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REVIEW

Adipose tissue in obesity and obstructive sleep apnoea

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ABSTRACT: A European Respiratory Society research seminar on ''Metabolic alterations in obstructive sleep apnoea (OSA)'' was jointly organised in October 2009 together with two EU COST actions (Cardiovascular risk in the obstructive sleep apnoea syndrome, action B26, and Adipose tissue and the metabolic syndrome, action BM0602) in order to discuss the interactions between obesity and OSA.

Such interactions can be particularly significant in the pathogenesis of metabolic abnormalities and in increased cardiovascular risk in OSA patients. However, studying the respective role of OSA and obesity is difficult in patients, making it necessary to refer to animal models or *in vitro* systems. Since most OSA patients are obese, their management requires a multidisciplinary approach.

This review summarises some aspects of the pathophysiology and treatment of obesity, and the possible effects of sleep loss on metabolism. OSA-associated metabolic dysfunction (insulin resistance, liver dysfunction and atherogenic dyslipidaemia) is discussed from the perspective of both obesity and OSA in adults and children.

Finally, the effects of treatment for obesity or OSA, or both, on cardio-metabolic variables are summarised. Further interdisciplinary research is needed in order to develop new comprehensive treatment approaches aimed at reducing sleep disordered breathing, obesity and cardiovascular risk.

KEYWORDS: Adipocyte, dyslipidaemia, hypoxia, liver dysfunction, obesity

The worldwide obesity epidemic has fostered investigation on adipose tissue, in order to prevent obesity-linked morbidity and develop effective treatment. Obesity is a risk factor for diabetes and cardiovascular events [1, 2] and increases mortality, especially in middle-aged adults [3]. Obesity rates are also increasing in children [4, 5]. Since obese children tend to become obese adults [6], the cardio-metabolic disease associated with obesity could begin in childhood [7].

Adipose tissue is a central player in metabolic regulation through the production and release of multiple adipokines [8]. Moreover, adipocytes and inflammatory cells, such as macrophages, show a high degree of interaction in obesity [9, 10]. The resulting picture is complex and, at present, incomplete. Recent research has explored new directions, such as the pathophysiology of different fat depots in the body [11], the role of hypoxia [12], and the interactions between adipose tissue and the central nervous system in response to nutrient excess [13]. Obesity has also been related to chronic sleep loss, typical of the current lifestyle in both adults and children [14, 15].

Obesity is a common finding and a major pathogenetic factor in obstructive sleep apnoea (OSA) in adults [16, 17] and children [18–20]. OSA is characterised by recurring episodes of upper airway obstruction during sleep [21], intermittent hypoxia [22], sleep fragmentation [23], excessive daytime sleepiness [21] and increased cardiovascular risk [24]. Upper airway collapse during sleep can be prevented by the application of nasal continuous positive airway pressure (CPAP), which is the treatment of choice for moderate-to-severe OSA in adults. In children, OSA is traditionally considered as a ''local'' disease due to high prevalence of adenotonsillar hypertrophy, and adenotosillectomy is usually performed; however, partial resolution of OSA is often observed, which probably reflects the additional impact of obesity [25, 26].

Changes in body weight are known to affect OSA severity [27–29]. Most adult patients with OSA

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have central obesity and increased visceral fat [30], the latter being associated with neck adiposity, increased upper airway fat [31] and metabolic abnormalities [32], even in normal weight subjects. Sex-related differences in the amount of visceral fat could contribute to the higher prevalence of OSA in males [33]. In children, besides the classic OSA phenotype associated with adenotonsillar hypertrophy [34] and growth failure [35], it is possible to identify an obese OSA phenotype, similar to adult OSA [34].

It is conceivable that OSA and obesity may interact and potentiate their detrimental consequences. OSA-associated metabolic abnormalities have been reproduced in animal models exposed to a pattern of intermittent hypoxia similar to that found in humans with sleep disordered breathing [36, 37]. However, hypoxia of adipocytes could play an important role in the metabolic disturbances associated with obesity [8, 38]. In addition, OSA and obesity share common mechanisms such as inflammatory activation [39], oxidative stress [39] and increased sympathetic activity [40].

In order to discuss the complex relationship between OSA and obesity, a second research seminar on the ''Metabolic effects of OSA'' was organised in October 2009 by the European Respiratory Society and two EU-funded actions of the COST programme (Cooperation in Scientific and Technological Research), namely COST actions B26 (Cardiovascular risk in the obstructive sleep apnoea syndrome) and BM0602 (Adipose tissue and the metabolic syndrome). The first research seminar took place in 2007, and its focus was primarily on the pathogenesis of insulin resistance (IR) in OSA [36].

The purpose of this review is to provide an overview on the pathophysiology of obesity, including an essential description of the main aspects of adipose tissue biology, the pathogenesis and the implications of IR in tissues such as skeletal muscle and liver, the possible role of sleep loss in obesity, and current treatment for obesity. With this background, the role played by OSA in the pathogenesis of metabolic abnormalities in adults and children will be briefly reviewed, together with the effects of OSA treatment. As for genetic interactions between OSA and obesity, which were also discussed during the seminar, the interested reader is referred to several recently published reviews [41–43].

ADIPOSE TISSUE PATHOPHYSIOLOGY, IR AND METABOLIC SYNDROME

The aim of this section is to discuss some features of obesity that are important in the context of OSA, namely the types and distribution of adipose tissue in obesity, and the mechanisms of adipocyte dysfunction.

Types and distribution of adipose tissue in obesity

Adipose tissue exerts important endocrine functions involving multiple crosstalk with other organs and tissues [44]. Adipocytes produce hormones, cytokines and many other proteins and peptides, collectively called ''adipokines'', leading to fine tuning of fuel utilisation, energy homeostasis and cardiovascular function [8, 45–47]. In addition, pre-adipocytes, lymphocytes, macrophages and endothelial cells contribute to the secretory output of adipose tissue and play a key role for the endocrine activity of the different fat depots.

Obesity is characterised by the expansion of white adipose tissue, as a result of increased size (hypertrophy), and, additionally, by an increased number of adipocytes (hyperplasia) [48]. The number and size of adipocytes vary according to localisation of fat [48], diet [49], genetic factors [50], sympathetic innervation [51] and sex [52]. Visceral adiposity is generally associated with hypertrophy of adipocytes [53]. A modest amount of brown adipose tissue (BAT) is also present in humans, its main function being heat production rather than energy storage. The peculiar anatomical and functional characteristics of BAT have been recently summarised [54–56].

The localisation of excess white adipose tissue in the body carries relevant metabolic consequences. Increased visceral fat mass is associated with more severe health effects compared to peripheral obesity, which is characterised by predominant accumulation of subcutaneous fat [57]. The expansion of visceral fat increases the risk of developing IR, type-II diabetes, atherosclerosis, OSA, steatohepatitis, and cardio- and cerebrovascular disease [3, 58, 59]. Many clinical and biochemical factors associated with increased cardiovascular risk (*i.e.* dyslipidaemia, arterial hypertension, hyperglycaemia, hyperuricaemia and microalbuminuria) are often present in visceral (or central) obesity. The term ''adiposopathy'' has been proposed to indicate the strong link between visceral fat and obesity-associated metabolic abnormalities [60].

Recent data highlight the role of fat localisation in modulating adipocyte function. Besides the classic distinction between visceral and subcutaneous fat, the latter can be subdivided into superficial and deep, with the deep fraction sharing many features with visceral fat [61]. Ectopic fat depots can be found in the epicardial, periadvential and perirenal regions, and in the pancreas, skeletal muscle and bone marrow [47]. The physiology of adipose tissue in these localisations, and the cellular source of adipokines and inflammatory mediators, are incompletely understood but could contribute to the pathogenesis of obesity-associated abnormalities [47]. Specifically, epicardial fat is a true visceral fat depot, and a tight association of epicardial fat mass with risk of cardiovascular disease has been recently reported [62].

Clinically, increased abdominal circumference is the best marker of visceral obesity and predicts overall mortality [3]. To improve the clinical recognition of central obesity, the metabolic syndrome (MetS) has been defined as the association of some risk factors (*i.e.* increased waist circumference, high blood pressure and dyslipidaemia) [59]. The widely used National Health and Nutrition Examination Survey/Adult Treatment Panel III definition is based on simple criteria [63], but its clinical or epidemiological usefulness is not entirely clear [64].

