Chronic Fatigue in Type 1 Diabetes: Highly Prevalent but Not Explained by Hyperglycemia or Glucose Variability

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OBJECTIVE

Fatigue is a classical symptom of hyperglycemia, but the relationship between chronic fatigue and diabetes has not been systematically studied. We investigated prevalence, impact, and potential determinants of chronic fatigue in patients with type 1 diabetes mellitus (T1DM).

RESEARCH DESIGN AND METHODS

Out of 324 randomly selected T1DM outpatients, 214 participated in this cross-sectional observational study. Participants were compared with age- and sex-matched population-based controls. Chronic fatigue, functional impairments, current health status, comorbidity, diabetes-related factors, and fatigue-related cognitions and behaviors were assessed with questionnaires, and HbA_{1c} values and comorbidity were assessed with medical records. Sixty-six patients underwent continuous glucose monitoring combined with an electronic fatigue diary for 5 days. Acute fatigue and four glucose parameters were determined: mean, variability, and relative time spent in hypoglycemia and hyperglycemia.

RESULTS

T1DM patients were significantly more often chronically fatigued (40%; 95% CI 34–47%) 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. Age, depression, pain, sleeping problems, low self-efficacy concerning fatigue, and physical inactivity were significantly associated with chronic fatigue. Chronically fatigued patients spent slightly less time in hypoglycemia (proportion 0.07 ± 0.06 vs. 0.12 ± 0.10; $P = 0.025$). Glucose parameters were not related to acute fatigue.

CONCLUSIONS

Chronic fatigue is highly prevalent and clinically relevant in T1DM. Its significant relationship with cognitive behavioral variables and weak association with blood glucose levels suggests that behavioral interventions could be helpful in managing chronic fatigue in T1DM.

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Fatigue is one of the classical presenting symptoms of diabetes. For example, in newly diagnosed type 2 diabetes mellitus, 61% of the patients were fatigued, and fatigue was the second most frequently reported symptom (1). It is often assumed that once diabetes is treated and glucose levels are controlled, fatigue diminishes. This has, however, not been empirically tested. Furthermore, glucose control is often suboptimal with persistent episodes of hyperglycemia that may result in sustained fatigue. Fatigue may also sustain in diabetic patients because it is associated with the presence of a chronic disease, as has been demonstrated in patients with rheumatoid arthritis and various neuromuscular disorders (2,3).

It is important to distinguish between acute and chronic fatigue, because chronic fatigue, defined as severe fatigue that persists for at least 6 months, leads to substantial impairments in patients' daily functioning (4,5). In contrast, acute fatigue can largely vary during the day and generally does not cause functional impairments.

Literature provides limited evidence for higher levels of fatigue in diabetic patients (6,7), but its chronicity, impact, and determinants are unknown. In various chronic diseases, it has been proven useful to distinguish between precipitating and perpetuating factors of chronic fatigue (3,8). Illness-related factors trigger acute fatigue, while other factors, often cognitions and behaviors, cause fatigue to persist. Sleep disturbances, low self-efficacy concerning fatigue, reduced physical activity, and a strong focus on fatigue are examples of these fatigue-perpetuating factors (8–10). An episode of hyperglycemia or hypoglycemia could trigger acute fatigue for diabetic patients (11,12). However, variations in blood glucose levels might also contribute to chronic fatigue, because these variations continuously occur.

The current study had two aims. First, we investigated the prevalence and impact of chronic fatigue in a large sample of type 1 diabetic (T1DM) patients and compared the results to a group of age- and sex-matched population-based controls. Secondly, we searched for potential determinants of chronic fatigue in T1DM. A multifactorial model for fatigue in patients with type 2 diabetes mellitus (13) was used for selecting potential determinants. This model encompasses not only physiological factors, such as hyperglycemia, hypoglycemia, and glucose variability (11,12,14), but also psychological factors, such as diabetes-related emotional distress. In addition to the aforementioned variables, demographic variables, specific fatigue-related factors, and current health status, including depressive mood, pain (6), and the presence of comorbidities, (15) may also determine chronic fatigue. We established the relationship between these factors and chronic fatigue in T1DM. An overview of the factors expected to affect chronic fatigue in T1DM is schematically depicted in Supplementary Fig. 1. T1DM was chosen, as it has fewer interactions with significant comorbidities. In a substudy, we assessed the contribution of mean glucose levels, glucose variability, hyperglycemia, and hypoglycemia, determined by continuous glucose monitoring (CGM), to both chronic and acute fatigue.

