Decreased coronary flow reserve in obese women

Obez kadınlarda azalmış koroner akım rezervi

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Objectives: Obesity is associated with an increased rate of cardiovascular disease and risk factors. It is a common problem in apparently healthy women. We aimed to investigate the association between obesity and coronary flow reserve (CFR) in obese women.

Study design: The study included 80 consecutive women (mean age 55.6±10.2 years) without diabetes mellitus and clinical coronary artery disease. Body mass index (BMI) was calculated and obesity was defined as BMI ≥30 kg/m^2. Based on BMI, the patients were grouped as normal weight (n=13; 18.5-24.9 kg/m^2), overweight (n=32; 25-29.9 kg/m^2), obese (n=32; ≥30-39.9 kg/m^2), and morbid obese (n=3; ≥40 kg/m^2). Peak diastolic coronary flow velocities were measured in the distal left anterior descending artery by transthoracic pulsed wave Doppler echocardiography at baseline and after dipyridamole infusion and CFR was calculated as the ratio of hyperemic to baseline peak diastolic velocities.

Results: There were 35 obese women (43.8%). Coronary flow reserve was significantly lower in obese women than in nonobese subjects (2.2±0.5 *vs.* 2.5±0.4; p=0.022). The lowest CFR was seen in patients with a BMI of ≥40 kg/m^2; overweight women did not differ significantly from women of normal weight. Coronary flow reserve was correlated with BMI (r=-0.314, p=0.005), waist circumference (r=-0.316, p=0.005), C-reactive protein (CRP) (r=-0.342, p=0.011), and adiponectin level (r=0.410, p=0.011). In regression analysis, BMI (p=0.017), waist circumference (p=0.048), systolic blood pressure (p=0.025), fasting glucose (p=0.035), and adiponectin level (p=0.037) were found to be independent predictors for impaired CFR. In ROC analysis, the cut-off value for BMI to predict impaired CFR was ≥30 kg/m^2, with 76% sensitivity and 72% specificity (ROC area 0.805, p<0.001, 95% CI 0.669-0.96).

Conclusion: Impaired CFR in obese women suggests the presence of microvascular dysfunction. Treatment of obesity is important for the prevention of atherosclerosis.

Key words: Blood flow velocity; body mass index; coronary circulation; echocardiography; female; obesity/complications; risk factors; vascular resistance.

Amaç: Obezite artmış kardiyovasküler hastalık ve risk faktörleri ile ilişkilidir. Obezite sağlıklı olduğu düşünülen kadınlarda sık karşılaşılan bir sorundur. Bu çalışmada obez kadınlarda obezite ile koroner akım rezervi (KAR) arasındaki ilişki araştırıldı.

Çalışma planı: Çalışmaya, diabetes mellitus ve klinik koroner arter hastalığı olmayan 80 ardışık kadın hasta (ort. yaş 55.6±10.2) alındı. Tüm olgularda beden kütle indeksi (BKİ) ölçüldü ve BKİ ≥30 kg/m^2 olanlar obez olarak kabul edildi. Beden kütle indeksine göre hastalar normal kilolu (n=13; 18.5-24.9 kg/m^2), fazla kilolu (n=32; 25-29.9 kg/m^2), obez (n=32; ≥30-39.9 kg/m^2) ve aşırı obez (n=3; ≥40 kg/m^2) olarak sınıflandırıldı. Zirve diyastolik koroner akım, distal sol ön inen koroner arterden dipiridamol infüzyonu öncesi ve sonrasında transtorasik nabız dalga Doppler ile ölçüldü ve hiperemik zirve diyastolik hızın başlangıç zirve diyastolik hıza oranı KAR olarak kabul edildi.

