Metabolic Syndrome and Arterial Stiffness in Peritoneal Dialysis Patients

Periton Diyalizi Hastalarında Metabolik Sendrom ve Arteriyel Sertlik

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ABSTRACT

OBJECTIVE: The metabolic syndrome (MetS) is an endocrinopathy that increases the risk of cardiovascular disease. Arterial stiffness is commonly used to evaluate the risk of cardiovascular disease, which is quantified by pulse wave velocity (PWV) and augmentation index (AIx). Our study aim was evaluate the prevalence of MetS and arterial stiffness in peritoneal dialysis patients.

MATERIAL and METHODS: A total of 36 peritoneal dialysis patients were included. Patients' waist circumference, body mass index (BMI), blood pressure, glucose, triglyceride, and HDL-cholesterol levels were recorded. PWV and AIx measurements were performed by means of the Mobil-O-Graph device. Adult Treatment Panel III criteria were used for the diagnosis of MetS.

RESULTS: 47.2% of peritoneal dialysis patients had MetS, and the prevalence of MetS was found to be 61% above the age of 55 years. Patients with MetS had higher BMI, waist circumference, glucose, triglyceride levels. Median age was significantly higher in the MetS group (p=0.044). Age-adjusted analysis revealed significantly higher Alx@75 in the MetS group (p=0.025); but no significant difference was observed in PWV. In regression analysis, the age, central systolic blood pressure, and augmentation pressure appeared as the independent determinants of PWV.

CONCLUSION: Metabolic Syndrome prevalence was found to be 47.2%, and it was more common in subjects older than 55 years. In the MetS group, the Alx@75 values were found to be significantly higher.

KEY WORDS: Arterial stiffness, Augmentation index, Metabolic syndrome, Peritoneal dialysis, Pulse wave velocity

ÖZ

AMAÇ: Metabolik Sendrom (MetS) kardiyovasküler hastalık riskini artıran bir endokrinopatidir. Nabız Dalga Hızı (NDH) ve Augmentasyon İndeksi (Alx) ölçümleri ile değerlendirilen arteriyel sertlik kardiyovasküler hastalık risk belirlenmesinde sıklıkla kullanılmaktadır. Çalışmamızda periton diyaliz hastalarındaki MetS sıklığını ve arteriyel sertlik durumlarını değerlendirmeyi amaçladık.

GEREÇ ve YÖNTEMLER: Çalışmaya 36 periton diyalizi hastası alındı. Hastaların bel çevresi, Vücut kitle indeksi (VKİ), kan basıncı, glukoz, Trigliserid, HDL-Kolesterol değerleri kaydedildi. Nabız dalga hızı ve Alx ölçümleri Mobil-O-Graph cihazı ile yapıldı. Metabolik Sendrom tanısında, Adult Treatment Panel III ölçütleri kullanıldı.

BULGULAR: Periton diyalizi hastalarının %47,2'sinde MetS saptandı ve 55 yaş üstünde sıklığı %61 bulundu. MetS grubunda VKİ, bel çevresi, glikoz, trigliserid düzeyleri yüksekti. MetS grubu ortanca yaşı anlamlı yüksekti (p=0,044). Yaş ile düzeltilmiş analizde Alx@75 MetS grubunda anlamlı yüksek saptandı (p=0,025), fakat NDH'ında anlamlı fark saptanmadı. Regresyon analizinde NDH'nın bağımsız belirleyicileri yaş, santral sistolik kan basıncı ve augmentasyon basıncı olduğu saptandı.

SONUÇ: Metabolik sendrom sıklığı % 47,2'dir ve 55 yaş üstünde daha yaygındır. Alx@75 değerleri MetS grubunda anlamlı yüksektir.

