

Fatigue is Related to Insulin Use by Acting Via Depressive Mood in Patients with Diabetes Mellitus

Diyabet Hastalarında Gözlenen Yorgunluk, İnsülin Kullanımına Bağlı Oluşan Depresif Duygudurum ile İlişkilidir

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Abstract

Objective: Fatigue is a common symptom in diabetes mellitus. The aim of this study was to determine the factors leading to fatigue and to investigate the effect of insulin use on fatigue among the diabetic population. **Material and Methods:** One-hundred diabetic patients attending the diabetes clinic of Cerrahpaşa Medical Faculty between October 2017-January 2018 and 42 healthy controls were evaluated in this cross-sectional study. Questionnaires including demographic and disease characteristics, Fatigue Impact Scale (FIS), Fatigue Severity Scale (FSS), Beck Depression Inventory (BDI), quality of life scale (SF-36), Epworth Sleepiness Scale (ESS), and Pittsburgh Sleep Quality Index (PSQI) were used. **Results:** Ages (47.6 ± 14.8 and 45.7 ± 14.1 years; $p=0.47$) and body mass indices (26.6 ± 4.1 and 25.3 ± 3.5 kg/m²; $p=0.08$) of 100 patients with diabetes (Type 1 Diabetes/Type 2 Diabetes= 29/71) and 42 healthy volunteers were similar. The diabetic group had worse FIS total ($p=0.05$), FIS psychological ($p=0.04$) scores and SF-36 scores compared to the healthy controls. When the patients with diabetes were divided into two groups according to insulin use and compared with healthy controls, the ESS and PSQI were similar but all FIS parameters (total $p=0.005$, cognitive $p=0.007$, physical $p=0.01$, psychological $p=0.009$) and BDI ($p=0.05$) were significantly worse in patients with insulin use than non-insulin and control groups. The relationship between fatigue and insulin use was independent of glycemic control and duration of diabetes but was affected by the BDI ($p=0.001$). **Conclusion:** Insulin use leads to fatigue in patients with diabetes, regardless of diabetes type, and this effect is influenced by depressive mood. Psychotherapeutic approaches prior to insulin treatment might yield fruitful results.

Keywords: Depression; diabetes mellitus; fatigue; quality of life; sleep

Özet

Amaç: Yorgunluk, diabetes mellitusta sık rastlanan bir semptomdur. Bu çalışmanın amacı diyabetik hastalarda yorgunluğa sebep olabilecek faktörlerin belirlenmesi ve insülin kullanımının yorgunluk üzerine olan etkisinin değerlendirilmesidir. **Gereç ve Yöntemler:** Bu kesitsel çalışmada, Ekim 2017-Ocak 2018 tarihleri arasında İstanbul Üniversitesi Cerrahpaşa-Cerrahpaşa Tıp Fakültesi Diyabet Polikliniğinde takip edilen 100 diyabet hastası ve 42 sağlıklı kontrol değerlendirilmiştir. Hastaların demografik ve hastalık özelliklerinin yanı sıra Yorgunluk Etki Ölçeği (YEÖ), Yorgunluk Şiddet Ölçeği (YŞÖ), Beck Depresyon Envanteri (BDE), hayat kalitesi ölçeği (SF-36), Epworth Uykululuk Ölçeği (EUÖ) ve Pittsburgh Uyku Kalitesi Ölçeği (PUKÖ) anketleri değerlendirilmiştir. **Bulgular:** Çalışmada değerlendirilen 100 diyabetik hastanın (Tip 1/Tip 2: 29/71) ve 42 sağlıklı gönüllünün yaşları ($47,6 \pm 14,8$ ve $45,7 \pm 14,1$ yıl; $p=0,47$) ve beden kitle indeksleri ($26,6 \pm 4,1$ ve $25,3 \pm 3,5$ kg/m²; $p=0,08$) benzerdi. Diyabet grubunda kontrol grubuna göre toplam YEÖ ($p=0,05$), psikolojik YEÖ alt grubu ($p=0,04$) ve SF-36 skorları daha kötü saptandı. Diyabet grubu insülin kullanımına göre 2'ye bölündüğünde, EUÖ ve PUKÖ skorları her 3 grupta benzer iken, tüm YEÖ parametreleri (toplam $p=0,005$; kognitif $p=0,007$, fiziksel $p=0,01$, psikolojik $p=0,009$) ve BDR skoru ($p=0,05$) insülin kullanan grupta, kullanmayanlar ve kontrol grubuna göre daha kötü saptandı. Yorgunluk ve insülin kullanımı ilişkisi, glisemik kontrol ve diyabet süresinden bağımsız, ancak BDE'den etkilenmekteydi ($p=0,001$). **Sonuç:** Diyabetli bireylerde insülin kullanımı yorgunluğa sebep olmakta ve bu etki diyabet tipinden bağımsız olarak depresif durumdaki etkilenmektedir. İnsülin tedavisi başlangıcında psikoterapötik yaklaşımlar uygun olabilir.

