REVIEW

Sleep-related disorders in patients with type 1 diabetes mellitus: current insights

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Abstract: Type 1 diabetes mellitus (T1DM) is an autoimmune condition that results from destruction of beta cells in the pancreas. Several reviews have concluded that sleep contributes to poor glycemic control, diabetes management, and diabetes-related complications in individuals with T1DM and represents an untapped opportunity for intervention. However, at the current juncture, the American Diabetes Association's Standards of Medical Care are devoid of recommendations about how to address sleep in the management of T1DM. This article summarizes reviews of sleep in youth and adults with T1DM and empirical studies that have examined various sleep parameters ranging from sleep disturbances (general, perceived sleep quality, sleepiness, awakenings, and sleep efficiency), sleep duration, sleep consistency, sleep-disordered breathing (SDB), and sleep architecture. The data show that many individuals with T1DM sleep less than recommendations; individuals with the poorest sleep have difficulties with diabetes management; and sleep deficiency including SDB often corresponds to several disease morbidities (neuropathy, nephropathy, etc). Mixed findings exist regarding direct associations of various sleep parameters and glycemic control. SDB appears to be just as prevalent, if not more, than other conditions that have been recommended for universal screening in individuals with T1DM. The article concludes with recommendations for collaborative research efforts to further elucidate the role of sleep in diabetes-related outcomes; investigations to test behavioral strategies to increase sleep quantity and consistency; and considerations for clinical care to address sleep.

Keywords: type 1 diabetes, sleep duration, quality, and consistency

Introduction

Type 1 diabetes mellitus (T1DM) is one of the most commonly diagnosed medical conditions in school-age youth, ranking third in the prevalence of pediatric conditions. About 2–3 youth per every 1,000 are currently diagnosed with T1DM.[1] The pathogenesis of T1DM is autoimmune destruction of pancreatic islet β-cells. T1DM management typically includes exogenous administration of basal and bolus insulin via syringe, pen, or pump. Insulin doses are prescribed based on the individual's carbohydrate intake, glucose levels, and needs. If the amount of insulin is insufficient to lower blood glucose concentrations, hyperglycemia resulting in polydipsia, polyuria, nocturia, and visual problems may occur. Sustained hyperglycemia may potentially lead to diabetic ketoacidosis (DKA), as acid accumulates in the blood stream due to the absence of insulin needed to convert glucose into energy for the cells.[2] Conversely, excess insulin relative to carbohydrate intake can result in hypoglycemia.

The Diabetes Control and Complications Trial was a landmark study of over 1,000 individuals with T1DM, which demonstrated that intensive treatment with insulin was

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more effective in controlling diabetes and preventing morbidities relative to conventional treatment.[3,4] However, maintaining strict glycemic control may lead to hypoglycemia, which if unaddressed may result in seizures, loss of consciousness, or mortality.[3] Chronic glycemic dysregulation has been causally linked to several adverse outcomes, such as increased risk of cardiovascular disease, hypertension, and neuropathy.[5,6] Another microvascular complication is retinopathy, which is caused by damage to retinal blood vessels, potentially leading to blindness. Poor management can also lead to nephropathy and end-stage kidney disease requiring dialysis or a renal transplant.[6]

Disease progression and management follow a developmental trajectory that reflects notable glucose dysregulation during adolescence. In addition to hormonal changes during puberty, adolescents struggle with self-care behaviors.[7] Self-monitoring of blood glucose levels often creates distress attributable to the physical discomfort, increased burden over typical adolescent responsibilities, varying comfort and self-acceptance around peers, and the delicate balance of parental involvement and self-sufficiency.[8] Adherence to self-management is often measured through self-report or parent-report inventories or based on the frequency of self-monitoring of blood glucose with a glucometer.

In contrast to T1DM, type 2 diabetes mellitus (T2DM) is not an autoimmune disease and develops as a result of metabolic dysfunction and inflammation. The glycemic dysregulation stems from insufficient production and inefficient cellular absorption of insulin.[6] In 2017, the Standards of Medical Care in Diabetes (Standards), published annually, introduced recommendations to assess sleep quality, quantity, and sleep-disordered breathing (SDB), as part of the comprehensive evaluation to identify comorbidities in T2DM.[9] The Standards referenced data substantiating sleep duration and SDB as causal factors in the etiology of T2DM to support this inclusion. Although there is burgeoning evidence supporting the role and influence of sleep in T1DM, the Standards have not adopted recommendations based on extant findings.

There may be important distinctions in how sleep influences disease outcomes in individuals with T1DM vs T2DM as a result of interactions between autonomic nervous system (ANS) activity and mediators of systemic inflammation. The ANS is composed of two primary branches – the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). Short sleep duration and/or larger standard deviations of total sleep time (TST) have been linked with greater heart rate variability, suggesting compromised cardiac autonomic modulation,[1,11] elevated systemic inflammatory responses,[1] and disruptions in the hypothalamic–pituitary–adrenal (HPA) axis such as increased adrenocorticotropic hormone (ACTH) and cortisol.[1,12] Experimental studies have demonstrated causal pathways between sleep restriction and inflammation,[13] HPA axis disruption,[14] and brain responses to food assessed via functional magnetic resonance imaging.[15]

SDB has been conceptualized as a cluster of respiratory abnormalities during sleep. Similar to the physiological impact of sleep loss, SDB has been associated with 1) cortisol elevations as a result of activation of the HPA; 2) increased SNS activity due to chronic intermittent hypoxia; and 3) elevated inflammatory markers such as tumor necrosis factor alpha, IL-6, and C-reactive protein.[16] The sleep cycle comprises two sleep states: rapid eye movement (REM) and non-rapid eye movement (NREM). Three sleep stages (N1, N2, and N3) occur in NREM.[1] Compared to REM and wake states, stage N3 (slow wave sleep [SWS]) is characterized by increased production of growth hormone[17] and brain glucose utilization, reduced HPA activity,[18] and imbalances in the proportion of SNS (increased) to PNS (decreased) activity.

The physiological pathways for how sleep affects glycemic regulation in T2DM have been established in experimental and meta-analytic studies.[19–21] Specifically, deficient sleep contributes to reduced insulin release after meals, thereby maintaining glucose in the bloodstream.[22] Additionally, insulin production is increased in an attempt to lower the elevated glucose levels attributable to increased cortisol circulating in the body following sleep loss. Concurrently, elevations in epinephrine due to increased SNS activity inhibit insulin release and promote glycogenolysis.[23,24]

The hormonal and physiological associations with sleep for T1DM are less clear; even with sufficient sleep or treated sleep disorders, in T1DM, the pancreas would not be able to respond to variations in sleep due to the absence of functional beta cells. Therefore, sleep debt, irregular sleep schedules, and untreated SDB may impact glycemic control via elevations in cortisol and an imbalance in PNS and SNS activity. Furthermore, the role of sleep in T1DM may also contribute to behaviors that interfere with optimal diabetes management. For instance, sleep restriction has been linked with executive functioning difficulties, memory impairment, and behavioral dysregulation;[25–28] these are essential skills for effective diabetes management.[29]

This article aims to provide a comprehensive summary of empirical studies and previous reviews to identify trends in findings, summarize implications, and address gaps in

research. Accordingly, the review describes empirical studies from peer-reviewed publications, consolidates findings from recent reviews of sleep in T1DM, and offers suggestions for future directions for sleep as a target in diabetes clinical care and research endeavors. The first objective was to conduct a systematic review of the literature to ascertain the prevalence and severity of various sleep parameters among individuals with T1DM. The second objective was to describe the findings that characterized differences in various sleep parameters between those with T1DM and those without. The third objective of this review was to elucidate the associations between sleep parameters and diabetes-related outcomes such as hyperglycemia, hypoglycemia, diabetes comorbidities, and diabetes management.

Article selection

The main goal of this article was to provide an up-to-date comprehensive overview of peer-reviewed publications containing empirical data that targeted a sleep parameter as a variable in the investigation (eg, sleep was an independent or dependent variable, or as a variable examined in relation to a diabetes-related outcome). The following sleep parameters were searched in tandem with T1D, T1DM, type 1 diabetes, or diabetes: sleep, sleep quality, sleep-disordered breathing, SDB, sleepiness, insomnia, sleep disturbance, or sleep architecture. The primary search engine used was PubMed. The search included articles through June 2018. Articles had to be peer-reviewed and published in English. Results of each paired search (eg, T1DM and sleep) were recorded in a spreadsheet. Duplicate articles that appeared in more than one search were removed. The abstract of each individual article was initially reviewed to confirm that the study measured or examined sleep in some capacity among individuals with T1DM. The second-level screening included reviewing the full article for abstracts that met inclusion criteria or for those articles for which eligibility could not be verified based upon the abstract review alone.