ANAHTAR SÖZCÜKLER: Arteriyel sertlik, Augmentasyon indeksi, Metabolik sendrom, Nabız dalga hızı, Periton diyalizi

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INTRODUCTION

Metabolic syndrome (MetS) is an endocrinopathy that develops on the basis of insulin resistance and characterized by systemic disorders i.e. hyperglycemia, abdominal obesity, dyslipidemia, and hypertension. It is associated with an increased risk of cardiovascular disease (CVD) (1). Diagnostic criteria for diagnosis of Metabolic syndrome were defined by the National Cholesterol Education Program/Adult Treatment Panel III (NCEP-ATP III), the World Health Organization (WHO), and the International Diabetes Federation (IDF) (2). Most epidemiological clinical studies have utilized NCEP-ATP III criteria due to its ease of use (3).

Advanced chronic kidney disease (CKD) and MetS have many similarities and multiple interactions, such as glucose intolerance and insulin resistance, hypertension, atherogenic dyslipidemia, proinflammation, hypertriglyceridemia, and low HDL (4).

Cardiovascular disease is the most important cause of mortality in dialysis patients, and the presence of MetS is an independent risk factor for the mortality of CVD. Arterial stiffness is closely related to hypertension, coronary artery disease, stroke, heart failure, and atrial fibrillation, and is used to determine the risks associated with CVD (5). Arterial stiffness can be non-invasively determined by the measurement of pulse wave velocity (PWV) and augmentation index (AIx) using a Mobil-O-Graph device. Pulse wave velocity is the speed of arterial pulse pressure wave that travels in the arterial system, and can be measured from palpable arterial segments (6). As arterial stiffness increases, pressure wave travels more rapidly and returns back to heart before diastole, resulting in reduced coronary perfusion and left ventricular hypertrophy (5, 6)

The factors commonly involved in MetS, such as oxidative stress, proinflammation, and high blood pressure, also increase arterial stiffness (5). Only a few studies have evaluated MetS in patients undergoing peritoneal dialysis (4, 7). The aim of the present study was to evaluate the prevalence of MetS and co-occurrence with arterial stiffness in patients undergoing peritoneal dialysis.

METHODS

A total of 36 patients, whose clinical condition was stable for at least the last two months and who had been undergoing peritoneal dialysis for at least three months, were included in the study. The patients who have experienced an episode of peritonitis in the last three months were excluded from the study. The patients were informed about the nature of the study and informed consent was obtained.

Diagnosis of Metabolic Syndrome

According to the NCEP-ATP-III criteria, having three or more of the following conditions is considered diagnostic for MetS: Abdominal obesity (waist circumference: men > 102 cm, women > 88 cm), elevated fasting plasma triglycerides (≥ 150 mg/dL), low high-density lipoprotein cholesterol (Men < 40 mg/dL, Women < 50 mg/dL), high blood pressure (≥ 130/85 mmHg or on treatment), dysglycemia (fasting glucose ≥ 100 mg/dL or known diabetes mellitus) (8, 9).

The waist circumference was measured at the midpoint between the lower costal margin and iliac crest while the patient was in a standing position. Body mass index (BMI) was calculated by using the following formula: BMI = weight/height^2 (kg/m^2). Fasting blood samples were obtained for the measurement of glucose, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, uric acid, serum albumin, C-reactive protein (CRP), and hemoglobin. Daily glucose exposure was calculated from the dialysis regimen. The product of the volume and the glucose concentration for each exchange was calculated as described by Davies et al (10). The duration of peritoneal dialysis, weight gain in comparison to start of peritoneal dialysis, and the etiology of CKD recorded from the medical chart for each patient.

Measurement of Arterial Stiffness

A single-cuff arteriograph device (Mobil-O-Graph PWA, a model pulse wave analysis device, I.E.M. GmbH, Stolberg, Germany) was employed using the oscillometric method, which is independent from the operator and has validated reliability. The patients remained at rest for 15 minutes before the measurement. After entering date of birth, height, weight, and smoking status into the device program for each patient, the appropriate blood pressure cuff was placed on the upper arm on the projection of the brachial artery while the patient was in a seated position. The cuff was kept at the level of the heart, and three successive measurements were obtained at 30-sec intervals.

