

Review

Sleep habits and diabetes

S. Larcher^a, P.-Y. Benhamou^a, J.-L. Pépin^{b,c}, A.-L. Borel^{a,b,*}

^a Grenoble University Hospital, Pôle DIGIDUNE, Endocrinology Department, Grenoble, France

^b HP2 laboratory, Inserm U1042, Grenoble Alpes University, Grenoble, France

^c Grenoble University Hospital, Pôle Thorax et Vaisseaux Clinique Physiologie, Sommeil et Exercice, Grenoble, France

Received 29 August 2014; received in revised form 9 December 2014; accepted 29 December 2014

Available online 23 January 2015

Abstract

Sleep duration has been constantly decreasing over the past 50 years. Short sleep duration, sleep quality and, recently, long sleep duration have all been linked to poor health outcomes, increasing the risk of developing metabolic diseases and cardiovascular events. Beyond the duration of sleep, the timing of sleep may also have consequences. Having a tendency to go early to bed (early chronotype) compared with the habit of going to bed later (late chronotype) can interfere considerably with social schedules (school, work). Eventually, a misalignment arises in sleep timing between work days and free days that has been described as ‘social jet lag’. The present review looks at how different sleep habits can interfere with diabetes, excluding sleep breathing disorders, and successively looks at the effects of sleep duration, chronotype and social jet lag on the risk of developing diabetes as well as on the metabolic control of both type 1 and type 2 diabetes. Finally, this review addresses the current state of knowledge of physiological mechanisms that could be linking sleep habits and metabolic health.

© 2015 Elsevier Masson SAS. All rights reserved.

Keywords: Diabetes; Sleep duration; Chronotype; Social jet lag; Melatonin

1. Introduction

Sleep habits are changing. It is well demonstrated that sleep duration has constantly decreased over the past 50 years. In the US population, the National Sleep Foundation reports that sleep duration has decreased from 9 h in 1910 to 7.5 h in 1975 and 6.8 h in 2005 (see <http://sleepfoundation.org/sleep-polls-data/white-papers/how-much-sleep-do-adults-need/page/0%2C8/>), while French surveys into sleep habits have revealed the same trends [*Sommeil et rythme de vie* (Sleep and lifestyle); 2009; p. 1–22; www.institut-sommeil-vigilance.org/documents/Presse-JNS-2009.pdf]. A meta-analysis based

on eight sleep-related US studies, carried out between 1975 and 2006, showed that the proportion of short sleepers (defined as those sleeping < 6 h per night) has increased from 6.6% to 9.3% during this period. Sociodemographic factors associated with short sleep were having full-time work, being a man and being < 65 years of age. Married people and those of Asian or Hispanic ethnicity had less risk of being short sleepers [1]. Short sleep duration, poor sleep quality and, recently, long sleep duration have all been linked to poor health outcomes that have stimulated a new field of research addressing the characteristics of sleep habits as well as their impact on health.

Indeed, beyond duration of sleep, the timing of sleep has a significant impact. For instance, shift workers demonstrate numerous adverse health events compared with day workers [2]. In the general population, having a tendency to go to bed early (early chronotype) compared with the habit of going to bed later (late chronotype) can have an impact on health [3,4]. Moreover, social schedules (such as school and work) interfere

* Corresponding author. CHU de Grenoble, pavillon des Ecrins, CS10217, 38043 Grenoble cedex 9, France. Tel.: +33 04 76 76 55 09; fax: +33 04 76 76 50 42.

E-mail address: alborel@chu-grenoble.fr (A.-L. Borel).

considerably with individual sleep preferences in the majority of the population. Subjects having late chronotypes are more likely to accumulate a sleep debt during work days that will be recovered during work-free days. The misalignment of sleep timing between work and free days has been described as ‘social jet lag’.

The present work reviews how different sleep habits can interfere with diabetes, excluding the sleep breathing disorders that are frequently seen in patients with diabetes. This report will also successively look at the effects of sleep duration, chronotype and social jet lag on the risk of developing diabetes as well as on metabolic control in both type 1 and type 2 diabetes (T1D and T2D, respectively). Finally, the current state of knowledge of the physiological mechanisms that could be linking sleep habits and metabolic health are addressed.

2. Sleep duration and diabetes

Numerous studies have addressed the question of the relationship between sleep duration and the prevalence of T2D in cross-sectional studies [5–12]. These studies are summarized in [Table 1](#). In fact, the majority of studies found just such an association in a wide range of populations from different geographical areas, and in both adult men and women. However, these studies used different definitions for short sleep duration and took into account either previously known or newly diagnosed T2D, or both. T2D also appears to be more frequent in subjects with long sleep durations, albeit with less robust evidence.

Causality in the relationship between sleep duration and diabetes, however, cannot be determined from cross-sectional analyses. Having a chronic disease like T2D could in itself have an impact on sleep quality and quantity. For this reason, several prospective studies have been conducted in large population-based cohorts to assess the link between chronic, self-reported sleep habits and T2D incidence. The European Prospective Investigation into Cancer and Nutrition (EPIC) study is an ongoing large-scale cohort study of diet and chronic diseases across Europe. In the 23,620 men and women followed for a mean duration of 7.8 years, the hazard ratio (HR) for developing T2D according to sleep duration was not significant in the fully adjusted model [13]. However, in a prospective occupation-based study in Japan, 3073 men and 1122 women showed higher risk of developing T2D when they slept <5 h per night compared with those who slept >7 h per night (adjusted OR: 5.37, 1.38–20.91) [14].

Other prospective studies have demonstrated a significant risk of developing T2D in patients having either short sleep duration [15–20] or long sleep duration [16–18,20,21]. These studies are summarized in [Table S1](#) (see [supplementary material associated with this article online](#)). Two meta-analyses of data from these prospective studies have also been performed. The first, by Cappuccio et al. [22], analyzed the results of nine prospective studies and found that short duration of sleep determined a greater risk of developing T2D with no evidence of publication bias. The effect in men (RR: 2.07, 95% CI: 1.16–3.72) tended to be larger than in women (RR: 1.07, 95% CI: 0.90–1.28; heterogeneity test $P=0.04$). Yet, long duration of sleep was also associated with greater risk of T2D (RR: 1.48, 95% CI:

1.13–1.93) with no evidence of publication bias and no statistically significant heterogeneity. One hypothesis is that long sleep duration could be a marker of associated sleep disorders, typically sleep apnoea.

