Carotid Intima Media Thickness and Parameters Related to Blood Flow in Obese Patients

Obez Hastalarda Karotis İntima Media Kalınlığı ve Kan Akımının İlişkili Olduğu Parametreler

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ABSTRACT Objective: Obesity increases the risk of atherosclerotic diseases. The relation between carotid intima-media thickness (CIMT) and subclinical atherosclerosis is known. In this study; we investigated the relationship between CIMT and clinical and laboratory parameters related to carotid blood flow. **Material and Methods:** We enrolled 64 obese and 40 overweight and a total of 104 patients in the study. Body mass index (BMI), waist circumference (WC), hip circumference (HC) and waist to hip ratio (WHR) of the patients were recorded. Patients' fasting blood glucose (FBG), insulin, triglyceride (TG) and LDL-cholesterol (LDL-C) levels were measured. Insulin resistance (HOMA-R) was calculated. Carotid intima-media thickness and blood flow were measured by Doppler ultrasound. **Results:** The average age was 46.6±11.1 years. The subjects were subdivided into two groups as overweight and obese. FBG, insulin and HOMA-R were elevated in both groups. TG levels were elevated in the obese group, but not in the overweight group. LDL levels were normal in both groups. Increased intima-media thickness was observed in 32 patients. The correlation between carotid blood flow peak systolic velocity (PSV) of 29-127 cm/min (average 74.76 cm/min) and WHR was weak (r=0.37; p=0.030). EDV (11- 51 cm/min, average 31.62+10.52 cm/min) showed weak correlations with BMI and WHR (r=0.33; p=0.170). **Conclusion:** Ultrasonographic evaluation of atherosclerotic changes in arteries should be used in clinical practice more often, as it is relatively easy and noninvasive. Resistivity index of internal carotid artery may also be used as a marker of atherosclerosis in addition to intima media thickness.

Key Words: Obesity; carotid intima-media thickness; blood flow velocity

ÖZET Amaç: Obezite, aterosklerotik hastalık riskini arttırır. Karotis intima-media kalınlığının (KIMK) subklinik ateroskleroz ile ilişkisi bilinmektedir. Bu çalışmada vasküler hastalığı olmayan obez hastalarda, KIMK ve karotis kan akımının ilişkili olduğu klinik ve loboratuvar parametreler arasındaki ilişkiyi araştırdık. **Gereç ve Yöntemler:** Bu çalışmaya 64 obez ve 40 fazla kilolu olmak üzere toplam 104 hasta dahil edildi. Hastaların beden kitle indeksi (BKİ), bel çevresi (BÇ), kalça çevresi (KÇ) ve bel-kalça oranı (BKO) ölçüldü. Açlık kan şekeri (AKŞ), insülin, trigliserid (TG), LDL-kolesterol (LDL) düzeyleri bakıldı. İnsülin direnci (HOMA-R) hesaplandı. Karotis intima media kalınlığı ve kan akımı Doppler ultrasonografi ile ölçüldü. **Bulgular:** Hastaların ortalama yaşı 46,6±11,1 yıl idi. Gruplar fazla kilolu ve obez olarak iki gruba ayrıldı. Her iki grupta da AKŞ, insulin ve HOMA-R düzeyleri artmıştı. TG obez hastalarda artmakla birlikte, fazla kilolu hastalarda normal sınırlar içerisindeydi. LDL düzeylerinde ise iki grupta da artış saptanmadı. Karotis intima media kalınlığı artışı 32 hastada gözlendi. Karotis kan akımı pik sistolik hızı (PSV) olan 29-127 cm/dk (ort. 74,76 cm/dk) ile BKO arasındaki korelasyon zayıftı (r=0,37; p=0,030). End diyastolik hız (EDV) (11-51 cm/dk, ort. 31,62+10,52 cm/dk) ile VKİ ve BKO arasında anlamlı korelasyon yoktu (p=0,170). **Sonuç:** Klinik pratikte, arterlerdeki aterosklerotik değişiklikleri değerlendirmek için diğer yöntemlere göre daha kolay ve noninvazif bir yöntem olduğundan, ultrasonografik metod daha sık kullanılabilir. İnternal karotid arterin rezistivite indeksi de intima media kalınlığına ek olarak ateroskleroz belirteci olarak kullanılabilir.

