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Cognitive Functions and Intelligence Quotient in Patients with Metabolic Syndrome Through the Window of Type 2 Diabetes Mellitus

Tip 2 Diabetes Mellitus Penceresinden Metabolik Sendromlu Hastalarda Bilişsel Fonksiyonlar ve Zeka Katsayısı

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ÖZ

Amaç: Metabolik sendrom (MetS) olan hastalarda bilişsel işlevleri ve zeka katsayısı (IQ) değerini, tip 2 diabetes mellitus (DM) hastalığını dikkate alarak değerlendirmek.
Araçlar ve Yöntem: Ocak-Mart 2020 tarihleri arasında kesitsel bir çalışma yürütüldü. Bu çalışmaya katılanlar üçüncü basamak bir hastanedendir. Sağlık kontrolü veya DM takibi ile polikliniğe başvuran hastalar çalışmaya dahil edildi. Çalışmaya 18-75 yaşlarında toplam 80 hasta (44 MetS'li ve 36 MetS'siz hasta) art arda dahil edildi. Hastaların klinik ve laboratuvar parametreleri, Mini Mental Durum Muayenesi (MMSE) ve Kent E-G-Y skorları ile ölçüldü.
Bulgular: MetS'li hastalarda glikozile hemoglobin (HbA1c) ve trigliserid düzeyleri daha yüksek, yüksek dansiteli lipoprotein-kolesterol (HDL-c) ve ferritin düzeyleri daha düşüktü. MMSE skoru MetS'li katılımcılarda MetS'siz katılımcılardan daha düşükken, Kent E-G-Y skoru her iki grupta da benzerdi. Tüm hastaların DM ve/veya MetS olup olmadığına bağlı olarak, alt grup analizleri yapıldı ve değerlendirildi. Diyabetli hastalar, diğer alt gruplara kıyasla daha düşük IQ puanlarına sahipti.
Sonuç: MetS, bilişsel işlevleri azaltır, ancak bunun genel olarak IQ üzerinde bir etkisi olmadığı gösterilmiştir. Bununla birlikte, DM varlığının MetS'lu hastalarda zeka üzerine kötüleştiren bir faktör olduğu gösterilmiş olsa da, daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: bilişsel işlev; diyabetes mellitus; metabolik sendrom; zekâ katsayısı

ABSTRACT

Purpose: To evaluate the cognitive functions and intelligence quotient (IQ) in patients with metabolic syndrome (MetS) by also considering Type 2 diabetes mellitus (DM).
Materials and Methods: A cross-sectional study was conducted from January to March 2020. Participants in this study are from a tertiary care hospital. Patients admitted to the outpatient clinic with health check-up, or follow-up of DM were included in the study. A total of 80 patients (44 patients with MetS and 36 patients without MetS), 18-75 years old, were recruited to the study consecutively. Clinical and laboratory parameters, Mini Mental State Examination (MMSE) and Kent E-G-Y scores of patients were measured.
Results: Glycated hemoglobin (HbA1c) and triglycerides levels were higher, whereas high-density lipoprotein-cholesterol (HDL-c) and ferritin levels were lower in patients with MetS. MMSE score was lower in participants with MetS than without MetS, whereas Kent E-G-Y score was similar in both groups. Depending on whether all patients have DM and/or MetS, subgroup analyzes were performed and evaluated. Patients with diabetes had lower IQ scores compared to the other subgroups.
Conclusion: MetS reduces cognitive functions, whereas it has been shown that this generally does not have any effect on IQ. However, even though DM presence has been shown to be a worsening factor on intelligence in MetS, further studies are needed.

Keywords: cognitive function; diabetes mellitus; intelligence quotient; metabolic syndrome

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INTRODUCTION

Metabolic syndrome (MetS), which has become a more common public health issue, is associated with diseases, including non-alcoholic fatty liver, cardiovascular disease, diabetes mellitus, hypertension, and dyslipidemia.[1] Diabetes Mellitus (DM) is a progressive complex disease, and achieving normoglycaemia is the first goal in diabetics. On the way to the target, it is necessary to increase the quality of life of the patients, to reduce the complications and to consider the comfort of the patient while performing this.[2,3]

Health is defined as "not only the absence of illness and disability but a state of complete physical, mental and social well-being" by the World Health Organization.[4]The importance of cognitive functions and intelligence is increasing day by day while suffering from chronic diseases.[5]It is already known that the factors increased on intelligence quotient (IQ) improve the quality of life.[6] From this perspective, the effect of MetS and DM on mental functions is as important as its effect on physical functions. A Turkish proverb says: healthy mentality takes place in the healthy body.

