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RESEARCH

Investigation of fatigue, mental well-being and tachycardia in short- and long-term metformin use

Kısa ve uzun süreli metformin kullanımında yorgunluk, ruhsal iyilik hali ve taşikardinin incelenmesi

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Abstract

Purpose: The current study aimed compare short and long-term metformin users according to socio-demographic characteristics and to examine the relationships between fatigue, tachycardia and psychological well-being.

Materials and Methods: In cross-sectional study were reached 92 patients, 46 short-term and 46 long-term metformin users. It was measured fatigue with the Functional Assessment of Chronic Illness Treatment-Fatigue Scale (FACIT-F), tachycardia with saturation device, well-being with the World Health Organization Well-Being Index (WHO-5).

Results: For the group using short-term metformin, the mean; year of metformin use was 1.82±0.77 and pulse rate was 82.48±8.80, FACIT-F score was 20.37±7.25, and WHO-5 score was 15.70±3.23. The group using long-term metformin mean year of metformin use was 5.93±2.68, pulse rate was 84.57±9.64, FACIT-F score was 25.33±5.65 and WHO-5 score was 12.63±3.70. Well-being is negatively correlated with the year of diabetes, year of metformin use, pulse rate and fatigue. FACIT-F, metformin year and pulse rate explain a total of 41.9% of the variance in well-being. FACIT-F (β=-.51, t=-5.82, p= .000) and the year of metformin use (β=-.19, t=-2.12, p= .037) significantly decrease well-being, while pulse rate does not have a significant effect on well-being.

Conclusions: Long-term use of metformin has been found cause fatigue and negative psychological well-being. Fatigue, year of metformin use and pulse rate number are important predictors of psychological well-being in Type II diabetes patients using metformin.

Keywords:. Metformin, mental well-being, fatigue, tachycardia

Öz

Amaç: Çalışmada kısa ve uzun süreli metformin kullanıcılarının bazı sosyo-demografik özelliklerine göre karşılaştırılması ve yorgunluk, taşikardi ve ruhsal iyilik hali arasındaki ilişkilerin incelenmesi amaçlandı.

Gereç ve Yöntem: Kesitsel tarama tasarımlı çalışmada, 46'sı kısa süreli, 46'sı uzun süreli metformin kullanıcısı olmak üzere 92 hastaya ulaşıldı. Yorgunluk, Kronik Hastalık Tedavi-Yorgunluk Fonksiyonel Değerlendirmesi Ölçeği (FACIT-F), taşikardi saturasyon cihazı, iyilik hali Dünya Sağlık Örgütü İyilik Hali İndeksi (WHO-5) ile ölçüldü.

Bulgular: Kısa süreli metformin kullanan grupta ortalamalar; metformin kullanım yılı 1,82±0,77, nabız 82,48±8,80, FACIT-F skoru 20,37±7,25, WHO-5 skoru 15,70±3,23 olarak bulundu. Uzun süreli metformin kullanan grupta ortalamalar; metformin kullanım yılı 5,93±2,68, nabız 84,57±9,64, FACIT-F skoru 25,33±5,65, WHO-5 skoru 12,63±3,70 olarak bulundu. İyilik hali diyabet yılı, metformin kullanım yılı, nabız hızı ve yorgunlukla negatif korelasyon göstermektedir. FACIT-F, metformin yılı ve nabız hızı iyilik halinin toplam %41,9'unu açıklıyor. FACIT-F'nin (β=-.51, t=-5.82, p= .000) ve metformin kullanım yılının (β=-.19, t=-2.12, p= .037) iyilik halini önemli ölçüde azalttığı, nabız hızının ise iyilik halinde önemli bir etkiye sahip olmadığı görüldü.

Sonuç: Metforminin uzun süreli kullanımının yorgunluğa ve olumsuz psikolojik iyilik haline neden olduğu bulunmuştur. Yorgunluk, metformin kullanım yılı ve nabız sayısı metformin kullanan Tip II diyabet hastalarında ruhsal iyi oluşun önemli belirleyicileridir.

Anahtar kelimeler: Metformin, ruhsal iyi oluş, yorgunluk, taşikardi.

