Adipose tissue as a key player in obstructive sleep apnoea

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ABSTRACT Obstructive sleep apnoea (OSA) is a major health concern worldwide and adversely affects multiple organs and systems. OSA is associated with obesity in >60% of cases and is independently linked with the development of numerous comorbidities including hypertension, arrhythmia, stroke, coronary heart disease and metabolic dysfunction. The complex interaction between these conditions has a significant impact on patient care and mortality. The pathophysiology of cardiometabolic complications in OSA is still incompletely understood; however, the particular form of intermittent hypoxia (IH) observed in OSA, with repetitive short cycles of desaturation and re-oxygenation, probably plays a pivotal role. There is fast growing evidence that IH mediates some of its detrimental effects through adipose tissue inflammation and dysfunction. This article aims to summarise the effects of IH on adipose tissue in experimental models in a comprehensive way. Data from well-designed controlled trials are also reported with the final goal of proposing new avenues for improving phenotyping and personalised care in OSA.

Adipose tissue: physiology, modifications in obesity and the role of hypoxia

Initially thought to be an organ of pure energy storage, the adipose tissue has now evolved as a highly active endocrine organ participating in numerous physiological and pathophysiological processes. In mammals, adipose tissue can be distinguished as white adipose tissue (WAT) or brown adipose tissue (BAT) based on several criteria including developmental lineage, functionality and morphology. BAT is predominantly present in newborns and in small quantities in adults, and plays a role in thermoregulation [1]. Most of the human adipose tissue is WAT, mainly located beneath the skin (subcutaneous WAT) and surrounding internal organs (visceral WAT (vWAT)). The physiological functions of WAT include thermal insulation,

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energy regulation and lipid storage. Furthermore, it plays a key role in metabolism, mediated predominantly through the secretion of multiple hormones, cytokines, chemokines and other proteins, collectively referred to as adipokines [2]. Lipid-laden adipocytes represent the predominant cellular compartment of the adipose tissue. In addition, it also contains the stromal-vascular fraction (SVF) which includes the extracellular matrix, pre-adipocytes, endothelial cells, fibroblasts and immune cells, such as macrophages and lymphocytes (figure 1).

In obesity, the adipose tissue undergoes significant morphological and phenotypic changes, which play a central role in the mediation of the detrimental effects associated with this state [3, 4]. With persistent excessive calorie intake, WAT is forced to expand to facilitate lipid storage which is achieved by an increase in adipocyte number (hyperplasia) and enlargement in adipocyte size (hypertrophy) [5]. While hyperplasia represents a healthy expansion of WAT, hypertrophy results in adipose tissue dysfunction and inflammation contributing to insulin resistance, increased immune cell infiltration, local hypoxia and fibrosis (figure 1) [6, 7]. In obesity, adipocyte hypertrophy and dysfunction are paralleled by quantitative and qualitative changes of the SVF. Cells of both the innate and adaptive immune system, including total T-cells, B-cells, macrophages, leukocytes and mast cells, increase in obese WAT, particularly in the visceral compartment [2]. Macrophages infiltrating the obese adipose tissue typically form so-called crown-like structures surrounding necrotic adipocytes [8]. The function of these crown-like structures probably includes clearance of cell debris and performance of adaptive tasks, but they are a definite sign of metabolic dysfunction as numbers of crown-like structures correlate with adipose tissue inflammation and insulin resistance [9]. In addition, immune cells undergo significant phenotypic alterations in obesity. In lean insulin-sensitive adipose tissue, anti-inflammatory regulatory T-cells (Tregs) and macrophages of an M2 alternatively activated phenotype are the predominant cells contributing to tissue repair processes and resolution of inflammation. In contrast, adipose tissue expansion is associated with a decrease in $CD4^+$ helper and Treg cells, infiltration of $CD8^+$ cytotoxic T-cells and macrophage polarisation towards an M1-proinflammatory phenotype. Subsequently, the production of numerous proinflammatory adipokines, such as tumour necrosis factor (TNF)-α, interleukin (IL)-6 and resistin, increases leading to insulin resistance and metabolic dysfunction [2, 10, 11].

