Title

Chronic fatigue in type 1 diabetes: highly prevalent but not explained by hyperglycaemia or glucose variability.

Running head

Chronic fatigue in type 1 Diabetes Mellitus.

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Structured abstract

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 (DM1).

Research Design and Methods: Out of 324 random selected DM1 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, HbA_{1c} values and comorbidity with medical records. Sixty-six patients underwent continuous glucose monitoring combined with an electronic fatigue diary for five days. Acute fatigue and four glucose parameters were determined; mean, variability and relative time spent in hypo- and hyperglycemia.

Results: DM1 patients were significantly more often chronically fatigued (40%; 95%CI: 34%-47%) compared to matched controls (7%; 95%CI 3%-10%; $p<.001$). Chronically fatigued patients had significantly more functional impairments. Fatigue was the most troublesome symptom. Age (Odds Ratio (OR): depression (OR: 28.0), pain (OR: .965), sleeping problems (OR: 1.02), low self-efficacy concerning fatigue (OR: .826) and physical inactivity (OR: .995) were significantly associated with chronic fatigue. Chronically fatigued patients spent slightly less time in hypoglycemia (proportion: .07± 0.06 versus .12± 0.10; $p=.025$). Glucose parameters were not related to acute fatigue.

Conclusions: Chronic fatigue is highly prevalent and clinically relevant in DM1. 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 DM1.

Fatigue is one of the classical presenting symptoms of diabetes mellitus (DM). For example, in newly diagnosed type 2 DM 61% of the patients was 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 hyperglycaemia that may result in sustained fatigue. Fatigue may also sustain in DM 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 six 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 DM 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 behaviours 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 hyper- or hypoglycaemia, could trigger acute fatigue for DM 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 DM patients (DM1) 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 DM1. A multi-factorial model for fatigue in patients with

type 2 diabetes (13) was used for selecting potential determinants. This model not only encompasses physiological factors, such as hyperglycaemia, hypoglycaemia 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, 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 DM1. An overview of the factors expected to affect chronic fatigue in DM1 is schematically depicted in appendix figure 1. DM1 was chosen as it has fewer interactions with significant comorbidities. In a sub study, we assessed the contribution of mean glucose levels, glucose variability, hyperglycaemia and hypoglycaemia, determined by continuous glucose monitoring (CGM), to both chronic and acute fatigue.

Methods

Sample

DM1 outpatients between 18 to 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; unable to spreak, read and write Dutch, being hospitalised 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=1900) 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 DM1 patients were requested 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 DM1 patients. For the substudy, patients were followed for five days to investigate the contribution of blood glucose levels to acute – in a longitudinal design- and chronic fatigue – in a cross sectional design.

Procedure

From an outpatient cohort of 831 DM1 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 about two hours 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 non-participants with that of participants. Patients who didn't 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 CGM system and EFD was explained. The Freestyle Navigator® CGM system was used in accordance with the guidelines of Abbott. Data were collected between June 2011 and Januari 2012.

Instruments

Main study

Sex, age and HbA_{1c} were retrieved from the medical records. The prescence of a comorbidity was assessed in two ways. First, patients were asked if they had other illnessess in addition to DM1 (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 Strenght was used to assess *fatigue severity* over the past two weeks (Cronbach alpha = .95). This subscale consists of eight items (8-56). A score of 35 or higher, being two standard deviations 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 to suffer from fatigue for 6 months or longer and scored >35 were viewed as being *chronically fatigued*. The Short fatigue questionnaire (SFQ) was used to assess fatigue severity in non-participants. The SFQ consists of four items of the CIS-fatigue subscale (17) (Cronbach alpha = .926). All other instruments used are described in Appendix 1.

Substudy

Blood glucose

Glucose levels were continuously monitored for five days using the Freestyle Navigator®, which records glucose levels (mmol/L) every ten minutes. Operationalisation of glucose parameters are described in the statistical analyses.

Acute fatigue

The severity of acute fatigue was assessed using the EFD. Patients were asked to indicate how fatigued they were on that particular moment on a visual analogue scale ranging from "not at all fatigued" (0) to "very severely fatigued" (100). This question was presented on a personal digital assistant (pda) on six moments, evenly divided over the day from 8:30 to 22:30.

Power calculation

Main study: We selected 20 potential predictors for chronic fatigue. With ten patients needed per predictor, 200 participants yielded adequate statistical power. An estimated response rate of sixty percent 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 non-chronically fatigued patients.