Identification of specific metabolic phenotypes may help to focus on high-risk patients. For example, ~20% of the obese population are metabolically healthy (MHO) [65]. The MHO phenotype is associated with early onset of obesity, predominance of subcutaneous over visceral fat, and a more favourable cardiovascular profile compared to patients with central obesity [66]. Adipose tissue in the gluteofemoral region may play an important protective role against metabolic abnormalities and the associated cardiovascular risk, by acting as a metabolic sink for excess fat storage [67, 68]. The MHO phenotype might be more common in obese pre-menopausal females, who appear relatively protected from cardio-metabolic risk [33] but show

increased mortality associated with the MetS in the post-menopausal period [69]. Conversely, normal-weight metabolically obese subjects show an apparently lean phenotype, but their amount of visceral fat is larger than normal and associated with IR [32, 65]. There are some uncertainties about definitions [70], and longitudinal studies on cardio-metabolic risk in obesity subtypes are still lacking.

The functional attitudes of visceral and subcutaneous adipocytes are programmed quite early during development and differentiation [71]. Adipocyte precursors are multi-potent cells that reside in each fat depot and possess depot-specific genetic, biochemical and metabolic features [72]. Metabolic activity is higher in visceral than in subcutaneous fat [11], and adipocytes located in the abdominal region display distinct features compared to adipocytes from other depots [73, 74] in both normal-weight and obese subjects. Visceral adipose tissue from non-obese humans responded faster and more intensely than subcutaneous adipose tissue to glucose or insulin exposure *in vitro*, with larger release of adiponectin, tumour necrosis factor (TNF)-α and leptin [11]. Visceral adipocytes from obese subjects released larger amounts of inflammatory cytokines, such as interleukin (IL)-1β, IL-6 and IL-8, and adipokines such as leptin, compared to visceral adipocytes from lean subjects [75]. Increased visceral fat and inflammation of adipose tissue were recently found in morbidly obese insulin-resistant subjects compared to weight-matched insulin-sensitive subjects, while the amount of subcutaneous fat was similar in the two groups [53]. Thus, a specific dysfunction of visceral adipocytes is considered as the pathophysiological basis for the negative consequences of abdominal obesity.

A thorough discussion of adipokines is beyond the scope of this paper, but can be found in several recent articles [8, 45–47, 76]. Leptin and adiponectin will be briefly discussed since they exert complex and unique actions, and have been studied in patients with OSA. For both adipokines, higher circulating levels are found in females than in males [76], indicating that sex-related fat distribution may affect their expression and release [67].

Leptin is a polypeptide hormone produced by adipocytes in proportion to their triglyceride content, and is a major player in appetite regulation in the hypothalamus. Subcutaneous fat is the main site of production of leptin, and leptin release from samples of subcutaneous fat cultured *in vitro* correlates with the circulating leptin levels found *in vivo* in the same individuals [76]. Human obesity is usually associated with high plasma leptin and attenuated leptin signalling (leptin resistance) [77], while defects in the leptin or leptin receptor genes are rare in clinical practice but have been fundamental to the understanding of the physiology of leptin in animal models [78]. Leptin might be involved in the pathogenesis of hypoventilation disorders [79] and its transcription is activated by exposure to continuous severe hypoxia *in vitro* [80]. In recent years, the role of leptin in immune function and inflammation has been increasingly studied [81], and some data indicate that leptin could contribute to the pathogenesis of atherosclerotic lesions by promoting inflammation [82]. All these data make leptin an interesting adipokine in the context of sleep disordered breathing.

Adiponectin exerts an insulin-sensitising action, and its levels are decreased in obesity [83–85]. Adiponectin has anti-atherogenic and anti-inflammatory properties, and its circulating levels are lower than normal in patients with type-II diabetes, MetS, hypertension and coronary artery disease [84]. Adiponectin is produced almost exclusively by mature adipocytes, and its expression is higher in subcutaneous than in visceral fat [86]. Importantly, adiponectin is found in the circulation in different oligomeric forms and it is now accepted that the so-called high-molecular-weight form is of key importance for the biological effects of this hormone [87]. Inflammatory mediators, such as TNF-α [88], and both continuous [89] and intermittent [90] hypoxia were found to inhibit adiponectin production *in vitro*. Adiponectin levels increase after weight loss or treatment with several drugs, such as fibrates, angiotensin-converting enzyme inhibitors, angiotensin II type I receptor blockers, thiazolidinediones, statin and some calcium channel blockers [91]. The protective role of adiponectin and its modulation by hypoxia suggest that it may be a useful marker of metabolic dysfunction in obesity and OSA.

Mechanisms of adipose tissue dysfunction in obesity

Inflammation

The recognition of inflammation as a major player in adipocyte dysfunction has been an important advance in obesity research. Inflammation was first reported to contribute to the pathogenesis of IR in 1993, when TNF-α expression was demonstrated in adipose tissue of obese rodents and insulin sensitivity was restored after treatment with anti-TNF-α antibodies [92]. There is a long list of inflammatory mediators involved in obesity and IR [93], and obesity is considered as a state of chronic, low-grade inflammation [9]. As obesity develops, adipose tissue becomes infiltrated with macrophages [94]. Adipocyte–macrophage interactions contribute to the development of IR, but other immune cells, such as mast cells or lymphocytes, probably play a role [10, 95].

The adipocyte can secrete inflammatory cytokines and attract monocytes by producing monocyte chemoattractant protein (MCP)-1 [94]. *In vitro*, adipocytes and macrophages show considerable similarities in their gene expression and functional aspects [10]. Both hypoxia [96] and decreased adiponectin [97] may play a role in macrophage activation in obesity. In obese animals, macrophages are found in close relationship with dead adipocytes (crown-like structures) [98], suggesting that their recruitment is linked to phagocytosis of cellular debris. In addition, a shift from an anti- to a pro-inflammatory phenotype in adipose tissue macrophages has been demonstrated in both murine [99] and human [100] obesity. In obese subjects, adipose tissue macrophages show increased expression of TNF-α and inducible nitric oxide synthase, according to the classic pro-inflammatory activation pattern (M1). Conversely, in lean subjects, adipose tissue macrophages predominantly show the alternative pattern of activation (M2) characterised by over-expression, among other molecules, of the anti-inflammatory cytokine IL-10 [99].

Although inflammation contributes to the development of IR and MetS [9, 93], the sequence of events leading to the inflammatory response in the adipose tissue is incompletely defined. An increased adipocyte size may be an important signal, through dysregulation of insulin signalling at the level of insulin receptor substrates (IRS). Phosphorylation of IRS-1, an early event in insulin signalling [101], is decreased in large adipocytes [102]. Adipocyte size in visceral fat correlated with IR in severely obese

patients, and a smaller adipocyte size was found in MHO patients compared to patients with the classic visceral obesity phenotype [103]. Adipocyte size also correlated with proliferation of adipose tissue-derived progenitor cells [104].

Activation of the nuclear factor-κB pathway further interferes with IRS-1 phosphorylation [10]. Nutrient excess causes endoplasmic reticulum (ER) stress, characterised by a complex disturbance in protein synthesis, in the adipocyte [105]. The pathways of inflammation and ER stress appear to intersect at some crucial points, involving the protein kinases JNK1 and IKKβ [95]. Finally, mitochondrial dysfunction was also demonstrated in adipocytes exposed to hyperglycaemia [106]. Therefore, inflammation impacts on several cellular pathways, deeply disturbing adipocyte function.

Hypoxia

Expansion of adipose tissue causes oxygen deprivation in large adipocytes as their distance from the vasculature increases [12, 107]. *In vitro* exposure of human and murine adipocytes to prolonged hypoxia decreased phosphorylation of IRS-1 and IRS-2 and caused IR [108, 109]. Hypoxia in adipose tissue has been documented in obese humans [110–112] and mice [113, 114]. In adipocytes in culture, continuous hypoxia stimulated the expression and secretion of several inflammation-related adipokines, including IL-6, leptin, angiopoietin-like protein-4 and vascular endothelial growth factor [113–115]. Continuous hypoxia inhibited the production of adiponectin [89], while intermittent hypoxia (12 cycles per h for 6 h per day) was recently found to inhibit adiponectin secretion while upregulating its expression in adipocytes [90].

