Sleep apnoea, insulin resistance and diabetes: the first step is in the fat

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Intermittent hypoxia's effect on adipose tissue induces insulin resistance: a first step in the OSA–diabetes link http://ow.ly/UzIm309kEMi

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Over the last few years, the relationship between obstructive sleep apnoea (OSA) and various metabolic disorders, especially type 2 diabetes (T2D), has emerged strongly. This circumstance is particularly relevant in terms of public healthcare, considering that 415 million people were affected by diabetes in 2015, with an expected prevalence of 642 million by 2040. To this, we must also add another 318 million individuals with features indicating future risk for developing T2D, including fasting hyperglycaemia, impaired glucose tolerance and insulin resistance [1]. The healthcare expenditure for diabetes in Europe was about €75 billion in 2011, which is projected to increase to €90 billion by 2030 [1, 2].

The development of T2D is the consequence of a series of concatenated alterations. In healthy individuals, insulin secretion by the pancreatic β-cells allows for normal glucose disposal in insulin-sensitive tissues, mainly adipose tissue, the liver and muscles. In predisposed individuals, there is a reduced response to insulin-stimulated glucose uptake in adipose tissue and the liver, known as insulin resistance, which is compensated by a rise in insulin production [3]. However, the compensatory capacity of the increased peripheral insulin demand is lost when the insulin-secretory capacity of the pancreatic β-cells is compromised. In a first phase, insulin resistance and impaired insulin secretion only cause postprandial hyperglycaemia, a characteristic of impaired glucose tolerance. In more advanced phases with a more pronounced deterioration of insulin production, persistent hyperglycaemia originates in the fasting state, corresponding with T2D [4].

To date, there is much clinical–epidemiological evidence to support the relationship of OSA with both insulin resistance and T2D [5]. Overall, it has been reported that the prevalence of prediabetes, assessed by insulin resistance and glucose intolerance, is higher in OSA patients than in controls, with estimates varying from 20 to 67% [6]. Several cross-sectional studies have shown that OSA impairs insulin sensitivity and glucose tolerance [7, 8], and it has been demonstrated that OSA is independently related to the development of insulin resistance, while the oxygen desaturation index is the main determining factor [9]. This latter finding, which has been corroborated by other studies [10], is particularly important, as it involves the hypoxic stress of OSA in the development of insulin resistance. Finally, OSA has also been independently associated with T2D [11]. In fact, in a very large nationwide study of a health insurance claims database, T2D was significantly more prevalent in OSA patients than in matched controls from all age groups [12]. In the same vein, in a cross-sectional analysis of the European Sleep Apnoea Cohort

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study, T2D prevalence increased with OSA severity from 6.6% in subjects without OSA to 28.9% in those with severe OSA, and OSA severity was associated with glycaemic control in patients with T2D [13].

In order to consolidate the relationships between OSA, insulin resistance and diabetes, it is necessary to identify pathogenic pathways connecting the two key elements of OSA – intermittent hypoxia (IH) and sleep fragmentation – with loss of sensitivity to insulin in its target tissues and pancreatic islet β-cell dysfunction. In addition to providing biological plausibility to the OSA–T2D relationship, the characterisation of pathogenic pathways could provide for the identification of targets on which to act or the definition of patient profiles for those at risk or susceptible to intervention. Thus far, potential mechanisms have been proposed that could explain the association between OSA and metabolic dysfunction, including activation of the sympathetic nervous system, changes in hypothalamic–pituitary–adrenal axis activity, formation of reactive oxygen species, and increases in inflammatory cytokines and adipocyte-derived factors, such as adiponectin, leptin and resistin [2, 14].