Anahtar kelimeler: Depresyon; diabetes mellitus; yorgunluk; hayat kalitesi; uyku

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Introduction

Diabetes mellitus (DM) is a chronic disease, increasing at an alarming rate. It is a serious public health problem all over the world. Apart from the most widely known microvascular and macrovascular complications associated with diabetes, comorbidities such as fatigue, depression, and sleep disturbances affect the quality of life and the compliance to treatments of patients with diabetes (1,2).

Fatigue is a common symptom in the general population that is known to be associated with different etiologies, negatively affecting both physical and mental capacity. It is very often encountered in patients suffering from diabetes and seriously affects the quality of life (3-5). The literature studies concerning patients affected with type 1 (T1D) and 2 (T2D) diabetes mellitus suggest the duration of diabetes mellitus, glycemic control, the frequency and severity of hypoglycemic attacks, depression, sleep problems, microvascular complications, pain, and body mass indices are the major predisposing factors for developing fatigue (2,6,7). Fatigue is also known to impair the compliance of treatment and disturb the glycemic control of patients with diabetes (1,2).

Depression is frequent comorbidity associated with diabetes, as recent studies documented that depression affects up to 25% of patients and the risk of major depression is doubled in patients with T2D (8). Depression hampers the quality of life, diminishes self-care, and impairs the glycemic control of patients with diabetes, leading to enhanced risks of micro- and macrovascular complications (9).

Insulin is one of the cardinal anti-diabetic treatments worldwide, but patients are often reluctant to start and use this medication. Various studies have demonstrated that diabetic patients suffering from comorbid conditions of depression or anxiety disorders avoided insulin therapy more than patients without these comorbidities (10). In addition, a study from France showed that fatigue was more frequently witnessed in T2D patients, especially in the insulin-treated T2D patients as compared to the T1D patients, coupled with significant impairment of the motivation scale (11). To our knowl-

edge, this study from France is unique in literature in terms of evaluation of the insulin-fatigue relationship. However, the factors affecting this association were not estimated in detail.

In light of these findings, we aimed to investigate whether the use of insulin caused fatigue and to determine the factors responsible for developing fatigue in insulin-treated patients. For this purpose, we assessed the frequency of fatigue, sleep disturbances, and depression and the impact of these comorbidities on the quality of life of both T1D and T2D patients. The relationship between these parameters and insulin use were also estimated.

Material and Methods

Subjects and Study Design

One hundred patients with T1D and T2D who attended the Diabetes outpatient clinic of Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty between October 2017 and January 2018 and 42 age and sex-matched healthy volunteers were enrolled in the study. Patients suffering from cancer, end-stage kidney disease, rheumatologic diseases, fibromyalgia, depression, symptoms of snoring or diagnosis of obstructive sleep apnea (OSA), recent acute cardiovascular events, acute and chronic infections, those who were hospitalized in 3-months period prior to the start of the study or who were pregnant, were excluded from the study.