Bulgular: Otuz beş kadın (%43.8) obez olarak kabul edildi. Koroner akım rezervi obez kadınlarda obez olmayanlara göre anlamlı derecede düşük bulundu (2.2±0.5 ve 2.5±0.4; p=0.022). En düşük KAR değeri BKİ ≥40 kg/m^2 olan kadınlarda gözlendi; fazla kilolu kadınlar ve normal kilolu kadınlarda KAR benzer bulundu. Koroner akım rezervi, BKİ (r=-0.314, p=0.005), bel çevresi (r=-0.316, p=0.005) ve C-reaktif protein (CRP) (r=-0.342, p=0.011) ve adiponektin (r=0.410, p=0.011) düzeyleriyle anlamlı ilişki gösterdi. Regresyon analizinde KAR düşüşünü öngören bağımsız etkenler şunlardı: BKİ (p=0.017), bel çevresi (p=0.048), sistolik kan basıncı (p=0.025), açlık kan şekeri (p=0.035) ve adiponektin düzeyi (p=0.037). ROC analizinde, KAR'daki bozulmayı öngörmede kullanılabilecek BKİ kesim değeri ≥30 kg/m^2 bulundu (duyarlık %76, özgüllük %72; ROC alanı 0.805, p<0.001, %95% GA 0.669-0.96).

Sonuç: Obez kadınlarda KAR değerindeki düşüş mikrovasküler disfonksiyon varlığının bir göstergesidir. Obezitenin tedavisi aterosklerozun önlenmesi için önemlidir.

Anahtar sözcükler: Kan akım hızı; beden kütle indeksi; koroner dolaşım; ekokardiyografi; kadın; obezite/komplikasyon; risk faktörü; vasküler direnç.

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Obesity is a health, social, and economic problem in women. It is highly prevalent in Turkish postmenopausal women and 30% of women are estimated to have a body mass index of ≥30 kg/m^2.[1] Although obesity is known as an independent risk factor[2,3] for coronary artery disease together with diabetes mellitus, hypertension, and dyslipidemia,[4] currently a new concept of 'obesity paradox' has emerged.[5] There are some findings showing that obesity is associated with impaired microvascular function[6,7] and loss of weight improves coronary flow reserve (CFR).[8]

In this study, we aimed to investigate the association between obesity and CFR determined by transthoracic Doppler echocardiography in Turkish women without diabetes and coronary artery disease.

PATIENTS AND METHODS

Study population. A total of 80 consecutive women (mean age 55.6±10.2 years) without diabetes mellitus and clinical coronary artery disease were enrolled. Coronary artery disease was defined as the presence of the following: a past history of a myocardial infarction/revascularization; typical angina; ST-segment or T-wave changes specific to myocardial ischemia or Q waves on the electrocardiogram; wall motion abnormality on echocardiography; a noninvasive stress test demonstrating ischemia or any perfusion abnormality; coronary artery stenosis on angiography. Patients were excluded if they had coronary artery disease, diabetes mellitus, uncontrolled hypertension, dyslipidemia, severe valvular disease, congenital heart disease, hypertrophic cardiomyopathy, chronic heart failure, cardiac rhythm other than sinus, hypo- or hyperthyroidism, chronic obstructive pulmonary disease, cor pulmonale, systemic diseases such as collagenosis, hemolytic, hepatic, and chronic renal disease, or inadequate transthoracic echocardiographic images.

The study was conducted in compliance with the Declaration of Helsinki. All participants gave informed consent and the study protocol was approved by the institutional ethics committee.

Demographic, clinical and laboratory parameters. Waist circumference, height, and weight were obtained. Body mass index (BMI) was calculated as body weight divided by height squared. Obesity was defined as BMI ≥30 kg/m^2. Patients with a BMI 18.5-24.9 kg/m^2 were categorized as having normal weight, 25-29.9 kg/m^2 as overweight, ≥30-39.9 kg/m^2 as obese, and ≥40 kg/m^2 as morbid obese.