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INTRODUCTION

The biguanide agent metformin, is the first-stair drug used in the treatment of Type II diabetes which is reported to reduce by 30% mortality and diabetes complications[1]. Metformin used the most commonly oral hypoglycemic agent, reduces glucose levels without increasing insulin secretion. It shows this effect either by strengthening the cells' response to insulin or by suppressing the liver's glucose synthesis[2]. In addition, it contributes positively to plasma lipid concentration and weight loss. Considering frequency of use of metformin, which is preferred because it is cheap, effective and doesn't have many side effects, it reported that 150 million diabetic patients worldwide use it[3]. When examining the side effects, the most common are; diarrhea, nausea, loss of appetite, gas and metallic taste in the mouth. Another reported side effect is decreased absorption of vitamin B12 (cobalamin)[4]. After Tomkin et al[5]. reported a relationship between metformin using and B12 absorption, studies on this subject gained momentum[6-9].

B12 is a water-soluble vitamin with important roles in maintaining hematopoiesis and central nervous system health, DNA synthesis, amino acid and fat metabolism[10]. Deficiency may go unnoticed for a long time due to the high storage of vitamin B12 by the liver. Vitamin B12 deficiency occurs in cases of inadequate intake, malabsorption and increased demand. For this reason, it recommended that adults take 2.4 micrograms (μg) of vitamin B12 daily[11]. Although the process of impairment of vitamin B12 absorption in metformin use hasn't been fully clarified, it has been claimed that metformin antagonizes the calcium cation and inhibits the binding changes in bile acid metabolism or decreases its absorption of calcium-dependent intrinsic factor (IF) with B12 complex[12]. Decreased absorption of vitamin B12 begins after 3 months metformin use[13]. Clinically, deficiency occurs after 4 years but rarely causes megaloblastic anemia[6,14]. Vitamin B12 deficiency can lead to megaloblastic anemia, as it causes changes in the shape of red blood cells and delays in their maturation[8,9]. Symptoms of long-term B12 deficiency such as pernicious anemia, peripheral neuropathy, weakness, fatigue and memory loss may also occur. Symptoms weakness and fatigue may precede anemia[15,16]. It is known that anemia causes tachycardia[17]. Also, declines in cognitive functioning have been reported to be associated with some depressive symptoms[18,19]. If vitamin B12 deficiency isn't diagnosed and treated, serious adverse effects such as anemia and neuropathy may occur for Type II diabetes patients[20]. Considering the low consumption of animal products other than milk and meat in Turkey[21] lack of access to animal foods containing vitamin B12 is associated with a higher risk of vitamin B12 deficiency[22].

When the literature is examined; although there are many studies in which meformin use causes B12 deficiency[6-9] it has not been investigated what complaints such as fatigue and psychological well-being due to vitamin B12 deficiency in diabetic patients. Considering the inadequacy of individual-centered care and psychological support in diabetic patients, it is important to examine their psychological well-being and fatigue. In this context, this study aimed to evaluate the fatigue, psychological well-being and pulse rate measurements of Type II diabetic patients using metformin for long time. Hypotheses of the study are as type II diabetes patients using long and short-term metformin follows; there is a difference between their psychological well-being, fatigue levels and pulse rates; there is a relationship between psychological well-being and disease and socio-demographic characteristics; some characteristics have an effect on psychological well-being.

The study aims to examine some socio-demographic characteristics, fatigue and psychological well-being of Type II diabetic patients on short and long-term metformin by comparing them. Another aim is to determine the factors that may be related to psychological well-being. The determined objectives, the study planned as a cross-sectional survey research. Cross-sectional studies are used to make measurements of the variables examined in a certain period of time and to examine the relationship of these measurements with various factors[23].

MATERIALS AND METHODS

Study design

The data of the study collected from patients who applied to the internal medicine outpatient clinic and were hospitalised in the internal clinics of Bayburt State Hospital between 08.00-17.00 hours on weekdays between April-November 2024 after obtaining ethics committee and institutional permission. The institution, which provides services

in accordance with the Inpatient Treatment Institutions Operating Regulations, regularly records and stores patient files. The manuscript was written according to the STROBE guidelines.