The second meta-analysis, by Holliday et al. [23], analyzed data from 10 studies, involving 447,124 participants of predominantly European ancestry, except for two studies (combined $n=10,079$) conducted in Japanese populations. The overall association of short sleep with diabetes risk was highly significant (OR: 1.33, 95% CI: 1.20–1.48; $P=4 \times 10^{-8}$) with no evidence of publication bias (Egger’s test, $P=0.15$).

Furthermore, in patients with previously known diabetes, inadequate sleep duration has been associated with several adverse outcomes. In the Korea National Health and Nutrition Examination Survey (KNHANES), 2134 men and women with T2D provided their self-reported sleep durations [24]. HbA_{1c} levels according to sleep duration were U-shaped, with those subjects sleeping 7 h/day having the lowest HbA_{1c} levels. However, the odds ratio (OR) for having an HbA_{1c} level >7%, indicating insufficient glycaemic control, was not significantly associated with sleep duration after adjusting for confounding factors. In the Fukuoka Diabetes Registry, 4870 Japanese men and women with T2D also demonstrated a U-shaped relationship between HbA_{1c} and sleep duration. The quadratic relationship remained significant even after adjusting for confounding factors [25]. In addition, short and long sleep durations have been associated with elevated urinary albumin excretion in patients with T2D [26,27].

In 79 patients with T1D, those having an objectively determined short sleep duration (<6.5 h per night), as measured by a wrist actimetry sensor, had higher levels of HbA_{1c} compared with patients who slept >6.5 h per night ([Fig. S1](#); see [supplementary material associated with this article online](#)) [28]. In addition, patients with T1D who presented with a non-dipping pattern of their night-time blood pressure had shorter sleep durations than those who presented with a physiological nocturnal dip in blood pressure [28,29].

In summary, sleep duration, whether too short or too long, appears to be linked with an increased risk of developing T2D. On the other hand, in patients with either T1D or T2D, both short and long sleep durations may have deleterious effects on glycaemic control as well as on other mediating factors (blood pressure, urinary albumin excretion) that contribute to target organ damage.

3. Chronotype and diabetes

A person’s ‘chronotype’ refers to their preferred schedules for sleep and daily activities. Those with morning, or early, chronotypes prefer to get up early and to have activities in the morning, whereas subjects with late, or evening, chronotypes go to bed later in the night and favour evening activities. Chronotype is also dependent on age: adolescents are likely to have a late chronotype, which will evolve towards an earlier chronotype with increasing age [30]. Thus, the ‘diurnal type’ is considered a biologically determined trait-like preference that can be environmentally modified. Circadian rhythms are generated

Table 1
Odds ratio (OR) for having type 2 diabetes according to sleep duration in cross-sectional analyses.

	Study design	<i>n</i>	Populations	Covariates	Sleep duration	OR (95% CI)
Tare et al. [5]	Case-control, five cohort studies	9797	European American, FW, M	Age, gender, BMI	Short sleep (< 5 h) Long sleep (> 9 h)	1.32 (1.0–1.61) 1.14 (0.9–1.38)
Jackson et al. [6]	Cross-sectional study, eight survey years (2004–2011) of US NHIS	130,943	White American, African American, W, M	Age, gender, socioeconomic factors, alcohol consumption, smoking status, physical activity, marital status, heart disease, hypertension, standard BMI categories	<i>African American:</i> Short sleep (< 7 h) Long sleep (> 7 h) <i>White American:</i> Short sleep (< 7 h) Long sleep (> 7 h)	PR (95% CI) 1.08 (0.95–1.23) 1.01 (0.89–1.15) 1.16 (1.07–1.25) 1.17 (1.09–1.26)
Najafian et al. [7]	Cross-sectional study	12,514	Iranian, W, M	Age, gender, BMI, waist circumference	Short sleep (< 5 h) Long sleep (> 9 h)	1.62 (1.33–1.99) 1.10 (0.83–1.44)
Lou et al. [8]	Cross-sectional study	16,893	Chinese with no known diseases, W, M	Age, gender, education levels, smoking, employment status, alcohol intakes, BMI categories, regular exercise	Short sleep (< 6 h) Long sleep (> 8 h)	1.25 (1.03–1.51) 0.87 (0.77–1.11)
Kachi et al. [12]	Cross-sectional study	20,744	Japanese, M	Age, obesity, smoking status, alcohol intakes, physical activity	Short sleep (< 5 h) Long sleep (> 9 h)	1.52 (1.22–1.90) 1.39 (1.05–1.85)
Cumberbatch et al. [9]	Cross-sectional study, Jamaica lifestyle survey 2007–2008	2432	Jamaican, W, M	Age, BMI, family history of diabetes	<i>Men:</i> Short sleep (< 6 h) Long sleep (> 10 h) <i>Women:</i> Short sleep (< 6 h) Long sleep (> 10 h)	4.25 (1.01–17.92) 6.35 (1.32–30.59) 0.39 (0.19–0.81) 0.92 (0.47–1.80)
Chao et al. [10]	Cross-sectional study	3470	Taiwanese, W, M	Age, gender, smoking, alcohol intakes, coffee-drinking habits, physical exercise, family history of diabetes, obesity	Short sleep (< 6 h) Long sleep (> 8.5 h)	1.55 (1.07–2.24) 2.83 (1.19–6.73)

PR: Poisson regression; W: women; M: men; BMI: body mass index; NHIS: National Health Interview Survey.

through the precisely controlled, cyclical expression of a number of genes designated ‘clock genes’ [31]. The nearly bell-shaped distribution for diurnal preferences is consistent with a polymorphic trait created by genetic polymorphisms of these clock genes. Yet, the chronotype can also come under pressure from environmental and behavioural factors. Increased self-reported light exposure advances sleep time, and the sleep debt accumulated during working days has an impact on the chronotype of work-free days [32].