Despite many studies on cognitive functions, there are comparatively scarce data on IQ in people with MetS. With this study, we aimed to evaluate the cognitive functions and IQ in patients with MetS by also considering type 2 DM for the first time in the literature (PubMed and Google Scholar) to our best knowledge.

MATERIALS and METHODS

Participants

A cross-sectional study was conducted from January to March 2020. Participants are from a tertiary care hospital in this study. Patients admitted to the outpatient clinic with health check-up or follow-up of DM were included in the study. Participants without metabolic syndrome consist of healthy or diabetic subjects. A total of 80 patients (44 patients with MetS and 36 patients without MetS), 18-75 years old, were recruited to the study consecutively. Waist circumference, height and weight of patients were measured, then they were used to calculate body mass index (BMI), weight in kilograms divided by height in meters squared.

Renal disorders (nephrotic syndrome, lupus, vasculitis, recent urinary tract infection, urinary calculus, chronic kidney disease stage 3 and above), endocrinological disorders (clinically significant thyroid dysfunctions, Cushing disease, acromegaly, Type 1 DM), chronic neuropsychiatric diseases (Parkinson's disease, schizophrenia, multiple sclerosis, Alzheimer's disease, bipolar disorders, cerebrovascular disease) malignancies, treatment with corticosteroids, acute or chronic infection, chronic anemias, pregnancy, malabsorption syndrome, gastrointestinal surgery, chronic hepatitis, chronic alcohol abuse, smokers, being vegetarian who do not consume eggs or meat were exclusion criteria, because of their effects on the cognitive function.

Ethics approval needed for the study is received from Erciyes University Local Ethical Committee (Date and Decision number: 29.01.2020-2020/57). This trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. All study participants gave written consent before any trial-related activities, and the researcher retained the consent forms.

Measurement of Laboratory Parameters

A fasting venous blood sample was collected after an overnight fast for at least 8-hour for biochemical investigations and samples were processed at the hospital laboratory on the same day. FPG, serum blood urea nitrogen (BUN), serum creatine (SCre), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), aspartate transaminase (AST), alanine transaminase (ALT), total cholesterol, low-density lipoprotein-cholesterol (LDL-c), high-density lipoprotein-cholesterol (HDL-c), triglycerides, thyroid-stimulating hormone (TSH), hemoglobin, folate, vitamin B12 and ferritin were estimated using a Roche Cobas 8000 immunoassay analyzer (Roche Diagnostics, USA). Glycated hemoglobin (HbA1c) was estimated using an Adams A1c HA-8180V automatic analyzer (Arkray Diagnostics, USA). All assays were performed with specific kits and calibrators supplied by the manufacturers.

Diagnostic criteria of MetS[7]

1. Elevated waist circumference (obligatory component): ≥94 cm in man; ≥80 in woman.
2. Elevated triglycerides: ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides.
3. Reduced HDL-c: <40 mg/dL (1.0 mmol/L) in man; <50 mg/dL (1.3 mmol/L) in woman or drug treatment for reduced HDL-c.
4. Elevated blood pressure: Systolic ≥130 and/or diastolic ≥85 mm Hg; or antihypertensive drug treatment.
5. Elevated fasting glucose ≥100 mg/dL or drug treatment of elevated glucose is an alternate indicator.

Diagnostic criteria of DM[8]

1. Elevated HbA1c: ≥6.5 %
2. Elevated FPG: ≥126 mg/dL (7.0 mmol/L)
3. Elevated 2nd hour plasma glucose level after oral glucose tolerance test: ≥200 mg/dL (11.1 mmol/L)
4. Elevated random plasma glucose level: ≥200 mg/dL (11.1 mmol/L)

Mini Mental State Examination (MMSE)

MMSE consists of a set of questions that evaluate different aspects of cognitive functioning, which are categorized as orientation to place, registration, attention, and calculation, recall and language.[9] Neither severe hypoglycemia (<70mg/dl) nor severe hyperglycemia (>400 mg/dl) was observed during the evaluation of MMSE.