The device automatically inflates above the systolic blood pressure to occlude the brachial artery. This allows the detection of fluctuations in the pressure of the brachial artery. The fluctuations are amplified by the tonometric sensor and transmitted to the device. The software installed on the device discriminates between early, late systolic and diastolic waves. The software calculates PWV, pulse pressure, and systolic and diastolic pressure from the central pressure changes, early (direct, P1), late (backward, P2) systolic and diastolic wave date. Augmentation pressure is calculated as the difference between the first and second systolic peak, and the Alx is calculated by the software as the proportion of augmentation pressure to pulse pressure (5,11,12).

Statistical Analysis

The Statistical Package for Social Sciences for Windows version 17 [SPSS Inc.; Chicago, IL, USA] software package was used for the statistical analyses. Descriptive statistics were expressed as number (n, %), median (25–75 percentile). The Mann-Whitney U-test was used in the comparison of data without normal distribution. The chi-square test was used for comparison of frequencies in both groups. The relationship between the

variables was evaluated using Pearson's correlation coefficient. Backward multiple linear regression analysis was performed to determine variables associated with arterial stiffness. A p value < 0.05 was considered statistically significant.

RESULTS

A total of 36 patients (24 males and 12 females) who were on follow-up in the peritoneal dialysis unit were included in the study. Metabolic syndrome was detected in 17 patients (47.2%). The causes of end-stage renal disease in the MetS and non-MetS group were diabetes at 13.9% - 8.3%, hypertension at 22.2% - 13.9%, glomerulonephritis at 2.8% - 8.3%, other/unknown at 8.3% - 22.2% respectively. Distribution of etiologies was not statistically different. The median age was significantly higher in the MetS group (p=0.044). The prevalence of MetS increased with age. 18 patients were aged above 55 years, and 11 of them (61%) had MetS. The patients gained 4.1 kg on average in a period of 39.3 months on peritoneal dialysis. Total cholesterol and CRP levels were significantly higher in the MetS group. The weight gain, systolic and diastolic blood pressure, duration of peritoneal dialysis, LDL-cholesterol, serum albumin, uric acid and hemoglobin levels were similar between the two groups. Median daily total glucose exposure was higher and urine volume was lower in MetS, however the differences were not significant (Table I).

Waist circumference, BMI, serum triglyceride, and glucose levels were significantly higher in the MetS group, as expected. The HDL-cholesterol level was lower in the MetS groups but this was not statistically significant (Table I).

The evaluation of individual prevalence rates for the components of MetS in patients undergoing peritoneal dialysis revealed that 55.5% had high blood pressure, 50% had hypertriglyceridemia, 50% had hyperglycemia, 47.2% had high waist circumference, and 69.46% had low HDL-cholesterol (Table II). Individual prevalence rates of the components of MetS according to gender was not significantly different.

The median PWV was 8.7 m/sec in the MetS group and 6.5 m/sec in the other group, and the difference was statistically significant (p=0.017). However, there was no significant difference between the groups in age-adjusted analysis, although PWV was higher in the MetS group (8.09 m/sec versus 7.82 m/sec, p=0.368). The median Alx normalized with 75/min heart rate (Alx@75) values were 29.6 in the MetS group and 18.7 in the other group (p= 0.025), and age-adjusted univariate analysis confirmed that Alx@75 was higher in MetS group (p= 0.025) (Figure 1, 2).

The correlation analysis involving all patients revealed a positive correlation between PWV and age (r=0.921, p< 0.001), waist circumference (r= 0.543, P= 0.001), augmentation pressure (r=0.420, p=0.011), central systolic blood pressure (r=0.448, p=0.006), and BMI (r=0.389, p=0.019). Multiple regression analysis was performed to detect the independent determinants of PWV among the parameters that were found to be correlated. Age, central systolic blood pressure, and augmentation pressure appeared as independent determinants of PWV. These parameters accounted for 96.8% of the PWV (Table III). Augmentation index normalized with 75/min heart rate (Alx@75) correlated only with waist circumference (r=0.380, p=0.022), and BMI (r=0.359, p=0.032).