Of all the possible pathways involved, numerous studies have investigated the relationship between IH and insulin resistance, assessing the effect of hypoxia–reoxygenation cycles on insulin target tissues. In several rodent models, it has been reported that chronic exposure to IH induces insulin resistance [15] and impairs glucose tolerance [16]. It has also been shown that healthy subjects who have undergone acute episodes of IH experience a decrease in insulin sensitivity [17]. However, although IH appears to be responsible for insulin resistance, the mechanisms involved remain unclear. The article in this issue of the *European Respiratory Journal* by Murphy *et al.* [18] provides important novel data demonstrating that IH decreases insulin sensitivity in lean and obese mice as well as cultured adipocytes, impeding insulin-mediated glucose uptake and, subsequently, inducing insulin resistance. In both murine epididymal visceral fat and adipocytes, IH down-regulates insulin-receptor substrate 1 (IRS-1) mRNA, decreasing insulin-induced tyrosine phosphorylation of the insulin receptor (IRβ) and IRS, as well as phosphorylation of Akt in adipocytes. Thus, IH leads to decreased functionality of adipose tissue, with inhibition of the insulin signalling pathway and down-regulation of IRS-1 mRNA. In addition, interesting information is also provided about the impact of IH on the adipose inflammatory phenotype. In studies in murine and *in vitro* models, it was observed that IH induces a pro-inflammatory phenotype of visceral adipose tissue with pro-inflammatory M1 adipose-tissue macrophage polarisation correlating with the degree of insulin resistance. These results are also in accordance with a very recent approach carried out by Gozal and co-workers [19, 20]. In the absence of a definitive mechanistic connection between M1 inflammation of adipose tissue and IRS down-regulation, the data generated provide new insights into understanding the effect of IH on one of the main target tissues of insulin.

In line with the M1 polarisation identified in adipose tissue, Murphy *et al.* [18] also describe that, in subjects without comorbidities, OSA severity correlates with serum levels of CD163, a surface marker characteristic of M2 macrophages, but whose soluble fraction requires M1-dependent cleavage [21]. It has therefore been considered a pro-inflammatory biomarker of several cardiovascular diseases, including insulin resistance and T2D [22]. Along the same lines, the demonstration of systemic M1 polarisation in patients with OSA related to nocturnal hypoxia intensity could contrast with the previous description of M2 polarisation in animal models with tumour infiltration subjected to intermittent hypoxia [23]. However, it should be kept in mind that this change in IH-induced macrophage polarisation could represent a merely local effect, relative to the proximity of tumour cells, because it has been described that while macrophages surrounding the tumour and those from the ipsilateral adipose tissue exhibit an M2 phenotype, an infiltration of preferentially M1 macrophages is observed in the contralateral adipose tissue [24]. Nonetheless, current knowledge of IH-induced macrophage polarisation does not allow us to conclude whether the two patterns identified are attributable solely to a local effect or whether there could be contributing systemic factors leading to different risk patterns in the development of comorbidity: metabolic–vascular (M1) *versus* pro-tumour (M2).

Identification of the effect of hypoxia on the inflammatory response of adipose tissue, as well as a better definition of the pathways involved in the reduced insulin sensitivity of this insulin target organ, will enable us to complete part of the sequence of glucose metabolism alterations induced by OSA, which will necessarily involve more organs and mechanisms (figure 1). In particular, some information is available on the effect of sleep fragmentation (SF). In a similar manner to IH, a shift towards the M1 phenotype in macrophages of mice subjected to chronic SF has been reported [25]. In addition, some evidence seems to indicate that it could intervene in the metabolic dysfunction observed in OSA. Thus, it has been demonstrated that shorter sleep duration negatively affects glucose metabolism [26], and, in a recent meta-analysis, the relative risk for the development of T2D associated with short sleep was estimated at 1.28 [27]. Although specific information on the metabolic consequences of sleep fragmentation is still limited, two independent groups have also shown negative effects of sleep fragmentation on insulin sensitivity in healthy participants [28, 29]. In addition, prospective population-based studies have shown an association between self-reported poor sleep quality and the incidence of T2D [30].