Articles were screened to identify studies that analyzed outcomes for individuals with T1DM separately from other groups (T2DM or those without diabetes). Retained articles needed to report data on at least one sleep metric among individuals with T1DM. The search process was replicated in the additional search engines of EMBASE and SCOPUS to determine additional unique articles. An a priori decision was made to include articles that were not yielded in the search, but were encountered during the writing process as searches often miss relevant references.[3] Additionally,

reference lists from the articles identified were also reviewed for any publications that had not been identified in the formal search. The final number of retained, empirical articles was 54; these appear in Table 1. An additional five review articles are also summarized in this article. A flowchart reflecting the results of the article selection process is shown in Figure 1.

Diabetes-related outcomes included glucose levels via HbA1c or a continuous glucose monitor (CGM); insulin sensitivity or requirements (disposal rates or doses); co-morbidities such as nephropathy, neuropathy, retinopathy, cardiovascular disease, hypertension, and DKA; and diabetes management variables (number of fingersticks and diabetes care or management inventories).

Summary of sleep-related findings from studies of individuals with T1DM

The summary of findings is organized by sleep disturbances, sleep duration, sleep consistency, SDB, and sleep architecture. Table 1 presents the empirical articles reviewed in order of publication year (and month if possible); number of T1DM participants and controls if included or subgroups of those with T1DM; sleep assessments used; sleep parameters that were examined in relation to T1DM status, experiences, or a diabetes-disease outcome; and the primary findings. Findings were not highlighted if differences in the sleep parameters were examined based on non-diabetes factors (eg, sleepiness in those with SDB vs not) or if associations were not linked with a diabetes-related variable (eg, sleep and mood).

Sleep disturbances

Sleep disturbances have been conceptualized as general disruptions in sleep. Indicators that individuals have disturbed sleep include awakenings or arousals; poor sleep quality measured subjectively or as an objectively measured index of sleep efficiency (SE); insomnia symptoms of difficulty falling or staying asleep; or self- or caregiver-reported daytime sleepiness. With regard to Objective 1, sleep disturbances have been documented to be a prevalent phenomenon in individuals with T1DM across the lifespan, beginning in early childhood. In a preschool sample of 10 children with T1DM, 9 met the clinical cutoff value on a parent-reported measure of sleep disturbance.[31] Another study noted that 29%–50% of the 24 parents of preschoolers with T1DM reported that at least once per week, their child had problems following the bedtime

Table I Summary of findings with sleep-related differences or associations in individuals with T1DM

Study	Participants	Sleep assessment	Sleep parameters assessed	Findings
Mondini and Guilleminault (1985)[83]	12 adults with T1DM	PSG	• SDB	• 42% (5/12) had respiratory problems (1 OSA, 2 central apnea, and 3 irregular breathing) • 80% (4/5) with SDB had neuropathy, whereas 6 of the 7 without SDB did not
Blanz et al (1993)[111]	93 children with T1DM; 91 without	Interview	• Sleep disturbances	• Greater prevalence of sleep disturbances in youth with T1DM
Sturrock and Moriarty (1995)[112]	300 adults with T1DM; 143 without	Nottingham Health Profile	• Sleep quality	• Self-reported well-being was rated worse across 6 criteria including sleep in adults with T1DM vs controls
Porter et al (1996)[87]	20 adolescents with T1DM (6 experienced hypoglycemia, 14 did not)	PSG	• Sleep architecture	• No differences in sleep architecture in those who experienced hypoglycemia from those who did not
Villa et al (2000)[75]	25 children with T1DM; 20 without	PSG	• SDB	• Children with T1DM had more apneas than controls • More apneas positively correlated with higher HbA1c
Matyka et al (2000)[38]	29 children with T1DM (14 with hypoglycemia; 15 without); 22 children without T1DM	PSG	• Sleep disturbances • Sleep architecture	• No sleep architecture differences in children with hypoglycemia compared to those without • Children with T1DM had more awakenings but no other sleep architecture differences
Pillar et al (2003)[39]	15 with T1DM; 15 without	PSG	• Sleep disturbances • Sleep architecture	• Rapid decline in glucose associated with awakenings (severity of hypoglycemia did not relate) • Nocturnal hypoglycemia was associated with more efficient sleep, SWS, and increased delta power) • No significant differences in sleep architecture between T1DM and controls
Radan et al (2004)[37]	18 adolescents with T1DM	Accelerometer	• Sleep disturbances	• Participants experienced more motor activity during periods of nocturnal hypoglycemia than hyperglycemic participants or normoglycemic participants
Low et al (2004)[113]	83 adults with T1DM; 245 without	Autonomic Symptom Profile (including a subscale of sleep dysfunction); Composite Autonomic Severity Score	• Sleep disturbances	• Mean ASP scores of sleep dysfunction were higher for T1DM patients than for controls

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Table 1 (Continued).

Study	Participants	Sleep assessment	Sleep parameters assessed	Findings
Happe et al (2005)[41]	46 youth with T1DM; 50 youth without; and 75 parents	A 3-question self-report questionnaire regarding Restless Leg Syndrome symptoms	• Sleep disturbances • Sleepiness	• No differences in rates of Restless Leg Syndrome in youth with T1DM and youth without • No differences in insomnia symptoms • No difference in daytime sleepiness
Jauch-Chara et al (2008)[86]	14 adults with T1DM; 14 adults without	PSG	• Sleep architecture	• There was a trend for less SWS during the first half of the night • Those with T1DM spent more time in Stage N2 during the whole night • No differences found in REM based on diabetes status
Borel et al (2009)[11]	20 adults with T1DM	PSG	• Sleep duration • SDB	• 55% (11/20) did not have nocturnal blood pressure dipping and they had shorter TST than those who did • 55% (11/20) had OSA
Borel et al (2010)[8]	40 adults with T1DM	Oximeter; ESS; PSG for those with abnormal oximetry data and 10% of those with normal oximetry data	• Sleepiness • SDB	• Participants had a mean ESS score of 6 (higher normal daytime sleepiness) • 13 had normal oximetry, 9 had borderline, and 15 had abnormal • 40% (16/40) had confirmed SDB (AHI >15 an hour) • 25% (10/40) had an AHI >30
Donga et al (2010)[63]	7 adults with T1DM	PSG	• Sleep duration	• Sleep restriction of 4 hours in a laboratory setting resulted in reduced glucose tolerance, insulin sensitivity, and acute insulin response to glucose
Yeshayahu and Mahmud (2010)[114]	75 adolescents with T1DM; 54 without	Self-reported sleep timing from the Habitual Activity Estimation Scale	• Sleep duration • Sleep consistency	• Adolescents with T1DM slept longer during school nights • All adolescents sleep significantly more on non-school nights demonstrating inconsistent sleep • TST and bed/wake times did not correlate with HbA1c
Schober et al (2011)[81]	58 adults with T1DM	ApneaLink device that measured air flow and pulse oximetry	• SDB	• 10.3% (6/58) had an AHI cutoff of 15+ • Higher rates of neuropathy, nephropathy, hypertension, retinopathy, and heart conditions among those with SDB than those without
van Dijk et al (2011)[44]	99 adults with T1DM and 99 without diabetes	PSQI; ESS; and BQ	• Sleep disturbances • Sleep duration • SDB	• No differences in continuous PSQI scores, but 35.4% of those with T1DM met the cutoff for poor sleep quality vs 19.2% • No difference in self-reported TST • 17.2% of the T1DM participants were at high risk of OSA on the BQ compared to 5.1% of the controls

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Table 1 (Continued).

