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Socioeconomic, psychological and health-related correlates of fatigue in adults with longstanding type 1 diabetes**

Socjoekonomiczne, psychologiczne oraz związane ze zdrowiem wykładniki zmęczenia u osób dorosłych z długim wywiadem cukrzycy typu 1

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Keywords

diabetes-related distress, fatigue, type 1 diabetes

Słowa kluczowe

napięcie emocjonalne związane z cukrzycą, zmęczenie, cukrzyca typu 1

Summary

Introduction. Type 1 diabetes is a chronic disease requiring continuous insulin therapy. Adjusting the rules of treatment to the existing lifestyle can be a source of emotional distress and fatigue.

Aim. The aim of this study was to assess factors determining fatigue in subjects with long history of type 1 diabetes.

Material and methods. 285 subjects (151 women), median age 43 years [interquartile range (IQR): 34-52], type 1 diabetes duration over 20 years, HbA1c 7.8% (IQR: 7.1-8.9) were included. Subjects diagnosed with chronic complications causing disability were excluded. Patients completed questionnaire comprising the question: Do you feel fatigue due to living with diabetes? Additionally, Problem Areas in Diabetes Questionnaire (PAID), Beck Depression Inventory (BDI), Neuroticism Extraversion Openness Five-Factor Inventory (NEO-FFI), Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) were completed. Socioeconomic status and parameters of metabolic control were assessed.

Results. 55.8% of subjects declared fatigue due to diabetes. There was a relationship between fatigue assessment based on single question and scores exhibited in MFSI-SF Total ($r = 0.38$; $p < 0.001$). Employed and married participants less frequently declared fatigue ($p < 0.05$). The fear of hypoglycemia and insulin injections was more frequent in group declaring fatigue ($p < 0.05$). Fatigue was strongly associated with scores exhibited in BDI, PAID questionnaire as well as with neurotic personality. No relation of HbA1c with fatigue was found. Multivariate regression analysis showed that the fear of hypoglycaemia, fear of insulin injections, degree of education, physical activity and microangiopathy were associated with fatigue.

Conclusions. Fatigue in type 1 diabetes is determined by comorbid depressive disorder, coping with diabetes, neurotic personality and particular socioeconomic factors.

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

Streszczenie

Wstęp. Cukrzyca typu 1 jest chorobą przewlekłą wymagającą stałej insulinoterapii. Konieczność dopasowania zasad leczenia do aktualnego stylu życia może stanowić źródło napięcia emocjonalnego i zmęczenia.

Cel pracy. Celem badania była ocena czynników warunkujących zmęczenie u osób z długim wywiadem cukrzycy typu 1.

Materiał i metody. Do badania włączono 285 osób (151 kobiet); mediana wieku 43 lata [rozstęp międzykwartylowy (IQR): 34-52], czas trwania cukrzycy ponad 20 lat, HbA1c 7,8% (IQR: 7,1-8,9). Wykluczono osoby z rozpoznanymi przewlekłymi powikłaniami powodującymi niesprawność. Pacjenci wypełniali kwestionariusz zawierający pytanie: „Czy jest Pani/Pan zmęczona/y życiem z cukrzycą?" oraz Kwestionariusz Obszarów Problemowych w Cukrzycy (PAID), Kwestionariusz Depresji Becka (BDI), Inwentarz Osobowości NEO-FFI, Skalę Poczucia Zmęczenia (MFSI-SF). Oceniono status socjoekonomiczny pacjentów oraz wyrównanie metaboliczne cukrzycy.

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Wyniki. 55,8% osób deklarowało zmęczenie związane z życiem z cukrzycą. Wykazano zależność pomiędzy oceną zmęczenia opartą o jedno pytanie a wynikami uzyskanymi w skali MFSI-SF ($r = 0,38$; $p < 0,001$). Osoby posiadające zatrudnienie oraz pozostające w stałym związku partnerskim rzadziej deklarowały zmęczenie ($p < 0,05$). Lęk przed niedocukrzeniem oraz przed wstrzyknięciami insuliny występował częściej w grupie deklarującej zmęczenie ($p < 0,05$). Wykazano związek zmęczenia z wynikami uzyskanymi w skalach BDI, PAID oraz z osobowością neurotyczną. Nie obserwowano związku zmęczenia z HbA1c. W analizie regresji wieloczynnikowej wykazano, że lęk przed niedocukrzeniem, lęk przed wstrzyknięciami insuliny, poziom wykształcenia, mała aktywność fizyczna oraz przewlekłe powikłania mikronaczyniowe były niezależnie związane ze zmęczeniem.

