The handle http://hdl.handle.net/1887/33966 holds various files of this Leiden University dissertation.

**Author:** Dijk, Marieke van  
**Title:** Type 1 diabetes and sleep : implications for glucoregulation  
**Issue Date:** 2015-06-18
CHAPTER 1

GENERAL INTRODUCTION
CONTENTS

I. Introduction

II. Type 1 diabetes mellitus (T1DM)
   1. Epidemiology
   2. Pathogenesis
   3. Diagnosis
   4. Complications
   5. Management

III. Sleep
   1. Definition
   2. Sleep architecture and stadia
   3. Determinants of sleep
   4. Function of sleep

IV. Sleep and glucose regulation
   1. Effect of sleep characteristics on glucose regulation
      a. Sleep duration
      b. Sleep quality
   2. Sleep characteristics in patients with T1DM

V. Consequences of impaired glucose regulation on sleep characteristics

VI. Sleep and cognition
I. INTRODUCTION

Type 1 diabetes mellitus (T1DM) is characterized by absolute insulin-deficiency, resulting from immune-mediated destruction of insulin-producing \( \beta \)-cells of the pancreas.\(^{(1)} \) Insulin replacement and frequent monitoring of blood glucose by patients themselves (SMBG) are the hallmarks of optimal treatment of T1DM.\(^{(2)} \)

Despite advances in insulin therapy during the past 25 years, relatively few patients with T1DM are able to reach the glycemic and HbA\(_1c\) target levels, obtained by normal metabolic control in non-diabetic subjects\(^{(3)} \), and they generally have relatively large intra-individual variations in blood glucose levels. Although insulin analogues and insulin pumps enable a level of insulin replacement that approaches the finesses of normal physiological control, it still remains impossible to achieve fully normal glucose physiology. This inability might be related to normal intra-individual variations in physiological factors, which may interfere with glucoregulation in healthy subjects and also in patients with T1DM, e.g. food intake, physical activity, and stress.\(^{(4-7)} \)

Voluntary sleep curtailment is common in our modern 24-h society. Increasing evidence exists for an important role of sleep as another physiological determinant of glucose metabolism in healthy people.\(^{(8-13)} \) Because altered sleep characteristics are known to affect glucoregulation in healthy controls, we hypothesized that this may also hold true for patients with T1DM. In this concept, altered sleep characteristics may be another factor challenging optimal glucoregulation in these patients. The effects of impaired sleep as a physiological determinant of impaired glucose regulation in patients with T1DM had not been studied previous to the studies documented in this thesis. Although there is only limited evidence that T1DM is associated with altered sleep patterns and sleep disorders\(^{(14-18)} \), metabolic dysregulation, frequently found in patients with T1DM, could still impair sleep characteristics; in turn, disturbed sleep could impair glucose metabolism, creating a vicious circle.

The studies described in this thesis focus on the interaction between sleep and glucose regulation in adult patients with T1DM. We studied effects of both shortened sleep duration and altered sleep composition on insulin sensitivity in adult patients with T1DM and healthy controls. In addition, we evaluated sleep patterns in T1DM, and studied the effect of hyperglycemia, induced by reduced insulin therapy, on sleep characteristics in patients with T1DM. Since T1DM was associated with cognitive impairment\(^{(19,20)} \), we also studied the effect of sleep characteristics on sustained attention in T1DM.

II. TYPE 1 DIABETES MELLITUS (T1DM)

1. Epidemiology

T1DM accounts for 5-10% of all cases of diabetes. Although it most commonly presents in patients younger than 16-18 years of age\(^{(2)} \) it may develop at any age.\(^{(23)} \) There is an enormous geographical variation in incidence of DM1 around the world, ranging from fewer than 4 cases per 100,000 children and adolescents(younger than 18 years) in much of Africa and Asia to more than 20 per 100,000 in Canada, Australia, and parts of Europe, with the highest reported incidences in Finland and Sardinia (about 50 and 37-45 cases per 100,000 children younger than 15 years,
respectively. The incidence of T1DM increases rapidly by 2% to 5% per year worldwide, especially in the youngest age group of who are less than 5 years of age. If these trends continue, a doubling of new cases of T1DM in European children younger than 5 years is predicted to occur between 2005 and 2020. Likewise the number of cases younger than 15 years will rise by 70%. There is no overall gender difference in the incidence of childhood DM1, but in select populations (e.g., older Europeans), there seems to be an increased risk for males (3:2 male to female ratio).