Broms et al. [33] reported the results of three prospective Finnish cohorts in which age and diurnal type were subjectively assessed at several time points. Analysis of the cross-sectional component showed that evening types became more prevalent between the 1980s and 2000s, a finding also reported by Roenneberg et al. [4]. Thus, the proportion of subjects having the evening chronotype has apparently increased in European populations over three decades. Such an evening chronotype appears to be associated with adverse health outcomes, including a higher mortality risk [33].

In the DILGOM substudy of the 2007 National FINRISK Study, subjects provided a blood sample in addition to their self-reported sleep habits. For the 2500 women and 2089 men included, cross-sectional analyses found an increased risk of T2D (OR: 2.6, 1.5–4.4) and of hypertension (OR: 1.3, 1.0–1.8) in those with the evening chronotype compared with subjects having the morning chronotype [34]. These associations were independent of sleep duration and sleep quality. In addition, in 194 patients with T2D, having a self-reported late chronotype was associated with deteriorated glycaemic control (as estimated by glycated haemoglobin levels) [35]. This association was mediated in part by a greater percentage of total daily calories consumed at dinner in patients presenting with the evening chronotype. In addition, the same subjects demonstrated a significant association between having an evening chronotype and a habit of skipping breakfast, both characteristics that have been independently linked to poorer glycaemic control in T2D [36]. In the study, people who skipped breakfast reported having no appetite in the morning compared with those who regularly ate

breakfast, suggesting that circadian regulation of appetite may play a role in skipping breakfast through factors related to either social schedules or genetic determination.

Overall, beyond sleep duration, the diurnal type—in particular, the evening chronotype—seems to have become more frequent in the general population and is associated with an increased prevalence of T2D as well as poorer glycaemic control in T2D patients. Nevertheless, only a few studies have addressed the potential impact of chronotype on diabetes, which now calls for further studies to document whether chronotype might be predictive of incident T2D or have an impact on metabolic control in patients with T1D.

4. Social jet lag and diabetes

Normal work schedules—typically starting early in the day—are best suited for subjects characterized as early chronotypes. Later sleep onset (whether controlled by the endogenous clock or by voluntary sleep behaviour) combined with early arousal (controlled by the external, social clock) cause late chronotypes to accumulate a substantial sleep debt over the working week, for which they have to compensate for by extending sleep duration on weekends. This interaction between the biological and social clocks can lead to a chronic form of sleep misalignment, depending on the chronotype and social situation ('social jet lag'). This social jet lag relates to the relatively infrequent jet lag experienced by people who travel across time zones, but with the peculiarity of being of small amplitude, yet recurring every week. This social jet lag can be quantified by calculating the absolute difference between mid-sleep time on work days and mid-sleep time on free days [37]. To some extent, social jet lag may also be observed in early chronotypes on free days if they stay up late into the night without the possibility of sleeping longer the next morning due to their normal circadian wake-up time. It is therefore possible that it is not simply chronotype, but also its consequences (such as social jet lag) that are the primary cause behind the adverse health outcomes in late chronotypes.

A population-based, cross-sectional study was performed by Roenneberg et al. [4], using an online questionnaire to assess sleep habits on work days and free days. This Munich Chrono-Type Questionnaire (MCTQ) was completed by more than 65,000 participants who were primarily from Central Europe. Their responses revealed that sleep duration decreased between 2002 and 2010, mainly by sleep curtailment on work days. Thus, social jet lag also increased during the same period. In addition, the respondents reported spending less and less time outdoors during work days as well as on free days. Thus, the authors hypothesized that the usual alignment of our sleeping behaviour on the light–dark cycle is impacted by spending more daylight hours indoors, under poor lighting conditions, while the nighttime hours are spent under artificial-light pollution. They also demonstrated, through multiple logistic regression, that social jet lag is associated with a prevalence of overweight and obesity, independently of age, gender, sleep duration and chronotype [4].

The impact of social jet lag on health outcomes has also been evaluated in shift workers, which found it to be positively associated with resting heart rate [38]. In the study by Reutrakul et al. [35], which addressed the impact of sleep habits on glycaemic control in patients with T2D, people with social jet lag of > 30 min tended to have higher HbA_{1c} levels than those with a misalignment of < 30 min, although this result was only a trend.

Thus, beyond sleep duration and chronotype, it is possible that the consequences of circadian misalignment on diabetes risk and/or glycaemic control is also influenced by social jet lag. This hypothesis deserves further study in patients with either T2D or T1D as well as prospective cohort studies to assess the relationship with the risk of developing T2D.

5. Study limitations

Human behaviour is torn between biological and social time, and influenced by natural timing signals ('zeitgebers', or light–dark cycles) that are 'polluted' by artificial light. However, natural zeitgebers are also influenced by the time of the year due to, for example, longer daylight exposure in summer. The amplitude of change in daylight hours throughout the year is also dependent on the latitude at which subjects live. In addition, seasonal adaptation, a continuous process that is itself 'polluted' by social time, which imposes an abrupt 1-h advance in time in spring and a 1-h loss in autumn. This social adaptation, aimed at minimizing the need for artificial lighting during work time, is another challenge for the biological clock. Allebrandt et al. [39] measured, in several European cohorts living at various latitudes, the influence of seasons on sleep habits, focusing on the two periods separated by the transition to 'daylight saving time' in spring and the return to the standard zone time in autumn. They demonstrated that these seasonal changes could influence chronotype, sleep duration and social jet lag, with various effects depending on the geographical location of the cohort. Such observations call for the inclusion of seasonal assessment as a potential confounder in further studies addressing the effects of sleep habits on health.