Wnioski. Zmęczenie w cukrzycy typu 1 jest związane ze współistniejącymi zaburzeniami depresyjnymi, stopniem radzenia sobie z chorobą, neurotyczną osobowością oraz szczególnymi czynnikami socjoekonomicznymi.

INTRODUCTION

Type 1 diabetes is a chronic disease requiring complex and demanding treatment based on insulin therapy. Patient is obliged to perform daily diabetes self-management tasks, as performing regular glucose checks, exercising, following proper diet to maintain good metabolic control. The treatment goals include appropriate glycated hemoglobin (HbA1c) < 7% due to low, not high blood glucose variability, prevention of acute and chronic complications such as microvascular retinopathy, chronic kidney disease, neuropathy or macrovascular myocardial infarction or stroke (1). The treatment regimen is usually individualized, with respect to patient's behaviours, needs, mental skills as well as social and economic status. Different educational approaches are used to implement therapeutic regimens, most of them comprising issues of patient empowerment (2, 3). Since the results of The Diabetes Control and Complications Trial have been published in 1993, a need for good metabolic control in terms of prevention of chronic complications was emphasized in diabetes management guidelines (4). Then, intensive functional insulin therapy has been recommended as a method for well-educated patients, when an insulin dose is calculated on a basis of actual glucose level, amount of carbohydrate in a meal and planned physical activity. However, adjusting the rules of treatment to the existing lifestyle may be a source of emotional distress and fatigue, that in turn may affect motivation and ability to perform necessary self-management tasks, resulting in poorer metabolic control. High levels of diabetes-related stress are also likely to reduce the patient's quality of life. As a result, the risk of disease complications may be increased. Moreover, widely understood non-diabetes-related stress, i.e. due to social or economic status may influence treatment compliance and metabolic control in diabetic patients. Therefore it is important to early diagnose diabetes- and non-diabetes-related distress and to understand factors determining the feeling of fatigue. Still, not every subject diagnosed with chronic disease, such as diabetes, declares fatigue and decreased quality of life. Fatigue as a complaint is common among general population. According to Eurobarometer Mental Health, 27% of responders from 27 European countries reported to be "tired most of the time" (5). However, the term fatigue is multidimensional, includes physiological, psychological and environmental aspects and origins (6).

AIM

The aim of this study was to assess fatigue in subjects with longstanding type 1 diabetes.

MATERIAL AND METHODS

A total of 312 patients were identified as eligible from our outpatient clinic to participate in the study. Of these, 1 refused participation because of lack of interest, 26 failed to complete baseline data. Finally, 285 subjects were included, 53% of women. The median age was 43 years [interquartile range (IQR): 34-52], type 1 diabetes duration over 20 years [median duration time 26 years (IQR: 22-31)], median age at onset 14 years (IQR: 9-23), HbA1c 7.8% (IQR: 7.1-8.9). We excluded patients diagnosed with chronic complications causing disability, such as blindness, end stage renal disease, manifested by estimated glomerular filtration rate (eGFR) < 15 ml/min/1.72 m^2 [eGFR was calculated using Modification of Diet in Renal Disease (MDRD) study equation], history of limb amputation or painful peripheral neuropathy as irreversible disability or chronic pain are recognized factors of chronic distress and fatigue themselves. We also established the upper age border at 60 years, as older patients are more often retired which can affect their questionnaire answers concerning lifestyle. 191 subjects had a positive history of using reusable needles requiring sterilization for insulin injections, 225 subjects a history of using bovine or porcine insulin.

To assess fatigue participants were asked to complete the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) and to answer the question: "Do you feel fatigue due to living with diabetes?". MFSI-SF is a 30-item self-report measure designed to assess multidimensional aspects of fatigue that include general, physical, emotional, mental fatigue and vigor. The vigor subscale score is subtracted from the sum of the 4 fatigue subscales to yield a total fatigue score. Subscale scores range from 0 to 24, and MFSI-SF total scores range from -24 to 96, with