Many effects of hypoxia are mediated by the hypoxia-inducible factor (HIF)-1, a transcription factor resulting from the dimerisation of an α-subunit, which is continuously degraded in the cytoplasm under normoxic conditions, and a β-subunit constitutively expressed by the cell [116]. When the oxygen level decreases, degradation of HIF-1α is inhibited and its cytoplasmic level increases, making dimerisation of HIF, its translocation to the nucleus and the subsequent activation of transcription of several hypoxia-responsive genes all possible [116].

Exposure to continuous hypoxia causes multiple adjustments in cell metabolism, including a switch to anaerobic glycolysis. In adipocytes, continuous hypoxia increased the expression and protein level of the glucose transporter GLUT-1 [117], glucose uptake and release of lactate [118, 119], but decreased the expression of the insulin-dependent glucose transporter GLUT-4 [119]. Among the genes upregulated by hypoxia, expression of metallothionein-3 increased 600-fold, suggesting a role possibly linked to its antioxidant properties [120]. Thus, *in vitro* data indicate that HIF-1α activation may directly cause IR in adipocytes [108]. However, a recent study in mice with defective expression of HIF-1α in adipose tissue found that these animals became more obese and insulin resistant when exposed to a high-fat diet compared to wild-type mice [121]. Decreased energy expenditure associated with dysfunction of BAT appeared more important than IR in this *in vivo* model [121]. Therefore, further studies are needed to assess the role of hypoxia on brown and white adipose tissue in animal models and humans.

Recent measurements of tissue partial pressure of oxygen (P_{O_2}) in lean rats during intermittent hypoxia or obstructive apnoea cycles of comparable duration, showed that tissue P_{O_2} oscillations were blunted in visceral adipose tissue [122], suggesting the possibility that changes in blood flow to adipose tissue might also occur in this model. More data are needed to better understand the effects of intermittent hypoxia on adipose tissue in order to assess whether specific alterations are responsible for the metabolic consequences of OSA.

The lipoxygenase pathway and oxidative stress

Besides hypoxia, other pathways may contribute to adipocyte dysfunction in obesity. Adipose tissue from high calorie-fed obese mice showed increased expression of lipoxygenases [123], whose products could promote recruitment and activation of macrophages to and within adipose tissue [124]. Knock-out mice for the 12-lipoxygenase gene on a high-calorie diet showed normal TNF-α, IL-6 and adiponectin release; in addition, MCP-1 concentration and the number of macrophages in adipose tissue were normal [123].

Oxidative stress could also play a role. 12-Hydroxyeicosatetraenoic acid (12-HETE) directly controls the increased expression of MCP-1 in macrophages [125], and peroxidation products of HETEs may act as signalling molecules in adipocytes. For instance, 4-hydroxynonenal (4-HNE) exerts pro-inflammatory effects [126], but is normally neutralised by the enzyme glutathione-*S*-transferase (GST). Mice with a disrupted GST gene gained more weight and accumulated more visceral fat in comparison with control mice, and showed high levels of 4-HNE in tissues [127].

To summarise this section, adipocyte dysfunction in obesity shows both metabolic and pro-inflammatory effects, probably reflecting disturbance of different cellular pathways. Even though knowledge of adipocyte biology has expanded greatly, the many facets of human obesity deserve further investigation. The emerging role of hypoxia and oxidative stress in the pathophysiology of obesity suggest possible interactions with OSA, in particular the activation of mechanisms common to both diseases.

IR AND METS IN OSA

Increasing severity of OSA in adults is associated with IR and the MetS [36, 37, 128], suggesting a link between OSA, metabolic abnormalities and cardiovascular morbidity and mortality [24, 129–133]. However, the independent role of OSA is still unclear, due to the difficulty in separating the effects of obesity and sleep disordered breathing in human studies.

Characterisation of non-obese adult OSA patients is extremely poor as far as metabolic abnormalities are concerned. No MetS component was found in ~10% of OSA patients referred for a sleep study; these patients were younger and showed mild-to-moderate OSA compared to all other patients [134]. Absence of metabolic abnormalities might characterise an early stage in the natural history of OSA; alternatively, non-obese OSA patients could represent a distinct phenotype, as proposed for paediatric OSA [34].

However, increased visceral fat may also be a critical factor in non-obese OSA patients, who show increased fat deposition in the abdomen and neck compared to controls [135]. In a Japanese study, neck circumference normalised for height correlated with severity of OSA independent of visceral obesity, especially in

non-obese subjects [136]. Finally, two studies in the general population recently reported that neck circumference is an independent predictor of cardio-metabolic risk [137] and of both MetS and OSA [138], but sleep studies were not performed in either study.

Clearly, the role of neck fat deposition, which has been extensively studied in the past for its relationship to upper airway dimensions and function, deserves further attention with regard to metabolic problems in OSA. Non-obese OSA patients appear strikingly similar to the phenotype of metabolically obese normal weight subjects [65]. However, to date, no study has assessed cardiovascular risk or outcomes specifically in non-obese OSA patients.

While the association of OSA with increased visceral fat has been known for a long time, the impact of increased subcutaneous fat on OSA and metabolic variables is much less clear. A recent epidemiological study reported that visceral and subcutaneous fat are associated with IR with different strength [139], indicating that more work is needed in this field as clinical cardiovascular outcomes are concerned.

This section briefly discusses some results of human and animal studies on the effects of intermittent hypoxia and OSA on IR and the MetS.

Clinical studies on metabolic abnormalities in OSA

Clinical and epidemiological studies have shown a progressive worsening of IR or MetS with OSA severity [140–143], even in severe obesity [144], suggesting a causal role of OSA in metabolic derangements. In addition, there is evidence that IR develops during acute exposure to intermittent hypoxia in healthy humans [145]. For further information, the reader is referred to recent reviews on the complex relationship between OSA, glucose metabolism, IR and diabetes [37, 128, 146–151].

The main finding against a role of OSA in altered glucose metabolism is that IR did not improve after CPAP treatment in many studies (see later section). At least part of the variability in results may be accounted for by the sensitivity of methods to detect IR, especially if one considers the peculiar condition of OSA patients who develop respiratory events only at night. For example, acute CPAP application in diabetic patients was found to decrease glucose level variability, as assessed by continuous glucose monitoring [152, 153]. Similarly, glycosylated haemoglobin (HbA1c) could be a sensitive marker of altered glucose metabolism in OSA in patients with [154] or without diabetes [155], or with the MetS [156].

Both leptin and adiponectin have been studied in clinical OSA. Several studies have reported that OSA patients show increased leptin levels compared to body mass index (BMI)-matched controls [157–159]. Some studies found that apnoea/hypopnoea index (AHI) or severity of nocturnal hypoxaemia were independent predictors of plasma leptin concentration [160, 161], while others only confirmed the known association of leptin with obesity but no independent effect of OSA [162–165]. Most studies examined male OSA patients, and sex-related differences are still unknown.

Adiponectin, a metabolically protective adipokine, was found to be decreased in OSA patients compared to controls in proportion to the severity of nocturnal hypoxaemia [166–168], suggesting a possible pathophysiological role of oxidative stress in decreased adiponectin levels in OSA. Other studies, however, reported a closer relationship of low adiponectin levels with obesity than with OSA [165, 169]. A recent study found that, while daytime adiponectin levels correlated with several measures of obesity, the nocturnal fall in circulating adiponectin in OSA patients correlated only with the waist-to-hip ratio, suggesting that adipose tissue distribution may modulate nocturnal adiponectin levels [170].

Case–control studies conducted in MetS patients have provided other pieces of evidence on the effects of OSA on cardio-metabolic variables. Compared to patients with MetS but no OSA, patients with MetS and OSA showed: 1) more severe vascular dysfunction [171]; 2) independent associations of OSA with triglyceride and glucose levels, C-reactive protein, uric acid and increased total/high-density lipoprotein (HDL) cholesterol ratio [143]; and 3) higher blood pressure and more severe autonomic dysfunction [172]. Similarly, in hypertensive patients, metabolic abnormalities were the strongest predictors of OSA [173]. It has been proposed that OSA should be considered an additional component of MetS [147, 174]. Recent findings in patients with MetS suggest that OSA may contribute to worse metabolic abnormalities or could represent a marker of MetS severity [143, 171, 172].