Clinical Assessments

The demographic characteristics of the participants were obtained from the patients themselves and the disease characteristics were evaluated from their medical files. A detailed medical history and physical examination were performed by an endocrinologist and hypoglycemia symptoms in the last month were evaluated and classified as mild, severe, and nocturnal. When the patient was able to treat the symptoms of hypoglycemic episodes unaided, it was considered minor. If patients needed help or medical intervention from others, then it was recorded as major. Any minor or major hypoglycemic episodes that occurred at night during sleeping was documented as

nocturnal hypoglycemia. The Douleur Neuropathique 4 (DN4) questionnaire was used to assess neuropathic pain. The patients were then asked to complete 6 questionnaires under the supervision of a diabetes nurse: the Fatigue Impact Scale (FIS), Fatigue Severity Scale (FSS), Beck Depression Inventory (BDI), 36-Item Short Form (SF-36) quality of life scale, Epworth Sleepiness Scale (ESS), and Pittsburgh Sleep Quality Index (PSQI).

Diabetic neuropathic pain assessment: Douleur neuropathique 4 (DN-4) questionnaire

DN-4 is a ten-item questionnaire prepared by the clinician. It contains seven items to estimate the pain quality and evaluated through self-reports of the patients. The rest three items are assessed in physical examinations made by a physician. Painful neuropathy is signified by a value of ≥ 4 points. It was developed in France and the Turkish validation was reported by Unal-Cevik et al. (12).

Fatigue impact scale (FIS)

The FIS is a multi-dimensional scale that comprises of 40 questions measuring the physical (10 questions), cognitive (10 questions), and social (20 questions) effects of fatigue. Every question is scored between 0-4 and total scoring is between 0-160. The score is proportional to the impact of fatigue. The Turkish validation of FIS was performed by Armutlu et al. (13).

Fatigue severity scale (FSS)

The FSS is a 9-item questionnaire that quantifies the effect of fatigue on functioning. Every question has a score of 1-7 points and the mean of the points is determined as the total score. A score of ≥ 4 points indicates 'severe fatigue.' The first Turkish validation of the FSS was performed by Gencay-Can et al. (14).

Beck depression inventory (BDI)

The BDI is a 21-item, self-reporting scale that identifies the symptoms of depression. Every question has a score of 0-3 points. Depression is reflected by a score of ≥ 17 . The Turkish validation of BDI was conducted by Hisli N. in 1989 (15).

36-item short form (SF-36) quality of life scale

The SF-36 has 36 questions with 8 subscales based on role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, physical functioning, social functioning, general health, and pain. Every subscale has a score of 0-100 and the score is proportional to the quality of life. The Turkish validation of SF-36 was performed by Kocyigit et al. (16).

Epworth sleepiness scale (ESS)

The daytime sleepiness is estimated by a simple and self-reported questionnaire namely ESS. It has 8 questions and a total score of 0-24. A score of ≥ 10 points directs patients to be examined using polysomnographic methods. The Turkish validation of ESS was made by Agargun et al. (17).

Pittsburgh sleep quality index (PSQI)

The PSQI is another self-reported questionnaire that evaluates sleep quality over a period of 1 month. It has 19 items that generate seven subscales: overall sleep quality, sleep disturbances, sleep latency, sleep duration, sleep efficiency, use of sleeping medication, and daytime dysfunction. A high total score indicates poor sleep quality. The Turkish validation of the PSQI was conducted by Agargun et al. (18).

The study was approved by the local ethics committee of Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty in accordance with the 1964 Helsinki Declaration. Written informed consent was obtained from all the participants prior to the study.

Statistical analysis

The data were statistically analyzed by the Statistical Package for the Social Sciences for Windows version 21.0 software package (SPSS, Chicago, IL). The results were expressed as mean \pm standard deviation (SD). In two group comparisons, the independent Student's t-test was used for continuous variables and the Chi-square (χ^2) test was used for categorical variables. One-way analysis of variance (followed by Tukey's post-hoc multiple analyses) together with Bonferroni correction was performed to compare three or four groups. In order to compute the potential effects of age, gly-

cated hemoglobin (HbA1c), and BDI on the fatigue scales, the analysis was performed by using these parameters as covariates. Pearson's and Spearman's correlations were used for parametric and nonparametric values, respectively. Receiver operating characteristic (ROC) curve analyses were used and the cut-off for the FIS was found to be 22.5 points. A stepwise multiple regression analysis was performed to define the predictors of FIS. Statistical significance was established at $p \leq 0.05$.

Results

One hundred patients and 42 age and sex-matched healthy volunteers were enrolled in the study. The demographic characteristics of the study groups are represented in Table 1.