Systolic and diastolic blood pressures were measured after at least five minutes of resting. Blood samples were obtained after overnight fasting. Plasma glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, C-reactive protein (CRP) levels were measured. Serum insulin (Immulite 2000 Insulin, Diagnostic Products Corporation, Los Angeles, USA) and adiponectin (Human adiponectin ELISA kit, Linco Research, Inc, Missouri, USA) levels were determined. Homeostasis model assessment for insulin resistance (HOMA) index was calculated with the following formula: fasting plasma glucose (mg/dl) x fasting plasma insulin (μU/ml) / 405.[9]

Echocardiographic examination and evaluation of coronary flow reserve. All the patients underwent transthoracic echocardiography using an Acuson Sequoia C-256 (Acuson Corporation, California, USA) machine with a 3.5 MHz transducer. Two-dimensional and transthoracic Doppler echocardiographic examinations were performed according to the recommendations of the American Society of Echocardiography.

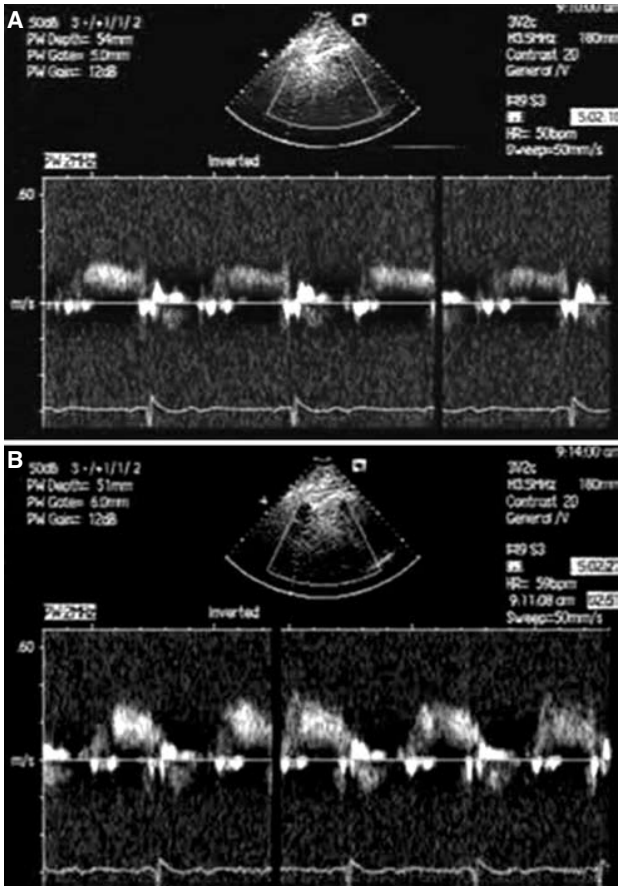

Figure 1. Demonstration of coronary flow velocity at **(A)** baseline and **(B)** hyperemia obtained by transthoracic pulsed wave Doppler echocardiography in the distal left anterior descending coronary artery.