Sample

The population of the study consisted of patients admitted to and hospitalized in the internal medicine outpatient clinic of Bayburt State Hospital. The sample size to be used in the study was calculated prior to the study using the G Power 3.1 power analysis programme. As there were no similar studies in the literature, the error rate was 0.05 when comparing the two unequal group means (26.80 and 25.40) of the FACIT-F scale[27]. It was determined that the effect size should be 0.744 for 95% power. Following this analysis, it was determined that the minimum number of participants in each group should be 40. The sample size was increased by 20% (six people) because the standard error would decrease and the study power would increase if the sample size was increased. A total of 92 people were included in the study, 46 people for each group. A total of 215 patients were contacted until a total of 92 people were reached. Patients who did not agree to participate in the study (n=87) and did not meet the inclusion criteria (n=36) were excluded from the study. The distribution of patients who met the inclusion criteria was determined according to the year of metformin use. Patients in the long-term metformin users group were composed of patients who had been using metformin for 4 years or more[6,14] while patients in the short-term metformin users group were composed of patients who had been using metformin for less than 4 years. Patients who did not meet the specified criteria were identified and excluded from the study.

Inclusion criteria were being at least 18 years old, type II diabetes and metformin use for at least 3 months[13], coming for examination in internal outpatient clinics or hospitalization in internal medicine clinics at Bayburt State Hospital. Exclusion criteria were **h**aving received insulin treatment in the last 6 months[24], pernicious anemia[6], chronic consumer of alcohol, serious medical illnesses[6], vitamin B12 or any multivitamin preparation had taken during the last 6 weeks were excluded from the study.

Measures

Data were collected using the Patient Information Form and Functional Assessment of Chronic Illness Treatment-Fatigue Scale (FACIT-F) scale and the WHO Well-being Index (WHO-5).

Patient Information Form

This form includes 16 questions in total (gender, age, height, weight, marital status, working status, education status, place of living, smoking, alcohol using, years of Type II diabetes, year of metformin use, daily metformin doses, acetylsalic acid use, another chronic diseases, pulse rate)[25].

Functional Assessment of Chronic Illness Treatment-Fatigue Scale (FACIT-F)

Cronbach's alpha coefficient of the scale developed by Cella et al[26]. was found to be .95. The adaptation study into the Turkish language was conducted by Yava and Çınar (2018) in 133 Type II diabetes patients. Cronbach's alpha coefficient was reported as .98. The scale used to evaluate the fatigue of chronic patients includes the evaluation of the statements in the last 7 days. The answers given in the scale consisting of 13 questions are scored between 0-4. Items other than items 7 and 8 of the scale are reverse-scored. A decrease in the total score ranging between 0-52 indicates an increase in fatigue[27]. In the present study, since it aimed to measure fatigue, items 7 and 8 were reverse scored and aimed to determine fatigue with increasing total score. In the current sample, the internal consistency coefficient was calculated as .758.

WHO Well-Being Index (WHO-5)

Developed by the World Health Organization (1998), this tool measures participants' psychological well-being and mood. The tool, adapted into Turkish by Eser et al[28]. has a total score range of 0-25 points. An increase in the total score indicates an improvement in positive psychological well-being, quality of life, and positive mood. For a more understandable calculation, the total scores can be multiplied by 4 to obtain a score out of 100. In the adaptation study, the Cronbach alpha value of the scale was reported as .83, while the internal consistency coefficient calculated in the current study was .885.

Procedure

Approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Bayburt University (Decision Date: 23.02.2024, Decision No: 29/2) and the Provincial Health Directorate of Bayburt (Decision Date: 05.04.2024, Decision No: 198143) before starting the study.The study, for

which ethical and institutional permissions were completed between February and April 2024, collected data between April and November 2014. Data collectied by reaching out to patients who agreed to participate in the study and met the inclusion criteria. At this stage, 123 patients who needed to be excluded were also interviewed. Participants who met the inclusion criteria for the study were informed by the Declaration of Helsinki, and their written consent was obtained by signing the informed consent form and verbal consent. Data were collected face-to-face by a nurse researcher with expertise in internal medicine. The researcher and pulse rates then completed the patient information form were measured. The FACIT-F and WHO-5 scales were then completed face-to-face. These procedures took about 20 minutes per patient. The researcher measured the pulse rate to measure tachycardia, which could be caused by anaemia. Pulse rates were measured by the researcher using a saturation device. Informed consent was obtained from all participants and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