Kent E-G-Y

The Kent E-G-Y is a short, individually administered verbal test, composed of 10 simple questions (What are used when building a house? Where is sand used? If a flag is flying south, which side is the wind blowing from? Tell me the names of some fish/birds? At what time of day is our shadow the shortest? Tell me the name of some big cities? Why does the moon appear larger than the stars? Which mine does the magnet attract? If our shadow falls towards the north-east, where is the sun? How many cusps does a star on the Turkish flag have?), originally intended to provide a rough estimate of the intellectual ability of children. Since its development, it has frequently been used as a brief test of IQ in adults and has been found useful as a quick screening instrument.[10] Neither severe hypoglycemia (<70 mg/dl) nor severe hyperglycemia (>400 mg/dl) was observed during the evaluation of the Kent E-G-Y.

Statistical Analysis

SPSS 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) program was used for statistical analyses. Frequencies were expressed in percentage (%). For comparison of categorical data, the Chi-square test was used. Whether the numeric (digital) data is distributed normally or not was determined by Kolmogorov-Smirnov test and Histogram graphs. Numeric (digital) data relating to independent groups demonstrating a normal distribution were compared by the Student's t-test. Variables, which demonstrated normal distribution, were expressed as mean ± standard deviation. If it was a non-normal distribution, the Mann-Whitney U test was used. Variables, which were demonstrating non-normal distribution, were expressed in median (interquartile range). p<0.05 was accepted and considered as significant.

RESULTS

Age, weight, educational status, and waist circumference were similar in both groups (p=0.162, p=0.537, p=0.740, and p=0.256, respectively). When the levels of FPG, BUN, Creatin, CKD-EPI, AST, ALT, total cholesterol, LDL-c, hemoglobin, vitamin B12 and folate were evaluated, there was no statistical difference between the groups (p=0.082, p=0.109, p=0.656, p=0.262, p=0.373, p=0.735, p=0.448, p=0.977, p=0.711, p=0.433, and p=0.095, respectively). MetS was more common in women (p<0.001). While patients with MetS were shorter, their BMI was higher (p<0.001 and p=0.002, respectively). HbA1c and triglycerides levels were higher, whereas HDL-c, ferritin, and TSH levels were lower in patients with MetS (p=0.034, p<0.001, p<0.001, p=0.011, and p=0.041 respectively). The total score of MMSE was lower in participants with MetS than without MetS, whereas Kent E-G-Y scores were similar in both groups (p=0.006 and p=0.627, respectively). Data on these comparisons are presented in Table 1.

Table 1. Clinical status and laboratory parameters of patients with and without MetS.