Increasing evidence points to a critical role of hypoxia in mediating the proinflammatory responses of obese adipose tissue [12]. With expansion of the adipose tissue, there is increased angiogenesis to ensure sufficient supply of oxygen and nutrients; however, as adipocyte hypertrophy continues, local tissue hypoxia develops leading to the activation of hypoxia-inducible transcription factors, in particular hypoxia-inducible factor (HIF)-1 [13]. This in turn triggers the expression of key angiogenic factors (*e.g.* vascular endothelial growth factor [14] and plasminogen activator inhibitor-1), thus contributing further to angiogenesis and adipocyte and metabolic dysfunction. In support of the pivotal role of hypoxia, recent studies have shown that adipocyte-specific depletion of HIF-1 prevents high-fat diet-induced adipose tissue inflammation and insulin resistance, and tissue vascularisation was comparable to wild-type controls [15].

Adipose tissue and IH: insight from rodent and reductionist models

Abundant literature states that obstructive sleep apnoea (OSA) syndrome is an independent risk factor for metabolic and vascular disturbances, such as insulin resistance and atherosclerosis [16, 17], and IH-induced adipose tissue dysfunction probably plays a key role in the pathogenesis. The effects of IH have been dissected in rodent experiments in which animals were exposed to cyclic and repetitive episodes of reduced inspiratory oxygen fraction (F_{IO_2}), with the most frequently used protocol consisting of cyclic reduction of F_{IO_2} in animal cages from 21% F_{IO_2} (room air) to 4–6% F_{IO_2}, mimicking hypoxaemic conditions found in patients with severe OSA [18]. This IH condition, applied for at least 2 weeks, induces vascular dysfunctions and reproduces glucose and lipid homeostasis disturbances similar to those observed in OSA patients. In particular, IH exposure increases levels of circulating free fatty acids and triglyceride-rich lipoproteins [19, 20], induces vascular remodelling and accelerated atherosclerosis [21, 22], and also leads to insulin resistance in both lean and obese mice [23, 24]. However, the mechanisms involved remain unclear and growing evidence suggest that adipose tissue could be a key player in these IH-associated deleterious consequences. As a proof of concept, visceral lipectomy in lean atherogenic mice prevented IH-induced atherosclerosis progression [25]. Furthermore, specific alterations of vWAT insulin signalling pathways have been described in both lean and obese mice exposed to IH [23, 24, 26, 27]. These examples illustrate the pivotal role of the adipose tissue in mediating IH-associated cardiovascular and metabolic dysfunctions (figures 1 and 2).

Several lines of evidence suggest that the IH-induced metabolic perturbations are accompanied by morphological changes of the adipose tissue [17]. The increase in fat mass and adipocyte enlargement, the key features of obesity, are not always present in response to IH and some studies even showed reduced fat mass and the presence of shrunken adipocytes (figure 1) [25, 28, 29]. Poulain *et al.* [25] suggest a

