Biological risk factors and sleep-related risk factors of type 2 diabetes mellitus

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Chapter 1

General introduction

Diabetes Mellitus

Diabetes Mellitus is a chronic, metabolic disease characterized by elevated levels of blood glucose, which over time leads to serious damage of the heart, blood vessels, eyes, kidneys and nerves. The number of people with diabetes nearly quadrupled since 1980 to 425 million people in 2017 and it is estimated to increase to an impressive number of 629 million people in 2045 [1]. Type 2 Diabetes Mellitus (T2DM) accounts for more than 90% of the people with diabetes [2]. T2DM results from the body's ineffective use of insulin and is characterized by deficient beta-cell function, insulin resistance, impaired insulin secretion and hyperglycemia [2].

However, several heterogeneous processes underlie the pathophysiology of T2DM [3]. This is evident from the fact that among people with prediabetes, defined as those not meeting the threshold for diabetes, only about 5-15% annually will actually progress to T2DM [4], while the remainder converts back to normoglycemia or remains at levels associated with prediabetes. According to an ADA expert panel, approximately 70% of people with prediabetes will develop T2DM eventually [5]. This suggests that there are different underlying pathophysiological processes underlying T2DM. Indeed, some of these processes are predominantly associated with obesity and insulin resistance, while others are associated with a loss of beta cell function as the primary abnormality [6]. Hence, information on the different mechanisms that play a role in the development of T2DM is essential for personalized T2DM prevention strategies and T2DM precision medicine and underlines the need to refine the characterization of people who will develop T2DM. For example, Ahlqvist et al. 2018 [7] identified five clusters (severe autoimmune diabetes, severe insulin-deficient diabetes, severe insulin-resistant diabetes, mild obesity-related diabetes and mild-age related diabetes), characterized by different abnormalities, of people with T2DM with differing disease progression and risk of diabetes complications, which could help to tailor and target early treatment. In this thesis, we will examine non-modifiable biological factors that may contribute to elucidating the heterogeneity in the pathophysiological processes to incident T2DM.

Risk factors for T2DM

T2DM results from a complex interaction between genetic, environmental and lifestyle factors. Numerous factors have been associated with the development of T2DM and among them several are considered established risk factors for T2DM.

First, it is well accepted that T2DM has an important *genetic component*. The high concordance rates of T2DM observed in identical twins support the involvement of genetic factors in the development of T2DM [8, 9]. Although a specific gene or genes have yet to be found, genome-wide association studies (GWAS) have successfully identified susceptibility loci associated with T2DM and related metabolic characteristics, which together explain about 10% of the heritable component of T2DM risk [9, 10].

A second well-known risk factor is *ethnicity*. Among ethnic minority groups, such as African, Turkish, Moroccan, and particularly South-Asian origin groups, a higher prevalence of T2DM is observed as compared with European host populations [11-13]. The prevalence of T2DM also differs between ethnic groups in the Netherlands. For example, men of different ethnic minority groups had 3 to 8 times higher odds to have T2DM and for women the odds were 6 to 12 times higher, compared to Caucasian participants [12].

A third risk factor is *age*. For years, T2DM was known as "older-onset diabetes,'' emphasizing that the prevalence of T2DM increases with age. Impaired beta-cell compensation in the context of age-related insulin resistance predisposes older people to develop T2DM [14]. However, in the last years, the age of T2DM diagnosis is decreasing [15]. This is mainly due to our current lifestyle patterns that result in obesity and less physical activity.

The fourth and leading risk factor for T2DM is *obesity* [16]. The risk of T2DM is not only determined by the degree of obesity, but also by the location of the fat accumulation. A recent Japanese population-based study [17] revealed that compared to non-obese group, obesity and visceral fat obesity alone each had little effect on the risk of incident T2DM with a Hazard Ratio (HR) of around 1.8 and 2.3, but that the presence of ectopic fat obesity resulted in the greatest risk of incident T2DM, with a HR of 4.7 (95%CI: 1.9–11.7) in men and 14.0 (7.2–27.1) in women. The pathophysiology linking obesity and diabetes is in generally attributed to insulin resistance and insulin deficiency [18]. In addition, free fatty acids (FFAs) play an important role. An *unhealthy lifestyle* is a fifth risk factor for T2DM.

