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Research Paper

Patients with type 1 diabetes in Sweden experience more fatigue than the general population

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ABSTRACT

Aims: Type 2 diabetes has been linked to fatigue, but results on type 1 diabetes are ambiguous. Our aim was to determine if type 1 diabetes is associated with fatigue and whether the fatigue is due to complications or to the disease itself.
Methods: The Multidimensional Fatigue Inventory (MFI-20), was submitted to all 435 adult patients with type 1 diabetes in the National Diabetes Register at the Sunderby Hospital clinic and to a control group of 2500 persons. The participation rate was 62% in both groups.
Results: Type 1 diabetes was associated with greater fatigue, with a 1.4-point difference (0.9–1.9, 95% CI) in *general fatigue* on a scale of 4–20. Type 1 diabetes was an independent predictor of fatigue, as were cardiovascular and cerebrovascular disease. Women with long diabetes duration but without complications experienced more fatigue than women in the general population (difference in *general fatigue* = 2.5, $p = 0.021$), whereas men showed no significant difference.
Conclusions: Type 1 diabetes is associated with greater fatigue, partly ascribed to vascular disease. Type 1 diabetes of long duration might be associated with fatigue regardless of classical complications, but further research is needed to confirm results.

Introduction

Type 1 diabetes is a chronic condition prevalent in about 30 000 people in Sweden [1]. The consequences of the condition vary among patients – common complications include nephropathy, diabetic foot disease, retinopathy, ischemic heart disease (IHD), and stroke. Possible effects upon quality of life, cognition and vitality are little studied.

Fatigue is defined by Medical Subject Headings (MeSH) as "[t]he state of weariness following a period of exertion, mental or physical, characterized by a decreased capacity for work and reduced efficiency to respond to stimuli." However, fatigue can be defined in many ways [2], and the definition above seems applicable primarily to healthy individuals. Amongst individuals with a disease, fatigue might be experienced as tiredness at rest, lack of endurance or loss of vigor [3]. Associations have been found between fatigue and several chronic conditions, including multiple sclerosis (MS) [4], chronic obstructive pulmonary disease (COPD) [5], systemic lupus erythematosus (SLE) [6], rheumatoid arthritis (RA) [7], and cancer [8]. Type 2 diabetes and the metabolic syndrome are also associated with fatigue [9]. Fatigue could be the consequence of disturbances in cognition.

Both type 1 and type 2 diabetes have been linked to cognitive decrements [10]. Studies on fatigue amongst type 1 diabetic patients are scarce and ambiguous: Pediatric type 1 diabetic patients showed more fatigue than their healthy peers in a 2009 study [11]. Amongst adults, one small study indicated that type 1 diabetes is not associated with increased fatigue [12]. However, a larger study from 2013 found a significant association between type 1 diabetes and fatigue [13]. Patients even reported fatigue as the most troublesome diabetes-related symptom. The prevalence of fatigue amongst patients with type 1 diabetes is most likely influenced by both lifestyle and the psychological stress related to the burden of living with a chronic condition [14]. Stroke and IHD, two possible complications of type 1 diabetes, have been linked to fatigue [15–17].

Our main aim was to determine if fatigue is more common amongst patients with type 1 diabetes than in the general population. A secondary aim was to determine whether a possible difference in fatigue might be related to complications or type 1 diabetes itself.

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Material and methods

Design

In a cross-sectional study, a questionnaire was distributed to all patients over 18 years of age with type 1 diabetes registered in the Swedish National Diabetes Register (NDR) at the Section of Endocrinology, Department of Medicine, Sunderby Hospital – a sample of convenience consisting of 435 persons. That clinic follows all patients with type 1 diabetes, classification was determined by the treating clinician, in the cities of Luleå and Boden, with an approximate catchment area of 100 000. The patients receiving the questionnaire comprised an estimated 90% of all patients with type 1 diabetes in the area.

Data were collected from August 2012 to August 2014. The questionnaire was sent out by mail, and by the end of the specified time frame, non-responders still living in the county were contacted by telephone and asked about their intention to participate in the study. Between May and August 2014, the questionnaire was also available at doctors' and nurses' appointments. Information about diabetes duration and complications was retrieved from patients' medical records. The registered complications included nephropathy (microalbuminuria, macroalbuminuria, end-stage renal disease – ESRD), IHD, stroke (amongst the patients also including transient ischemic attack – TIA), retinopathy (defined as laser treated retinopathy), diabetic foot disease (including neuropathy with or without pain) and amputation.

The reference group consisted of participants in the 2014 Northern Sweden MONICA population survey, which primarily investigated cardiovascular disease in relation to public health and socioeconomic factors. The study was carried out in a manner similar to the previous six surveys, which started in 1986 [18]. Each survey included 2500 people between 25 and 74 years of age in the counties of Norrbotten and Västerbotten, and that included the cities of Luleå and Boden. Since MONICA is a population survey, some people with diabetes were included in the reference group. We did not exclude these.