2. Pathogenesis

In the early 1980s Eisenbarth first describes the main phases of the pathogenesis of the immune form of T1DM. Available evidence suggests a strong genetic component, the most important of which relates to the HLA class II locus on chromosome 6, and with lesser contribution from other non-HLA genes, including the insulin gene on chromosome 11, and the cytotoxic T lymphocyte antigen 4 (CTLA4) on chromosome 2q33. Genes located within the HLA class II region on chromosome 6p21 are considered to be the major susceptibility genes for T1DM and account for approximately 50% of the genetic susceptibility. Both susceptibility, associated with diabetes resistance, and protective HLA haplotypes, associated with protection from the disease, are identified. The HLA haplotypes, DR4-DQ8 and DR3-DQ2, contribute to the greatest risk and are present in more than 90% of the children with T1DM. About 30% of patients with T1DM have both haplotypes, which combination confers the greatest susceptibility. These HLA susceptibility genes are thought to be important regulators of the immune response and have a major role in presentation of antigens involved in the pathogenesis of T1DM to antigen receptors on T-cells, the main effector cells of the destructive autoimmune process. The abnormal activation of the T-cell-mediated immune system by one or more environmental triggers in susceptible individuals leads to an inflammatory response in the islets of Langerhans, as well as to an humoral response with production of antibodies to β-cells antigens. Several autoantibodies have been identified that may play an important role in initiation or progression of auto-immune islet injury, including antibodies to insulin (IAA), glutamic acid decarboxylase (GAD-65), protein tyrosine phosphatase IA2 (IA-2AA), and zinc transporter (ZnT8). The presence and persistence of these autoantibodies facilitates the likelihood of progression to clinical disease, but there is no evidence that any of these antibodies have an active role in the pathogenesis of T1DM. The lifelong risk of DM1 is markedly increased in close relatives of patients with T1DM, averaging about 6 percent in their offspring, 5% in siblings, and 50% in identical twins (versus 0.4% in subjects with no family history). Environmental factors that trigger the onset of clinical disease are not well understood, but an interaction between genetic susceptibility and environmental factors is thought to be the fundamental element for the disease. Putative triggers include viruses (e.g., enteroviruses, coxsackie B, congenital rubella), environmental toxins (e.g., nitrosamines), or foods (e.g., early exposure to cow’s milk proteins, cereals, or gluten). Several pregnancy related and perinatal factors were associated with a small increase in risk of T1DM. There is evidence for a protective role of omega-3 fatty acids and vitamin D supplements in the inflammatory response associated with autoimmune islet cell destruction.
3. Diagnosis
The symptoms of T1DM are caused by hyperglycemia and include polydipsia, meaning excessive drinking, polyuria, or excessive urination, and considerable weight loss. Other symptoms may include lethargy, polyphagia, frequent yeast infections and urinary tract infections, blurred vision, impotence, nausea, vomiting, and dehydration. Diagnostic criteria for diabetes described by the WHO and American Diabetes Association (ADA) are a fasting plasma glucose >7.0 mmol/L, or a 2-hour glucose >11.1 mmol/L during a 75 gram oral glucose tolerance test (OGTT), confirmed by repeat testing on a different day in the absence of unequivocal hyperglycemia, or when classical symptoms of hyperglycemia are present and a random plasma glucose level is >11.1 mmol/L. (2) The presence of T1DM is suggested by presence of serum auto-antibodies to glutamic acid decarboxylase (GAD-65), protein tyrosine phosphatase IA2 (IA-2AA) and/or insulin (IAA). (39)