Variables	Patients with MetS (n=44)	Patients without MetS (n=36)	p
Gender (F/M), n (%)	35/9 (79.6/20.4)	13/23 (36.1/63.9)	<0.001
Age (year), median (IQR)	55.5 (21.5)	45.0 (13.5)	0.162
Education, n (%)			
Illiteracy	3 (6.8)	2 (5.6)	
Primary school	31 (70.5)	24 (66.7)	0.740
High school	8 (18.2)	6 (16.7)	
University	2 (4.6)	4 (11.1)	
Weight (kg), mean ± SD	84.5 ± 15.0	82.2 ± 13.4	0.537
Height (cm), mean ± SD	163.6 ± 7.61	171.1 ± 6.86	<0.001
BMI (kg/m2), mean ± SD	31.63 ± 5.47	27.95 ± 3.52	0.002
Waist circumference (cm), median (IQR)	98.5 (18.5)	98.0 (12.0)	0.256
FPG (mg/dL), median (IQR)	124.5 (139.0)	98.0 (45.0)	0.082
HbA1c (%), median (IQR)	6.7 (4.0)	5.8 (1.4)	0.034
Serum BUN (mg/dL), median (IQR)	11.2 (5.7)	12.6 (3.3)	0.109
Serum Creatin (mg/dL), median (IQR)	0.7 (0.3)	0.7 (0.3)	0.656
CKD-EPI (mL/m/1.73m2), mean ± SD	96.1 ± 24.1	102.0 ± 16.2	0.262
AST (U/L), median (IQR)	19.0 (6.0)	19.0 (7.0)	0.373
ALT (U/L), median (IQR)	20.5 (12.3)	21.0 (8.0)	0.735
Total cholesterol (mg/dL), median (IQR)	196.0 (54.5)	186.0 (45.0)	0.448
LDL-c (mg/dL), median (IQR)	105.0 (43.8)	100.0 (57.0)	0.977
HDL-c (mg/dL), median (IQR)	40.0 (10.5)	48.0 (16.0)	<0.001
Triglycerides, median (IQR)	233.0 (112.8)	116.0 (101.0)	<0.001
Hemoglobin (g/dL), mean ± SD	14.14 ± 1.40	14.90 ± 1.64	0.711
Ferritin (µg/L), median (IQR)	54.0 (84.8)	119.0 (97.5)	0.011
Vitamin B12 (ng/L), median (IQR)	265.5 (204.8)	277.0 (159.5)	0.433
Folate (ng/mL), median (IQR)	8.8 ± 3.5	10.2 ± 3.9	0.095
TSH, (mU/L), median (IQR)	1.34 (1.13)	1.95 (1.37)	0.041
MMSE, median (IQR)	28.0 (3.0)	29.0 (2.0)	0.006
Kent E-G-Y, median (IQR)	90.0 (13.0)	90.0 (9.0)	0.627

F/M: female/male; MetS: metabolic syndrome; BMI: body mass index; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; BUN: blood urea nitrogen; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; AST: aspartate transaminase; ALT: alanine transaminase; LDL-c: low-density lipoprotein-cholesterol; HDL-c: high-density lipoprotein-cholesterol; TSH: thyroid-stimulating hormone; MMSE: Mini Mental State Examination. (p<0.05 considered statistically significant)

Depending on whether all patients have DM and/or MetS, subgroup analyzes were performed and evaluated. Patients with Type 2 DM had lower IQ scores compared to other subgroups (p<0.001 and p<0.001, respectively). Detailed statistical evaluations are given in Table 2.

Table 2. Comparison of cognitive and intelligence status in subgroups.

IQR	DM (-) MetS (-)	DM (+) MetS (-)	DM (-) MetS (+)	DM (+) MetS (+)	p
MMSE, median	30.0 (1.0)a,g	27.5 (3.0)a,e	29.5 (2.0)b,e	26.0 (3.0)b,g	<0.001
Kent E-G-Y, median	90.0 (7.3)d,h	88.0 (14.0)f	98.0 (6.0)c,d,f	86.0 (4.0)c,h	<0.001
pa<0.001; pb<0.001; pc<0.001; pd<0.001; pe<0.005; pf<0.049; pg<0.001; ph<0.017					

DM: Diabetes mellitus; MetS: Metabolic syndrome; MMSE: Mini Mental State Examination.
(Firstly, the groups were compared collectively to determine the p values in the rightmost column. Secondly, significant p values were reported in the bottom line by comparing groups with the same letter in pairs with each other. p<0.05 considered statistically significant.)

DISCUSSION

We evaluated the cognitive functions and IQ in patients with MetS in terms of the presence of DM. As expected, patients with MetS had lower levels of cognitive function. Also, there was no difference between the two groups in IQ values. When the scores of IQ in patients without MetS were evaluated, it was found that patients with DM were at lower levels than those without. When the scores of IQ in patients with DM were evaluated, there was also no difference between patients with MetS and those without. When evaluated by subgroup analyzes, the presence of DM has been shown to have an important contribution to intelligence in MetS.

Comparing the frequency of MetS in terms of gender varies between countries, it is more common in men in the USA.[11] However, it is more common in women in Turkey.[12] In many societies, various conditions have been shown to decline cognitive functions in women more than men[13,14]. The majority of people with MetS were women in our study, which also covers these data in the literature.

