

Relationship Between Microalbuminuria and Metabolic Parameters in a Normotensive Population with Obesity

Normotansif Obez Bireylerde Mikroalbuminürinin Metabolik Parametrelerle İlişkisi

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ABSTRACT

Objective: Today, the second-most common cause of preventable death after smoking is obesity. Microalbuminuria is defined as an albumin to creatinine ratio (ACR) of more than 30 mg per gram of creatinine. Obesity increases the incidence of microalbuminuria by affecting the kidneys.

Method: This study was carried out by retrospectively examining the files of obese [Body mass index (BMI) ≥ 30 kg/m²] individuals between the ages of 18 and 65 with spot microalbuminuria test in urine who were admitted to the obesity outpatient clinic of a tertiary hospital between January 2013 and June 2015. Four hundred and ninety subjects were included in the study. The physical parameters, blood and urine tests of the subjects included in the study at the time of first admission to the obesity clinic were examined.

Results: Microalbuminuria was found in 5.7 % of the study participants. The glycated hemoglobin (HbA1c) and uric acid levels for subjects in the microalbuminuria-positive group were higher than in the levels of subjects in the microalbuminuria-negative group [5.6 (5.8-5.5) vs 5.5 (5.7-5.2); P=0.012 and 5.2 (6-4.5) vs 4.7 (5.5-4.2); P=0.038, respectively]. In the microalbuminuria-negative group, 25-hydroxyvitamin D3 (25-OH D3) levels were higher than in the microalbuminuria-positive group [12 (18-7.1) vs 8.4 (12.9-6.9); P=0.032]. Urine albumin to creatinine ratio was positively associated with BMI, and fasting insulin (FI), triglyceride (TG) and c-reactive protein (CRP) levels, and Homeostatic model assessment for insulin resistance (HOMA-IR).

Conclusion: Obesity increases microalbuminuria by affecting the kidneys. Microalbuminuria is associated with insulin resistance, dyslipidemia and low 25-OH D3 levels. Microalbuminuria must be checked in obese individuals. The prevalence of obesity should be reduced for a healthier life.

Keywords: microalbuminuria, urine albumin to creatinine ratio (ACR), body mass index (BMI), microalbuminuria, obesity, urine albumin to creatinine ratio (ACR)

ÖZ

Amaç: Günümüzde önlenabilir ölümlerin sigaradan sonra gelen ikinci en önemli nedeni obezitedir. Mikroalbuminüri; albümin/kreatinin oranının 30 mg/g üzerinde olması olarak tanımlanmaktadır. Obezite böbrekleri etkileyerek mikroalbuminüriyi artırmaktadır.

Yöntem: Ocak 2013-Haziran 2015 tarihleri arasında üçüncü basamak bir hastanenin obezite polikliniğine başvuran obez [Vücut kitle indeksi (VKİ) ≥ 30 kg/m²] bireyleri retrospektif olarak değerlendirildi. Çalışmaya hipertansiyon, diyabet, böbrek hastalığı olan hastalar dahil edilmedi. 18-65 yaş aralığındaki 490 obez birey çalışmaya alındı. Bireylerin obezite polikliniğine ilk başvuru sırasındaki fiziksel ve biyokimyasal parametreleri incelendi.

Bulgular: Çalışmaya dahil edilenlerin %5,7'sinde mikroalbuminüri saptandı. Mikroalbuminüri olan gruptaki bireylerin glikozillenmiş hemoglobin A1c (HbA1c) ve ürik asit seviyeleri mikroalbuminüri olmayan gruptaki bireylerden daha yüksekti [5.6 (5.8-5.5) vs 5.5 (5.7-5.2); P=0.012 ve 5.2 (6-4.5) vs 4.7 (5.5-4.2); P=0.038, sırasıyla]. Mikroalbuminüri olmayan grupta 25-hidroksivitamin D3 (25-OH D3) seviyeleri mikroalbuminüri olan gruptan daha yüksekti [12 (18-7.1) ve 8.4 (12.9-6.9); P=0.032]. VKİ, açlık insülini, insülin direnci (HOMA-IR), trigliserid ve C-reaktif protein (CRP) ile mikroalbuminüri düzeyi arasında ilişki bulundu.

