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Fatigue Among Adults With Type 1 Diabetes Mellitus and Implications for Self-Management

Stephanie Griggs, PhD, RN and

Yale University, Orange, Connecticut

Nancy S. Morris, PhD, ANP-BC

University of Massachusetts Medical School, Worcester, Massachusetts.

Abstract

Purpose—The aim of this review was to integrate empirical and theoretical literature on fatigue among adults with type 1 diabetes mellitus (T1DM). A methodological review using an integrative approach was used. Databases MEDLINE via Pubmed, CINAHL, PsycINFO, and Science Direct were searched for peer-reviewed articles published in English from 2007–2017, using the following search terms and Boolean operators: “Type 1 Diabetes” and “Fatigue.” Of 199 articles initially retrieved, 14 were chosen for inclusion. These articles included 13 quantitative (7 cross-sectional, 2 cohort, 2 secondary data analyses, 2 experimental) and 1 qualitative phenomenology. Fatigue was identified as one of the most troublesome symptoms reported in persons with T1DM. Four main themes emerged: fatigue in T1DM is multidimensional and related to psychological, physiological, situational, and sociodemographic factors.

Conclusions—Fatigue is considered a classic symptom of hyperglycemia; however, there were minimal data to support the theory that fatigue is related to hyperglycemia or hypoglycemia. Studies on fatigue among persons with T1DM are limited to small samples and cross-sectional designs with few randomized controlled trials addressing fatigue and diabetes-related symptoms. Evidence is conflicting regarding the onset of fatigue among persons with T1DM and the relationship between fatigue and diabetes duration. The prevalence of fatigue is likely influenced by disease physiology, psychological stress, and lifestyle factors, but more research is needed to confirm these relationships as causal inference is unclear.

Introduction

With 23% to 42% of adults with type 1 diabetes mellitus (T1DM) reporting fatigue^{1–3} and 31% to 35% reporting subjective sleep impairment,^{4–6} further attention is warranted regarding the potential impact on school and work performance, glycemic management, and overall quality of life. T1DM is a heterogeneous disorder leading to beta cell destruction and absolute insulin deficiency.⁷ Poor sleep quality and reduced sleep duration are related to fatigue. The multidimensional nature of fatigue is compounded in the 1.25 million Americans with T1DM⁸ who require self-monitoring and self-care interventions multiple times a day to optimize glycemic targets.⁹

Correspondence to Stephanie Griggs, Yale University, 400 West Campus, Drive, Orange, CT, 06477, USA (stephanie.griggs@yale.edu).

Fatigue is a distressing symptom in persons with T1DM,¹⁰ particularly central fatigue, which is defined as a “failure to initiate and/or sustain attentional tasks (mental fatigue) and physical activities (physical fatigue) requiring self-motivation.”^{11(p35)} Fatigue has implications for diabetes self-management with negative effects on daily functioning and well-being.⁴ For example, fatigue may result in a decreased ability to carry out activities necessary to optimize glucose targets such as checking blood glucose and responding to results, preparing optimal foods, and engaging in regular physical activity. Glycemic stability is the cornerstone of T1DM management and care.^{7,12} A number of therapeutic options exist for persons with T1DM including multiple daily injections of rapid-acting insulin combined with daily basal insulin as well as a continuous infusion of insulin subcutaneously via an insulin pump.⁷

One systematic review of research addressing fatigue in persons with T1DM was identified that only included 3 studies with fatigue as the primary endpoint.² Our review expanded these findings to also include the association of fatigue with self-management and to general quality of life. The aim of this review was to integrate the empirical and theoretical literature on fatigue in adults with T1DM. The following questions framed this review: What are the correlates and factors related to fatigue among adults with T1DM? Is fatigue associated with self-management in adults with T1DM?

Materials and Methods

Literature Search Strategy

The focus of this review is on correlates and related factors of fatigue among persons with T1DM. Databases MEDLINE via PubMed, CINAHL, PsycINFO, and Science Direct in addition to an ancestry approach were searched for peer-reviewed articles published in English from 2007 to 2017, excluding dissertations. We used the following search terms and Boolean operators: “Type 1 diabetes” and “fatigue.” Titles and abstracts were read and evaluated to ascertain relevance for this review. Inclusion criteria included primary research studies that specifically addressed T1DM and fatigue in adults. Articles were excluded if the population of interest was only people with type 2 diabetes. The review of searches were performed independently by the first author and verified by the second author.