4. Complications
The quality of long term glycemic control, as reflected in HbA1c values, is associated with the onset and progression of the complications of T1DM. (61-64) Long-term diabetes-related complications are divided into microvascular disease – i.e. nephropathy, retinopathy, and peripheral neuropathy-, and macrovascular disease – i.e. cardiovascular, cerebrovascular, and peripheral vascular disease-, which account for most of the increased morbidity and mortality associated with the disease. (2) Risk factors for diabetes-related complications include poor glycemic control, early onset and long duration of T1DM, genetic susceptibility, gender, hypertension, hyperlipidemia, and lifestyle factors (e.g., smoking, obesity, exercise). (3) The mechanism by which poor glycemic control predisposes to vascular disease is not completely understood. Putative mechanisms, associated with hyperglycemia, include: 1) accumulation of advanced glycosylation end products that contribute to microvascular disease, 2) accumulation of sorbitol, which interferes with cellular metabolism, 3) end-organ response with activation of cytokines, profibrotic elements, vascular growth factors, inflammation and activation of protein kinase C. Genetic susceptibility is another important factor for the development of complications. (62,65)

5. Management
Insulin therapy and frequent monitoring of blood glucose by patients themselves is fundamental to account for deficient endogenous insulin secretion and to attain normoglycemia. (2) Long-term glycemic control is best measured by HbA1c concentrations, which reflects the average glycemic concentration during the previous three months. (66) Most patients use basal-bolus approaches to insulin delivery with either multiple daily insulin injections (MDII) or continuous subcutaneous insulin pumps (CSII). (67,68) There is a small but clinically significant improvement in HbA1c levels with use of CSII compared to MDII. (69,70) Despite advances in insulin therapy during the past 25 years, only a few individuals with T1DM are able to reach glycemic and HbA1c target levels consistently, reflected in large intra-individual variations in blood glucose. (3) Intervention studies on the effect of short treatment with CSII therapy showed some improvement of insulin resistance after CSII in patients with T1DM, but their insulin sensitivity remained lower than that of healthy subjects. (71-74) Other components of management of patients with T1DM...
include nutritional planning and carbohydrate counting\textsuperscript{(75-77)}, screening for and treatment of diabetes-related complications, screening for and treatment of diabetes-associate disorders, attention to psychological and psychosocial well-being, and avoidance or treatment of severe hypoglycemia and diabetic ketoacidosis.\textsuperscript{(3)} There is an inverse relation between glycemic control and the risk of hypoglycemic episodes. Repeated episodes of severe hypoglycemia are a risk factor for cognitive impairment in patients with T1DM\textsuperscript{(78,79)}.

\textbf{III. SLEEP}

\textbf{1. Definition}

Sleep is a natural and reversible periodic state, characterized by reduced or absent awareness and attention, limited sensory activity and inactivity of nearly all striated muscles. The reversible nature and predictable cycling of sleep stadia are features that distinguish sleep from pathological unconsciousness.\textsuperscript{(80)}

\textbf{2. Sleep architecture and stadia}

Normal sleep is composed of rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep, with NREM being subdivided into 3 stages representing a continuum of relative depth: stage N1, N2, and N3 with stage N3 designated as deep sleep or ‘slow-wave sleep’ (SWS).\textsuperscript{(81)} Each sleep stage has unique characteristics, including brain wave patterns on electroencephalography (EEG), eye movements and muscle tone. NREM and REM sleep stages alternate cyclically and display an ultradian rhythm, with a 90-120 minute cycle. Ultradian rhythms are recurrent periods or cycles repeated throughout a 24-hour circadian day. The cycle repeats 4-5 times throughout a normal 8-hour sleep period. Sleep begins in NREM and progresses through deeper NREM stages before the first episode of REM sleep begins approximately 90 minutes later. Although this cycle repeats through the night, the duration of REM sleep increases and the duration and depth of SWS decreases with each cycle. As a consequence of these shifts in duration, SWS predominates in the first third of the night and REM-sleep in the last third.\textsuperscript{(82,83)} Most of the entire sleep time (75-85\%) is spent in NREM-sleep. About 1-5\% of nocturnal sleep is accounted for by short normal periods of wakefulness.\textsuperscript{(80)} Polysomnography describes the recording of various signals including the EEG, electro-oculography (EOG), and electromyography (EMG) used to distinguish between different sleep stages as well as to record additional signals such as respiratory or circulatory ones to diagnose sleep disorders.\textsuperscript{(80,81)}