The mean age of the participants with diabetes (female/male: 51/49) was 47.6 ± 14.8 years. The mean duration of diabetes was 12.0 ± 7.8 years. The comorbidities as observed in the present study reflected 14% cases of retinopathy, 16% nephropathy, and 37% neuropathic pain according to the DN-4 criteria. Macrovascular complications comprised of ischemic heart disease in 14% of the patients, cerebrovascular disease in 1%, and peripheral arterial disease in 2% of the diabetic subjects. Hypoglycemic symptoms were manifested in 70 patients, 53 being mild symptoms, 9 severe symptoms, and 8 had nocturnal hypoglycemia. On estimating

the questionnaires according to the complications, higher scores of FIS total ($p < 0.001$) and all FIS subscales ($p < 0.001$ for all), FSS ($p = 0.004$), BDI ($p < 0.001$) were revealed for the patients suffering from painful neuropathy. These patients also exhibited lower scores for physical functioning ($p = 0.001$), social functioning ($p = 0.04$), pain ($p < 0.001$), and general health ($p = 0.04$) subscales of the SF-36. The patients with nephropathy also showed a high FSS score ($p = 0.008$). It is noteworthy that the FIS total (0.004), FIS cognitive ($p = 0.002$), FIS physical ($p = 0.006$), FIS psychosocial ($p = 0.01$), and BDI ($p = 0.02$) scores were elevated in patients suffering from hypoglycemic symptoms. In addition, the patients with BDI scores of >17 had higher FIS (cognitive: $p = 0.001$, physical: $p < 0.001$, psychosocial: $p < 0.001$, total: $p < 0.001$) and FSS ($p = 0.005$) scores than those with BDI of <17 . The scores of the questionnaires depicted a similar outcome for the patients suffering from other diabetic complications. However, no significant correlation between the scales and glycemic control (HbA1c and fasting plasma glucose) was noted.

When the subjects with diabetes were compared with the healthy volunteers, the patients with DM had higher FIS total ($p = 0.05$) and FIS psychological ($p = 0.04$) subscale scores and worse physical functioning ($p = 0.005$), social functioning ($p = 0.02$), pain ($p = 0.01$), and general health ($p = 0.04$) sub-

Table 1. Demographic characteristics of the study group.

	Type 1 DM (n=29)	Type 2 DM with insulin use (n=35)	Type 2 DM without insulin use (n=36)	Healthy controls (n=42)
Age	$32.9 \pm 11.1^{*,\alpha,\beta}$	$53.5 \pm 10.9^{\dagger}$	$53.8 \pm 12.5^{\dagger}$	45.7 ± 14.1
Sex (F/M)	11/18	18/17	22/14	28/14
Educational status				
Primary education	8	19	18	10
Higher education	21	16	18	32
Monthly income (TL)	$2865 \pm 1519^{\dagger}$	$2938 \pm 1881^{\dagger}$	$2556 \pm 1142^{\dagger}$	4342 ± 2507
Exercise				
No exercise	7	12	11	11
Intermittent	11	14	10	15
Regular	11	9	15	16
BMI (kg/m ²)	$23.4 \pm 3.3^{*,\alpha}$	$28.3 \pm 4.0^{\dagger}$	$27.8 \pm 3.2^{\dagger}$	25.3 ± 3.5
HbA1c (%)	8.7 ± 1.2	8.2 ± 2.1	$7.0 \pm 1.1^{*,\gamma}$	ND

* $p < 0.001$ vs. Type 2 DM with insulin use; $^{\alpha}p < 0.001$ vs. Type 2 DM without insulin use; $^{\beta}p < 0.001$ vs. healthy controls; $^{\dagger}p < 0.05$ vs. healthy controls; $^{\gamma}p < 0.05$ vs. healthy controls; $^{\eta}p < 0.001$ vs. Type 1 DM.

scale scores of the SF-36 index. However, the FSS, BDI, ESS, and PSQ indices were statistically similar between the two groups. On classifying the diabetic patients based on the diabetes type and insulin usage, FIS total ($p=0.03$) and FIS cognitive ($p=0.01$) subscales were significantly lower and pain subscale ($p=0.01$) of SF-36 index were higher in T2D patients without insulin use than in those with T1D and T2D with insulin therapy.

