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Author: Dijk, Marieke van
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I. INTRODUCTION

Intensive insulin therapy and frequent self-monitoring of blood glucose values (SMBG) are the main strategies for optimal replacement of endogenous insulin secretion and to attain normoglycemia in patients with T1DM. Unfortunately, despite more physiological insulin replacement approaches and intensive treatment strategies, relatively few patients reach the glycemic and HbA1c targets, and in general large intra-individual variations in blood glucose persist.

Previous studies showed an important role for sleep as another physiological determinant of intra-individual variations in glucose metabolism in healthy controls. The impact of impaired sleep characteristics on glucose regulation had not been studied in patients with T1DM prior to the studies described in this thesis. We hypothesized that altered sleep characteristics might be one of the physiological factors contributing to impaired glucose regulation in patients with T1DM. In addition, we hypothesized that hyperglycemic dysregulation could impair sleep characteristics, which, in turn, could create a vicious circle by disturbing glucose metabolism.

In the present thesis we explored the interaction between sleep characteristics and glucose regulation in adult patients with T1DM and healthy controls. In addition, we assessed the impact of impaired sleep characteristics on sustained attention in patients with T1DM.

The major conclusions and implications of these studies are discussed in this chapter.

II. SLEEP AND GLUCOREGULATION

1. Effect of sleep characteristics on glucose regulation
   a. Sleep restriction

   Healthy subjects:

   Previous studies showed a negative impact of (partial) sleep restriction during multiple nights on glucose tolerance in healthy controls. These studies were in some aspects limited as they did not assess insulin sensitivity by the euglycemic hyperinsulinemic clamp method, the gold standard for measurement of insulin sensitivity. In Chapter 2 we aimed to compare the impact of one single night of reduced sleep duration (4 hr) with that of a night of normal sleep duration (8.5 hr) on insulin sensitivity in healthy controls. We assessed insulin sensitivity with the hyperinsulinemic euglycemic clamp technique using stable isotopes. The results of that study indicate that even a single night of partial sleep deprivation reduces insulin sensitivity by 19-25% in multiple metabolic pathways in healthy controls. In addition, our data also indicate that insulin sensitivity is not static in healthy controls, and can be modulated by sleep duration. This has also been observed to hold for other environmental factors, including exercise, and dietary macronutrient composition and content.

   Clinical implications:

   Sleep duration has been shortened considerably in Western societies during the past decades, together with a simultaneously increase in the prevalence of insulin resistance and T2DM. Our study confirmed that shortened sleep duration is another physiological determinant that contributes to insulin resistance and consequently to diabetes risk in healthy controls. Sleep
restriction, even of a single night, can induce such effects, indicating that they are most likely present on a daily basis in many people. Strategies to increase sleep duration might be considered as a potential intervention to prevent or delay the development of T2DM in high-risk populations.

**Patients with type 1 diabetes mellitus:**

In most patients with T1DM glucose regulation cannot be completely normalized, despite intensive insulin treatment and large intra-individual variations in blood glucose levels persist. Subtle intra-individual variations in glucose regulation depend on variations in physiological determinants, such as dietary factors, stress and exercise. In Chapter 3 we aimed to explore whether sleep restriction was another physiological determinant of impaired glucose regulation in patients with T1DM. We evaluated the effects of a single night of partial sleep restriction (4 hr) with those of a night of normal sleep duration (8.5 hr) on insulin sensitivity in patients with T1DM. Our results showed that one night of partial sleep deprivation reduced insulin-mediated peripheral glucose uptake by 14-21%. The studies in Chapter 2 and Chapter 3 did not address the potential pathophysiological mechanisms involved in the negative effects of reduced sleep duration on insulin sensitivity. We speculate that these mechanisms involve alterations in the activity of the autonomous nervous system, in additions to the endocrine effects of shortened sleep duration.