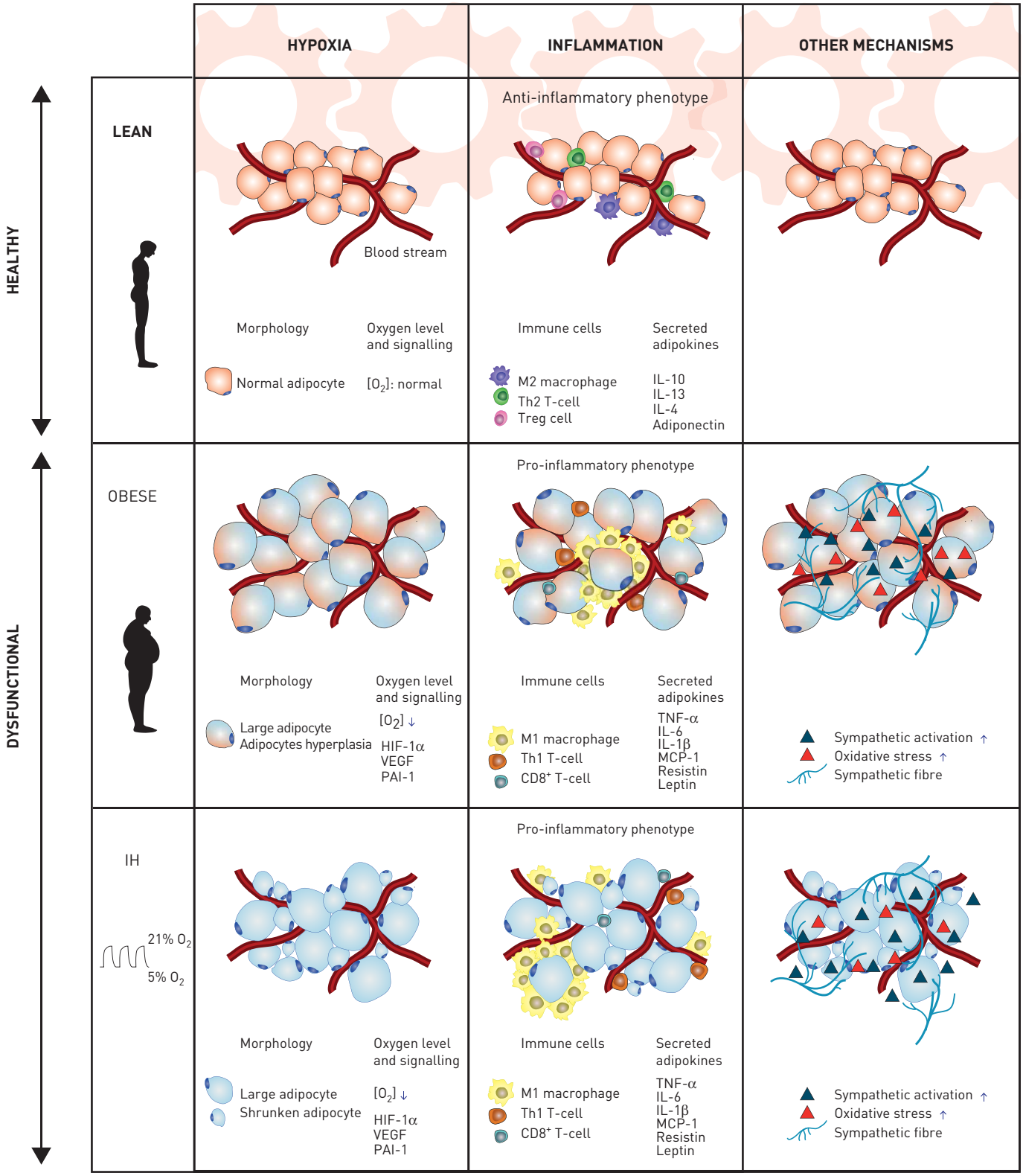

FIGURE 1 Obesity and intermittent hypoxia (IH) share common mechanistic pathways leading to adipose tissue dysfunction. Healthy adipose tissue contains small adipocytes and anti-inflammatory immune cells (M2 macrophages, T-helper 2 (Th2) cells and regulatory T-cells (T regs)), leading to the production of anti-inflammatory adipokines (interleukin (IL)-10, IL-13, IL-4 and adiponectin). Whereas adipocyte size and number differ between obesity and IH, the molecular alterations are strikingly similar. Indeed, adipocytes from obese and IH exhibit lower oxygen tension levels ($[O_2]$ ↓), increased expression of hypoxia-inducible factor (HIF)-1 and target genes (vascular endothelial growth factor (VEGF) and plasminogen activator inhibitor (PAI)1) and increased oxidative stress and sympathetic activation. In addition, proinflammatory immune cells ($CD8^+$ cytotoxic T-cells and Th1 cells) infiltrate the dysfunctional tissue and macrophages polarised to the M1 proinflammatory phenotype. This results in the secretion of proinflammatory adipokines (tumour necrosis factor (TNF)-α, IL-6, IL-1β, monocyte chemotactic protein (MCP)-1, resistin and leptin).

