

MULTİPLE SKLEROZ ALT GRUPLARI ARASINDAKİ AKİMA BAĞLI DİLATASYON ÖLÇÜMLERİNDEKİ FARKLILIKLAR

DIFFERENCES IN FLOW-MEDIATED DILATATION MEASUREMENTS BETWEEN MULTIPLE SCLEROSIS SUBGROUPS

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ÖZET

AMAÇ: Multiple skleroz (MS) alt grupları ile normal kontrol grubu arasındaki akıma bağlı dilatasyon (ABD) ölçümlerindeki farklılıkları göstermeyi amaçladık.

GEREÇ VE YÖNTEM: Çalışmaya 96 katılımcı (ortalama yaş: 42,7 ± 14,1 yıl) alındı. Katılımcıları şu şekilde gruplandırdık: 47 MS hastası (ortalama yaş: 40,2 ± 12,2 yıl) ve 49 normal kontrol grubu (ortalama yaş: 45,22 ± 15,27). MS hastaları şu şekilde alt sınıflara ayrıldı: Grup 1 – Tekrarlayan ve düzelen MS (Relapsing-remitting) (RRMS): 37 hasta (ortalama yaş: 36,9 ± 11,2); Grup 2 – İkincil ilerleyici MS (Sekonder Progressif) (SPMS): 5 hasta (ortalama yaş: 49,0 ± 6,0); Grup 3 – Birincil ilerleyici MS (Primer Progressif) (PPMS): 5 hasta (ortalama yaş: 55,4 ± 10,6 yıl). Brakial arterin shear strese verdiği tepkiyi ve periferik vazodilatör nitrik oksit (NO) üretim kapasitesini akıma bağlı dilatasyon yöntemini kullanarak değerlendirdik.

BULGULAR: Normal kontrol grubu ile MS alt grupları arasında akıma bağlı bazal, akıma bağlı hiperemi ve akıma bağlı bazal/hiperemi değerleri açısından istatistiksel olarak anlamlı farklar vardı (sırasıyla p = 0,001, p = 0,029 ve p = 0,020). Yaş ve cinsiyet faktörleri istatistiksel olarak kontrol edildiğinde, genişletilmiş özüllülük durumu ölçeği (EDSS) puanları ile diğer ölçümler arasında korelasyon bulunmadı (p > 0,05).

SONUÇ: Verilerimiz MS hastalarında ABD ölçümlerinin normal kontrollere göre daha fazla azaldığını göstermektedir. Birincil ilerleyici MS grubu, diğer gruplara kıyasla ABD ölçümleri açısından daha şiddetli bozulma gösterdi. ABD bazal/hiperemi oranı değerleri, normal kontrol ve tekrarlayan ve düzelen MS gruplarına kıyasla ilerleyici MS gruplarında daha fazla azaldı.

ANAHTAR KELİMELE: Nitrik oksit, Multiple skleroz, Vasküler endotel-bağımlı gevşeme.

ABSTRACT

OBJECTIVE: We aimed to show the differences in flow-mediated dilatation (FMD) measurements between multiple sclerosis (MS) subgroups and normal control participants.

MATERIAL AND METHODS: There were 96 participants (mean age: 42.7 ± 14.1 years) in this study. We grouped the participants as follows: 47 MS patients (mean age: 40.2 ± 12.2 years) and 49 normal control participants (mean age: 45.22 ± 15.27). The MS patients were subclassified as follows: Group 1 – relapsing-remitting multiple sclerosis (RRMS): 37 patients (mean age: 36.9 ± 11.2); Group 2 – secondary progressive multiple sclerosis (SPMS): 5 patients (mean age: 49.0 ± 6.0); and Group 3 – primary progressive multiple sclerosis (PPMS): 5 patients (mean age: 55.4 ± 10.6 years). We used FMD methods for an indirect evaluation of the brachial artery's reaction to shear stress and peripheral vasodilatory nitric oxide (NO) production capability.