RESEARCH DESIGN AND METHODS

Sample

T1DM outpatients between 18 and 75 years old were recruited from April to October 2011 from a large university diabetes clinic (Radboud University Nijmegen Medical Centre, the Netherlands). Exclusion criteria were inability to speak, read, and write Dutch; being hospitalized or terminally ill; and—additionally for the substudy—suffering from significant comorbidity. The ethics committee approved the study, and written informed consent was obtained from all participants.

Matched population-based controls were derived from a cohort (n = 1,900) of panel members of CentERdata. Fatigue data were collected in summer 2012. CentERdata is a Dutch research institute at Tilburg University consisting of Dutch households (16) representative of the Dutch population with respect to age, sex, education, and social economic status.

Design

In this cohort study, T1DM patients were asked to complete questionnaires. Patients were matched on age and sex with a population-based control group. With a cross-sectional design, we answered the research questions on prevalence, impact, and possible determinants of chronic fatigue in T1DM patients. For the substudy, patients were followed for 5 days to investigate the contribution of blood glucose levels to acute (in a longitudinal design) and chronic (in a cross-sectional design) fatigue.

Procedure

From an outpatient cohort of 831 T1DM patients, 350 patients were randomly selected (see POWER CALCULATION). Eligible patients were informed about the study in writing and contacted by telephone. Patients who agreed to participate could complete the questionnaires using Internet or by paper and pencil. It took participants approximately 2 h to complete the set of questionnaires. Patients who refused to participate were asked to complete the short fatigue questionnaire (SFQ) (17) with the aim to compare the level of fatigue of nonparticipants with that of participants. Patients who did not return the questionnaires were send up to two reminders with the SFQ attached.

All participants received an additional letter with information about the substudy. Subsequently, a subset of eligible patients was contacted for an appointment. During the appointment, the use of the CGM system and the electronic fatigue diary (EFD) was explained. The FreeStyle Navigator CGM system was used in accordance with the guidelines of Abbott. Data were collected between June 2011 and January 2012.

Instruments

Main Study

Sex, age, and HbA_{1c} were retrieved from the medical records. The presence of a comorbidity was assessed in two ways. First, patients were asked if they had other illnesses in addition to T1DM (patient-reported comorbidity: comorbidity_pr). Second, the first two authors screened the medical records to

identify the presence of a significant comorbidity defined as a comorbidity affecting patients' daily functioning (comorbidity based on medical records: comorbidity_mr). The two authors discussed arbitrary cases to reach consensus. All other data were collected using questionnaires.

Fatigue

The subscale fatigue of the Checklist Individual Strength (CIS) was used to assess *fatigue severity* over the past 2 weeks (Cronbach α = 0.95). This subscale consists of eight items (scores range from 8 to 56). A score of 35 or higher, being two SDs above the mean of the original healthy reference group, is indicative for severe fatigue (18). The CIS is a well-validated instrument (18,19) and frequently used (2,3,20). Patients who indicated suffering from fatigue for 6 months or longer and scored >35 were viewed as being *chronically fatigued*. The SFQ was used to assess fatigue severity in nonparticipants. The SFQ consists of four items of the CIS-fatigue subscale (Cronbach α = 0.926) (17). All other instruments used are described in Supplementary Data (21–35).

Substudy

Blood Glucose. Glucose levels were continuously monitored for 5 days using the FreeStyle Navigator, which records glucose levels (mmol/L) every 10 min. Operationalization of glucose parameters are described in STATISTICAL ANALYSES.

Acute Fatigue. The severity of acute fatigue was assessed using the EFD. Patients were asked to indicate how fatigued they were at that particular moment on a visual analog scale ranging from "not at all fatigued" (0) to "very severely fatigued" (100). This question was presented on a personal digital assistant at six moments, evenly divided over the day from 0830 h to 2230 h.

Power Calculation

Main Study

We selected 20 potential predictors for chronic fatigue. With 10 patients needed per predictor, 200 participants yielded adequate statistical power. An estimated response rate of 60% resulted in 350 patients to be contacted. For the substudy, CGM sensors were available for approximately 60 participants, and although no formal power calculation was performed for the substudy, we expected to have sufficient power to determine significant relationships between fatigue and glucose levels with repeated measures analyses and to compare chronically and nonchronically fatigued patients.