Excessive daytime sleepiness (EDS) is a major symptom of OSA, and could be a marker of OSA severity. Two case–control studies reported that EDS predicts IR in OSA patients [175, 176]; only sleepy patients showed improved insulin sensitivity after CPAP treatment for 3 months [175]. EDS in OSA patients was also found to be associated with type-II diabetes [177]. Other studies, however, did not confirm the association of subjective EDS and a worse metabolic profile in MetS patients [143], in morbidly obese patients [142] or in unselected consecutive OSA patients [134]. Therefore, the significance of EDS as a marker of metabolic abnormalities remains to be ascertained and is the focus of current clinical research.

The intermittent hypoxia mouse model

To better dissect the mechanisms by which OSA may affect metabolism, a mouse model of intermittent hypoxia has been developed which reproduces some of the effects of human OSA [178]. The main advantage is the possibility to study the response to intermittent hypoxia in lean and fat animals in several tissues by mimicking the intermittent hypoxia pattern that occurs during sleep in humans with OSA. The model also has some disadvantages, such as absence of intermittent hypercapnia [122] and occurrence of sleep disruption, characterised by a deficit in rapid eye movement sleep and decreased delta power during non-rapid eye movement sleep [179]. To overcome these limitations, a model of OSA in rats was recently developed [180] but, to date, has been used only in short-term studies.

In lean mice, acute intermittent hypoxia caused IR [181], but intermittent hypoxia for several days did not [182], possibly because prolonged exposure to intermittent hypoxia was associated with failure to gain weight, which exerted positive effects on insulin sensitivity. In contrast, in mice with genetic or diet-induced obesity, chronic intermittent hypoxia worsened IR [182].

There is no evidence that intermittent hypoxia impairs pancreatic β-cell function, although β-cell proliferation and apoptosis

occurred in mice exposed to intermittent hypoxia [183, 184]. IR during intermittent hypoxia can be mediated *via* multiple pathways [178]. Among them, activity of the sympathetic nervous system did not appear to play a major role in the effects of acute intermittent hypoxia in lean mice [181]. Acute intermittent hypoxia increased corticosterone release, which could have contributed to IR [181]. The metabolic effects of intermittent hypoxia were larger in obese compared to lean animals, suggesting that isolated intermittent hypoxia may be insufficient to cause significant damage. The results of such experimental studies suggest the hypothesis that OSA could worsen metabolism in obese subjects, while its effects might be limited in non-obese subjects, as recently found in a randomised controlled trial on the effects of CPAP on IR [185]. However, a previous study had reported different results, *i.e.* insulin sensitivity improved more in non-obese than in obese OSA subjects after CPAP treatment [186]. Therefore, the clinical impact of OSA and its treatment on IR requires further evaluation, especially in lean patients.

To summarise, studies in both OSA patients and animal models indicate that OSA probably contributes to IR, even though its effect may be relatively minor compared to the effect of obesity. However, it should be underlined that human OSA is a multiple component disease, including intermittent hypoxia and sleep fragmentation. The respective contribution of respiratory and polysomnographic parameters to metabolic variables in OSA patients is also a clinically important issue, but could not be addressed in this review.

ECTOPIC FAT AND DYSLIPIDAEMIA

The metabolic abnormalities of adipocytes in obesity are further amplified by ectopic fat deposition [44]. As storage capacity of adipose tissue is overwhelmed, decreased insulin action in adipose tissue increases lipolysis and release of free fatty acids (FFA) into the circulation, and IR develops in peripheral tissues (the ''lipotoxicity'' picture) [187–191]. The main targets of FFA in this ''overflow hypothesis'' [44] are skeletal muscle and the liver (fig. 1).

Obesity increases the amount of perivascular adipose tissue. Previously considered to mainly exert a mechanical support function, perivascular fat has recently been shown to normally exert a vasorelaxant action [192]. Obesity and the associated IR appear to blunt the physiological effect of perivascular fat, causing vascular dysfunction in obese animals [193] and humans [194], with obvious implications for the pathogenesis of cardiovascular disease associated with obesity.

The possibility that ectopic fat deposition may affect pancreatic exocrine function has been recently explored. Pancreatic fat deposition was found in mice fed a high-fat diet and in pathology specimens from patients with type-II diabetes, in the form of adipocyte infiltration and modified lipid content of pancreatic exocrine tissue [195]. In obese subjects, pancreatic fat deposition

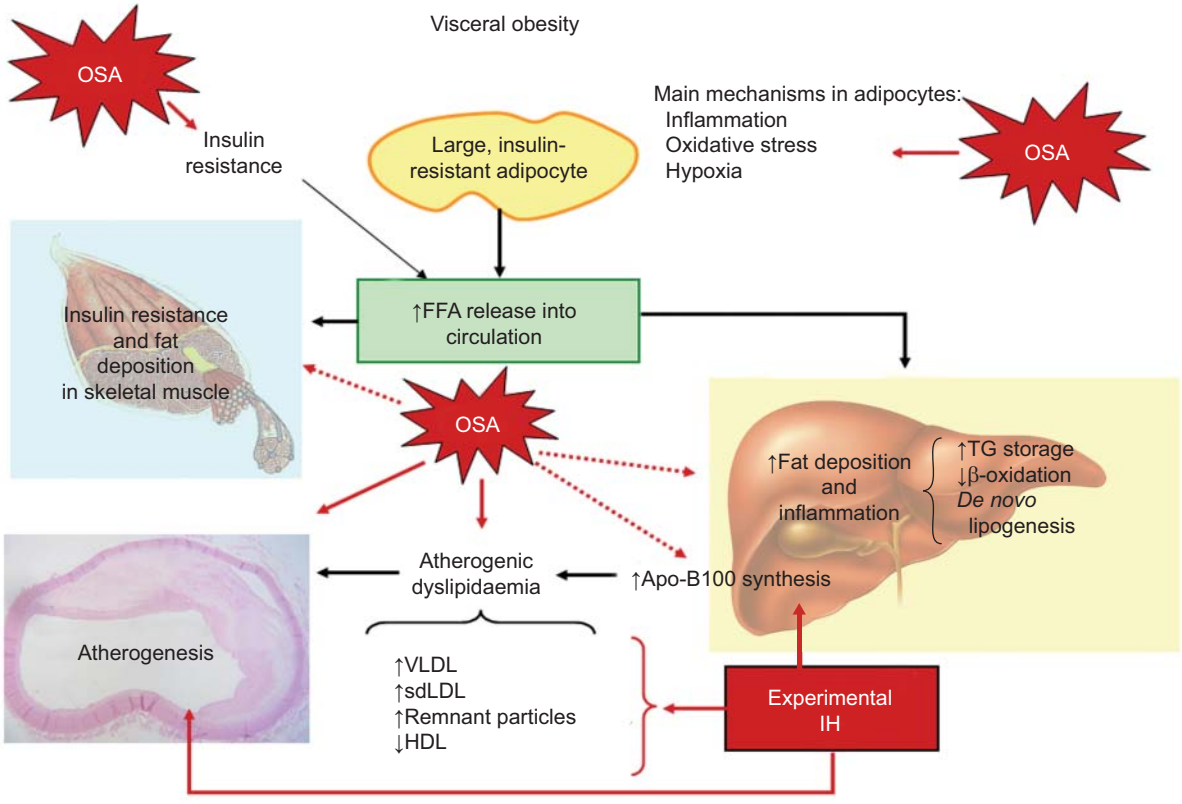

FIGURE 1. Schematic diagram summarising the functional consequences of visceral obesity in adipocytes, skeletal muscle, the liver and the vessel wall. The effects of obstructive sleep apnoea (OSA) or intermittent hypoxia (IH) on the same variables are also summarised. TG: triglyceride; FFA: free fatty acid; Apo-B100: apolioprotein B100; VLDL: very low-density lipoproteins; sdLDL: small dense low-density lipoproteins; HDL: high-density lipoprotein. For further details, refer to the text.

increased with increasing visceral fat in males [196] but, besides its association with IR, no clear effect of β-cell function could be demonstrated [197]. Therefore, the pancreas might also be a target in visceral obesity, but more studies are needed to verify the clinical importance of pancreatic fat accumulation on exocrine and endocrine function.