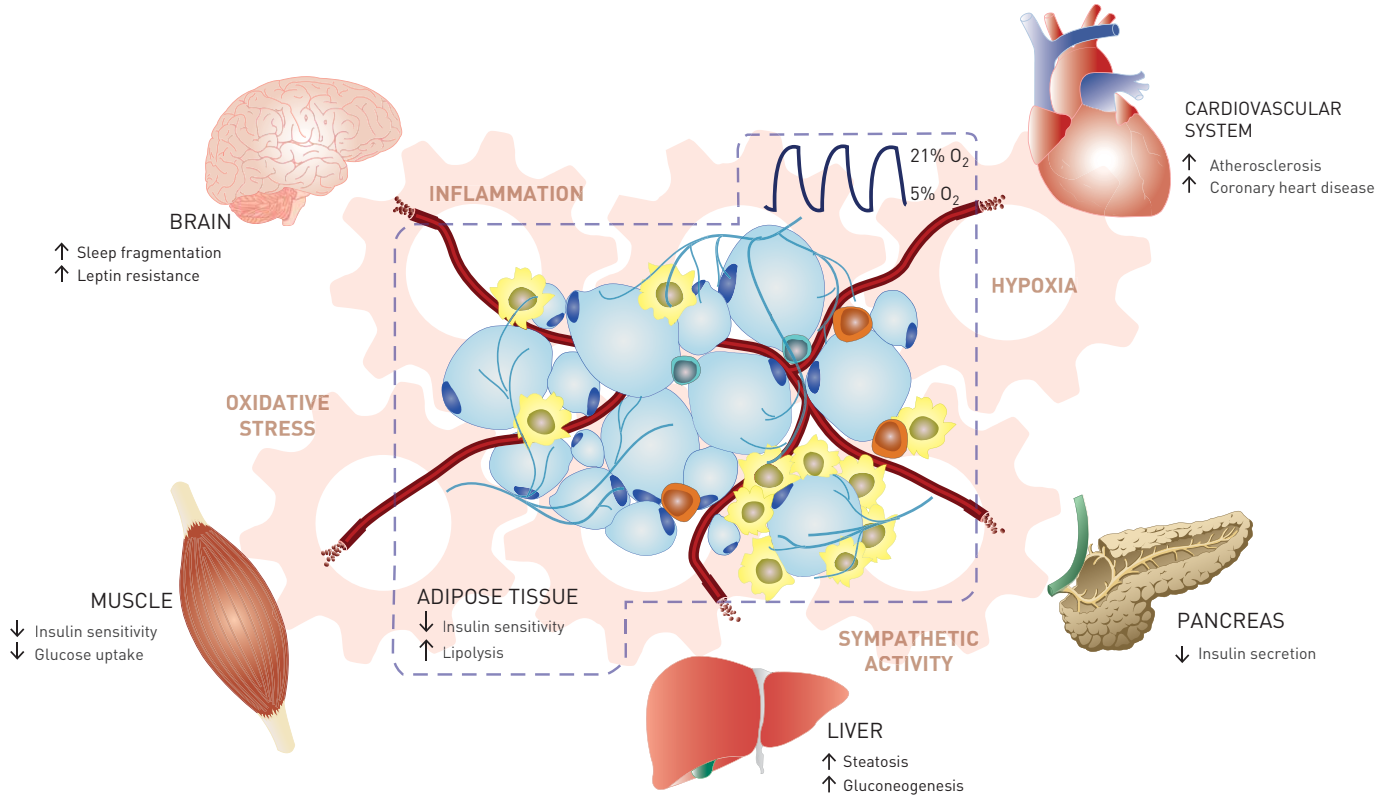

FIGURE 2 Adipose tissue as a key player in systemic consequences of intermittent hypoxia. Physiological consequences of intermittent hypoxia on adipose tissue, the brain, the cardiovascular system, the pancreas, the liver and muscle. Intermittent hypoxia systemic effects may be direct and/or originated through the adipose tissue dysfunction.

browning of the visceral adipose tissue and demonstrated that IH induces the expression of UCP-1, a marker of brown adipocytes (thermogenic fat). A recent study from Gozal *et al.* [30] showed the opposite effects by suggesting that IH induces preferential whitening of visceral adipose tissue, as opposed to prominent browning induced by sustained hypoxia.

Interestingly, although adipose tissue morphology may differ between IH and obesity, these two stimuli share common molecular disturbances. IH is a potent proinflammatory stimulus [31] particularly in the vWAT [17]. In lean mice, IH-induced vWAT inflammation is characterised by the increased expression of monocyte chemotactic protein-1, which contributes to the recruitment of macrophages in vWAT [23, 25, 26, 32]. These macrophages are organised in a crown-like structure around necrotic adipocytes [23, 25] and acquire a M1 proinflammatory phenotype that contributes to the release of proinflammatory cytokines, such as IL-6 and TNF-α [23, 25, 26]. These vWAT proinflammatory disturbances are potentiated in obese mice under IH [23]. Similar proinflammatory features have also been found in isolated cells in cultures exposed to IH. For example, isolated human adipocytes exposed to IH exhibit a robust increase in nuclear factor (NF)-κB activity and subsequent expression and release of proinflammatory cytokines [33, 34] and an increase in M1-related gene expression in cultured macrophages exposed to IH has been shown [23].