Empirical reports included a wide variety of methods: quantitative, instrument development, mixed-methods, and qualitative. All reports were coded according to 2 criteria: methodological or theoretical rigor and data relevance on a 2-point scale (high or low).¹³ As suggested by Whittemore and Knafl,¹³ reports with a high rigor and relevance contributed more to the analytic process. The quantitative studies were considered to have high rigor if the design was appropriate for the research question, valid and reliable instruments were used, methodology was clearly described, and primary threats to internal validity were addressed. The qualitative studies were considered to have high rigor if they described their strategies of scientific merit. Relevance was coded as high if the study was directly related to question of interest. Consensus was reached by both authors on the rating of each paper. Data display matrices were developed to visualize the coded data from each report by category and were iteratively compared (Table 1).

Results

Of 199 articles initially retrieved, 8 were removed because of duplication among the 4 databases and 176 were removed that did not meet inclusion criteria, leaving a total of 14 articles for inclusion (Figure 1). These articles included 13 quantitative (7 cross-sectional, 2 cohort, 2 secondary data analyses, 2 experimental), and 1 qualitative (phenomenology). The 14 papers were read, and data were extracted and placed into a matrix table highlighting the purpose, sample, method, setting, variables studied, and relevant findings (Table 1). In addition, each paper was given a rigor/relevance score determined by review of the rigor of the research method or the theoretical approach and the relevance of the data to fatigue among adults with T1DM. Contrasts and comparisons were noted throughout the iterative process as new papers were added to the matrix table. Our goal was to be inclusive of all data; we incorporated supportive as well as conflicting data in our synthesis of factors related to fatigue among adults with T1DM.

Fatigue was identified as one of the most troublesome symptoms reported in persons with T1DM.^{1,14} Both Goedendorp et al¹ and Segerstedt et al¹⁵ report that participants with T1DM had higher fatigue than matched controls. In a study of 214 outpatients, those with T1DM were significantly chronically fatigued (40%; 95% CI 34–47%) significantly more than matched controls (7%; 95% CI 3–10%; $P < .001$).¹ In a second study, fatigue scores were significantly higher among 268 patients with T1DM compared with the 1557 patients in the control group.¹⁵ Fatigue in people with T1DM was consistently discussed as being multidimensional and related to 4 main themes: (1) diabetes-related physiologic factors, (2) psychological symptoms, (3) situational factors, and (4) sociodemographic differences (Figure 2).

Physiologic Factors Associated With Fatigue

Based on the 30-year Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (EDIC), it is recommended that patients with T1DM achieve glycemia as close to the range found in people without diabetes as safely as possible.¹² Several authors suggest that one reason for fatigue among people with T1DM is alterations in blood glucose levels.^{1,4,16} These alterations include hyperglycemia,^{1,3,14} hypoglycemia,^{1,4} and glucose variability.^{15,17} Segerstedt et al¹⁵ report that fatigue was higher in participants who had a longer duration of T1DM (1.4-point difference, 95% CI 0.9–1.9, $P < .001$), yet it was not related to complications; the mechanism for the association with duration of diabetes is not clear. In contrast, Lasselin et al¹⁸ in a small study with 21 adults with T1DM report that diabetes duration and symptoms of fatigue were not significantly related.

Hyperglycemia—Fatigue is considered a classic symptom of hyperglycemia^{1,14}; however, the evidence between fatigue and hyperglycemia is minimal. To illustrate, Goedendorp et al¹ report that glucose parameters were not related to fatigue in a cross-sectional study of 214 outpatients with T1DM.

Hypoglycemia—The intensive management recommendations to achieve glucose levels comparable to healthy ranges in people without diabetes increase the risk of hypoglycemia.

¹² Specifically, improved glycemia in the DCCT was associated with a 2–6-fold increase in severe hypoglycemia in intensive as compared to conventionally treated subjects.⁷ Hypoglycemia and worry about hypoglycemia are major barriers for persons with T1DM to achieve glycemic stability and quality of life.¹ In a phenomenological study of 9 college students, a predominant theme among respondents was that diabetes affected academic performance because of the fatigue associated with hypoglycemia and hyperglycemia.¹⁶ Similarly, among a cohort of 192 adults with T1DM, 28% report that hypoglycemia, or fear of hypoglycemia, was a common cause of disrupted sleep due to awakening during the night.⁴ Hypoglycemia interrupts sleep for many with T1DM. However, once people with T1DM become chronically fatigued, they report less hypoglycemia.¹ This may be related to having less energy to manage glycemia, with resultant hyperglycemia being the default.

Glucose Variability—The frequency and magnitude of blood glucose fluctuations may be greater in individuals with T1DM who are more sensitive to exogenous insulin and have altered responses to hypoglycemia.⁷ This may lead individuals to overtreat hypoglycemia.⁷ Glucose fluctuations during the postprandial period may trigger inflammatory markers and oxidative stress.¹⁹ Goedendorp et al¹ did not find an association between glucose variability and fatigue in a sample of 214 adults with T1DM; further study is warranted to confirm these findings due to the small sample size.