Study	Participants	Sleep assessment	Sleep parameters assessed	Findings
Olsson et al (2012)[43]	30 adults with T1DM	A few survey questions asking about falling asleep or staying asleep	• Sleep disturbances	• Sleep disturbances were not related to having T1DM
Monaghan et al (2012)[32]	24 parents of children with T1DM	Demographic and Medical Questionnaire Child Sleep Questionnaire	• Sleep disturbances • Sleep duration	• 33% (8/24) reported that their children had trouble falling asleep more than once or twice a week • 8.3% (2/24) reported that their children woke up during the night and had trouble falling back asleep more than once or twice a week • Mean TST was 10.42 (8–13 hours) overnight and 11.69 inclusive of naps
Perfect et al (2012)[35]	50 children and adolescents with T1DM	Accelerometer; PSG; School Sleep Habits Survey; CSHQ (survey items for matched controls)	• Sleep disturbances • Sleepiness • Sleep quality • Sleep duration • SDB • Sleep architecture	• No differences in self-reported sleep disturbances between groups • Mean SE was 78.5% • Mean TST was 6.96 with actigraphy • TST did not predict glucose levels the next day • 35% (14/40) met AHI cutoff for SDB of 1.5 • No difference in rates of SDB between those with T1DM and matched controls, but significantly more central apneas in youth with T1DM • CGM readings were significantly higher in youth with SDB than those without
Palladino et al (2013)[49]	117 adolescents and young adults with T1DM; 122 without	A "sleep index" using 5 questions from the PSQI	• Sleep disturbances	• There were no differences with individuals with T1DM and controls • Males with T1DM experienced worsening sleep between two time points, but males without diabetes showed improved sleep and females did not show any changes
Bot et al (2013)[116]	277 adults with T1DM	PHQ-9	• Sleep disturbances	• 20.58% (57/277) reported sleeping difficulties
Feupe et al (2013)[88]	17 adults with T1DM	Zeo sleep monitor; ESS	• Sleepiness • Sleep architecture	• 29% (5/17) scored 10 or more on ESS (cutoff for excessive sleepiness) • Stage N3 sleep negatively correlated with HbA1c
Borel et al (2013)[61]	79 adults with T1DM	Accelerometer; BQ; International Restless Leg Syndrome Questionnaire	• Sleep duration • SDB	• Those sleeping <6.5 hours had higher HbA1c than those >6.5 • Non-dipping blood pressure pattern was more likely in those with shorter sleep • 27% (22/79) had positive scores on the BQ indicating risk for SDB
Caruso et al (2014)[4]	49 youth with T1DM; 36 without	SDSC	• Sleep disturbances	• Youth with T1DM had higher ratings on the SDSC and subscales (Initiating and Maintaining Sleep and Sleep–Wake Transitions) • Sleep disturbances mediated the relations between diabetes status and outcomes

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Table 1 (Continued).

Study	Participants	Sleep assessment	Sleep parameters assessed	Findings
Janovsky et al (2014)[48]	20 adults with T1DM (9 with cardiovascular autonomic neuropathy, 11 without); 22 without	PSG; ESS	• Sleep quality • Sleepiness • SDB	• 55% (5/9) of those with cardiovascular neuropathy scored >9 on ESS vs 45% (5/11) of the T1DM patients without cardiovascular neuropathy and 18% (4/22) of the controls • Sleep efficiency was significantly lower for those with cardiovascular neuropathy compared to both other groups • Higher rates on the measure of sleep apnea in adults with T1DM who had cardiovascular neuropathy vs both other groups
Perfect (2014)[36]	50 youth with T1DM	SSHS; CSHQ-sleep diaries	• Sleep disturbances • Sleep duration	• 30/50 (60%) met the cutoff score on the CHSQ • Average TST per the diary was 8.76 hours • Average TST on school nights was 8.34 hours and average TST on non-school nights was 9.43 hours • Self-reported TST was significantly related to HbA1c
Manin et al (2015)[79]	67 adults with T1DM	PSG; ESS	• Sleepiness • SDB	• Participants mean ESS scores were 5 • 46% (31/67) had AHI of at least 10 (the cutoff for mild-to-moderate OSA) • 19% (13/67) had AHI over 30 (the cutoff for severe OSA) • No BMI differences based on SDB • Those with SDB had more micro- and macrovascular complications and longer duration of diabetes
Miculis et al (2015)[115]	50 youth with T1DM	Activity questionnaire	• Sleep duration	• HbA1c was significantly related to sleep duration
Bachle et al (2015)[117]	202 adults with T1DM	PHQ-9	• Sleep disturbances	• 21.78% (44/202) reported sleep difficulties
Vale et al (2015)[78]	23 adults with T1DM	Respiratory polygraphy	• SDB	• 44% (13/23) had OSA • 30% (7/23) had at least AHI of 5 and 26% (6/23) had AHI >15 • AHI not correlated with BMI

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Table 1 (Continued).

Study	Participants	Sleep assessment	Sleep parameters assessed	Findings
Barone et al (2015)[54]	18 adults with T1DM; 9 adults without	Accelerometers and sleep diaries; ESS; PSG; and a visual analog sleep quality scale	• Sleep quality • Sleepiness • Sleep duration • Sleep consistency • SDB • Sleep architecture	• Sleep quality did not relate to average or SD of glucose levels, but among those in the lower glucose group (<154 mg/dL), sleep quality negatively related to glucose levels • No differences in self-reported or accelerometer TST • No differences in sleepiness, however, 39% (7/18) of the T1DM and 11% (1/9) of the controls met the ESS score of 10 • Time to fall asleep positively correlated with SD of glucose levels • Average glucose levels related to PSG awakenings • TST was not related to glucose levels measured via meter or glucose variability glucose group, shorter sleep duration related to higher glucose levels • Those with T1DM had an increased sleep variability on non-work nights relative to non-work nights compared to the controls • No differences in SDB between groups • No significant differences between T1DM and controls on sleep stages • No differences in SDB between groups
Bischoff et al (2015)[118]	25 children and adults with T1DM; 25 without	PSQ	• Sleep quality	• 24% of those with T1DM fell in the at-risk range for the PSQ sleepiness score • 10% of those with T1DM fell in the at-risk range for the PSQ snoring score • No differences in the PSQ snoring score
Hazen et al (2015)[34]	72 adolescents with T1DM in poor metabolic control	4 sleep-related items from the Child Behavior Checklist	• Sleep disturbances • Sleep duration	• 15% (11/72) of the parents reported adolescents had trouble sleeping • 22% (16/72) reported adolescent was tired • 29% (21/72) reported adolescents slept more than other children • 18% (13/72) reported their child sleeps less than other children • Ratings for sleeping more than other children correlated with higher HbA1c and CGM values and lower adherence • Sleeping more did not relate to number of fingersticks, but it did relate to reported self-care
Matejko et al (2015)[6]	148 adults with T1DM	Self-reported TST	• Sleep duration	• 26.3% (39/148) slept <6 hours • Those who slept < 6 hours had higher HbA1c than those with >6 hours • Those who slept longer had more episodes of hypoglycemia
Nefs et al (2015)[45]	267 adults with T1DM	PSQI	• Sleep quality	• 31% (83/267) met cutoff on PSQI • No difference in HbA1c based on sleep quality

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Table 1 (Continued).

Study	Participants	Sleep assessment	Sleep parameters assessed	Findings
Jaser and Ellis (2016)[53]	159 adolescents and young adults with TIDM across two sites	PSQI	• Sleep disturbances • Sleep duration	• Those without an insulin pump reported more sleep disturbances • Those without a pump reported shorter TST • TST did not relate to HbA1c • TST related to blood glucose monitoring
Turner et al (2016)[52]	236 adolescents with TIDM	14 days of single item (5-point Likert scale) asking "How well did you sleep last night?"	• Sleep quality	• Sleep quality and variability in sleep quality ratings related to self-reported challenges with checking glucose and risk for elevated glucose levels • Better sleep quality on one night predicted success for diabetes management the next day
Farabi et al (2016)[89]	27 adults with TIDM	PSG	• Sleep disturbances	• HbA1c and SD of CGM readings negatively correlated with coherence in the Alpha band during a 10- to 30-minute block • Average CGM readings in the 10- to 30-minute block and HbA1c inversely associated with average significant coherence in the Delta band
Larcher et al (2016)[62]	81 adults with TIDM (41 classified as having social jetlag)	Accelerometer; dim light melatonin onset	• Sleep duration • Sleep consistency	• TST was not related to HbA1c • Participants who exhibited a difference of 49 minutes (referred to as "social jetlag") had higher HbA1c • Insulin sensitivity, retinopathy, nephropathy, neuropathy, and cardiovascular neuropathy did not differ based on social jetlag
Menting et al (2016)[46]	194 adult patients with TIDM	Checklist Individual Strength; Sickness Impact Profile	• Sleep disturbances	• 58.2% (113/194) reported sleep disturbances
Chontong et al (2016)[5]	41 adults with TIDM	Accelerometer; BQ	• Sleep quality • Sleepiness • Sleep Duration • Sleep Consistency • SDB	• SE, Sleepiness, and TST were not related to HbA1c • SD of TST related to HbA1c • SD in mid-sleep related to HbA1c • High insulin requirements predicted greater SD of TST and mid-sleep • Higher OSA risk per the BQ had higher HbA1c
Denic-Roberts et al (2016)[47]	222 adults with TIDM in a longitudinal, epidemiological study	BQ; ESS; and PSQI	• Sleep quality • Sleepiness • Sleep Duration • SDB	• 41% (91/222) poor sleep quality • 13% (29/222) sleepiness • 46.3% (89/222) slept <7 hours • TST negatively correlated with HbA1c in participants with good control • TST positively related to HbA1c in those with poor control • Longer TST related to more insulin requirements • 26.6% were at-risk for SDB

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Table 1 (Continued).