Information on the effects of obesity, OSA and experimental intermittent hypoxia on muscle and liver metabolism is summarised in the following sections.

Skeletal muscle adipose tissue in obesity and OSA

Obese subjects show increased intra- and intercellular fat deposition in skeletal muscle [190, 198]. By releasing endocrine and metabolic mediators (including TNF-α, IL-6, leptin and adiponectin), adipose tissue crosstalks with skeletal muscle, a process that precedes and underlies the development of muscle IR [190]. IR in skeletal muscle is strongly linked to elevated adipose tissue mass [189, 190].

IR in skeletal muscle was initially hypothesised to be secondary to the increased availability of FFA, with subsequent activation of fat oxidation and inhibition of glucose utilisation. This hypothesis predicted intracellular accumulation of glucose-6-phosphate (G6P), due to inhibition of the early steps of glycolysis. However, exposure to FFA was shown to decrease, not increase, intracellular G6P concentration. Therefore, similar to what happens in adipose tissue, impaired insulin-dependent glucose transport plays a major role in skeletal muscle IR [199]. Macrophage infiltration of adipose tissue interspersed between myofibres occurs in obesity [190], and inflammation also exerts negative effects in skeletal muscle [200]. A thorough description of muscle IR is beyond the purpose of this review, but has been given elsewhere [190, 199].

There are no studies on IR in skeletal muscle in OSA patients, but one study in mice subjected to intermittent hypoxia for 9 h found that glucose utilisation decreased and IR increased in oxidative (soleus) but not in glycolytic (vastus) muscles [181]. Some studies have reported a low exercise capacity in OSA patients, suggesting that OSA may impact on muscle metabolism [201].

Hepatic steatosis and non-alcoholic fatty liver disease

Obesity

Obesity causes intracellular accumulation of lipids in the liver [188, 202], leading to hepatic steatosis which is pathologically defined as presence of fat in >5% of hepatocytes. Activation of macrophage-like Kupffer cells in the liver is also common in obesity [203].

Hepatic steatosis is the first step of non-alcoholic fatty liver disease (NAFLD), which includes a spectrum of pathological conditions: steatosis without inflammation; non-alcoholic steatohepatitis (NASH) and liver fibrosis [204–207]. NAFLD increases the risk of developing cryptogenic cirrhosis and hepatocarcinoma [208]. NAFLD is common in obese adults [202, 205, 209–212] and children [213], and is considered as the hepatic manifestation of MetS. NAFLD could develop in steps, with IR and obesity acting as the ''first hit'' and causing hepatic steatosis [206, 207], and oxidative stress, lipid peroxidation and inflammation probably implicated in the ''second hit'' [206–208]. Although skeletal muscle is of major importance for insulin-regulated glucose disposal, liver IR will lead to enhanced hepatic glucose production, which may significantly contribute to impaired glucose tolerance and/or hyperglycaemia.

Different mechanisms have been proposed to explain the pathogenesis of NAFDL in obesity [214]. The main view considers hepatic accumulation of fat as a consequence of obesity and IR [199]. Conversely, other studies suggested that fat accumulation in the liver may cause IR independent of visceral fat [215, 216]. Finally, accumulation of triglycerides in the liver may not be detrimental *per se*, and could actually exert a protective role by limiting the accumulation of FFA [217].

According to the main view, the liver in obesity is loaded with excess FFA from dietary sources, adipose tissue and *de novo* synthesis of lipids [202, 218]. Release of FFA from the adipose tissue accounts for a large proportion of liver fat [218], and is favoured by IR at the adipocyte level, as insulin normally promotes lipid storage and inhibits lipolysis and FFA release by adipocytes [219]. While FFA uptake in the liver is increased [215], their β-oxidation is impaired [202, 220]. Moreover, hyperglycaemia and hyperinsulinaemia enhance *de novo* lipogenesis in the liver [214]. Therefore, in very simplified terms, liver steatosis in obesity results from disturbance in several steps of FFA/lipid handling.

The cause of the transition from steatosis to steatohepatitis is not completely defined. Inflammation is a major culprit [188, 214], since liver Kupffer cells could play a role similar to that of macrophages in adipose tissue [100]. Indeed, depletion of Kupffer cells in an animal model prevented the development of IR and lipid accumulation in the liver [203].

Obstructive sleep apnoea

The link between altered metabolism and inflammation in obesity may be amplified in OSA [221]. Increased circulating FFA have been recently reported in patients with OSA without MetS compared to sex-, age- and BMI-matched controls [222] and in patients with chronic heart failure and OSA during sleep [223], suggesting an effect of OSA on lipid metabolism independent of concurrent obesity.

The association of OSA and fatty liver has been recently reviewed [224]. Approximately 50% of patients with NAFLD refer symptoms of OSA [225], and some case reports suggest that severe OSA may lead to liver injury [226–228]. Noninvasive imaging techniques, such as ultrasound or computed tomography scans, do not currently help to distinguish between simple steatosis and NASH [229–231]. Since liver enzymes are neither sensitive nor specific predictors of NAFLD-related liver damage [208, 209], data on NAFLD have mostly been obtained by liver biopsy in obese patients undergoing bariatric surgery [208, 232].

In morbidly obese subjects, the degree of pathological liver abnormalities and/or enzymes increased with OSA severity in some [233–236] but not all studies [237, 238]. Table 1 summarises the main studies on liver function in OSA patients. In subjects with OSA and elevated liver enzymes in the absence of any known liver disease, an AHI >50 was associated with more severe hepatic steatosis, necrosis and fibrosis compared to patients with an AHI ⩽50, despite similar degree of obesity [239]. Other studies reported an association of intermittent hypoxia during sleep with NASH and liver fibrosis [233, 235, 240] or high serum aminotransferase levels [241]. Severity of

TABLE 1 Studies on liver dysfunction, obesity and obstructive sleep apnoea (OSA)

First author [ref.]	Patients	Methods	OSA	Results
SINGH [225]	190 NAFLD patients	AST/ALT, liver biopsy, modified Berlin Questionnaire	46% of the sample reported symptoms of OSA	No difference in liver damage between patients with and without OSA
JOUËT [237]	62 morbidly obese (54 females)	AST/ALT, liver biopsy	OSA in 84.7% of the sample	Male sex and OSA increased the risk for increased AST/ALT NASH and fibrosis not different between OSA and non-OSA
KALLWITZ [234]	85 morbidly obese (61 females)	AST/ALT, liver biopsy	AHI $\geqslant$15 in 51% of the sample	Increased ALT in OSA patients; OSA tended to be associated with progressive liver disease
MISHRA [235]	101 morbidly obese	AST/ALT, liver biopsy	OSA in 83.5% of NASH positive and 72.7% of NASH negative patients (NS)	Higher liver enzymes and OSA severity in NASH positive compared to NASH negative patients
CAMPOS [236]	200 morbidly obese (168 females)	Liver biopsy	OSA diagnosed in 13.5% of the sample	OSA increased the risk of NASH (OR 4.0, 95% CI 1.3–12.2)
POLOTSKY [233]	90 morbidly obese (75 females)	AST/ALT, liver biopsy	RDI >5 in 81.1% of the sample; RDI 15±29	NASH in patients with severe O_2 desaturation during sleep
DALTRO [238]	40 morbidly obese (26 females)	AST/ALT, liver biopsy	AHI >5 in 80% of the sample; median AHI 11 (6–30)	No significant association between OSA and liver enzymes or NASH
TANNÉ [239]	163 suspected OSA	AST/ALT, liver biopsy	Moderate to severe OSA in 79% of the sample	Liver enzymes associated with BMI and OSA (OR 5.9, 95% CI 1.2–29.2) NASH more severe in patients with AHI >50, but insulin resistance was a stronger factor
TATSUMI [240]	83 OSA, 41 controls	Serum type III pro-collagen (latent NASH), CT liver/spleen ratio	Mean AHI 32.5	Non-obese patients (mean BMI 25.6 $kg \cdot m^{-2}$) Correlation between serum type III pro-collagen (marker of fibrosis) and O_2 desaturation during sleep Hepatic steatosis unaffected by OSA
NORMAN [241]	109 OSA	AST/ALT	Mean AHI 53	AST/ALT correlated with nocturnal hypoxaemia
CHIN [242]	40 obese OSA	AST/ALT	Mean AHI 57	Increase in AST/ALT from evening to morning in untreated patients, blunted by acute and prolonged CPAP treatment
KOHLER [243]	94 OSA	AST/ALT	Mean ODI 42.4	Randomised controlled trial Decrease in AST after both therapeutic and subtherapeutic CPAP
KHEIRANDISH-GOZAL [244]	518 snoring children, 142 overweight/obese	AST/ALT	OSA in 66.2% of the sample	Increased liver enzymes (>40 $U \cdot L^{-1}$) in obese OSA children, associated with insulin resistance and hyperlipidaemia Improvement after treatment
VERHULST [245]	75 children and adolescents	AST/ALT	OSA in 44% of the sample	Increased liver enzymes associated with RDI and hypoxaemia during sleep