6. Mechanisms implicated linking sleep habits and diabetes

The circadian environment has generated a central nervous system mechanism essential for adapting and anticipating environmental fluctuations. Circadian body clocks are organized hierarchically, with the central clock located at the suprachiasmatic nucleus (SCN) of the hypothalamus, and peripheral clocks at other brain regions and peripheral tissues such as muscles, liver, adipose tissue and pancreas [40]. Environmental light–dark cycles reset the SCN pacemaker through the retina and retinohypothalamic (RHT) tract. The SCN in turn synchronizes oscillators in the peripheral tissues. However, the SCN is connected to numerous regions in the brain that, in turn, integrate with other zeitgebers such as social information, nutritional intakes and exercise. Also, there are numerous connections to the reward regions of the brain. It is estimated that circadian machinery controls the cyclical expression of about 10–20%

of genes in cells. In addition, the expression of these genes is modulated by epigenetic factors. Epigenetic regulation of the circadian transcription of cell genes is particularly controlled by the nicotinamide adenine dinucleotide (NAD⁺)-dependent silent mating type information regulation 2 homolog 1 (SIRT1) histone deacetylase, which is central to the regulation of circadian activity of the peripheral metabolic pathways as well as the circadian epigenetic expression of circadian-regulated genes [41].

SCN activity is one of the factors implicated in the central nervous system that directs both behavioural and metabolic adaptations, leading to circadian regulation of food intake. In turn, food intake and, as a consequence, metabolic pathways provide feedback to the central nervous system and modulate SCN activity (Fig. 1). Thus, given a different social environment where subjects are less exposed to light–dark cycles and more under the influence of social zeitgebers, SCN activity is then subjected to a new pattern of stimuli that subsequently changes the regulation of peripheral clocks as well as the circadian regulation of food intake.

The mammalian pineal gland is a neuroendocrine transducer. Photic information from the retina is transmitted to the pineal gland through the SCN in the hypothalamus and the sympathetic nervous system. Neural input to the gland is norepinephrine, while the output is melatonin. The synthesis and release of melatonin are stimulated by darkness and inhibited by light [42]. Recent evidence suggests that melatonin may be one of the endocrine mediators of circadian regulation of insulin sensitivity [43]: both melatonin receptor type 1 (MT1) and type 2 (MT2) are present on β cells, where they inhibit insulin secretion; conversely, insulin receptors are present on pinealocytes. Furthermore, removal of MT1 induces insulin resistance, while melatonin administration restores glucose homeostasis [44,45]. Several variants of encoding melatonin receptor 1B (MTNR1B; also known as MT2) have been associated with an increased risk of diabetes [46,47]. Following these genome-wide studies, a more recent study was carried out with the Nurses' Health Study

cohort, using a case–control design [48]. In 2000, melatonin secretion in nurses who provided urinary samples was estimated by measuring urinary concentrations of its major metabolite, 6-sulphatoxymelatonin. Nurses who developed T2D between the 2000 and 2012 surveys ($n = 370$) were then matched with control nurses without T2D during the same period ($n = 370$). Those with lower melatonin secretion had a significantly higher incidence of T2D. This association was not confounded by any of the established diabetes risk factors, or sleep duration or snoring; however, data for past exposures to shift work or genetic background were not available in the study. Melatonin secretion at night might have been disrupted by short sleep duration, circadian misalignment and/or light exposure. Several pieces of evidence point to melatonin as a potential mediating mechanism to link poor sleep habits and incidence of T2D.

7. Understanding the mechanisms associated with sleep restriction

Human laboratory studies conducted in healthy volunteers have demonstrated that sleep curtailment was associated with a decrease in insulin sensitivity, as estimated by homeostatic model assessment (HOMA) and euglycaemic–hyperinsulinaemic clamp studies [49–53]. Broussard et al. [50] demonstrated that sleep restriction was associated with a decrease in subcutaneous adipose cell insulin sensitivity in seven healthy adults. The mediating mechanisms that might have been involved in such an association are multiple. Sleep restriction is associated with an increase in sympathetic nervous activity [49,51]. Increased sympathetic nervous system activity has inhibitory effects on insulin secretion and promotes insulin resistance. In addition, increased sympathetic activity stimulates lipolysis [54] and, thus, increases levels of plasma free fatty acids, which can lead to ectopic fat depots in the liver and muscles, thereby inducing insulin resistance. Sleep deprivation has also been linked to an increase in salivary and serum cortisol levels, with loss of the physiological dip in serum cortisol at the end

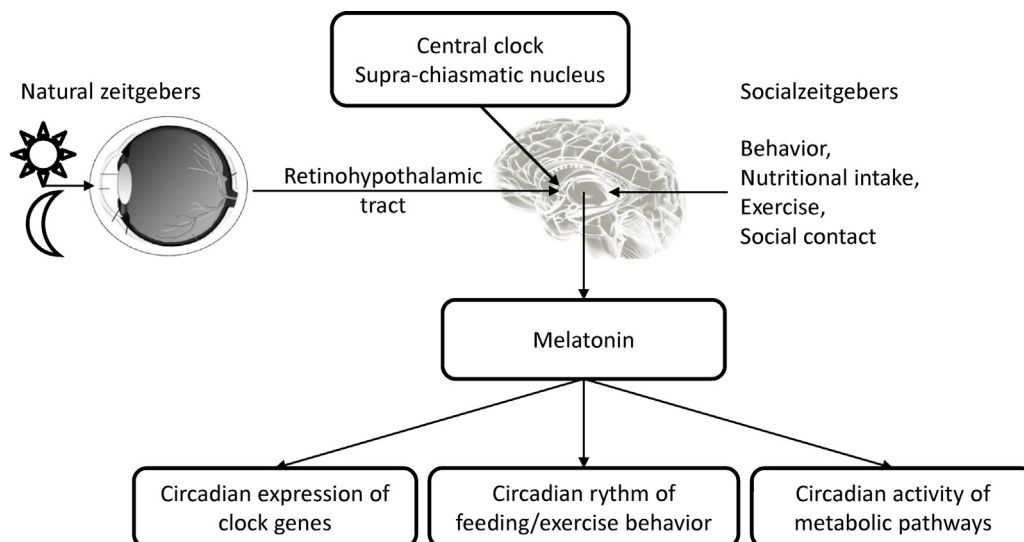


Fig. 1. Physiology of the circadian regulation of metabolic pathways.

of the day [49,52,55,56]. While inversion of the cortisol circadian pattern has been demonstrated to induce insulin resistance [57], increases in cortisol following sleep restriction were not correlated with changes in insulin sensitivity [52]. Nevertheless, the link between sleep restriction and low-grade inflammation has been robustly demonstrated and carefully reviewed by Mullington et al. [58], with low-grade inflammation found to participate in the genesis of insulin resistance.