When the patients with diabetes were divided into two groups based on the use of insulin, viz., patients with insulin therapy and patients without insulin therapy, and compared with the healthy volunteers, FIS total ($p=0.005$) and all FIS subscales (cognitive: $p=0.007$; physical: $p=0.01$; psychological: $p=0.009$) and BDI ($p=0.05$) scores were higher and physical functioning ($p=0.008$), social functioning ($p=0.01$), and pain ($p=0.001$) subscales of SF-36 were lower in the group comprising of diabetic patients under insulin therapy (Table 2). Similar results were obtained after controlling for the HbA1c and age of the participants.

The parameters related to FIS were examined using correlation analysis, both in the entire diabetic population and in each diabetes type. FIS scores were positively associated with FSS ($r=0.45$; $p<0.001$), total PSQI ($r=0.32$; $p=0.001$), and BDI scores in

patients with diabetes ($r=0.74$, $p<0.001$) (Figure 1a-c). Linear regression analyses depicted a one-unit increase in BDI led to a two-and-a-half-point increase in FIS total score ($F=12.2$; $\text{Beta}=0.74$; $p<0.001$). ROC curve analysis for FIS was performed with 60% sensitivity and 60% specificity and a cut-off value of 22.5 was found. The parameters considered for the multivariate logistic regression model included age, sex, BMI, BDI score, PSQI, duration of diabetes, presence of hypoglycemia, insulin use, and fasting plasma glucose. Insulin use ($p=0.01$) and BDI scores ($p=0.001$) were shown to significantly influence the FIS score. Moreover, the exemption of the BDI parameter from the model was found to withdraw the effect of insulin use on fatigue (Table 3).

Discussion

In our study, we demonstrated that fatigue was more prevalent among the diabetic population as compared to the healthy volunteers and the impact of fatigue affected their quality of life. Interestingly, as far as fatigue severity and sleep disturbances were concerned, a significant difference was absent between the two groups. Patients with diabetes with frequent hypoglycemic attacks were more prone to be affected by fatigue but hypoglycemia itself failed to explain the relationship between fatigue and insulin use.

Table 2. The comparison of the fatigue, sleep quality, depression, and SF-36 scales of the patients with diabetes according to the usage of insulin with healthy volunteers.

	Patients with diabetes with insulin use (n=64)	Patients with diabetes without insulin use (n=36)	Healthy volunteers (n=42)	p
Fatigue impact scale	45.2±34.3	28.5±22.9	28.1±30.0	0.005
Fatigue severity scale	3.9±1.7	3.6±1.7	3.7±1.5	0.73
Beck depression inventory	13.9±9.8	9.9±7.9	10.1±9.4	0.05
SF-36				
Physical functioning	66.9±21.3	72.7±21.1	80.1±20.7	0.008
Role limitations due to physical health	61.7±28.5	72.2±27.8	71.4±32.9	0.13
Role limitations due to emotional problems	58.5±24.3	67.5±23.2	61±30.2	0.25
Energy/fatigue	54±20.9	57.6±19.8	57±21.2	0.63
Emotional well-being	64.2±15.9	69.7±16.7	70.1±14.2	0.09
Social functioning	63.2±22.4	71.6±17.1	75.1±22.5	0.01
Pain	61.6±21.6	75±21.6	77.2±24.1	0.001
General health	54.1±24.8	57.9±21.3	63.8±18	0.09
Epworth Sleepiness Scale	5±3.6	4.9±3.8	4.8±3.3	0.96
Pittsburgh Sleep Quality Index	7±3.9	6.5±3.4	6.6±5	0.79