RESULTS: There were statistically significant differences between the normal control group and the MS subgroups regarding flow-mediated basal, flow-mediated hyperemia, and FMD ratio values (p = 0.001, p = 0.029, and p = 0.020, respectively). No correlation was found between the expanded disability status scale (EDSS) scores and other measurements after statistically controlling for age and gender factors (p > 0.05).

CONCLUSIONS: Our data indicate that FMD measurements decreased more in the MS patients compared to the normal controls. The PPMS group exhibited more severe deterioration with regard to FMD measures than the other groups. FMD ratio values decreased more in the progressive MS groups compared to the normal control and RRMS groups.

KEYWORDS: Nitric Oxide, Multiple Sclerosis, Vascular Endothelium-Dependent Relaxation.

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INTRODUCTION

Endothelial dysfunction, which has a key role in most pathological processes related to the cardiovascular system, has also a critical role in many neurodegenerative diseases (1). Multiple sclerosis is one of the most important neurodegenerative diseases in clinical practice (2). Because of multifactorial characteristics of multiple sclerosis (MS), pathophysiological mechanisms of factors about MS symptomatology, disease processes, morbidity, surviving and mortality were not clearly shown yet (3). Many of the studies have shown that MS is associated with autoimmunological mechanisms which have destructive effect on blood brain barrier and increased vascular permeability in brain (4). Nitric oxide, reactive oxygen species, reduced antioxidant capacity, mitochondrial dysfunction, increased amount of intracellular Na and Ca demyelization and abnormal and remyelination processes are all effective on Astroglial, oligodendrocyte and neuronal levels in MS (5-8). On the other hand, numerous observation about MS patients have clearly shown that there is increased cardiovascular morbidity and mortality in patients with MS (9). In patients with MS have also increased ratio of hypertension, acute coronary syndromes, and stroke which are mainly based on endothelial dysfunction in clinical practice (10-13). Besides, endothelial dysfunction is clearly defined as decreased NO production, increased and abnormal NO utilities in arterial bed (14). Increased Thromboxane A₂, leukotrienes, cytokines, chemokines, decreased PGI₂ levels, platelet aggregation, chronic inflammation and vasoconstriction are all main characteristics of endothelial dysfunction (15,16). In the literature numerous studies have shown that there is increased amount of NO in BOS specimens in patients with MS (17). On the other hand, MS patients have decreased NO production capacity at peripheral arterial bed during shear stress which is indirectly shown by Flow Mediated Dilatation measurements. (18,19). It seems that, in patients with MS, the process of production, distribution and utilization of NO are deteriorated with progressively especially in the later stages of MS. Flow mediated dilation

(FMD) is the most used method for non-invasive assessment of endothelial function. Accordingly, FMD can be useful in evaluation of nitric oxide releasing capacity in MS patients (20-23). There is small data about peripheral endothelial dysfunction in patients with flow mediated in the literature. In this study, we aimed to show the differences about FMD measurements among MS subgroups and normal participants.

MATERIALS AND METHODS

This is a cross-sectional study of 68 patients with multiple sclerosis admitted to the Neurology Department of the Medical School of Kırıkkale University, and the relevant symptoms were screened between January 2010 and January 2023. After the objectives of the study were described to the patients and their written informed consents were obtained, baseline characteristics and clinical data of the participants were collected by an interview and recorded in the study questionnaire and data from FMD analysis.

Patients

All participants were evaluated in Neurology and Cardiology clinics. Cardiologic evaluation and measurements, including FMD measurements, were performed by a cardiologist.