In addition to inflammation, other mechanisms have been proposed to participate to IH-induced adipose tissue dysfunctions. As previously reported in obesity, adipose tissue hypoxia itself could represent a convincing mechanism contributing to adipose tissue dysfunction in response to IH [13]. In lean rodents exposed to different pattern of hypoxia, a recent study demonstrated that IH induces a deleterious response in vWAT, through HIF activation [30]. Similarly, Thomas *et al.* [24] demonstrated in lean mice that IH increases HIF-1α expression in vWAT, which parallels the decreased insulin signalling and sensitivity. However, whereas adipocyte-specific depletion of HIF-1α prevents insulin resistance in obesity [15], heterozygous HIF-1α deficiency (HIF-1$\alpha^{+/-}$) had no beneficial effect on IH-induced systemic insulin resistance [24], suggesting more complex regulating mechanisms in the deleterious metabolic response to IH.

IH induces autonomic dysfunction characterised by sympathetic activation and associated increases in circulating catecholamines [35, 36]. This sympathetic activation represents a well-described mechanism

responsible for the release of free fatty acids and glycerol, as a result of adipose tissue lipolysis by hormone sensitive lipase [37]. In rodents, IH exposure induces adipose tissue lipolysis, and pharmacological inhibition of lipolysis by acipimox prevents IH-induced insulin resistance in mice [25, 29, 38]. However, sympatholytic strategies using adrenergic blockade or adrenal medullectomy only abolish IH-induced lipolysis without a beneficial effect on peripheral insulin resistance [39–41], again supporting a more complex signalling pathway involving complementary mechanisms. In response to IH, adipose tissue represents the main source of circulating free fatty acids, which constitute an essential substrate for the liver to generate triglyceride-rich lipoproteins, well-known for their proatherogenic properties [42]. In addition to IH-induced adipose tissue lipolysis, Drager *et al.* [43] demonstrated that IH delays the clearance of triglyceride-rich lipoproteins. They demonstrated that IH upregulated angiopoietin-like protein 4 expression in adipose tissue through HIF-1 activation, resulting in the inhibition of lipoprotein lipase activity and atherosclerosis progression [44].

Finally, as a response to this complexity, a transcriptomic analysis in vWAT from mice exposed to IH revealed modification of expression of more than 3000 genes, with the main changes in genes involved in metabolic processes, the mitochondrion and oxidative stress responses [45]. To date, only a few studies have investigated the role of IH on vWAT-specific oxidative stress. A recent report demonstrated that macrophages from adipose tissue of mice exposed to IH exhibit increased reactive oxygen species production and alterations in the electron transport chain, indicating coupling of IH-induced adipose tissue inflammation with mitochondrial dysfunctions and oxidative stress [27]. In addition, resveratrol, a natural polyphenolic flavonoid known for its anti-inflammatory and antioxidative properties, abolishes both systemic and vWAT insulin resistance induced by IH, and prevents macrophage recruitment and M1 polarisation within vWAT [26]. Thus, IH induces many deleterious and complementary mechanisms in vWAT (figure 1) that contribute directly to systemic, cardiovascular and metabolic disturbances (figure 2).

Adipose tissue, ectopic fat and lipids in OSA: insights from clinical studies

OSA is independently associated with the different components of the metabolic syndrome, particularly visceral obesity, hypertension, insulin resistance and abnormal lipid metabolism [46]. There is a bidirectional relationship between OSA, adipose tissue/obesity and metabolic diseases. Obesity and ectopic fat depots exacerbate sleep apnoea through a decrease in lung volumes, increased mechanical load and narrowing of the upper airway. IH and sleep fragmentation exacerbate the metabolic impact of obesity by increasing sympathetic activity, oxidative stress, inflammation and lipolysis.