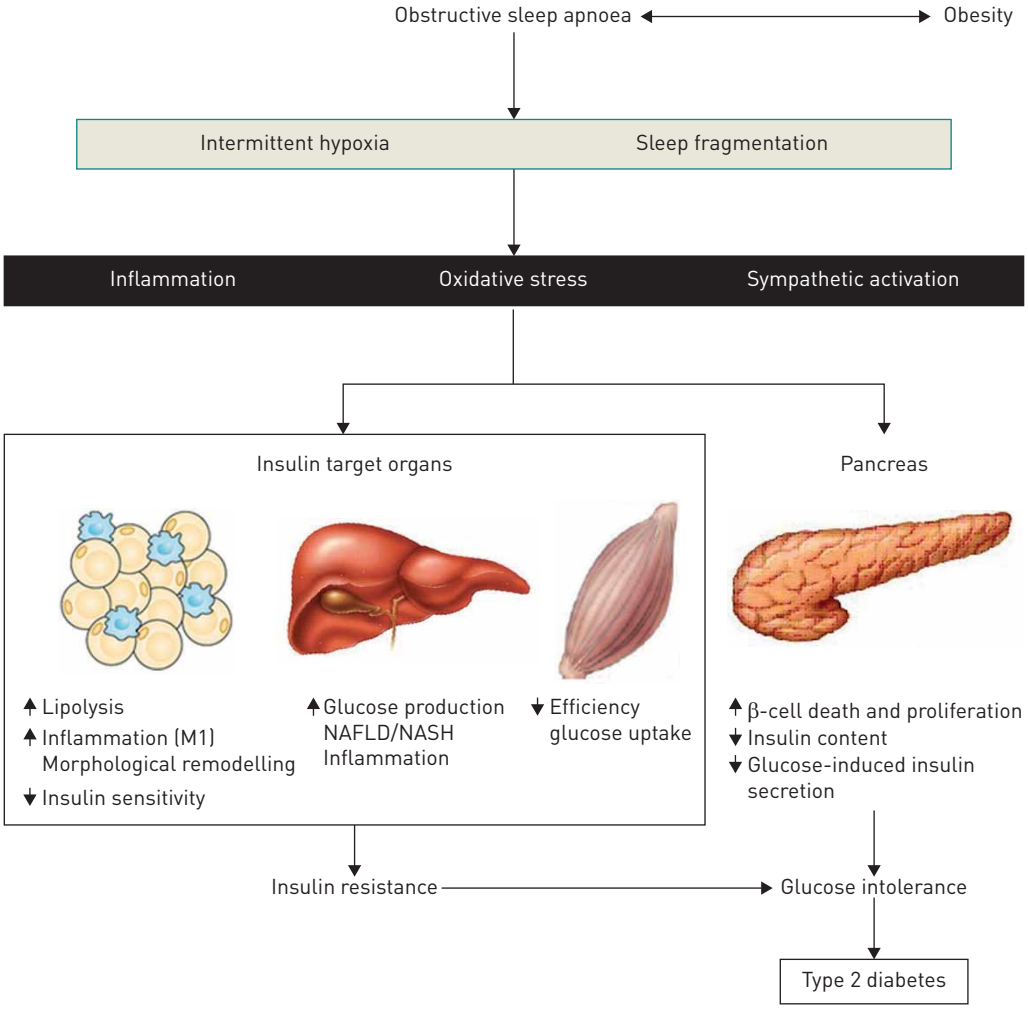

FIGURE 1 Potential mechanisms linking obstructive sleep apnoea to alteration in glucose metabolism. M1: pro-inflammatory macrophages; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis.

Another important aspect pending clarification lies in the identification of OSA factors that contribute to the dysfunction of pancreatic β-cells and justify the transition from pre-diabetes (insulin resistance) to T2D [31]. Although still preliminary, some data have suggested the involvement of inflammation, oxidative stress and increased sympathetic tone induced by OSA [2, 3]. Finally, in order to establish a partnership between OSA and T2D, it is necessary to determine the effect of apnoea–hypopnoea suppression on insulin resistance and glycaemic control in patients with OSA and T2D, the latter of which is still the subject of considerable debate [32, 33].

In short, the relationship between OSA and diabetes, which is supported by considerable epidemiological evidence, will be reinforced by the precise characterisation of its pathogenic mechanisms. Identification of the routes of action of IH on adipose tissue to induce insulin resistance is a first step in this regard.

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