

TYPE 1 DIABETES ASSOCIATED WITH SLEEP DISORDERS

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ABSTRACT

Although the number of published studies regarding the interaction between T1DM and the sleep-wake cycle is limited, the findings on the subject are nevertheless significant. Glycemic variation, as well as poor glycemic control, in T1DM seems to affect the sleep-wake cycle as a whole. Some important evidences available in the literature, comparing sleep in subjects with T1DM with control subjects, are: a trend towards increased total sleep time, decreased sleep latency, increased sleep efficiency, higher blood levels of growth hormone, epinephrine and ACTH throughout the night, and higher cortisol levels during the first half of the night. It is likely that not only the long-term consequences of hyperglycemia affect nocturnal sleep, but also the acute responses to hypoglycemia. In our view, the latter affects sleep in individuals with T1DM regardless of whether the hypoglycemic event occurred during the day or night. On the other hand, there are evidences that a poor night's sleep and sleep disorders may not only result in diurnal sleepiness, but could also worsen diabetes control, revealing a vicious circle. We suggest that improved glycemic control and avoidance of hypo- and hyperglycemia would minimize the impact of T1DM on circadian rhythms, lessening sleep disorders and improving both sleep duration and quality. At the same time, it would favor the maintenance of a good metabolic control.

Keywords: type 1 diabetes, glycemia, sleep, sleep-wake cycle, sleep quality.

Several authors have reported an association between type 2 diabetes and sleep impairment. Previous studies have clearly established that sleep quality influences glucose utilization (1-3), and have implicated sleep debt as a cause for decreases in glucose tolerance (4). Furthermore, sleep-disordered breathing has been associated with glucose intolerance and insulin resistance, which may lead to type 2 diabetes mellitus (T2DM) (5-7). Other authors have argued that T2DM in adults is associated with higher rates of sleep-related disorders such as insomnia, excessive sleepiness,

breathing pauses, snoring, daytime sleepiness, restless legs or sleep debt (8-10). A study conducted by Knutson et al in individuals with T2DM determined not only that low sleep quality and high scores for perceived sleep debt are associated with poor glycemic control, but that poor diabetes control can then contribute to a higher perceived sleep debt and lower sleep quality (11). These results reveal a vicious circle, in which sleep debt and sleep quality impact glucose metabolism; in turn, glucose intolerance, insulin resistance or T2DM influence sleep length and quality, thereby

creating a feedback loop.

The serum level of glycosylated hemoglobin (HbA1c) is known to reflect average glycemia over the preceding 2–3 months (12). Studies that have evaluated HbA1c levels offer further substantiation for the link between glucose metabolism and perceived sleep debt or quality in people with T2DM (11). In a cohort of non-obese and non-diabetic children, HbA1c levels strongly correlated with the severity of sleep-disordered breathing (SDB) (13).

Unlike T2DM, the interaction between type 1 diabetes mellitus (T1DM) and the sleep-wake cycle has not been extensively studied. Although the number of published studies regarding this association is limited, the findings on the subject are nevertheless significant. Villa *et al.* showed that children with T1DM have more frequent and longer lasting apneas than those without diabetes (14). They also demonstrated that apnea events during sleep correlate significantly with poor glycemic control and with the duration of diabetes (14). Moreover, rapid changes in glucose levels that are independent of absolute glucose values may affect night sleep, resulting in awakening (15). Considering these and other data, along with complaints of excessive daytime sleepiness (16) and low sleep quality among people with T1DM, we hypothesize that glycemic variation in T1DM might affect the sleep-wake cycle as a whole.

Interestingly, Pillar *et al.* have reported a trend toward increased total sleep time, decreased sleep latency, and increased sleep efficiency in children with T1DM (15). Furthermore, they indicate an association between hypoglycemia during night sleep and an increase in sleep efficiency (15). In light of these findings, we are led to conclude that the tendency towards increased night sleep duration in T1DM individuals is potentially a result of a higher frequency of hypoglycemia during the night. In our view, it is likely that hypoglycemia affects night sleep duration and efficiency in individuals with T1DM, regardless of whether the hypoglycemic event occurred during the day or night.

The physiological path that links exposure to intermittent or prolonged hypoglycemia with sleep disorders is unknown. We do know, however, that acute or chronic hypoglycemia may act as a stressor that elicits physiological responses from the sympathoadrenal and sympathoneuronal systems as well as the hypothalamopituitary-adrenocortical (HPA) axis (18). Both humans and animals with poorly controlled or uncontrolled diabetes display diurnal hypersecretion of glucocorticoids, as well as altered regulation of the HPA axis (19). These effects could be related to the deterioration of sleep quality, as seen in patients with depression (20).

Jauch-Chara *et al.* recently reported that 14 individuals with T1DM displayed higher blood levels of growth hormone, epinephrine and ACTH throughout the night, as well as a tendency toward higher cortisol levels during the first night-half, compared with healthy control subjects (21). Even though their blood glucose had been monitored throughout the experimental night, these patients spent slightly less time in slow wave sleep during the first night-half and reported less restorative sleep than the healthy subjects. Nocturnal hypoglycemia was prevented in this study, which indicates that the increased level of counterregulatory hormones detected was not a result of hypoglycemia during the experimental night. The authors suggest that the slightly,

but persistently, elevated concentrations of glucose and insulin observed might be responsible for stimulating HPA activity and the release of epinephrine (21).

Although T1DM subjects were monitored during a single night, it is possible that changes in hormone levels and sleep architecture (21) were associated with disruption of the sleep-wake cycle and other circadian rhythms, leading to a phase shift of daily glucose tolerance (2). Taking into account all presented data, we suggest that improved glycemic control and avoidance of hypo- and hyperglycemia would minimize the impact of T1DM on circadian rhythms, improving both sleep duration and quality.

Further investigation is necessary in order to clarify the pathways through which T1DM and glycemic excursions may affect the sleep-wake cycle, and vice versa. We understand that it will be difficult to establish a cause-effect interaction, given the reciprocal nature of the influence between sleep and glucose metabolism. Glycemic excursions or poor glycemic control can lead to a poor night's sleep in terms of quality and/or length (11). In turn, a poor night's sleep and sleep disorders can not only result in diurnal sleepiness, but could also worsen diabetes control by raising pro-inflammatory cytokines. These cytokines inhibit glucose uptake by fat and muscle tissue as well as increase the secretion and plasmatic concentrations of counterregulatory hormones (22–24), which can lead to insulin resistance and glucose intolerance (25), thereby worsening the glycemic control.

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