Statistical analysis

The data were analyzed using the Statistical Package for Social Science (SPSS) 27 program. Before analyzing the data, the distribution of the data was examined. The normality of the data was assessed using skewness-kurtosis test. In the present study, the skewness and kurtosis coefficients were within the limits of +2 and -2 (between -1.441 and 0.498) and acceptable for all variables[29]. The presence of outliers was checked by observing whether any responses were above the z-score ±3.29. It is concluded that there are no extreme values in the data set. Q-Q plots, box plots, and histograms were also examined. When the assumptions for parametric tests were met, the Independent Samples t-test and the Chi-square test were used to compare the means between groups. Descriptive statistics were reported using mean, standard deviation, minimum-maximum, frequency, and percentage. To examine relationships, Pearson correlation was used for normally distributed ratio variables, Spearman correlation for ordinal variables, and ETA correlation for nominal variables. Hierarchical regression analysis was used to examine multivariable causal relationships. The regression analysis, certain assumptions had to be met. These included that the variables were continuous, that there were significant relationships between them, that the Durbin-Watson coefficient was close to 2 to eliminate autocorrelation, that there were no outliers in the data set, and that the absence of multicollinearity was confirmed by observing that the tolerance and variance inflation factors (VIF) were close to 1 and that the calculated standardized residuals (ZRE) did not exceed (3). In testing these assumptions, it was observed that the variables included in the regression analysis were continuous and that well-being was related to fatigue, year of metformin use, year of diabetes, and pulse rate. In addition, the Durbin-Watson statistic calculated as 1.942 suggests that there is no autocorrelation problem in the data set, and the standardized residuals ranging from (1.93-2.48) suggest that there are no outliers. Due to collinearity between year of diabetes and year of metformin use (tolerance: .10, VIF: 9.60), year of diabetes was excluded from the analysis. Since the tolerance and VIF values of the predictors are close to 1, it can be said that there was no multicollinearity problem among the predictors.

RESULTS

Among the participants who used short-term metformin; 71.1% were female, 80.4% were married, 56.5% were not working, 45.7% were high school graduates, 60.9% lived in the city center, 69.6% did not smoking, 93.5% did not drink alcohol, 63.0% used two doses of metformin daily, 87.0% did not use acetylsalicylic acid, and 82.6% did not have any additional chronic disease. Among the participants using long-term metformin, 65.2% were female, 78.3% were married, 50.0% were not working, 50% had completed primary school, 56.5% lived in the city center, 76.1% did not smoking, 95.7% did not drink alcohol, 69.6% used two doses of metformin daily, 82.6% did not use acetylsalicylic acid, and 65.2% did not have an additional chronic disease. No significant difference ($p>0.05$) was found between the short-term and long-term metformin use groups (Table 1).

Fatigue and psychological well-being were measured using appropriate questionnaires, and these characteristics were compared between short-term and long-term metformin users, with the results presented in Table 2. The mean age of the short-term metformin group was 55.78±11.00 (min=28, max=78), years of diabetes mellitus 2.37±0.68 (min=1, max=3), years of metformin use 1.82±0.77 (min=1, max=3), body mass index 30.35±5.53 (18.43-45.17), and pulse rate 82.48±8.80 (min=64, max=102).

Table 1. Descriptive characteristics of participants (N=92)