NAFLD: non-alcoholic fatty liver disease; AST: aspartate aminotransferase; ALT: alanine aminotransferase; NASH: non-alcoholic statohepatitis; NS: nonsignificant; RDI: respiratory disturbance index; AHI: apnoea/hypopnoea index; BMI: body mass index; CT: computed tomography; CPAP: continuous positive airway pressure; ODI: oxygen desaturation index.

nocturnal hypoxaemia also correlated with markers of liver dysfunction in non-obese OSA patients [240]. In children, OSA was associated with elevated liver enzyme levels [244, 245], which normalised after adenotonsillectomy [244]. Therefore, some clinical data support the possibility that OSA may worsen liver function.

Intermittent hypoxia in animal models

In mice fed a high-calorie diet, intermittent hypoxia converted hepatic steatosis to steatohepatitis and liver fibrosis, and caused oxidative stress in the liver by upregulating an important enzyme of oxidative stress, NADPH oxidase [246]. Similarly, exposure of rats to chemically induced hypoxaemia enhanced the development of NASH induced by high-fat diet [247]. In lean mice on regular chow diet, exposure to intermittent hypoxia for 12 weeks caused only minor liver injury [248]. These data suggest that intermittent hypoxia alone is insufficient to cause steatohepatitis but could amplify the damage caused by obesity.

Dyslipidaemia in obesity and OSA

Obesity, MetS and type-II diabetes are characterised by a specific pattern of plasma lipids, called atherogenic dyslipidaemia [249], which is a powerful cardiovascular risk factor [250–252]. Atherogenic dyslipidaemia is also common in OSA, and a role

for OSA in worsening dyslipidaemia is suggested by several experimental and clinical studies.

Obesity

The hallmarks of atherogenic dyslipidaemia associated with obesity and type-II diabetes are: high fasting levels of triglycerides, total cholesterol, and cholesterol associated with very low- and low-density lipoproteins (VLDL and LDL, respectively), and low HDL cholesterol [250]. The liver plays a central role in lipoprotein metabolism [253–255]. Briefly, synthesis, modification and clearance of lipoproteins are complex processes, modulated by insulin at several steps. A major feature of obesity is the overproduction of VLDL, due to increased release of FFA by visceral adipose tissue [254].

Apolipoprotein (Apo)-B is an essential constituent of atherogenic particles, and its plasma level is increasingly used as a clinical marker of atherogenesis [255, 256]. The size of lipoproteins is a crucial determinant of their atherogenetic potential, since small particles remain trapped in the subintimal vascular layer, where they initiate and sustain plaque formation. While the role played by small dense LDL in atherogenesis has been known for a long time [257], recent research has examined the risk linked to remnant lipoproteins, derived from metabolism of triglyceride-rich lipoproteins (TRLs) [258].

Obesity is also characterised by low levels of HDL cholesterol, which is considered to exert protective cardiovascular effects. Decreased HDL is, in part, secondary to an exchange of cholesterol triglycerides between HDL and TRL particles, which occurs when TRL levels increase [254]. Hepatic and endothelial lipases have also been shown to modulate HDL levels in obesity [254].

Obstructive sleep apnoea

The association between OSA and dyslipidaemia has been explored in several studies. In a large community-based sample (the Sleep Heart Health Study), OSA severity correlated with fasting total cholesterol levels independent of BMI [259]. In elderly subjects, OSA was associated with low HDL cholesterol levels independent of age and BMI [260].

In a case–control study, patients with OSA had higher total and LDL cholesterol levels compared to controls matched for age, BMI and smoking status [261]. Increased Apo-B levels have been found in adult [262] and paediatric [263] OSA patients, and Apo-B decreased after effective OSA treatment [262–264].

OSA patients show decreased levels of lipoprotein lipase [265] and pro-atherogenic dyslipidaemia [142, 266–268]. Severity of nocturnal hypoxaemia predicted increased liver levels of stearoyl coenzyme A desaturase (SCD-1), an enzyme involved in triglyceride biosynthesis and lipopotein secretion, in obese OSA patients [233]. In contrast, other studies found similar plasma lipids in patients with OSA and controls [171, 269–271]. HDL dysfunction has also been found in OSA [270]. Therefore, OSA appears to be associated with dyslipidaemia, but data are still insufficient to confirm a causal relationship.

Intermittent hypoxia in animal models

In lean mice, chronic intermittent hypoxia increased serum total cholesterol, triglycerides, VLDL cholesterol, LDL cholesterol and lipid liver content [272–274] proportionally to the severity of the hypoxic stimulus [274]. In obese *ob/ob* mice, chronic intermittent hypoxia exacerbated dyslipidaemia, hepatic steatosis and IR [182, 272]. While isolated chronic intermittent hypoxia was not sufficient to cause atherosclerosis, it greatly potentiated the pro-atherogenic effects of a high-cholesterol diet [275].

Studies in mice have identified some steps of hepatic lipid biosynthesis which are affected by intermittent hypoxia [214, 276]. Intermittent hypoxia increases hepatic levels of the transcription factor sterol regulatory element binding protein (SREBP)-1 and of SCD-1 [272, 273, 277]. Dyslipidaemia and hepatic steatosis in mice exposed to chronic intermittent hypoxia were associated with upregulation of SCD-1 [271–275, 278], while depletion of SCD-1 reversed hyperlipidaemia [277]. Thus, chronic intermittent hypoxia may induce metabolic dysfunction *via* SCD-1.

The mechanisms by which intermittent hypoxia impacts on hepatic lipid biosynthesis are poorly understood. Hypoxic activation of HIF-1α may play a role, since mice with partial deficiency of HIF-1α exposed to intermittent hypoxia showed attenuated hyperlipidaemia, IR, hepatic steatosis and SCD-1 induction [279]. However, other pathways may also be involved. First, acute hypoxia induces lipolysis, possibly *via* sympathetic activation [280]. Secondly, hypoxia may suppress β-oxidation of fatty acids [281]. Finally, intermittent hypoxia decreases the activity of lipoprotein lipase in adipose tissue [282], which plays a primary role in the hydrolysis of triglycerides in circulating chilomicrons and VLDL [283, 284].

As a summary of this section, figure 1 schematically reports the metabolic abnormalities found in visceral obesity and OSA, and highlights points of possible detrimental synergies of both conditions.

THE METABOLIC EFFECTS OF SLEEP LOSS

Sleep loss may play a role in the pathogenesis of obesity and metabolic abnormalities, as suggested by epidemiological and mechanistic studies [14, 15]. An association of self-reported short sleep and/or sleep disruption with MetS has been found in the general population [285–287] and shift workers [288, 289]. Short sleep duration may increase the risk of incident diabetes [290, 291] and stroke [292]. Some studies suggest that sleep loss may contribute to the pathogenesis of cardiovascular disease in shift workers [293–295].