Table 1. Clinical and laboratory characteristics

	Overall (n=80)			Nonobese group (n=45)			Obese group (n=35)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			55.6±10.2			54.0±10.0			57.0±9.2	NS
Height (cm)			158.4±5.9			158.8±5.4			157.8±5.3	NS
Weight (kg)			73.3±12.1			65.8±7.1			82.8±10.4	**<0.001**
Body mass index (kg/m^2)			29.4±4.7			26.1±2.4			33.8±3.1	**<0.001**
Waist circumference (cm)			92.2±11.8			86.0±9.1			100.0±10.1	**<0.001**
Systolic blood pressure (mmHg)			125.8±16.1			123.7±16.0			128.6±16.2	NS
Diastolic blood pressure (mmHg)			75.3±8.7			75.2±8.4			75.6±9.3	NS
Hypertension	44	55.0		22	48.9		22	62.9		NS
Dyslipidemia	42	52.5		21	46.7		21	60.0		NS
Smoking	15	18.8		8	17.8		7	20.0		NS
Menopause	62	77.5		30	66.7		32	91.4		**<0.01**
Fasting glucose (mg/dl)			95.5±13.5			92.8±10.8			99.0±15.8	**<0.05**
LDL-cholesterol (mg/dl)			121.6±26.8			117.8±28.4			126.6±23.9	NS
HDL-cholesterol (mg/dl)			51.7±14.1			53.4±16.1			49.1±10.5	NS
Triglyceride (mg/dl)			128.5±61.1			118.4±58.0			140.3±63.4	NS
Insulin (μU/ml)			7.6 (5.5-11.3)			6.8 (4.9-8.8)			10.1 (5.7-13.9)	**<0.05**
HOMA index			1.4 (1.1-2.6)			1.44 (0.98-2.10)			2.25 (1.21-3.25)	**<0.05**
C-reactive protein (mg/l)			2.9 (1.3-5.6)			2.0 (1.0-4.0)			3.3 (2.0-6.5)	**<0.05**
Adiponectin (μg/ml)			10.9±7.0			13.2±8.1			8.3±4.5	**<0.05**
Ejection fraction (%)			56.4±3.8			56.6±3.8			56.2±3.8	NS
Left ventricle mass (g)			118.1±44.6			115.7±47.3			121.3±41.1	NS
Basal diastolic coronary flow (cm/sec)			30.9±6.2			30.0±5.3			31.9±7.2	NS
Peak diastolic coronary flow (cm/sec)			71.9±13.5			74.4±13.8			68.8±12.6	**<0.05**
Coronary flow reserve			2.4±0.5			2.5±0.4			2.2±0.5	**<0.05**

HOMA: Homeostasis model assessment for insulin resistance.

Left anterior descending (LAD) coronary artery was visualized using a modified, foreshortened, 2-chamber view, and an optimal alignment to the interventricular sulcus was obtained. The color gain was adjusted to provide optimal images and coronary flow in the distal LAD was examined by color Doppler flow mapping over the epicardial part of the anterior wall. Pulsed wave Doppler recordings of the mid-to-distal LAD coronary artery were obtained from each subject. Spectral Doppler of the LAD coronary artery displayed a characteristic biphasic flow pattern, with a larger diastolic and a smaller systolic component. Hyperemia was induced by infusion of dipyridamole at a rate of 0.56 mg/kg over 4 min. Coronary peak diastolic velocities were measured at baseline and at hyperemia (Fig. 1). The highest three Doppler recordings were averaged for each measurement. Coronary flow reserve was calculated as the ratio of hyperemic to baseline peak diastolic velocities.[10]

Statistical analysis. Statistical analyses were performed with SPSS software (Statistical Package for Social Sciences, version 10.0). Continuous variables were expressed as mean±standard deviation (SD) or median (interquartile range) and categorical variables as percentages. The Kolmogorov-Smirnov test was used to test the normality of distribution. Variables with a normal distribution were compared by an unpaired t-test. Variables that showed a nonhomogenous distribution were compared by the Mann-Whitney U-test. Categorical variables were compared with the chi-square test. Correlations were sought by the Spearman's correlation test. Multivariate linear regression analysis was performed to determine independent parameters associated with CFR. The cut-off value for BMI to predict impaired CFR was estimated by receiver operating characteristic (ROC) curve analysis. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

Demographic and clinical features of the study population are presented Table 1. Coronary artery disease was eliminated with normal coronary angiography (n=52), radionuclide myocardial perfusion imaging (n=6), or exercise stress test (n=22).

There were 35 obese women (43.8%). Waist circumference, BMI, CRP, fasting glucose, insulin levels, and HOMA index were significantly higher in the obese group (Table 1). Coronary flow reserve was significantly lower in obese women than in nonobese

subjects (2.2±0.5 *vs*. 2.5±0.4; p=0.022). In addition, adiponectin levels were significantly decreased in the obese group (Table 1).

Coronary flow reserve was correlated with BMI (r=-0.314, p=0.005), waist circumference (r=-0.316, p=0.005), CRP (r=-0.342, p=0.011), and adiponectin level (r=0.410, p=0.011).