Statistical Analyses

DM1 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 DM1 patients and matched population-based controls, and differences between chronically fatigued and non-chronically fatigued DM1 patients were tested using unpaired *t*-test and chi-square. 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 standard deviation of all glucose measurements of each participant (Gvar) (21). 3. *Relative time spend in hyperglycaemia* was assessed by dividing the number of CGM observations above 10 mmol/L by the total number of CGM observations of each participant (hyper). 4. *Relative time spend in hypoglycaemia* 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 standard deviations 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 non-responders filled in the SFQ (see appendix figure 2). Mean age of responders was 48±13 years, 53% were female, 52% had a higher education and 76% was married or lived together. Average diabetes duration was 29±14 years. Based on cut-off scores on the BDI-PC(22) 16% had clinically relevant depressive symptoms. Comorbidity_mr was 24% and comorbidity_pr was 49% based on patients 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 cut-off score are described in table 1 of the appendix.

Differences between participants and non-participants.

There was no significant difference on the mean scores on the Short Fatigue Questionnaire (SFQ) between participants (mean 15.7 sd 7.8) and non-participants (mean 16.2 sd 7.9) (p=.702) completing questionnaires. Non-participants. including non-responders did not differ significantly from participants on sex (p=.710). Participants and non-participants did differ significantly from each other on age and HbA_{1c}. Participants were older (mean 47.9 sd 12.9) had lower HbA_{1c} values (mena 7.8 NGSP, sd 1.1; 62 mmol/mol) and their latest HbA_{1c} was measured more recently (3.0 months, sd 10.5 months) compared to non-participants. The mean age of non-participants was 43.6 (sd 15.3), mean HbA_{1c} values was 8.6 NGSP (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 DM1 patients were chronically fatigued (40%; 95% Confidence Interval (CI) 34%-47%) than of matched controls (7%; 95% CI 3%-10%). Mean fatigue severity was also significantly higher in DM1 patients (31±14) compared to matched

controls (17±9, p<.001). DM1 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=.014) or without clinically relevant depressive symptoms (88% vs 31%; p<.001). Patients who reported neuropathy, nephropathy or cardiovascular disease as complications of diabetes we more often chronically fatigued (see Table 1).

Chronically fatigued DM1 patients were significantly more impaired compared to non-chronically fatigued DM1 patients on all aspects of daily functioning (see appendix 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, sleepiness or drowsiness (see appendix 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).

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 five 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 (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>=.271). The prevalence of chronic fatigue in the substudy was 37% compared to 40% in the total sample.

Chronically fatigued DM1 patients (n=25) spent in proportion less time in hypoglycaemia (.07±.06) compared to non-chronically fatigued patients (n=41) (.12±.10; p=.025). There was no significant difference between the two groups in GLmean (8.63±1.63 vs 7.84±1.73 mmol/L; p=.068), Gvar (3.13±0.90 vs 3.08±0.92 mmol/L; p=.816) and hyper (.32±.20 vs .25±.17; p=.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=.656), Gvar (r=-0.132, p=.291), hyper (r=0.056, p=.652) or hypo (r=-0.157, p=.209). GEE's showed no significant between or within subject effects of GLmn_hour and Gvar_hour on acute fatigue (Table 4).

Discussion

This study establishes that chronic fatigue is highly prevalent and clinically relevant in DM1 patients. While current blood glucose level was only weakly associated with chronic fatigue, cognitive behavioural 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 DM1 patients, as many as 40% was chronically fatigued, compared to 7% found in a matched population-based sample. Our results confirm earlier findings that DM1 patients experience higher levels of fatigue than healthy controls (6), although chronic fatigue was previously not

incorporated. Another study found that DM2, but not DM1 patients had higher levels of fatigue compared to 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 DM1 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 DM1 patients. Chronically fatigued DM1 patients had more functional impairments than non-chronically fatigued patients, and DM1 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 DM1 patients spent slightly less time in hypoglycaemia, but average glucose levels, glucose variability, hyperglycaemia or HbA1c were not related to chronic fatigue. In type 2 diabetes also no relationship was found between fatigue and HbA1c (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 hyper- and hypoglycaemia and acute fatigue. Although other studies have reported a relationship between hyper- and hypoglycaemia and acute fatigue, those studies interviewed patients about symptoms retrospectively or were performed under laboratory settings (11,12,14). In the present study with real life situations it seems that the effect of a single episode of hyper- or hypoglycaemia on fatigue cannot be isolated.