Spiegel et al. [59] performed the very first study assessing changes in appetite-regulating hormones after sleep restriction. Healthy normal-weight young men were submitted to two nights of 4 h in bed vs two nights of 10 h in bed. During sleep restriction, leptin (anorexigenic) decreased by 18% and ghrelin (orexigenic) increased by 28%. These changes were associated with a 23% increase in hunger ratings and a 33% increase in appetite for carbohydrate-rich foods. Numerous studies have subsequently addressed the same question and found global evidence that restricted sleep affects energy balance because of upregulation of orexigenic hormones and downregulation of anorexigenic hormones [60]. In addition, some studies have looked at changes in energy expenditure during sleep restriction. It appears that resting energy expenditure is not increased by sleep restriction [61], whereas physical activity decreases after sleep restriction [62,63].

Thus, sleep restriction in laboratory studies has been demonstrated to induce insulin resistance, possibly mediated by an increase in sympathetic activity, elevation of cortisol levels and low-grade inflammation. Sleep restriction also increases hunger and caloric intake without increasing energy expenditure. These mechanisms may explain why self-reported short sleep duration is associated with an increased incidence of obesity and T2D in epidemiological studies (Fig. 2).

8. Understanding the mechanisms associated with circadian misalignment

Circadian clock genes are expressed in nearly all mammalian cells, where they coordinate the cell cycle, cell growth and cell metabolism. Mice presenting with homogeneous mutations of

the *Clock* (circadian locomotor output cycles kaput) gene are characterized by a profound alteration in behavioural circadian rhythm. In particular, it has been shown that the *Clock* gene mutant mice have an attenuated diurnal rhythm of feeding behaviour, and develop obesity, hyperphagia, reduced energy expenditure and visceral adiposity, as well as dysregulation of glucose and lipid metabolism [64]. In addition, when such male mice are subjected to dim or bright light during the usual dark phase, they demonstrate a shift in their food consumption towards the usual inactive phase. They gain more body weight and develop glucose intolerance compared with mice subjected to the usual dark–light cycle, despite similar daily caloric intakes and locomotor activity [65].

In one human experiment in a laboratory setting, 10 adults (including five women) underwent a 10-day laboratory protocol wherein they ate and slept at all phases of the circadian cycle—achieved by scheduling a recurring 28-h ‘day’. The subjects ate four isocaloric meals during each 28-h day. This short-term circadian misalignment, similar to that which occurs acutely with jet lag and chronically with shift work, resulted in systematic increases in postprandial glucose, insulin and mean arterial pressure, systematic decreases in leptin and sleep efficiency, and complete inversion of the cortisol profile across the diurnal–nocturnal period [66]. Likewise, Leproult et al. [67] conducted a sleep restriction study (5 h per night) for eight nights, of which four were spent respecting circadian alignment and four were spent with 8.5 h of circadian misalignment. The 26 healthy subjects showed a decrease in insulin sensitivity and an increase in low-grade inflammation with sleep restriction, but these changes were approximately doubled when the subjects were also subjected to circadian misalignment.

9. Bidirectional relationship between sleep quality and diabetes

Having focused on the consequences of sleep disturbances on glycaemic control and the risk of diabetes, it is also necessary to consider the fact that diabetes is a chronic disease in which symptoms are likely to interfere with sleep quality. One patient out of

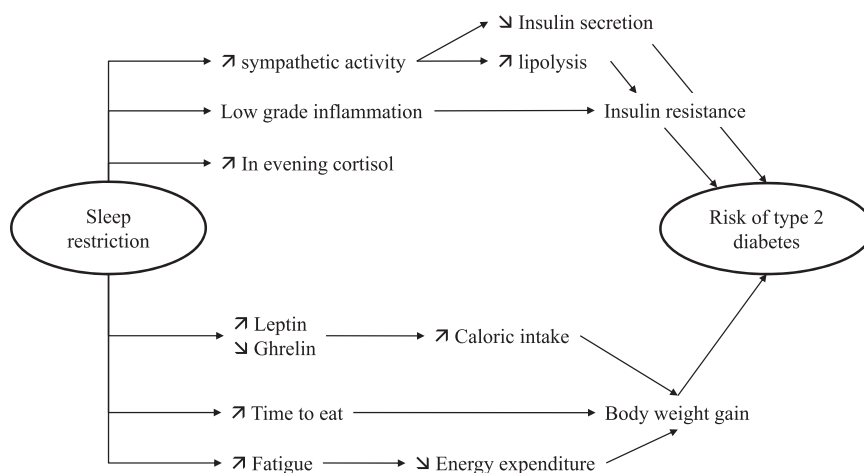


Fig. 2. Mechanisms underlying the impact of sleep restriction on metabolism.

five suffered from chronic pain related to sensitive neuropathy in a French cross-sectional study of 766 patients with either T1D or T2D. In these patients, chronic pain was associated with a poorer quality of life and more sleep disturbances [68]. Accordingly, in 100 patients with T2D, poor sleep quality (as measured by the Pittsburgh Sleep Quality Index, PSQI) was reported in 45% of cases and associated with age ($P=0.04$), peripheral neuropathy ($P=0.001$) and restless legs syndrome ($P<0.001$). Excessive daytime sleepiness (on the Epworth Sleepiness Scale) was found in 26% of patients, too [69]. Van Dijk et al. [70] addressed the question of sleep quality in patients with T1D compared with control patients matched for age and gender. Poor sleep quality (as assessed by PSQI) was found in 35% of patients with T1D compared with 20% in the controls ($P=0.021$). Depression, peripheral polyneuropathy, habitual snoring and other sleep disturbances (such as hypoglycaemia) were independently associated with poor sleep quality. Thus, symptoms associated with either T1D or T2D can influence sleep quality. In turn, sleep disturbances can alter glycaemic control, leading to a vicious circle where diabetes and sleep disorders exacerbate each other.

