[107] However, results have not been consistent and inadequate control for the confounding or possibly interacting effects of adiposity on these inflammatory markers remains a hurdle to the interpretation of results. In a recent study, lean mice exposed to IH led to elevation of tumour necrosis factor-α secretion by fat.[108] Other animal models, apart from IH exposure, have been used to address the question of whether OSA causes inflammation. In a rat model, recurrent obstructive apnoeas produced by occluding the airway (i.e. simultaneously subjecting rats to strenuous breathing and hypoxia/hypercapnia) led to a significant increase in various leucocyte-endothelial cell interactions such as leucocyte rolling and firm adhesion of leucocytes in comparison with a sham group.[109] By subjecting piglets acutely to a pattern of IH/hypercapnia by modifying the O_2 and CO_2 concentration of the air being breathed in, a transient increase in the inflammatory cytokine IL-6 was found.[110]

Because of the close association between inflammation and insulin resistance, it has been suggested that visceral obesity is a potential pathogenetic factor promoting inflammation and leading to insulin resistance and sleep apnoea.[107] Nuclear factor kappa B (NF-κB) is the transcription factor that is involved in inflammatory pathways that might be involved in

modulating insulin sensitivity.[111] Importantly, NF-κB is increased not only with OSA but also with obesity and MS, and it has major implications for activation of inflammatory pathways in OSA as it upregulates expression of adhesion molecules, inflammatory cytokines and adipokines, the downstream gene products of NF-κB.[112]

In a study using *in vitro* model of IH/reoxygenation in HeLa cells, the regulation of inflammatory and adaptive pathways on hypoxic stimulation was mapped.[113] HeLa cells exposed to IH demonstrated selective activation of the pro-inflammatory transcription factor NF-κB whereas the adaptive regulator hypoxia inducible factor-1 was not activated, suggesting that selective activation of inflammatory over adaptive pathways with IH might be an important molecular mechanism of cardiometabolic dysfunction in OSA. Activation of NF-κB and increased activity of downstream products of NF-κB activation has been confirmed in a mouse model of IH.[114] In contrast, it has been reported that IH increased hypoxia inducible factor-1α protein levels in PC12 and endothelial cell cultures due to oxidative stress.[85,115]

CRP is an inflammatory serum protein that is produced in adipose tissue and the liver.[116] Elevated levels correlated positively with worsening HOMA in a general population followed up for 5 years.[117] The association between OSA and elevated levels of CRP has been investigated in many studies with conflicting results, probably related to the confounding effects of obesity and presence of comorbidities.[118,119] Our group has demonstrated an independent association between severity of OSA and elevated CRP level in men free of comorbidities, after careful consideration of the confounding effect from visceral obesity measured by magnetic resonance imaging.[120] Nevertheless, two interventional studies showed different results,[121,122] and no change after CPAP treatment was found in the randomized controlled trial.[122]

In summary, the data for a causal role of OSA, independent of obesity, on expression of inflammatory markers in sleep apnoea subjects is still highly controversial.

Adipocyte-derived hormones/proteins

Many biomolecules produced by adipose tissues may affect glucose and lipid metabolism. They are thought to be pro-inflammatory, and could be involved in pathobiochemistry of cardiometabolic diseases.

Adiponectin

Adiponectin is a cytokine that is produced in white adipose tissues. A reduction in adiponectin contributes to insulin resistance in obesity. It is still not clear why adiponectin levels are decreased in obesity.[123] Serum levels of adiponectin correlate with insulin sensitivity, and it has anti-inflammatory and protective vascular effects.[48,124,125] Hypoadiponectinaemia has been demonstrated to be closely associated with endothelial dysfunction and cardiovascular morbidity in clinical studies.[126,127]

It has been postulated that OSA may downregulate adiponectin expression in adipose tissue. Studies on serum adiponectin levels in OSA have been controversial.[75,128,129] In a Japanese study of 200 male patients with cardiovascular diseases, hypoadiponectinaemia was significantly associated with visceral adiposity and insulin resistance but not with any of the sleep indices.[128] In another study of 68 subjects with no known comorbidity undergoing sleep studies, OSA subjects actually had a higher level of adiponectin compared with BMI-matched non-OSA subjects, but their blood samples were taken in a non-fasting state in the evening.[129] In a case-control study of 28 otherwise healthy subjects with moderate OSA, there was no difference in adiponectin levels between OSA and BMI-matched non-OSA subjects, though significant differences were seen in other metabolic parameters.[75] Our group found that serum adiponectin levels was suppressed in OSA and independently associated with sympathetic activity, and severity of sleep apnoea, suggesting that sympathetic activation is a pathway through which sleep disordered breathing may contribute to the determination of adiponectin levels.[130] This was supported by previous work that showed that adiponectin gene expression in preadipocyte cell lines was severely suppressed by the synthetic beta-adrenergic agonist, isoproterenol.[131] The use of CPAP treatment for 2 to 3 months has been reported to increase serum adiponectin levels significantly in OSA subjects in a few observational studies[132,133] but not in a randomized controlled study of diabetics with OSA.[134]