One could question the relevance of chronic fatigue in diabetes 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 for diabetes patients. Furthermore, it is not unlikely that chronic fatigue makes it also more difficult for patients to be actively involved in their diabetes regulation, e.g. by becoming more physical active.

Regarding demographic characteristics, current health status, diabetes-related factors, and fatigue-related cognitions and behaviours 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 DM1. Although depression was strongly related, it could not completely explain the presence of chronic fatigue (23) as 31% was chronically fatigued without having clinically relevant depressive symptoms. Age was also 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. (2003) also reported this finding (14).

Most obvious factors such as diabetes complications, or comorbidities did not strongly contribute to chronic fatigue in DM1. One might argue that the methods chosen to assess comorbidities might be less reliable than for example the Charlson Index (24), however, independent of the chosen method, comorbidity was not the most important factor explaining the large presence of chronic fatigue.

Our study has limitations. DM1 patients were selected from the diabetes clinic of one university hospital, so the sample may not be representative for the DM1 population in general. We only included DM1 patients, because they have fewer comorbidities than DM2, however, we expect that chronic fatigue is relevant in all DM types.

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' behaviour. The fact that patients'

glucose levels did not improve over the five 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 designed 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 DM1 patients. Complementary measurements of fatigue and glucose control were performed using state-of-the-art methods, EFD and CGM, as well as conventionally assessments; questionnaires and HbA_{1c} levels. This is also the first study that quantifies the contribution of specific fatigue-related cognitions and behaviours in DM1.

In summary, chronic fatigue is a highly prevalent and burdensome symptom for DM1 patients. In the search for potential determinants of chronic fatigue in DM1 specific fatigue-related cognitive behavioural factors were more important than prevailing glucose levels. Our findings may have clinical implications. Cognitive behaviour therapy aimed at fatigue-perpetuating factors can lead to a significant decrease of fatigue and disabilities (20,25). 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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Table 1: Specification of diabetes complications: Associations with fatigue severity.

	n		CIS-fatigue Mean (sd)	p-value
Retinopathy	92	Yes	32.2 (14.0)	.264
	122	No	30.0 (14.7)	
Neuropathy	58	Yes	36.1 (14.5)	.001
	156	No	29.0 (14.0)	
Loss of feeling in feet	32	Yes	33.2 (13.7)	.328
	182	No	30.5 (14.5)	
Nephropathy	22	Yes	39.4 (12.5)	.003
	192	No	30.0 (14.4)	
Cardiovascular disease	28	Yes	40.0 (13.8)	.001
	186	No	30.0 (14.1)	
Heart attack	11	Yes	36.1 (15.0)	.226
	203	No	30.7 (14.4)	
Stroke	2	Yes	49.0 (9.9)	.076
	212	No	30.7 (14.4)	

Table 2: Potential determinants of fatigue: Associations with fatigue severity.

			CIS-fatigue Mean (sd)	CIS-fatigue Pearson R	P-value
Demographic variables	Age			-,192	.005
	Sex	Male	27.9 (14.3)		.003
		female	33.6 (14.1)		
	Education	Lower	31.3 (15.5)		.693
		higher	30.6 (13.5)		
	Marital status	Married	30.2 (14.3)		.153
		Not married	33.5 (14.7)		
Current health status	Sign. Comorbidity (Medical record)	Yes	37.1 (14.5)		<.001
		No	29.0 (12.6)		
	Other illnesses (self-reported)	Yes	34.7 (13.6)		<.001
		No	27.2 (14.4)		
	Pain			-.520	<.001
	Depression			.467	<.001
Specific diabetes-related factors	Diabetes duration			-.116	.091
	Age of diabetes onset			-.084	.221
	Number of complications due to diabetes			.241	<.001
	HbA_{1c}			.097	.156
	Diabetes-specific self-efficacy			-.299	<.001
	Diabetes-related distress			.342	<.001
Fatigue-related cognitions	Self-efficacy concerning fatigue			-.635	<.001
	Fatigue catastrophizing			.635	<.001
	Ilness-related attributions with regard to fatigue			-.491	<.001
	Focusing on fatigue			.598	<.001
Fatigue-related behaviours	Self reported physical activity			-.163	.018
	Sleeping problems			.525	<.001

Table 3: Results of logistic regression analysis of potential determinants of chronic fatigue.