10. Conclusion

Sleep habits appear to have changed towards more frequent sleep curtailment, circadian misalignment, late chronotypes and the consequences of social jet lag. Short sleep duration has been clearly associated with an increased prevalence and incidence of T2D, as well as poor metabolic control in both T1D and T2D. Yet, only limited data have emerged regarding the potential link between circadian misalignment and the prevalence of T2D and its glycaemic control. Such a possibility is sustained by the fact that circadian genetic and epigenetic machinery has an impact on food-related behaviours and peripheral metabolic pathways through a feedback loop. In addition, the neuroendocrine hormone melatonin, regulated *via* the SCN by the dark–light cycle, has metabolic effects that can affect insulin sensitivity and β -cell function. Mediating mechanisms have been revealed by sleep restriction and circadian misalignment laboratory studies, including sympathetic overactivity, and unfavourable changes due to dysregulation of the hypothalamic–pituitary–adrenal axis and appetite/satiety hormones that can induce body weight gain and glucose intolerance.

Further studies are now warranted to better understand how social changes affect the physiology of circadian regulation, and may have an impact on the development and control of chronic metabolic disorders, especially T2D and T1D. Our team is currently evaluating how sleep habits, assessed both subjectively and objectively, may affect melatonin secretion and metabolic control in patients with T1D.

However, interventional studies are also needed to address the effectiveness of lifestyle modifications such as extending sleep duration and correcting circadian misalignment. In addition, environmental adaptations such as the quality of artificial light at night and school or work schedules need to be considered in relation to the physiology of our circadian pattern. Finally, the administration of melatonin or prescribed light exposure needs

to be tested for its ability to restore the physiological dialogue between circadian mechanisms and metabolic pathways.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgments

Funding: we thank the *Société francophone de diabétologie* (French Society of Diabetology), the *Association nationale pour les traitements à domicile, les innovations et la recherche* (ANTADIR; National Association for Treatment at Home, Innovations and Research) and the *Fond de dotation Agir pour les maladies chroniques* (Endowment Fund for Action Against Chronic Diseases) for their grants, which sustained our research project addressing the role of sleep habits in the glycaemic control of patients with type 1 diabetes.

Appendix A. Supplementary data

Supplementary materials (Fig. S1 and Table S1) associated with this article can be found at <http://www.sciencedirect.com> at <http://dx.doi.org/10.1016/j.diabet.2014.12.004>.

References

- [1] Knutson KL, Van Cauter E, Rathouz PJ, DeLeire T, Lauderdale DS. Trends in the prevalence of short sleepers in the USA: 1975–2006. *Sleep* 2010;33:37–45.
- [2] Boivin DB, Tremblay GM, James FO. Working on atypical schedules. *Sleep Med* 2007;8:578–89.
- [3] Levandovski R, Dantas G, Fernandes LC, Caumo W, Torres I, Roenneberg T, et al. Depression scores associate with chronotype and social jetlag in a rural population. *Chronobiol Int* 2011;28:771–8.
- [4] Roenneberg T, Allebrandt KV, Mewes M, Vetter C. Social jetlag and obesity. *Curr Biol* 2012;22:939–43.
- [5] Tare A, Lane JM, Cade BE, Grant SF, Chen TH, Punjabi NM, et al. Sleep duration does not mediate or modify association of common genetic variants with type 2 diabetes. *Diabetologia* 2014;57:339–46.
- [6] Jackson CL, Redline S, Kawachi I, Hu FB. Association between sleep duration and diabetes in black and white adults. *Diabetes Care* 2013;36:3557–65.
- [7] Najafian J, Mohamadifard N, Siadat ZD, Sadri G, Rahmati MR. Association between sleep duration and diabetes mellitus: Isfahan Healthy Heart Program. *Niger J Clin Pract* 2013;16:59–62.
- [8] Lou P, Chen P, Zhang L, Zhang P, Yu J, Zhang N, et al. Relation of sleep quality and sleep duration to type 2 diabetes: a population-based cross-sectional survey. *BMJ Open* 2012;2.
- [9] Cumberbatch CG, Younger NO, Ferguson TS, McFarlane SR, Francis DK, Wilks RJ, et al. Reported hours of sleep, diabetes prevalence and glucose control in jamaican adults: analysis from the Jamaica lifestyle survey 2007–2008. *Int J Endocrinol* 2011;2011:716214.
- [10] Chao CY, Wu JS, Yang YC, Shih CC, Wang RH, Lu FH, et al. Sleep duration is a potential risk factor for newly diagnosed type 2 diabetes mellitus. *Metabolism* 2011;60:799–804.
- [11] Chaput JP, Despres JP, Bouchard C, Tremblay A. Association of sleep duration with type 2 diabetes and impaired glucose tolerance. *Diabetologia* 2007;50:2298–304.
- [12] Kachi Y, Ohwaki K, Yano E. Association of sleep duration with untreated diabetes in Japanese men. *Sleep Med* 2012;13:307–9.