Patient Selection

Exclusion criteria were stable or unstable angina pectoris, acute myocardial infarction, systolic heart failure (EF<50%), hypertension, valvular heart disease, aortic aneurysm, acute or chronic renal failure (serum creatinine level >1.5 mg/dl), diabetes mellitus, asthma or chronic obstructive lung disease and psychiatric diseases, alcohol and drug abuse. 21 patients were excluded because of developing a condition included in exclusion criteria during the study period. 96 participants (49 Normal control participants and 47 MS patients) (mean age: 42.74 ± 14.07 years) were enrolled in the study. A total of 47 MS patients (33 female and 14 male patients, minimum age: 18 maximum age: 64, mean age of MS patients: 40.15 ± 12.35 years) and 49 normal control participants (33 female and 16 male patients, minimum age: 18 maximum age: 68, mean age of normal control

group 45.22 ± 15.27 years) were enrolled into the study. We divided the study participants as normal control group and the patients with MS. Additionally we also classified the patients with MS as following:

Group 1: RRMS (Relapse Remitting Multiple Sclerosis): 37 patients mean age (36.89 ± 11.16 years)

Group 2: SPMS (Secondary Progressive Multiple Sclerosis) 5 patients mean age (49.00 ± 5.96 years)

Group 3: PPMS (Primary Progressive Multiple Sclerosis) 5 patients mean age (55.40 ± 10.55 years)

Neurologic Evaluation

MS patients followed in our neurology outpatient clinic were included in the study. The diagnosis of MS was made according to the 2017 McDonald's revised criteria. MS patients consisted of RRMS, SPMS and PPMS patients (24).

Expanded Disability Status Scale (EDSS) scores, duration of disease and disease modifying agents used by the patients were recorded (25).

Cardiologic Evaluation

Following a detailed medical history taking, all subjects were physically examined, and their blood pressures were measured in both arms using a sphygmomanometer. 12-channel electrocardiography (ECG) recordings and transthoracic echocardiography (Ge-Vivid 7 Pro, General Electric; FL, USA), FMD tests were performed.

Flow-Mediated Dilatation (FMD)

We used Flow mediated dilatation (FMD) methods for indirect evaluation of the reaction to shear stress of brachial artery and peripheral vasodilatory and Nitric oxide production capability. A Ge-Vivid 7 Pro, 12 L Doppler probe (General Electric, Florida, USA) was used to detect the measurements of flow mediated dilatation.

Flow mediated dilatation measurements were performed as defined by Hayward, C.S et al. (23). In the present study,

- Basal brachial artery diameter measurements

were represented as FMD BASAL (mm):

- Brachial artery diameter at Hyperemia phase was represented as FMD HYPEREMIA (mm):

- We also calculated *FMD RATIO*: $[(FMD\ HYPEREMIA - FMD\ BASAL)/FMD\ BASAL] \times 100$ (%) (20-23).

Ethical Committee

Ethical approval for this study was obtained from the Kirikkale University Clinical Research Ethics Committee on September 7, 2023 (Decision No: 13/1).

Statistical Analysis

All statistical analyses were conducted using SPSS version 20.0 (SPSS; Chicago, IL, USA). All variables were tested for normal distribution using the Shapiro Wilk test. According to statistically distribution types, we showed the data as mean $\pm$ standard deviation (SD) which data have normally distribution. Besides we showed the data as median (25%-75%) which data have non-normally distribution. Student T test and ANOVA (Analysis of Variance) and Bonferroni adjustment tests were employed to compare data of the groups which have normal distribution. Mann Whitney U Test and Kruskal Wallis test were used to compare data of the groups which have non-normal distribution. For the evaluation of statistical correlation among the measurements we used Partial Correlation Analyses. A p value of <0.05 was accepted as statistically significant.