Sonuç: Obezite böbrekleri etkileyerek mikroalbuminüriyi artırmaktadır. Mikroalbuminüri; insülin direnci, dislipidemi ve düşük 25-OH D3 ile ilişkilidir. Mikroalbuminüri obez bireylerde mutlaka bakılmalıdır. Daha sağlıklı bir yaşam için obezite prevalansı azaltılmalıdır.

Anahtar kelimeler: mikroalbuminüri, idrar albümin kreatinin oranı, vücut kitle indeksi, obezite

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INTRODUCTION

By the end of the 20th century, changing lifestyles and nutritional habits increased the prevalence of obesity worldwide. Today, the second most common cause of preventable death after smoking is obesity. The World Health Organization (WHO) has announced that obesity will likely be the most prevalent health problem of the 21st century. The World Health Organization considers obesity to be a disease that must absolutely be treated (1).

Obesity leads to many health, social, and economic problems. When obesity is not treated, individuals are at higher risk for diabetes mellitus, insulin resistance (IR), hypertension, dyslipidemia, heart failure, atrial fibrillation, stroke, cholelithiasis, hepatosteatorosis, osteoarthritis, obstructive sleep apnea and cancer (2).

The kidneys are substantially affected by obesity. Obesity is associated with hypertension, which can lead to the development of diabetes mellitus and atherosclerosis, but can also independently affect the kidneys and increase the risk of developing chronic kidney disease (3-6). Obesity can also increase the risk of developing focal segmental glomerulosclerosis, obesity-related glomerulopathy, nephrolithiasis, urinary incontinence and renal cancers (7-9). The impact of obesity on the kidneys can also lead to microalbuminuria. Numerous medical studies assist the idea that insulin resistance may precede or make contributions to improvement of microalbuminuria (10-12). Insulin signaling in podocytes appears to be important to keep the integrity of the glomerular filtration barrier (12). These data may additionally suggest that reduced insulin sensitivity is associated with the initial pathogenesis of albuminuria (13).

Therefore, in this study, we aimed to investigate the association of microalbuminuria with anthropometric, metabolic and inflammatory parameters in normotensive obese population.

MATERIALS AND METHODS

Subjects

This study was carried out by retrospectively

examining the files of obese individuals with spot microalbuminuria test who applied to the obesity outpatient clinic of the Kartal Dr. Lutfi Kirdar Training and Research Hospital between January 2013 and June 2015. Exclusion criteria included present and past history of prevalent diabetes mellitus, arterial hypertension, renal disease. Further exclusion criteria were systolic/diastolic blood pressure $\geq 140/90$ mmHg, fasting plasma glucose (FPG) ≥ 126 mg/dL, glycated hemoglobin (HbA1c) $\geq 6.5\%$, using any medication and pregnancy. Four hundred and ninety subjects with obesity (aged 18–65 years) were included in the study.

This study approved by the Kartal Dr. Lutfi Kirdar Training and Research Hospital Ethical Committee. The approval number is 2016/514/82/1.

Measurement of anthropometric parameters and laboratory analysis

The physical parameters, blood and urine tests of the subjects included in the study at the time of first admission to the obesity clinic were examined. Physical examination findings [height (m), weight (kg)] and body mass index (BMI; kg/m²) of the patients measured by the researchers were recorded. Body fat percentages (PBF) of the subjects were calculated using bioelectrical impedance analysis.

Blood samples were taken from the study participants in the morning after 12 hours of fasting for biochemical and hormone tests. Venous blood samples were taken from the left arm to measure, and evaluate fasting plasma glucose (FPG), fasting insulin (FI), HbA1c, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), creatinine, uric acid, 25-hydroxyvitamin D3 (25-OH D3), C-reactive protein (CRP) levels and white blood cell (WBC) counts in the same day. Urine samples were also collected and were sent to determine urine albumin/creatinine ratios.