Neuropathic Pain and High Number of Diabetes Complications—Fatigue is associated with neuropathic pain^{1,3} and with having a high number of diabetes complications.³ Neuropathic pain is a common debilitating and distressing symptom that can impair sleep, lower mood, and have a negative impact on daily activities.^{1,20} In a cross-sectional study of 120 severely fatigued patients with T1DM, both pain ($\beta = -.31$, $t(117) = -3.39$, $P = .001$) and fatigue severity ($\beta = .18$, $t(117) = 2.04$, $P = .044$) contributed to functional impairment.¹⁷ Pain (chronic neuropathic or joint) is associated with fatigue in 4 additional studies.^{1,3,20,21}

Menting et al¹⁷ studied fatigue among 194 outpatients with T1DM over 43 months and reported that those who had persistent fatigue had significantly more diabetes complications ($P < .001$) including cardiovascular disease, neuropathy, nephropathy, retinopathy, and numbness in the feet. Sleeping difficulties were associated with a higher A1C among a group of 277 adults with both T1DM and depression.²² This is in contrast to Lasselin et al¹⁸ who reported no association between diabetes complications and fatigue symptoms.

Fatigue and Psychological Factors

Fatigue in people with T1DM is associated with several psychological factors: increased depression,^{1,3,22} increased anxiety symptoms,⁵ increased diabetes-related distress,¹⁴ lower self-efficacy,^{1,3} and lower quality of life.²⁰ Depression is common in people with diabetes and related to higher A1C levels.²² In an observational study of 214 outpatients with T1DM, depression was significantly associated with chronic fatigue.¹ In a longitudinal study of 277 patients with T1DM from 3 outpatient clinics, fatigue was one of the most commonly reported symptoms, and associations with depressed mood were more pronounced in people with type 1 diabetes vs type 2.²² Lower self-efficacy significantly predicted severe fatigue (β

= $-.191$, $P = .028$) in 214 adults with T1DM¹ and in 194 adults with T1DM (OR = 0.44, $P < .05$).³

Fatigue and Situational Factors

The following situational factors are associated with T1DM-related fatigue: decreased physical activity,^{1,3,18} increased BMI,^{3,18} sleep disturbances and difficulties,^{1,3,4,5,20,22} problems with concentrating,²² less confidence in diabetes self-care,³ and competing demands of higher education.¹⁶ Fatigue and quitting sports when younger were predictive of lower quality of life among a group of adults with T1DM.²³

Decreased Physical Activity and Increased BMI—A number of situational factors affect fatigue in persons with T1DM; however, physical inactivity and increased BMI have a marked clinical relevance for this population. Specifically, increased BMI and decreased physical activity increase macrovascular complication risk (eg, coronary vascular disease).⁷ In 3 studies, physical inactivity was significantly associated with fatigue,^{1,3,18} and in a fourth study, abandoning sports at a younger age was predictive of a lower quality of life.²⁴ In a cross-sectional study of 21 patients with T1DM, increased BMI was associated with increased general fatigue ($r = 0.355$, $P < .05$), physical fatigue ($r = 0.369$, $P < .05$), and mental fatigue ($r = 0.501$, $P < .001$).²³

Sleep Disturbances and Difficulties—Several studies support that chronic sleep interruption is prevalent in adults with T1DM.^{3–5,22} In persons with T1DM from 3 outpatient clinics in the Netherlands, sleeping problems were strongly related to higher A1C.²² In a cross-sectional study of Dutch adults with T1DM ($n = 267$), poor sleep quality was related to higher levels of daytime sleepiness, fatigue, depressive and anxiety symptoms, and diabetes-specific distress.⁵ Sleeping problems predicted chronic fatigue in 2 studies.^{1,3} In a mixed-methods study of 192 participants with T1DM, chronic sleep interruptions had a detrimental impact on the lives of participants, with 49% reporting exhaustion.⁴

Problems With Concentration—Problems with concentration was a commonly reported symptom in adults with T1DM.^{4,16,22} In a phenomenological study of 9 Canadian university students with T1DM, the following comments reflect concerns with concentration: “I think the greatest difficulty for me is concentrating in class. If my blood sugars aren’t spot on, like if I’m low, I just feel so awful, for me, I just feel like I’m drunk. I can’t do anything, I can’t walk right or speak right, I’m just clumsy. So I don’t want to go to class, and if I’m in class, I’ll just leave if my blood [glucose] is high, I’m tired, I can’t concentrate, I feel like I’m going to fall asleep at the drop of a hat. So again, if my blood sugars aren’t spot on, I tend to miss the class or just not go.”¹⁶ In a mixed-methods study ($n = 192$, ages 19–89), 32% ($n = 17$) reported poor concentration/lack of focus, and 49% ($n = 49$) reported exhaustion/tiredness.⁴ In another study, lack of concentration was related to higher A1C levels over a 1-year follow-up.²²

