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ORIGINAL RESEARCH

DOES ENDOTHELIAL DYSFUNCTION CORRELATE BETTER WITH WAIST-TO-HIP RATIO THAN WITH BODY MASS INDEX OR WAIST CIRCUMFERENCE AMONG OBESE PATIENTS?

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Villela NR, Aguiar LGK, Bahia L, Bottino D, Bouskela E. Does endothelial dysfunction correlate better with waist-to-hip ratio than with body mass index or waist circumference among obese patients? Clinics. 2006;61(1):53-8.

PURPOSE: Obesity is associated with cardiovascular disease, affecting large arteries and the microcirculation. Waist circumference and body mass index are routinely employed as measures for assessing obesity-related health risk, whereas waist-to-hip ratio is not. We aimed to investigate the association between brachial vascular reactivity and body mass index, waist circumference, and waist-to-hip ratio.

METHODS: Eighty-five volunteers (21 men/66 women), aged between 20 and 55 years, underwent determination of waist circumference, body mass index, waist-to-hip ratio, and endothelial function by venous occlusion plethysmography. Forearm blood flow was measured in response to intrabrachial artery infusions of 3 different concentrations of endothelium-dependent (acetylcholine 7.5, 15, and 30 mg/min) and endothelium-independent (sodium nitroprusside 2, 4, and 8 mg/min) vasodilators.

RESULTS: There was an inverse correlation of body mass index and waist circumference with forearm blood flow increments after acetylcholine and sodium nitroprusside infusions, while waist-to-hip ratio showed an inverse correlation with forearm blood flow increments only after acetylcholine. When subjects older than 40 years (n = 25) were excluded from the analysis, the inverse correlation of body mass index with forearm blood flow increments after acetylcholine infusion no longer existed, while waist circumference and waist-to-hip ratio showed the same results observed before.

CONCLUSION: The waist-to-hip ratio is probably a better estimator of endothelial dysfunction and possibly of cardiovascular risk than body mass index. These findings underscore the importance of routinely collecting hip circumference as an obesity index and risk estimator.

KEYWORDS: Endothelium. Vascular Reactivity. Waist-to-Hip Ratio. Body Mass Index. Waist Circumference.

INTRODUCTION

Obesity is a chronic disease, the incidence of which is growing alarmingly, affecting not only adults but also children and adolescents. Obesity is a risk factor for a host of pathologies from arthritis to cardiovascular diseases. In cardiovascular disease, obesity increases the risk not only of large artery disease, such as myocardial infarction and stroke,[1,2] but also of disease entities that are in part caused by microangiopathy, notably retinopathy, nephropathy, and heart failure.[3–5] These associations cannot be entirely explained by obesity-associated insulin resistance, hypertension, or dyslipidemia.[3,5,6] Responsible mechanisms are likely to include metabolic and inflammatory responses to the increased amount of stored fat[7] that may deeply and negatively influence endothelial physiology, a condition which may lead to the formation of the atherosclerotic plaque.[8]

Waist circumference (WC) is widely viewed as a sim-

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ple but effective measure for assessing obesity-related health risks, whereas the measurement of hip circumference is not currently a priority. In a population-based study, Lisner et al[9] showed that hip circumference was a significant independent inverse risk estimator for diabetes and cardiovascular endpoints. Recently Yusuf et al[10] demonstrated, in the Interheart study, that waist-to-hip ratio (WHR) was a strong predictor of myocardial infarction, again suggesting that hip measurement should not be excluded from health surveys.

Endothelial dysfunction precedes and predicts clinical macrovascular disease.[11] Abnormal vasomotor responses occur in obesity and insulin resistance states.[12] Severe endothelial dysfunction even in the absence of obstructive coronary disease is associated with increased cardiac events,[13] and the impairment of brachial artery endothelium-dependent vasodilation correlates with the same alteration in coronary arteries[14].

The purpose of the present study was to define the relationship between brachial vascular reactivity and body mass index (BMI), WC, and WHR in Brazilian subjects.

METHODS

Subjects

Eighty-five volunteers (21 men – 66 women), aged between 20 and 55 years, from the Cardiometabolic Clinic for outpatient care at the State University of Rio de Janeiro participated in this study after giving written informed consent. The exclusion criteria were current tobacco use and any established cardiovascular and respiratory disease.