Obesity is defined as a BMI greater than or equal to 30 kg/m². Obesity is frequently subdivided into categories as follows: Grade 1 obesity: BMI:

30-35 kg/m², Grade 2 obesity: BMI: 35-40 kg/m² and Grade 3 obesity: BMI \geq 40 kg/m². Grade 3 obesity is sometimes categorized as morbid obesity. The degree of insulin resistance was estimated at the baseline by homeostatic model assessment for insulin resistance (HOMA-IR) according to the method described by Matthews et al.¹⁴. Insulin resistance was accepted as positive for subjects with HOMA-IR score \geq 2.7 (15).

For the purpose of this study, microalbuminuria was defined as an albumin to creatinine ratio (ACR) of more than 30mg per gram of creatinine (16).

Venous plasma glucose levels were measured using the hexokinase method. Glycosylated hemoglobin was measured by high-performance liquid chromatography (HPLC) method. Serum

insulin levels were determined using immunoassay method. Serum uric acid, TC, HDL-C and TG levels were studied using an enzymatic calorimetric measurement technique. Low-density lipoprotein cholesterol was estimated by Friedewald Equation [LDL-C = TC - (TG/5) - HDL-C]. CRP was determined using by the nephelometric technique. 25-hydroxyvitamin D3 levels were measured by chemiluminescence technique.

Statistical analysis

Continuous variables with normal distribution were presented as mean [standard deviation (SD)]; non-normally distributed variables were reported as median [interquartile range (IQR)]. The normality of distribution of continuous variables was tested by one-sample Kolmogorov-Smirnov test. Means of 2 continuous normally distributed variables

Table 1. Characteristics of the study population and differences by gender

	All subjects (n=490)	Female (n=427)	Male (n=63)	P
Main characteristics				
Age (year)	38 \pm 10	39 \pm 10	35 \pm 10	0.003
Current smoker (%)	34	28	46	0.011
Weight (kg)	94 (104-85)	91 (102-84)	111 (126-101)	<0.001
BMI (kg/m ²)	36 (40-33)	36 (40-33)	35 (40-32)	0.28
PBF (%)	42 (47-38)	43 (47-40)	34 (37-31)	<0.001
Microalbuminuria (%)	5.7	5.4	7.9	0.386
Insulin resistance positivity (n)	66	65	79	0.031
Metabolic and inflammatory parameters				
FPG (mg/dl)	96 (103-90)	97 (104-90)	93 (101-88)	0.061
HbA1c (%)	5.5 (5.7-5.2)	5.5 (5.7-5.2)	5.5 (5.8-5.2)	0.466
FI (IU/ml)	13.7 (18.6-10.3)	13.6 (18-9.8)	17 (24.9-12.2)	0.001
TC (mg/dl)	194 \pm 40	194 \pm 40	194 \pm 37	0.968
HDL-C (mg/dl)	45 (52-38)	46 (53-39)	39 (42-34)	<0.001
LDL-C (mg/dl)	121 \pm 32	121 \pm 32	121 \pm 31	0.980
TG (mg/dl)	120 (161-89)	116. (155-88)	149 (223-105)	<0.001
CRP (mg/l)	5.3 (9.2-3.4)	5.5 (9.3-3.4)	4.1 (6.8-3.3)	0.083
WBC ($\times 10^3$ /mm ³)	7 (8.7-6)	7 (8.7-6)	8 (9-7)	0.072
Creatinine (mg/dl)	0.6 (0.7-0.5)	0.6 (0.6-0.5)	0.7 (0.8-0.7)	<0.001
Uric acid (mg/dl)	4.8 (5.6-4.2)	4.6 (5.3-4.1)	6.1(7-5.3)	<0.001
25-OH D3 (ng/ml)	11.5 (18-7)	11 (17-6.9)	15.5 (22.1-10.9)	<0.001

BMI: Body mass index, PBF: Percent body fat, FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, FI: Fasting insulin, TC: Total cholesterol, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, TG: Triglyceride, CRP: C-reactive protein, WBC: White blood cell, 25-OH D3: 25-hydroxyvitamin D3 Continuous variables are expressed as means \pm SD or median (interquartile range), and categorical variables as percentages (%). Differences between groups assessed with Student's t -test or Mann-Whitney U-test according to distribution of the data and chi-square test was used for categorical variables.

were compared by independent samples Student's t test. Mann-Whitney U test was used to compare means of variables not normally distributed. The frequencies of categorical variables were compared using chi-square test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