Lifestyle factors

Lifestyle factors, such as smoking, physical inactivity, sedentary lifestyle and dietary intake are among the most important modifiable factors that have been suggested to play a role in the development of obesity and in turn T2DM. *Smoking* increases the risk of T2DM by around 30% for active smokers, compared to nonsmokers [19]. *Physical inactivity* refers to insufficient levels of moderate to vigorous intensity physical activity, so not meeting the recommendation of physical activity of at least 150 minutes moderate intensity or 75 minutes vigorous intensity physical activity per week [20], while *sedentary behavior* refers to prolonged sitting [21]. A recent meta-analysis reported a dose-response relation of physical activity with a pooled risk reduction of 26% (95%CI: 20-31%) for T2DM among those who adhered to the physical activity recommendations, compared to inactive people [22]. In addition, a significant association between sedentary time and incidence of T2DM with a pooled HR of 1.9 (95%CI: 1.6-2.2) was shown [23]. The underlying mechanism suggests that physical inactivity induces weight gain, obesity and eventually T2DM. Furthermore, sedentary behavior, in particular television viewing, is

also associated with unhealthy eating [24], aggravating the predisposition to obesity and T2DM.

In addition to being associated with sedentary behavior, *an unhealthy diet* is thought to be an important independent risk factor for the development of T2DM. When single food items are investigated, consumption of red meat [25], processed meat [26] and sugar sweetened beverages [27-29] are associated with an increased risk of T2DM, whereas consumption of fruits [30], vegetables [31] and whole grains [32, 33] are associated with a reduced T2DM risk [34]. When studying dietary patterns, the western diet, which is characterized by high consumption of red and processed meat, high fat dairy products, French fries, sweets and desserts, was associated with an increased T2DM risk independent of BMI, physical activity, age and family history (Relative Risk(RR): 1.6; 95%CI: 1.3-1.9)[35]. In contrast, a prudent diet, characterized by higher consumption of vegetables, fruit, fish, poultry and whole grains, resulted in a reduced risk (RR: 0.8; 95%CI: 0.7-1.0)[35].

A novel lifestyle factor that is suggested to be associated with risk of T2DM is sleep, which we will further investigate in this thesis.

Characterizing different pathophysiological processes of T2DM

Besides insulin, a variety of other biological factors are involved in the maintenance of glucose metabolism. To date, these factors however received less attention in relation with the development of T2DM than insulin. Among these biological factors are the incretin hormones, glucagon and GAD65 antibodies. A better understanding of the underlying processes associated with the development of T2DM, and in particular the possible role of glucagon, incretin hormones and GAD65 antibodies, could further refine the characterization of people who are at high risk of T2DM. In addition, people with T2DM also show differences in treatment responses and not all people achieve good glycemic control with their current treatment. Therefore, knowledge on glucagon, incretin hormones and GAD65 antibodies could also contribute to developing targeted prevention strategies and to a better guiding of treatment choices.

The two most important **incretin hormones** are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Food intake stimulates the secretion of these incretin hormones, which in turn regulate the release of both insulin and glucagon from pancreatic islet cells in order to control blood glucose levels. The important role of the incretin hormones with regard to insulin secretion becomes apparent when the same amount of glucose is infused intravenously as opposed to orally ingested; oral glucose enhances insulin secretion much more than infused glucose: the so-called incretin effect [36, 37]. However, in people with T2DM, the incretin effect is severely reduced [38]. Given the glucoregulatory actions of the incretin hormones and their importance in maintaining glucose homeostasis, it was hypothesized that impaired

incretin responses could be associated with the future development of T2DM, however this is yet to be studied.

Contrary to the beta-cells that release insulin, the pancreatic alpha-cells release **glucagon**, which breaks down hepatic glycogen and thereby releasing glucose to maintain glucose levels when blood glucose levels drop. Dysregulated release of glucagon by alpha-cells, which shows as increased fasting glucagon levels and reduced suppression of glucagon after a meal, contributes to the development of hyperglycaemia[39]. Because these abnormal glucagon responses already exist in people with prediabetes [40-42], impaired glucagon suppression could be associated with increased future risk of T2DM, however this is yet to be studied.

GAD65 antibodies, which are involved in the regulation of the beta-cells of the pancreas, are autoantibodies against the enzyme glutamic acid decarboxylase (GAD) [43]. GAD is involved in the production of the neurotransmitter gamma-aminobutyric acid (GABA). It is known that in T2DM, autoimmunity for GAD65, reflected by GAD65 antibody positivity, is associated with rapid progression to insulin deficiency [44-47]. In people without diabetes, GAD65 antibody positivity was associated with a decrease in maximal insulin secretory capacity, suggesting that the presence of GAD65 antibodies is a pancreatic marker of a subclinical autoimmune process which could lead to insulin deficiency and T2DM [48]. Several prospective studies [49-53] investigated the association of GAD65 antibody positivity with incident T2DM with inconsistent results. In this thesis, we will further explore whether GAD65 antibody positivity is associated with future risk of T2DM.