	Chronic fatigue	B	SE	Wald	Exp (b) (OR)	p-value	95% CI Lower	95% CI Upper
(Constant)		10.4	4.72	4.81	31320	.028		
Demographic variables	Age	-.081	.028	8.50	.923	**.004**	.874	.974
	Sex	.398	.515	.597	1.49	.440	.542	4.09
	Education	-1.07	.553	3.74	.343	.053	.986	8.61
	Marital status	.429	.616	.485	1.54	.486	.459	5.13
Current health status	Depression	3.33	1.05	9.99	28.0	**.002**	**3.55**	**221**
	Pain	-.036	.014	6.24	.965	**.013**	**.938**	**.992**
	Significant comorbidity	.657	.628	1.09	1.93	.296	.563	6.61
Specific diabetes-related factors	Diabetes duration	-.006	.023	.073	.994	.786	.950	1.04
	Number of complications due to diabetes	.169	.198	.730	1.19	.393	.803	1.75
	HbA_{1c}	.075	.225	.112	1.08	.738	.694	1.68
	Diabetes-specific self-efficacy	.001	.026	.001	1.00	.969	.951	1.05
	Diabetes-related distress	-.041	.023	3.28	.959	.070	.917	1.00
Fatigue-related cognitions	Self-efficacy concerning fatigue	-.191	.087	4.83	.826	**.028**	**.696**	**.980**
	Fatigue catastrophizing	.055	.060	.832	1.06	.362	.939	1.19
	Illness-related attributions with regard to fatigue	-.226	.115	3.85	.798	.050	.636	1.00
	Focusing on fatigue	.061	.038	2.57	1.063	.109	.986	1.15
Fatigue-related behaviours	Self reported physical activity	-.005	.002	8.67	.995	**.003**	.992	.998
	Sleeping problems	.015	.005	8.14	1.02	**.004**	1.01	1.03

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OR: odd ratio, CI: confidence interval

Table 4: Result of GEE of blood-glucose values on acute fatigue.

	Mean	Sd	B	Standard error	p-value	95% Wald Confidence Interval	
						Lower	Upper
Between subject							
(Intercept)			39.0	4.40	.000	30.4	47.6
GLmean_hour	8.41	3.61	-.025	.342	.941	-.695	.645
Gvar_hour	.684	.552	-1.13	1.37	.411	-3.81	1.56
Within subjects							
(Intercept)			37.1	3.07	.000	31.1	43.1
GLmean_hour			.043	.211	.840	-.371	.456
Gvar_hour			.021	.825	.979	-1.60	1.64

Appendix 1: Description of the questionnaires used.

Impact of fatigue

Functional impairments in daily life were assessed using the Sickness Impact Profile 8 (SIP) (26) which consists of eight subscales and a total score (0-5799). The *burden of fatigue* was determined by using the Diabetes Symptom Checklist (DSC) (27,28) in which the burden of 34 diabetes-related symptoms, including fatigue, is rated from zero to five.

Potential determinants of chronic fatigue

Current health status

To assess *comorbidities* patients were asked to if they had other illnessess in addition to their type 1 diabetes. This item was scored yes or no. In addition, the presence of a significant comorbidity was also rated based on patient's medical status. *Pain severity* was assessed using the pain subscale of the Health Survey Short Form-36 (SF36). The Dutch language version of the SF-36 has been proven to be a reliable and valid instrument in the general population and in chronic disease populations (29).

Depression

Depression was assessed with the Beck Depression Inventory Primary Care (BDI-PC) (30). This is a seven item questionnaire with scores ranging from zero to 21. A score of four or higher on the BDI-PC is indicative for a clinical depression (22).

Diabetes-related factors

Patients had to fill in the date when DMI was diagnosed. Using this date and the date patients completed the questionnaire *diabetes duration* was calculated. The *number of complications due to diabetes* were assessed by asking patients if they had damage to their eyes, kidneys,

nerves, feet, cardiovascular system, and if they had a heart attack or stroke. The total number of complications was calculated, varying from 0-7. HbA_{1c} values, determined closest to the date patients completed the questionnaires, were obtained from the patients' medical files. The confidence in diabetes self-care scale (CIDS) was used to assess *diabetes-specific self-efficacy*, i.e. the perceived ability to perform diabetes self-care tasks. This scale is a 20-item questionnaire. Each item is a 5-point Likert scale and total CIDS scores range from 0 to 100. The CIDS scale is a reliable and valid measure of diabetes-specific self-efficacy in patients with type 1 diabetes (31). The problem areas in diabetes scale (PAID) was used to assess *diabetes-related distress* (32). It is a 20-item questionnaire. Each item is a 5-point Likert scale and total PAID scores range from 0 to 100. The PAID is a validated instrument (32,33).