Anahtar Kelimeler: Obezite; karotıs iç-orta kalınlığı; kan akım hızı

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Obesity is a widespread disease of increasing prevalence, which is associated with multiple co-morbidities including atherosclerotic diseases. General obesity as indicated by high body mass index (BMI) has been related to increased risk of clinical events of atherosclerotic diseases.[1] Many significant cardiovascular risk factors have been well-established as common conditions accompanying obesity, most notably insulin resistance, hypertension and dyslipidemia.[2,3] There is some evidence that abdominal obesity which is characterized by high waist-to-hip ratio (WHR) or waist circumference (WC) is even a stronger predictor of atherosclerotic diseases.[4] Atherosclerosis affects the major elastic and muscular arteries, but some vessels are largely spared while others may be markedly diseased. The carotid bifurcation, the coronary arteries, the infrarenal abdominal aorta, and the vessels supplying the lower extremities are at the highest risk. Local mechanical factors such as wall shear stress and mural tensile stress potentiate atherogenesis. Plaques tend to occur where flow velocity and shear stress are reduced.[5,6] Carotid intima-media thickness (IMT) is a validated marker of subclinical atherosclerosis, and is a predictor of future myocardial infarction and stroke.[1,7] There is a great need for a noninvasive, safe and technically straightforward tool for screening asymptomatic patients.[8,9]

We have analyzed the relation of carotid IMT and blood flow with anthropomorphic characteristics, insulin resistance and triglyceride, low-density-lipoprotein cholesterol (LDL-C) levels in overweight and obese patients.

MATERIAL AND METHODS

This is a cross-sectional study. One hundred and four patients, who were followed up at Outpatients Clinics of Internal Medicine and who did not have any established vascular diseases (coronary, cerebrovascular and peripheral artery disease) were included. Eighty four of these patients were women, and 20 of them were men. All patients were weighed while wearing light clothing and without shoes, and their standing heights were measured. BMI was calculated by body weight in kilograms divided by squared body height in meters. The waist circumference and hip circumference were measured, and waist to hip ratio was calculated. All subjects had at least 12 h of fasting before blood sampling for biochemical evaluation. Fasting blood glucose (FBG), triglyceride (TG) and LDL-cholesterol (LDL-C) levels were measured spectrophotometrically using Abbot Aeroset 2.0 (Abbot Diagnostic USA). The insulin level was measured with electro-chemiluminescence immunoassay method using Roche-Hitachi E 170. Insulin resistance was calculated using the homeostasis model assessment (HOMA-R) which simplifies to fasting insulin X glucose product divided by 22.5. The intima media thickness was measured using B- Mode of carotid ultrasonography (USG) and carotid blood flow was measured using Doppler USG, performed by the same specialist in the Radiology Clinic. Carotid IMT measurements were made using ATL HDI 5000 with lineer array transducer L 12-5MHz, by using LOGIQ-7 GE. Carotid IMT measurements were made in both right and left common carotid arteries three times, at the thickest point on the far wall of the distal common carotid artery, approximately 1.5 cm proximal to the flow diviter. The carotid IMT was measured in a plaque-free section. For each subject, the IMT was calculated by averaging six measurements from both sides. IMT over 0.8 mm was accepted positive. Blood flow rate and peripheral flow resistance were evaluated by means of resistivity index (RI) which is used to evaluate vascular hemodynamic alterations. We evaluated Carotid IMT and Carotid blood flow as an indicator of atherosclerosis by using Doppler USG. We also calculated resistivity index using the Pourcelot formula. According to the formula; Resistivity index= Peak systolic velocity-End diastolic velocity/Peak systolic velocity.[10,11]

Our study was approved by and carried out according to the instructions of our Ethics Committee And was conducted in accordance to the principles of the Declaration of Helsinki. All patients gave their informed consents.