RESULTS

Table 1 shows the comparisons of anthropometric, biochemical, echocardiographic and FMD measurements in control and multiple sclerosis groups. There were no statistically significant differences of anthropometric, biochemical, echocardiographic measurements between the control and patient groups. However, there were statistically significant differences in FMD hyperemia and FMD ratio values between the groups ($p = 0.042$ and $p < 0.001$, respectively) (Table 1). **Table 2** shows the comparisons of anthropometric, biochemical, echocardiographic and FMD measurements among multiple

sclerosis groups. There were some statistically significant differences of anthropometric, biochemical, echocardiographic and FMD measurements among the MS groups. (For Age $p = 0.001$, creatinine $p = 0.019$, EDSS $p = 0.001$, aortic root measurement $p = 0.037$, ejection fraction (EF) $p = 0.001$, FMD basal $p = 0.001$, FMD hyperemia $p = 0.029$ and FMD ratio $p = 0.020$, respectively) (Table 2). After Bonferroni adjustment, we detected that there are statistically significant differences about FMD measurements between PPMS and RRMS groups (For FMD Basal $p = 0.001$, FMD Hyperemia $p = 0.034$ and FMD Ratio $p = 0.031$).

Table 3 shows the comparisons of anthropometric, biochemical and FMD measurements in normal control, Relapse Remitting MS (RRMS) group and Progressive MS groups (SPMS and PPMS). There are statistically significant differences about (For age $p < 0.001$, FMD basal $p = 0.003$, FMD hyperemia $p = 0.011$ and FMD ratio $p < 0.001$, respectively).

We also detected that some echocardiographic values are also shown statistically differences among the groups (For Ejection Fraction $p = 0.047$, Interventricular septum $p = 0.016$). After Bonferroni adjustment we detected that there are statistically significant differences about FMD between Normal Control Group and RRMS and Progressive MS ($p = 0.028$ and $p < 0.001$, respectively). Besides there is statistically significant difference about FMD between Progressive MS and RRMS ($p = 0.011$) (**Figure 1**).

We performed partial correlation analyses to reveal that the associations among the EDSS scores, anthropometric, biochemical, echocardiographic and FMD measurements. After statistically controlling the effects of age and gender effects we did not detect any correlation between EDSS scores and the other measurements ($p > 0.05$).

Besides similarly, after controlling the effects of age and gender we determined that there is statistically significant negative correlation between MS groups and FMD ratio. According to our results developing of more severe MS forms was getting more reduced FMD ratio results ($r = -0.444$, $p = 0.004$).

Table 1: Comparisons Of anthropometric, Biochemical And Fmd Measurements in Control And Multiple Sclerosis.

	GROUPS		
	NORMAL CONTROL GROUP N:49 Mean±SD	MULTIPLE SCLEROSIS GROUP N:47 Mean±SD	P
ANTHROPOMETRIC MEASUREMENTS			
AGE (years)	45.22±15.27	40.15±12.35	0.077
WEIGHT(kg)	75.24±16.55	71.57±14.01	0.245
HEIGHT(cm)	165.06±9.61	165.85±7.20	0.651
BODY MASS INDEX (kg/m ²)	27.58±5.26	26.06±5.00	0.151
WAIST CIRCUMFERENCE (cm)	93.04±15.91	89.51±14.11	0.254
BLOOD PRESSURE MEASUREMENTS			
SYSTOLIC BLOOD PRESSURE	122.7±9.1	125.0±7.40	0.176
DIASTOLIC BLOOD PRESSURE	80.0±6.8	78.3±6.2	0.198
BIOCHEMICAL MEASUREMENTS			
Hemoglobin	13.95±1.31	13.41±1.51	0.063
White Blood Cell	7.85±2.00	7.18±3.35	0.232
Platelets	271.88±62.97	278.62±84.97	0.659
SERUM BLOOD GLUCOSE LEVEL (Fasting) (mg/dl)	96.90±13.48	97.98±9.02	0.648
SERUM UREA LEVEL (mg/dl)	26.47±8.07	27.62±8.45	0.498
CREATININE	0.75±0.14	0.70±0.13	0.075
TOTAL CHOLESTEROL (mg/dl)	185.64±40.77	185.69±39.27	0.995
LDL CHOLESTEROL (mg/dl)	106.52±3.75	107.38±35.25	0.913
HDL CHOLESTEROL (mg/dl)	49.36±12.56	53.25±14.66	0.182
Triglyceride	149.13±66.37	125.32±61.62	0.083
CRP*	5.04±3.38	6.31±4.57	0.241
SEDIMENTATION*	14.82±9.69	17.85±12.38	0.287
T3*	2.90(2.50-3.10)	3.00(2.70-3.30)	0.147
T4*	1.10(1.00-1.30)	1.20(1.00-1.28)	0.947
TSH*	1.30(0.90-3.10)	1.77(1.22-2.43)	0.422
ECHOCARDIOGRAPHIC MEASUREMENTS			
Left atrium (mm)	32.04±4.58	31.28±2.90	0.333
Aort(mm)	32.12±3.78	31.68±3.08	0.442
Left ventricular Ejection Fraction (EF)(%)	62.6±6.5	64.23±3.29	0.129
Interventricular septum thickness(mm)*	1.00(0.90-1.10)	1.00(0.90-1.00)	0.146
Posterior wall thickness(mm)*	1.00(0.90-1.10)	1.00(0.90-1.10)	0.338
FLOW MEDIATED DILATATION MEASUREMENTS			
FMD BASAL (mm)	3.74±0.52	3.68±0.51	0.533
FMD HYPEREMIA (mm)	4.26±0.61	4.02±0.50	0.042
FMD RATIO	12.50(10.00-17.11)	9.38(6.06-12.12)	<0.001