Statistical Analyses

T1DM patients were matched by age and sex with 214 population-based controls from the sample of CentERdata. Precision matching was done with STATA/SE 12.1. Differences between T1DM patients and matched population-based controls and differences between chronically fatigued and nonchronically fatigued T1DM patients were tested using unpaired *t* test and χ^2. The mean burden of each diabetes symptom was calculated and ordered from the least to the most troublesome symptom. To identify potential determinants, Pearson's correlations were calculated with fatigue severity, followed by a logistic regression analysis with chronic fatigue as dependent variable.

To assess whether blood glucose contributed to acute or chronic fatigue, between-subject effects (whether patients with high variability had more fatigue than those with low variability) and within-subject effects (whether, within one patient, blood glucose values were related to fatigue) were tested with *t* test, Pearson correlations, and generalized estimating equations (GEE).

Four different parameters of blood glucose were determined: *1*) mean glucose level was assessed by calculating the mean of all glucose measurements of each participant (GLmean); *2*) glucose variability was assessed by calculating the SD of all glucose measurements of each participant (Gvar) (36); *3*) relative time spent in hyperglycemia was assessed by dividing the number of CGM observations above 10 mmol/L by the total number of CGM observations of each participant (hyper); and *4*) relative time spend in hypoglycemia was calculated with CGM observations lower than 4 mmol/L (hypo). The severity of *acute fatigue* was assessed by calculating the mean of all EFD scores of each participant (EFDmean).

GEE was used to determine whether acute fatigue was predicted by blood glucose values in the preceding hour. GEE enables determination of *between*-subject effects using independent structure and *within*-subject effects using exchangeable structure. The *mean glucose level* (GLmean_hour) and the *glucose variability* (Gvar_hour) was assessed by calculating means and SDs of the recorded glucose values in the hour preceding an EFD score. GEE was performed with GLmean_hour, Gvar_hour as independent, and EFD scores as dependent variables. All analyses were performed with SPSS, version 16.0 (SPSS Inc., Chicago, IL). A level of $P < 0.05$, two-sided, was considered significant.

RESULTS

Because of a high response rate, only 324 patients were approached. Twenty-one approached patients did not meet the eligibility criteria. Two hundred fourteen eligible patients returned questionnaires (response rate 71%). Thirty-five of 89 nonresponders filled in the SFQ (see Supplementary Fig. 2). Mean age of responders was 48 $\pm$ 13 years, 53% were female, 52% had a higher education, and 76% were married or lived together. Average diabetes duration was 29 $\pm$ 14 years. Based on cutoff scores on the Beck Depression Inventory for Primary Care (37), 16% had clinically relevant depressive symptoms. Comorbidity_mr was 24% and comorbidity_pr was 49% based on patient self-report. There were 65% true positive and negative cases between comorbidity_pr and comorbidity_mr. Mean scores on the questionnaires used and the proportion of patients scoring above the cutoff score are described in Supplementary Table 1.

Differences Between Participants and Nonparticipants

There was no significant difference on the mean scores on the SFQ between participants (mean 15.7; SD 7.8) and nonparticipants (mean 16.2; SD 7.9; P = 0.702) completing questionnaires. Nonparticipants, including nonresponders, did not differ

significantly from participants on sex (P = 0.710). Participants and nonparticipants did differ significantly from each other on age and HbA_{1c}. Participants were older (mean 47.9; SD 12.9), participants had lower HbA_{1c} values (mean 7.8, National Glycohemoglobin Standardization Program; SD 1.1; 62 mmol/mol), and their latest HbA_{1c} was measured more recently (3.0 months; SD 10.5 months) compared with nonparticipants. The mean age of nonparticipants was 43.6 (SD 15.3) years, mean HbA_{1c} values were 8.6 (National Glycohemoglobin Standardization Program; SD 1.6; 70 mmol/mol), and HbA_{1c} was measured 8 months previously (SD 19 months).

Prevalence and Impact of Chronic Fatigue

A significantly higher percentage of T1DM patients were chronically fatigued (40%; 95% CI 34–47%) than matched controls (7%; 95% CI 3–10%). Mean fatigue severity was also significantly higher in T1DM patients (31 ± 14) compared with matched controls (17 ± 9; $P < 0.001$). T1DM patients with a comorbidity_mr or clinically relevant depressive symptoms were significantly more often chronically fatigued than patients without a comorbidity_mr (55 vs. 36%; P = 0.014) or without clinically relevant depressive symptoms (88 vs. 31%; $P < 0.001$). Patients who reported neuropathy, nephropathy, or cardiovascular disease as complications of diabetes were more often chronically fatigued (see Table 1).

