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Physical Activity, Insulin Sensitivity, and Metabolic Control in Type 1 Diabetes Mellitus

Tip 1 Diabetes Mellitusta Fiziksel Aktivite, İnsülin Duyarlılığı ve Metabolik Kontrol

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Abstract

Objective: To assess insulin sensitivity and physical activity level (PAL) and their relationship with demographic, clinical, and laboratory parameters in patients with Type 1 diabetes mellitus (T1DM).

Material and Methods: We evaluated 150 adults with T1DM using the International Physical Activity Questionnaire (IPAQ) to determine PAL and estimated glucose disposal rate (eGDR) for insulin sensitivity. The patients were divided into three groups according to PAL [inactive (n=48), moderately active (n=55), and highly active (n=47)] and into two groups according to eGDR [<8.16 mg·kg^{-1}·min^{-1} [n=67] and ≥8.16 mg·kg^{-1}·min^{-1} (n=83)].

Results: According to eGDR values, 44.6% of 150 patients were insulin resistant. Insulin resistant patients were older and heavier and had higher body mass index, waist circumference, blood pressure, and serum glycemic and lipid parameters than insulin sensitive patients, and had nephropathy and a family history of DM. No significant differences in PAL were found according to insulin sensitivity between the groups. According to eGDR values, high-density lipoprotein cholesterol and glomerular filtration rate were positively correlated. In terms of clinical and metabolic parameters, except for gender distribution, no differences were found among the PAL groups.

Conclusion: The prevalence of insulin resistance was high in Turkish adults with T1DM and a meaningful correlation was evident between eGDR and disease control parameters. PAL assessed by the IPAQ was similar between insulin-resistant and insulin-sensitive patients.

Keywords: Type 1 diabetes mellitus; physical activity; insulin sensitivity; metabolic control; estimated glucose disposal rate

Özet

Amaç: Tip 1 diabetes mellitus (Tip 1 DM) lu hastalarda insülin duyarlılığı ve fiziksel aktivite düzeyi (PAL) ile bunların demografik, klinik ve laboratuvar parametreleri ile ilişkisini değerlendirmektedir.

Gereç ve Yöntemler: PAL ve insülin duyarlılığı için tahmini glukoz atılım oranı (eGDR) nı belirlemek amacıyla Uluslararası Fiziksel Aktivite Anketi (IPAQ) kullanılarak 150 erişkin Tip 1 DM'li hasta değerlendirildi. Hastalar PAL'ye göre 3 gruba [inaktif (n=48), orta derecede aktif (n=55) ve yüksek derecede aktif (n=47)] ve eGDR'ye göre iki gruba [<8.16 mg·kg^{-1}·min^{-1} (n=67) ve ≥8.16 mg·kg^{-1}·min^{-1} (n=83)] ayrıldı.

Bulgular: eGDR değerlerine göre, 150 hastanın %44,6'sı insülin dirençli idi. İnsülin dirençli hastalar; daha yaşlı ve kiloluydu, insülin duyarlı hastalardan daha yüksek beden kitle indeksi, bel çevresi, kan basıncı ve serum glisemik ve lipit parametrelerine sahipti ve diyabet aile öyküsü ve nefropatileri mevcuttu. Gruplar arasında insülin duyarlılığına göre PAL'de anlamlı farklılık bulunmadı. eGDR değerlerine göre; yüksek yoğunluklu lipoprotein, kolesterol ve glomerüler filtrasyon hızı ile pozitif korelasyon olduğu gösterildi. Klinik ve metabolik parametreler açısından cinsiyet dağılımı dışında PAL grupları arasında fark bulunamadı.

Sonuç: Tip 1 DM'li Türk erişkinlerde, insülin direnci prevalansı yüksek idi ve eGDR ile hastalık kontrol parametreleri arasında anlamlı bir ilişki olduğu görüldü. IPAQ ile değerlendirilen PAL'nin insülin dirençli ve insülin duyarlı hastalarda benzer olduğu gözlendi.