The statistical analysis was performed using the Statistical Package for the Social Science (SPSS) for Windows, version 9.0. Data are expressed as

means ± standard deviation and the Student's t- test was used for comparing the mean values. Pearson correlation analysis was used to examine the relationships between carotid IMT and various data, and Mann Whitney U test was used for comparison of FBG, TG, insulin and HOMA-R values. Statistical significance was accepted as $p<0.05$.

RESULTS

In this study, the average age was 46.60+11.1 years. There was no significant age difference between men and women (p=0.170). Patients with hypertension were excluded, smoking was not interrogated, and the genetic background was unknown. The subjects were categoried for obesity according to the World Health Organization (WHO) criteria as overweight (BMI: 25.00-29.90 kg/m^2) and obese (BMI ≥30.00 kg/m^2).[10] Forty patients were overweight (12 men, 28 women) and 64 patients were obese (8 men, 56 women). The anthropomorphic parameters of the patients are presented in Table 1. In the overweight group, HOMA-R showed no correlation with BMI (p=0.560) and showed a moderate correlation with WHR (r=0.40; p=0.030). There was a moderate correlation with BMI (r=0.44; p=0.025), and a strong correlation with WHR (r=0.66; p=0.010) in the obese group. In the overweight group, there was no relation between TG, BMI and WHR, but a moderate relation was observed between TG and HOMA-R (r=0.54; p=0.035). In the obese group, there was moderate relation between TG, BMI and WHR; but strong relation existed between TG and HOMA-R (r=0.64; p=0.015).We also found moderate correlations of LDL-C with BMI and WHR (r=0.41; p=0.045 and r=0.43; p=0.040, respectively). The IMT increased in 32 patients in the obese group (Figure 1). Forty percent of the patients with increased IMT, had high RI. RI was between 0.50-0.68 and mean RI was 0.5±0.01 in the overweight group and it was 0.6±0.11 in the obese group. Resistivity index showed a weak correlation with WHR (r=0.38; p=0.04) and fasting blood glucose (r=0.30; p=0.04), no correlation with LDL (r=0.25; p=0.15) and a moderate correlation with HOMA-R (r=0.35; p=0.04) and TG (r=0.34; p=0.05). On Doppler USG, correlation between carotid blood flow peak systolic velocity (PSV) of 29.00-127.00 cm/min (an average of 74.76 cm/min) and WHR was weak (r=0.37; p=0.030) in the obese group. There was no correlation between end diastolic velocity (EDV) of 11.00-51.00 cm/min, and WHR (p=0.170) (Table 2, Figure 2)

TABLE 1: Antropomorphic data and laboratory findings of the patients.

	Overweight	Obese
n	40	64
BMI (Kg/m^2)	29.00±4.40	42.44±10.50; p=0.001
WC (cm)	98.20±7.10	116.29±16.03; p=0.022
HC (cm)	108.00±10.35	132.79±15.95; p=0.080
WHR	0.90±0.01	0.87±0.01; p=0.550
FBG (mg/dl)	141(87-168)	180(115-209); p=0.015
LDL-C (mg/dl)	138.00±14.00	134.00±42.04; p=0.500
Triglyceride (mg/dl)	140 (114-189)	221(165-310); p=0.045
Insulin (µg/ml)	11(5.1-22)	20(14-28); p=0.620

BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHR: Waist to hip ratio; FBG: Fasting blood glucose; LDL-C: Low density lipoprotein cholesterol). The values within the normal range are shown as (mean±standard deviation) and the values out of range are shown as Median (Min-Max).

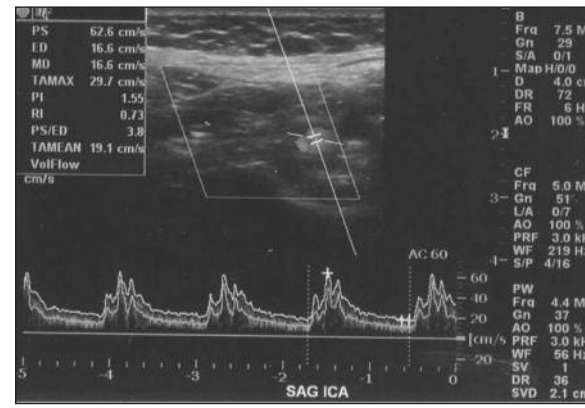

FIGURE 1: An example of increased intima media thickness on carotid Doppler ultrasonography.