Chronically fatigued T1DM patients were significantly more impaired compared with nonchronically fatigued T1DM patients on all aspects of daily functioning (see Supplementary Table 3). Fatigue was the most troublesome symptom of the 34 assessed diabetes-related symptoms. The five most troublesome symptoms were overall sense of fatigue, lack of energy, increasing fatigue in the course of the day, fatigue in the morning when getting up, and sleepiness or drowsiness (see Supplementary Table 2).

Potential Determinants of Chronic Fatigue

All but four of the tested univariate correlations between fatigue severity and potential determinants were significant. Fatigue severity was not significantly related to education, marital status, age of diabetes onset and HbA_{1c} (see Table 2).

Logistic regression analysis showed that chronic fatigue was predicted by being younger, having clinically relevant depressive symptoms, more pain and sleeping problems, lower level of self-reported physical activity, and self-efficacy concerning fatigue (see Table 3).

Table 1—Specification of diabetes complications: associations with fatigue severity

	n	CIS fatigue, mean (SD)	*P* value
Retinopathy			
Yes	92	32.2 (14.0)	0.264
No	122	30.0 (14.7)	
Neuropathy			
Yes	58	36.1 (14.5)	0.001
No	156	29.0 (14.0)	
Loss of feeling in feet			
Yes	32	33.2 (13.7)	0.328
No	182	30.5 (14.5)	
Nephropathy			
Yes	22	39.4 (12.5)	0.003
No	192	30.0 (14.4)	
Cardiovascular disease			
Yes	28	40.0 (13.8)	0.001
No	186	30.0 (14.1)	
Heart attack			
Yes	11	36.1 (15.0)	0.226
No	203	30.7 (14.4)	
Stroke			
Yes	2	49.0 (9.9)	0.076
No	212	30.7 (14.4)	

Contribution of Blood Glucose to Chronic and Acute Fatigue

For the substudy, the majority of patients (n = 116) was willing to participate. Twenty-one patients were excluded because of the presence of a comorbidity (medical records). A subset of 68 patients participated. From two patients, no data were obtained. Sixteen patients had incomplete 5-day data sets but were included in the analyses. Reasons for incomplete or absent data were premature sensor removal (n = 4), technical problems with the CGM system (n = 13) or EFD (n = 1). In this substudy, participants did not differ from patients not willing to participate regarding age, sex, fatigue severity, and HbA_{1c} (all $P \geq 0.271$). The prevalence of chronic fatigue in the substudy was 37% compared with 40% in the total sample.

Chronically fatigued T1DM patients (n = 25) spent in proportion less time in hypoglycemia (0.07 ± 0.06) compared with nonchronically fatigued patients (n = 41; 0.12 ± 0.10; P = 0.025). There was no significant difference between the two groups in GLmean (8.63 ± 1.63 vs. 7.84 ± 1.73 mmol/L; P = 0.068), Gvar (3.13 ± 0.90 vs. 3.08 ± 0.92 mmol/L; P = 0.816) and hyper (0.32 ± 0.20 vs. 0.25 ± 0.17; P = 0.133).

None of the four blood glucose parameters were significantly associated with acute fatigue. Correlations between EFD scores and glucose parameters were GLmean (r = 0.056; P = 0.656), Gvar (r = −0.132; P = 0.291), hyper (r = 0.056; P = 0.652) or hypo (r = −0.157; P = 0.209). GEEs showed no significant between- or within-subject effects of GLmean_hour and Gvar_hour on acute fatigue (Table 4).

CONCLUSIONS

This study establishes that chronic fatigue is highly prevalent and clinically relevant in T1DM patients. While current blood glucose level was only weakly associated with chronic fatigue,