Fatigue-related cognitions

Self-efficacy concerning fatigue was assessed using the Self-efficacy scale (SES), This scale consists of 7 questions and was based on the self-efficacy scale used in CFS patients (34). Total scores range from 7 to 28. *Fatigue catastrophising* was assessed using the Fatigue Catastrophising Scale (FCS) (35). This scale consists of 10 items. Respondents rated each item on a 5-point scale. A total score was derived by computing the mean of the 10 ratings. The FCS is a reliable instrument (36). *Causal attributions with regard to fatigue* was assessed using the causal attribution list (CAL) which consists of 12 items divided over two subscales; psychological attributions (7 items) and illness-related attributions (5 items). For each item patients were asked to indicate their opinion regarding the cause for their fatigue complaints on a 4-point scale (1 very applicable to 4 not at all applicable). This questionniare was based on the CAL developed by Servaes et al., (2002) (37). In the CAL used for this study was adjusted. The breast cancer-related attributions were replaced by illness-related attributions (fatigue is attributed to diabetes, high blood-glucose levels, low blood-glucose levels, diabetes

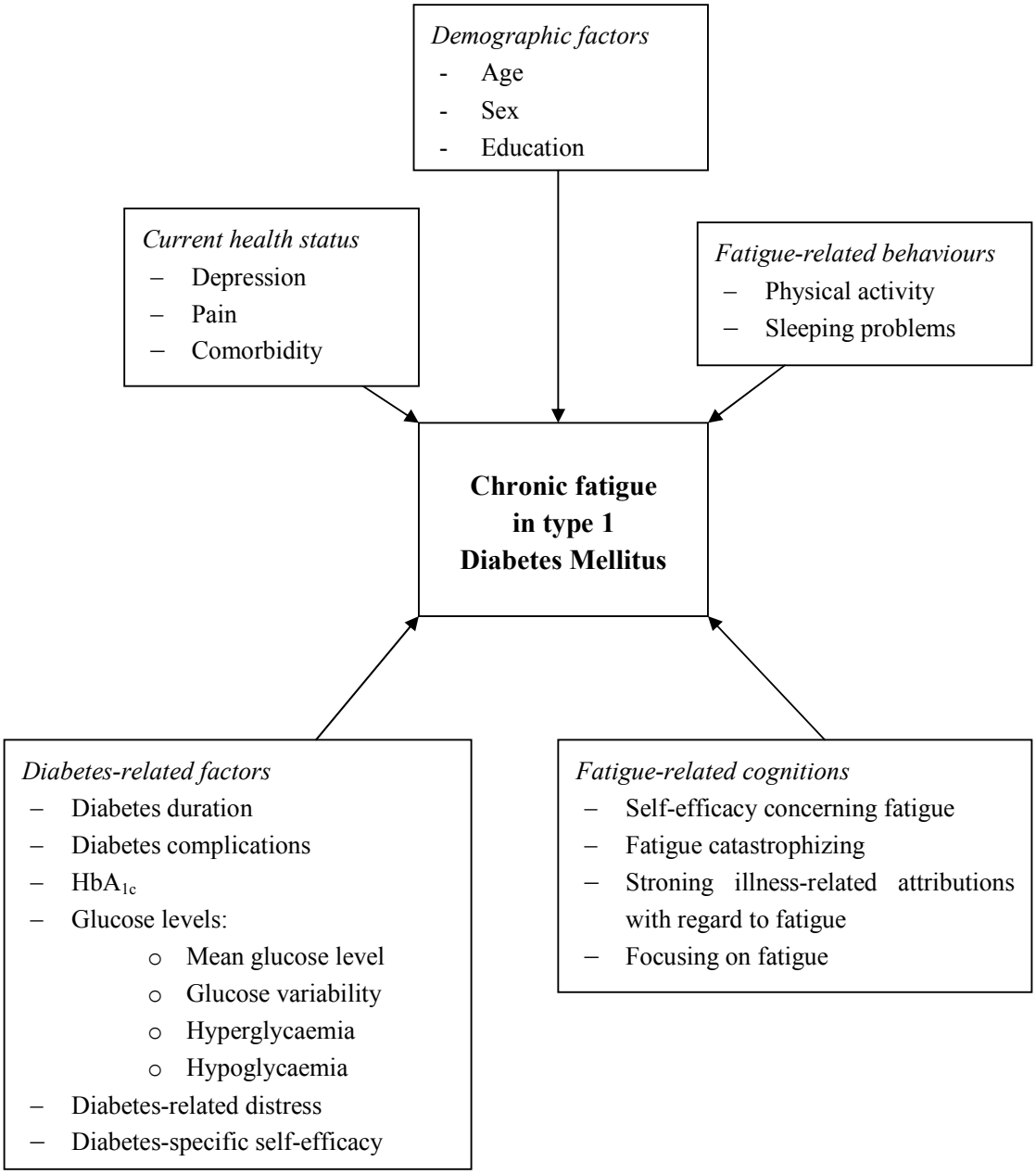
complication and illnesses different from diabetes). The illness management questionnaire (IMQ) (38) was used to assess *focusing on fatigue*. With this questionnaire patients were asked to indicate their overall approach to their illness during the last 6 months on nine items. The score on each item ranges from 1 (never) to 6 (always) and item scores are added to form a total score.

