Sleep: How quality and duration affects insulin sensitivity and glucose control

In the third part of the Journal's coverage of the 80th Scientific Sessions of the American Diabetes Association, Pam Brown focuses on two sessions that discussed the complex and often overlooked relationship between sleep and metabolic health. The article reminds clinicians to be mindful that poor-quality sleep and short duration of sleep are risk factors for the development of type 2 diabetes and for poor glycaemic control in type 1 and type 2 diabetes.

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"Diabetes meets the Sandman – sleep, diabetes and glycaemic management" provided a background primer on sleep medicine and its specific application to glycaemic control in children with type 1 diabetes*. It highlighted the usefulness of taking a detailed sleep history when speaking with adolescents or parents of children with type 1 diabetes, even if we are not otherwise involved in helping them manage their condition.

The symposium began with discussion of the critical functions of sleep – a restorative process involved in energy regulation and conservation, immune function, motor-skill learning and memory consolidation from short-term to long-term memory. A recap on the five stages of sleep and the associated physiological changes followed:

- Non-REM stage 1 – transition between waking and sleeping.
- Non-REM stage 2 – body temperature drops and heart rate slows.
- Non-REM stage 3 – muscles relax, blood pressure and breathing rates decrease, and deepest sleep occurs. Described as deep sleep, this occurs earlier in the night.
- REM (rapid-eye movement) sleep – body is relaxed and immobilised; brain is more active, eyes move rapidly and dreams occur. More REM sleep occurs later in the night, towards morning.

People cycle through the stages of non-REM and REM sleep in roughly 90-minute cycles each night.

The audience were reminded that sleep recommendations for children and teenagers differ from those for adults – ranging from 11–14 hours for toddlers to 8–10 hours for teenagers aged 13–18 years – and are not always known by parents or acknowledged by teenagers.

With adolescents, 50–70% do not meet recommendations. Children with type 1 diabetes are 3 times more likely and adolescents with type 1 diabetes are 6 times more likely to experience insufficient sleep duration than their peers without type 1 diabetes. Speakers highlighted that higher rates of sleep apnoea and sleep-disordered breathing occur in children with type 1 diabetes unrelated to BMI status, and a campaign is underway to have this included in the *ADA Standards of Care*, where it is currently only discussed in relation to children with type 2 diabetes.

The brain is described as "glucose hungry", but a sleep-deprived brain uses less glucose during Stage 3 sleep than a sleep replete brain. This was demonstrated in the seminal paper by Spiegel et al (1999), although this study was carried out in young, healthy people without type 1 diabetes who were sleep deprived, with only 4 hours sleep compared to their normal 8 hours. When glucose tolerance was also measured, the sleep-deprived 21–30-year-olds had a glucose tolerance comparable to that of 61–80-year-olds known to suffer from impaired glucose tolerance. Several studies since have confirmed that sleep restriction

*The symposium was chaired by Sarah Westen (University of Florida), with Faculty Members Sara Jaser (Vanderbilt University Medical Center), Susana Patton (Nemours Children's Health System), Erin Hanlon (University of Chicago), Michelle Perfect (University of Arizona) and Michelle van Name (Yale School of Medicine).

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decreases insulin sensitivity by 16% to 32%, as measured by intravenous glucose tolerance tests.

It is believed that not just total sleep deprivation but also limiting Stage 3 slow-wave sleep increases insulin resistance and the risk of type 2 diabetes (Tasali et al, 2008). Sleep fragmentation, as may occur in those with obstructive sleep apnoea, has similar effects to decreased slow-wave sleep and is associated with around a similar 25% decrease in insulin sensitivity.

When short sleep or circadian misalignment as occurs in shift workers were compared, both were associated with reduced insulin sensitivity but, for the same amount of sleep deprivation, circadian misalignment was associated with greater reduction in insulin sensitivity. If allowed to sleep as much as needed, the circadian misalignment group did not completely normalise their insulin sensitivity, whereas insulin sensitivity returned to normal in those with pure sleep deficit.