Table 2—Potential determinants of fatigue: associations with fatigue severity

	CIS fatigue mean (SD)	CIS fatigue Pearson *R*	*P* value
Demographic variables			
Age		–0.192	0.005
Sex			
Male	27.9 (14.3)		0.003
Female	33.6 (14.1)		
Education			
Lower	31.3 (15.5)		0.693
Higher	30.6 (13.5)		
Marital status			
Married	30.2 (14.3)		0.153
Not married	33.5 (14.7)		
Current health status			
Significant comorbidity (medical record)			
Yes	37.1 (14.5)		<0.001
No	29.0 (12.6)		
Other illnesses (self-reported)			
Yes	34.7 (13.6)		<0.001
No	27.2 (14.4)		
Pain		–0.520	<0.001
Depression		0.467	<0.001
Specific diabetes-related factors			
Diabetes duration		–0.116	0.091
Age of diabetes onset		–0.084	0.221
Number of complications due to diabetes		0.241	<0.001
HbA_{1c}		0.097	0.156
Diabetes-specific self-efficacy		–0.299	<0.001
Diabetes-related distress		0.342	<0.001
Fatigue-related cognitions			
Self-efficacy concerning fatigue		–0.635	<0.001
Fatigue catastrophizing		0.635	<0.001
Illness-related attributions with regard to fatigue		–0.491	<0.001
Focusing on fatigue		0.598	<0.001
Fatigue-related behaviors			
Self-reported physical activity		–0.163	0.018
Sleeping problems		0.525	<0.001

cognitive behavioral factors were by far the strongest potential determinants. It could be that glucose levels induce fatigue but are not involved in its perpetuation.

The first part of our conclusion is based on the fact that a substantial part of T1DM patients, as many as 40%, was chronically fatigued, compared with 7% found in a matched population-based sample. Our results confirm earlier findings that T1DM patients experience higher levels of fatigue than healthy controls (6), although chronic fatigue was previously not incorporated. Another study found that type 2 diabetic, but not T1DM, patients had higher levels of fatigue compared with healthy controls (7). This apparent discrepancy may be explained by the relatively small sample size of this latter study, potential selection bias (patients were not randomly selected), and the use of a different fatigue questionnaire. Comparing T1DM patients with the Dutch population has the advantage that the general population also includes individuals with various diseases.

Not only was chronic fatigue highly prevalent, fatigue also had a large impact on T1DM patients. Chronically fatigued T1DM patients had more functional impairments than nonchronically fatigued patients, and T1DM patients considered fatigue as the most burdensome diabetes-related symptom.

Contrary to what was expected, there was at best a weak relationship between blood glucose level and chronic fatigue. Chronically fatigued T1DM patients spent slightly less time in hypoglycemia, but average glucose levels, glucose variability, hyperglycemia, or HbA_{1c} were not related to chronic fatigue. In type 2 diabetes mellitus also, no relationship was found between fatigue and HbA_{1c} (7).

We assumed that variations in blood glucose could trigger acute fatigue and therefore investigated the relationship between acute fatigue and blood glucose in detail. Again, no relationship was found between mean glucose level, glucose variability, time spent in hyperglycemia and hypoglycemia, and acute fatigue. Although other studies have reported a relationship between hyperglycemia and hypoglycemia and acute fatigue, those studies interviewed patients about symptoms retrospectively or were performed under laboratory settings (11,12,14). In the current study with real-life situations, it seems that the effect of a single episode of hyperglycemia or hypoglycemia on fatigue cannot be isolated.

One could question the relevance of chronic fatigue in diabetic patients, as it seems unrelated to glucose control. The fact that fatigue is seen as the most burdensome symptom by patients and is associated with more severe disability makes it a relevant issue in the care of diabetic patients. Furthermore, it is not unlikely that chronic fatigue also makes it more difficult for patients to be actively involved in their diabetes regulation, e.g., by becoming more physically active.

Regarding demographic characteristics, current health status, diabetes-related factors, and fatigue-related cognitions and behaviors as potential determinants of chronic fatigue, we found that sleeping problems, physical activity, self-efficacy concerning fatigue, age, depression, and pain were significantly associated with chronic fatigue in T1DM. Although depression was strongly related, it could not completely explain the presence of chronic fatigue (38), as 31% was chronically fatigued without having clinically relevant depressive symptoms. Age was also

Table 3—Results of logistic regression analysis of potential determinants of chronic fatigue

