The Impact Of Adiposity And Insulin Resistance On Endothelial Function In Middle-Aged Subjects

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Citation

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Abstract

Objectives: To investigate the relationship between adiposity, adipose distribution, insulin resistance (IR) and vascular endothelial function.

Methods: Flow-mediated endothelium-dependent dilation (EDD), body mass index (BMI), waist circumference, waist hip ratio and IR index (HOMA-IR) were measured in 527 healthy subjects (328 males) aged between 35 to 55 years. The relations between these parameters and endothelial function was studied using univariate and multivariate linear regression analysis.
Results: Waist circumference, waist hip ratio and HOMA-IR were greater in the overweight or obese subjects ($p<0.01$). They were also greater in males than in females within the same body weight group ($p<0.05$). The incidence of vascular endothelial dysfunction in the normal body weight, overweight and obese was 30.7%, 69.5% and 75.4% respectively ($p<0.05$). A higher waist circumference and waist hip ratio was also found in male subjects with endothelial dysfunction than those without. A greater HOMA-IR was identified in both male and female subjects with impaired endothelial function ($p<0.05$). Multivariate linear regression analysis showed a small but significant inverse correlation between endothelial function and BMI ($r= -0.285$, $p<0.001$), waist hip ratio ($r= -0.179$, $p<0.001$) and HOMA-IR ($r= -0.164$, $p<0.001$).

Conclusions: Adiposity and adipose distribution have an important impact on endothelial function in male subjects. An increase in HOMA-IR is associated with vascular endothelial dysfunction in both males and females.

INTRODUCTION

Endothelial dysfunction has been shown to be an early marker of atherosclerotic disease. [1]Previous studies have demonstrated a close correlation between vascular endothelial dysfunction and insulin resistance, which was commonly seen in those who are obese. [2] To further illustrate the relationships between obesity, insulin resistance and vascular endothelial function, we investigated the adiposity and adipose distribution, insulin resistance and endothelial function in middle-aged subjects.

PATIENTS AND METHODS

PATIENTS

This study was approved by the Human Ethics Committee of our hospitals. Five hundred and twenty seven healthy subjects (25-55 years old) from the city of Shijiazhuang in Northern China were enrolled in the study. Body mass index (BMI) were used to define overweight or obesity as below: normal: 18.5~24.9 kg/m2; overweight: 25~29.9 kg/m2; obese: BMI > 30 kg/m2.

METHODS

Plasma glucose was measured by glucose oxidase technique. Plasma insulin level was tested after 12 hours of fasting using dextran-charcoal radioimmunoassay method. Insulin resistance was estimated by the homeostasis-model assessment (HOMA-IR): insulin resistance = (fasting glucose x fasting insulin) / 22.5. [3]

Weight and height were measured in light clothing without shoes. BMI was calculated as weight (kg) divided by height

(m) squared and was used as an index of overall adiposity. Waist circumference was measured at the level of the umbilicus with the subject standing and breathing normally. Hip circumference was measured at the level of greatest hip girth. Waist circumference and waist hip ratio was used as a measure of body fat distribution.

Vascular endothelial function was assessed from brachial artery from B-mode ultrasound images using a standard NAS-1000 HE system and a 7.0-MHz linear array transducer. The ultrasound method for assessing endothelium-dependent and independent dilatation was performed as described previously. [4, 5] The brachial artery was scanned in longitudinal section above the elbow, and the center of the artery was identified when the clearest picture of the anterior and posterior intimal layers was obtained. Depth and gain settings were set to optimize images of the lumen/arterial wall interface.

In all studies, scans were obtained at rest, during reactive hyperemia (with increased flow leading to endothelium-dependent dilatation (EDD)). When a satisfactory transducer position was found, the skin was marked, and the arm remained in the same position throughout the study. A resting scan was recorded, and arterial diameter was measured using B-mode. Increased flow was then induced by inflation of a pneumatic tourniquet placed around the forearm (distal to the scanned part of the artery) to a pressure of 300 mm Hg for 4.0 minutes, followed by release. After 60-90 seconds of cuff deflation, the diameter of the brachial artery was measured. An increase of more than 10% in artery diameter after cuff release was defined as normal endothelial function. [6]

STATISTICAL ANALYSIS

Data were expressed in means + SD. SPSS10.0 statistical software was used to analyze the difference between groups (t and ?2 tests). The relationship between age, gender, waist circumference, waist hip ratio, BMI, HOMA-IR and EDD was assessed by a univariate and a multiple linear regression analysis. P<0.05 was considered statistically significant.

RESULTS

GENERAL FINDINGS (TABLE 1)

There was no significant difference in the average age between normal body weight, overweight and obese group (p>0.05). There was an increased waist circumference and waist hip ratio in the overweight and obese group compared with the normal body weight group (p<0.01). The HOMA-IR was also increased in the latter two groups (p<0.01). In the overweight and the obese group, the waist circumference and waist hip ratio was greater in males than in females (p<0.01).