Variable		Short-term metformin use (n=46)	Long-term metformin use (n=46)		
		n (%)	n (%)	χ^2	p
Gender	Female	33 (71.7)	30 (65.2)	.45	.501
	Male	13 (28.3)	16 (34.8)		
Marital status	Single (Divorced/Widow)	9 (19.6)	10 (21.8)	.07	.797
	Married	37 (80.4)	36 (78.3)		
Working status	Working	20 (43.5)	23 (50)	.39	.531
	Not working	26 (56.5)	23 (50)		
Education status	Literate/illiterate.	9 (19.6)	8 (17.5)	1.04	.791
	Primary school	21 (45.7)	23 (50.0)		
	Middle school	13 (28.3)	10 (21.7)		
	High school and above	3 (6.5)	5 (10.9)		
Place of living	Rural	18 (39.1)	20 (43.5)	.18	.672
	City	28 (60.9)	26 (56.5)		
Smoking	Yes	14 (30.4)	11 (23.9)	.49	.482
	No	32 (69.6)	35 (76.1)		
Alcohol using	Yes	3 (6.5)	2 (4.3)	.21	.646
	No	43 (93.5)	44 (95.7)		
Metformin doses (daily)	1	10 (21.7)	9 (19.6)	.53	.766
	2	29 (63.0)	32 (69.6)		
	3	7 (15.2)	5 (10.9)		
Use of acetylsalicylic	Yes	6 (13.0)	8 (17.4)	.34	.562
	No	40 (87.0)	38 (82.6)		
Another chronic disease	Yes	8 (17.4)	16 (34.8)	3.06	.058
	No	38 (82.6)	30 (65.2)		

n:number, %:percentage, χ 2 : Chi-square test.

The mean FACIT-F score was 20.37±7.25 (min=9, max=24) and the mean WHO-5 score was 15.70±3.23 (9-25). The mean age of the long-term metformin users was 54.85±12.15 years (min=26, max=77), years of diabetes mellitus 7.20±2.93 (min=1, max=17), years of metformin use 5.93±2.68 (min=1, max=13), body mass index 30.45±5.26 (21.94-48.15), and pulse rate 84.57±9.64 (min=64, max=104). The mean FACIT-F score was 25.33±5.65 (min=8, max=22) and the mean WHO-5 score was 12.63±3.70 (min=4, max=22). Age, body mass index, and pulse rate were not significantly different between short-term and long-term metformin users (p>0.05) (Table 2).When considering long-term metformin users, it is expected that the year of diabetes and metformin use would be higher in this group. However, compared to short-term users, FACIT-F mean values are higher, whereas WHO-5 mean values are lower.

Table 3, based on the second research question, shows the correlation results of ratio variables that could be related to patients' psychological well-being. Well-being is negatively correlated with year of diabetes, year of metformin use, pulse rate, and fatigue. According to the results of the ETA statistic on the relationship with categorical variables, the following coefficients were obtained: gender (.148), marital status (.192), employment status (.110), education level (.315), place of residence (.099), smoking (.071), alcohol use (.092), acetylsalicylic acid use (.026), and the presence of another chronic disease (.119).

Because fatigue,[15,16] metformin use,[18,19] year of diabetes,[30] and pulse rate[31] may negatively affect well-being, they were included in the hierarchical regression analysis (Table 3). Gender and age, which are known to influence well-being,[32] were controlled for

Table 2. Comparison of groups using short- and long-term metformin (N=92)

Variable	Short-term metformin use (n=46)	Long-term metformin use (n=46)	t	p
	X̄±SD (Min-Max)	X̄±SD (Min-Max)		
Age (years)	55.78±11.00 (28-78)	54.85±12.15 (26-77)	.39	.700
Diabetes year	2.37±.68 (1-3)	7.20±2.93 (1-17)	-10.90	.000*
Metformin years	1.82±.77 (1-3)	5.93±2.68 (1-13)	-10.00	.000*
Body mass index	30.45±5.26 (21.94-48.15)	30.35±5.53 (18.43-45.17)	.09	.930
Pulse rate	82.48±8.80 (64-102)	84.57±9.64 (64-104)	-1.08	.281
FACIT-F	20.37 ±7.25 (9-24)	25.33±5.65 (8-22)	-3.37	.000*
WHO-5	15.70±3.23 (9-25)	12.63± 3.70 (4-22)	4.23	.000*

*p<.001, X̄±SD: Arithmetic average-standard deviation, min: minimum, max: maximum. t: Independent samples t testi, FACIT-F: The Functional Assessment of Chronic Illness Treatment-Fatigue Scale, WHO-5: WHO Well-Being Index

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Table 3. Correlation results regarding relationships with WHO-5 (N=92)