Study Protocol

The study was approved by the Ethical Committee of the State University of Rio de Janeiro.

The same trained examiner collected the anthropometric measurements in duplicate: waist at its smallest point with the abdomen relaxed; hip circumference at the level of the widest diameters around the buttocks; and body mass (weight) using a digital scale (Filizola®, São Paulo, SP, Brazil). Body mass index was defined as weight (in kg) divided by squared height (in meters).

Vascular reactivity was evaluated by measuring forearm blood flow (FBF) responses to intra-arterial infusions of acetylcholine (Ach; Acetilcolina®, USP, São Paulo, SP, Brazil) and sodium nitroprusside (SNP; NPS®, Lebon, Porto Alegre, RS, Brazil) to evaluate endothelium-dependent and -independent vasodilation, respectively. The study was performed in the morning after an 8 to 10-hour overnight fast and in a temperature controlled room (20° to 22°C). A 27-gauge steel spinal needle (Becton, Dickinson Indústrias Cirúrgicas Ltda, Juiz de Fora, MG, Brazil) was inserted into the left brachial artery, anterior to the elbow, under sterile conditions and after local anesthesia with 1% lidocaine. A mercury-filled silastic strain-gauge was placed on the upper third of the forearm, which rested slightly above the level of the heart. Venous occlusion was accomplished using a blood pressure cuff applied proximal to the elbow and inflated to 40 mm Hg by a rapid cuff inflator. Wrist cuff was inflated to at least 50 mm Hg above systolic blood pressure, 1 minute before each flow measurement, to avoid hand shunt. Blood pressure was noninvasively measured simultaneously in the right arm at each period, and a 1-lead electrocardiogram was recorded continuously. Baseline blood flow was recorded after a 20 min infusion of NaCl 0.9%, at a rate of 0.8 mL/min, delivered by a Harvard pump (Harvard Apparatus Inc, South Natick, Massachusetts, USA). Acetylcholine and SNP were always infused in progressive dosages: 7.5, 15, and 30 mg/min and 2, 4, and 8 mg/min, respectively, for 5 minutes at each dose. Acetylcholine was always infused first, with an interval of 20 minutes between each drug. Blood flow was measured during the last 2 minutes for each dose and recorded for 10 seconds in every 15 seconds. The plethysmograph (Hokanson EC6, D.E. Honkanson Inc, Bellevue, WA, USA) was connected to an analog-to-digital converter (8SP, AD Instruments Pty Ltd, Castle Hill, Australia), and data were analyzed by Power Lab software on an IBM PC. Evaluations of FBF were made by calculation of the mean of at least 4 consecutive recordings.

Analysis

Forearm blood flow was expressed as mL/min per 100 mL forearm tissue. Responses to Ach and SNP were quantified as the increase in FBF above baseline value.

Data were analyzed using SPSS 8.0.0. Correlation analysis was performed by Spearman rank order test, and significant differences were assumed to be present at $P < .05$.

RESULTS

Table 1 displays the main characteristics of the subjects enrolled in the study.

Basal FBF before Ach correlated with basal FBF before SNP ($r = 0.61$, $P < .001$), which is an index of the good reliability of the method. It should be noted that 5 subjects received only Ach infusions, so FBF after SNP could not be evaluated in these subjects.

Table 1- General characteristics of the sample of the 85 subjects investigated

Variables	Quartiles	n
Age (years)	18 – 27	22
	27 – 37	26
	37 – 41	16
	41 – 55	21
BMI (kg/m^2)	19.8 – 30.8	20
	30.8 – 35.4	23
	35.4 – 40.4	21
	40.4 – 54.1	21
Waist (cm)	60 – 94	24
	94 – 101	19
	101 – 109	23
	109 – 129	19
WHR	0.68 – 0.83	23
	0.83 – 0.88	26
	0.88 – 0.92	17
	0.92 – 1.05	19

We observed significant inverse correlations of BMI and WC with FBF increments after Ach and SNP infusions ($P < .05$) (Table 2). The inverse correlation of WHR with FBF increment was significant after Ach ($P < .05$), but not after SNP infusion (Table 2).