						95% CI	
Chronic fatigue	B	SE	Wald	OR	*P* value	Lower	Upper
Constant	10.4	4.72	4.81	31,320	0.028		
Demographic variables							
Age	–0.081	0.028	8.50	0.923	**0.004**	0.874	0.974
Sex	0.398	0.515	0.597	1.49	0.440	0.542	4.09
Education	−1.07	0.553	3.74	0.343	0.053	0.986	8.61
Marital status	0.429	0.616	0.485	1.54	0.486	0.459	5.13
Current health status							
Depression	3.33	1.05	9.99	28.0	**0.002**	3.55	221
Pain	–0.036	0.014	6.24	0.965	**0.013**	0.938	0.992
Significant comorbidity	0.657	0.628	1.09	1.93	0.296	0.563	6.61
Specific diabetes-related factors							
Diabetes duration	–0.006	0.023	0.073	0.994	0.786	0.950	1.04
Number of complications due to diabetes	0.169	0.198	0.730	1.19	0.393	0.803	1.75
HbA_{1c}	0.075	0.225	0.112	1.08	0.738	0.694	1.68
Diabetes-specific self-efficacy	0.001	0.026	0.001	1.00	0.969	0.951	1.05
Diabetes-related distress	–0.041	0.023	3.28	0.959	0.070	0.917	1.00
Fatigue-related cognitions							
Self-efficacy concerning fatigue	–0.191	0.087	4.83	0.826	**0.028**	0.696	0.980
Fatigue catastrophizing	0.055	0.060	0.832	1.06	0.362	0.939	1.19
Illness-related attributions with regard to fatigue	–0.226	0.115	3.85	0.798	0.050	0.636	1.00
Focusing on fatigue	0.061	0.038	2.57	1.063	0.109	0.986	1.15
Fatigue-related behaviors							
Self-reported physical activity	–0.005	0.002	8.67	0.995	**0.003**	0.992	0.998
Sleeping problems	0.015	0.005	8.14	1.02	**0.004**	1.01	1.03

Nagelkerke R Square, 720. Boldface values are $P < 0.05$. B, B weight (unstandardized); OR, odds ratio.

found to be related to fatigue; younger patients experienced more fatigue. Although age is not consistently found to be related to fatigue in other chronic illnesses (2,3), Warren et al. also reported this finding (14).

Most obvious factors such as diabetes complications or comorbidities did not strongly contribute to chronic fatigue in T1DM. One might argue that the methods chosen to assess comorbidities might be less reliable than, for example, the Charlson Index (39), however, independent of the chosen method, comorbidity was not the most important factor explaining the large presence of chronic fatigue.

Our study has limitations. T1DM patients were selected from the diabetes clinic of one university hospital, so the sample may not be representative for the T1DM population in general. We only included T1DM patients, because they have fewer comorbidities than type 2 diabetes mellitus; however, we expect that chronic fatigue is relevant in all diabetes mellitus types.

Table 4—Result of GEE of blood glucose values on acute fatigue

						95% Wald CI	
	Mean	SD	B	SE	*P* value	Lower	Upper
Between-subject							
Intercept			39.0	4.40	0.000	30.4	47.6
GLmean_hour	8.41	3.61	–0.025	0.342	0.941	–0.695	0.645
Gvar_hour	0.684	0.552	−1.13	1.37	0.411	−3.81	1.56
Within-subject							
Intercept			37.1	3.07	0.000	31.1	43.1
GLmean_hour			0.043	0.211	0.840	–0.371	0.456
Gvar_hour			0.021	0.825	0.979	−1.60	1.64

B, B weight (unstandardized).

The CGM system could not be blinded. Although patients were asked to regulate their blood glucose in the way they were used to and not to use CGM data, we cannot rule out the possibility that CGM readings have affected patients' behavior. The fact that patients' glucose levels did not improve over the 5 days of using CGM argues against this possibility.

Another limitation of our study is the fact that we did not use a disease-specific instrument to assess quality of life.

The total duration patients suffered from fatigue was determined retrospectively, which is less accurate than prospective determination. However, in the matched population-based controls, the duration of fatigue was established in the same way. Furthermore, we used this cross-sectional design study to identify potential determinants, but this design can only provide associations. A limitation is the lack of data on the health status of the control group. It might be that somatic comorbidity

other than diabetes is more prevalent in patients than in the control group, and this could potentially partly explain the difference in the prevalence of chronic fatigue in both groups.

Our study also has strengths. It is a large, randomly selected cohort of T1DM patients. Complementary measurements of fatigue and glucose control were performed using state-of-the-art methods, EFD and CGM, as well as conventional assessments, questionnaires and HbA_{1c} levels. This is also the first study that quantifies the contribution of specific fatigue-related cognitions and behaviors in T1DM.

In summary, chronic fatigue is a highly prevalent and burdensome symptom for T1DM patients. In the search for potential determinants of chronic fatigue in T1DM, fatigue-related cognitive behavioral factors were more important than prevailing glucose levels. Our findings may have clinical implications. Cognitive behavior therapy aimed at fatigue-perpetuating factors can lead to a significant decrease of fatigue and disabilities (20,40). However, whether such an intervention will lead to a reduction in fatigue and better diabetes self-care remains to be established.

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