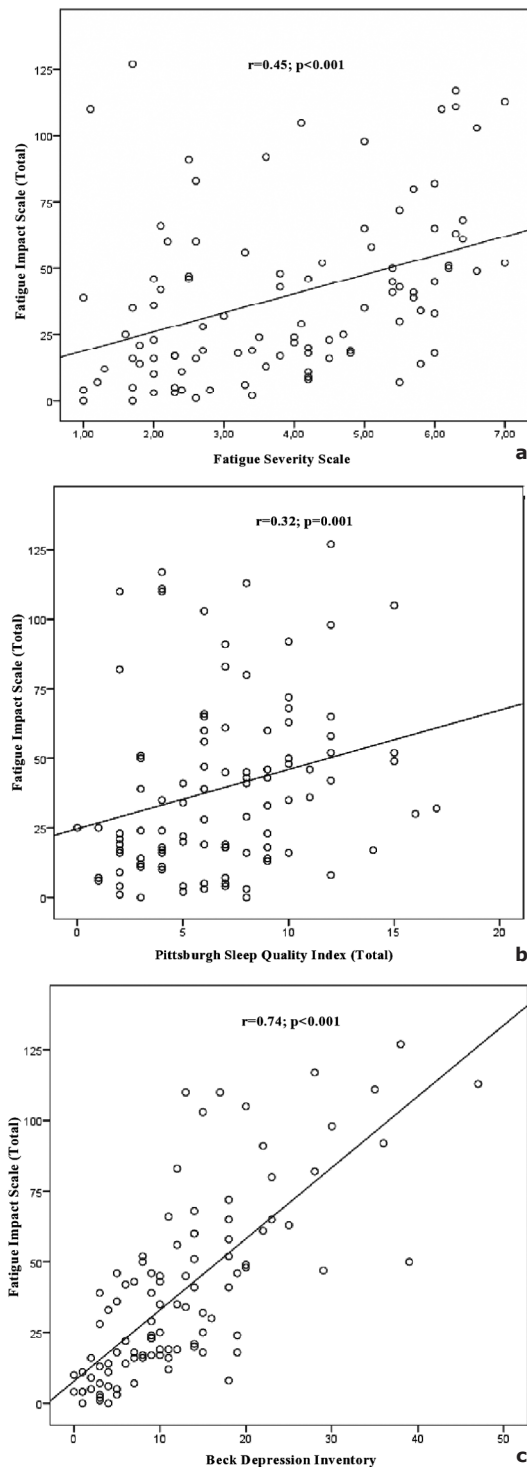


Figure 1: The correlation plot of the Fatigue Impact Scale with; Fatigue Severity Scale (a), Pittsburgh Sleep Quality Index (Total) (b), and the Beck Depression Inventory (c) in patients with diabetes mellitus.

The impact of fatigue was not related to diabetes type, glycemic control or disease duration, but it was more prominently

observed in diabetic patients treated with insulin. The most impressive finding of this study was the significant correlation between the impact of fatigue with insulin use and depression, which has not been demonstrated previously. The difference in the fatigue impact scale, which shows the fatigue perception of the patient rather than the FSS, which reflects objective fatigue parameters, was important evidence with regards to the influence of the psychological factors. Fatigue is a common clinical finding among patients suffering from T1D and T2D (2,4,5). Various studies published in the literature have dealt with the causes of fatigue. Age, disease duration, BMI, glycemic control, acute and chronic complications, depression, and sleeping problems were the most common predisposing factors associated with acute and chronic fatigue (1,4-6,19). However, there are different schools of thought regarding the association between glycemic control and fatigue. Few studies revealed no relationship between glycemic control and fatigue (4,5). In our study, we demonstrated that fatigue was associated with hypoglycemia, painful neuropathy and nephropathy, quality of sleep, and depression, but we observed no significant relationship between the other parameters listed above.

Hypoglycemia is one of the most frequently seen complications among diabetic populations, particularly, those associated with insulin treatment. Fatigue is one of the most frequent findings following hypoglycemic episodes and it impairs the quality of life (20). In our study, we reported that 70% of patients with diabetes had hypoglycemia and we also demonstrated that patients with hypoglycemia had higher FIS and BDI scores in all subscales. However, we failed to establish any effects of hypoglycemia on the SF-36 quality of life index.

Painful neuropathy is one of the most common and debilitating complications of diabetes mellitus, seriously distressing the quality of life (21,22). Nocturnal pain in patients suffering from painful neuropathy is a major cause of sleep disturbances (23). Moreover, it has been shown that painful diabetic neuropathy enhances levels of anxiety and depression and is responsible for pain-induced disability (24). In line with the

Table 3. Stepwise logistic regression analysis of parameters affecting Fatigue Impact Scale.