While there is a paucity of studies demonstrating adipose tissue inflammation and dysfunction in response to IH in rodents we are, as yet, lacking clear and precise data in human subjects with OSA. Indirect information is represented by studies looking at circulating levels of leptin and adiponectin, which are sole adipokines. Human obesity is characterised by leptin deficiency with higher circulating levels of leptin [47]. In adipocyte cultures and rodent models, IH has been reported as exacerbating hyperleptinemia and higher circulating levels of leptin are generally found in obese patients with OSA even after adjustment for body mass index (BMI). These elevated leptin levels remain unaltered by continuous positive airway pressure (CPAP) treatment. As leptin activates the autonomous nervous system, hyperleptinemia in patients with OSA might contribute to sympathetic overactivity and frequent occurrences of difficult-to-control hypertension. Low circulating adiponectin levels are also associated with obesity and predictors of late cardiovascular events. Induction of HIF-1α in adipocytes, as demonstrated during IH, is known to lead to downregulation of adiponectin expression [48]. In a relatively large group of 486 obese subjects, plasma adiponectin levels gradually decreased with the increasing severity of OSA [49]. Adiponectin levels were particularly low in OSA associated with hepatic fat and non-alcoholic fatty liver disease (NAFLD) [50]. In a meta-analysis of three randomised controlled trials (RCTs) [51], CPAP did not improve total circulating levels of adiponectin. Accordingly, in a recent RCT, effective oral appliance was not superior to sham oral appliance in increasing adiponectin levels [52]. Potentially, low adipokine production in response to IH might reflect a greater propensity for ectopic and visceral fat deposition in patients with OSA. In overweight males, after controlling for confounders, OSA is specifically associated with a higher amount of visceral adiposity whereas in females, OSA is associated with global adiposity [53, 54]. Independently of BMI, OSA is involved in the development of ectopic fat depots contributing to the progression of insulin resistance in the different metabolic organs, including the pancreas, liver and muscle (figure 2) [23, 24, 55]. The local fat depots might contribute differently to some of the deleterious consequences of OSA. For instance, in epicardial adipose tissue, the cross-talk between epicardial adipocytes and cells of the vascular wall or myocytes modulates cardiac remodelling and the risk of developing atrial fibrillation [56] both being cardiovascular alterations frequently observed in OSA. Epicardial adipose tissue is highly sensitive to IH and, after bariatric surgery, the loss in epicardial adipose tissue mass is limited in morbidly obese subjects with untreated OSA [56]. Among other OSA-related ectopic fat depots, liver steatosis and NAFLD have been extensively studied, both in rodent models and humans [57]. NAFLD is an increasingly

prevalent condition paralleling the growing epidemic of obesity and type-2 diabetes with associated increased risk of late cardiovascular events and higher mortality. NAFLD shows a continuous spectrum of severity ranging from simple steatosis to overt non-alcoholic steatohepatitis that can progress further towards cirrhosis and hepatocarcinoma. OSA and particularly the severity of IH contribute to the deleterious progression into overt non-alcoholic steatohepatitis whereas the absence of OSA seems to protect morbidly obese patients from developing NAFLD. Among the multiple mechanisms that have been described to explain the link between IH and NAFLD [57], emerging studies in children with OSA suggest that insulin resistance and NAFLD severity could be related to low-grade endotoxaemia and impaired gut-barrier integrity [58–60]. Such IH-induced gut microbiome alterations have also been reported in rodent models [61, 62], with no beneficial effect of normoxic recovery [62]. Thus, in accordance with the abundant literature from the past decade linking gut microbiota dysbiosis with metabolic pathologies [63], microbiota dysfunctions might also be involved in OSA-related metabolic disorders and further studies are needed to decipher the exact mechanisms.

This accumulation of hepatic fat and the development of hepatic insulin resistance is also one of the mechanisms underlying lipid abnormalities in OSA [64]. As previously described in rodents, IH results in an increase in metabolic dyslipidaemia in patients with OSA [65] favoured by upregulated triglycerides and phospholipids biosynthesis, and inhibited triglyceride uptake in the liver. A recent study in OSA patients corroborates the previous results from rodents exposed to IH, showing a decreased lipolysis of triglyceride-rich lipoproteins in patients with severe OSA [66]. Furthermore, delayed triglyceride-rich lipoproteins clearance through adipose tissue lipoprotein lipase inhibition were associated with increased carotid intima-media thickness [66]. The majority of observational studies support a link between OSA and dyslipidaemia [64], while in a meta-regression analysis, apnoea–hypopnoea index had a significant effect on low density lipoprotein and triglycerides [67]. Data from the European Sleep Apnea Database group have recently confirmed that there is a dose–response relationship between triglycerides and the severity of IH but this was modulated by geographical variations, suggesting that genetic background and lifestyle habits alter the relationship [68].

Personalised medicine is among the next challenges in OSA [69]. To better define the appropriate treatment for a single patient, we need combinations of biomarkers that are able to characterise IH consequences at the level of the different metabolic organs. Metabolomic and lipidomic profiles in OSA have been reported as distinct from a control group matched for age, BMI and body composition [70]. Also, in a relatively large sample of nonobese and obese OSA, we recently found an independent correlation of OSA severity with the M1 macrophage inflammatory marker sCD163 [23]. These findings need to be replicated in much larger, more diverse OSA populations, where proper adjustment can be made for comorbid diseases. However, a combination of biomarkers remains to be tested and developed to enhance their discriminative power in characterising adipose tissue remodelling, constituting a target for therapy and being potential predictors of treatment response.