Study	Participants	Sleep assessment	Sleep parameters assessed	Findings
Barnard et al (2016)[56]	258 guardians of youth with T1DM/192 adults with T1DM	Survey about overnight testing	• Sleep disturbances	• 19% (49/258) of the guardians reported nighttime awakenings to affect bolus calculations • 12% (23/192) of the adults reported nighttime awakening to affect bolus calculations • 35% (90/258) of the guardians reported nighttime-disrupted sleep affected decisions • 33% (63/192) of the adults with T1DM reported nighttime-disrupted sleep affected decisions
Tang et al (2016)[119]	131 adult cancer survivors with T1DM; 5,574 adult cancer survivors without	EORTC QLQ-C30	• Sleep disturbances	• Individuals with T1DM had higher scores on the Insomnia subscale than individuals without
Jaser et al (2016)[31]	10 preschoolers with T1DM	Actigraphy; CSHQ (parent-reported)	• Sleep disturbances • Sleep quality • Sleep duration	• 90% (9/10) met the cutoff on the CHSQ • Mean SE of 82.5% • Sample averaged 8.1 hours TST
Farabi et al (2016)[55]	24 young adults with T1DM	PSG	• Sleep disturbances	• Number of arousals related to HbA1c • Decrease in IL-6 before and after sleep was greater in those in poor glucose control
McDonough et al (2017)[58]	45 adolescents with T1DM	2-week sleep diary; SDSC	• Sleep duration	• Mean TST was 8.6 hours • A 15-minute increase in sleep corresponded with an additional glucose check and 1 more bolus of insulin
Adler et al (2017)[42]	45 children with T1DM and 45 without; 45 adolescents with T1DM and 45 without; 64 young adults with T1DM and 64 without	SDSC; Adolescents Sleep–Wake Scale; PSQI (all self-reported); ESS	• Sleep disturbances • Sleepiness • Sleep quality	• No significant differences were found in reported sleep disorders between any of the groups of T1DM participants vs controls • PSQI scores showed higher rates of problems in sleep disturbances, subjective sleep quality, sleep latency, nightly SE, and TST

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Table 1 (Continued).

Study	Participants	Sleep assessment	Sleep parameters assessed	Findings
Banghoej et al (2017)[77]	200 adults with T1DM	ApneaLink (pulse oximetry; nasal respiratory flow; thorax movements); ESS; and BQ	• SDB	• 46% (92/200) met AHI cutoff of 5 • 31% (60/200) had AHI between 5 and 14 • 8% (16/200) had AHI between 15 and 20 • 6% (11/200) had AHI of 30+ • 27% (53/200) had AHI ≥10 • Those with OSA had diabetes longer, higher BMI, and higher rates neuropathy, nephropathy, cardiovascular disease, retinopathy, and hypertension • No difference in HbA1c, retinopathy, or cardiovascular disease
Jaser et al (2017)[33]	515 parents of children with T1DM	CSHQ (parent-reported)	• Sleep quality • Sleep duration	• 67% (346/515) met the cutoff for poor sleep quality on the CSHQ • 20% (103/515) had a TST of <9 hours • Shorter TST was associated with higher HbA1c (those who slept <9 hours had HbA1c of 8% and those who slept >9 hours had HbA1c of 7.8%)
von Schnurbein et al (2018)[51]	191 adolescents with T1DM	Munich ChronoType Questionnaire; SQS	• Sleep disturbances • Sleep quality • Sleep duration • Sleep consistency	• Self-reported increases in average sleep quality correlated with a small decrease in HbA1c • Average TST was 7.7 hours, with a mean 2.5 hours in mid-point on school/work and non-school/work days • TST did not relate to HbA1c nor insulin requirements
Patel et al (2018)[59]	65 adolescents with T1DM	Accelerometer; PSQI; and 7-day sleep diary	• Sleep quality • Sleep duration	• Average PSQI score of 5.37 (exceeds 5, the cutoff for poor sleep quality) • Average TST of 6 hours and 54 minutes • Participants slept an average on 1 more hour on weekends vs weeknights
Kostkova et al (2018)[76]	44 youth with T1DM; 60 without	PSG	• Sleep quality • Sleep architecture • SDB	• No significant differences in TST or SE between youth with T1DM and youth without • 23% (10/44) of T1DM participants had SDB • No differences in AHI between those with diabetes and those without • Those with T1DM assigned to the high glucose group had significantly more respiratory arousals and a higher AHI than those in the lower glucose group • No significant differences in SWS or sleep stages between the two groups

Abbreviations: AHI, apnea–hypopnea index; BQ, Berlin Questionnaire; BMI, body mass index; CGM, continuous glucose monitor; CSHQ, Children's Sleep Habits Questionnaire; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; ESS, Epworth Sleepiness Scale; OSA, Obstructive Sleep Apnea; PHQ-9, Patient Health Questionnaire; PSQ, Pediatric Sleep Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SDSC, Sleep Disturbance Scale for Children; SE, sleep efficiency; SQS, sleep quality scale; SSR, sleep self-report; SSHS, School Sleep Habits Survey; SDB, sleep-disordered breathing; PSG, polysomnography; SWS, slow wave sleep; T1DM, type 1 diabetes mellitus; TST, total sleep time.
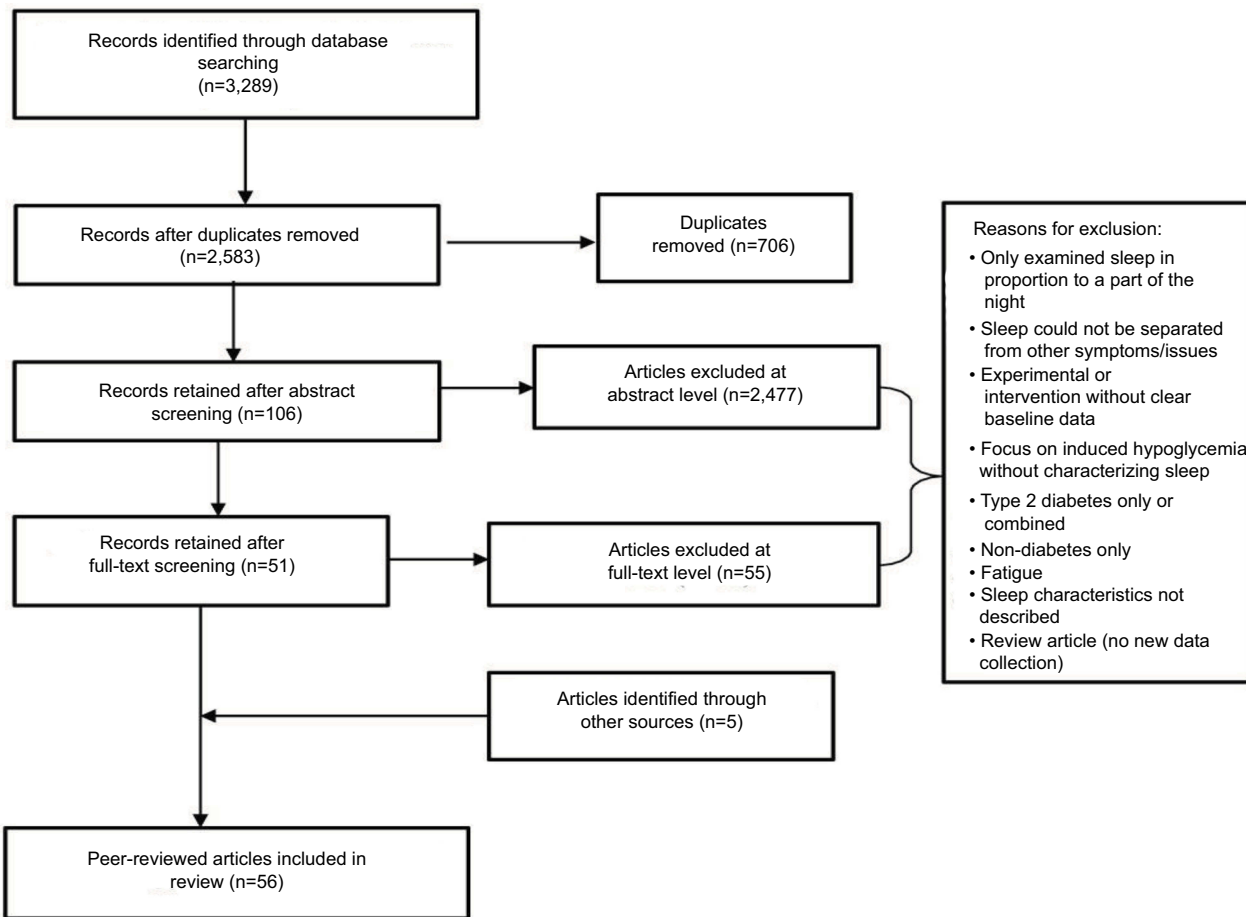
Records identified through database searching (n=3,289)