higher scores indicating more fatigue (7). The scale has no established cut-off scores, although Stein et al. showed that MFSI-SF Total scores above 0.85 represented significant fatigue (8). While the validity and reliability of MFSI-SF was shown on cancer patients, it is not a disease-specific fatigue scale and may be used in other chronic diseases (9, 10). Participants of our study fulfilled some additional questionnaires assessing their personality, depressive symptoms, coping with diabetes. We based the assessment of personality on Neuroticism Extraversion Openness Five-Factor Inventory (NEO-FFI) by Costa and McCrae (11, 12), a 60-item psychological personality inventory measuring The Big Five personality traits: Extraversion, Agreeableness, Conscientiousness, Neuroticism, and Openness to Experience. The Beck Depression Inventory, a 21-question multiple-choice tool was used for screening for emotional and physical symptoms of depression. We also used The Problem Areas in Diabetes Questionnaire (PAID), a 20-item scale measuring and classifying diabetes-related emotional distress into subgroups of: emotional burden, physician-related distress, regimen distress and interpersonal distress (13, 14). Body mass index (BMI) was obtained in all participants. We collected blood samples in fasting state defined as no caloric intake for at least 8 hours. Serum concentration of total cholesterol (T-Chol), high density lipoproteins (HDL) cholesterol, low density lipoproteins (LDL) cholesterol, triglicerides (TG), creatinine, thyroid-stimulating hormone (TSH) and high-sensitivity C-reactive protein (hsCRP) were measured using standard methods. The glycemic control was expressed by measuring HbA1c with the use of high-performance liquid chromatography (HPLC). The information on participants' social and economic status, educational degree, lifestyle habits and diabetes-related issues was collected based on survey prepared for the purpose of this study. Chronic complications were assessed via medical chart review. We assumed the presence of microangiopathy when either retinopathy or nephropathy or neuropathy was diagnosed.

All participants provided written informed consent after reading the description of the study. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the local Ethics Committee.

Statistical analysis

The MFSI-SF has no cut-offs and the higher score means more severe fatigue. Furthermore there was a relationship between assessment of fatigue based on single question and scores exhibited in MFSI-SF Total ($r = 0.38$, $p < 0.001$). Thus we divided participants of our study into two groups according to their answer to question about feeling fatigue (tab. 1-3). The results are shown as median values and IQR when the data were skewed or as number and percentage of participants for categorical data. The Kolmogorov-Smirnov test with Lilliefors correction was used to test for normality. The comparison between groups was assessed by Mann-Whitney test for continuous variables and chi-square test for categorical variables. Multivariable linear regressions were carried out to determine independent relationship of variables with the declared fatigue. The independent variables in these analyses were diabetes duration, degree of education, BMI, diagnosed microangiopathy, fear of hypoglycaemia, fear of insulin injections, physical activity. Statistical analyses were conducted using Statistica version 10 (StatSoft Inc., Tulsa, USA). For all results, a p-value below 0.05 was considered significant.

Tab. 1. Clinical characteristics of study participants according to declared fatigue (median and IQR or number)

Variable	Declared fatigue		p-value
	Yes	No	
Age [years]	42 (34-52)	43.5 (34-54)	**0.398****
Sex [m/f]	66/93	68/58	**0.036***
HbA1c [%]	7.9 (7.3-9.0)	7.7 (6.9-8.7)	**0.198****
BMI [kg/m^2]	24.6 (22.6-27.3)	24.9 (22.6-27.8)	**0.448****
T-Chol [mg/dl]	201 (177-228)	196 (171.5-222.0)	**0.362****
HDL [mg/dl]	66 (56-77)	66 (53-82)	**0.987****
LDL [mg/dl]	110 (89-128)	111 (94-133)	**0.682****
TG [mg/dl]	97 (78-125)	92 (71-121)	**0.145****
Creatinine [mg/dl]	0.86 (0.76-1.0)	0.88 (0.77-0.99)	**0.744****
hsCRP [mg/l]	1.15 (0.56-2.61)	1.07 (0.56-2.52)	**0.604****
TSH [uIU/ml]	1.64 (1.1-2.45)	1.58 (0.89-2.49)	**0.464****
Microangiopathy [n, yes/no]	128/27	88/35	**0.028***
Retinopathy [n, yes/no]	125/30	89/32	**0.161***
Neuropathy [n, yes/no]	69/76	45/72	**0.138***
Chronic kidney disease [n, yes/no]	37/104	23/93	**0.226***

hsCRP – high-sensitivity C-reactive protein; *chi^2 test; **Mann-Whitney test; $p \leq 0.05$ in bold font

Tab. 2. Demographic, socioeconomic, lifestyle and diabetes-related characteristics of study participants in association with fatigue. N = 285, fatigue declared by 159 subjects, chi^2 test

Variable		Declared fatigue		p-value
		Yes	No	
Education	primary school education vocational education secondary school education higher education	8 32 76 43	3 17 55 50	0.08
Marital status[b]	single/married	66/93	34/92	**0.011**
Employment status[a]	unemployed/employed	92/66	41/81	**0.00001**
Children	yes/no	106/51	91/35	0.392
Smoking cigarettes	yes/no	56/102	33/92	0.104
Regular exercise[c]	yes/no	102/57	98/27	**0.009**
Fear of hypoglycaemia	yes/no	95/61	51/73	**0.001**
Fear of insulin injections	yes/no	70/89	30/96	**0.0004**

