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Therapy for Insomnia and Glycemic Control in T2DM

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Abstract

Diabetes mellitus (DM) patients have been reported to have higher rates of sleep disorders and additional research is needed, as sleep restriction leads to striking alterations in endocrine function including increased insulin resistance, activated sympathetic tone, and elevated stress hormone secretion. An appropriate sleep environment is necessary for prevention of onset and worsening of DM, thus we consider therapy for insomnia to be an important target for improving glycemic control in insomniac DM patients.

Commentary

The prevalence of diabetes mellitus (DM) has been increasing rapidly throughout the world and publication of research findings is important. Therapy is considered essential for glycemic control in type-2 DM (T2DM) patients, such as diet and exercise, oral hypoglycemic agents, and insulin therapy, while new agents including sodium glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) have also become available. However, some patients cannot achieve good control with any of those approaches.

Patients with T2DM have been reported to have higher rates of sleep disorder and use more hypnotics as compared to control subjects [1]. Complications related to DM, e.g., nycturia and peripheral neuropathy, may lead to sleep loss, while a sleep disorder in DM patients can worsen glycemic control. In fact, it has been reported that reduced sleep quality is independently associated with a higher incidence of T2DM in the general population [2] as well as worse glycated hemoglobin A1c (HbA1c) status in affected patients [3]. Therefore, an appropriate sleep environment for prevention of onset and worsening of DM is considered to be important, though few studies have examined the relationship between therapy for insomnia and T2DM.

Mussa BM et al. [4] conducted a randomized controlled study with 51 patients with T2DM. Stress levels, recovery levels, and sleep habits were determined using heart-rate variability (HRV), followed by personalized approaches consisting of information, feedback, action, and follow-up examinations. Those results demonstrated that personalized intervention strategies that reduce stress levels, increase recovery levels, and promote healthy sleep patterns improve glycemic control in patients with T2DM. Gerfinkel D et al. [5] reported a randomized, double-blind, crossover study of 36 patients with T2DM and insomnia, who were treated with either melatonin, the major hormone produced nocturnally by the pineal gland and involved in entrainment into the light dark cycle, or a placebo. Subjects who received melatonin showed improved sleep efficiency and reduced wake time after sleep onset, as evaluated using wrist actigraphy, while mean HbA1c levels were significantly lower than at the baseline. As noted above, it is considered that treatment for insomnia may improve glycemic control in T2DM patients.

Other reports have noted that short-term partial sleep restriction in healthy subjects leads to striking alterations in metabolic and endocrine functions, including decreased carbohydrate tolerance, increased insulin resistance, activated sympathetic tone, and elevated serum cortisol concentrations [6,7], thus it is suggested that long-term sleep curtailment may predispose individuals to overt clinical DM. Several studies have demonstrated a strong association between insomnia and psychologic factors, especially in relation to perceived stress [8]. Mental and/or physical stress has been associated with activation of sympathetic tone [9], as well as accelerated secretion of various stress hormones, such as serum growth hormone, cortisol, and adrenaline [10]. Nocturnal excessive secretion of these stress hormones causes a steep rise in serum glucose levels during the early morning, termed 'dawn phenomenon' [11], which has been shown to cause an increase in average 24-hour mean glucose level, making glycemic control difficult in patients with T2DM [12].

These background issues prompted us to examine whether insomnia therapy can improve glycemic control with deactivation of sympathetic tone, reduction in insulin resistance, and suppression of dawn phenomenon in patients with T2DM and insomnia. We conducted a 7-day open-label, single-arm, intervention trial that included 18 subjects with T2DM and insomnia who were treated with suvorexant [13], a dual orexin receptor antagonist that suppresses wakefulness and promotes sleep without affecting neural systems other than the orexin system. Suvorexant treatment for 3 days significantly increased total sleep time and sleep efficiency, with partial suppression of sympathetic nerve activity expressed by SDNN from 109.5 to 113.2 ms ($p=0.044$). In addition, the mean glucose level noted in continuous glucose monitoring (CGM) for 24 hours was significantly decreased from 157.7 ± 22.9 to 152.3 ± 17.8 mg/dL ($p=0.010$), and especially during the dawn phenomenon period from 28.3 ± 15.0 to 18.2 ± 9.9 mg/dL ($p=0.002$), with a significant improvement in homeostasis model assessment of insulin resistance (HOMA-IR) from 4.0 ± 2.8 to 2.9 ± 1.6 ($p=0.044$) also noted. Those results demonstrated that therapy for insomnia in patients with T2DM can achieve improved glycemic control by reducing sympathetic nerve activity and insulin resistance, and improving dawn phenomenon.

Therapy for insomnia is important for DM patients who have difficulties with glycemic control by use of conventional

pharmacotherapy. Nevertheless, additional interventional examinations with qualitative sample sizes and adequate observation periods are necessary to clarify this potential relationship.

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