Anahtar kelimeler: Tip 1 diabetes mellitus; fiziksel aktivite; insülin duyarlılığı; metabolik kontrol; tahmini glukoz atılım oranı

Introduction

Sedentary lifestyle, lack of exercise, inadequate diet, and poor treatment compliance are considered the main causative factors for obesity, insulin resistance, and ultimately increased cardiometabolic risk in patients

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with type 1 diabetes mellitus (T1DM) (1-3). Most patients with T1DM are characterized by varying degrees of insulin resistance, which is characterized by limited stimulation of glucose metabolism in muscles and the liver. Approximately 30-50% reduction in insulin-mediated glucose uptake has been demonstrated in such patients (4-8). Some insulin-dependent patients may have phenotypic features that are associated with type 2 DM. The term "double diabetes" has been used to describe such patients. These patients are more prone to develop macrovascular and microvascular complications. They have a higher incidence of morbidity and mortality rates than insulin-sensitive and lean patients (4).

Regular physical activity has several benefits such as a decrease in cardiovascular risk and mortality and better quality of life. Physical exercise may act as a powerful stimulus for homeostasis, and physical exercise distributes the energy balance and enhances peripheral insulin sensitivity (9-13). Hormonal and metabolic responses to exercise depend on the intensity, duration, and individual training status. Skeletal muscles are not simply a movement organ, but also an endocrine organ producing and releasing numerous myokines, growth factors, and metallopeptidases in response to contraction (14). Secreted myokines can influence metabolism. Muscle contraction increases glucose uptake by itself and results in the recruitment of glucose transporters to the cell membrane independent of insulin (14-20).

In our daily practice, the number of uncontrolled diabetic patients is quite high despite the intensive insulin treatment and close follow-up. In this study, we assess the reasons that could lead to this situation. We hypothesized that daily physical activity affects insulin resistance and required insulin dose in T1DM. In this study, we aimed to investigate the relationship between calculated insulin resistance and exercise questionnaire with demographic, clinical features and laboratory results in patients with poorly controlled diabetes.

Material and Methods

This is a cross-sectional, single-center study among Turkish patients with T1DM being followed in a tertiary hospital. The study was conducted between March 2014 and March 2015, following the Ethics Committee approval from the University of Health Sciences, Bursa Yuksek Ihtisas Training & Research Hospital (formerly Sevket Yilmaz Training & Research Hospital).

During the study period, 185 patients with T1DM were screened and 35 of them were excluded because they did not meet the inclusion criteria or because of lack of sufficient data. In total, 150 outpatient clinic patients between 18 and 65 years of age, capable of physical exercise and having a diagnosis of T1DM with a minimum duration of one year were included after providing written informed consent. T1DM was diagnosed with patients' clinical and laboratory evaluations according to the American Diabetes Association criteria (21). Prior weight loss, symptomatic acute hyperglycemia, the presence of initial ketosis, and permanent requirement of insulin treatment after six months of diagnosis were accepted as clinical criteria. Low c-peptide and insulin levels despite concomitant hyperglycemia and positive serum auto-antibodies were used as laboratory criteria. Estimated Glucose Disposal Rate (eGDR), which can be calculated by using routine clinical measures such as waist circumference (WC) or waist-to-hip ratio, glycosylated hemoglobin (HbA1c) levels, and presence of hypertension, was derived to measure insulin resistance. As an insulin sensitivity index, eGDR is well correlated with the results obtained from a euglycemic hyper-insulinemic clamp study which is the gold standard for the measurement of insulin sensitivity in patients with T1DM. In an eGDR validation study, the clamp-measured glucose disposal rate was 3.8-13.4 $mg \cdot kg^{-1} \cdot min^{-1}$, with a range of ~9-11 $mg \cdot kg^{-1} \cdot min^{-1}$ in those with normal IR (22) and it should be emphasized that lower eGDR levels indicate greater insulin resistance (23-26).

International physical activity questionnaire (IPAQ), which is generally accepted survey, using a simplified questionnaire to assess the physical activity level (PAL). It is validated for different societies and an instrument designed primarily for adult population surveillance. Also, it has been shown that this test is appropriate and reliable for young Turkish population similar to our study population (27, 28).

Patients with severe retinopathy, end-stage renal disease, established cardiovascular diseases, and physical disability were excluded to reduce the disease-related exercise intolerance bias. In addition, patients with a history of taking medications that might affect glucose metabolism and insulin sensitivity were excluded.

Body weight (kg) and height (cm) were measured in suitable conditions. Body mass index (BMI) was calculated as weight divided by height in meters squared ($kg \cdot m^{-2}$). WC was measured at the midpoint between the lowest rib and the anterior iliac. Blood pressure (BP) was measured in a seated position using an automated BP monitor. Individuals using antihypertensive medications and/or those with a systolic BP (SBP) of ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg were considered hypertensive.