[a]students included into 'employed' group
[b]seperated/widowed/divorced included into 'single' group
[c]at least 45 min. of physical activity three times a week
$p \leq 0.05$ in bold font

Tab. 3. Association of personality factors, depressive symptoms and coping with diabetes with fatigue, Mann-Whitney test

Variable	Declared fatigue		p-value
	Yes (n = 159)	No (n = 126)	
MFSI-SF			
General [score]	7.0 (3-12)	3.0 (1-6)	**0.000005**
Physical [score]	6.5 (2-10)	2 (0-6)	**0.00004**
Emotional [score]	7.0 (4-12)	4.0 (1-6)	**0.000006**
Mental [score]	6.0 (3-10)	4.0 (2-7)	**0.003**
Vigor [score]	10.0 (6-13)	12.0 (8-16)	**0.004**
Total [score]	16.0 (6.0-33.0)	0.0 ((-9.0)-14.0)	**0.000001**
BDI [score]	11.5 (6-19)	5.0 (3-9)	**0.000001**
PAID [score]	35.0 (22.5-51.25)	16.25 (10-27.5)	**0.000001**
Personality factors			
Conscientiousness [score]	33.0 (29-37)	35.0 (31-39)	0.0668
Openness to Experience [score]	24.0 (21.5-28)	25.0 (22-29)	0.263
Extraversion [score]	26.0 (22-31)	30.0 (25-34)	**0.00008**
Neuroticism [score]	25.0 (18-30)	16.0 (12-22)	**0.0000001**
Agreeableness [score]	31.0 (26-34.5)	31.0 (29-35)	**0.04**

BDI – Beck Depression Inventory; PAID – Problem Areas in Diabetes questionnaire; MFSI-SF – Multidimensional Fatigue Symptom Inventory-Short Form; $p \leq 0.05$ in bold font

RESULTS

55.8% of participants declared fatigue. There was significant difference in scores exhibited in MFSI-SF between group declaring and not declaring fatigue (tab. 3). No correlation of glycemic control assessed by HbA1c measurement with declared fatigue ($r = 0.08$, $p = 0.178$) or MFSI-SF Total score ($r = 0.11$, $p = 0.166$) was found. Married and employed participants less frequently reported fatigue compared with unemployed or single ones. No significant relationship between education level, having offspring or smoking cigarettes and fatigue was found. We found a negative association between active lifestyle, performing regular physical activity and fatigue ($r = -0.16$, $p = 0.009$). When analyzing issues concerning insulin therapy, fatigue was significantly more frequent among participants declaring fear of hypoglycemia and fear of insulin injections (tab. 2). There was a direct relationship of fatigue and depression symptoms exhibited in BDI ($r = 0.36$, $p = 0.000005$), as well as difficulties due to coping with diabetes indicated by PAID questionnaire ($r = 0.43$, $p = 0.000001$). For personality factors, neuroticism positively, extraversion and agreeableness negatively correlated with fatigue ($r = 0.41$, $p = 0.0000001$; $r = -0.20$, $p = 0.013$; $r = -19$, $p = 0.02$ respectively).

In the multivariate regression analysis the fear of hypoglycaemia and the fear of insulin injections, degree of education, physical activity and microangiopathy remained predictors of fatigue after adjustment for age and sex (tab. 4).

Tab. 4. The relationship between investigated parameters and fatigue, with multivariate analysis adjusted for age and sex

Variable	Multivariate regression analysis		
	β	95% CI	p-value
Duration of diabetes	0.001	-0.009; 0.009	0.986
HbA1c	0.003	-0.041; 0.043	0.960
BMI	-0.041	-0.020; 0.009	0.485
Microangiopathy	**0.131**	**0.017; 0.296**	**0.03**
Fear of hypoglycaemia	**0.146**	**0.030; 0.261**	**0.014**
Fear of "the needle"	**0.191**	**0.079; 0.323**	**0.0013**
Degree of education	**-0.117**	**-0.144; -0.0008**	**0.047**
Physical activity	**-0.138**	**-0.275; -0.023**	**0.02**

β – standardized regression coefficient; 95% CI – 95% confidence intervals; $R = 0.361$, $R^2 = 0.130$, $p < 0.00001$; $p \leq 0.05$ in bold font