- [13] von Ruesten A, Weikert C, Fietze I, Boeing H. Association of sleep duration with chronic diseases in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study. *PLoS One* 2012;7:e30972.
- [14] Kita T, Yoshioka E, Satoh H, Saijo Y, Kawaharada M, Okada E, et al. Short sleep duration and poor sleep quality increase the risk of diabetes in Japanese workers with no family history of diabetes. *Diabetes Care* 2012;35:313–8.
- [15] Beihl DA, Liese AD, Haffner SM. Sleep duration as a risk factor for incident type 2 diabetes in a multiethnic cohort. *Ann Epidemiol* 2009;19:351–7.
- [16] Chaput JP, Despres JP, Bouchard C, Astrup A, Tremblay A. Sleep duration as a risk factor for the development of type 2 diabetes or impaired glucose tolerance: analyses of the Quebec Family Study. *Sleep Med* 2009;10:919–24.
- [17] Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG, et al. Sleep duration as a risk factor for diabetes incidence in a large US sample. *Sleep* 2007;30:1667–73.
- [18] Yaggi HK, Araujo AB, McKinlay JB. Sleep duration as a risk factor for the development of type 2 diabetes. *Diabetes Care* 2006;29:657–61.
- [19] Mallon L, Broman JE, Hetta J. High incidence of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population. *Diabetes Care* 2005;28:2762–7.
- [20] Ayas NT, White DP, Al-Delaimy WK, Manson JE, Stampfer MJ, Speizer FE, et al. A prospective study of self-reported sleep duration and incident diabetes in women. *Diabetes Care* 2003;26:380–4.
- [21] Tuomilehto H, Peltonen M, Partinen M, Lavigne G, Eriksson JG, Herder C, et al. Sleep duration, lifestyle intervention, and incidence of type 2 diabetes in impaired glucose tolerance: The Finnish Diabetes Prevention Study. *Diabetes Care* 2009;32:1965–71.
- [22] Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* 2010;33:414–20.
- [23] Holliday EG, Magee CA, Kritharides L, Banks E, Attia J. Short sleep duration is associated with risk of future diabetes but not cardiovascular disease: a prospective study and meta-analysis. *PLoS One* 2013;8:e82305.
- [24] Kim BK, Kim BS, An SY, Lee MS, Choi YJ, Han SJ, et al. Sleep duration and glycaemic control in patients with diabetes mellitus: Korea National Health and Nutrition Examination Survey 2007–2010. *J Korean Med Sci* 2013;28:1334–9.
- [25] Ohkuma T, Fujii H, Iwase M, Kikuchi Y, Ogata S, Idewaki Y, et al. Impact of sleep duration on obesity and the glycaemic level in patients with type 2 diabetes: the Fukuoka Diabetes Registry. *Diabetes Care* 2013;36:611–7.
- [26] Ohkuma T, Fujii H, Iwase M, Ogata-Kaizu S, Ide H, Kikuchi Y, et al. Association between sleep duration and urinary albumin excretion in patients with type 2 diabetes: the Fukuoka diabetes registry. *PLoS One* 2013;8:e78968.
- [27] Afsar B. The relationship between self-reported nocturnal sleep duration, daytime sleepiness and 24-h urinary albumin and protein excretion in patients with newly diagnosed type 2 diabetes. *Prim Care Diabetes* 2013;7:39–44.
- [28] Borel AL, Pepin JL, Nasse L, Baguet JP, Netter S, Benhamou PY. Short sleep duration measured by wrist actimetry is associated with deteriorated glycaemic control in type 1 diabetes. *Diabetes Care* 2013;36:2902–8.
- [29] Borel AL, Benhamou PY, Baguet JP, Debaty I, Levy P, Pepin JL, et al. Short sleep duration is associated with a blood pressure nondipping pattern in type 1 diabetes: the DIAPASOM study. *Diabetes Care* 2009;32:1713–5.
- [30] Roenneberg T, Kuehnle T, Juda M, Kantermann T, Allebrandt K, Gordijn M, et al. Epidemiology of the human circadian clock. *Sleep Med Rev* 2007;11:429–38.
- [31] von Schantz M. Phenotypic effects of genetic variability in human clock genes on circadian and sleep parameters. *J Genet* 2008;87:513–9.
- [32] Roenneberg T, Wirz-Justice A, Mrosovsky M. Life between clocks: daily temporal patterns of human chronotypes. *J Biol Rhythms* 2003;18:80–90.
- [33] Broman JE, Pitkanen J, Backlund H, Heikkilä K, Koskenvuo M, Peltonen M, et al. Long-term consistency of diurnal-type preferences among men. *Chronobiol Int* 2014;31:182–8.
- [34] Merikanto I, Lahti T, Puolijoki H, Vanhala M, Peltonen M, Laatikainen T, et al. Associations of chronotype and sleep with cardiovascular diseases and type 2 diabetes. *Chronobiol Int* 2013;30:470–7.
- [35] Reutrakul S, Hood MM, Crowley SJ, Morgan MK, Teodori M, Knutson KL, et al. Chronotype is independently associated with glycaemic control in type 2 diabetes. *Diabetes Care* 2013;36:2523–9.
- [36] Reutrakul S, Hood MM, Crowley SJ, Morgan MK, Teodori M, Knutson KL. The relationship between breakfast skipping, chronotype, and glycaemic control in type 2 diabetes. *Chronobiol Int* 2014;31:64–71.
- [37] Wittmann M, Dinich J, Mrosovsky M, Roenneberg T. Social jetlag: misalignment of biological and social time. *Chronobiol Int* 2006;23:497–509.
- [38] Kantermann T, Duboutay F, Haubruge D, Kerkhofs M, Schmidt-Trucksass A, Skene DJ. Atherosclerotic risk and social jetlag in rotating shift-workers: first evidence from a pilot study. *Work* 2013;46:273–82.
- [39] Allebrandt KV, Teder-Laving M, Kantermann T, Peters A, Campbell H, Rudan I, et al. Chronotype and sleep duration: the influence of season of assessment. *Chronobiol Int* 2014;31:731–40.
- [40] Cermakian N, Sassone-Corsi P. Environmental stimulus perception and control of circadian clocks. *Curr Opin Neurobiol* 2002;12:359–65.
- [41] Orozco-Solis R, Sassone-Corsi P. Epigenetic control and the circadian clock: linking metabolism to neuronal responses. *Neuroscience* 2014;264:76–87.
- [42] Brzezinski A. Melatonin in humans. *N Engl J Med* 1997;336:186–95.
- [43] Cizza G, Reuena M, Galli G, de Jonge L. Chronic sleep deprivation and seasonality: implications for the obesity epidemic. *J Endocrinol Invest* 2011;34:793–800.
- [44] Contreras-Alcantara S, Baba K, Tosini G. Removal of melatonin receptor type 1 induces insulin resistance in the mouse. *Obesity (Silver Spring)* 2010;18:1861–3.
- [45] Sartori C, Dessen P, Mathieu C, Monney A, Bloch J, Nicod P, et al. Melatonin improves glucose homeostasis and endothelial vascular function in high-fat diet-fed insulin-resistant mice. *Endocrinology* 2009;150:5311–7.
- [46] Bouatia-Naji N, Bonnefond A, Cavalcanti-Proenca C, Sparso T, Holmkvist J, Marchand M, et al. A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. *Nat Genet* 2009;41:89–94.
- [47] Bonnefond A, Clement N, Fawcett K, Yengo L, Vaillant E, Guillaume JL, et al. Rare MTNR1B variants impairing melatonin receptor 1B function contribute to type 2 diabetes. *Nat Genet* 2012;44:297–301.
- [48] McMullan CJ, Schernhammer ES, Rimm EB, Hu FB, Forman JP. Melatonin secretion and the incidence of type 2 diabetes. *JAMA* 2013;309:1388–96.
- [49] Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999;354:1435–9.
- [50] Broussard JL, Ehrmann DA, Van Cauter E, Tasali E, Brady MJ. Impaired insulin signaling in human adipocytes after experimental sleep restriction: a randomized, crossover study. *Ann Intern Med* 2012;157:549–57.
- [51] Nedeltcheva AV, Kessler L, Imperial J, Penev PD. Exposure to recurrent sleep restriction in the setting of high caloric intake and physical inactivity results in increased insulin resistance and reduced glucose tolerance. *J Clin Endocrinol Metab* 2009;94:3242–50.
- [52] Buxton OM, Pavlova M, Reid EW, Wang W, Simonson DC, Adler GK. Sleep restriction for 1 week reduces insulin sensitivity in healthy men. *Diabetes* 2010;59:2126–33.
- [53] van Leeuwen WM, Hublin C, Sallinen M, Harma M, Hirvonen A, Porkka-Heiskanen T. Prolonged sleep restriction affects glucose metabolism in healthy young men. *Int J Endocrinol* 2010;2010:108641.
- [54] Hucking K, Hamilton-Wessler M, Ellmerer M, Bergman RN. Burst-like control of lipolysis by the sympathetic nervous system in vivo. *J Clin Invest* 2003;111:257–64.
- [55] Reynolds AC, Dorrian J, Liu PY, Van Dongen HP, Wittert GA, Harmer LJ, et al. Impact of five nights of sleep restriction on glucose metabolism, leptin and testosterone in young adult men. *PLoS One* 2012;7:e41218.
- [56] Guyon A, Balbo M, Morselli LL, Tasali E, Leproult R, L'Hermite-Baleriaux M, et al. Adverse effects of two nights of sleep restriction on the hypothalamic-pituitary-adrenal axis in healthy men. *J Clin Endocrinol Metab* 2014;jc20134254.
- [57] Plat L, Leproult R, L'Hermite-Baleriaux M, Fery F, Mockel J, Polonsky KS, et al. Metabolic effects of short-term elevations of plasma cortisol are more pronounced in the evening than in the morning. *J Clin Endocrinol Metab* 1999;84:3082–92.