\textbf{NREM sleep}

NREM sleep is defined as ‘a relatively inactive yet actively regulating brain in a movable body’.\textsuperscript{(82)} During NREM sleep, cognitive activity is typically fragmented, and body activity periodically occurs as a person moves through the three stages of the NREM sleep. The three NREM stages roughly parallel a depth of sleep continuum with arousal thresholds generally lowest in N1 and highest in N3. Stage N1, drowsiness, is the transition from wakefulness to sleep and the lightest stage of sleep. It is characterized by relatively fast EEG frequencies with low amplitude. During
N1, muscle tone starts to decrease and attention and awareness of the external environment diminish. This stage accounts for 2 to 5 percent of the total sleep time (TST) in young adults. An increased proportion of stage N1 suggests sleep fragmentation due to a sleep disorder. Stage N2 is called ‘intermediate’ sleep and is characterized by a slowing of the main EEG frequency, the appearance of typical EEG phenomena such as sleep spindles and K-complexes, a further decrease in muscular activity, and loss of awareness of the external environment. Stage N2 sleep typically accounts for 40-50 percent of the total sleep time (TST). Benzodiazepines increase N2 sleep time at the expense of stage N3. The final NREM stage, N3 or SWS, is characterized by low frequency high-amplitude delta EEG waves, and accounts for 20 percent of the TST.

**REM sleep**
REM sleep is defined as a ‘highly activated brain in a paralyzed body’.\(^{(82)}\) It makes up about 20-25 percent of the total sleep time (TST) and is characterized by: 1) episodic bursts of rapid eye movements; 2) a low-voltage relatively fast EEG that resembles an active, awake pattern; 3) atonia of most skeletal muscles, excepting some such those involved in respiration; and 4) bursts of autonomic activity. REM sleep can be divided as having tonic and phasic periods, distinguished by short clusters of REM activity (phasic) that are followed by periods of relative inactivity (tonic).\(^{(80)}\)

### 3. Determinants of sleep
Sleep is thought to be regulated by several processes. The ultradian rhythm controls the NREM-REM cycle, whereas homeostatic drive (e.g. increased sleepiness follows longer periods of wakefulness) and circadian sleep-wake rhythms determine the amount and timing of sleep.\(^{(80,82)}\) Age, prior sleep history and the sleep environment, circadian rhythm disorders, external temperature, drugs, medical, neuropsychiatric, sleep and behavioral disorders are important factors which affect both sleep duration and stage distribution.\(^{(82;84-86)}\)

### 4. The function of sleep
Several theories have been proposed to describe the function of sleep, but the ‘restorative theory of sleep’ is most accepted. SWS is thought to be the most ‘restorative’ of all sleep stages.\(^{(87)}\) Several important physiological activities occur during SWS, including reductions in heart rate, blood pressure, sympathetic nervous activity, while vagal tone increases.\(^{(88)}\) SWS is also associated with a decrease in brain glucose metabolism.\(^{(89)}\) Additionally, hormone release is modulated by SWS. The release of the hypothalamic-pituitary-adrenal (HPA) system is inhibited\(^{(90)}\), whereas growth hormone (GH) and prolactin secretion are increased. The counterregulatory hormones GH and cortisol have both important roles in glucose metabolism and their levels are influenced by impaired sleep.\(^{(90)}\) Studies evaluating the effect of sleep deprivation indicated impairments in cognitive and physical performance\(^{(92,93)}\), and chronic sleep deprivation is associated with numerous cardiometabolic disturbances, including obesity, hypertension, dysfunction of glucose metabolism, increased diabetes risk, and even mortality.\(^{(94,95)}\)
IV. SLEEP AND GLUCOSE REGULATION

1. Effect of sleep characteristics on glucose regulation

In physiological conditions glucose metabolism shows a circadian rhythm with intra-individual daytime and nighttime variations in glucose tolerance. Various mechanisms operate during nocturnal sleep to maintain stable glucose levels during the night. In addition to circadian rhythmicity, sleep plays an important role in the regulation of glucose regulation during the night. During the first half of the sleep period glucose tolerance markedly decreases by diminished glucose utilization because of the predominance of SWS. The initiation of SWS is temporally associated with transient metabolic, hormonal, and neurophysiological changes, all of which could affect glucose metabolism, including a 30-40% decrease in cerebral glucose uptake, suppression of corticotropic and sympathetic activity, rapid anti-insulin-like effect by an increased growth hormone (GH) release, and decreased muscle tone. During the latter part of the sleep, plasma glucose levels progressively decrease towards pre-sleep values, reflecting increased glucose utilization due to the increase in awakenings and REM stages.