In addition to comparing the groups above, patients with none of the aforementioned complications but with 30 years or more of diabetes duration were also analyzed separately from other diabetes patients. The cut-off age was chosen according to ongoing the PROLONG study at Lund University, investigating mechanisms protecting against diabetes complications.

Instruments

The questionnaires contained the Multidimensional Fatigue Inventory (MFI-20) and background questions concerning sex, age and smoking habits. The reference group was also asked about previous or current cardio- and cerebrovascular disease. The MFI-20 consists of 20 questions and measures fatigue on five subscales: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue [19]. Each subscale ranges from 4 to 20, with higher scores indicating more fatigue. The Swedish translation of MFI-20 has been previously accepted for scientific purposes [20].

Statistical analyses

To investigate any difference in fatigue between the patients and the control group, MFI-20 scores were compared using independent samples *t*-test. Differences between groups are denoted by Δ. When comparing small groups, the Mann–Whitney *U* test was used (stated in the results).

Table 1
Number of participants and participation percentage in the patients and control group according to age

Age	MONICA	Patients	MONICA	Patients
	n		Participation rate	
18–34	239	60	48%	41%
35–44	290	52	58%	66%
45–54	340	59	68%	74%
55–64	362	44	72%	70%
65–81	326	51	65%	80%

Using data from all patients and controls, linear regression was performed with *general fatigue* as dependent variable and type 1 diabetes, IHD, stroke, age, sex and daily smoking as independent variables. Factors previously linked to fatigue or with large differences between the groups were included in a linear regression model including the control group and patients with 30 years or more of diabetes duration but without major complications. Investigated independent factors were sex, age, smoking, IHD, stroke and type 1 diabetes.

Statistical analyses were performed with IBM SPSS Statistics (version 22). All confidence intervals (CI) are 95%. Given regression model coefficients are unstandardized. If any participant failed to answer a question, which resulted in a missing value, the participant was excluded from that particular analysis, but included in other analyses that did not require the variable in question. For none of the fatigue dimensions was the rate of missing values higher than 2.4 percent.

This study was approved by the Regional Ethics Review Board at Umeå University, Sweden. All participants were provided with information in writing and consented to taking part in the study.

Results

A total of 268 patients with type 1 diabetes and 1557 subjects from the control group (MONICA) participated in the study, resulting in a participation rate of 62% in each group (Table 1). Participation frequencies varied with age: the lowest rate was found amongst the youngest patients, whereas the oldest patients were more prone to participate. The participation rate did not differ between patients and controls according to gender (60% among men and 63.5% among women). The mean age was about the same in both groups, while the percentage of women was lower amongst the patients. The frequencies of IHD and stroke were also higher amongst the patients (Table 2).

Fatigue scores in all dimensions were significantly higher amongst the patients than in the control group (Table 3). When

Table 2
Characteristics of participants, means (SD) or percentages. Patients with type 1 diabetes and the control group from the MONICA study

Characteristics	MONICA $n = 1557$	Patients $n = 268$
Age (years)	50.8 (13.8)	48.0 (16.1)
Women	51.6%	46.6%
Daily smokers	7.8%	6.0%
IHD	4.6%	9.0%
Stroke	2.4%	3.7%
Foot disease	N/A	18.9%
Amputation	N/A	1.1%
Nephropathy	N/A	16.1%
Laser treated retinopathy	N/A	25.2%
Diabetes duration (years)	N/A	26.4 (15.0)
Age of onset (years)	N/A	21.6 (14.3)

Table 3
Fatigue scores for the patients with type 1 diabetes and for the control group from the MONICA study

Means	General fatigue	Physical fatigue	Reduced activity	Reduced motivation	Mental fatigue
Men					
MONICA $n = 753$	9.7	9.0	9.0	7.4	8.4
Patients $n = 143$	11.0	9.6	9.6	8.0	9.4
Δ	1.3	0.6	0.7	0.7	1.0
95% CI	0.6; 1.9	−0.1; 1.3	0; 1.3	0.1; 1.2	0.4; 1.7
p	<0.001	0.1	0.044	0.013	0.001
Women					
MONICA $n = 804$	10.8	9.7	9.3	7.6	8.7
Patients $n = 125$	12.5	10.9	9.9	8.2	9.1
Δ	1.7	1.2	0.6	0.6	0.4
95% CI	0.9; 2.5	0.4; 2	−0.2; 1.4	0; 1.2	−0.3; 1.1
p	<0.001	0.005	0.1	0.039	0.2
Both sexes					
MONICA $n = 1557$	10.3	9.4	9.1	7.5	8.5
Patients $n = 268$	11.7	10.2	9.8	8.1	9.3
Δ	1.4	0.8	0.6	0.6	0.7
95% CI	0.9; 1.9	0.3; 1.4	0.1; 1.1	0.2; 1	0.3; 1.2
p	<0.001	0.003	0.015	0.002	0.002