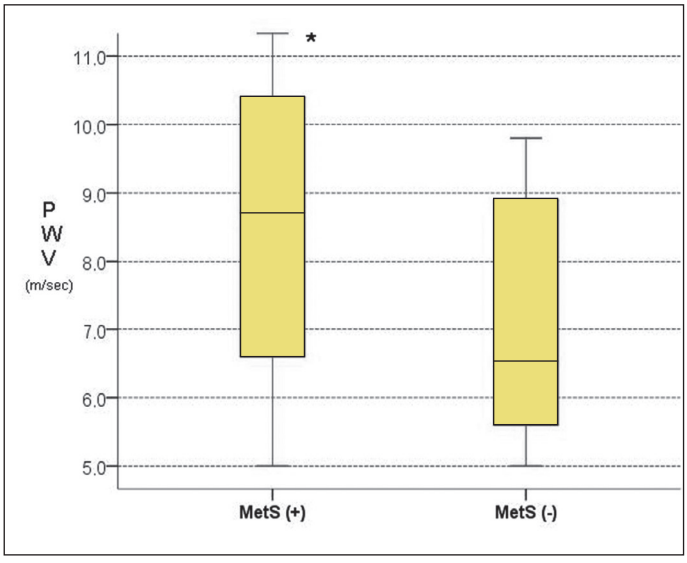

Figure 1: *Pulse wave velocity values of the groups.*
****:*** *Difference between groups,* ***p=*** *0.017,* ***MetS:*** *Metabolic syndrome,* ***PWV:*** *Pulse wave velocity, median (25–75 percentile) ± min, max value.*

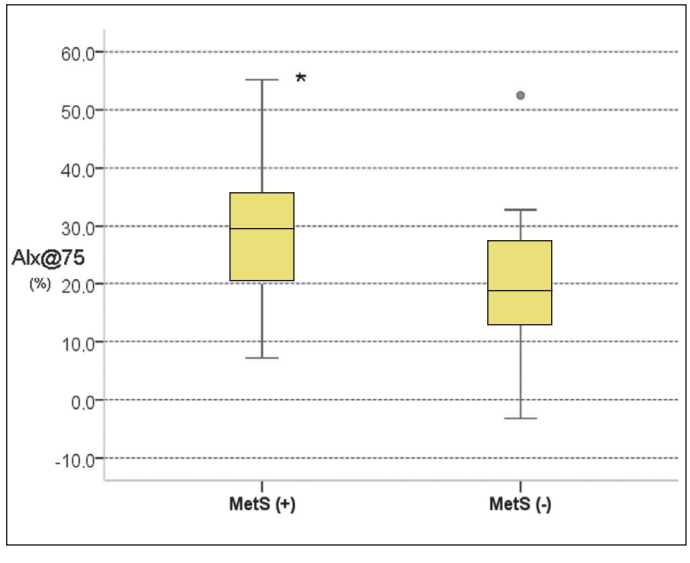

Figure 2: *Alx@75 values of the groups.*
****:*** *Difference between groups,* ***p=*** *0.010,* ***Alx@75:*** *Augmentation index normalized with 75/minute heart rate,* ***MetS:*** *Metabolic syndrome, median (25–75 percentile) ± min, max value.*

Table I: Demographical, clinical, and biochemical characteristics of the groups.