When subjects older than 40 years were excluded (n = 25) from the analysis, a significant inverse correlation of WC and WHR, but not BMI, with the FBF increment after Ach was observed, with no significant correlation of WHR with SNP infusion (Table 3).

DISCUSSION

Obesity is associated with increased cardiovascular morbidity and mortality and is now regarded as a major independent risk factor.[15] Obesity is still routinely diagnosed when the BMI equals or exceeds 30 kg/m^2. Our findings suggest that there is a stronger positive correlation of WHR with impaired nitric oxide-dependent vasodilation than of BMI or WC.

Data from long-term follow-up studies in adults show that impaired endothelium-dependent arterial vasorelaxation in response to muscarinergic stimulation with acetylcholine precedes cardiovascular events by years.[11] Fichtlscherer et al[16] found a good correlation between impaired endothelium-dependent FBF and recurrence of instability and cardiovascular event rates in patients with acute coronary syndrome. Numerous studies have evaluated lifestyle and pharmacological interventions to improve endothelial function and to limit cardiovascular risk.[17] Woo et al[18] reported an improvement of endothelial function in young obese after dietary modification alone or in combination with exercise training, showing that a primary intervention can change the cardiovascular risk.

Atherosclerosis is an inflammatory process, with metabolic disturbances such as obesity, hyperglycemia, and dyslipidemia considered to be proinflammatory triggers that initiate a chronic subclinical inflammatory status.[19] Excessive fat accumulation plays a major role in initiating and maintaining this inflammatory process. The adipocyte is a

Table 2 - Correlations (Spearman *r*) between forearm blood flow and obesity indexes in all patients

	Body mass index		Waist circumference		Waist-to-hip ratio	
	r	*P*	*r*	*P*	*r*	*P*
Ach (7.5 µg/min) (n = 85)	-0.26	0.010	-0.32	0.003	-0.16	0.080
Ach (15 µg/min) (n = 85)	-0.22	0.020	-0.28	0.010	-0.24	0.020
Ach (30 µg/min) (n = 85)	-0.26	0.010	-0.27	0.012	-0.22	0.020
SNP (2 µg/min) (n = 80)	-0.31	0.001	-.027	0.014	-0.16	0.100
SNP (4 µg/min) (n = 80)	-0.37	0.001	-0.32	0.005	-0.14	0.120
SNP (8 µg/min) (n = 80)	-0.37	0.001	-0.31	0.006	-0.16	0.090

Ach = acetylcholine; SNP = sodium nitroprusside

Table 3 - Correlations (Spearman *r*) between forearm blood flow and obesity indexes in patients aged ≤ 40 years

	Body mass index		Waist circumference		Waist-to-hip ratio	
	r	*P*	*r*	*P*	*r*	*P*
Ach (7.5 µg/min) (n = 60)	-0.19	0.180	-0.29	0.040	-0.35	0.010
Ach (15 µg/min) (n = 60)	-0.23	0.110	-0.27	0.050	-0.28	0.050
Ach (30 µg/min) (n = 60)	-0.28	0.060	-0.32	0.020	-0.28	0.050
SNP (2 µg/min) (n = 55)	-0.27	0.070	-0.30	0.030	-0.25	0.090
SNP (4 µg/min) (n = 55)	-0.35	0.010	-0.34	0.010	-0.17	0.260
SNP (8 µg/min) (n = 55)	-0.39	0.008	-0.36	0.010	-0.19	0.200

Ach = acetylcholine; SNP = sodium nitroprusside

complex and active endocrine cell, releasing numerous products, including free fatty acids, leptin, adiponectin, PAI-1, interleukin-6, tumor necrosis factor alpha, resistin, and angiotensin.[20]

Although there is no doubt that intra-abdominal fat has the greatest impact as a cardiovascular risk factor, the metabolic role of peripheral fat has not been completely clarified. Ferreira et al[21] showed that only visceral fat is adversely associated with large artery stiffness, whereas some degree of protection is conferred by peripheral fat and lean mass. There is a good positive correlation of intra-abdominal or visceral adipose tissue with insulin resistance, and it should be noted that patients of normal weight can also be insulin resistant.[22] These findings call into question the usefulness of BMI as a risk marker, especially in lean persons.