T1DM duration, educational level, marital status, family history of DM, and daily used insulin dose (U/day) were obtained from the clinical history.

Assessments of physical activity

Freely available (www.ipaq.ki.se) short form of the IPAQ (26, 27) was employed for determining PAL. The short form of the IPAQ asks about the frequency (days/week) and duration (min/day) of walking, moderate intensity activities, and vigorous intensity activities. A metabolic equivalent-min (MET-min) is computed by multiplying the MET score by the minutes of an activity. An average MET score was derived for each type of activity:

- Walking MET-min/week= 3.3×duration×frequency
- Moderate MET-min/week= 4.0×duration×frequency
- Vigorous MET-min/week= 8.0×duration×frequency
- Total Physical Activity= Walking+Moderate + Vigorous MET-min/week

According to their PAL, patients were divided as follows: inactive (n=48) (<600MET-min/week), moderately active (n=55) (601-3000 MET-min/week), and highly active (n=47) (>3000 MET-min/week).

Insulin sensitivity

The eGDR was calculated as follows:

21.158+(-0.009×WC)+(-3.407×HTN)+(-0.51×HbA1c),

HTN indicates hypertension and is expressed as 0 (no) or 1 (yes or still on antihypertensive medications). Patients were divided according to their eGDR values using 8.16 $mg \cdot kg^{-1} \cdot min^{-1}$ as the cutoff level as previously described by Chillaron et al. (28), who found a strong correlation between this eGDR value and all types of diabetes-related complications. Patients with eGDR values <8.16 $mg \cdot kg^{-1} \cdot min^{-1}$ (n=67) were recognized as insulin resistant, whereas patients with eGDR values ≥8.16 $mg \cdot kg^{-1} \cdot min^{-1}$ (n=83) were recognized as insulin sensitive.

Laboratory methods

Blood samples were analyzed for fasting plasma glucose (FPG), blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs) using an autoanalyzer (Abbott Aeroset System; Abbott Laboratories, Abbott Park, IL, USA). LDL-C levels in patients with TG values <400 mg/dL were calculated using the Friedewald formula:

LDL-C=total cholesterol-[(TG/5)-HDL-C]

HbA1c levels were measured using high-performance liquid chromatography (HPLC; Bio-Rad Diagnostic Group, Hercules, CA, USA), and 24-hour urine albumin excretion was measured by a chemiluminescence immunoassay (Immulite 2500 analyzer; Siemens, Los Angeles, CA, USA).

The solid-phase enzyme-linked immunosorbent assay method was used with a High Sensitivity CRP Enzyme Immunoassay (DRG International Inc., Mountainside, NJ, USA) for measuring high-sensitivity C-reactive protein (h-CRP). The measurable range was <0.1-10 mg/L, and intra- and interassay coefficients of variation were 2.5% and 2.3%, respectively.

Statistical analysis

Statistical analyses were performed using the IBM-Statistical Package for the Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to determine the normality of data. Comparisons between groups were performed using Analysis of variance for normally distributed variables, and the Mann-Whitney and

Kruskal-Wallis tests for non-normal variables. The Mann-Whitney *U* test was used to compare means and medians of continuous variables, and Pearson's c^2 test was used for comparing proportions of insulin resistance between or among categorical variables (or Fisher's exact test for 2×2 tables when c^2 test assumptions were not satisfied). Independent samples t-tests were used for comparing insulin-resistant and non-insulin-resistant subjects with respect to discrete or continuous variables. Spearman's correlation coefficient was used to evaluate the correlation between eGDR and PAL and clinical findings, laboratory parameters, and family history of any types of DM. Continuous variables are expressed as the mean ±standard deviation or median (minimum-maximum), as appropriate; categorical variables are expressed as frequencies (n,%). The significance level was considered as $p<0.05$.

Results

During the study period, a total of 185 patients with T1DM were screened and 35 patients were excluded. Of the 150 participants, 85 were women and 65 were men. Mean disease duration was 10.7±6.9 years. All the patients were literate and approximately two-thirds of patients had a high educational degree. Sixty-two percent of the patients were married. Furthermore, 75 (50%) patients did not have a family history of DM, 21 (14%) had T1DM, and 54 (36%) had a family history of type 2 diabetes mellitus (T2DM). Mean FPG was 229.1±120.6 mg/dL and HbA1c was 9.3%±2.3% which indicated uncontrolled diabetic disease. Body measurements reflected a lean body structure, mean weight was 65.1±10.5 kg, WC was 67.6±10.8 cm, and BMI was 23.8±4.1 $kg \cdot m^{-2}$. Mean eGDR was 8.22±2.09 $mg \cdot kg^{-1} \cdot min^{-1}$ that is higher than our cut-off value of 8.16 $mg \cdot kg^{-1} \cdot min^{-1}$ for describing insulin sensitivity. All the participants, except 22 patients who were using an insulin pump, were receiving intensive subcutaneous insulin therapy. Demographic, clinical, and some laboratory data are listed in Table 1.

