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Sleep apnea in relation to metabolism: An urgent need to study underlying mechanisms and to develop novel treatments for this unmet clinical need

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Obesity is a disease state of epidemic proportions in the United States and other industrialized countries, which can cause and/or exacerbate diabetes (DM), obstructive sleep apnea (OSA), cardiovascular disease, cancers, and liver and renal disease [1,2]. OSA is a relatively common problem with about 20% of adults presenting with at least mild OSA and about one in 15 presenting with moderate or severe OSA [3]. OSA often occurs as a comorbidity of obesity and DM, but it also contributes to worsening of DM, at least in part independently from obesity, and leads to increased morbidity and mortality from DM, cardiovascular disease, and accidents caused by excessive daytime sleepiness [4–7]. Indeed, the risk of OSA increases with both age and BMI with a prevalence of up to 80% in the highest risk categories [8] for this unmet clinical need.

Several studies have linked OSA with worsened obesity and related comorbidities including DM and cardiovascular disease as well as increased all-cause mortality [9–11]. Disrupted sleep itself repeatedly leads to weight gain and poorer metabolic outcomes [9,10,12–15], which makes OSA and obesity a cycle which can be difficult to break (Fig. 1). OSA has been associated with the development of insulin resistance and DM [16,17] and is known to be a common comorbidity of obesity and DM [18]. Significant data link OSA and nocturnal intermittent hypoxia with poor glycemic control, and increasing severity of OSA correlates with worsening DM outcomes [16–19]. Several studies also show increased systolic blood pressure and hypertension, as well as cardiovascular disease risk with OSA [20,21]. Furthermore, the lipid profile is worsened with OSA, demonstrating increased total and low-density lipoprotein cholesterol levels and decreased high-density lipoprotein cholesterol levels [22]. Similar to the other comorbidities of obesity, large studies, such as the Look AHEAD study, have found that OSA symptoms improve with weight loss [23,24], suggesting that obesity and OSA are parts of a vicious cycle that can be broken with targeted therapy.

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Evidence from sleep restriction, fragmentation, and circadian misalignment studies has consistently demonstrated impaired insulin sensitivity, which was decreased by about 25% [14,15,25–37]. The combination of sleep restriction and circadian misalignment, in the short-term, results in a 58% decrease in insulin sensitivity [30], suggesting that complex states such as OSA may have the most dramatic effects on insulin resistance. Notably, adipocytes appear to respond to insulin differently after sleep deprivation, suggesting that there may be involvement of multiple cell types and networks which lead to these changes [25]. Systemically, changes in c-reactive protein (hsCRP), tumor necrosis factor alpha (TNF- α), and interleukins (IL-6, IL-8, IL-1 β) have been observed with sleep deprivation, suggesting systemic changes in inflammatory markers with OSA [30,38–41]. Ghrelin, leptin, and cortisol, hormones important in energy homeostasis and stress, are also altered by sleep deprivation and OSA [25,36]. Adiponectin, another adipokine, has been shown to be decreased in individuals with OSA [42,43], which does not change, in most studies, with treatment (meta-analysis: [44]). Irisin, a myokine which promotes the browning of white adipose tissue, and has thus been proposed to induce weight loss, was found to be lower in individuals with OSA [45]. Fasting incretin levels, glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), are increased with OSA [46]. Altogether, there is evidence of abnormal inflammatory markers, adipokines, and GI-secreted hormone levels leading to adiposity and altered metabolic hormonal (insulin, leptin) signaling, resulting in insulin resistance and abnormal metabolism, and leading to worsening insulin resistance/DM and eventually cardiovascular disease.

Furthermore, a rather limited number studies on underlying molecular mechanisms have focused on how OSA alters metabolism at the cellular level. OSA decreases the uptake of glucose by muscle tissue [47] and may stimulate hypoxia in adipose tissue, leading to inflammation [48,49]. These effects may be mediated by changes in insulin and leptin signaling. Insulin binds to insulin receptors, which activate the PI3K/Akt pathway and stimulate glucose uptake [50]. Leptin binds to the leptin receptor to activate a number of downstream signaling molecules, including AMPK, ERK1/2, STAT3, Akt, and mTOR [51–54]. Studies in rodents have shown changes in these pathways with models of OSA, contributing to insulin resistance at the cellular level and systemically [55]. One small study has examined how this may be altered in humans, discovering that short-term sleep deprivation altered Akt signaling in adipocytes, decreasing cellular insulin sensitivity [25]. More studies are needed to fully explore these potential signaling pathways in humans with greater sleep deprivation such as in OSA, in different tissue types, and for longer periods of time.

Most recently, Trzepizur and colleagues [56] examined how maternal gestational sleep fragmentation may impact metabolism in the offspring. Male offspring demonstrated increased body weight, fat mass, and systemic and adipocyte insulin resistance. Their exosomes also showed increased adipocyte proliferation. Using a double knock-out for C/EBP homologous protein (CHOP) and growth-arrest and DNA-damage-inducible protein 34 (GADD34) blocked these changes, suggesting that these genes, as part of the stress response, may mediate the metabolic dysfunction caused by gestational sleep fragmentation. This study raises the hypothesis that changes in sleep before birth may predispose

individuals to obesity and metabolic dysfunction. As this study was performed in rodents, it needs to be expanded and confirmed in humans.

While we are striving to understand the full spectrum of metabolic consequences of sleep disorders, including OSA, and we have initiated significant efforts towards understanding the underlying mechanisms, we do not yet know whether these changes may be corrected, and if yes, to what extent, by treatments for OSA, such as continuous positive air pressure (CPAP) for which conflicting evidence exists [57]. A greater understanding of underlying pathophysiological mechanisms, including mechanisms in utero or during early life, which may contribute to the development of OSA and/or metabolic dysfunction resulting from OSA later in life, is urgently needed. Such mechanisms can in turn inform the design of clinical trials to address this unmet clinical need. One could also argue that, in turn, clinical trials are also needed to further inform our knowledge about underlying mechanisms and thus the design of even better trials of novel potential treatments to address the metabolic consequences of OSA.

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Fig. 1.

Obesity leads to insulin resistance (IR, in many organs; shown: PBMCS, liver, brain, muscle, kidneys, adipocytes, pancreas) and cardiovascular disease as well as sleep apnea. Sleep apnea also leads to metabolic changes that in turn influence obesity.