**Clinical implications:**

This was the first study to assess the adverse effect of sleep restriction on insulin sensitivity in patients with T1DM. This study stresses that shortened sleep duration, even during only a single night, is another physiological determinant of insulin sensitivity in patients with T1DM and might become another therapeutic target to optimize glucoregulation in patients with T1DM. Endocrinologists perhaps ought to start explaining to their patients that not getting enough sleep may impair their insulin sensitivity, since it can be expected that sleep restriction increases postprandial glucose levels in the absence of concurrent adaptations of exogenous insulin dose. Further research of the underlying pathophysiologic mechanisms responsible for the effect of short sleep duration on insulin sensitivity in patients with T1DM is warranted.

**b. Sleep composition**

In addition to sleep duration, sleep composition is a determinant of glucose metabolism in healthy controls. The clear ‘restorative’ role of slow-wave-sleep (SWS) in the maintenance of glucose metabolism has been described before. The initiation of SWS coincides with neurophysiological, hormonal, and metabolic alterations, which can affect glucose regulation. Tasali et al. assessed the effect of multiple subsequent nights of SWS suppression on glucose tolerance, and documented that this intervention decreased glucose tolerance. However, these authors did not include the assessment of insulin sensitivity by the euglycemic hyperinsulminemic clamp method. The impact of one single night of selective on glucose regulation had not been studied in patients with T1DM previously. Chapter 4 described the effects of a single night of SWS suppression compared to a night of normal sleep on insulin sensitivity in healthy controls.
We used acoustic stimuli of varying frequency and intensity to suppress the SWS. Our study showed that a single night of selective suppression of SWS, without a change in total sleep duration, did not affect insulin sensitivity in healthy controls.

**Clinical implications:**
Although we showed a negative impact of shortened sleep duration on insulin sensitivity in healthy controls and patients with T1DM in Chapter 2 and Chapter 3, respectively, there was no effect of a single night of suppression of SWS during maintained sleep duration on insulin sensitivity in healthy controls. Therefore, sleep duration rather than sleep quality, is an important determinant of insulin sensitivity in healthy controls.

2. **Sleep in patients with T1DM**
Patients with T2DM report sleep disturbances more frequently than the general population does. This is relevant for glucose regulation, since previous publications have shown that reduced sleep duration and/or decreased sleep quality markedly reduce glucose tolerance and insulin sensitivity in healthy controls and patients with type 1 diabetes. Sleep characteristics, and their relation with glucoregulation, have not been studied in a large cohort of well-characterized adult patients with T1DM. In Chapter 5 we describe a cross-sectional study in which we compared subjective sleep characteristics between a well-characterized large cohort of adult patients with T1DM and individually age, sex and BMI matched healthy controls. In addition, we related these sleep characteristics to glycemic control, i.e. HbA1c values, and assessed possible risk factors for impaired sleep. We used validated sleep questionnaires to assess different features of sleep. We reported significant disturbed sleep quality and a higher risk for obstructive sleep apnea (OSA) compared with matched healthy controls. Several aspects influenced the outcome parameters: the HADS depression score, presence of polyneuropathy, habitual snoring, and other sleep disturbances were independently associated with poor sleep quality. We found no significant association between individual sleep characteristics and impaired glucoregulation.

**Clinical implications:**
This explorative, cross-sectional, study is important, since disturbed subjective sleep characteristics are apparently part of the complex syndrome of long-standing TIDM. Although the presumed relationship between sleep characteristics and impaired glucose metabolism, assessed by HbA1c values, was not observed in this study using questionnaires, additional studies with objective sleep measurements to assess the impact of impaired sleep characteristics on insulin sensitivity in patients with T1DM are described in Chapter 2-4.