DISCUSSION

The WHO estimates that over 1 billion people are overweight globally.[12] Abdominal pattern of fat distribution is associated with metabolic abnormalities and atherosclerotic disease.[13,14] Quantitative measurement of IMT of the distal common carotid artery is increasingly accepted as an indica-

TABLE 2: Carotid Doppler ultrasonography findings of the patients.

	Overweight	Obese
IMT (mm)	0.7±0.2	0.9±0.3
PSV (cm/min)	70.26±13.04	74.26±24.33
EDV (cm/min)	34±11.01	51±24.01
RI	0.5±0.01	0.6±0.11

IMT: Intima media thickness; PSV: Peak systolic velocity; EDV: End diastolic velocity; RI: Resistivity index.

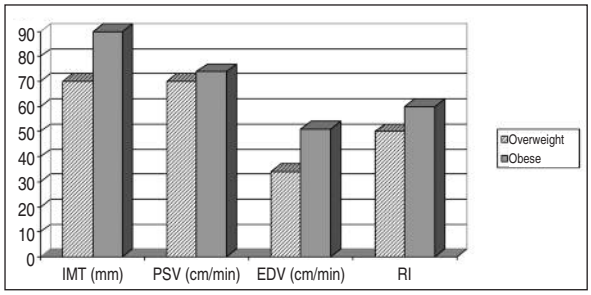

FIGURE 2: Comparison of carotid Doppler ultrasonography findings of obese and overweight patients.

IMT: Intima media thickness; PSV: Peak systolic velocity; EDV: End diastolic velocity; RI: Resistivity index.

tor of atherosclerosis, and is frequently used as a strong marker for cardiovascular morbidity and mortality.[7,9,15-17] Although the relationship of obesity and atherosclerosis is not clearly established, it is suggested that adipose tissue might mediate proinflammatory and prothrombotic state and alterations in cardiac structure and function.[18,19] Early atherosclerosis may be diagnosed by measuring carotid IMT by using Doppler USG. Ultrasonic quantitative flow measurement system has made it possible to measure noninvasively and quantitatively the absolute blood flow volume in the common carotid artery that constitutes the input end of the cerebral arteries. Cases with decreased blood flow volumes generally possess stenotic lesions. However, it is important to note that blood flow reduction is not always due to atherosclerosis, but may also be seen in Alzheimer's disease, severe low-output heart failure, and other conditions.[20] Increased IMT is related to several cardiovascular risk factors like age, diabetes mellitus, hypercholesterolemia and smoking. It is also related to angina pectoris, myocardial infarction, aortic aneurysm and peripheral artery disease. Every 0.1 mm increase in IMT increases the risk of myocardial infarction from 10% up to 15% and ischemic cerebrovascular accident from 13% up to 18%. Ultrasound has advanced the noninvasive diagnosis of carotid and cerebral atherosclerosis, but quantitative measurement only recently has been possible.[21,22]

Lakka et al. have observed for the first time that abdominal obesity, as indicated by high WHR and high WC, is associated with accelerated progression of carotid atherosclerosis independent of overall obesity and other risk factors in middle-aged man with no prior atherosclerotic diseases.[1] Michele et al. found BMI and WHR were significant predictors of carotid IMT, independent of age, blood pressure, lipid abnormalities and fasting insulin.[15] Increased carotid IMT has been associated with LDL-C, diabetes, smoking and clinically overt atherosclerosis. BMI is a risk factor for unstable angina and myocardial infarction in patients with confirmed coronary artery disease.[15] Another index of obesity, WHR, may have greater predictive value for arteriosclerotic vascular events.[23] We also observed a moderate correlation of IMT with BMI and WHR in the overweight and obese subjects without known atherosclerosis. This correlation was more pronounced for WHR. In their study, Bobbioni-Harsch et al. also found that weight gain was significantly associated with the development of cardiometabolic risk factors.[24] Similarly; Alpsoy et al. and Ozcetin et al. established that overweight and obese children were also potentially at risk of early atherosclerosis.[25,26]