comparing both sexes together, the difference between means in *general fatigue* score was 1.4 on a scale of 4–20 (0.9–1.9, 95% CI). Furthermore, fatigue scores, with the exception of mental fatigue, were greater in women than in men in both the patient and the control groups. In a linear regression model, type 1 diabetes, as well as IHD and stroke, remained significant predictors for higher scores in all fatigue dimensions, after adjusting for age, sex and daily smoking ($p < 0.05$). The association and the impact was strongest in the *general fatigue* dimension ($p < 0.001$; $B = 1.18$; $R^2 = 10\%$).

Women with a diabetes duration of 30 years or more but without major complications (micro- or macroalbuminuria, diabetic foot disease, IHD, stroke or laser treated retinopathy) showed significantly higher *general fatigue* scores than women in the general population ($n = 16$, $\Delta = 2.5$, $p = 0.021$, comparison by Mann–Whitney U). However, there was no such difference seen in the men ($n = 20$, data not shown). When adjusting for IHD, stroke, sex, age and daily smoking, having a diabetes duration of 30 years or more but no major complications was significantly associated with higher *general fatigue* ($p = 0.047$, $B = 1.26$, $R^2 = 10\%$). In a univariate comparison between patients with and without the aforementioned complications, only stroke ($\Delta = 3.0$, $p = 0.067$) and female sex ($\Delta = 1.5$, $p = 0.014$) were associated with greater *general fatigue* scores (comparisons by Mann–Whitney U).

Discussion

This study indicates that there is an association between type 1 diabetes and fatigue. These findings contradict one previous, small study [12] and support a recent, large Dutch study [13]. By and large women had higher fatigue scores than men, which is to be expected according to results in earlier studies [21,22]. The associations found between IHD, stroke and fatigue were also consistent with earlier findings [16,17]. However, it is interesting that type 1 diabetes was found to be an independent predictor of fatigue when controlling for the age, sex, smoking, stroke and IHD.

While type 1 diabetes might be associated with fatigue regardless of major complications, further research is needed to find out which patients are more likely to experience fatigue. One such group identified in this study was women with 30 or more years of diabetes duration but without major complications. While the finding might be of clinical importance, the results should be interpreted with caution due to a small group size ($n = 16$). The fact that some patients seem protected from complications despite long diabetes duration has been previously observed [23].

Some indications on mechanisms mediating the association between type 1 diabetes per se and fatigue comes from studies of patients with type 2 diabetes where an association with brain atrophy and cognitive impairment [24], and a link between high blood glucose levels and dementia has been established [25]. In type 2 diabetes patients who reported hypoglycemic symptoms, the risk of excessive fatigue was almost doubled, compared with patients not reporting such symptoms [26]. A decrease in cognitive performance and impaired sustained attention is associated with type 1 diabetes [27,28]. Amongst patients with long-standing type 1 diabetes, cognitive dysfunction is associated with subcortical volume loss, regardless of microangiopathy [29].

Fluctuation in blood glucose levels, in the short and long term, may thus be an important factor for impairment in higher mental functions, possibly leading to fatigue. Research on the association between recurrent, moderate hypoglycemia and cognitive impairment amongst rats has given ambiguous results [30,31]. Severe hypoglycemia is associated with worse cognitive functioning in patients with type 1 diabetes [32]. However, the association between glucose levels, including variability, time in hyperglycemia, HbA1c, and acute fatigue is reported as weak; instead, cognitive behavioral factors are found to be related to chronic fatigue [13]. Results in the present study give no indications of possible mechanisms accounting for the difference in fatigue between patients with type 1 diabetes and the general population. Although no association was found between hypoglycemia and acute fatigue in previous studies, a possible link between severe hypoglycemic events in patients with type 1 diabetes and chronic fatigue cannot be ruled out yet.

In our department all patients with type 1 diabetes are screened for thyroid disease, deficiency of vitamin B12 or folic acid every two years. We are also liberal with testing for Addison's disease and coeliac disease in patients with fatigue, weight loss or decreasing insulin demand. Therefore we do not believe that undiagnosed autoimmune disease explains our findings.