3. **Effect of metabolic dysregulation on sleep**
Various aspects of diabetes could be linked to disturbed sleep characteristics in patients with TIDM, including complications of TIDM, psychological factors and high prevalence of sleep disturbances (see Chapter 5).
In Chapter 6, we aimed to investigate the effect of controlled metabolic dysregulation, frequently found in patients with T1DM, on sleep characteristics in well-controlled patients with T1DM on stable CSII. Hyperglycemic dysregulation was induced and maintained during the hyperglycemic night by 50% reduction of the basal and bolus insulin infusions compared with the euglycemic night. The results showed that hyperglycemia induced by reduction of insulin infusion did not affect objective sleep parameters. Therefore, a single night of hyperglycemic dysregulation does not constitute an important determinant of disturbed sleep duration and sleep quality in T1DM patients.

Clinical implications:
Although we showed that sleep duration is a determinant of glucose regulation in both healthy controls and T1DM patients in Chapter 2 and 3, hyperglycemic dysregulation did not turn out to be a determinant of impaired sleep in patients with T1DM. Since even well-controlled patients experience large daily fluctuations in glucose values, these fluctuations do not explain the potential disturbed sleep characteristics found in the patients.

Further objective research is warranted to elucidate the underlying mechanisms of the impaired sleep characteristics in patients with T1DM, since impaired sleep characteristics could impair glucoregulation in these patients.

IV. SLEEP AND SUSTAINED ATTENTION
Patients with T1DM perform less well on different neuropsychological tests, including sustained attention. Although different disease-related variables are associated with cognitive impairment, the exact pathophysiology is not completely elucidated. The role of impaired sleep characteristics on sustained attention has been documented in healthy controls and patients with sleep disorders. The Sustained Attention to Response Task (SART) has been proven to be sensitive to sleep deprivation in healthy controls and to excessive sleepiness in sleep-disorders. However, sleep characteristics and their relation with sustained attention had not been studied previously in patients with T1DM.

In Chapter 7 we describe a cross-sectional study exploring the relation between subjective sleep characteristics, assessed by validated sleep questionnaires, and sustained attention in patients with T1DM and healthy controls. We used the SART to assess sustained attention. The results of this explorative study indicate the presence of impaired sustained attention in patients with T1DM compared to healthy controls. In addition, the presence of T1DM per se was an risk factor for impaired sustained attention. However, disturbed sleep characteristics were not associated with impaired sustained attention in our patients. Additional studies with objective sleep characteristics are warranted.

Clinical implications:
The results of this cross-sectional study are relevant, since even mild forms of cognitive dysfunction, as observed in our study, might influence everyday activities.
V. SUMMARY AND CONCLUDING REMARKS

The present thesis described the interaction between impaired sleep characteristics and glucose regulation in adult patients with T1DM and healthy controls. In addition, we described the impact of impaired sleep characteristics on sustained attention in patients with T1DM.

From the studies described in this thesis we can conclude that:

1. A single night of partial sleep restriction decreased insulin sensitivity of multiple metabolic pathways in healthy controls. (Chapter 2)

2. A single night of partial sleep deprivation reduced insulin-mediated peripheral glucose uptake in patients with T1DM. (Chapter 3)

3. A single night of selective SWS suppression did not induce insulin resistance in healthy controls; reduced sleep duration rather than altered sleep composition is therefore an important determinant of insulin sensitivity in healthy controls. (Chapter 4)

4. Disturbed sleep characteristics are part of the complex syndrome of patients with longstanding T1DM. (Chapter 5)

5. There is no effect of short-term controlled hyperglycemic dysregulation on objective sleep characteristics in patients with T1DM. (Chapter 6)

6. Diabetes per se is independently associated with impaired sustained attention in patients with T1DM. (Chapter 7)

Optimizing sleep duration could be a therapeutic target to optimize glucoregulation in these patients, since voluntary sleep curtailment is extremely common in this 24-hr modern society. Although we showed that reduced sleep duration has a negative impact on glucose regulation, short-term controlled hyperglycemia did not affect sleep characteristics, and, therefore, no vicious circle between sleep characteristics and dysregulation of glucose metabolism appears to be present.
REFERENCE LIST