Several mechanisms were proposed for these changes in insulin sensitivity and glucose tolerance:

- Decreased brain glucose utilisation.
- Alterations in sympatho-vagal balance: higher sympathetic nervous activity inhibits beta-cell release and promotes insulin resistance.
- Increased evening cortisol levels: promotes insulin resistance (IR).
- Prolonged nocturnal secretion of growth hormone may also have hyperglycaemic effects.

In another study, the effects of sleep deprivation on adipocytes at cellular level were explored using fat biopsies (Broussard et al, 2012). It was demonstrated that sleep deprivation is associated with decreased insulin sensitivity not just at the whole-body level (demonstrated with the intravenous glucose tolerance test), but also at the cellular level. Biopsies taken from those who had had only 4 hours of sleep demonstrated decreased insulin sensitivity, proving that, at a cellular level, cells have a memory of the sleep deprivation.

From carefully controlled laboratory studies where scientists were able to measure energy intake and output over 24 hours, there is evidence that although there is a small energy cost of extended wakefulness, this is low and measured at around 150 kcal extra/day, while in the young healthy youths studied, there was an additional food intake of around 300 kcal/day in the form of salty, starchy and sweet foods. It is, therefore, easy to see how this could rapidly translate into increased weight and obesity. Leptin levels are decreased, ghrelin levels increased and endocannabinoid levels increased – all changes that promote food intake.

Applying this information to children with type 1 diabetes, there is an association between poor sleep and detrimental changes to glycaemic control (Reutrakul et al, 2016). Clinicians were, therefore, reminded of the importance of taking a comprehensive sleep history, particularly if poor glycaemic control – exploring insomnia, sleep-disordered breathing (include apnoea in youth with type 1 diabetes), poor sleep quality, daytime sleepiness, inconsistent sleep habits/circadian misalignment or "social jet lag", and inadequate sleep duration, all of which may contribute to sleep deficiency. The associated poorer glycaemic control may partly relate to poorer self-management associated with sleep deprivation, and it was questioned whether increasing sleep can improve this.

Indeed, sophisticated sleep studies and prescribing increased sleep opportunity have demonstrated improved attention, memory, problem-solving skills and classroom behaviours as well as improvements in time in range on continuous glucose monitoring (CGM).

Using technology such as CGM to monitor glycaemia overnight in children with type 1 diabetes of different age ranges resulted in decreased moderate or severe hypoglycaemia, but did not improve time in range overnight (Tamborlane et al, 2005). Since insulin requirements are so variable in young children overnight, hybrid closed-loop systems improved not just hypoglycaemia but also time in range and hyperglycaemia. Using technology reduced the burden on caregivers, who also suffer significant sleep loss due to worry about their child.

Adolescents have been demonstrated to commonly have a shift in circadian rhythm, sometimes referred to as "social jet lag", staying awake late but forced to get up early for school on weekdays and often staying awake even later

at weekends, then oversleeping. This has been shown to be associated with mood problems, poor academic performance and obesity in the general population (Owens, 2014), as well as poorer glycaemic control and greater insulin requirements in those with type 1 diabetes. These changes have been demonstrated to relate not to duration of sleep/total sleep time, but more to inconsistency of the mid-point of each night's sleep throughout the week. Possible solutions include caregivers enforcing earlier bedtimes and limiting evening distractions, and sleep coaching studies covering general sleep hygiene educating about the potential impact of inconsistent sleep on type 1 diabetes control.

Metabolic changes and circadian rhythm

In "Metabolic changes related to alteration in circadian rhythm", Josiane Broussard (Colorado State University) and Andrew McHill (Brigham and Women's Hospital and Harvard Medical School, Boston) debated whether it is sleep or food that contributes most to the metabolic changes seen in the circadian misalignment which occurs in shift workers and, potentially, in adolescents with social jet lag.