General characteristics, ACR levels and metabolic parameters of the obese population

Four hundred and ninety study participants including 427 (87.1%) female and 63 (12.9%) male patients with a mean age of 38 ± 10 years were evaluated. The mean BMI of the subjects was 36 kg/m^2 . Microalbuminuria was detected in 5.7% of all subjects. Rates of microalbuminuria positivity were similar in women and men ($P = 0.386$). Homeostatic model assessment for insulin resistance positivity was significantly higher in men than women (79% vs 65%; $P = 0.031$) (Table 1). Body mass index was similar in women and men ($P = 0.28$). However, PBF was significantly higher in women than men [43(47-40) vs 34 (37-31); $P < 0.001$]. Fasting insulin, TG, creatinine, uric acid, 25-OH D3 levels were significantly higher in men than women [17 (24.9-12.2) vs 13.6 (18-9.8); $P = 0.001$, 149 (223-105) vs 116.5 (155.7-88); $P < 0.001$, 0.7 (0.8-0.7) vs 0.6 (0.6-0.5); $P < 0.001$, 6.1(7-5.3) vs 4.6 (5.3-4.1); $P < 0.001$, 15.5 (22.1-10.9) vs 11 (17-6.9); $P < 0.001$, respectively]. However, HDL-C levels were significantly higher in women than men [46 (53-39) vs 39 (42-34); $P < 0.001$].

Albumin to creatinine ratio levels in subjects with morbid obesity

Among study participants, 26% ($n = 128$) were morbidly obese. ACR levels of subjects with grade 1 and grade 3 obesity were compared

(Table 2). In the first group (BMI = $30\text{--}34.9 \text{ kg/m}^2$; $n = 189$), the average ACR was 4.6 mg/g. In the second group (BMI $\geq 40 \text{ kg/m}^2$; $n = 128$), the average ACR was 6.1 mg/g. ACR levels were significantly higher in subjects with grade 3 obesity than subjects with grade 1 obesity ($P = 0.013$).

Metabolic parameters according to microalbuminuria

Two groups were created based on the presence of microalbuminuria (Table 3). We found that HbA1c and uric acid levels were significantly higher in microalbuminuria-positive group than the microalbuminuria-negative group [5.6 (5.8-5.5) vs 5.5 (5.7-5.2); $P = 0.012$ and 5.2 (6-4.5) vs 4.7 (5.5-4.2); $P = 0.038$, respectively]. However, we also found that 25-OH D3 levels were lower in microalbuminuria-positive group than the microalbuminuria-negative group [8.4 (12.9-6.9) vs 12 (18-7.1); $P = 0.032$]. Age, smoking status, BMI, PBF, glucose, FI, HOMA-IR, TC, HDL-C, LDL-C, TG, CRP, WBC and creatinine were similar among subjects in two groups.

Correlation between ACR and metabolic parameters

The correlation between ACR and metabolic parameters is given in Table 4. Albumin to creatinine ratio was positively correlated with BMI, IR, HOMA-IR, TG and CRP. We did not find any correlations among other metabolic parameters.

DISCUSSION

Obesity increases microalbuminuria by affecting the kidneys. The relationship between microalbuminuria and obesity has been of interest to researchers.

In our study, we distinguished two groups according to whether subjects had microalbuminuria or not. We found that HbA1c and uric acid levels were higher and 25-OH D3 levels were lower in the group with microalbuminuria. When we assessed the relationship between ACR levels and metabolic parameters in the study population, we found a

Table 2. Comparison of ACR levels in subjects with grade 1 and grade 3 obesity

	BMI 30-34.9 kg/m ² (n=189)	BMI $\geq 40 \text{ kg/m}^2$ (n=128)	P
ACR (mg/g)	4.6 (8.1-3.2)	6.1 (10.6-3.8)	0.047

ACR: Albumin to creatinine ratio, BMI: Body mass index Variables are expressed as median (interquartile range). P is derived from Mann-Whitney U-test.