Although accurate quantification of body fat compartments requires expensive techniques such as magnetic resonance imaging or computed tomography, clinical anthropometric measurements such as WC or WHR can be used to assess regional fat distributions. Yusuf et al,[10] in a case-control study of acute myocardial infarction enrolling 27098 participants from 52 countries, showed a strong correlation between WHR and myocardial infarction risk, while BMI showed only a modest relation with it.

Impairment in endothelium-dependent vasodilation was also found by Higashi et al[23] in patients with a BMI higher than 30 kg/m^2. We found that BMI and WC had a negative correlation with FBF under the condition of endothelial-dependent vasodilation, but also under the condition of endothelial-independent vasodilation. When only young patients were included in the analysis we found a signficant inverse correlation only of WHR with FPB under the condition of endothelial-dependent vasodilation; this finding could be reflecting the probability that older subjects had higher rates of established arterial disease.

Our data show a stronger correlation of blunted responses to endothelium-dependent arterial vasorelaxation with WHR than with BMI, suggesting that WHR could be a precocious and more specific obesity index for endothelial dysfunction in this group. Findings in conduit arteries were also observed by Brook et al[24] who studied obese subjects and found a significantly blunted response in brachial artery flow-mediated dilation in subjects with a WHR ^{3} 0.85.

These findings underscore the importance of the collection of hip circumference as an obesity index and risk estimator. Considering that there is a good correlation of WHR with endothelial dysfunction of coronary and brachial arteries, it is possible that redefining obesity based on WHR, as proposed by Yusuf et al,[10] would greatly increase the accuracy of estimation of myocardial infarction risk from obesity.

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RESUMO

Villela NR, Aguiar LGK, Bahia L, Bottino D, Bouskela E. Em obesos, a disfunção endotelial correlaciona melhor com a relação cintura-quadril do que com a medida da cintura ou índice de massa corpórea. Clinics. 2006;61(1):53-8.

OBJETIVO: A obesidade é associada a doenças cardiovasculares e compromete tanto a macro como a microcirculação. As medidas da cintura e do índice de massa corpórea são rotineiramente empregadas para avaliação do risco cardiovascular em obesos, enquanto a relação cintura-quadril é pouco utilizada. O objetivo do trabalho foi determinar que medida antropométrica, entre as rotineiramente usadas, avalia melhor o risco cardiovascular em obesos.

MATERIAL E MÉTODO: Oitenta e quatro voluntários (21 homens/ 66 mulheres), idade entre 20 e 55 anos foram avaliados quanto ao diâmetro da cintura, ao índice de massa corpórea, à relação cintura-quadril e à função endotelial pela técnica de pletismografia com oclusão venosa para medida do fluxo sanguíneo braquial, em resposta a injeção intrabraquial de três doses de acetilcolina (7,5; 15 e 30 mg/min) ou de nitroprussiato de sódio (2; 4 e 8 mg/min), para avaliação da vasodilatação endotélio-dependente e -independente.

RESULTADO: Houve correlação inversa entre o índice de massa corpórea, diâmetro da cintura e aumento do fluxo sanguíneo após injeção de acetilcolina e nitroprussiato de sódio, enquanto que a relação cintura-quadril mostrou uma correlação negativa apenas com o aumento no fluxo de sangue no antebraço, após as infusões de acetilcolina. Quando os indivíduos com mais de 40 anos foram retirados da análise, não observamos mais a relação inversa entre índi-

ce de massa corpórea e aumento do fluxo sanguíneo após injeção de acetilcolina, enquanto que a cintura e a relação cintura-quadril mantiveram os resultados observados anteriormente.

CONCLUSÃO: A relação cintura-quadril é provavelmente um melhor índice para estimar a disfunção endotelial, e consequentemente o risco cardiovascular, que o índice de massa corpórea e esses achados reforçam a importância da aferição da circunferência do quadril como um índice de obesidade e para estimativa do risco cardiovascular.

UNITERMOS: Disfunção endotelial. Vasodilatação. Diâmetro da cintura. Índice de massa corpórea. Relação cintura-quadril.

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