	B	S.E.	Wald	p
Sex	-0.303	0.709	0.183	0.669
BMI	-0.121	0.090	1.820	0.177
BDI	0.254	0.075	11.391	0.001
PSQI	0.191	0.117	2.633	0.105
Age	0.043	0.03	2.063	0.151
Duration of diabetes	-0.057	0.05	1.263	0.261
Fasting plasma glucose	-0.002	0.006	0.077	0.782
Insulin use	-2.017	0.86	5.506	0.019
Hypoglycemia	-0.141	0.700	0.04	0.840

BDI: Beck depression inventory; BMI: Body mass index; PSQI: Pittsburgh sleep quality index.

published reports, our study also documented that 34% of patients had painful neuropathy and it was related to fatigue, depressive symptoms, and compromised quality of life. Importantly, we used a validated tool (DN-4) for diagnosing painful neuropathy in order to prevent bias due to the self-reporting of the patient. However, no relationship between sleep problems and neuropathy could be detected in the present study.

Published articles in the literature showed that the prevalence of minor and major depression was augmented in individuals with diabetes mellitus (7). Younger age, female sex, low income, poor glycemic control, and comorbidities and complications were factors associated with depression in diabetes mellitus (25,26). Interestingly, some studies in the literature demonstrated that insulin treatment might be associated with depression (27). Similar symptoms of depression between diabetic patients and healthy controls were recorded in our study. However, in the diabetes group, BDIs were found to be worse in patients with painful neuropathy and with hypoglycemia.

It is known that there is a negative appraisal regarding insulin treatment in patients with diabetes, the so-called 'psychological insulin resistance' (28,29). Makine et al. demonstrated that higher levels of depression and diabetes distress were associated with more negative beliefs about insulin in insulin-naïve patients with T2D (10). Iversen et al also showed that patients suffering from anxiety and depression were less likely to

start insulin therapy (30). On the other hand, Lasselín et al. employed 21 T1D patients and 24 T2D patients and found that fatigue was more pronounced in the insulin-treated patients with T2D than in patients with T1D (11). In line with the literature, our study focused on the causes of fatigue and found that the positive correlation between insulin treatment and fatigue was mostly related to depressive symptoms.

Limitations

Our study has some limitations. The first is the cross-sectional design of the study. The cause-effect relationship could be more clearly identified if it was prospectively designed. A small sample size of the control group is another limitation of the present study. This limitation may reduce the statistical power of the study. Nevertheless, to our knowledge, this is the largest-scaled study in the literature to evaluate the relation between fatigue and insulin use.

Conclusion

The present study revealed that the use of insulin therapy in diabetic patients was associated with fatigue, regardless of the diabetes type and this effect was mostly related to depression. A significant difference in the FIS parameters, rather than FSS, proved the effect of psychological factors. The quality of life of diabetic patients was severely compromised as a result of fatigue. Before initiating insulin therapy in these patients, psychotherapeutic approaches may be an important intervention that may improve the compliance of the treatment and also the quality of life.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Özlem Haliloğlu, Zeynep Oşar Siva; Design: Özlem Haliloğlu, Mesude Tütüncü, Zeynep Oşar Siva; Control/Supervision: Özlem Haliloğlu, Serdar Şahin, Özge Polat Korkmaz, Melis Dila Özer, Zeynep Oşar Siva; Data Collection and/or Processing: Özlem Haliloğlu, Mesude Tütüncü, Serdar Şahin, Zeynep Oşar Siva; Analysis and/or Interpretation: Özlem Haliloğlu, Mesude Tütüncü, Serdar Şahin, Zeynep Oşar Siva; Literature Review: Özlem Haliloğlu, Serdar Şahin, Özge Polat Korkmaz, Melis Dila Özer, Zeynep Oşar Siva; Writing the Article: Özlem Haliloğlu, Mesude Tütüncü, Zeynep Oşar Siva; Critical Review: Zeynep Oşar Siva; References and Fundings: Özlem Haliloğlu, Zeynep Oşar Siva; Materials: Özlem Haliloğlu, Özge Polat Korkmaz, Melis Dila Özer.

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