Table 3. Anthropometric, metabolic and inflammatory parameters in groups with and without microalbuminuria

	Microalbuminuria (+) group (n=28)	Microalbuminuria (-) group (n=462)	P
Main characteristics			
Age (year)	38±8	38±10	0.902
Current smoker (%)	44	34	0.306
BMI (kg/m ²)	36 (41-33)	36 (40-32)	0.39
PBF (%)	45 (46-41)	42 (47-38)	0.342
Metabolic and inflammatory parameters			
FPG (mg/dl)	99 (110-90)	96 (103-89)	0.146
HbA1c (%)	5.6 (5.8-5.5)	5.5 (5.7-5.2)	0.012
FI (IIU/ml)	15 (23.7-11.7)	13.7 (18.6-10.1)	0.221
HOMA-IR	3.5 (5.5-2.8)	3.2 (4.4-2.3)	0.128
TC (mg/dl)	196±38	195±40	0.838
HDL-C (mg/dl)	42 (50-37)	45 (52-39)	0.417
LDL-C (mg/dl)	121±29	121±32	0.924
TG (mg/dl)	125 (167-89)	119 (160-89)	0.778
CRP (mg/l)	6.2 (13.6-4)	5.1 (9-3.4)	0.113
WBC (x10 ³ /mm ³)	7 (8.6-6.1)	7 (8.7-6)	0.688
Creatinine (mg/dl)	0.53 (0.6-0.5)	0.6 (0.7-0.5)	0.225
Uric acid (mg/dl)	5.2 (6-4.5)	4.7 (5.5-4.2)	0.038
25-OH D3 (ng/ml)	8.4 (12.9-6.9)	12 (18-7.1)	0.032

BMI: Body mass index, PBF: Percent body fat, FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, FI: Fasting insulin, HOMA-IR: Homeostatic model assessment for insulin resistance, TC: Total cholesterol, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, TG: Triglyceride, CRP: C-reactive protein, WBC: White blood cell, 25-OH D3: 25-hydroxyvitamin D3

Continuous variables are expressed as means ± SD or median (interquartile range), and categorical variables as percentages (%). Differences between groups assessed with Student's t-test or Mann-Whitney U-test according to distribution of the data or chi-square test for categorical variables.

positive correlation between ACR and BMI, FI, HOMA-IR, TG, CRP.

As BMI increases, the muscle mass of the individual increases, so the level of microalbuminuria is expected to increase. There are a number of studies that have indicated the presence of a relationship between BMI and microalbuminuria. In the CREDIT study, the mean microalbuminuria in obese subjects was significantly higher than non-obese subjects (17). In a study, involving 290 obese individuals conducted by Esen et al.¹⁸, there was a significant correlation between BMI and microalbuminuria. A study by Zheng et al.¹⁹ showed a correlation between BMI and microalbuminuria. However, these studies compared obese and non-obese subjects, while our study has focused only on

obese subjects. Additionally, the CREDIT study did not exclude subjects who had chronic diseases such as hypertension, diabetes mellitus and chronic kidney disease, which can independently cause microalbuminuria. Inclusion of subjects with these conditions could result in misleading conclusions about the relationship between obesity and microalbuminuria levels.

Homeostatic model assessment for insulin resistance is a strong indicator of insulin resistance, which is a component of many metabolic syndromes. In our study, we found a positive correlation between HOMA-IR and microalbuminuria. A study involving 752 obese individuals performed by Utsunomiya et al.²⁰ also showed a significant positive correlation between HOMA-IR and microalbuminuria. The correlation

Table 4. Correlation between ACR and metabolic parameters in the study population

	R	P
Main characteristics		
Age (year)	-0.02	0.97
BMI (kg/m ²)	0.108	0.017
PBF (%)	0.017	0.784
Metabolic and inflammatory parameters		
FPG (mg/dl)	0.57	0.210
HbA1c (%)	0.044	0.328
FI (IU/ml)	0.122	0.007
HOMA-IR	0.128	0.005
TC (mg/dl)	0.018	0.690
HDL-C (mg/dl)	-0.063	0.168
LDL-C (mg/dl)	0.001	0.980
TG (mg/dl)	0.130	0.004
CRP (mg/l)	0.108	0.018
WBC (x10 ³ /mm ³)	0.067	0.138
Creatinine (mg/dl)	-0.064	0.169
Uric acid (mg/dl)	0.053	0.241
25-OH D3 (ng/ml)	-0.057	0.211