Impact of CPAP treatment on adipose tissue and ectopic fat

Assuming that IH is linked with the amount of ectopic fat and specific lipidomic and metabolic profiles, the next question is to know whether or not sleep apnoea treatment is able to improve metabolic parameters and reduce metabolic risk. First of all, untreated OSA attenuates reduction in body weight, loss of ectopic fat depots and metabolic improvements expected with lifestyle intervention programmes [71] or bariatric surgery [56]. Effective treatment of OSA by CPAP was expected to reduce cardiovascular and metabolic morbidity. The improvement in metabolic dysfunction in response to CPAP was hypothesised as occurring in relation to changes in the amount of ectopic fat or reduction in local inflammation and oxidative stress in metabolic organs. It was argued that this would occur not only by suppression of IH but also due to consequent increases in physical activity after CPAP use at night. This is unlikely to be the case as, in the only available RCT, West *et al.* [72] demonstrated that obese patients with OSA do not actually increase their physical activity on CPAP. Accordingly, two RCTs assessing visceral abdominal fat and liver fat by computed tomography scan or magnetic resonance imaging failed to demonstrate any reduction in body fat tissues after CPAP treatment [73–75]. A systematic analysis of randomised studies comparing therapeutic *versus* sham CPAP intervention, also including studies using a CPAP withdrawal design, showed no difference after therapy in changes in glucose, lipids, insulin resistance levels or the ratio of patients with metabolic syndrome [76]. Also, after 2 months of treatment with a mandibular advancement device or a sham device, the mandibular advancement device had no effect on circulating biomarkers compared with the sham device despite high treatment adherence (6.6 h·night^{-1}) [52]. Finally, data from RCTs showed that noninvasive tests characterising liver steatosis were increased in untreated OSA, potentially contributing to cardiometabolic risk, but did not improve after 6–12 weeks of effective CPAP treatment [77]. In summary, neither adiposity nor metabolic biomarkers appear to be improved by effective OSA treatment, contributing to the modest impact of CPAP in reducing mortality and late

cardiovascular events [78]. Even more concerning, a first meta-analysis suggested that CPAP promotes a small but significant increase in BMI and weight [79]. In subsequent individual patient's meta-analysis addressing the dose-dependent effects of CPAP [80], weight gain was greater with high-use therapeutic CPAP compared with high-use placebo CPAP (mean difference: 1.45 kg). However, this limited weight gain was not accompanied by any adverse metabolic effects. In the European Sleep Apnea Database cohort, CPAP response was heterogeneous and CPAP usage was not found to systematically change BMI. Weight gain and increases in waist circumference were restricted to an OSA phenotype without established obesity [81]. As recently supported by American Thoracic Society consensus guidelines, these data together suggest that additional therapies for body weight reduction must be recommended for overweight or obese patients with OSA initiated on CPAP [82]. Moreover, weight loss plus CPAP have synergistic effects on weight and metabolic parameters compared with each intervention alone [83]. In obese patients with OSA on CPAP, noninvasive ventilation or respiratory muscle training as adjuncts to exercise have recently been shown to significantly reduce waist circumference and blood pressure [84].The evidence supports a combined treatment strategy in obese OSA.

Current limitations and future directives

As summarised here, a fast growing body of studies using experimental models has provided substantial support of the key role of IH-induced adipose tissue inflammation in metabolic dysfunction in rodents. However, the adipose tissue in these animals differs in many aspects from that in humans, both in distribution and function, and hence, the detailed role of this response for the human condition of OSA remains to be determined. In humans, increased vWAT rather than extension of the subcutaneous fraction is linked to impaired glucose metabolism, insulin resistance and mortality [85]. Depending on the anatomical location, vWAT can be divided into omental, mesenteric, retroperitoneal, gonadal and pericardial depots. Similar to humans, vWAT in rodents consists of different parts. The largest and by far best studied parts are the paired fat pads in the gonadal region, which are attached to the uterus and ovaries in females and the epididymis in males. However, there is no true equivalent to these fat pads in human and, hence, results obtained from rodent studies using this tissue cannot be easily translated into human conditions. Mesenteric fat in rodents is believed to be most representative of human vWAT due to its high vascularity and access to the portal drainage system; however, in mice, it forms a glue-like web and is not easily dissectible from surrounding structures and, hence, studies on this vWAT compartment are limited. Additionally, the careful translation of animal data into human conditions has been hindered by the difficulties in routine sampling of vWAT in humans. In relation to OSA, only one study so far has been performed, sampling omental adipose tissue in morbidly obese subjects during bariatric surgery [86]. The study found no association of OSA with total macrophage infiltration of the adipose tissue, but detailed phenotyping of the macrophages or further functional/morphological evaluations were not performed. Thus, the results of the adipose tissue studies employing models of IH must be interpreted with caution. Furthermore, the widely used rodent model of IH has several limitations which are reviewed in detail elsewhere [87, 88]. Moreover, we are still lacking experimental data combining IH with other potential pathophysiological triggering factors in OSA, such as sleep fragmentation, intra-thoracic pressure swings and hypercapnia. Thus, future studies need to focus on overcoming these limitations in order to provide a more representative model of the human condition.