FMD RATIO :[(FMD HYPEREMIA - FMD BASAL)/FMD BASAL]x100 Shapiro-Wilk Test $p > 0.05$ Student T test, Mean±SD, $p < 0.05$, *Shapiro-Wilk Test $p < 0.05$, Mann-Whitney U Test, Median (%25- %75), $p < 0.05$

Table 2: Comparisons Of Anthropometric, Biochemical, Echocardiographic And Fmd Measurements Among Multiple Sclerosis Groups.

	GROUP 1 MULTIPLE SCLEROSIS RRMS N:37 MEAN±SD	GROUP 2 MULTIPLE SCLEROSIS SPMS N:5 MEAN±SD	GROUP 3 MULTIPLE SCLEROSIS PPMS N:5 MEAN±SD	P
ANTHROPOMETRIC MEASUREMENTS				
AGE (years)	36.89±11.16	49.00±5.96	55.40±10.55	0.001
WEIGHT(kg)	70.30±13.51	70.80±10.66	81.80±18.87	0.229
HEIGHT(cm)	165.65±7.25	168.40±8.79	164.80±5.98	0.692
BODY MASS INDEX (kg/m ²)	25.66±4.84	25.28±5.66	29.85±4.89	0.199
WAIST CIRCUMFERENCE (cm)	88.03±13.98	87.00±14.41	103±8.34	0.074
BLOOD PRESSURE MEASUREMENTS				
SYSTOLIC BLOOD PRESSURE (mmHg)	125.2±7.8	126.6±5.5	124.8±5.2	0.559
DIASTOLIC BLOOD PRESSURE (mmHg)	79.0±5.8	72.0±7.6	79.0±4.2	0.051
BIOCHEMICAL MEASUREMENTS				
HGB	13.32±1.58	13.74±1.32	13.74±1.29	0.745
WBC	6.71±2.73	9.07±6.21	8.78±3.54	0.175
PLT	279.89±86.15	284.00±90.59	263.80±87.80	0.917
SERUM BLOOD GLUCOSE LEVEL (Fasting) (mg/dl)	96.95±8.60	99.80±9.20	103.80±11.39	0.255
SERUM UREA LEVEL (mg/dl)	31.11±4.60	27.00±4.63	27.20±3.27	0.053
CREATININE (mg/dl)	0.69±1.2	0.62±0.07	0.84±0.16	0.019
TOTAL CHOLESTEROL (mg/dl)	181.1±6.89	200.5±14.36	194.6±16.93	0.590
LDL CHOLESTEROL (mg/dl)	104.2±36.57	114.75±28.50	123.80±30.05	0.472
HDL CHOLESTEROL (mg/dl)	54.94±14.98	54.25±13.35	40.60±6.77	0.121
TRIGLISERID (mg/dl)	117.34±60.23	157.00±55.96	155.80±70.01	0.243
CRP*	4.00(2.29-8.00)	4.00(3.10-8.60)	7.10(6.00-12.50)	0.174
SEDIMENTATION*	13.0(11.0-23.0)	16.0(5.0-32.5)	19.0(9.5-34.0)	0.794
T3	3.10(2.75-3.40)	2.60(2.30-3.15)	2.70(2.45-3.00)	0.069
T4	1.15(1.00-1.24)	1.20(1.05-1.35)	1.25(1.17-1.40)	0.233
TSH	1.80(1.10-2.53)	1.77(1.25-2.97)	1.70(1.44-1.83)	0.882
MULTIPLE SCLEROSIS MEASUREMENTS				
EDSS*	1.00(0.00-1.00)	5.00(4.50-6.00)	7.00(6.00-7.50)	<0.001
ECHOCARDIOGRAPHIC MEASUREMENTS				
LA	31.16±2.96	33.20±1.30	30.20±3.11	0.232
AO	31.11±3.06	34.40±0.55	33.20±3.03	0.037
EF	65.00±2.90	63.20±2.86	59.60±2.70	0.001
IVS	0.95±0.14	1.02±0.05	1.06±0.09	0.059
FLOW MEDIATED DILATATION MEASUREMENTS				
FMD BASAL (mm)	3.55±0.43	3.92±0.36	4.38±0.59	0.001
FMD HYPEREMIA (mm)	3.93±0.46	4.18±0.40	4.52±0.58	0.029
FMD RATIO*	10.00(8.89-12.70)	5.40(4.96-8.94)	2.70(2.05-4.76)	0.020