↓

Records after duplicates removed (n=2,583) → Duplicates removed (n=706)

↓

Records retained after abstract screening (n=106) → Articles excluded at abstract level (n=2,477)

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Records retained after full-text screening (n=51) → Articles excluded at full-text level (n=55)

Articles identified through other sources (n=5) →

↓

Peer-reviewed articles included in review (n=56)

Reasons for exclusion:
- Only examined sleep in proportion to a part of the night
- Sleep could not be separated from other symptoms/issues
- Experimental or intervention without clear baseline data
- Focus on induced hypoglycemia without characterizing sleep
- Type 2 diabetes only or combined
- Non-diabetes only
- Fatigue
- Sleep characteristics not described
- Review article (no new data collection)

Figure 1 Flowchart highlighting inclusion of articles for manuscript.

routine, falling asleep, calling parents back to the bedroom, and winding up in parents' beds. In contrast, these parents reported less frequent concerns with prolonged (>10 minutes) nighttime awakenings.[32] Actigraph (a wrist-sized device that estimates sleep based on a movement sensor) findings from a study of preschoolers with T1DM revealed that average SE was 82.5%, which is lower than the 85% threshold considered to be good sleep quality.[31] With regard to Objective 2, the search did not identify studies that had examined if differences existed in sleep disturbances between those with and without diabetes in the preschool population.

Returning to Objective 1 in the school-age population, Jaser et al[33] found that over two-thirds (67%) of 511 children with T1DM, aged 2–12 years, met the score cut-off on a parent-reported measure of disturbed sleep. A study that examined four items on a parent rating scale found that adolescents with T1DM experienced problems related to sleeping (15%), being tired (22%), sleeping more than peers (29%), or sleeping less than peers (18%).[34] Perfect et al[35] conducted a cross-sectional, case-

controlled study that examined sleep using actigraphy, polysomnography (PSG), sleep diaries, and self- and parent-reported questionnaires in youth with T1DM (aged 10–16 years). The researchers compared sleep in youth with T1DM to sleep in a healthy control sample matched for sex, age, and body mass index (BMI). The matched control participants were obtained from the second examination of a large observational cohort study that had recruited from the same geographic region, used the same PSG equipment, and had the same scoring technician as the youth with T1DM.[35,36] Responses to a sleep disturbance questionnaire completed by parents about the youth with T1DM revealed that 60% met the clinical cutoff.[36] Meanwhile, the average actigraph-measured SE in youth with T1DM was 78.5%.[35]

With regard to Objective 2 in school-aged children, two PSG studies found disparate findings, with one revealing more awakenings in young children with T1DM than those without T1DM,[38] whereas the other study did not find more awakenings or differences in SE.[39] One study

reported that compared to children and adolescents without diabetes, youth with T1DM had higher ratings on an overall measure of sleep disturbances, with particular difficulties related to sleeping too much, falling and staying asleep (eg, insomnia symptoms), and symptoms of restless leg syndrome and teeth grinding.[4] In contrast, another study did not find higher rates of restless leg syndrome and insomnia symptoms between school-age youth with T1DM compared to their siblings.[41] A recent study compared sleep concerns reported by those with T1DM to a convenience sample of those without diabetes (eg, friends and family members) at different age intervals (eg, children, adolescents, and adults). Compared to those without diabetes, children with T1DM actually showed fewer problems with sleeping too much and had lower scores on a subscale reflecting nighttime arousals. Adolescents with T1DM reported fewer respiratory problems during sleep and less daytime sleepiness.[42] In the aforementioned case-controlled study,[35] youth with T1DM did not report more sleepiness, trouble falling asleep, and early morning awakening than those without diabetes. However, direct comparisons were not possible as the diabetes and control samples used different assessment tools to capture those sleep disturbances.

Findings related to the occurrence of sleep disturbance in adults have been mixed (Objective 1). Using a few survey items, adults with T1DM were not characterized by sleep disturbances such as difficulties falling or staying asleep.[43] In cross-sectional studies, rates of participants who were classified as reporting enough symptoms commensurate with sleep disturbances have ranged from 31% to 48%.[44–47] In one of those studies, sleep disturbances were more prevalent in females than in males.[47] With regard to daytime sleepiness, males and females had similar scores, with about 10% reporting difficulties in this area.[47]

A few studies have compared reports of sleep disturbances in adults with T1DM and those without T1DM (Objective 2). van Dijk et al[44] did not find significant differences in scores on a measure of sleep disturbance, but they found that more adults with T1DM met the clinical cutoff for impairment relative to those without diabetes. Janovsky et al[48] reported that a greater number of adult patients with T1DM met the cutoff on a measure of sleepiness than those without T1DM. In the aforementioned study that compared individuals with T1DM to a convenience sample from different age spans, adults who had T1DM evidenced more sleep-related complaints. Accordingly, although average scores on a sleep disturbance measure did not differ between the two groups, adults with T1DM reported higher rates of poor subjective sleep quality, delayed sleep onset, short sleep, and lower SE.[42] Palladino et al[49] found that self-reported sleep disturbances collected over two different time points did not differ between females with and without T1DM, but there was an interaction effect between males and diabetes status on sleep disturbance scores. Accordingly, males with T1DM reported significantly more disturbed sleep between time points, whereas males without T1DM noted improved sleep at follow-up.

With regard to Objective 3, several studies did not find associations between self-reported sleep disturbance, sleep quality, sleepiness, or SE with disease outcomes (glucose, comorbidities) in preschool children,[32] children,[42] adolescents,[42,44] and adults.[42,45,5] However, some data have supported that delays or disruptions in sleep may be linked to poor glycemic control, diabetes-related complications, and inconsistent diabetes management.[39,41,51,52] For instance, Pillar et al[39] found that a swift decline in glucose levels paralleled more PSG-recorded awakenings in children with T1DM. Supporting these findings, higher HbA1c, DKA, and more frequent hypoglycemic episodes were more likely to have been experienced by children with a higher severity of parent-reported sleep disturbances, but the number of finger-sticks did not associate with sleep disturbance severity.[33] In a cross-sectional study of 191 adolescents with T1DM, better sleep quality uniquely predicted better glycemic control (eg, lower HbA1c).[51] Another study that utilized electronic daily self-reports of older adolescents with T1DM demonstrated that both sleep quality and variability in sleep quality synergistically predicted risk for elevated blood glucose levels and perceived challenges to checking their blood glucose levels. Regardless of youth's typical sleep quality, better sleep quality ratings on the preceding night positvely related to improved diabetes management the next day.[52] Hazen et al[34] found that parents' ratings that their adolescent slept more than his or her same age peers significantly related to higher glucose levels, based on both HbA1c and CGM. Sleeping more than others of their age also related to poorer self-reported diabetes management. None of the sleep-related items correlated with the number of glucose meter readings. Although it is possible that hypersomnolence can negatively affect glycemic control, the sample consisted exclusively of adolescents who were in poor control (eg, HbA1c >7.5%). Furthermore, sleeping more than peers may still not reflect adequate or consistent sleep. Another study of adolescents and young adults found a significant correlation between sleep quality and HbA1c for males, but not for females.[53] In a study focused on

hypoglycemia, adolescents evidenced more motoric activity using an accelerometer during hypoglycemic episodes, suggesting that more restless sleep occurred when blood glucose levels were too low.[37]