Figure 1

Table 1a: General findings

Group	n	Age (years)	BMI (kg/m²)
Normal weight Total	166	44.97±4.85	22.79±1.66
Male	102	44.82±5.20	22.63±1.72
Female	64	45.27±4.52	22.41±1.53
Overweight Total	223	44.23±5.62	27.30±1.24
Male	135	43.98±5.23	27.27±1.26
Female	88	44.75±6.16	27.48±1.15
Obesity Total	138	45.21±7.03	31.20±1.42**□
Male	91	44.06±7.66	31.08±1.32**□
Female	47	46.83±6.91	31.62±1.50**□

BMI body mass index; W: waist circumference; WHR: Waist hip ratio; IR: insulin resistance. Compared with normal weight group: *P<0.01, **P<0.001; Compared with overweight group: ?P< 0.01??P<0.001; Compared with males in the same group, ?P<0.01, ??P<0.001.

Figure 2

Table 1b: General findings

Group	Waist (cm)	WHR	HOMA-IR
Normal weight Total	78.83±6.15	0.84±0.05	0.39±0.30
Male	81.32±5.26	0.87±0.04	0.37±0.31
Female	75.29±5.44▲	0.80±0.04▲	0.42±0.28
Overweight Total	92.27±6.11**	0.91±0.05**	0.61±0.39*
Male	95.13±5.36**	0.94±0.04**	0.59±0.38*
Female	86.77±4.58**▲▲	0.87±0.03**▲▲	0.64±0.39*
Obesity Total	101.34±6.25**□□	0.94±0.06**□	0.64±0.35*
Male	103.82±5.42**□□	0.97±0.04**□	0.66±0.35*
Female	97.67±6.79**□□▲	0.87±0.05**▲▲	0.61±0.36*

BMI body mass index; W: waist circumference; WHR: Waist hip ratio; IR: insulin resistance. Compared with normal weight group: *P<0.01, **P<0.001; Compared with overweight group: ?P< 0.01??P<0.001; Compared with males in the same group, ?P<0.01, ??P<0.001.

COMPARISON OF ADIPOSITY, ADIPOSE DISTRIBUTION AND HOMA-IR BETWEEN NORMAL AND ABNORMAL ENDOTHELIAL FUNCTION GROUP (TABLES 2 AND 3)

Endothelial dysfunction was detected in 51 (30.7%), 155 (69.5%) and 104 (75.4%) in normal weight, overweight and obese group, respectively. The incidence of vascular endothelial dysfunction in females (52.3%, 104/199) was lower than that in males (64.3%, 211/328, p<0.01).

In the obesity group, subjects with abnormal vascular endothelial function had a greater BMI. In those with endothelial dysfunction of normal weight and overweight groups, a greater waist circumference was found in males than in females (p<0.05). Waist hip ratio was greater in males who have endothelial dysfunction of all body weight groups (p<0.05).

A greater HOMA-IR was found in all subjects with endothelial dysfunction (p<0.05) except the male subjects of the normal body weight group.

In all subgroups, the waist circumference and waist hip ratio was greater in males than in females (p<0.01).

CORRELATION BETWEEN ADIPOSITY, ADIPOSE DISTRIBUTION, HOMA-IR AND ENDOTHELIAL FUNCTION

Univariate analysis showed a significant inverse correlation between EDD and BMI, waist circumference, waist hip ratio or HOMA-IR (r=-0.418, -0.366, -0.424 and -0.263 respectively, P<0.001). Multivariate analysis of the correlation between EDD and age, gender, BMI, waist circumference, waist hip ratio and HOMA-IR revealed a small but significant inverse correlation between EDD and BMI (r=-0.285, p<0.001), waist hip ratio (r=-0.179, p<0.001) and HOMA-IR (r=-0.164, p<0.001).

Figure 3

Table 2a: Comparison of body mass index and waist circumference between groups with normal and impaired endothelial function.

			Waist (cm)	
Group	Endothelial function	n	Male	Female
Total	Normal	209	89.81±9.71	79.94±9.57##
	Impaired	318	95.67±7.96**	87.37 ± 8.32**##
Normal weight	Normal	115	79.33±5.37	74.83±5.29#
	Impaired	51	83.57±5.15**	75.50±5.74##
Overweight	Normal	68	92.18±5.63	85.50±3.45##
	Impaired	155	96.20±4.75*	87.92±5.33##
Obesity	Normal	34	102.71±5.50	96.67±6.66#
	Impaired	104	104.87±5.46	97.15±7.19##

The abbreviations are as in the Table 1. Compared with normal endothelial function: *P<0.05, ** P<0.01; Compared with males in this group: #P<0.01, ##P<0.001

Figure 4

Table 2b: Comparison of body mass index and waist circumference between groups with normal and impaired endothelial function.