In regression analysis, BMI, waist circumference, systolic blood pressure, fasting glucose, LDL-cholesterol, and adiponectin level were found to be independent predictors for impaired CFR (Table 2).

In ROC analysis, the cut-off value for BMI to predict impaired CFR was ≥30 kg/m^2, with 76% sensitivity and 72% specificity (ROC area 0.805, p<0.001, 95% CI 0.669-0.96).

When the patients were dichotomized according to the BMI subgroups, the lowest CFR was seen in patients with a BMI of ≥40 kg/m^2. With respect to CFR, overweight women did not differ significantly from women of normal weight (Fig. 2).

Table 2. Multivariate linear regression analysis for prediction of impaired coronary flow reserve

	ß	(95% CI)	*p*
Age	-0.245	-0.047; 0.015	0.096
Obesity	-1.224	-1.745; -0.869	**0.017**
Waist circumference	0.475	0.001; 0.043	**0.048**
Fasting glucose	-1.284	-0.083; -0.015	**0.035**
LDL-cholesterol	0.344	0.000; 0.012	**0.052**
HDL-cholesterol	-0.086	-0.043; 0.031	0.298
Triglyceride	0.048	-0.005; 0.006	0.478
C-reactive protein	1.380	0.029; 0.563	**0.045**
HOMA index	-0.451	-0.666; 0.069	0.062
Adiponectin	0.421	0.013; 0.086	**0.037**
Systolic blood pressure	-0.943	-0.034; 0.015	**0.025**
Diastolic blood pressure	-0.114	-0.042; 0.029	0.255
Menopause	-0.072	-0.849; 0.675	0.384

HOMA: Homeostasis model assessment for insulin resistance.

DISCUSSION

This study demonstrated that CFR was impaired in obese women when compared to nonobese women, implying coronary microvascular and endothelial dysfunction in obese women.

Several studies have shown microvascular dysfunction in obesity.[6,11] De Jongh et al.[6] examined microvascular function by skin capillary recruitment and skin endothelium-dependent vasodilatation by acetylcholine and sodium nitroprusside. They found that obesity was characterized by impaired microvascular function and that microvascular dysfunction was associated with increased blood pressure and decreased insulin sensitivity. Another study that investigated coronary endothelial function in obese subjects with normal and mildly diseased coronary arteries showed that obesity was independently associated with coronary endothelial dysfunction.[11] Our results are in accordance with these findings and demonstration of an association between coronary microvascular dysfunction and obesity in Turkish women has important implications.

Coronary microvascular dysfunction is considered to represent an early stage of coronary atherosclerosis. Obesity impairs coronary microvascular function. Some potential mechanisms could be postulated to explain how obesity causes microvascular dysfunction. Obesity is associated with insulin resistance and insulin resistance leads to endothelial dysfunction. Although our study population had normal levels of glucose, obese women had a higher insulin level and HOMA index. As a consequence, obesity-related insulin resistance can lead to coronary microvascular dysfunction and impaired CFR. Another possible mechanism can be related to inflammation. Adipose tissue presents a milieu of chronic low level of inflammatory state with increased levels of interleukin-6, tumor necrosis factor-alpha, and CRP. These inflammatory mediators in turn induce insulin resistance and endothelial dysfunction,[12] potentially leading to impaired CFR in obese women. Our study supports these finding as CRP levels were also increased in obese women compared with the levels in nonobese subjects and CRP was found to be an independent factor for impaired CFR.