With regard to Objective 3 in adults, one study found that sleepiness scores were higher for those with T1DM who had cardiovascular neuropathy relative to those who had not yet developed neuropathy.[48] During an overnight sleep study of 18 adults who had T1DM, average glucose levels were positively associated with awakenings, and those with the most variability in glucose levels experienced the greatest number of awakenings.[54] Likewise, a study with adults with T1DM found that more PSG-recorded arousals related to higher HbA1c levels.[55]

Although the objectives of this review focused on the frequency and impact of sleep disturbances in T1DM, aspects of nocturnal management of diabetes may also interfere with or facilitate restful sleep. For instance, parental ratings of sleep disturbances were lower when preschool children were on a fixed insulin administration schedule compared to those who received more intensive treatments consisting of blood glucose monitoring and variable insulin shots adjusted for glucose levels.[32] A study that examined sleep disturbances in children, adolescents, and young adults found that sleep disturbances were higher in children who used a CGM compared to those who used a glucose meter. Additionally, children who used a CGM and/or those who wore a pump reported more insomnia symptoms than those who used a meter or those who delivered insulin via an injection, respectively.[42] In contrast, Jaser and Ellis[53] found fewer sleep disturbances among adolescents with T1DM who used a pump relative to those who did not. A mixed methods survey study with forced choice and open-ended responses completed by guardians of youth with T1DM, as well as by adults with T1DM, revealed that nearly one-fifth experienced nighttime awakenings to manage diabetes.[56] Youth with T1DM were not included as part of that sample; thus, perspectives of youth's own sleep were not captured.

In summary, scores on sleep disturbance measures have not consistently differentiated adults with and without diabetes. Nonetheless, adults with T1DM appear to exhibit higher rates of sleep disturbances when evaluating cutoff scores specified by the instruments that were used. Consequently, relative to those without diabetes, more individuals with T1DM may endorse more frequent and severe sleep problems. Moreover, factors such as poor sleep quality, daytime sleepiness, insomnia symptoms, or awakenings may contribute to worse glycemic control or

difficulties engaging in diabetes self-management. In youth, there has been less support for a direct association between self-reported sleep disturbances and glycemic control. However, some of the youth studies and three of the adult studies found that disturbed sleep related to management aspects of diabetes. The preponderance of studies relied on self-reports of sleep disturbance, which may be appropriate given that in some respects, characteristics of sleep disturbances are subjective. Ambulatory technologies such as the CGM and actigraphy, or even home-based PSG, would provide objective assessments that would complement self-reported methods. The current methodologies that have been employed have not enabled researchers to ascertain if sleep disturbances are a causal contributor or a consequence of poor disease control. For example, although sleep disturbances could precede glycemic dysregulation or disease co-morbidities, significant pain associated with microvascular and macrovascular complications could disrupt sleep. Sophisticated longitudinal designs that incorporate analytic techniques, such as a dynamical systems approach,[57] would elucidate how changes in diabetes disease outcomes and sleep disturbances affect the other over time.

Insufficient sleep duration

Several studies have examined the prevalence of inadequate sleep duration in individuals with diabetes from a cross-sectional perspective (Objective 1). Developmentally, a few studies with young children with T1DM have indicated early problems with sleep. Although Monaghan et al noted adequate average sleep duration per parent report for 24 children with T1DM aged 2–5 years, many did not meet the recommended TST, even with naps and overnight sleep periods combined.[32] Using a wrist accelerometer, another study of 10 preschoolers found average TST to be only about 8 hours.[31] In an epidemiological study of youth with T1DM, parents of preschool children reported an average of ~11 hours of sleep per night, whereas the average sleep duration of children between the ages of 5 and 12 years was 9.5 hours. These averages were still within the lower end of the recommended range for each age group, with 20% of the youth sleeping <9 hours.[33] Among studies with adolescent samples, self-reported averages have consistently ranged below the recommended amount of sleep (7.4–8.6 hours/night).[51,53,58,59]

The method of assessing sleep duration may yield different amounts of sleep. Accordingly, two published studies of youth from the same cohort of adolescents with T1DM revealed that

objectively measured mean TST was 6.96 hours,[35] whereas the average self-reported sleep duration from sleep diaries was 8.76 hours across 5 days.[36] Additionally, when asked about typical school night and non-school night sleep using a validated survey, these adolescents reported their sleep durations to be 8.34 and 9.43 hours, respectively.[36] Similarly, Patel et al[59] reported school night TST to be 7.26 hours and non-school night TST to be 6.26 hours using actigraphy, whereas TSTs computed from diaries for school nights and non-school nights were 7.75 and 8.75 hours, respectively. Several studies have examined the associations between TST and both glycemic control and diabetes management in youth (Objective 3). In the epidemiological study of participants with T1DM, parents' reports of their child's sleep duration were significantly related to parent-reported HbA1c, with those sleeping >9 hours per night having lower HbA1c.[33] Although the findings were based on parent report and practical significance is unknown, a difference of 0.2% in HbA1c between the two sleep groups is consistent with the average change in HbA1c following adherence-promoting interventions.[12] Further, in the adolescent sample of youth with T1DM from the case-controlled study, night-to-night TST measured via actigraphy did not predict CGM-recorded glucose levels the following day;[35] however, the researchers did not report the overall correlation between actigraph-measured sleep duration and overall average glucose levels. Nonetheless, self-reported average TST significantly related to HbA1c in the same sample.[36] Other studies with adolescents and young adults diagnosed with T1DM did not reveal a significant relation between self-reported sleep duration and HbA1c.[51,53,58,59] With regard to management, sleep amount did not predict how much insulin the adolescents with T1DM required,[51] but two studies found that youth who slept more tested their glucose levels more often,[53,58] were more likely to use a pump,[53] and were more likely to adjust their insulin when needed.[58]

With regard to Objective 1 in adults, Denic-Roberts et al[47] reported that nearly half of their sample of adults with T1DM obtained less than the recommended sleep duration (7 hours). Meanwhile, another study found that 26% of the sample of adults with T1DM averaged <6 hours per night.[6] With regard to Objective 2, one study did not find self-reported sleep duration to differ between adults with T1DM and those without.[44] An observational study also did not find statistically significant differences between TST of adults with T1DM (n=18) and those without (n=9) using accelerometers and sleep diaries. However, participants with T1DM still reported 25 minutes less sleep and had larger within group variability, as expressed by a larger SD.[54]

Regardless of whether adults with T1DM sleep the same or worse than those without diabetes, evidence exists that inadequate sleep duration relates to diabetes outcomes (Objective 3). With regard to glycemic control, studies have found that adults with short sleep duration (6–6.5 hours) based on self-reported[6] and objectively[61] measured TST had significantly higher HbA1c than those with more sleep. Yet, when objectively measured sleep duration has been examined as a continuous value in other adult studies, the correlations with HbA1c have not been significant.[5,54,62] There may be other factors that enhance or mitigate the contribution of sleep duration to disease outcomes. For instance, an epidemiological study found a moderating effect, such that shorter sleep was associated with lower HbA1c among participants with poor control, but sleep duration negatively related to glucose levels among those with good control. Moreover, those with longer self-reported sleep duration also appeared to have higher insulin need.[47] It is important to keep in mind that due to the large sample size, the correlations were significant but indicated relatively small effects.

In summary, based on the extant data, similar to individuals without T1DM, as individuals with T1DM move through the developmental stages, the prevalence of inadequate sleep duration is likely to increase. To date, there have been mixed findings related to the contribution of sleep duration on glycemic control and diabetes management. However, the exclusive reliance on correlational research obfuscates the fact that there are a myriad of confounding factors that might affect the diabetes–sleep relationship. Few studies have examined the impact of inadequate sleep using controlled designs for individuals with T1DM. However, one experimental sleep restriction study in a laboratory setting showed that adults with T1DM who were limited to 4 hours of sleep exhibited lower glucose tolerance and insulin sensitivity compared to when they were provided the opportunity to obtain the recommended TST.[63] Thus, very limited data are available that experimentally elucidate the mechanistic underpinnings and potential causal role of sleep duration in glycemic control and vice versa in individuals with T1DM. Experimental sleep manipulation studies using in-lab or at-home protocols have demonstrated that sleep restriction and extension cause changes in mood,[64,65] behaviors,[65,66] cognition,[14,22,27,28,67,68] aspects of immune functioning,[69,7] and metabolic control.[71] Accordingly, prescribed sleep conditions as part of a multiday protocol such as in a residential program that mimics a camp-like environment

would allow for control and precise monitoring of environmental and intraindividual factors that moderate the effects of sleep duration on metabolic health. Given the momentary fluctuations in glycemic control, microlongitudinal designs that utilize ambulatory technologies such as the CGM and actigraphy, or even home-based PSG, would provide evidence regarding unique temporal resolution of sleep, glucose, and daytime functioning in naturalistic settings. Moreover, a clinical trial[72] aimed at increasing sleep duration has been developed to investigate the efficacy of a sleep extension intervention on diabetes-related outcomes. Such studies are needed to be able to test the effects of prescribing a lengthened sleep duration on the prognosis of T1DM.