Decreased Self-management—Fatigue and self-management of diabetes likely have reciprocal effects; however, not much work has been done in this area. Several participants in the studies reviewed reported having less confidence in diabetes self-care.^{3,5,16} Barnard et

al⁴ hypothesize that not having enough energy to effectively self-manage T1DM may contribute to decreased confidence. Fatigue is both a precipitant and consequence of poor glycemic management. In a study of 214 outpatients with T1DM conducted in the Netherlands, suboptimal glucose management ($r = 0.18$, $P < .05$) predicted severe fatigue.⁵ In contrast, participants in a study by Barnard et al⁴ reported that fatigue contributed to suboptimal glucose management: “Because of being tired, I feel that I might not be making the best diabetes choices during the night” and “Exhaustion impedes all decisions, and taking too little or too much insulin or over-writing a low.”^{4p.765–766} In this study, 64% reported a negative impact of inadequate sleep on diabetes-related decision making (effective calculation of bolus doses).⁴

Competing Demands—Another struggle for people with T1DM is finding the balance between their health and meeting academic demands.¹⁶ As one Canadian college student stated, “The more things that get put on the list, then the further down the list my diabetes gets put. Especially in my program, a degree won’t matter if I don’t have a good portfolio. So those things take priority, because I’m going to be a diabetic [sic] for the rest of my life, and I only have a small window of time to get my foot in the door to start my career.”¹⁶

Sociodemographic Differences in Fatigue Among Adults With T1DM

Several differences were noted in sociodemographic characteristics: specifically age, gender, education/academic performance, and social support of people with T1DM and fatigue. The results among studies, however, are variable.

Age and Gender—Different studies report varied gender and age differences for fatigue. Younger age predicted chronic fatigue ($\beta = -.081$, $P = .004$),¹ and no significant relationship was found in other studies between age and symptoms of fatigue.^{3,18,24}

Two studies report more “physical” fatigue in women than men,^{15,24} with more men reporting “mental” fatigue.¹⁵ Additionally, women with diabetes 30 years had higher fatigue scores compared with men.¹⁵

Education and Academic Performance—Goedendorp et al¹ reported no significant association between fatigue and education among adults with T1DM. However, Hempler et al²⁴ reported that higher fatigue is associated with an overall lower educational level.

Social Support—A lack of social or family support was associated with more fatigue among persons with T1DM living without a partner or with little-to-no contact with family and friends.²⁴ People with T1DM who experienced social discrimination also reported more fatigue.²³ In contrast, Goedendorp et al¹ reported no association between fatigue and marital status among adults with T1DM.

Interventions Related to Fatigue

Two intervention studies were included in this review.^{20,25} Menting et al²⁵ conducted a web-based cognitive behavior therapy (CBT) with 120 patients to target cognitions and behaviors that perpetuate chronic fatigue among adults with T1DM. Those in the CBT group had

significantly lower fatigue severity scores (mean difference 13.8, 95% CI 10.0–17.5; $P < .0001$) and significantly lower scores for functional impairment after 5 months (mean difference 513, 95% CI 340–686; $P < .0001$).²⁵ Boyle et al²⁰ conducted a double-blind, randomized, parallel-group investigation to examine the effect of pregabalin, amitriptyline, and duloxetine on sleep, daytime functioning, and quality of life among 11 adults with T1DM and 72 adults with type 2 diabetes, all of whom had peripheral neuropathy. Duloxetine enhanced central nervous system arousal and performance on sensory motor tasks,²⁰ which may have potential value in treating fatigue (Table 2).

Discussion

Fatigue among adults with T1DM is prevalent and has a negative impact on quality of life and active engagement in the day-to-day management of glycemia. Overall, studies on fatigue among persons with T1DM are limited to small samples and cross-sectional designs with only 1 randomized controlled trial specifically addressing fatigue in this population. This review nonetheless highlights the multidimensional nature of fatigue and factors and characteristics associated with fatigue among adults with T1DM.

Fatigue is related to various physiologic, psychologic, situational, and sociodemographic factors, but the findings are not consistent among all studies. Results may be confounded due to the following: different instruments used to measure fatigue and variables of interest, an inconsistent definition of fatigue across all studies, diverse research methods, different durations of T1DM among participants, and varying contextual factors at the time of each study. Some of the studies report potential causative factors of fatigue, while others examined the impact of fatigue on select outcomes.