Broussard began by defining circadian misalignment as an altered or inappropriate relationship between sleep–wake and associated behaviours. Shift workers are 44% more likely to have type 2 diabetes and the risk has been shown to correlate with nights worked per month. This is likely to have a significant impact on the type 2 diabetes burden, since large numbers of people undertake shift work all or some of the time (20% of adults in the US workforce). She shared a meta-analysis by Anothaisintawee et al (2015) which showed that poor sleep and circadian rhythm misalignment can contribute to the risk of developing type 2 diabetes as much as conventional risk factors. For example, after adjustment for confounders, the risk of type 2 diabetes due to difficulty initiating or maintaining sleep is slightly less than having a family history of diabetes but more than being physically inactive, while diabetes risk with too little or too much sleep or shift working is comparable to being physically inactive. Highlighting population decreases in overall sleep duration, Dr Broussard stressed that, in addition, shift workers get not only less sleep but poorer quality sleep, with increased sleep disturbance. Mechanisms for the way sleep decreases insulin sensitivity were less clearly defined in adults than in children.

Dr Broussard shared evidence of not just whole-body decreases in insulin sensitivity, but changes in insulin sensitivity and fatty acid metabolism at the cellular level in adipocytes harvested on fat biopsy in those with circadian misalignment and sleep deprivation.

Dr McHill argued that it is all about food and the timing of food rather than sleep *per se* that causes the metabolic changes (McHill and Wright, 2017). If people only sleep for 5 hours, rather than 9 hours, they expend more energy and, therefore, you would expect them to lose weight. However, when sleep deprived, they increased food intake with 6% extra calories in post-dinner high-carbohydrate and salty snacks, which resulted in weight gain. When looking at the energy expenditure in a group of healthy volunteers undergoing simulated circadian misalignment, there was an increase in total daily energy expenditure in the day they transitioned to night shift, but they expended less energy during sleep on the two nights on night shift, which was down by around 12%. There was also a decreased thermic effect of food, which reduced from around 5% at baseline to 1%.

In a real-world study of 110 lean, young volunteers who were allowed to work a sleep–wake cycle that suited them, the lean group consumed 50% of their calories well prior to the nocturnal measured melatonin increase. Those eating later, nearer to their melatonin surge, had decreased thermic effect of food. There was no correlation with 24-hour total sleep time. Correlation with the timing of eating relative to their melatonin surge was the most significant parameter influencing metabolic impact. Eating later or having circadian misalignment resulted in higher glucose impact of the same meal.

Several studies have demonstrated sleep deprivation may promote adverse food timing. Weekend recovery sleep is a common sleep-loss countermeasure, as discussed earlier in relation

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"It is likely that both sleep duration and quality, and food intake and timing contribute to the metabolic changes seen in circadian misalignment."

to adolescents. Depner and colleagues (2019) showed that short sleep led to later timing of energy intake, weight gain and reduced insulin sensitivity, which weekend recovery sleep failed to prevent.

In rebuttal, Dr Broussard stressed that the timing of food intake did not play a role in any of the studies which she cited. She stressed that daytime sleep is inherently disturbed and disrupted. "Wake after sleep onset" was described as a useful marker and this showed that even when the sleep opportunity may be the same, the actual sleep quality is very different during daytime sleep. She also stressed that disruption to sleep causes metabolic impairments even when the timing is adequate, as her team proved when they were able to decrease slow-wave sleep, rather than shortening overall sleep time.

During his rebuttal, Dr McHill explained how it is possible to separate the effects of sleep loss and food intake, disassociating the two processes using a 20-hour day in a laboratory and then superimposing sleep restriction.

Both speakers shared sophisticated human sleep laboratory studies, which included intravenous glucose tolerance tests and CGM evidence to support their individual arguments, before agreeing that it is likely that both sleep duration and quality, and food intake and timing contribute to the metabolic changes seen in circadian misalignment.

My take-home messages were the importance of asking about sleep quality and duration in anyone with poor diabetes control, particularly children and adolescents with type 1 diabetes, and to be more aware of shift work and sleep disturbances as risk factors for developing type 2 diabetes and less good control, and to build this into our screening and prevention strategies. ■

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