Cross-sectional epidemiological data in adults and children have shown an association between obesity and self-reported short sleep duration and/or poor quality of sleep [14, 296–298]. A negative linear association between baseline habitual sleep duration and later obesity has been demonstrated by prospective longitudinal data in children [298] but not in adults [299]. However, there are no experimental data in children or adults demonstrating that shortened sleep and/or poor sleep quality are causally related to the increased prevalence of obesity. Furthermore, in mice, chronic sleep restriction induced a catabolic state and weight loss despite increased feeding [300]. Reduced sleep duration (at least in the short-term) may increase the risk of weight gain by altering the regulation of appetite and by reducing insulin sensitivity [301–303]. Slow wave sleep (SWS) appears to play a protective role [304], in agreement with cross-sectional population data showing an inverse association between the amount of SWS and BMI. In addition, even a modest sleep restriction is associated with increased release of inflammatory cytokines in healthy young adults [305]. Finally,

circadian rhythms are increasingly studied with special attention to the role of peripheral clock genes in obesity, diabetes and cardiovascular disease [306–310].

Little is known about the effects of sleep fragmentation, as it occurs in OSA patients, on metabolic variables. A recent study showed decreased insulin sensitivity and increased sympathetic activation in normal subjects after acute sleep fragmentation [311].

In the future, studies will need to closely examine compartment-specific adipose tissue (especially visceral fat) under conditions of sleep restriction and/or disruption. Experimental manipulation of sleep requires intensive sampling during the day and the night under conditions of constant routine. The role of OSA-associated sleep disruption in promoting visceral obesity is still an open question.

EFFECTS OF TREATMENT FOR OBESITY AND OSA

The aim of this section is to briefly discuss some aspects of obesity and OSA with regard to treatment. In particular, the major problem of weight loss by pharmacological treatment or bariatric surgery is addressed in obese and OSA patients, as well as the changes in metabolic variables observed after CPAP treatment.

Therapeutic strategies in obesity and the metabolic impact of weight loss

Interventions aiming at correcting visceral adipocyte dysfunction may positively modulate the clinical phenotype and cardiometabolic outcomes of MetS patients [312]. Non-pharmacological approaches, such as diet to reduce calorie intake and exercise to increase energy expenditure, are the most effective interventions to improve metabolism and prevent type-II diabetes in individuals at risk [313, 314].

Other modalities of weight loss, such as bariatric surgery or medications, may have more success in the long-term than diet alone, as summarised in a recent review [315]. Laparoscopic gastric banding in severe obesity is a safe and effective method to achieve long-term weight reduction [316–318]. The Swedish Obesity Study has shown long-term weight loss and decreased 10-yr mortality in severely obese patients randomised to bariatric surgery compared to those undergoing conventional dietary treatment [319].

A comprehensive discussion of the treatment of obesity is beyond the scope of this review. It is worth noting that the development of new drugs to improve insulin sensitivity and reduce body weight is a major continuing challenge for the pharmaceutical industry. For example, drugs that improve insulin action are available (*i.e.* specific agonists of the peroxisome proliferator activated receptor-γ nuclear receptor), but their usefulness in obese patients is limited since they may also promote weight gain [312]. Thiazolidinediones are also a class of medications with severe side-effects. In addition, the development of drugs for obesity has been, until now, hampered by significant side-effects, as recently shown by the experience with rimonabant, a selective antagonist of endocannabinoid CB1 receptor. Endocannabinoid CB1 receptors initially appeared to be a good target for treatment, since they are highly expressed in regions of the brain involved in feeding and energy regulation, but also in adipose tissue, the gastrointestinal tract, liver and skeletal muscle [320]. In phase-III clinical trials, rimonabant caused weight loss and improved the metabolic profile [312], but had to be withdrawn from the market because of major psychiatric side-effects [321]. Another recent target for obesity treatment is represented by the incretin system [322]. The results are promising for the treatment of obese patients, since incretin mimetics were found to reduce overall body fat with prominent effects on visceral adipose tissue [323, 324].

Inflammation in visceral obesity is another potential intervention target, and salicylate derivatives are currently under intense investigation [325–328]. However, efficacy of new drugs needs to be tested not only for reduction of body weight, but also for prevention of cardiovascular events in the long term. In addition, new drugs should be specifically studied in patients of different ages, given the significant prevalence of obesity in young and old subjects [329].

Metabolic impact of CPAP treatment in OSA

CPAP intervention studies can provide information on whether specific health effects in obese patients can be modified by reversal of OSA. In general, analysis of the effects of CPAP is complicated by the variable compliance and adherence to treatment by OSA patients. CPAP treatment does not promote weight loss [330], and did not clearly affect diabetes [331] or other metabolic disorders [37]. The majority of recent studies, including randomised controlled trials [332–334], showed no effect of CPAP treatment on metabolic variables despite improvements in sleepiness and blood pressure, as recently summarised [37, 128, 150, 151, 335, 336]. However, a recent randomised controlled trial in Chinese male OSA patients without significant comorbidities reported improved insulin sensitivity in the effective CPAP group after 1 week of treatment, which was maintained at 3 months only in overweight/obese patients [185].

Circulating leptin decreased after CPAP treatment [157, 337], especially in non-obese [157, 337] and CPAP-compliant [339, 340] patients. CPAP treatment also reversed low serum adiponectin levels in obese OSA patients [166, 167], even though IR was unaffected [167]. These data are in agreement with the experimental findings that both continuous and intermittent hypoxia *in vitro* inhibit adiponectin production or secretion by adipocytes [37, 89, 90, 114], but firm evidence is still missing, given the negative result of a randomised controlled trial [334].

A similar uncertainty exists with regard to the effects of CPAP treatment on liver dysfunction. In an observational study, CPAP treatment for OSA for a single night slightly, but significantly, decreased serum alanine aminotransferase and aspartate aminotransferase levels [242]. In contrast, a randomised controlled trial found no difference in liver enzymes after effective or sham CPAP treatment [243]. Whether CPAP treatment for OSA affects liver pathology, *i.e.* the amount of fat deposition and NAFLD severity, is currently unknown.

Several non-randomised and randomised studies have examined the effect of OSA treatment on plasma lipids. CHIN and coworkers [341, 342] first showed that CPAP treatment decreased LDL cholesterol and increased HDL cholesterol levels. Positive effects of CPAP on lipids were reported in three non-randomised studies [262, 264, 337]. A large randomised controlled trial found decreased plasma cholesterol levels after therapeutic but not after sub-therapeutic CPAP for 1 month [343]. Three other randomised studies showed no effect of CPAP, but they included small numbers of subjects [262, 332, 337]. Therefore, current evidence suggests that CPAP treatment may decrease total and LDL

cholesterol levels. Unfortunately, none of the available studies stratified patients for obesity.

Metabolic impact of weight loss in OSA

Although changes in weight were associated with changes in OSA severity in both population and clinic-based studies [28–31], weight loss research for OSA has been hampered with doubts about the long-term effectiveness of weight loss as the only treatment in OSA. It is still unknown whether OSA patients could lose weight in the short or long term, and by what method this might be best achieved [344]. A recent randomised controlled trial of diet-induced weight loss for mild OSA reported positive results [345], but mild OSA may carry limited or no morbidity. In moderate-to-severe OSA, a therapeutic approach combining CPAP with diet to reduce weight might be more appropriate, as suggested by two recent randomised controlled trials in obese diabetic [346] or non-diabetic [347] OSA patients. Data after 1-yr of follow-up suggest that long-term maintenance of weight after initial very low energy diet in obese OSA patients is associated with persistent improvement of OSA [348]. Other studies reported less optimistic results after a 2-yr follow-up [349].

Bariatric surgery has also been used in OSA patients. In the Swedish Obesity Study cohort, prevalence of OSA-related symptoms at 2 yrs of follow-up decreased proportionally to weight loss [350]. According to a meta-analysis conducted in 2004, OSA resolved in 85% of the patients after bariatric surgery [350], as confirmed by studies including polysomnographic assessment [351–353].

As for use of medications to treat obesity, the effects of sibutramine have been recently assessed in obese OSA patients. Sibutramine did not affect sleep [354], and weight loss was associated with improved AHI and daytime sleepiness over a 6-month period [355]. The metabolic profile improved in obese OSA patients treated with sibutramine, low-calorie diet and exercise for 6 months [356]. Another study compared the effects of sibutramine to those of CPAP in patients who had been allowed to choose between the two treatments [357]. Sibutramine treatment caused a 5-kg weight loss over 1 yr and positively modified oxygen saturation during sleep, but did not affect AHI or cardiovascular variables. Conversely, CPAP-treated patients improved their respiratory variables during sleep and daytime blood pressure but did not lose weight [357]. Unfortunately, the results of these studies are not going to impact on the clinical management of OSA patients as sibutramine was withdrawn in Europe in early 2010 due to increased cardiovascular events associated with prolonged administration of the drug [358].