Many large studies in the literature have already shown that MetS worsen cognitive functions.[15-17] There are studies known that obesity deteriorates cognitive functions.[18,19]

HDL-c level has been shown to be an independent risk factor that adversely affects cognitive functions in men.[20] In addition, the height of the triglyceride level is negatively correlated with cognitive functions in adults.[21] The relationship of ferritin levels is positively correlated with cognitive functions, whether the hemoglobin level is low or not, has been shown in both children and adults. Moreover, it has been emphasized in many studies that the condition that most affects cognitive functions in people with MetS is hyperglycemia.[17,22,23] In the study conducted by Wang et al., it was reported that hyperglycemia is a risk factor for cognitive functions in patients with MetS.[23] In our study, we revealed that cognitive functions of people with MetS are impaired, which was compatible with the literature. In addition, patients with MetS in our study had higher BMI and triglyceride values while having lower HDL and ferritin levels than those without MetS. These findings, which confirm previous studies, may be the causes of poor cognitive functions in MetS.

In our study, evaluation of cognitive functions according to the MMSE scale and the privileged location of the presence of DM with subgroups are shown in Tables 1 and 2. When the total score of MMSE in patients without DM was evaluated, there was no difference between patients with and with out MetS. When the MMSE scores of patients with DM were evaluated, there was also no difference between patients with and withoutMetS. When the MMSE scores of patients without MetS were evaluated, it was found that patients with DM were at lower levels than those without DM ($p^a<0.001$). When the MMSE scores of patients with MetS were evaluated, patients with DM were also found to be at lower levels than those without DM ($p^b<0.001$). These outcomes demonstrated that DM has a unique place and focal point in cognitive functions in patients with MetS.

To the best of our knowledge, IQ and its relationship with DM in MetS was compared firstly in the literature (PubMed and Google Scholar). Moreover, there are scarce data in the literature on DM and IQ. It has been shown that DM does not have a negative effect on intelligence, especially in studies in which the relationship between intelligence and DM in the population under the age of 18 has been revealed.[24] In another study, it was shown that DM in adults is associated with lower level of intelligence. In a study in the literature, a modest difference was found in Type 2 diabetics with a history of hypoglycemia when using insulin compared with a healthy population.[25]

In our study, evaluation of IQ according to the Kent E-G-Y are shown in Tables 1 and 2. When the Kent E-G-Y scores of patients without MetS were evaluated, there was also no difference between patients with DM and those without. When the Kent E-G-Y scores of patients with MetS were evaluated, it was found that those with DM had lower intelligence scores than those without ($p^c<0.001$). When the Kent E-G-Y scores of patients without DM were evaluated, it was found that those with MetS had higher intelligence ($p^d<0.001$). When the Kent E-G-Yscores of patients with DM were evaluated, there was also no difference between patients with MetS and those without. In addition, the group with DM without MetS had significantly lower intelligence scores than the group with MetS without DM. These outcomes demonstrate to us that intelligence deteriorates with the effect of the presence of diabetes in patients with metabolic syndrome.

Our study also has some limitations. Firstly, because of the cross-sectional design, cognitive function and metabolic status were measured once, and these could be changed over time. Therefore, we cannot make causal outcomes in our study. Secondly, the number of participants was only 80, which may affect results. This number was limited as we were very meticulous in exclusion criteria. Thirdly, we did not adjust for all confounding variables, such as age, education, family history of cognitive impairment. Despite all these limitations, our study is valuable due to the findings on the mental effects of MetS by looking at the literature through the window of diabetes.

MetS reduces cognitive functions, whereas it has been shown that this generally does not affect IQ. However, even though DM presence has been shown to be a worsening factor on IQ in MetS, further studies are needed.

Conflict of Interests

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Authors' Contributions

Concept/Design: UST, KD, MFG, EKU. Data Collection and/or Processing: UST, KD, MK, BS. Data analysis and interpretation: UST, KD, EKU, DMU, MFG. Literature Search: KD, MK, DMU. Drafting manuscript: UST. Critical revision of manuscript: KD, BS, MK, MFG. Supervision: KD, MFG, BS, EU, DMU.

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