On the basis of eGDR values, patients were divided as insulin resistant and insulin sensitive. Gender distribution and mean disease duration were similar in both groups, but patients in the insulin-resistant group were older and had higher blood pressure (SBP and DBP) than patients in the insulin-sensitive group. Body weight, BMI, and WC were also significantly higher in insulin-resistant patients and strongly reflected insulin resistance ($p<0.001$). Although the mean total dose of insulin used was higher in the insulin-resistant group than in the insulin-sensitive group, the difference was insignificant ($p=0.809$). Patients in the insulin-resistant group had higher FPG and HbA1c levels compared with patients in the insulin-sensitive group ($p>0.001$). Serum AST ($p=0.580$) and ALT ($p=0.512$) levels were similar in both groups. The kidney function of insulin-resistant patients was worse than that of insulin-sensitive patients (Table 2). The mean total cholesterol, LDL cholesterol, and TGs were

Table 1. Patients' demographic characteristics and clinical and laboratory data.

Parameter	Data (n=150)
Age (years)	31.07±8.83
Women/men, n	85/65
Disease duration (years)	10.7±6.9
Educational level, n (%)	
Elementary school	47 (31.3%)
High school	62 (41.3%)
University	41 (27.3%)
Family history of DM, n (%)	
None	75 (50%)
T1DM	21 (14%)
T2DM	54 (36%)
Marital status	
Unmarried	57 (38%)
Married	93 (62%)
Total daily insulin dose (U/day)	55.7±21.5
Body weight (kg)	65.1±10.5
BMI (kg/m^2)	23.8±4.1
WC (cm)	87.6±10.8
FPG (mg/dL)	229.1±120.6
HbA1c (%)	9.3±2.3
eGDR ($mg \cdot kg^{-1} \bullet min^{-1}$)	8.22±2.09
PAL, n (%)	
Low	47 (31.3%)
Moderate	54 (36.1%)
High	49 (32.6%)

BMI: body mass index; DM: diabetes mellitus; eGDR: estimated glucose disposal rate; FPG: fasting plasma glucose; HbA1c: glycosylated hemoglobin; PAL: physical activity level; WC: waist circumference.

Table 2. Demographic and metabolic characteristics according to eGDR.

	Low-eGDR group (n = 67, 41.9%)	High-eGDR group (n = 83, 58.1%)	p
Women/men	34/33	31/52	0.227
Age (years)	33.2±9.3	29.5±8.1	**0.016**
Family history of diabetes (n, %)	49 (73.1%)	26 (31.2%)	<0.05
Type 1 DM (n, %)	13 (19.4%)	8 (9.6%)	<0.01
Type 2 DM (n, %)	36 (53.7%)	18 (21.6%)	<0.001
Disease duration (years)	10.37±7.6	10.96±6.4	0.335
Insulin dose (U/day)	61.03±26.3	51.95±16.4	0.809
SBP (mmHg)	118.5±18.7	106.9±12.9	**<0.001**
DBP (mmHg)	75.6±12.3	70.0±9.15	**0.007**
Body weight (kg)	69.9±10.5	61.5±9.1	**<0.001**
BMI (kg/m^2)	25.6±4.0	22.5±3.6	**<0.001**
WC (cm)	93.9±9.3	83.0±9.5	**<0.001**
FPG (mg/dL)	274.6±125.4	196.2±106.2	**<0.001**
HbA1c (%)	10.9±2.46	8.17±1.3	**<0.001**
AST (U/L)	21.4±13.5	19.4±10.3	0.580
ALT (U/L)	20.1±10.8	20.7±11.4	0.512
BUN (mg/dL)	15.1±7.4	11.69±3.5	**0.002**
Creatinine (mg/dL)	0.87±0.34	0.77±0.14	**0.048**
Total C (mg/dL)	212.9±50.6	181.5±45.8	**<0.001**
HDL-C (mg/dL)	50.9±13.2	61.5±15.1	**<0.001**
LDL-C (mg/dL)	125.5±35.0	99.1±34.8	**<0.001**
TG (mg/dL)	179.7±117.5	100.8±71.6	**<0.001**
hs-CRP (mg/dL)	5.05±3.7	5.3±6.7	**0.017**
Microalbuminuria (mg/24 h)	186.2±560.1	98.4±340.7	**0.014**
GFR (mL·min^{-1}·1.73 m^{-2})	93.0±24.3	104.0±20.1	**0.008**
eGDR (mg·kg^{-1}·min^{-1})	6.35±1.77	9.59±0.91	**<0.001**
PAL, n			
Low (n)	22	25	**0.875**
Moderate (n)	24	30	**0.874**
High (n)	21	28	**0.609**