		Min	Max	X̄	SD	Skewness	Kurtosis	1	2	3	4	5	6	7	8
1	Age	26.00	78.00	55.32	11.54	-0.28	-0.40	1.00							
2	Diabetes year	1.00	13.00	4.78	3.22	1.05	0.17	.043	1.00						
3	Body mass index	18.43	48.15	30.40	5.37	.730	1.00	.072	.028	1.00					
4	Metformin year	1.00	13.00	3.88	2.85	1.25	1.21	.121	.940**	.031	1.00				
5	Metformin doses	1.00	3.00	1.92	0.58	-	-	.114	.015	.048	.034	1.00			
6	Pulse rate	64.00	104.00	83.52	9.24	-0.25	-0.37	.220*	.189	.143	.170	-.025	1.00		
7	FACIT-F	12.00	40.00	22.85	6.93	0.31	-0.78	-.091	.361**	.060	.312**	-.135	.072	1.00	
8	WHO-5	8.00	24.00	14.16	3.78	0.39	-0.64	-.042	-.365**	-.029	-.375**	.071	-.207*	-.584**	1.00

*p<.05, **p<.01, X̄±SD:arithmetic average-standard deviation, FACIT-F: The Functional Assessment of Chronic Illness Treatment-Fatigue Scale, WHO-5: WHO Well-Being Index, min: minimum, max: maximum

Table 4. Hierarchical regression findings (N=92)

Variables	B.	BSE	β	t	p	95% CI		Collinearity	
						Low	up	Tolr .	VIF
Step 1									
Gender	-1.17	.86	-.14	-1.36	.177	-2.88	.54	.97	1.03
Age	-.01	.03	-.02	-.16	.871	-.07	.06	.97	1.03
Step 2									
Gender	-1.09	.68	-.13	-1.60	.113	-2.45	.26	.95	1.05
Age	.00	.03	-.01	-.12	.909	-.06	0.05	.89	1.13
FACIT-F	-.28	.05	-.51	-5.82	.000	-.37	-.18	.88	1.14
Metformin year	-.25	.12	-.19	-2.12	.037	-.48	-.02	.87	1.15
Pulse rate	-.06	.04	-.15	-1.72	.089	-.13	.01	.91	1.10

B: Unstandardized coefficients , BSE: Standard error, Beta (ß): Standardized coefficient, t: value, 95% CI: Confidence ınterval , Collinearity: collinearity statistic, VIF: Variance inflation factor, Tolr.: Tolerance, FACIT-F: The Functional Assessment of Chronic Illness Therapy Scale, WHO-5: WHO Well-Being Index, R^2: Determination coefficient

Step 1: $R^2 = .022$, $F_{(2\text{-}89)} = .1.00$, $p = .371$; Step 2: $R^2 = .419$, $F_{(3\text{-}86)} = 19.59$. $p<.001$, $\Delta R^2 = .397$

Based on the third research question, Step 1 in Table 4, which controls for variables, explains 2.2% of the variance in well-being, but the model is insignificant. Step 2, which includes FACIT-F, metformin age, and

pulse rate in addition to the controlled gender and age, explains 41.9% of the variance in well-being, with 39.7% explained by the predictors alone. The model shows that FACIT-F (β=-.51, t=-5.82, p= .000) and age of metformin use (β=-.19, t=-2.12, p= .037) significantly decrease well-being, while pulse rate has no significant effect on well-being.

DISCUSSION

Metformin has significant protective and beneficial effects as well as side effects. Patients receiving long-term metformin treatment have been reported to be at risk for anemia. It inhibits B12 absorption by disrupting calcium-dependent membrane function in the terminal ileum[33]. When comparing those who used metformin for 3 years or more with those who used metformin for less than 3 years, the risk of vitamin B12 deficiency was reported to increase with dose and year of metformin use[34]. In this study, it was concluded that long-term use of metformin in patients with type II diabetes caused fatigue and negative psychological well-being. Fatigue is a common condition in diabetes due to increased or decreased glucose levels[35]. In addition, vitamin B12 deficiency can also cause symptoms of fatigue and tiredness[10]. As a result of the study conducted by Polat and Ayaz[4] 2019 to determine vitamin B12 deficiency in type II diabetics using metformin, they concluded that vitamin B12 deficiency was higher in patients using 2,000 mg/day metformin compared to patients using 1,000 mg/dL metformin. Diabetes, a chronic disease, is recognized as one of the most challenging diseases. In this case, it is expressed in negative psychological well-being[36]. Vitamin B12 deficiency has been associated with negative mood[37]. A similar study was not found in the literature, and it is thought that patients who use metformin for a long time have higher fatigue and negative psychological well-being due to lower vitamin B12 levels.