Fatigue-related behaviours

Physical activity was assessed using the short form International Physical Activity Questionnaire (IPAQ). This questionnaire is a 9-item scale, providing information on the amount of minutes spent in vigorous, moderate intense activity, and walking during the previous seven days. The total numer of minutes spend on activity was calculated. The IPAQ has reasonable measurement properties for monitoring population levels of physical activity among 18 to 65 year old adults in diverse settings (39). The *objective level of physical activity* was assessed using an actometer. It is a motion-sensing device based on a piezoelectric sensor, with highly reproducible readings (40). It records the number of movements in 5-minute intervals. The mean physical activity score across all worn days and nights was assessed to determine the level of physical activity. *Sleeping problems* were assessed using the subscale sleep/rest of the SIP (26).

Appendix Figure 1: Potential determinants of chronic fatigue in DM1 patients.

Appendix figure 2: Flow chart of accrual of patients.



Appendix Figure 1: Potential determinants of chronic fatigue in DM1 patients.

Appendix Table 1: mean scores, standard deviations and proportions of the sample on questionnaires

Outcome measure and used questionnaire	Mean & Sd	Proportion above cut-off
Fatigue severity / severe fatigue Checklist individual strenght – subscale fatigue, >=35	31 ± 14	44%
Pain Health Survey Short Form-36 - subscale pain	78 ± 23	
Depressive mood / clinically relevant depression Beck Depression Inventory Primary Care >=4	1.7 ± 2.3	16%
Diabetes-specific self-efficacy Confidence in diabetes self-care scale	87 ± 12	
Diabetes-related distress Problem areas in diabetes scale	16 ± 15	
Self-efficacy concerning fatigue Self-efficacy scale	20 ± 4.0	
Fatigue catastrophizing Fatigue Catastrophising Scale	16 ± 5.9	
Ilness-related attributions with regard to fatigue Causal attribution list – subscale illness-related attributions	14 ± 5.9	
Focusing on fatigue Illness management questionnaire	22 ± 9.5	
Self reported physical activity (minutes per week) International Physical Activity Questionnaire	246 ± 289	
Sleeping problems Sickness Impact Profile - subscale sleep/rest	54 ± 62	