DISCUSSION

In diabetic patients, suffering from chronic disease fatigue seems to be of physiological, psychological and environmental origins. Rapid fluctuations of glucose levels, chronic hyperglycemia, acute hypo or hyperglycemia may precipitate fatigue (15, 16). Moreover, we found the positive relation of the fear of hypoglycemia itself with fatigue. To emphasize, in our study, none of participants had symptoms of hypoglycemia or acute hyperglycemia during answering the survey. Although intensive functional insulin therapy is an only method that enables flexibility of one's lifestyle, it should be noted, that 79% of participants had a positive history of using bovine or porcine insulin, injected once or twice daily. At that times, a personal glucose meter was uncommon, therefore practically no dose adjustments were performed based on self-monitoring of blood glucose. Stable insulin doses regardless of actual insulin demands, unpredictable animal insulin absorption and action, common skin allergic reactions caused much higher glucose variability and more frequent hypoglycemic episodes than nowadays, when human insulin or insulin analogues are used. Moreover, 67% of participants begun their treatment with the use of uncomfortable reusable needles requiring sterilization, when disposable ones were still unavailable. Still, for some of them, the necessity of injecting insulin, even with the use of disposable needle, is frustrating. The inconvenient and unpleasant therapy may be a source of distress, discouragement and fatigue. The presence of chronic complications of diabetes has been associated with fatigue in previous studies (17, 18). In our study there was significant association of fatigue with microangiopathy as general, but no association with retinopathy, neuropathy or chronic kidney disease separately. One explanation may be the fact that participants with complications causing disability, as limb amputation due to diabetic foot, end stage renal disease requiring dialysis or blindness were excluded. Included participants were asymptomatic in relation to chronic microvascular complications. Fatigue is also one of the somatic symptoms connected with depression (19, 20). The necessity for "taking care of diabetes", performing complicated self-management tasks, with no day off, may be a source of emotional burden and fatigue called diabetes-related emotional distress (21). In our study participants getting higher scores in BDI or PAID questionnaire, as well as those afraid of insulin injections, declared fatigue more frequently. Finally, there may be the relationship between some lifestyle habits and fatigue. In our study there was an inverse correlation between reported physical activity and fatigue. Recent studies underline the positive impact of regular physical activity on well-being, mood and quality of life. Physical activity improves muscle mass and strength, enhance metabolic substrate use for energy and increases mood, yet might be perceived as antidepressant (22). This may account for a lower prevalence of fatigue among physically active participants. According to socioeconomic status of subjects included in the study, fatigue was less frequent among employed patients. Unemployed, with probably low income may need additional support in developing and using coping skills to deal with diabetes-related fatigue. Furthermore it may be also important to assess the ways they cope with stress related to socioeconomic situation and often poverty. There were no differences according to having offspring, but to marital status, which confirms previous reports available in literature (23). We found a positive association between neurotic personality and fatigue. For extravertive and agreeable personality, the association was reversed. The explanation may include the description of neuroticism as a degree of proneness to experience negative emotional states and by terms anxiety, depression, impulsiveness and vulnerability to stress. Personality traits have been associated with emotional well-being, health-related quality of life and some psychiatric symptoms. The association between neuroticism and extraversion with subjective well-being has been demonstrated before in patients with a somatic disease and in healthy subjects (24, 25). Therefore fatigue in type 1 diabetic patients may not only be determined by the health condition, but is also shaped by personality traits that are relatively stable throughout an individual's life time (26). In this study we used MFSI-SF, a structured diagnostic

tool for assessment of fatigue, which correlated with fatigue discrimination based on one question. Moreover subjects declaring fatigue due to diabetes gained significantly higher scores in PAID questionnaire. The assessment of fatigue based on one question might thus be a screening tool in patients with long duration of diabetes. Still, the sample size in our study was not large enough to achieve adequate statistical power in analyzing the relationships and this is a limitation.

In summary, patients with long duration time of type 1 diabetes experience fatigue due to chronic stress related to the disease and treatment issues or of other origin, as socioeconomic status and particular personality traits. Fatigue is strongly associated with depressive symptoms and coping with diabetes. That in turn seems to be a hurdle in achieving target metabolic control and successful prevention of chronic complications, although not indicated in our study. Therefore it is important to determine factors influencing the feeling of fatigue to be able to use the best interventions aimed to improving self-management and coping strategies for dealing with fatigue. There have been wide literature on diabetes-related distress and fatigue in type 2 diabetes, still few studies on this subject in patients with long type 1 diabetes duration time. Further research is needed using larger studied group and wider range of questionnaires and laboratory tests to better understand the association between type 1 diabetes and fatigue.

CONCLUSIONS

Fatigue is reported by more than a half of individuals with long duration of type 1 diabetes. It is determined by comorbid depressive symptoms, coping with diabetes, neurotic personality and some socioeconomic factors.

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