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BUN: blood urea nitrogen; C: cholesterol; DBP: diastolic blood pressure; eGDR: estimated glucose disposal rate; FPG: fasting plasma glucose; GFR: glomerular filtration rate; HbA1c: glycosylated hemoglobin; Hct: hematocrit; HDL: high-density lipoprotein; Hb: hemoglobin; hs-CRP: high-sensitivity C-reactive protein; LDL: low density lipoprotein; PAL; physical activity level; PLT: platelet count; SBP: systolic blood pressure; TG: triglycerides; WBC: white blood cell count; WC: waist circumference. Significant differences are shown in bold.

significantly higher and HDL cholesterol was significantly lower in the insulin-resistant group than in the insulin-sensitive group (p<0.001). Patients in both groups had similar exercise habits (Table 2).

We also divided our patients into three groups according to their PALs determined using the IPAQ survey. The distribution according to sex was the only significant difference between the groups, with a significantly higher proportion of women in the low and moderately active groups and a higher proportion of men in the high activity group. With respect to clinical and metabolic parameters, there were no significant differences between the groups, except for GFR that was significantly different between the low and highly active groups (p=0.015, Table 3).

Although significant positive correlations were observed among eGDR, AST, HDL cholesterol, and GFR, significant negative correlations were observed among eGDR, age,

Table 3. Demographic and metabolic characteristics according to PAL.

	Low-activity group (n=47)	Moderate-activity group (n=54)	High-activity group (n=49)	p
Women/men	32/15	35/19	21/28	**0.026**
Age (years)	30.7±8.2	31.2±9.0	31.1±9.2	0.972
Disease duration (years)	10.7±6.4	11.3±7.7	10.0±6.6	0.689
Insulin dose (U/day)	52.23±21.5	58.35±22.5	50.6±20.5	0.192
SBP (mmHg)	114.85±17.9	108.85±15.6	112.6±16.2	0.537
DBP (mmHg)	72.05±11.17	72.15±10.55	73.15±11.3	0.882
Body weight (kg)	65.34±10.7	65.85±11.01	64.09±10.1	0.207
BMI (kg/m^2)	24.4±3.9	24.1±4.8	23.0±3.2	0.256
WC (cm)	89.3±10.9	88.2±12.0	85.3±9.0	0.269
FPG (mg/dL)	251.1±140.2	237.0±115.1	198.6±100.9	0.150
HbA1c (%)	9.69±2.90	9.16±1.82	9.18±2.26	0.934
AST (U/L)	21.5±14.3	20.3±10.0	19.0±10.6	0.636
ALT (U/L)	19.64±9.5	20.5±13.8	20.1± 19.2	0.887
BUN (mg/dL)	13.2±7.3	13.1±5.1	13.0±4.6	0.382
Creatinine (mg/dL)	0.87±0.38	0.79±0.16	0.79±0.13	0.831
Total C (mg/dL)	188.5±47.0	193.7±45.9	202.6±57.5	0.601
HDL-C (mg/dL)	54.8±16.1	58.6±16.1	57.4±13.2	0.470
LDL-C (mg/dL)	104.1±33.3	110.8±35.7	115.4±41.9	0.456
TG (mg/dL)	144.1±121.8	123.4±88.7	137.0±92.6	0.767
hs-CRP (mg/dL)	5.81±6.98	4.96±4.81	4.93±5.27	0.394
Microalbuminuria (mg/24 h)	260.8±107	54.2±170.1	111.7±400	0.632
GFR (mL·min^{-1}·1.73 m^{-2})	93.7±27.2	98.2±21.2	106.1±17.1	0.590
eGDR (mg·kg^{-1}·min^{-1})	7.71±2.59	8.52±1.49	8.31±2.10	0.530