Inconsistent sleep schedules

Although sleep disturbances and duration have been the focal point of most studies, the potential influence of sleep inconsistency or variability has more recently been examined in relation to glycemic control and other disease-related outcomes (eg, insulin dosage; Objective 3). A standard indicator of sleep consistency is the standard deviation (SD) of TST. However, a few studies have examined the difference between sleep duration on school/work nights and non-school/work nights. Bed and wake times, the differences in the latest and earliest bedtime, and the difference between school and non-school nights, have also been used to characterize sleep schedules. These indicators of sleep timing and variability are distinguished from another circadian rhythm metric referred to as "social jetlag", which is derived by computing the difference between the halfway point between bedtime and awakening time on school/non-work nights and the midpoint of the sleep period on non-school/work nights. When examining social jetlag,[51] a study did not find that adolescents with T1DM who experienced greater social jetlag had higher HbA1c, but these adolescents required more insulin to manage their diabetes.[51] Another study of adolescents with T1DM using TST SD found that more pronounced variability significantly related to higher HbA1c.[59] In adults, one study did find that social jetlag positively correlated with HbA1c.[62] A different study with 41 adults with T1DM that characterized variability by examining the SD of both mid-sleep and sleep duration found that both these metrics predicted higher HbA1c and significantly associated with greater insulin need.[5]

The emphasis on sleep variability is nascent and has been overshadowed by the focus on sleep duration in studies with individuals with T1DM. The complexity of the sleep–wake cycle has not been fully realized in research with T1DM. Sleep misalignment can be captured through several metrics of circadian rhythm beyond that of differences in timing and social jetlag. For instance, more recent studies have considered daily variations, such as the sleep regularity index and the composite phase delay in adults samples.[73,74] Similarly, global metrics of glucose levels as opposed to day-to-day fluctuations in glycemic control may not capture the immediate and cumulative effects of having glucose levels out of the target range such as with chronic hyperglycemia or intermittent hypoglycemia.

Sleep-disordered breathing

Data have supported not only the potentially higher prevalence of SDB in individuals with T1DM but also the myriad of morbidities associated with SDB in this population. Only three studies have examined SDB in youth with T1DM (Objectives 1 and 2). A prospective, case-controlled study reported the rate of SDB to be 35% (14/40) using an apnea–hypopnea index (AHI) ≥1.5.[35] The rates of SDB were comparable between those with and without T1DM in these three studies.[35,75,76] However, in two of the pediatric studies, individuals with T1DM had more apneic[35,75] and central apneic events[35] than those without T1DM.

With regard to Objective 1 in adults, prevalence rates from an epidemiological study utilizing self-report at a single time point found that 23% of the 222 adults endorsed items suggestive of high SDB risk.[47] Using PSG, researchers have reported the rates of individuals who exhibited various AHIs. Using an AHI of 5, multiple studies have found high rates (45%–63%) of SDB.[77,78] Using an AHI cutoff of 10, studies reported the prevalence of SDB to be 27%–46%.[77,79] Using a cutoff of 15, the prevalence rates have ranged from 8% to 40%.[78,8,81] Using an AHI > or ≥ 30, studies have found rates from 6% to 25%.[78–8] These studies were based on samples ranging between 10 and 58 individuals. Therefore, it is difficult to compare the findings to studies that have been conducted in those without diabetes or those with T2DM to determine if the prevalence of SDB is equivalent or greater than those samples.[82] Nonetheless, the use of PSG provides an objective, "gold" standard metric that has revealed that roughly half of the patients with T1DM may have at least mild SDB. In regard to Objective 3, all three pediatric studies linked SDB with poor glycemic control. For instance, in comparison to youth with well-controlled diabetes, youth with poor control had more

respiratory difficulties, such as respiratory arousals,[76] higher AHIs,[76] more apneas,[75] and more central apneas.[75] In one of those pediatric studies,[35] when comparing glycemic control based on SDB status, although HbA1c did not differ, CGM-recorded glucose levels were significantly higher (>40 mg/dL difference) and individuals with T1DM who had SDB were more hyperglycemic relative to those without. In adults, untreated SDB may contribute to long-term microvascular and macrovascular complications. Some studies found nephropathy, neuropathy, hypertension, and heart complications to be more common among adults with T1DM who had SDB compared to adults with T1DM who did not show evidence of SDB.[79,81,83] One study did not find differences in the number of individuals with diabetic retinopathy based on their SDB status (AHI >15).[81]

Altogether, individuals with T1DM appear to be at high risk for at least mild SDB. Moreover, those with SDB evidence significantly worse glycemic control or experience more morbidities that arise from complications of having T1DM. Although it is not possible to experimentally induce SDB as a way to demonstrate that SDB causes poor disease control, a more important question is whether treatment of SDB will reduce the risk or existence of comorbidities. Accordingly, a meta-analytic study found evidence that treatment of SDB has led to improvements of metabolic control.[84] More recently, factors such as the duration of treatment, compliance with treatment, and severity of SDB have been postulated to influence whether continuous positive airway pressure (CPAP) has a secondary benefit of improving glucose regulation.[82,85] However, CPAP as a treatment concomitant with current T1DM standard of care practices is unknown. Thus, randomized controlled trials (RCTs) are needed to examine the effect of CPAP and surgical interventions (adenoidectomy and tonsillectomy) on alleviating SDB and improving diabetes control.

Sleep architecture

Regarding Objective 2, one study in adolescents found that individuals with T1DM spent a greater percentage of time in stage N2 than those without diabetes.[35] The study also found that those with T1DM spent less time in stage N3.[35] Similarly, one adult study found more stage N2 in those with T1DM compared to those without.[86] However, a few studies in children and adults have not shown differences in the percentage of time in NREM stages[38,39,76] compared to those without T1DM, nor have any of the studies noted a difference in REM[35,38,39,54,76,86] based on diabetes status.

With regard to relations with glycemic control (Objective 3), two studies did not find sleep architectural differences in youth who had experienced hypoglycemia during the sleep period,[38,87] whereas another study found that children who had experienced hypoglycemia spent more time in SWS compared to youth with T1DM who did not experience hypoglycemia.[39] A single night lab-based PSG did not reveal significant differences in the proportion of time spent in each sleep stage between youth with T1DM classified as in good control compared to those classified as poor control based on their CGM recordings during the sleep study. However, the authors noted that their previous research had demonstrated that when classified by HbA1c (>9 vs <9), youth with higher glucose spent significantly more time in lighter stages of sleep.[76] Perfect et al[35] reported that percentage of time in stages N2 (more) and N3 (less) both related to higher HbA1c and stage N2 significantly related to weekly average CGM levels in adolescents with T1DM. A greater proportion of time spent in SWS was associated with lower Hb1Ac in a small study with adults as well. Moreover, another study found that individuals experienced significantly less hypoglycemia as measured by CGM during stage N3.[88] Furthermore, when examining the correspondence between CGM recordings and sleep architecture via EEG patterns among adults with T1DM, researchers found strong associations between glucose levels and the variability of those levels with glucose-EEG power coherence in the alpha and delta bands. The direction of the relationship supports the possibility that brain activity and glucose may have greater influence on each other when individuals with T1DM are in better control.[89] Notably, no studies that met inclusion criteria in this review found an association between glycemic control and REM in either children[35,38,39,76,87] or adults.[88]

Summary of reviews of T1DM and sleep

Three comprehensive reviews have been published summarizing the empirical findings pertaining to sleep among individuals with T1DM.[9–92] A 2016 meta-analysis that involved an international collaboration of T1DM researchers spearheaded by the first author of that publication examined the differences in sleep quality, daytime sleepiness, sleep duration, SDB, and sleep architecture in youth and adults with T1DM compared to those without as well as those sleep parameters in relation to glycemic control.[9]

Reutrakul et al noted that at the time of their meta-analysis, studies examining sleep disturbance in children did not utilize a consistent measurement to aggregate the findings. With regard to sleep disturbances in adults, PSG-measured SE and rates of poor sleep quality did not differ between adults with T1DM and controls and were not related to HbA1c. However, adults with T1DM had significantly worse scores on sleep quality measures than those without, and HbA1c levels were significantly higher among those with poor sleep quality, relative to those with good sleep quality.