Notwithstanding these limitations, the current state of knowledge lends support for a key role of adipose tissue inflammation and dysfunction in metabolic and cardiovascular disease processes in OSA and, thus, interventions targeting this response may lead to improved outcomes in these patients. As outlined above, CPAP alone is often insufficient in improving glucose metabolism in OSA. Animal studies have provided a greater insight into the reasons of the lack of response demonstrating that the detrimental effects of IH may not be reversible even with prolonged periods of normoxic recovery [27, 89]. Thus, strategies to combine CPAP with other interventions are more compelling. Weight loss in addition to CPAP is more beneficial in improving metabolic parameters in comparison with either treatment alone [83]; however, it is difficult to achieve and maintain through lifestyle interventions alone. Surgical or pharmacological approaches may be more feasible but there is still a scarcity of studies which have tested the efficacy of such strategies in OSA populations. A potentially attractive approach is a glucagon-like peptide (GLP)-1-based weight loss regimen. Liraglutide is the best studied GLP-1 analogue and is administered at a dose of 3.0 mg daily in adjunct to diet and exercise is superior to placebo in achieving weight loss and metabolic control in nondiabetic subjects [90]. The mechanism of GLP-1-mediated weight loss is incompletely understood and likely multifactorial but the reduction in adipose tissue inflammation through the activation of invariable natural killer T-cells leading to the browning of white fat probably plays a key role [91]. In addition, a recent murine study demonstrated a reduction in atherosclerotic plaques with liraglutide accompanied by a decrease in M1-proinflammatory macrophages from bone marrow-derived cells, which are also believed to be the main source of adipose tissue macrophages [92].

Blackman *et al.* [93] compared the impact of liraglutide with placebo in nondiabetic patients with moderate-to-severe OSA and found a significant benefit in the reduction of weight and glycated haemoglobin (HbA_1C); however, so far, data are lacking comparing this intervention with CPAP or a combination of both.

Another suggested pharmaceutical intervention to target adipose tissue dysfunction is the anti-inflammatory compound resveratrol. It is contained in small amounts in grapes and wine and has gained widespread attention for its possible beneficial effects on obesity-related outcomes [94]. Evidence has mainly arisen from preclinical studies and relevant to OSA, Carreras *et al.* [26] reported a significant decrease with resveratrol in IH-induced macrophage M1-polarisation in lean mice. However, clinical trials using resveratrol as an anti-obesity agent have yielded conflicting and less convincing results and further large-scale RCTs are needed before definite conclusions of its effectiveness in obesity in general, and OSA populations specifically, can be drawn. Promising amelioration of adipose tissue inflammation has also been demonstrated with statin therapy possibly through inhibition of nuclear factor-κB activity and activation of the AMP-activated protein kinase leading to improved insulin sensitivity [95]. Following this approach, an RCT of statin therapy *versus* CPAP in patients with OSA investigating its impact on cellular damage in subcutaneous adipose tissue is currently underway at the Mayo Clinic (Rochester, MN, USA) and results may help identify the role of statins in adipose tissue dysfunction of patients with OSA. Beside bariatric surgery or pharmacological intervention to facilitate weight loss, a further unexplored strategy is physical exercise, which has been demonstrated to lead to adaptive changes of WAT associated with improvement in metabolic health [96]. Only a small number of studies have investigated this treatment approach in OSA demonstrating a minor improvement in quality of life with inconsistent decreases in OSA severity and weight [82, 97]. However, we are lacking long-term RCTs on this subject and specifically, data on metabolic outcomes.

In conclusion, despite fast emerging evidence of a key role of adipose tissue inflammation in IH-associated cardiometabolic complications in preclinical models, the detailed role of these responses in OSA needs to be further defined. Thus, future translational studies on this subject are urgently warranted in order to guide future interventional clinical trials.

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