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BUN: blood urea nitrogen; C: cholesterol; DBP: diastolic blood pressure; eGDR: estimated glucose disposal rate; FPG: fasting plasma glucose; GFR: glomerular filtration rate; HbA1c: glycosylated hemoglobin; Hct: hematocrit; HDL: high-density lipoprotein; Hb: hemoglobin; hs-CRP: high-sensitivity C-reactive protein; LDL: low density lipoprotein; PAL; physical activity level; PLT: platelet count; SBP: systolic blood pressure; TG: triglycerides; WBC: white blood cell count; WC: waist circumference.

disease duration, insulin dose, SBP, DBP, body weight, WC, FPG, HbA1c, total cholesterol, LDL cholesterol, and TGs. There were no significant correlations among eGDR, ALT, BUN, creatinine, h-CRP, and microalbuminuria. Regarding PAL, we found a positive correlation only between PAL and GFR and a negative correlation between PAL and FPG. Correlation analyses among eGDR, PAL, and metabolic and clinical parameters are shown in Table 4.

Discussion

In T1DM, insulin production by the b-cells diminishes long before the clinical onset of hyperglycemia, and this process is marked by the loss of pulsatile secretion and the first-phase insulin response to intravenous glucose. Decreased insulin efficiency results in progressive glucose intolerance and reduced insulin sensitivity by the time they are diagnosed with overt diabetes (29-32). The total daily insulin dose reflects insulin sensitivity, and, clinically, insulin resistance in patients with T1DM is often recognized by high insulin requirements. It is difficult to recognize whether insulin dose is normal and until now there are no age- and gender-specific normative data on daily insulin doses. Although the relationship between insulin dose and insulin resistance has been shown in previous studies (33-35), it was not so obvious in our study. Despite the higher insulin level observed in the insulin-resistant group, the difference was not significant (61.03±26.3 U/day vs. 51.95±16.4 U/day, p=0.809).

Table 4. Correlation analyses between eGDR and PAL and other patient data.

	eGDR		PAL	
	r	p value	r	p value
Women/men	0.074	0.383	-0.207	**0.013**
Age (years)	0.532	**<0.001**	-0.144	0.114
Disease duration (years)	-0.296	**0.001**	-0.041	0.626
Educational level	0.229	**0.006**	-0.022	0.790
Family history of DM	-0.244	**0.003**	0.051	0.547
Marital status	-0.207	**0.013**	-0.011	0.892
Insulin dose (U/day)	-0.265	**0.001**	0.074	0.380
SBP (mmHg)	-0.529	**<0.001**	-0.045	0.598
DBP (mmHg)	-0.404	**<0.001**	-0.041	0.631
Body weight (kg)	-0.489	**<0.001**	-0.048	0.571
BMI (kg/m2)	-0.489	**<0.001**	-0.137	0.105
WC (cm)	-0.589	**<0.001**	-0.147	0.081
FPG (mg/dL)	-0.276	**0.001**	-0.174	**0.037**
HbA1c (%)	-0.663	**<0.001**	-0.086	0.305
AST (U/L)	0.226	**0.007**	-0.071	0.402
ALT (U/L)	-0.047	0.580	0.016	0.848
BUN (mg/dL)	0.020	0.819	-0.140	0.096
Creatinine (mg/dL)	-0.024	0.781	-0.071	0.402
Total C (mg/dL)	-0.342	**<0.001**	0.113	0.184
HDL-C (mg/dL)	0.290	**0.001**	0.068	0.421
LDL-C (mg/dL)	-0.340	**<0.001**	0.121	0.158
TG (mg/dL)	-0.418	**<0.001**	-0.028	0.741
hs-CRP (mg/dL)	-0.067	0.430	-0.620	0.463
Microalbuminuria (mg/24 h)	-0.154	0.082	-0.128	0.147
GFR (mL·min^{-1}·1.73 m^{-2})	0.196	**0.021**	0.221	**0.009**
eGDR (mg·kg^{-1}·min^{-1})	-	-	0.103	0.222

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BUN: blood urea nitrogen; C: cholesterol; DBP: diastolic blood pressure; eGDR: estimated glucose disposal rate; FPG: fasting plasma glucose; GFR: glomerular filtration rate; HbA1c: glycosylated hemoglobin; Hct: hematocrit; HDL: high-density lipoprotein; Hb: hemoglobin; hs-CRP: high-sensitivity C-reactive protein; LDL: low density lipoprotein; PAL; physical activity level; PLT: platelet count; SBP: systolic blood pressure; TGs: triglycerides; WBC: white blood cell count; WC: waist circumference.
Significant differences are shown in bold.