Are the higher fatigue scores found among patients with diabetes of such magnitude as to imply impact on quality of life? The minimal clinically important difference (MCID) for MFI-20 has been assessed in a radiotherapy population, ranging from 1.4 to 2.4 on the different subscales [33]. The differences between the control group and the diabetic patients found in this study were below the MCID in all fatigue dimensions but no data on MCID in patients with diabetes have been presented. Given previous patient reports on the burden of fatigue [13], this is somewhat unexpected, but the concept of MCID is controversial and not easy to define. However, for women with long standing diabetes without complications, the difference in fatigue was found to be clinically significant.

It is unclear in what way the patients experience fatigue. The MeSH definition, quoted in the introduction, does not seem to capture the long-term weariness that might be associated with chronic conditions. Fatigue takes many different forms, and many definitions exist [2]. How do the patients describe their fatigue? Is it a subjective feeling, or does it influence performance at work or on daily activities? How is it affected by mental or physical activity and rest? Is it connected to muscular strength or endurance? Although the different scales of the MFI-20 try to grasp various aspects of fatigue, further investigation on fatigue amongst patients with type

1 diabetes is needed. Most likely, both quantitative and qualitative research is needed to answer the questions above.

Further research is needed to find the factors and mechanisms that account for fatigue amongst diabetic patients without classical complications and where the difference in fatigue cannot be explained by IHD and stroke. Both psychological and physiological factors are likely to contribute to fatigue symptoms, especially is the concept of "diabetes burnout" [14] a target for further studies. Since neuroimaging has shown associations between structural changes and both type 1 and 2 DM, such examinations might prove helpful to identify mechanisms for fatigue amongst diabetes patients [34]. Implications from the findings in this study suggest that clinicians should be more alert to identify patients with type 1 diabetes who have fatigue symptoms. For cancer patients, physical activity has been shown to reduce fatigue [35], and cognitive behavior therapy (CBT) has been proven efficient in patients with chronic fatigue syndrome [36]. Given that cognitive behavioral factors have been associated with chronic fatigue [13] amongst patients with type 1 diabetes, perhaps CBT might help them as well. For selected patients, a thorough neuropsychological examination would possible be helpful in order to individualize advice and support.

Strengths and limitations

The strengths of this study include using a database covering almost all known patients with type 1 diabetes in the area, use of established tools for measurement, and information about diabetes duration and complications from patients' medical records. The Northern Sweden MONICA Study supplies a credible population comparison and further increases the external validity of the results. Unfavorable factors included limited geographic coverage, low response rate amongst young people and self-reported data on IHD and stroke in the control group. Data on present or previous metabolic control and the incidence of hypoglycemia were not available but could have added important dimensions. All in all, the results obtained likely reflect the groups sampled and might be applicable to other populations. Results regarding nephropathy are not quite reliable, since most patients with severe nephropathy and end-stage renal disease are treated for their diabetes at the Section of Nephrology and were thus not included in this study.

A trend toward increasing response rates with age was found in both the patients and the control group. This pattern is familiar from other studies [37]. However, a low response in certain age groups might lead to problems with non-response bias. Indeed, fatigue scores found in this study were compared to a general German population [21], and young people in the present study report higher fatigue scores than young people in the German population. This suggests that our lower response rate in the lower ages might be a sign of non-response bias amongst less fatigued young people.

A large number of tests were performed, raising the issue of mass significance. No particular correction for multiple comparisons was made, mainly due to an ambition to keep the analysis as simple as possible. Low *p*-values in most comparisons between large groups indicate that results are significant. However, the number of patients with over 30 years of diabetes duration but without complications was low. Therefore, findings on these patients should be interpreted with caution. The linear regression models that investigated possible predictors for fatigue scores showed low R^2 values. This suggests that other factors than those accounted for in this study might explain the associations between type 1 diabetes and fatigue. Due to the nature of fatigue, this should be expected. It should be underlined that the aim of this study was not to set up a model of independent predictors, which could explain fatigue, but to find a possible association between type 1 diabetes and fatigue, taking basic confounders into account. A prospective study using repeated measures of fatigue along with details on hypoglycaemia, HbA1c, physical activity, anthropometry and socio-economy would in the future serve well to entangle which factors that are most important in predicting fatigue among patients with type 1-diabetes.

Conclusions

Type 1 diabetes is associated with fatigue. Part of the association can be explained by macrovascular complications due to diabetes, but even when taking vascular problems into account, the link remains. Some of our findings might be of clinical importance. Women with a long duration of diabetes without complications experienced more fatigue than the control group, suggesting that fatigue might be a complication of type 1 diabetes *per se*.

Future studies on the associations between type 1 diabetes and fatigue should aim for higher participation rates and advanced cognitive assessment. Fields of interest include the interaction between type 1 diabetes and its complications, sex and fatigue as well as the possible links between biochemical markers and fatigue. Neuroimaging could contribute to a better understanding of mechanisms.

Conflict of interest

The authors declare they have no conflicts of interest.

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