a. Sleep duration

Voluntary sleep curtailment has become a common behavior pattern in our modern ‘24-hour’ society. There is strong evidence that partial sleep restriction affects glucose regulation. A pioneering study by Van Cauter and colleagues showed a 40% reduction in glucose tolerance, measured with the intravenous glucose tolerance test (ivGTT), and other endocrine and metabolic changes associated with diabetes, after six consecutive nights of only four hours sleep per night in 11 healthy young men. Other experimental and epidemiological studies confirmed a strong association between (partial) sleep restriction during multiple nights and glucose tolerance in healthy subjects. Subsequent nights with partial sleep restriction result in impaired glucose tolerance in healthy controls, but the effect of one single night of partial sleep deprivation on insulin sensitivity had not been characterized in healthy controls. Moreover, previous studies did not include the assessment of insulin sensitivity by the hyperinsulinemic euglycemic clamp method, which is considered to be the gold standard for measurement of insulin sensitivity. We therefore evaluated the effect of a single night of partial sleep restriction on parameters of insulin sensitivity, assessed by the hyperinsulinemic euglycemic clamp studies combined with tracer dilution of [6,6-2H2] glucose in healthy controls (Chapter 2).

As said, glucose regulation cannot be normalized despite intensive insulin therapy in most patients with T1DM, apparent as large intra-individual variations in plasma glucose levels. Subtle intra-individual variations in glucose regulation and insulin sensitivity depend on variations in several physiological determinants, such as dietary factors, exercise and psychosocial factors. Since multiple nights of impaired sleep are known to impair glucose metabolism in healthy controls, we hypothesized that impaired sleep characteristics in patients with T1DM could contribute to the intra-individual variations in glucose regulation, and could be another physiological determinant of impaired glucose regulation seen in these patients. Therefore, we compared the effects of one single night of reduced sleep duration with those of a night of normal
sleep duration on hepatic and peripheral insulin sensitivity, as assessed by the hyperinsulinemic euglycemic clamp with stable isotopes, in adult patients with T1DM (Chapter 3).

b. Sleep composition

In addition to sleep duration, the composition of sleep in terms of sleep stages is also a determinant of glucose metabolism in healthy controls. Research has supported the clear role of SWS in the maintenance of normal glucose metabolism. Tasali and colleagues showed a markedly decreased insulin sensitivity and glucose tolerance measured with the ivGTT in young healthy controls after selective suppression of SWS, without a change in TST, during three consecutive nights. Selective SWS suppression was reached by delivering acoustic stimuli on varying frequency and intensity to speakers placed on each side on the bed of the subjects. However, the effects of one single night of controlled SWS suppression on insulin sensitivity, measured by the hyperinsulinemic euglycemic clamp method, have not been studied in healthy subjects before. Therefore, in Chapter 4, we compared the effects of one single night of impaired sleep quality – by selective SWS suppression - with those of a night of normal sleep on hepatic and peripheral insulin sensitivity, using a hyperinsulinemic euglycemic clamp with stable isotopes ([6,6-2 H2] glucose), in healthy controls. We hypothesized that selective suppression of SWS would decrease insulin sensitivity in healthy controls, which in turn may contribute to the intra-individual variations in plasma glucose in patients with T1DM.