Calculation of eGDR as an insulin sensitivity index is practical, and the results correlate well with the results obtained from glucose clamp studies. eGDR has first described in Pittsburgh epidemiological studies, and a low eGDR reflects a high resistance to insulin (23, 26, 33-35). Kilpatrick et al. (9) showed that patients with the highest insulin resistance at their baseline visit have more microvascular and macrovascular complication development risk independently of their assigned treatment group. Several studies have investigated insulin sensitivity according to eGDR and its different cut-off values in patients with T1DM (36-41). Similar to the determination of optimal HbA1c levels, Chillarón et al. (28) determined 8.16 mg·kg^{-1}·min^{-1} as a cut-off value for developing microvascular complications. They found that patients with microvascular complications had quite low levels of eGDR such as 5.97±1.2 mg/kg^{-1}.min^{-1} for diabetic retinopathy, 5.06±0.4 mg/kg^{-1}.min^{-1} for diabetic neuropathy and 5.79±1.5 mg/kg^{-1}.min^{-1} for diabetic nephropathy. Because of the cross-sectional nature of our study, we used a single cut-off point to establish different groups. Despite the single cut-off point, there

were significantly meaningful correlations between the levels of 8.16 $mg \cdot kg^{-1} \cdot min^{-1}$ for eGDR and metabolic parameters reflecting insulin resistance. This is the first such study in a Turkish population and we identified an acceptable eGDR value for describing insulin resistance. Unlike total daily insulin dose, the eGDR showed a strong correlation with most of the parameters investigated in our study, such as family history of T2DM, longer diabetes duration, older age, poor glycemic control, a greater amount of fat, and increased lipid levels (42-45). As shown in Table 2 and Table 4, insulin-resistant patients were older and had higher body weight, WC, BMI, SBP, DBP, total cholesterol, LDL-C, TG, FPG, HbA1c, and lower HDL-C than insulin-sensitive patients in the present study. Moreover, although the disease duration was similar in both groups, insulin-resistant patients had lower GFR and higher Urinary albumin excretion rate (UAER) than patients in the insulin-sensitive patients. With respect to renal parameters, our results were similar to those of Bulum et al. (36), where the authors found a strong correlation between eGDR and the markers of renal function, such as UAER, creatinine level, and creatinine clearance.

Teixeirra et al. (37) used two parameters for describing insulin resistance, eGDR and insulin sensitivity score (ISS). In addition to a moderate correlation between eGDR and ISS (r=0.612), the authors also found a positive correlation between BMI, body fat distribution, waist-to-height ratio, total daily dose of insulin, age, diabetes duration, and both formulas. As shown in Table 1, our study participants had acceptable mean body weight, BMI, and WC, reflecting healthy individuals measurements, and an eGDR value of 8.22±2.09 $mg \cdot kg^{-1} \cdot min^{-1}$. Mean body weight was 65.1±10.5 kg, mean BMI was 23.8±4.1 $kg \cdot m^{-2}$, and mean WC was 87.6±10.8 cm. Thus, our patients were lean and insulin sensitive according to our cut-off value. However, when patients were grouped according to eGDR, patients with low eGDR had higher body weight (69.9±10.5 vs. 61.5±9.1 kg), BMI (25.6±4.0 vs. 22.5±3.6 $kg \cdot m^{-2}$), and WC (93.9±9.3 vs. 83.0±9.5 cm) compared with patients with high eGDR. There were significant differences between the groups with p-values <0.001 for all those measurements. These results were similar to those presented by Teixeirra et al. There were 13 hypertensive patients (21.7%) in the low eGDR group, but no hypertensive patients in the high eGDR group. Patients with low eGDR had higher levels of total cholesterol, LDL cholesterol, and TGs but a lower level of HDL cholesterol.

In the Pittsburgh Epidemiology of Diabetes Complications Study experience, in patients with T1DM, Pambianco et al. (38) reported that having had more metabolic syndrome parameters initially is associated with developing of more chronic microvascular complication rates. The relation between eGDR and metabolic syndrome parameters was also consistent in our study and we found a strong correlation between low eGDR and worse metabolic and anthropometric parameters.