Fatigue is a symptom that has a basis in modifiable conditions such as impaired sleep or depression. With the exception of the study by Naegeli et al,¹⁴ there were no objective data to support the “classic” theory that fatigue is related to hyperglycemia or hypoglycemia. Modifiable factors associated with fatigue include BMI, serum glucose level, physical activity, social support, as well as occupational and educational demands. For example, people with T1DM can decrease their BMI, increase their physical activity, as well as decrease the demands of their occupation (reducing work hours, negotiating assignments, requesting accommodations) to potentially improve their fatigue symptoms. These modifiable factors are all potential targets of interventions to reduce fatigue. Nighttime hypoglycemia and fear of hypoglycemia at night may impact sleep quality for many with T1DM. This is a potentially modifiable factor that, if minimized, may contribute to better sleep and potentially less fatigue.

Neuropathic pain is another factor frequently reported to be associated with fatigue. Further research is needed to clarify if neuropathic pain disrupts sleep, which then contributes to fatigue, or if neuropathic pain itself causes fatigue. Age, gender, and duration of diabetes are associated with fatigue in some studies but not all. Although not modifiable, awareness of these characteristics and their potential association with fatigue is important as it may impact the timing and focus of select interventions to decrease fatigue.

It is not clear if the psychological factors associated with fatigue (depression, anxiety, diabetes-related distress, low self-efficacy, and decreased quality of life) precipitate the onset of fatigue or occur within the context of someone experiencing fatigue. Further investigation of these associations is warranted. A few studies reported a negative impact of fatigue on management of glycemia. It remains unclear if (a) disrupted sleep and fatigue predict inadequate glycemic management or (b) inadequate glycemic management leads to disrupted sleep and fatigue or (c) this is a reciprocal relationship that can go in either direction. Fatigue among adults with T1DM is also associated with less educational success and overall lower educational attainment. The degree and/or frequency of fatigue necessary to negatively impact educational efforts is not known.

Implications for Educators

Results from this integrative review have several implications for patient education and clinical practice. The authors found that fatigue and related variables can have a differential impact on self-care behaviors and several other important situational factors. This review supports the multidimensional nature of factors associated with fatigue. Sleep patterns and fatigue should be given consideration when working with patients to manage their glycemia. Given the varied research designs in most of the studies, we cannot infer causation. But the identified associations suggest a need to assess and consider the situational, psychological, physiological, and situational factors that may impact fatigue in adults with T1DM.

Educators and clinicians can help patients with T1DM to identify modifiable factors that have been associated with fatigue including BMI, serum glucose level, physical activity, and educational demands. Through use of mutual goal setting, patients can be encouraged to set reasonable targets to reduce BMI and increase physical activity if that is an identified issue for the patient. Also, with fear of hypoglycemia and disrupted sleep in mind, using technology such as continuous glucose monitors and insulin pumps that can sense and stop insulin infusions when blood glucose is low have the potential to reduce the fear of hypoglycemia and actual hypoglycemic events. These technologies may support improved sleep quality and reduce fatigue.

Based on the findings that a lack of social or family support was associated with more fatigue, diabetes educators may teach patients how to recognize available social support. To assist patients in recognizing social support available, providers can conduct a personal inventory of diabetes-related support and identify the available sources. As people with T1DM may struggle to find the balance between their health and meeting academic demands, patients and support persons should be encouraged to communicate effectively to ensure that educational needs are balanced with self-management demands.

Limitations

A strength of this review is the specific focus on fatigue among adults with T1DM despite the varying conceptualizations of fatigue among the studies. We included mixed research methods as well as theoretical papers to broadly capture current work in this targeted area. This review does have some limitations. Given pragmatic limitations of resources, this literature was not inclusive of gray literature such as unpublished dissertations or studies

published in languages other than English. Gray literature may have expanded or clarified the concept of fatigue in adults with T1DM. Also, this integrative review is limited to the years 2007 to 2017; therefore, periodic updates will be important.

Conclusion

The prevalence of fatigue among adults with T1DM is likely influenced by disease physiology, psychological stress, and lifestyle factors but, as causal inference is unclear, more research is needed to confirm these relationships. Fatigue is considered a classical symptom of hyperglycemia; however, the evidence between fatigue and hyperglycemia is minimal. Studies on fatigue among persons with T1DM are limited to small samples and cross-sectional designs with few randomized controlled trials addressing fatigue and diabetes-related symptoms. Evidence is conflicting regarding the onset of fatigue among persons with T1DM and the relationship between fatigue and diabetes duration and fatigue and diabetes-related complications. Fatigue creates an additional impediment to the daily self-care management of diabetes. Interventions to minimize the burden of fatigue among adults with T1DM are lacking. More research is needed to investigate potential mechanistic pathways to move the fatigue-symptom-management science forward.