Variable	MetS (+) (n=17, 47.2%)	MetS (-) (n=19, 52.8%)	P
Age (year)	58 (46.5-72.5)	49 (32.0-62.0)	0.044
BMI (kg/m^2)	31.0 (26.1-34.1)	24.7 (20.8-26.9)	0.002
Waist circumference (cm)	106 (95.5-115.5)	88 (79.0-98.0)	< 0.001
Triglyceride (mg/dl)	221 (153.5-259.5)	114 (86.0-145.0)	0.001
HDL- cholesterol (mg/dl)	33 (30.0-40.5)	37 (34.0-44.0)	0.059
Systolic BP (mmHg)	143 (112-149)	122 (110-148)	0.303
Diastolic BP (mmHg)	85 (72.5-104.5)	86 (73.0-94.0)	0.495
Glucose (mg/dl)	117 (98.5-156.5)	92 (80.0-105.0)	0.002
Weight gain (kg)	4.5 (1.1-6.3)	3.8 (0.8-6.8)	0.949
C-Reactive protein (mg/dl)	17.3 (7.4-36.5)	4.7 (3.2-7.0)	0.015
Peritoneal duration (month)	32 (9.5-41.0)	30 (9.0-73.0)	0.516
T-Cholesterol (mg/dl)	202 (176-253)	171 (155-200)	0.038
LDL-Cholesterol (mg/dl)	125 (108-162)	109 (101-122)	0.103
CSBP (mmHg)	133 (105-137)	116 (102-132)	0.274
CDBP (mmHg)	90 (73-107)	87 (74-95)	0.485
Creatinine (mg/dl)	7.6 (5.8-10.7)	9.0 (6.9-12.7)	0.680
Urea (mg/dl)	97 (77-122)	122 (79-153)	0.188
Serum albumine (g/dl)	3.5 (3.2-3.6)	3.4 (3.2-3.7)	0.811
Uric acid (mg/dl)	6.8 (5.4-8.9)	5.6 (5.2-6.5)	0.128
Hemoglobin (g/dl)	11.1 (10.1-12.7)	10.7 (10.1-11.3)	0.260
Glucose exposure (g/day)	163.2 (108.8-249.5)	136.0 (122.4-204.0)	0.751
Urine volume (ml/day)	400 (50-1750)	1000 (300-1950)	0.357
ESRD etiology			
Hypertension	8 (22.2%)	5 (13.9%)	0.344
Diabetes mellitus	5 (13.9%)	3 (8.3%)	0.433
Glomerulonephritis	1 (2.8%)	3 (8.3%)	0.605
Unknown etiology	2 (5.5%)	3 (8.3%)	1.000
Post renal	1 (2.8%)	5 (13.9%)	0.182
Total	17 (47.2%)	19 (52.8%)	-

BMI: Body mass index, **CDBP:** Central diastolic blood pressure, **CSBP:** Central systolic blood pressure, **ESRD:** End-stage renal disease, **MetS:** Metabolic syndrome. Variable values were expressed as number (n, %) or median (25-75 percentile).

DISCUSSION

Metabolic syndrome is an important cause of morbidity and mortality as insulin resistance, pro-inflammatory cytokines (e.g., IL-6, TNF- α) released from adipose tissue, hypercoagulability, and hypertension worsens vessel wall injury (13). Metabolic syndrome is becoming a worldwide pandemic. The prevalence was 34% in the 2003-2006 cohort of the National Health and Examination Survey (NHANES) and 33.9% in Turkey (14,15). The prevalence of MetS was reported to be 46% in CKD patients in Turkey, and was around 53% - 70% in dialysis patients (16-20).

The risk of MetS in patients undergoing peritoneal dialysis is higher than in hemodialysis and predialysis patients due to the

Table II: Prevalence of individual component of MetS in peritoneal dialysis patients.

Component of MetS	Normal n (%)	Abnormal n (%)	Total cases n (%)	Cut of values
Waist circumference	20 (55.5)	16 (44.5)	36 (100)	> 102 cm in men & > 88 cm in women
Triglyceride	18 (50)	18 (50)	36 (100)	≥ 150 mg/dl
HDL- cholesterol	11 (30)	25 (70)	36 (100)	< 40 mg/dl in men & < 50 mg/dl in women
Blood pressure	21 (58.3)	16 (41.7)	36 (100)	≥ 130/85 mmHg
Fasting glucose	18 (50)	18 (50)	36 (100)	≥ 100 mg/dl

MetS: Metabolic syndrome.

Table III: Multiple linear regression analysis of variables associated with pulse wave velocity.

Parameters	Regression coefficient	Standart error	Beta	p
Age (year)	0.112	0.006	0.855	< 0.001
CSBP (mmHg)	0.023	0.005	0.245	< 0.001
AuP (mmHg)	0.029	0.016	0.095	0.077

AuP: Augmentation pressure, **CSBP:** Central systolic blood pressure.

higher risk of metabolic disturbances, such as hyperglycemia and hyperlipidemia, and weight gain (4). According to the criteria of NCEP ATP III, the prevalence of MetS among patients undergoing peritoneal dialysis was reported to be 55%-60% (21, 22). Peritoneal dialysis solutions have high glucose content, and 60-80% of the glucose is absorbed by the peritoneal membrane (23). This corresponds to 100 - 300 gr of glucose per day, and glucose overload may cause worsening of the components of MetS including obesity, hyperlipidemia, hyperglycemia, and insulin resistance.