When examining sleep duration, the authors concluded that TST assessed via PSG was significantly shorter in children with T1DM relative to those without. Youth who slept the recommended number of hours per night did not differ in glycemic control compared to those who slept less than the recommended number of hours. Comparison of those in good vs poor control did not reveal differences in TST, although there was a trend for adolescents in good control to sleep longer. With regard to findings involving objective measurements of sleep duration in adults, differences in self-reported TST did not exist between adults with and without T1DM, and there was not a correspondence between those in good vs poor control and short vs adequate sleep. In contrast, those classified as having short sleep based on self-reported TST had significantly worse glycemic control, and those with poor control slept significantly less than those in good control.

In this meta-analysis, there were not enough pediaric studies to report SDB prevalence rates or examine AHI in relation to HbA1c. Similar to the current study, the authors noted that more than half of the adult participants with T1DM had at least mild SDB, with about one-sixth having moderate or severe SDB. The difference in HbA1c between those with and without SDB was not significant, although the difference in HbA1c in adults with more severe SDB approached significance. Moreover, those with poor glycemic control had more severe SDB than those in good control. Finally, there were not enough studies in either children or adults to report sleep architectural differences. However, there was a trend for adults with poor glycemic control to spend more time in lighter stages of sleep and less time in stage N3.[9]

In another review, Farabi[91] summarized the findings related to sleep disturbances and quality, sleep duration, SDB, and architecture. The author explained that the structure of sleep appears to differ in individuals with T1DM. Additionally, various difficulties with sleep onset, sleep maintenance, sleep duration, and depth of sleep have been noted. Moreover, SDB appears to be more prevalent among individuals with T1DM, and those with SDB may be at higher risk for diabetes complications. Nonetheless, the author noted that most studies in T1DM have been cross-sectional and did not explain how or why sleep duration and glucose may be related.

Perez et al[92] provided a more recent review of sleep duration, variability, and sleep architecture in youth with T1DM. The authors drew similar conclusions in that youth with T1DM appear to have insufficient and inconsistent sleep. Furthermore, sleep problems characterized by inadequate, inconsistent, and light sleep have been linked with poorer glycemic control. The authors also noted that there may be greater differences between the number of hours slept on non-school/work nights compared to school–work nights in individuals with T1DM than those without. Such a notion might not only reflect greater sleep inconsistency in this population but also suggest that average sleep duration aggregated across all days in a week may not capture that gap.[92]

Two additional meta-analytic studies focused on retinopathy in adults with T1DM. They each only identified one study, but these studies were not the same. Both concluded that there was a positive association between respiratory problems during sleep and retinopathy in adults with T1DM.[93,94]

Discussion

About 60 studies with varying sample sizes have now been published across the lifespan investigating the role of sleep in T1DM. Rates of sleep disorders and problems across studies were consistently 15% or higher. The current rates for Hashimoto's disease and celiac disease range from 1% to 15% and up to 30%, respectively.[6] The Standards for T1DM recommend routine screening for these two conditions given the high co-occurrence. Unlike T2DM patients, the Standards do not mention sleep as part of their practice parameters for T1DM. This gap is most likely due to the varying ways in which sleep has been assessed, smaller sample sizes, and absence of longitudinal, case-controlled, or experimental studies in individuals with T1DM. Nonetheless, as more studies are published, the significance of these findings may warrant inclusion of sleep recommendations in future iterations of these guidelines.

Implications for the practice setting

Given the prevalence, evaluation of sleep concerns and screening for disorders may facilitate diabetes

management and glycemic control efforts. With regard to perceived sleep disturbances in children, practitioners can incorporate one of the most commonly used questionnaires such as the Children's Sleep Habit Questionnaire[95] (parent report measure) or the Pittsburgh Sleep Quality Index[96,97] (older adolescents and adults). A newer measure that has not yet been utilized in youth with T1DM but can be administered to children and adolescents is the Children's Report of Sleep Patterns.[98–1] Furthermore, some CGM companies have been incorporating technological applications that integrate data from accelerometers that generate sleep metrics. Although these commercially available devices have not undergone the validation process relative to research-grade devices, they do have the potential to objectively depict sleep patterns and disruptions in restful sleep. Monitoring sleep on a daily basis is particularly relevant given that burgeoning evidence has supported that sleep variability or inconsistency may be related to negative outcomes.

Despite the risk for SDB, screening for SDB is not part of routine practice and both clinicians and patients lack awareness regarding the potential impact of SDB on disease outcomes.[1] Several screening approaches have been proposed in youth and adults, with varying predictive validity for SDB. For instance, the STOP-BANG[1,1] (or A modified version[1]) is an acronym for snoring, tired, blood pressure, BMI, age >50 years (or academic problems for children), neck circumference >95th percentile, and male gender. Studies have shown that positive indicators of three or more represent moderate risk for SDB, with SDB being more likely with an increasing number of criteria met.[1,1,1] A positive screen with a STOP-BANG may warrant a referral for a PSG. It is important to consider that this approach has not been validated in individuals with T1DM, and thus, it is not known if additional risk factors include poor glycemic control or comorbidities. In adults, the Berlin Questionnaire that was used in several studies included in this review has shown some promising predictive validity but is still problematic as it may yield false negatives.[1,1]

Directions for future research

Multiple study designs have been employed, yet notably absent have been longitudinal, experimental, or RCTs. The rigor of research on sleep in individuals with T1DM might increase if researchers formed a network to collaborate on a multisite, epidemiological study to characterize the phenotypical aspects of sleep in this population and determine the clinical relevance of different sleep parameters for disease

outcomes. Studies tracking sleep in participants' natural environments provide ecologically valid contexts; however, another approach could be a crossover study that includes experimentally manipulated sleep conditions (short, healthy sleep opportunity, perhaps alter sleep times to assess effects of variability) as part of a multiday protocol such as in residential summer program akin to an overnight camp setting. This would enable researchers to collect biomedical and psychosocial data, document environmental conditions, and precisely monitor physical activity, diet intake, and mood. Additionally, at the time of this review, no peer-reviewed publications exist that have systematically and comprehensively studied the treatment of sleep disorders or problems in individuals with T1DM. One study detailed the components of the intervention to extend sleep, with final results still pending.[17] Two other prospective studies are being developed or underway to facilitate youth obtaining adequate sleep and establishing healthy sleep schedules.[1,1]

Limitations

This review did not address the potential effects of sleep insufficiency on daytime functioning, such as internalizing symptoms, externalizing symptoms, academic achievement, neurobehavioral performance, and quality of life. A few studies have established or proposed the associations of sleep and neurobehavioral outcomes in individuals with T1DM.[35,36,4] Sensitive, longitudinal ambulatory cognitive assessments and ecological momentary assessments of mood and well-being would document the day-to-day influences of sleep and their interaction with glycemic control and intervention effects. To further support the integration of evaluation for sleep problems into clinical care, future research is needed to address critical issues such as establishing recommendations for universal screening practices; selecting tools that have the most clinical utility in identifying those with a sleep disorder that are cost effective, sensitive, and not burdensome; pinpointing the best timing to monitor and treat different aspects of sleep over the course of diabetes clinical care; and establishing evidence-based intervention components that are effective in reducing sleep disturbances, lengthening sleep, regularizing sleep schedules, and treating SDB.

Conclusion

The prevalence of sleep problems appears to be higher among individuals with T1DM. Although research has yielded mixed results, several sleep parameters are

associated with diabetes-related complications. On a final note, given that managing T1DM requires considerable resources and time for families, notably absent from the majority of studies was a cross-cultural or diversity perspective. Consequently, a multicultural framework with family systems thinking including examination of the socioeconomic influences on sleep patterns in this population would help to contextualize the role of sleep in the disease trajectory and potentially enhance interventions targeting sleep to maximize outcomes.

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