



The Role of OSA on Metabolic Disorders

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Obstructive Sleep Apnea (OSA) is a frequent disorder in the general population, and even more common in the diabetic population, with incidences reported ranging from 17 [1] to 48% [2], although these figures are probably an underestimation. As this disorder is so widespread, it is often accepted and dismissed. Patients themselves, often omit mentioning that they suffer from sleep apnea to the doctor. In extreme cases various surgical interventions have used, however with not great success, some reports do not show superiority of surgery over use of continuous positive air pressure device (CPAP). While CPAP can lessen the severity of OSA, poor compliance using the device is common.

Recent research casts this disorder in quite a different light. Breathing is a physiologic function that follows a circadian rhythm and is tightly related to the pattern of the cardiovascular system. The heart rate is synchronized with the respiratory rate and the same is for the blood pressure oscillations. Furthermore, respiratory function is capable of an immediate response to external circumstances that demand more or less oxygen delivery. All body systems require oxygen, and all metabolic functions depend precisely on oxygen to function. So it is no wonder that the respiratory function and the attendant oxygen delivery have an impact on blood glucose metabolism. In this line of thought, a pioneering study [3] showed that OSA disrupts blood glucose metabolism, insulin, TSH and cortisol secretion pattern. Subsequent work confirmed these results, showing that the presence of OSA is associated with high HbA1c values. A polysomnographic study of 60 consecutive diabetic patients demonstrated that the severity of OSA is inversely proportional to HbA1c level [4]. OSA has been also commonly found in pre-diabetes and incident diabetes irrespective of obesity in a population >2500 nondiabetic subjects with a questionnaire based cross sectional analysis [5]. OSA disrupts sleep, and many critical functions are apparently caused by short / disturbed sleep, and among these appetite. A recent metaanalysis demonstrated that adults who sleep less than 5 hs have 60% increase in the risk of obesity [6]. Due to the well known effects of obesity on glucose metabolism it is clear that this dysfunction can worsen blood glucose control. Sleep exerts its effects on appetite disrupting the secretion of Leptin, Ghrelin and other less well studied hormones in nondiabetic individuals [7] or inducing leptin resistance in the diabetic population [8,9]. This condition is self perpetuating because the excess fat accumulates in the respiratory muscles, in the retropharyngeal space, in the abdomen, reducing the excursion of the diaphragm, thus further reducing the respiratory space, and increasing the burden of OSA. The accumulation of fat

in the abdominal cavity is in turn cause of increased secretion of inflammatory kinins and is a contributor to atherosclerosis [10]. A consistent positive linear correlation between visceral fat and one of the main indexes of OSA, the Apnea: Hypopnea Index (AHI) has been demonstrated [11]. OSA itself seems also capable of increasing the blood levels of the proinflammatory C-reactive protein, thus adding to the diffuse atherosclerotic damage [12]. On the basis of these data and others a critical role for OSA has been recently hypothesized. In brief OSA may predispose to the appearance of Obesity and diabetes in genetically predisposed individuals, worsen the inflammatory condition caused by these alterations, and precipitate a vascular catastrophe depriving of oxygen for a critical time this atherosclerosis - prone individuals [13].

There are few doubts on a role of OSA, but the strict relationship of this respiratory disturbance with the sleep pattern is a matter of further confusion. Sleep architecture is deeply disturbed in diabetes as described in a large retrospective report [14]. An elegant study on 11 young men who underwent a period of sleep restriction to 4 hours with a subsequent recovery period of 12 hours, demonstrated that during sleep extension glucose tolerance, acute insulin response to glucose (AIR), glucose effectiveness (the capacity of glucose to enhance its own cellular uptake and suppress endogenous glucose production independent of insulin), and insulin sensitivity were significantly improved compared with the sleep restriction period [15]. Another more recent study with selective suppression of the slow wave sleep with acoustic stimuli without sleep interruption confirmed these alterations [16]. Of great relevance is the increase in the AIR to glucose, which is characteristically suppressed in diabetics.

We definitely know that the unit OSA Sleep disruption affects the metabolic and cardiovascular environment, but there are many additional metabolic derangements associated with this disorder still to be discovered. Is the altered pattern of sleep or the oxygen deficiency / stressful stimulus of OSA the true culprit of these alterations in blood glucose control? A limited answer comes from a recently published study of 97 patients with type 2 diabetes treated with diet, metformin, or gliptins. In this study, the day to day variability of the fasting blood glucose was evaluated over a period of seven days, and the respiratory pattern was studied for one night. In these subjects, the indexes of respiratory disturbance and the number of awakenings appeared to act simultaneously to increase the variability. However when the variability was mild the number of awakenings appeared to be the main driver of this condition [17].

Other aspects of OSA and the sleep pattern on glucose metabolism, such as depth, duration, frequency of the awakening episodes; the role of the different phases of sleep in which the OSA / awakenings occur; the role of time of day when sleeping starts; and the role of the many drugs that diabetes patients take are worth being explored. More important, what the term “awakening” really means needs to be further clarified: what is the role of awakening, which can happen in more or lesser stressful conditions, and what is the significance of the duration of each episode of awakening? These data should be related to the many aspects of blood glucose physiology that we know, like fasting blood glucose, postprandial blood glucose, HbA1c values, and glucose variability. It is time to shed light on this net of missing information. There is much more to study in this fascinating disease to elucidate the attendant derangements of metabolism. We hope that the pages of the Journal will host additional data to help “see through the glass”.

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