*FMD RATIO :[(FMD HYPEREMIA - FMD BASAL)/FMD BASAL]x100 Shapiro-Wilk Test $p > 0.05$, One-way ANOVA test, Mean±SD $p < 0.05$, *Shapiro-Wilk Test $p < 0.05$, Kruskal-Wallis Test, Median (%25-%75), $p < 0.05$

Table 3: Comparisons Of Anthropometric, Biochemical And Fmd Measurements in Normal Control, Relaps Remitting Ms Group And Progressive Ms Groups.

	NORMAL CONTROL GROUP N:49 Mean±SD	RELAPS REMITTING MS (RRMS) GROUP N:37 Mean±SD	PROGRESSIVE MS (SPMS+PPMS) GROUPS N:10 Mean±SD	P
ANTHROPOMETRIC MEASUREMENTS				
AGE (years)	45.22±15.27	36.89±11.16	52.20±8.75	0.001
WEIGHT(kg)	75.24±16.55	70.30±13.51	76.30±15.56	0.860
HEIGHT(cm)	165.06±9.61	165.65±7.25	166.60±7.34	0.280
BODY MASS INDEX (kg/m ²)	27.58±5.26	25.66±4.83	27.57±5.56	0.208
WAIST CIRCUMFERENCE (cm)	93.04±15.91	88.03±13.98	95.00±13.94	0.225
BLOOD PRESSURE MEASUREMENTS				
SYSTOLIC BLOOD PRESSURE	122.7±9.1	125.2±7.8	124.2±5.7	0.382
DIASTOLIC BLOOD PRESSURE	80.0±6.8	79.03±5.8	75.5±6.9	0.138
BIOCHEMICAL MEASUREMENTS				
Hemoglobin	13.95±1.31	13.32±1.58	13.74±1.23	0.126
White Blood Cell	7.85±2.00	6.71±2.73	8.92±4.76	0.035
Platelets	271.88±62.97	279.89±86.15	273.90±84.78	0.885
SERUM BLOOD GLUCOSE LEVEL (Fasting) (mg/dl)	96.90±13.48	96.95±8.60	101.80±10.00	0.449
TOTAL CHOLESTEROL (mg/dl)	185.64±40.77	182.60±40.74	197.71±32.13	0.602
LDL CHOLESTEROL (mg/dl)	106.52±37.75	104.19±36.57	119.78±27.91	0.519
HDL CHOLESTEROL (mg/dl)	49.36±12.56	54.94±14.97	46.67±11.90	0.110
Triglyceride	149.13±66.37	117.34±60.23	156.33±60.23	0.059
CRP*	4.00(2.50-7.00)	4.00(2.29-8.00)	7.05(4.00-8.43)	0.146
SEDIMENTATION*	13.00(9.00-21.00)	13.0(11.0-23.0)	17.50(6.75-27.25)	0.518
T3*	2.90(2.50-3.10)	3.10(2.75-3.40)	2.70(2.43-3.00)	0.290