- [58] Mullington JM, Simpson NS, Meier-Ewert HK, Haack M. Sleep loss and inflammation. *Best Pract Res Clin Endocrinol Metab* 2010;24:775–84.
- [59] Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* 2004;141:846–50.
- [60] Morselli L, Leproult R, Balbo M, Spiegel K. Role of sleep duration in the regulation of glucose metabolism and appetite. *Best Pract Res Clin Endocrinol Metab* 2010;24:687–702.
- [61] Nedeltcheva AV, Kilkus JM, Imperial J, Kasza K, Schoeller DA, Penev PD. Sleep curtailment is accompanied by increased intake of calories from snacks. *Am J Clin Nutr* 2009;89:126–33.
- [62] Bromley LE, Booth 3rd JN, Kilkus JM, Imperial JG, Penev PD. Sleep restriction decreases the physical activity of adults at risk for type 2 diabetes. *Sleep* 2012;35:977–84.
- [63] Booth JN, Bromley LE, Darukhanavala AP, Whitmore HR, Imperial JG, Penev PD. Reduced physical activity in adults at risk for type 2 diabetes who curtail their sleep. *Obesity (Silver Spring)* 2012;20:278–84.
- [64] Turek FW, Joshu C, Kohsaka A, Lin E, Ivanova G, McDearmon E, et al. Obesity and metabolic syndrome in circadian Clock mutant mice. *Science* 2005;308:1043–5.
- [65] Fonken LK, Workman JL, Walton JC, Weil ZM, Morris JS, Haim A, et al. Light at night increases body mass by shifting the time of food intake. *Proc Natl Acad Sci U S A* 2010;107:18664–9.
- [66] Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci U S A* 2009;106:4453–8.
- [67] Leproult R, Holmback U, Van Cauter E. Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. *Diabetes* 2014;63:1860–9.
- [68] Bouhassira D, Letanoux M, Hartemann A. Chronic pain with neuropathic characteristics in diabetic patients: a French cross-sectional study. *PLoS One* 2013;8:e74195.
- [69] Lopes LA, Lins Cde M, Adeodato VG, Quental DP, de Bruin PF, Montenegro Jr RM, et al. Restless legs syndrome and quality of sleep in type 2 diabetes. *Diabetes Care* 2005;28:2633–6.
- [70] van Dijk M, Donga E, van Dijk JG, Lammers GJ, van Kralingen KW, Dekkers OM, et al. Disturbed subjective sleep characteristics in adult patients with long-standing type 1 diabetes mellitus. *Diabetologia* 2011;54:1967–76.