A family history of T2DM and chronic hyperglycemia during the clinical phase of T1DM are associated with decreased peripheral glucose uptake and insulin resistance. This relationship has been supported in numerous studies (46-50) and this was a prominent finding in our study. There was a meaningful correlation between some demographics such as educational level, family history of DM, and marital status. Patients with a family history of DM had a lower eGDR, reflecting insulin resistance (p=0.003). There was a higher proportion of patients with a family history of T2DM in the insulin-resistant group than in the insulin-sensitive group (53.7% [36 of 67] vs. 21.6% [18 of 83]). The proportion of patients with a family history of T1DM was 19.4% (13 of 67) in the insulin-resistant group and 9.6% (8 of 83) in the insulin-sensitive group. There were significant differences between the two groups in terms of family history of DM (p<0.005, for all types). In addition, the proportion of patients who had high educational levels and who were married was higher in the insulin-sensitive group (p=0.006, r=0.229 for educational level; and p=0.013, r=-0.207 for marital status). We cannot explain these relationships as these may have been a coincidence. A high education level and being married may lead to a more regular lifestyle to achieve and sustain better glycemic control.

Exercise is one of the important cornerstones of diabetes management. Exercise can improve body weight control, cardiovascular disease risk, and insulin sensitivity. In addition, the frequency and severity of complications in individuals with T1DM are greater among those reporting little exercise (10-13, 15, 51-53). From the perspective of PAL, as assessed using IPAQ, we did not find such clear results in our study. We found no correlation between PAL and parameters reflecting good disease control (HbA1c levels, lipid parameters, BP, and anthropometric measurements).

In diabetic patients, exercise increases the prevalence of hypoglycemia. Hypoglycemia is the most important factor for the physical activity (54). The fear of hypoglycemia results in a serious limitation to the intensive glycemic control and exercise implementation. In addition, activation of counter-regulatory hormones, especially during intense activity, may be another possible explanation (55, 56). A recently published meta-analysis showed no evidence of improvement in HbA1c with exercise (13). Increased calorie intake, insulin dose reduction, and weakness are concluded as the reasons for this finding. In our study, men reported more intense activity than women and it may be associated with our sociological structure. Besides a negative correlation with FPG, there was a positive correlation between GFR and PAL, reflecting the physiological effects of exercise on glomerular filtration. All these results appear complex and somewhat contradictory, which may be related to our assessment methods. Exercise reduces cardiovascular disease and mortality by improving endothelial function with decreasing insulin requirement and lipid levels and promoting well-being in patients with T1DM (3). Although we did not observe a glycemic benefit in our study, we suggest exercise because of its well-defined benefits.

In conclusion, Turkish adults with T1DM have high insulin resistance prevalence. Older age, high WC, body weight, BMI, BP, lipid levels, glycemic parameters, BUN, creatinine, UAER, and low GFR and HDL cholesterol were the more common features among T1DM patients with insulin resistance. The effects of physical activity were not consistent with respect to metabolic control parameters in patients with T1DM in our study population. This consistency persisted when analyses were done according to eGDR groups.

Learning Points

According to the estimated glucose disposal rate, 44.6% of 150 Type 1 DM patients were insulin-resistant.

Insulin resistant patients were older, heavier and have higher body mass index, waist circumference, blood pressure, serum glycemic and lipid parameters than insulin sensitive patients, and had nephropathy and family history of DM.

No significant differences were found in the physical activity level between the insulin sensitive and resistant groups.

Prevalence of insulin resistance was high in Turkish type 1 diabetic adults and the meaningful correlation was evident between the estimated glucose disposal rate and disease control parameters.

The IPAQ alone was not sufficient to assess the exercise levels of type 1 diabetic patients.

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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: Nizameddin Koca, Metin Güçlü; Design: Nizameddin Koca, Metin Güçlü; Control/Supervision: Metin Güçlü, Nizameddin Koca; Data Collection and/or Processing: Nizameddin Koca, İrfan Esen, Gamze Emlek, Sinem Kıyıcı; Analysis and/or Interpretation: Metin Güçlü, Nizameddin Koca; Lit-

erature Review: Metin Güçlü, Sinem Kıyıcı; Writing the Article: Metin Güçlü, Nizameddin Koca; Critical Review: Metin Güçlü, Nizameddin Koca; References and Fundings: Metin Güçlü, Nizameddin Koca; Materials: Gamze Emlek, Gürcan Kısakol, İrfan Esen.

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