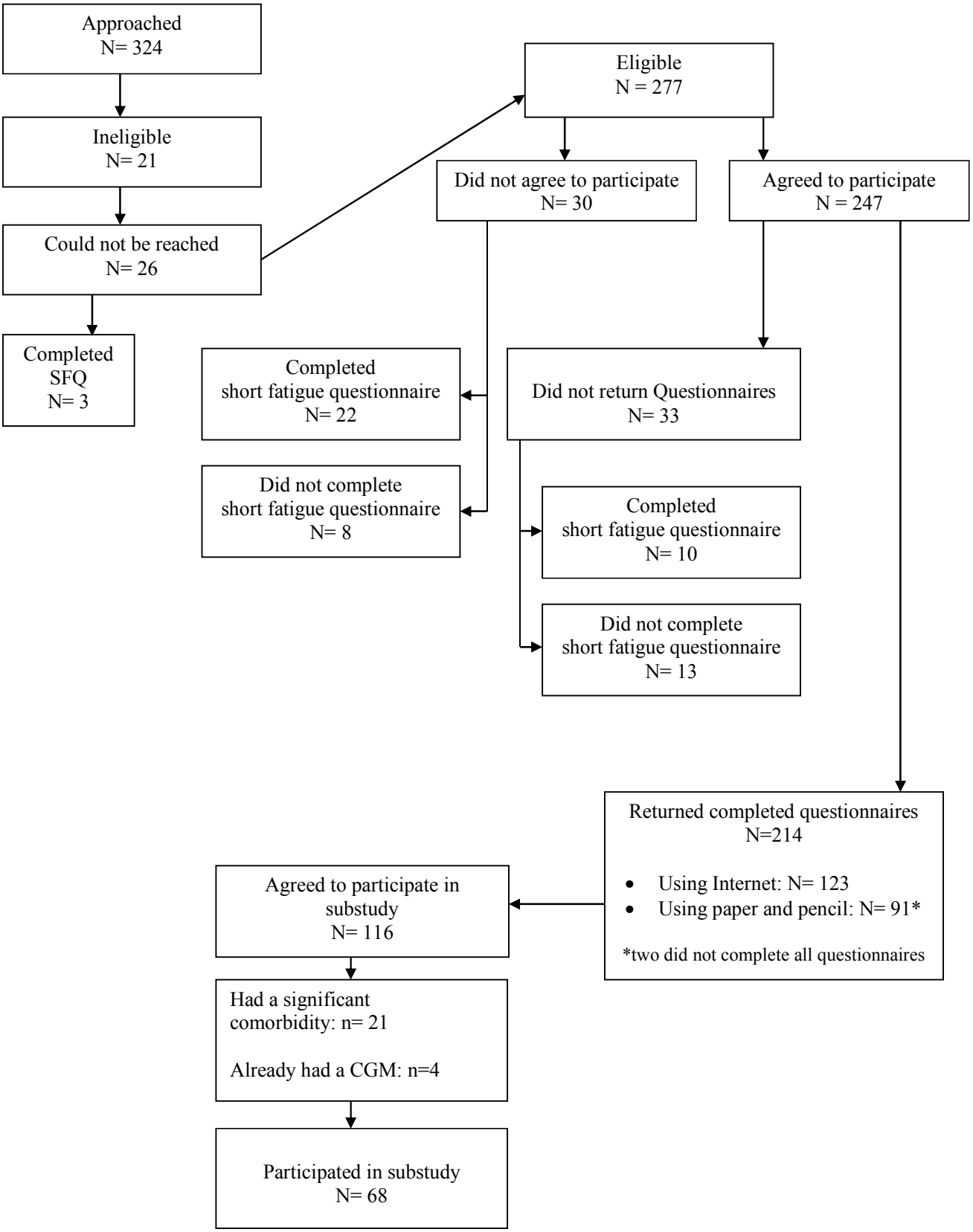
Appendix Table 2: Ten most reported troublesome symptoms of 34 diabetes symptoms (n=214).

1	**Overall sense of fatigue.**
2	**Lack of energy.**
3	**Increasing fatigue in the course of the day.**
4	**Fatigue in the morning when getting up.**
5	Sleepiness or drowsiness.
6	Moodiness.
7	Difficulty concentrating.
8	Tingling or prickling in the hands or fingers.
9	Aching calves when walking.
10	Numbness (loss of sensation) in the feet.

Appendix Table 3: Difference between chronically fatigued and non-chronically fatigued DM1 patients on functional impairments in daily life.

	Chronically fatigued DM1 patients (n=86) Mean (sd)	Non- chronically fatigued DM1 patients (n=128) Mean (sd)
SIP sleep and rest	94±69	27±39*
SIP homemaking	108±112	24±55*
SIP mobility	42±81	6 ±28*
SIP social interactions	191±184	50±76*
SIP ambulation	63±106	13±40*
SIP leisure activities	88±77	21±41*
SIP alertness behaviour	135±165	28±73*
SIP work limitations	96±136	27±78*
SIP total	816±568	195±237*

* Difference between severely and non-severely fatigued patients was significant $P<.001$.



Appendix figure 2: Flow chart of accrual of patients.