Recent data showed that IH led to suppression of adiponectin secretion by adipocytes *in vitro*.[135]

Leptin

Leptin is a hormone that is secreted by adipose tissue and its levels increase exponentially with increasing fat mass.[136] Most obese subjects have high serum leptin levels, indicating that obesity is a leptin resistant state.[137] The main role of leptin is to reduce appetite.[138]

Visceral obesity accounted for the increase in leptin levels in OSA in some studies,[75,139] whereas others reported that serum leptin levels were significantly higher in OSA subjects than in BMI-matched controls.[140–143] One study found that leptin levels correlated with cardiac sympathetic activity in OSA subjects.[144] OSA was shown to be associated with an increase in serum leptin levels, and the increase in leptin occurred in proportion to the severity of OSA.[138] These findings were related to endothelial dysfunction.[145,146] Thus, leptin may contribute to the pathogenesis of cardiovascular complications in OSA.

A few observational studies have shown a reduction of serum leptin levels after weeks or months of CPAP treatment[141,147] and in one of these studies, the impact was more pronounced in patients with a BMI <30.[148] However, the lack of a control group is a major

limitation due to potentially significant confounding effects from changes in body weight.

In a mouse model of OSA, the increase in insulin resistance in response to IH was dependent on the disruption of leptin pathways.[93]

Adipocyte-fatty acid-binding protein (A-FABP)

FABPs are a family of small intracellular lipid-binding proteins. A-FABP is abundantly present in adipocytes, and regulates intracellular fatty acid trafficking and glucose metabolism.[149] In animal experiments, the apparent functions of A-FABP were mediation of insulin resistance independent of the effects of obesity and the promotion of atherosclerosis.[150,151] A-FABP knockout mice were found to be partially protected from insulin resistance induced by dietary and genetic obesity.[152] Positive associations between serum A-FABP levels and adiposity, hyperglycaemia, insulin resistance, and the metabolic syndrome have been reported in cross-sectional and longitudinal studies.[153] In a recent large population-based genetic study, there was a reduced risk for hypertriglyceridaemia, type 2 diabetes and coronary artery disease in subjects who carried a functional genetic variant of the A-FABP gene that resulted in reduced adipose tissue A-FABP gene expression.[154]

In our previous study, A-FABP level was elevated in severe OSA subjects compared with non-OSA or less severe OSA subjects, and its level significantly correlated with insulin resistance.[155] These findings suggest that AFABP levels may be upregulated by severe OSA and may be one of the mediators that propagate metabolic dysfunction in sleep apnoea.

In support, our recent data found that IH led to upregulation of A-FABP and E-FABP expression in human aortic endothelial cells *in vitro*.[156]

CONCLUSIONS

OSA is associated with metabolic dysregulation in the complex human biological system. Intermittent hypoxemia and sleep fragmentation are postulated to trigger an array of downstream effects including sympathetic activation, neurohumeral changes, inflammation and oxidative stress, which are pathophysiological cascades common to the pathogenesis of cardiometabolic diseases. Obesity/visceral obesity are major risk factors for OSA, and are significant sources of inflammatory biomarkers, hormones and binding proteins that may play important roles in the pathogenesis of cardiometabolic complications at the molecular level. They may act in concert with OSA in the generation of metabolic aberrations. The majority of epidemiological and clinical studies have demonstrated independent associations of OSA with MS, but the evidence is not conclusive for the causality of the association. There is also experimental data in support of the occurrence of such pathways as a consequence of OSA, using *in vitro* or *in vivo* models of IH, and less commonly, sleep fragmentation. Prospective longitudinal cohort studies and interventional trials are needed to establish a definite direction of the relationship between OSA and MS or its components. However, in the human scenario, exogenous factors that have substantial influence on body metabolism can hardly be rigidly constant, and will always pose some confounding on the direction of effects in the relationship between OSA and metabolic dysfunction, including fat metabolism. A holistic approach with high index of suspicion of the concurrence of OSA and metabolic disorders is warranted, and a healthy diet and appropriate lifestyle modifications are no less important than CPAP treatment in the management of these individuals who may be suffering from OSA alone or all three conditions: OSA, obesity and metabolic syndrome.

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