The INTERHEART study identified obesity as an important risk factor for myocardial infarction which was expressed with four different measurements: BMI, WHR, WC and HC. INTERHEART showed us that WHR was an obesity measurement which was strongly associated with myocardial infarction. Waist circumference had a strong association with IMT progression. This observation may suggest that increased WC reflects long–term alterations in metabolic risk variables.[12,27,28]

Carotid IMT in obese subjects was independently associated with fasting blood glucose. This

may suggest that obesity-induced hyperglycemia may be a predictor of carotid atherosclerosis. In overweight and obese subjects, other parameters such as pulse pressure, age and the duration of hypertension were associated with IMT more strongly than fasting serum glucose.[29] We also found high FBG, insulin levels and HOMA-R in overweight and obese subjects without known risk factors. These values were more pronounced in the obese group.

Although IMT was not increased in the overweight group, we observed higher IMT values in the obese group. Torrejon et al. evaluated whether obese adolescents had higher IMT compared to non-obese ones, and similar to our study, they found that IMT was significantly higher in the obese group.[30]

Insulin levels and insulin resistance are also independently related to IMT progression and cardiovascular morbidity independent of other cardiovascular risk factors.[4] Hyperinsulinemia and cardiovascular disease is at least partly mediated by the clustering of several risk factors caused by insulin resistance.[23,31] Various adipokines secreted by adipose tissue may promote endothelial dysfunction, hypercoagulability, dyslipidemia and inflammation of atherosclerosis.[32]

We found high insulin levels and high insulin resistance determined by HOMA-R in both overweight and obese subjects. We also observed positive correlation with IMT and insulin or insulin resistance.

Several studies suggested that presence of plaques was a better predictor of future cardiovascular events compared to increased IMT.[33] Twenty six percent of the subjects with advanced subclinical atherosclerosis do not have carotid plaques.[18,23] Different blood flow values and ratios (one of which is resistivity index) are used to classify vascular obstruction by Doppler USG.

RI is associated with vascular resistance and compliance. Vascular compliance which affects RI significantly is termed a difference in vessel volume related to variations in pressure. Carotid plaques may result in alterations in blood flow.[10,11] Like IMT, the IR is clearly correlated with age and arteriosclerosis risk factors and manifestations. IR is related to the elasticity or extensibility of the vessel and its related vascular resistance. A low or normal RI may represent a still healthy vessel not damaged by arteriosclerosis.[10] We observed a weak correlation of obesity with PSV, EDV and RI. This situation resulted in a decrease in carotid blood flow in some patients. We did not observe a correlation of anthropomorphic measurements with PSV, EDV or RI in the overweight group.

Our study has some limitations. We measured IMT in the common carotid artery. Measuring IMT in the common carotid artery is more reliable and less difficult than IMT measuring it in the internal carotid artery, but less sensitive to local atherosclerotic changes.[34] We included patients without an established coronary heart disease, as revealed by their medical history and a normal electrocardiography. In addition, we did not perform treadmill test, sintigraphic evaluation or coronary angiography. Therefore, we may have underdiagnosed silent cardiac events.

Our study is a cross-sectional study, therefore we did not follow up IMT in obese patients in the long-term.

In conclusion, pre-clinic atherosclerotic changes were observed in one third of the obese patients who had no atherosclerotic disease history or cardiovascular events. We used both BMI and WHR as indices of obesity. We found a stronger relation between IMT and WHR when compared to BMI. We found that obesity was associated with accelerated carotid IMT and PSV, EDV, RI. Ultrasonographic method of evaluating atherosclerotic changes in arteries should be more frequently used in the clinical practice, as it is relatively easy, non-invasive and inexpensive. PSV, EDV and RI should also be measured as indicators of atherosclerosis.

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