Coppola et al.[8] investigated the effect of weight loss on coronary circulation and adiponectin levels in obese women. Coronary flow reserve was sig-

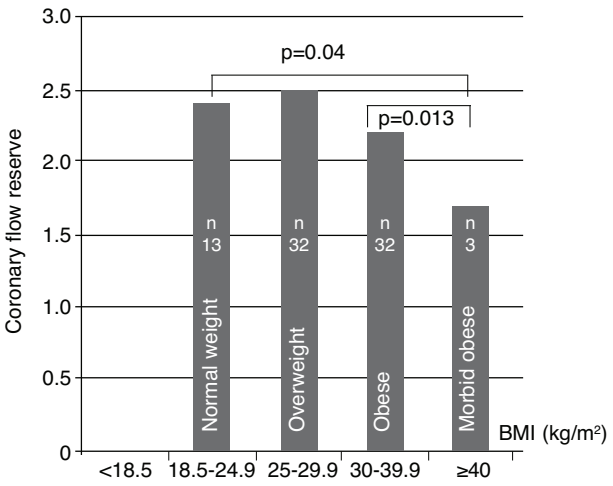

Figure 2. Coronary flow reserve in patients grouped by body mass index.

nificantly lower in obese subjects compared to that in normal-weight individuals. Our study yielded similar results, with obese women having impaired CFR and decreased adiponectin levels. On the other hand, weight loss in obese women is associated with improved coronary microcirculation and increased adiponectin levels.[8] In a previous study, we found that low adiponectin levels were associated with impaired CFR in women with a normal coronary angiography.[13] In the current study, we found decreased adiponectin levels in obese women and adiponectin was an independent predictor of impaired CFR.

Although obesity is considered to be an earlier presentation of coronary heart disease, a survival paradox has emerged from recent observations in overweight and obese patients.[14-16] In a meta-analysis which evaluated 40 studies including more than 250,000 patients with coronary disease, patients with a low BMI (<20 kg/m^2) had an increased risk for cardiovascular mortality, whereas overweight patients (BMI 25-29.9 kg/m^2) had the lowest risk for cardiovascular mortality.[17] While obese patients (BMI 30-35 kg/m^2) did not have an increased risk for cardiovascular mortality, patients with severe obesity (≥35 kg/m^2) had the highest risk for cardiovascular mortality.[17] Kaplan et al.[18] found that elevated BMI was associated with an increased risk for reinfarction and death, but they also observed high rates of mortality and risk for recurrent coronary disease among those with a low BMI. They reported a U-shaped mortality curve by the BMI distribution. The underlying mechanism of obesity is not fully understood. It may be that coronary artery disease is manifest in obese persons at an earlier age, and obese cardiac patients tend to better tolerate the catabolic stress of myocardial ischemia or heart failure than their normal-weight counterparts.[4,19] Obesity-related risk factors for coronary artery disease such as dyslipidemia, hypertension, and diabetes mellitus are recognized and treated earlier in obese patients than normal-weight persons. Conversely, weight loss due to chronic disease and cachexia may serve as a confounding factor, worsening outcomes in lower-weight individuals.[4] In our study, we did not evaluate the prognosis in patients with impaired CFR and obesity, but CFR was lowest in women with BMI ≥40 kg/m^2 while overweight women and normal-weight women had similar CFR. In our study population, we did not have patients with low BMI (<18.5 kg/m^2). Therefore, we could not determine whether a U-shaped effect of obesity on CFR was also present. This effect of obesity on CFR and prognosis should be examined by further studies.

Limitations. We evaluated CFR noninvasively by transthoracic echocardiography instead of using invasive catheter-based methods. Assessment of CFR by transthoracic Doppler echocardiography was reported to be a reliable and reproducible indicator of coronary microvascular function in previous studies.[20,21] Measurement of coronary flow velocity and CFR in the LAD by transthoracic Doppler echocardiography was found to be a clinically useful, feasible, and reliable method in a relatively obese American population.[22] We did not measure focal fat amount by body composition analyzer or computed tomography. We only evaluated abdominal obesity by measuring waist circumference, which is accepted to reliably reflect visceral obesity.

In conclusion, CFR is impaired in Turkish obese women. Treatment of obesity is important for the prevention of atherosclerotic coronary artery disease and the effects of treatment including diet, exercise, and medications should be investigated in larger studies.

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