Sleep Apnea, Glucose Regulation and Diabetes in Patients with Sleep Apnea

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Recent years have provided solid data on the huge importance of sleep in metabolic control in general, and glycemic control in particular. Both too-short sleep (less than 6 hours per night) and too-long sleep (more than 9 hours) are associated with increased risk for diabetes [1]. The mechanisms for these associations are still not completely clear, despite much progress in recent years. The association between sleep and glucose control is complex. While disturbed sleep may increase the risk for diabetes, it appears that diabetes in turn may result in sleep disturbances [2]. Experimental sleep deprivation in healthy volunteers resulted in insulin resistance, which normalized following recovery sleep [3]. On the other hand, obstructive sleep apnea (the most common cause of hypersomnia) has also been shown to result in insulin resistance and risk of diabetes [4,5].

Several studies have demonstrated an association between obstructive sleep apnea and diabetes. Epidemiologically, diabetes is significantly more prevalent in patients with OSA [4], and OSA is more prevalent in patients with diabetes [5]. The association between sleep apnea and diabetes may result from bidirectional relationships or is the outcome of a third factor affecting both glucose/insulin metabolism and breathing during sleep such as obesity or stress. Similarly, it has been shown that bidirectional relationships exist between OSA and obesity, likely resulting in a vicious cycle with positive feedback between the two [6]. Several recent studies have shown that treating only the sleep apnea may improve diabetic control, emphasizing the importance of OSA in the development of diabetes in these patients and providing evidence of a causal relationship between the two [7-10].

The paper by Elizur et al. [11] in the current issue of *IMAJ* describes a study that assessed the effect of respiratory indices in non-diabetic patients with OSA on glucose regulation. Although there was no correlation between the severity of OSA and glucose levels, they did find a significant correlation between lower mean 5 minute oxygen saturation (reflecting severity of OSA) and lower glucose variability, especially during REM sleep. Reduced glucose variability has been reported as a potential predictor of diabetes mellitus [12]. Thus, their study does support an association between OSA and increased risk for diabetes. The reason for the lack of correlation between respiratory indices and glucose levels may potentially be the small number of participants (only seven patients), which is the most important caveat in their study. On the other hand, the strength of their study is the continuous assessment of glucose levels, which provided solid data on the minute-by-minute glucose changes in patients with OSA but without diabetes. In addition, it should be kept in mind that several other studies that assessed the association between OSA and diabetes, as well as the effects of CPAP treatment, also failed to show positive results [13,14]. Thus, the relationship between sleep and diabetes is multifarious indeed. Several methodological issues may explain these conflicting results. These include small sample size, type of patients recruited, severity of OSA, concomitant diseases, medications used (especially glucose-lowering medications), duration of the study, lack of a control arm, lack of randomization, and/or blinded analyses of the results. Of special interest is the study by Chung et al. [14] of 25 patients with moderate-severe OSA who underwent 5 months of CPAP treatment but did not show improvement in glucose levels or insulin resistance. These results are in contradiction to other studies that showed clear improvement in glucose indices with CPAP treatment for OSA [7,9,10]. The reason for these conflicting results may stem from the relatively small sample size and relatively small baseline glucose metabolism impairment in the Chung study [14]. Recent careful and well-controlled studies concluded that in patients with OSA, CPAP treatment alone (with no treatment or unchanged treatment for diabetes) does result in improved glucose control [9,10].

Thus, the study by Elizur and co-authors [11] along with several other studies provide further substantial data linking sleep apnea with impaired glucose control and increased risk of diabetes [4,5,7,9-

OSA = obstructive sleep apnea

REM = rapid eye movement

CPAP = continuous positive airway pressure

11,15]. These studies show that diabetes is more common in patients with OSA, and that selective treatment for the sleep disorder results in a substantial amelioration of the glucose control impairment. Potential mechanisms to explain how sleep apnea causes insulin resistance and glucose intolerance consist of sympathetic activation, stress induced by hypoxemia, reoxygenation and sleep fragmentation, inflammatory processes involving adhesion molecules, and endothelial dysfunction [16,17]. The latter also links both sleep apnea and diabetes to cardiovascular diseases. Since CPAP treatment clearly alleviates both sleep apnea and the complications and potential development of diabetes, from the clinical point of view CPAP treatment is essential for patients with OSA. Successful treatment is expected to result in improved glucose metabolism, especially in patients with severe OSA and in those with relatively short disease duration [9,10]. With that in mind, we must question the factors affecting patients' decision to be treated with CPAP for OSA, since the major limitation for good treatment is patients' non-compliance with that treatment [18].

In conclusion, there is a growing body of evidence associating sleep apnea with metabolic disorders in general and glucose metabolism impairment in particular. Clearly, OSA can lead to glucose intolerance, decreased glucose variability, insulin resistance and diabetes, which may be relieved by treatment of only the sleep disordered breathing. This knowledge should continue to encourage clinicians to ensure that patients with OSA are effectively treated, particularly in this era of obesity and diabetes which have become a major public health problem.

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Capsule

BCAT1 promotes cell proliferation through amino acid catabolism in gliomas carrying wild-type IDH1

Tönjes et al. show that glioblastoma express high levels of branched-chain amino acid transaminase 1 (BCAT1), the enzyme that initiates the catabolism of branched-chain amino acids (BCAAs). Expression of BCAT1 was exclusive to tumors carrying wild-type isocitrate dehydrogenase 1 (IDH1) and IDH2 genes and was highly correlated with methylation patterns in the BCAT1 promoter region. BCAT1 expression was dependent on the concentration of α-ketoglutarate substrate in glioma cell lines and could be suppressed by ectopic overexpression of mutant IDH1 in immortalized human astrocytes, providing a link between IDH1 function and BCAT1 expression. Suppression of BCAT1 in glioma cell lines blocked the excretion of glutamate and led to reduced proliferation and invasiveness in vitro, as well as significant decreases in tumor growth in a glioblastoma xenograft model. These findings suggest a central role for BCAT1 in glioma pathogenesis, making BCAT1 and BCAA metabolism attractive targets for the development of targeted therapeutic approaches to treat patients with glioblastoma.

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