Insulin resistance is significantly more prominent in patients undergoing peritoneal dialysis compared to that of hemodialysis and predialysis patients. The incidence of diabetes in the general population is 0.5 - 0.9%, while the incidence is around 12.7% in patients undergoing peritoneal dialysis (24,25). It was found that 27.3% of the patients developed diabetes at the end of the first month after initiation of peritoneal dialysis (26). Another study reported increased insulin requirement in diabetic patients undergoing peritoneal dialysis (27). In addition, uremic toxins, inflammation, and oxidative stress increase the risk of MetS in patients with CKD (4). The prevalence of MetS was found to be 47.2% in the present study, and the above-mentioned factors were considered to contribute to the development of MetS.

The prevalence of MetS increases as the population gets older. The NHANES cohort between 2003 and 2006 reported an increased prevalence rate with increasing age; 20% in males versus 16% in females aged below 40 years, and 52% in males and 54% in females aged above 60 years (16). In the present study, the prevalence of MetS increased with age and we found that it was 61% in patients aged above 55 years.

Cross-sectional and longitudinal studies demonstrated increased arterial stiffness in patients with MetS (28-30). Holewijn et al. found higher PWV and AIx in patients with MetS and reported that it could be a marker of subclinical atherosclerosis (31). Metabolic syndrome co-occurring with CKD was found to be associated with increased PWV (32). There is a limited number of studies that have evaluated MetS and arterial stiffness in patients undergoing peritoneal dialysis. In a study conducted in 2008, the characteristics of MetS in patients undergoing peritoneal dialysis were found to be closely related to PWV (7). In the present study, age-adjusted AIx was found to be significantly higher in patients with MetS; however, the difference in PWV did not reach statistical significance. The lack of a significantly high level of PWV was attributed to the small number of patients in the study.

Hypertension is prevalent in MetS, and is mainly attributed to subclinical organ damage and arterial stiffness. However, it has been reported that increased arterial stiffness was independent from hypertension in CKD with MetS (30). Mechanisms other than hypertension might have played a role in arterial stiffness and the physiopathology remains currently unknown. Elevated levels of pro-inflammatory cytokines such as IL-6 and TNF-α,

and decreased levels of nitric oxide and adiponectin in MetS may accelerates the atherosclerotic process, which increases vasoconstriction and thrombosis (13).

Hyperinsulinemia increases sympathetic tone, promotes sodium reabsorption, activates the renin-angiotensin-aldosterone system, and can increase systemic and vascular inflammation (33). In addition, advanced glycosylation products produced by hyperglycemic state can cross-bind with the collagen molecules on the arterial wall. This can result in the loss of flexibility and increased arterial stiffness in the long-term (34).

The risk of cardiovascular mortality is 15 - 30 times higher in patients with end-stage renal disease compared to general population (35). Metabolic syndrome is associated with 2-fold increase in the risk of stroke, cardiovascular mortality and CVD and 1.5-fold increase in all-cause mortality (36). A 1 m/sec decrease in PWV decreases cardiovascular mortality risk by 21% in patients with end-stage renal disease, and the increase in arterial stiffness is associated with 1.5- to 6-fold increase in cardiovascular mortality (37-39). Considering the high mortality risk associated with CKD, MetS, and arterial stiffness, the researchers of the current study consider it appropriate to evaluate all patients undergoing dialysis for MetS and arterial stiffness.

CONCLUSION

Metabolic syndrome is common in peritoneal dialysis patients with a prevalence of 47.2% and was even more common in older patients. We found that Alx@75 increased in the MetS group. There is an increase in arterial stiffness in peritoneal dialysis patients with MetS. Therefore, prevention and treatment of MetS may be important to reduce or inhibit development of arterial stiffness in peritoneal dialysis patients.

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