ACR: Albumin to creatinine ratio, BMI: Body mass index, PBF: Percent body fat, FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, FI: Fasting insulin, HOMA-IR: Homeostatic model assessment for insulin resistance, TC: Total cholesterol, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, TG: Triglyceride, CRP: C-reactive protein, WBC: White blood cell, 25-OH D3: 25-hydroxyvitamin D3

P –value derived from Pearson's or Spearman's correlation according to the distribution of the data

between HOMA-IR and microalbuminuria was more prominent in those with central obesity and in the subgroup of those with central obesity and hypertension rather than general population. The study also included patients with hypertension that may lead to microalbuminuria, which differs from only obese population in our study. Again, this study indicated that diagnostic criteria of metabolic syndrome, i.e. insulin resistance and hypertension affect the kidneys and can lead to microalbuminuria. Hyperglycemia and increased levels of free fatty acids lead to endothelial injury (21). Endothelial injury is associated with microalbuminuria (22).

C-reactive protein levels show the extent of chronic inflammation and endothelial damage. Increasing CRP levels are associated with cardiovascular morbidity and mortality. Dyslipidemia, a metabolic syndrome parameter, is also common in obese individuals. In a study conducted by Pannacciulli et al.²³ in premenopausal overweight and obese subjects, microalbuminuria was found to be positively correlated with BMI, HOMA-IR, TG and CRP and negatively correlated with HDL. This study was performed only with female subjects, which differs from our study population. In our study, we found a correlation between microalbuminuria, CRP and TG. However, we found no correlation between microalbuminuria and HDL. C-reactive protein levels indicating arterial wall inflammation, and microalbuminuria indicating endothelial dysfunction, may increase together in the atherogenic process that occurs in obese people.

Uric acid is an oxidant and increases oxidative stress that can lead to endothelial dysfunction. Large-scale epidemiological studies have shown that high uric acid levels are associated with cardiovascular disease, hypertension, diabetes mellitus and chronic kidney disease (24). In a study by Yan et al.²⁵, which included 3212 patients with type 2 diabetes mellitus, a positive correlation was found between uric acid level and microalbuminuria. This study only included patients with type 2 diabetes mellitus, which differs from our study.

Glycosylated hemoglobin; is a parameter used in the diagnosis of diabetes mellitus and monitorization of hyperglycemia. As glucose levels increase, HbA1c levels also increase. In a study by Diouf et al.²⁶ in patients with type 2 diabetes mellitus, HbA1c levels were found higher in the group with microalbuminuria. Also, only patients with type 2 diabetes mellitus were included in this study, which differs from our study population.

Low levels of 25-OH D3 are associated with both skeletal system-related diseases and cardiovascular diseases. A research has shown that a low 25-OH D3 level increases the risk of

hypertension and cardiovascular disease. In a study by Dutta et al.²⁷ with prediabetic subjects, an association was found between microalbuminuria and low 25-OH D3 levels. This study was a cohort study and also included non-obese population, which differs from our study.

We could not find any study in the literature that investigated the relationship between microalbuminuria and uric acid, HbA1c, 25 hydroxy vitamin D in only obese people.

Our study had certain limitations. First, owing to the intrinsic feature of its cross-sectional design, this study can only evaluate the association rather than causality. Another limitation is that we used HOMA-IR method to evaluate the degree of insulin resistance. But the use of hyperinsulinemic-euglycemic clamp is the gold-standard method to assess insulin sensitivity. Thirdly, female subjects were more numerous than male subjects which could potentially affect the results.

CONCLUSION

Microalbuminuria must be checked in obese individuals. It should be kept in mind that obese individuals with microalbuminuria may have insulin resistance, dyslipidemia, high CRP and uric acid levels and low 25-OH D3 levels.

The prevalence of obesity should be reduced. This is necessary for individuals to have a healthier life and to use limited resources more effectively by reducing the costs caused by obesity. Health professionals and managers have a great responsibility in this regard.

Ethics Committee Approval: This study approved by the Kartal Dr. Lutfi Kırdar Training and Research Hospital Ethical Committee. The approval number is 2016/514/82/1

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Informed Consent:

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