2. Sleep characteristics in patients with T1DM

The interaction between T1DM and sleep characteristics has not been extensively studied. Jauch-Chara and colleagues reported altered sleep architecture in 14 non-hypoglycemic adult patients compared with healthy controls. The patients spent more time in lighter sleep stages and less time in SWS. The authors suggested that T1DM was associated with disruption of the sleep-wake cycle. A pilot study of Borel and colleagues showed a high prevalence of obstructive sleep apnea (OSA) in 37 non-obese adults with T1DM. Available evidence showed that children with T1DM have a more disrupted sleep with more frequent and longer awakenings, and more sleep disorders, such as more frequent and longer lasting apneas and restless legs syndrome, than healthy children. These studies investigated relatively few subjects or children with T1DM. The relation between sleep characteristics and glucoregulation has not been studied in adult patients with T1DM. Therefore, in Chapter 5 we compared subjective sleep characteristics measured by validated sleep questionnaires, between a large cohort of adult patients with T1DM with individually age, gender and BMI matched healthy controls. In addition, we related these sleep characteristics to the quality of glycemic control, i.e. HbA1c values, and assessed other possible risk factors for impaired sleep characteristics in adult patients with T1DM. Our primary hypothesis was that adult patients with T1DM have alterations in subjective sleep characteristics compared with individually matched healthy controls. In addition, we hypothesized that subjective sleep disturbances would be associated with impaired glucoregulation. If T1DM indeed causes disruptions of sleep patterns, this may in turn impair glucose regulation, creating a vicious circle.
3. Consequences of impaired glucose regulation on sleep characteristics

Various aspects of diabetes may be linked to disturbed sleep, including physical complications of the disease, metabolic fluctuations, psychological factors, and high prevalence of sleep disorders. A study of Perfect et al. showed an association between higher HbA1c and reduced SWS in diabetic children with T1DM. We hypothesized that metabolic dysregulation induced by reduction in insulin therapy in patients with T1DM may affect sleep characteristics. If so, this may induce a vicious circle: metabolic dysregulation would impair sleep and that in turn results in impaired glucose tolerance and insulin resistance. Therefore, we evaluated in Chapter 6 the effects of controlled hyperglycemia on sleep characteristics in well-controlled (HbA1c below 8% during the year prior to the start of the study) adult patients with T1DM on stable continuous subcutaneous insulin infusion (CSII). In order to obtain and maintain hyperglycemia during the night with glucose levels ~15 mmol/L, the basal and bolus insulin infusions of the patients with T1DM were reduced by 50%, compared with the euglycemic occasion.

V. SLEEP AND COGNITION

Patients with T1DM perform less well on neuropsychological tests including intelligence, psychomotor speed, visual and sustained attention, cognitive flexibility, visual perception, and speed of information processing. Although various disease-related variables are associated with cognitive impairment – e.g. chronic hyperglycemia, microangiopathy, age at onset, disease duration, and structural brain defects – the pathophysiology of cognitive dysfunction in T1DM is not well understood. Studies on the effect of severe hypoglycemia on cognitive function reported conflicting results. Whereas some retrospective studies suggested an association in adult patients, large prospective studies failed to conform this. Disturbed sleep might well be another determinant of impaired cognitive function in patients with T1DM. Disturbed sleep impairs daytime functioning, one expression of which is a decline in sustained attention, measurable as prolongation of reaction time (RT), i.e. speed, and an increased number of errors, i.e. accuracy. Decreased sleep duration was associated with decreased speed and the beginning of accuracy failure in healthy controls. Hence, disturbed sleep characteristics might contribute to cognitive problems in T1DM. Deficits in sustained attention have already in part been reported in previous studies of patients with T1DM. Those studies investigated sustained attention in children in a controlled setting to investigate the effect of acute hypo- or hyperglycemia, or used tests like the digit vigilance test, the lottery ticket test, or the elevator counting test. The Sustained Attention to Response Task (SART) that assesses sustained attention, has been shown to be sensitive to sleep deprivation in healthy controls and to reflect excessive sleepiness in sleep-disordered patients. Sustained attention and its relation with sleep characteristics, have, however, not been studied in adult patients with T1DM. The SART takes a short time to perform, and is easy to administer, which make the test useful in a clinical setting. Therefore, we examined sustained attention – i.e. RT and number of omission and commission errors – in adult patients with T1DM, compared to healthy controls, and explored if sleep related factors are an risk factor for sustained attention. The results of this study are described in Chapter 7.
REFERENCE LIST

3 Daneman D. Type 1 diabetes. Lancet 2006; 367(9513):847-858.


56 Vaarala O, Knip M, Paronen J et al. Cow’s milk formula feeding induces primary immunization to


63 The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 1995; 44(8):968-983.


101  Maquet P. Sleep function(s) and cerebral metabolism. Behav Brain Res 1995; 69(1-2):75-83.