T4*	1.10(1.00-1.30)	1.15(1.00-1.24)	1.23(1.13-1.40)	0.252
TSH*	1.30(0.90-3.10)	1.80(1.10-2.53)	1.74(1.37-1.92)	0.717
ECHOCARDIOGRAPHIC MEASUREMENTS				
Left atrium (mm)	32.04±4.58	31.16±2.96	31.70±2.75	0.582
Aort(mm)	32.12±3.78	31.11±3.06	33.80±2.15	0.073
Left ventricle Ejection Fraction (EF)(%)	62.6±6.50	65.00±2.90	61.40±3.45	0.047
Interventricular septum thickness(mm)*	1.00(0.90-1.10)	0.95±0.14	1.03±0.06	0.016
FLOW MEDIATED DILATATION MEASUREMENTS				
FMD BASAL (mm)	3.73±0.52	3.55±0.43	4.15±0.52	0.003
FMD HYPEREMIA (mm)	4.27±0.61	3.93±0.46	4.35±0.50	0.011
FMD RATIO	12.50(10.00-17.11)	10.00(8.89-12.70)	4.77(2.58-6.20)	<0.001

FMD RATIO = [(FMD HYPEREMIA - FMD BASAL)/FMD BASAL]x100, Shapiro-Wilk Test p>0.05, One-way ANOVA test, Mean±SD, p<0.05, *Shapiro-Wilk Test p<0.05, Kruskal-Wallis Test, Median (%25-%75), p<0.05

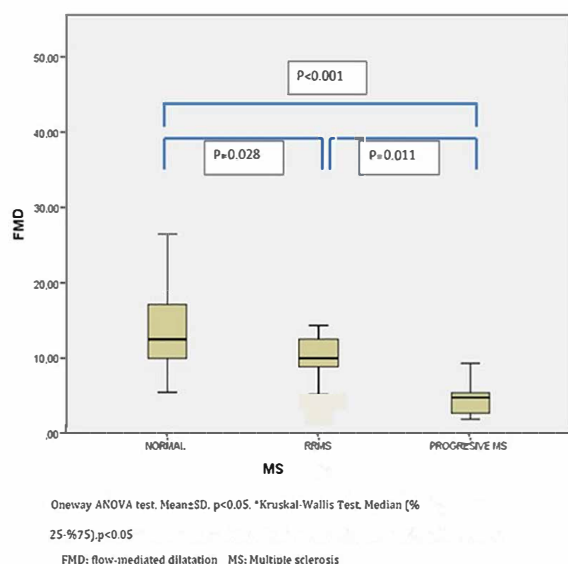


Figure 1: FMD measurements among normal, RRMS and progressive MS groups.

DISCUSSION

In the present study, we determined that there are decreased FMD hyperemia and FMD Ratio values in patients with MS compared to normal control participants. We detected that there is

statistically significant decrease in progressive MS groups compared to normal and RRMS groups. Especially PPMS group has more decreasing FMD value than the other groups.

Our study results have shown that the patients with MS have progressively increasing endothelial dysfunction during disease period especially getting progressive forms of MS. Although the patients with PPMS group have older appearance compared to the other groups, after controlling the effects of age and gender we still found that PPMS group has more severe endothelial dysfunction according to other groups.