Novel risk factors for T2DM

While physical inactivity and diet are established lifestyle related risk factors for T2DM, sleep is a relatively novel lifestyle factor that is suggested to be associated with T2DM. In today's society the prevalence of impaired sleep has been increasing [54, 55]. A recent meta-analysis conducted in the Netherlands, revealed that in 2017, 7-28% of the general adult population reported to have a specific form of impaired sleep, namely insomnia symptoms [56]. Insomnia is defined as chronic difficulty of falling asleep, staying asleep or waking up early, despite opportunity to sleep, for at least 3 times a week during 1 month, resulting in daytime impairment [57]. Several forms of impaired sleep, it being short sleep, long sleep, insomnia, napping, circadian rhythm disturbances, affect a wide range of body functions, including metabolic health and the endocrine system [58-63].

Impaired sleep as risk factor for T2DM is thought to be mediated by several mechanisms. First, impaired sleep is thought to affect the secretion of the hormones ghrelin and leptin [64]. As both hormones play an important role in regulating hunger and appetite, elevated hunger and appetite could lead to obesity and in turn increases insulin resistance, thereby predisposing people to T2DM [62]. Second, impaired sleep is

associated with daytime fatigue and sleepiness, thereby reducing physical activity and increasing weight gain [65]. Third, impaired sleep is thought to affect the stress response system. Hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis or sympathetic activation leads to an increase in cortisol levels, which in turn contributes to insulin resistance, dyslipidemia and obesity [65] Fourth, impaired sleep might cause decreased brain glucose utilization, which leads to hyperglycemia [66].

To date, when examining impaired sleep, sleep duration is most often investigated, making it the most established impaired sleep risk factor for developing T2DM. Insomnia is the second most important factor, which is predominantly studied in people without T2DM. A recent meta-analysis showed a clear pattern for impaired sleep as a risk factor for developing T2DM; ranging from an increased risk of 28% in people with sleep duration of ≤5-6h, compared to 6-8h per night to 84% in those with insomnia compared to those without [67]. The studies that analyzed the prevalence of insomnia in people with T2DM showed inconsistent results, ranging from 6 [68] to 80% [69] and its association with metabolic parameters and glycemic control in people with T2DM are largely unknown, and therefore will be studied in this thesis.

Additionally, there are several less known forms of impaired sleep for which there is not so much evidence on the association with T2DM. Among them is **social jetlag**, which is a less-known and less extreme form of disturbed circadian rhythm, compared to shift work and travelling to time zones. Social jetlag represents the discrepancy between circadian and social clocks, in the way that people often use alarm clocks and/or medication to align their sleep and wake times with social obligations rather than with their internally regulated sleep wake times [70, 71]. As 69% of adults report at least one hour of social jetlag, this is a highly prevalent sleep disturbance [71]. However, only a few studies have investigated the metabolic consequences of social jetlag [70, 72-74] and the association with T2DM is still lacking. As the different forms of impaired sleep, such as short sleep duration, napping and insomnia, often cluster, it is also important to assess the conjoint effect of these sleeping problems, both will be done in this thesis.

Main objective

This thesis aims to examine 1) the value of non-modifiable biological factors that could play a role in the development of T2DM and could contribute to the improved characterization of people at risk of developing T2DM and 2) impaired sleep as a possible novel modifiable lifestyle factor associated with T2DM development and progression.

Study populations

The studies described in this thesis, were performed in two prospective general population cohorts; the Hoorn Meal Study and the New Hoorn Study. The Hoorn Meal Study was initiated in the year 2005 and consisted of 208 participants at baseline [75].

After 7 years, a follow-up examination was carried out in which 129 people participated [76]. The New Hoorn Study is a cohort study with the main objective to investigate whether the increasing rates of longevity, physical inactivity and obesity affect the prevalence and risk factors of disturbances in glucose metabolism [77]. The New Hoorn Study was initiated in 2006-2007 and consisted of 2807 participants at baseline [78]. Between 2013-2015, a follow-up visit of the total cohort was conducted in which 1734 people participated [79].

Outline of the thesis

Following this general introduction (chapter 1), the first part of this thesis describes non-modifiable biological factors and their association with T2DM. Chapter 2 describes the prospective association between the incretin responses during an oral glucose tolerance test (OGTT) and mixed meal test (MMT) and fasting glucose levels in the Hoorn Meal Study. In Chapter 3, the prospective association between glucagon responses to an OGTT and MMT and fasting glucose levels in this same study is described. Chapter 4, describes the association between GAD65 antibody levels and incident diabetes in a systematic review and meta-analysis, including new data from the Hoorn Study. In part 2, impaired sleep as a novel modifiable risk factor for T2DM development and progression is described. Chapter 5 describes the cross-sectional association of social jetlag with presence of the metabolic syndrome and T2DM in the New Hoorn Study. In Chapter 6, the cross-sectional association of several sleep-related factors, namely sleep duration, insomnia, napping and sleep medication use with the metabolic syndrome is described. Chapter 7, describes the prevalence of insomnia and insomnia symptoms and its association with metabolic parameters and glycemic control in adults with T2DM in a systematic review and meta-analysis. In the general discussion (chapter 8), the main results are discussed and summarized.

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