Overall, these studies underline the need for individualised treatment of obesity in OSA patients. Life-long adherence to CPAP treatment is a problem in OSA treatment [359], justifying additional pharmacological approaches. It is likely that OSA treatment and metabolic risk management, possibly integrated in the same sleep centre, may be necessary to obtain optimal results, but evidence-based management strategies are still missing.

OBESITY AND OSA IN CHILDREN

Obesity and MetS in children have been increasingly studied in the past decade. Genetic defects, sedentary lifestyle and unhealthy food habits are considered the main culprits of paediatric obesity [360] and the increasing prevalence of type-II diabetes in the young population [361]. Clinically, the immediate and long-term effects of childhood obesity are strikingly similar to those of adult obesity [360]. There is evidence that cardiovascular lesions develop in obese children [362], raising concerns about the long-term impact of childhood obesity on health.

Prevalence of OSA in children is expected to increase due to the rise in obesity [18–20]. Besides its immediate effects (snoring and daytime symptoms), paediatric OSA may influence the natural history of sleep disordered breathing in adulthood [363], including metabolic dysfunction. However, not every child with OSA will manifest adverse consequences, suggesting modulation by genetic and environmental factors [364].

OSA and obesity probably interact at the level of upper airways. Obese children with OSA demonstrated larger tonsils and adenoids compared to controls [365, 366], and a higher risk of residual OSA after adenotonsillectomy [365, 367]. However, upper airway closure may occur in obese children for a smaller degree of tonsil and adenoid enlargement than in non-obese children [365]. The relative contribution of (central) obesity and adenotonsillar hypertrophy remains to be elucidated and may differ between young children, in whom adenotonsillar hypertrophy might play a major role, and adolescents, who show a predominant role of obesity [368]. Recent studies have tried to address the impact of fat distribution and neck anatomy in a case–control study of obese children with and without OSA [369], but more studies are needed before drawing any conclusion on this topic. It should be pointed out that hereditable factors influencing craniofacial structures represent important predisposing conditions to develop upper airway obstruction, together with the acquired factors of adenotonsillar hypertrophy and obesity [370].

Similar to adults, obese children and adolescents often develop MetS [371–375], which appears linked to visceral obesity and ectopic fat deposition [376], secondary to excess calorie intake and reduced physical activity. While obesity is known to increase the risk for OSA, it is unclear whether OSA in children is directly involved in the pathogenesis of MetS. In contrast to adults, the paediatric population is relatively free from prolonged exposure to cardio-metabolic risk factors, and childhood OSA causes a lesser degree of oxygen desaturation than adult OSA, resulting in milder intermittent hypoxaemia compared to adult patients. OSA-associated nocturnal hypoxaemia in children independently predicted MetS and glucose intolerance [377–379], and prevalence of MetS increased with increasing severity of OSA [380–382], together with markers of inflammation [382], arterial alterations [383], and excessive daytime sleepiness [382, 384]. In non-obese children, the HDL cholesterol level was recently found to be inversely correlated with OSA severity [385]. Conversely, other studies have suggested that IR in children with OSA is associated with obesity rather than OSA [386–388].

A similar degree of uncertainty surrounds liver dysfunction. Two studies reported increased elevated serum aminotransferase levels in obese children with OSA, suggesting that OSA could act as a ''second hit'' in the development of NAFLD in children [244, 245]. Increased leptin levels have been reported in children with OSA, in the absence of changes in either adiponectin or resistin [389]. Other studies suggested that adiponectin is a sensitive marker of OSA in obese pubertal children [387] or found a predominant effect of obesity on adipokine levels [390]. The

exact pathogenesis and long-term consequences of early perturbations in metabolism by paediatric OSA warrant urgent research efforts.

Effects of treatment of paediatric OSA

Therapeutic interventions in children should be aimed at correcting both sleep apnoea and concomitant obesity if present. There is no agreement in the criteria to define the success rate of treatment in paediatric OSA, making it hard to compare the results of available studies [391].

The results of adenotonsillectomy are conflicting. Adenotonsillectomy carries a low success rate [25]. In addition, BMI often increases post-operatively, due to increased appetite, decreased nocturnal energy expenditure and decreased total motor activity [392]. One study using a pre/post-surgery design to assess the effect of OSA on IR in non-obese and obese children found that OSA was clearly associated with IR in obese children only. Plasma lipids markedly decrease in obese patients with resolution of OSA, while they showed a minor improvement in patients with residual OSA post-surgery [261]. In another study, lipid profiles, C-reactive protein and Apo-B significantly improved after adenotonsillectomy in both obese and non-obese children [389]. Other studies failed to show any effect of adenotonsillectomy on fasting insulin or the HOMA (homeostatic model assessment) index, or found that the metabolic profile worsened after surgery due to increased BMI [393], or were insufficiently powered to detect differences between subsets of obese children after surgery [394]. As for liver dysfunction, serum aminotransferase levels decreased in the majority of obese OSA children after adenotonsillectomy [244], but further study is needed to confirm a cause–effect relationship between OSA and NAFLD [395].

Experience with CPAP in children is limited, and the problem of long-term compliance to treatment may be as crucial as in adults. A single study in children found a slight decrease in leptin after CPAP treatment, while insulin sensitivity, BMI and norepinephrine levels were unaffected [396]. Weight loss is a promising alternative [391], but long-term compliance to weight loss is also a relevant problem in children.

FUTURE RESEARCH DIRECTIONS

Several important areas can be identified for future research. We have started to understand some mechanisms by which OSA may worsen metabolism, and studies in mice have provided a large amount of data on the effects of chronic intermittent hypoxia. However, the effects of decreased or disrupted sleep on metabolism remain incompletely defined in both obesity and OSA. Interestingly, sleep loss may not only promote weight gain, but could also diminish fat loss during a low-calorie diet, as recently found in obese humans [301].

Studies on the effects of hypoxia on adipocyte function face some methodological problem, since *in vitro* exposure to room air actually represents a condition of hyperoxia compared to the value of tissue P_{O_2} measured in live animals [114, 115] and humans [112]. Testing the effects of intermittent hypoxia *in vitro* on adipose tissue is problematic, due to the technical difficulty of controlling the rate of gas diffusion in cell cultures. This problem can be partly overcome by reducing the number of intermittent hypoxia cycles per minute, in order to obtain measurable oscillations in oxygen levels in the supernatant to which the cells are exposed.

Knowledge on adipose tissue function in OSA patients is still insufficient, and the biology of adipocytes from different fat depots (visceral and subcutaneous) in obese and non-obese OSA patients has not been studied. The pattern of adipokines in OSA is incompletely defined, as well as their interaction with inflammation, which plays such an important role in both OSA and obesity.

The role of OSA and obesity in causing metabolic abnormalities in children is incompletely understood. Given the partial success of adenotonsillectomy, sleep studies and metabolic assessment should be performed in children after surgery in order to evaluate the need for further treatment. Randomised controlled studies are needed to identify the best therapeutic strategy in paediatric OSA according to the specific OSA phenotype. In addition, longitudinal studies to explore the long-term consequences of OSA in children are warranted.

A comprehensive approach, aimed at abolishing OSA but also at attaining long-term reduction in body weight, is desirable in both adults and children with OSA. In patients undergoing bariatric surgery, resolution or improvement of obesity improved OSA, especially in males. However, patients undergoing bariatric surgery may not be representative of the whole OSA population because of usual predominance of morbidly obese females. Bariatric surgery has provided important data on liver function in OSA, and remains a good opportunity for metabolic studies at the time of the intervention. Moreover, liver biopsies are easily obtained at the time of bariatric surgery, but collecting them during follow-up or in patients treated with CPAP is ethically problematic. Hopefully, improved noninvasive means of diagnosis of NAFLD will help to improve liver assessment in OSA patients.

From a clinical point of view, new models of integrated care, possibly in the same centre, are needed for treatment of obese OSA patients. A multidisciplinary approach seems necessary for both adult and paediatric patients in order to provide effective treatment and prevent metabolic and cardiovascular consequences of both obesity and OSA.

STATEMENT OF INTEREST

None declared.

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