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Figure 1.
Fatigue search strategy.

Figure 2.
Visual diagram of fatigue and correlates.

Table 1

Fatigue in T1 DM Variables Matrix^a

Source and Rigor/Relevance*	Purpose	Sample/Method/ Setting	Concepts of Interest	Key Findings Related to Fatigue in T1 DM	Fatigue Defined and/or Measurement Tool
Barnard et al, (2016) ⁴ Rigor: high Relevance: high	Quantify sleep interruption and explore personal experiences and determine the impact of impaired sleep on well-being and diabetes-related activities/decision making	Sample: 258 parent/ carers of children with T1DM and 192 adults with T1DM Method: Mixed-methods questionnaire Setting: University of Southampton, UK	Frequency and causes of night waking Impact of night waking Insulin delivery method	14.1% (n = 27) report awakening ☒ 1 time Actual or fear of hypoglycemia reported by 9.4% (n = 18) 33% (n = 63) reported a negative impact of sleep on diabetes-related decision making 78% (n = 151) reported a negative impact of awakening during the night on daily functioning 49% (n = 95 adults) reported exhaustion or tiredness	<i>Fatigue not defined</i> Concept arose from tree-text responses from adults with T1DM
Bot et al, (2013) ²² Rigor: high Relevance: high	Explore the associations of individual depressive symptoms with A1C in outpatients with diabetes	277 adults with T1DM 365 adults with T2DM Secondary data analysis 3 tertiary diabetes outpatient clinics in the Netherlands	Fatigue BMI Sleeping difficulties Appetite Concentration Psychomotor retardation Suicidal ideation A1C	Sleeping difficulties significantly related to higher baseline ($\beta = .16$, $P < .001$) and 1-year follow-up A1C ($\beta = .12$, $P = .004$) Symptoms reported most often in the total sample were fatigue, sleeping difficulties, problems with concentration, and appetite problems	<i>Item: Feeling tired or having little energy</i> (past 2 weeks) item 4 from Patient Health Questionnaire (PHQ)-9
Boyle, Eriksson, et al, (2012) ²⁰ Rigor: high Relevance: low	Compare the analgesic efficacy of pregabalin, amitriptyline, and duloxetine and their effect on polysomnographic sleep, daytime functioning, and quality of life in patients with diabetic peripheral neuropathic pain	11 adults with T1DM 72 adults with T2DM Double-blind randomized, parallel group, 8-day, placebo run-in followed by 14 days of lower-dose and 14 days of higher dose medication. Surrey Clinical Research Center, United Kingdom	Daytime functioning BMI Sleep Subjective pain Quality of life	Pregabalin improved sleep continuity ($P < .001$), duloxetine increased wake time ($P < .01$), and reduced total sleep time ($P < .001$) Duloxetine enhanced central nervous system arousal and performance on sensory motor tasks	<i>Items: Assessed energy, full of life, worn out, tired</i> (past 4 weeks) Short Form-36 (vitality subscale)
Goedendorp, et al, (2014) ¹ Rigor: high Relevance: high	Determine prevalence, impact, and potential determinants of chronic fatigue in patients with T1DM	214 outpatient adults with T1DM Cohort study University Diabetes Clinic in the Netherlands	Hypoglycemia Hyperglycemia Functional impairments Health status Comorbidity Diabetes-related factors Fatigue-related cognitions A1C Age, depression, pain, physical inactivity	Patients with T1DM were significantly more often chronically fatigued (40%; 95% CI 34–47%; $P < .001$) compared with matched controls (7%; 95% CI 3–10%; $P < 0.001$) Chronically fatigued patients had significantly more functional impairments Fatigue was the most troublesome symptom reported Chronically fatigued patients spent slightly less time in hypoglycemia Younger age, depression, pain, sleeping problems, sedentary lifestyle, low self-	<i>Acute fatigue: variable fatigue during the day that generally does not cause functional impairments</i> <i>Chronic fatigue: Severe fatigue that persists for at least 6 months, leads to substantial impairments in patients' daily functioning</i> Checklist of Individual Strength (CIS-fatigue subscale) Items: Fatigue severity, concentration problems,