Endothelial cells, which constitute one of the most important cell groups of the entire cardiovascular system, both structurally and functionally, have an indispensable importance in the holistic functioning of the cardiovascular system (20-26). Many pathological conditions affecting endothelial cells are known to constitute the basic pathophysiological mechanisms of cardiovascular diseases (22). It is well known fact that FMD tests create shear stress in the brachial artery, causing reactive NO release in the arterial bed (20-25). During this test, it shows how much the vessel can expand compared to basal values, according to the NO release capacity (20,25). Many of the studies have shown that there are decreased FMD measurements in patients with degenerative cardiovascular diseases like hypertension, atherosclerosis, diabetes mellitus and congestive heart failure (22). It seems that NO production capacity decreases progressively with the patients having endothelial dysfunction. There are increased incidences of cardiovascular disease which accompany with progressive endothelial dysfunction could also go with many of neurological disorders (27). Some studies also have shown that there is severe endothelial dysfunction in MS patients. Although many of factors could be effective on this results like age, immobility, increased body mass index, hyperlipidemia, hypertension and atherosclerotic processes which are inevitably increased incidences with MS progression, it was detected that independent characteristics of MS (28) Although EDSS scores have significant importance to clinical evaluation of the patients with MS (25), we

could not find any significant correlation with EDSS scores and FMD measures after statistically controlling the effects of age and gender.

Numerous studies have shown that increased NO and reactive oxygen species could be both initiating and promoting factors of blood-brain barrier (BBB) damage (5,17). The studies which were done in last few decades have shown us there are autoimmunological pathophysiological mechanisms which are accompany with increased NO and reactive oxygen species levels could be deteriorative effects on both astroglial and neuronal levels in brain by BBB damage, increased membrane permeability and mitochondrial damage (5,17). This pathophysiological process last myelin degeneration of neurons in both peripheral and autonomic nerve systems. This demyelination process in MS disease and the neuronal damage at the end of this process cause both neuronal conduction delays and a clinical pathological process accompanied by complete blockage of conduction (28-30). At that point data about NO in patients with MS in the literature pointed out that there is increased amount of NO in BOS specimens. On the other hand, MS patients have decreased NO production capacity at peripheral arterial bed (5,17,18).

According to our study, there is significant decreasing of FMD measures in patients with both RRMS and progressive MS groups compared to normal group. On the other hand, this decrease in FMD values is more pronounced in the progressive MS group. At that point, it seems that there are more severe and spreading BBB lesions which have decreased remyelination capacity accompanied with more severe NO distribution defects in patients with MS. We considered that the process of production, distribution and utilization of NO are deteriorated with progressively especially in the later stages of MS. In addition, the data obtained according to the results of our research show that monitoring FMD values in MS patients can be a monitoring criterion in terms of possible progression of the disease.

Our study is a single-center and cross-sectional study. One of the most important factors limiting our study was the small number of patients, particularly in some groups. Therefore, the subgroups with small patient numbers (SPMS and

PPMS) were also considered as a single combined group (Progressive MS) during statistical analysis. In this study, we evaluated the endothelial function with only FMD results. Although this is a very practical and useful method for indirect evaluation of brachial relaxation capacity due to shear stress related NO releasing, we could not measure serum NO levels directly. Moreover, both direct and indirect methods about the detection of peripheral NO could not reflect the levels in BOS and brain humors. Besides, data on smoking among study participants were not included in the statistical evaluation due to the small number of patients in some subgroups. Another limitation of our study is the lack of immunomodulatory/cardiovascular drug registration which could be effective on serum NO levels. Large studies could be effective in getting more detailed data and analyses.

Our data indicates that the patients with MS have decreased FMD measurements compared to normal controls. PPMS group has more severe deterioration about FMD measures than the other groups. There are decreased FMD ratio values in progressive MS groups compared to control and RRMS group.

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