Anemia can occur as a result of vitamin B12 deficiency. In anemia, which occurs due to decreased oxygen-carrying capacity of the blood, the body begins to beat faster and tachycardia occurs to deliver oxygen to the cells[17]. Symptoms such as weakness and fatigue may precede anemia[15,16]. It is thought that the lack of change in pulse rate (tachycardia) measurements in patients using metformin for a long time may be because fatigue develops before anemia.

Mental disorders, especially depression and anxiety, are reported to be more common in people with diabetes than in the general population. Psychological factors that may affect fatigue in people with diabetes are emotional stress and depression resulting from diabetes self-management[35]. Sönmez and Kasım[38] reported that depression increased with the duration of diabetes. Considering that the risk of developing complications increases with the duration of diabetes[36], it is assumed that diabetes and years of metformin use, which are the results of this study, are effective in decreasing psychological well-being as fatigue increases.

The sympathetic nervous system works harder than usual in stressful situations. The sympathetic nervous system is activated to protect the body's self-regulation against the stress or pain it perceives during stress. One of the resulting physiological effects is the acceleration of the heart rate[7]. It is believed that as the pulse rate increases, psychological well-being decreases, which is the result of the study.

The study results show that fatigue, years of metformin use, and pulse rate are essential predictors of psychological well-being in type II diabetes patients using metformin. Thus, the study results show that as fatigue and years of metformin use increase, psychological well-being decreases. In addition, it was concluded that fatigue was the variable that most and best predicted the level of psychological well-being in type II diabetes patients using metformin. However, the contribution of the year of metformin use to psychological well-being was found to be relatively low, and the number of pulse rates was found to have no contribution.

Fatigue in diabetes is often associated with various complications when glycemic control is not achieved[39]. One of the predisposing factors to fatigue in people with diabetes is depression. The fact that diabetes management is individualized, complex, and requires long-term follow-up can be considered among the causes of fatigue in people with diabetes. A study by Jain et al[40]. found that 68% of people with type II diabetes experienced fatigue and that fatigue was significantly associated with disease duration, fasting and postprandial blood glucose levels, depression, body mass index, and the number of diabetes complications. In this regard, it can be stated that the reason for the emergence of the relationship between fatigue and psychological well-being as a result of the study is the lack of glycemic control.

As a result, it was found that long-term use of metformin caused fatigue and negative psychological

well-being. In addition, it was found that the well-being of type II diabetic patients using metformin was negatively associated with fatigue, year of metformin use, and pulse rate; fatigue had significant effects on decreasing well-being when the variables that may be effective on well-being were controlled, the contribution of year of metformin use to psychological well-being was quite small, and the number of pulse rate did not contribute. In addition to annual measurement of vitamin B12 in type II diabetic patients who use metformin for a long time, it is recommended that fatigue and psychological well-being of patients be assessed and supported. Despite the prevalence of psychological problems and their negative consequences, person-centered chronic disease management and psychological support for patients with diabetes are inadequate. Therefore, the integration of a collaborative and patient-centered approach is recommended to improve health outcomes and fatigue status.

Because the sample of this study consisted of patients who presented to the Internal Medicine Outpatient Clinic of Bayburt State Hospital and were hospitalized, the results cannot be generalized to all type II diabetes patients using metformin. The results of this study may both recommend that all patients undergo annual serum B12 testing as recommended5 and provide guidance for initiating studies to alleviate the symptoms experienced by patients. Since there are no studies evaluating the subjective data of our patients who have used metformin for a long time due to vitamin B12 deficiency, the results of this study may guide us to initiate studies to alleviate the symptoms experienced by the patients. This study may instruct interventions to improve negative psychological well-being or fatigue in long-term metformin users.

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