			BMI (kg/m^2)	
Group	Endothelial function	n	Male	Female
Total	Normal	209	25.89±3.12	24.67±3.36#
	Impaired	318	27.72±2.79**	27.76±3.07**
Normal weight	Normal	115	22.43±1.86	22.65±1.66
	Impaired	51	22.91±1.64	23.15±1.35
Overweight	Normal	68	27.22±1.26	27.34±1.07
	Impaired	155	27.32±1.29	27.59±1.21
Obesity	Normal	34	30.91±1.38	31.10±1.42
	Impaired	104	31.18±1.20	32.39±2.30*

The abbreviations are as in the Table 1. Compared with normal endothelial function: *P<0.05, ** P<0.01; Compared with males in this group: #P<0.01, ##P<0.001.

Figure 5

Table 3a: Comparison of waist hip ratio (WHR) and insulin resistance (HOMA-IR) between group with normal and impaired endothelial function.

Group	Endothelial function	N	WHR (cm) Male	WHR (cm) Female
Total	Normal	209	0.91±0.06	0.82±0.05##
	Impaired	318	0.95±0.04**	0.86±0.05**##
Normal weight	Normal	115	0.85±0.03	0.80±0.04##
	Impaired	51	0.89±0.03**	0.80±0.04##
Overweight	Normal	68	0.91±0.04	0.86±0.03##
	Impaired	155	0.95±0.03*	0.87±0.05##
Obesity	Normal	34	0.95±0.03	0.87±0.06#
	Impaired	104	0.99±0.04*	0.87±0.04##

The abbreviations are as in the Table 1. Compared with normal endothelial function: *P<0.05, **P<0.01; Compared with males in the same group #P<0.01, ##P<0.001

Figure 6

Table 3b: Comparison of waist hip ratio (WHR) and insulin resistance (HOMA-IR) between group with normal and impaired endothelial function.

Group	Endothelial function	N	HOMA-IR Male	HOMA-IR Female
Total	Normal	209	0.45±0.35	0.38±0.32
	Impaired	318	0.64±0.39*	0.69±0.43**
Normal weight	Normal	115	0.34±0.29	0.33±0.31
	Impaired	51	0.42±0.34	0.58±0.25**
Overweight	Normal	68	0.50±0.37	0.55±0.29
	Impaired	155	0.65±0.39*	0.71±0.46*
Obesity	Normal	34	0.51±0.30	0.35±0.22
	Impaired	104	0.77±0.39*	0.76±0.43**

The abbreviations are as in the Table 1. Compared with normal endothelial function: *P<0.05, **P<0.01; Compared with males in the same group #P<0.01, ##P<0.001

DISCUSSION

Previous studies have shown that an increase in body adipose tissue, especially in the abdominal region, is a risk factor of vascular endothelial function impairment. 2 Our study demonstrated that BMI, waist circumference and waist hip ratio were greater in middle-aged subjects with endothelial dysfunction than in those with normal endothelial function. These results suggest that adiposity and adipose tissue distribution have a significant influence on vascular endothelial function. Our study also showed that waist circumference and waist hip ratio was greater in males than in females with or without endothelial dysfunction, indicating that male subjects have a more centrally distributed adipose tissue, which helps to explain the higher incidence of vascular endothelial dysfunction.

Although overweight is associated with vascular endothelial dysfunction, one third of our subjects with normal body weight also had impaired vascular endothelial function. These subjects, however, have an increased waist circumference and waist hip ratio, suggesting that adipose distribution is more important than body weight in predicting vascular endothelial function. A more recent study also demonstrated that the degree of vascular damage is predicted by body fat distribution independently of body weight and metabolic and other haemodynamic parameters.[7] Adipose distribution doesn't appear to play an important role in determining vascular endothelial function in females who have a normal body weight.

HOMA-IR appears to be an important contributing factor of vascular endothelial dysfunction, an early marker of atherosclerotic disease. [8] Patients with atherosclerosis are found to have both endothelial dysfunction and reduced insulin activity. 1 In female subjects, the endothelial dysfunction cannot be explained by adipose distribution alone, because there was no significant increase in waist circumference or waist hip ratio in those with endothelial function impairment. In these subjects, HOMA-IR increase appears more important than adipose distribution in leading to endothelial dysfunction. Multivariate analysis also demonstrated a small but significant correlation between the level of HOMA-IR and endothelial function in both male and female subjects.

The specific impact of insulin resistance on endothelial function seems complex. Insulin resistance is often accompanied by hyperinsulinemia, which abolishes endothelium-dependent vasodilation in large conduit arteries; probably by increasing oxidant stress. 8 Insulin has a vasodilative action in a number of tissues. Insulin resistant states exhibit diminished insulin-mediated glucose uptake into peripheral tissues and display impaired insulin-mediated vasodilation as well as impaired endothelium dependent vasolidation to the muscarinic receptor agonist acetylcholine. [9] Insulin resistance within the adipose tissue inhibits insulin-induced lipolysis and increases free fatty acids which are known to cause endothelial injuries. [10]

In summary, adiposity and adipose distribution have a close relationship with vascular endothelial dysfunction in uncomplicated obese subjects especially in males. In females, insulin resistance appears to play a more important rule than adipose distribution in determining endothelial dysfunction.

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