Source and Rigor/ Relevance*	Purpose	Sample/Method/ Setting	Concepts of Interest	Key Findings Related to Fatigue in T1 DM	Fatigue Defined and/or Measurement Tool
Hempler et al, (2014) ²⁴ Rigor: high Relevance: high	Determine association between fatigue, sociodemographic factors, and social network in people with T1DM	2419 adult outpatients with T1DM Cross-sectional Denmark	Fatigue Education Living situation	efficacy, and having diabetes complications predicted chronic fatigue Women had higher fatigue scores ($P < .03$) than men High fatigue associated with low education, living without a partner, and rare/no contact with family and friends	reduced motivation, reduced activity Multidimensional Fatigue Inventory (MFI-20) Subscales: General fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue
Hill et al, (2013) ¹⁶ Rigor: high Relevance: high	Examine the lived experiences of university students with T1DM	9 college students with T1DM Phenomenology, focus groups Canadian University	Academics Lived experience	Difficulties associated with dietary restrictions and food availability, lack of diabetes awareness on campus, and internal struggles related to coping with diagnosis of T1DM Challenging to meet the demands of diabetes management and academic requirements Fatigue associated with hypoglycemia and hyperglycemia and interfered with academic work Academic stress associated with A1C level Participant defined: "I think the greatest difficulty for me is concentrating in class. If my blood sugars aren't spot on, like if I'm low, I just feel so awful, for me, I just feel like I'm drunk. I can't do anything. I can't walk right or speak right, I'm just clumsy. So I don't want to go to class, and if I'm in class, I'll just leave. If my blood [glucose] is high, I'm tired, I can't concentrate, I feel like I'm going to fall asleep at the drop of a hat. So again, if my blood sugars aren't spot on, I tend to miss the class or just not go." (p. 240)	<i>Fatigue not defined</i> Concept of fatigue arose from participants responses
Lasseloin et al, (2012) ¹⁸ Rigor: high Relevance: high	Assess fatigue symptoms and cognitive performance using a dimensional approach in healthy adults and those with type 1 and type 2 diabetes	21 patients with T1DM 24 patients with T2DM 15 healthy subjects Cross-sectional Haut-Leveque Hospital in Pessac, France Controls from University Victor Segalen Bordeaux 2	Fatigue BMI Physical activity Cognitive function	Patients with T1DM scored similarly to healthy controls on all fatigue measures Increased BMI was associated with increased scores of general fatigue ($r = .355$, $P < .05$), physical fatigue ($r = .369$, $P < .05$), reduced motivation ($r = .353$, $P < .05$), and mental fatigue ($r = .501$, $P < .001$)	Multidimensional Fatigue Inventory (MFI-20) Subscales: General fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue
Mellerio et al, (2015) ²³ Rigor: high Relevance: high	Describe the socio-professional outcomes, health-related quality of life, and sexuality of adults with childhood-onset T1DM	388 adults with T1DM Cross-sectional Nationwide registry in France	Education SF-36 Physical Composite Score SF-36 Mental Composite Scores (MCS) Fatigue	Fatigue and abandoning sports were predictive of a lower HRQOL Physical Composite Scores and Mental Composite Scores were decreased moderately	Multidimensional Fatigue Inventory (MFI-20) Subscales: General fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue

Source and Rigor/ Relevance*	Purpose	Sample/Method/ Setting	Concepts of Interest	Key Findings Related to Fatigue in T1 DM	Fatigue Defined and/or Measurement Tool
Menting et al, (2016) ³ Rigor: high Relevance: high	Identify the course of severe fatigue, its predictors, and the relationship with A1C in patients with type 1 diabetes	214 adults with T1DM Cohort Outpatient clinic in Netherlands	BMI Depressive symptoms Pain Sleep disturbances Self-efficacy Fatigue Diabetes self-care confidence A1C	Participants with T1DM-related complications had preserved social outcomes, but altered HRQOL. Depressive symptoms, pain, sleep disturbances, lower self-efficacy concerning fatigue, less confidence in diabetes self-care, more fatigue severity at baseline, and more diabetes complications predicted severe fatigue at follow-up Baseline A1C was positively associated with fatigue severity at follow-up in both groups	Checklist of Individual Strength (CIS-fatigue subscale) Items: Fatigue severity, concentration problems, reduced motivation, reduced activity
Menting, J., Tack, C. J., & Knoop, H. (2017) ¹⁷ Rigor: high Relevance: high	Investigate the prevalence, location and severity of pain, association with psychosocial and clinical variables impact on functional impairment in fatigued patients with T1DM	120 severely fatigued patients with T1DM Cross-sectional Netherlands	BMI Pain Fatigue severity Depressive symptoms Functional impairment A1C Diabetes-related complications Actigraphy	Pain was associated with diabetes duration, the number of complications, fatigue severity, depressive symptoms, and functional impairment, but not with A1C or physical activity Both pain and fatigue severity contributed to functional impairment	Checklist of Individual Strength (CIS-fatigue subscale) Items: Fatigue severity, concentration problems, reduced motivation, reduced activity
Menting, Tack, van Bon, et al, (2017) ²⁵ Rigor: high Relevance: high	Investigate the efficacy of cognitive behavioral therapy in reducing fatigue severity in patients with T1DM	120 adults with T1DM RCT Netherlands	BMI Fatigue severity Functional impairment A1C Glucose variability	Compared to control group, patients in the CBT group had significantly lower fatigue severity scores and significantly lower scores for functional impairment after 5 months	Checklist of Individual Strength (CIS-fatigue subscale) Items: Fatigue severity, concentration problems, reduced motivation, reduced activity
Naegediet al, (2010) ¹⁴ Rigor: high Relevance: high	Explore Diabetes Symptom Checklist-Revised Cognitive Distress, Fatigue, Hyperglycemia, and Hypoglycemia subscales as measures of cut diabetes-associated symptoms in patients with both type 1 and 2 diabetes	481 with T1DM 372 with T2DM Secondary data analysis of data from a clinical trial Multicenter RCT conducted in the United States, India, Mexico, France, Germany, Argentina, Belgium, Italy, and Puerto Rico	Cognitive distress Fatigue Hyperglycemia Hypoglycemia	Cognitive distress, fatigue, hyperglycemia, and hypoglycemia are reliable and valid measures of acute symptoms of diabetes	Diabetes Symptom Checklist (fatigue subscale) Items: lack of energy, overall sense of fatigue, increasing fatigue during the course of the day, fatigue in the morning when getting up
Nets et al, (2015) ⁵ Rigor: high Relevance: high	Examine psychological aspects of living with T1DM and T2DM among adults in the Netherlands	267 adults with T1DM 361 adults with T2DM Cross-sectional Netherlands	Sociodemographic BMI Sleep quality Fatigue Daytime sleepiness Depressive symptoms Anxiety symptoms Diabetes-specific distress Clinical characteristics of diabetes	Poor sleep quality reported by 31% of adults with T1DM Poor sleep quality related to a higher self-care burden and higher levels of daytime sleepiness, fatigue, depressive and anxiety symptoms, and diabetes-specific distress	Fatigue Assessment Scale (FAS-10) Items I am bothered by fatigue I get tired very quickly I don't do much during the day I have enough energy for everyday life Physically, I feel exhausted I have problems to start things

Source and Rigor/ Relevance*	Purpose	Sample/Method/ Setting	Concepts of Interest	Key Findings Related to Fatigue in T1 DM	Fatigue Defined and/or Measurement Tool
Segersiedt et al, (2015) ¹⁵ Rigor: high Relevance: high	Compare prevalence of fatigue among adults with T1DM and general population. Determine if T1DM is associated with fatigue and whether the fatigue is due to complications or to the disease itself.	268 adults with T1DM 1557 control group Cross-sectional National Diabetes Register at the Sunderby Hospital clinic in Sweden	Fatigue (MFI-20) Time since diagnosis Cardiovascular disease Cerebrovascular disease	Type 1 diabetes is associated with fatigue Women with long diabetes duration but without complications experienced more fatigue than general population	I have problems to think clearly I feel no desire to do anything, mentally I feel exhausted When I am doing something I can concentrate quite well Multidimensional Fatigue Inventory (MFI-20) Subscales: General fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue

Abbreviations: HRQOL, health-related quality of life; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

^aRigor and relevance rated using Whittemore and Knafl (2005) recommendations. See text for details of how we applied their recommendations.

Table 2

Numeric Description of Study Population

	Total Sample Size	Sample % T1DM	Sex, % Male	Mean Age in Years (SD) or Range	Mean AIC
Barnard et al, (2016) ⁴	450	100	24.5	19–89 years	—
Bot et al, (2013) ²²	642	43	51	53.3 (15.1)	7.8
Boyle, Eriksson, et al, (2012) ²⁰	83	13.3	68.7	65.1 (8.9)	7.9
Goedendorp, et al, (2014) ¹	214	100	47	48.6 (13)	7.8
Hempler et al, (2014) ²⁴	2419	100	—	—	—
Hill et al, (2013) ¹⁶	9	100	33	—	—
Lasselín et al, (2012) ¹⁸	60	35	73.4	56.9 (9.6)	7.3
Mellerio et al, (2015) ²³	388	100	42.8	28.5 (3.1)	<8 (61%) >8 (39%)
Menting et al, (2016) ³	214	100	46.4	51.5 (12.7)	8.1
Menting, Tack, & Knoop (2017) ¹⁷	120	100	38	43.6 (12.3)	8
Menting, Tack, van Bon, et al, (2017) ²⁵	120	100	38	43.6 (12.3)	8
Naegeli et al, (2010) ¹⁴	853	56	57	57	7.2
Nefs et al, (2015) ⁵	628	42.5	41	47 (16)	7.2
Segerstedt et al, (2015) ¹⁵	1825	17.2	53.4	48 (16.1)	—