Association of waist circumference and body fat weight with insulin resistance in male subjects with normal body mass index and normal glucose tolerance

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Abstract

Objective: We investigated the relationship of the waist circumference (WC) and body fat weight (BF) with insulin resistance in subjects with normal body mass index (BMI) and normal glucose tolerance (NGT) during a routine medical check-up.

Methods: We categorized 167 male subjects in three groups as follows: a group with normal BMI but high WC (normal-BMI/high-WC group; 22≦BMI<25 kg/m^2, waist ≧85cm; n=31), a group with normal BMI and normal WC (normal-BMI/normal-WC group, waist <85cm; n=68), and a group with low normal BMI and normal WC (low normal-BMI/normal-WC group; 18.5≦BMI<22 kg/m^2 and waist< 85cm; n=68). We measured the plasma glucose and serum insulin levels before glucose loading and after 30 and 120 min and calculated several indexes of insulin secretion and sensitivity.

Results: Subjects from the normal-BMI/high-WC group showed significantly decreased Matsuda index and increased homeostasis model assessment for insulin resistance (HOMA-IR) compared with normal-BMI/normal-WC group. Univariate regression analyses showed significant correlation of HOMA-IR with WC (r=0.39) and BF (r=0.37). Matsuda index was significantly correlated with WC (r=-0.39) and BF (r=-0.47). The multiple regression analysis showed that the BF is significantly correlated with HOMA-IR ($p<0.05$) and Masuda index ($p<0.005$) among the

clinical variables and with HOMA-IR ($p<0.05$) and Masuda index ($p<0.0001$) among the anthropometric variables but not with WC in either analysis.

Conclusion: Decreased Matsuda index and increased HOMA-IR were observed in subjects from the normal-BMI/high-WC group. Multivariate analysis showed that BF is associated with decreased Matsuda index and increased HOMA-IR and that WC is not associated with either factors

Key words

Metabolically obese but normal body weight

Waist circumference

Insulin resistance

Visceral fat

Matsuda index

HOMA-IR

Abbreviations

ALT: alanine aminotransferase

AST: aspartate aminotransferase

BF: body fat weight

BMI: body mass index

eGFR: estimated glomerular filtration rate

HOMA-IR: homeostasis model assessment for insulin resistance

HOMA-β: homeostasis model assessment for β cell function

IGT: impaired glucose tolerance

JDS: Japan Diabetes Society

MONW: metabolically obese but normal body weight

NAFLD: non-alcoholic fatty liver disease

NGSP: National Glycoheaemoglobin Standardization Program

NGT: normal glucose tolerance

OGTT: oral glucose tolerance test

WC: waist circumference

Introduction

Visceral fat accumulation is one of the manifestations of metabolic syndrome and an important risk factor for atherosclerosis (1,2). Previous study has demonstrated that visceral fat accumulation promotes insulin resistance and that it affects glucose tolerance in the Japanese population (3). Individuals with obesity-like findings (eg, visceral fat accumulation) but with normal body weight are categorized as metabolically obese but normal weight (MONW) subjects; they have been categorized as a sub-phenotype of metabolic syndrome (4). We previously reported the presence of insulin resistance measured by the euglycemic-hyperinsulinemic clamp study in MONW subjects with normal glucose tolerance as evaluated by excess visceral fat accumulation detected by computed tomography; these observations suggested that visceral fat accumulation can induce insulin resistance in MONW subjects with normal glucose tolerance (5-7). Insulin resistance is a risk factor of type 2 diabetes and atherosclerosis in subjects with normal body mass index (BMI). Several reports demonstrated that Asian and Japanese people tend to be less obese but with increased body fat content compared with other ethnic populations with the same BMI (8-10).

Waist circumference is currently being used as an early indicator of visceral fat accumulation during routine medical check-up (11). Several reports demonstrated that insulin resistance is associated with waist circumference in subjects with normal glucose tolerance and normal BMI

(12,13). However, there is no report comparing clinical parameters and several indexes of insulin resistance and insulin secretion between subjects with high and normal waist circumference in the same range of BMI and normal glucose tolerance. In addition, a recent study has shown that the body fat weight is also a useful marker of insulin resistance (14.15); thus, we have also analyzed the association of body fat weight with insulin resistance.

In this study, we investigated the relationship of the waist circumference and body fat weight with insulin resistance measured by the 75g oral glucose tolerance test (OGTT) in male subjects with normal glucose tolerance and normal BMI

Materials and Methods

Subjects

The 75g OGTT was performed using Torelan G 75 (Shimizu, Japan) in 938 subjects undertaking medical check-up at Mihama town, Mie prefecture between 2000 and 2007. Based on the results of this 75g OGTT, 167 Japanese men with normal BMI and normal glucose tolerance were included in the study. Diabetes and impaired glucose tolerance (IGT) were excluded based on the criteria of the Japan Diabetes Association (16). The Mie University's Review Board for human investigations approved the study protocol and the investigation was carried out following the principles of the Helsinki Declaration. Written informed consent was obtained from all subjects before the beginning of the study. None of the subjects were receiving any medication that could

affect insulin levels and the subjects were not under dietary therapy before the beginning of this study. The waist circumference correlates with visceral fat accumulation, and Japanese men with waist circumference of more than 85 cm have excess visceral fat accumulation as measured by CT (11). Therefore, a waist circumference over 85 cm is considered abnormal based on the criteria of the Japan Society for the Study of Obesity (17). We categorized the subjects in three groups as follows: a group with normal BMI but high waist circumference (normal-BMI/high-WC group; 22.0≦BMI<25 kg/m^2, waist≧85cm; n=31), a group with normal BMI and normal waist circumference (normal-BMI/normal-WC group; 22.0≦BMI<25 kg/m^2,waist <85cm; n=68), and a group with low normal BMI and normal waist circumference (low normal-BMI/normal-WC group; 18.5≦BMI<22.0 kg/m^2 and waist< 85 cm; n=68). Because subjects with BMI<22.0 kg/m^2 had waist circumference less than 85 cm, they were categorized as low normal BMI subjects. Hypertension was diagnosed when the systolic blood pressure was ≧140mmHg or diastolic blood pressure ≧ 90mmHg including subjects under medication. Dyslipidemia was diagnosed when there were abnormal serum triglyceride (≧150 mg/dl) or HDL cholesterol levels (<40 mg/dl).

Methods

Blood was sampled in all subjects from an antecubital vein in the early morning after fasting overnight and after resting for 30 min in supine position. Serum and plasma were separated by centrifugation at 1500 x g at 4°C for 20 min and then stored at –80°C until use. Waist

circumference was measured at the umbilical level in the standing position before performing OGTT by same person for measurement. Blood pressure was measured on supine position at rest. Body fat weight was measured by bioelectric impedance using a TBF-101 (Tanita, Tokyo, Japan). The level of HbA1c (Japan Diabetes Society [JDS]) was measured by the latex-immunoturbidimetry methods. The value of HbA1c (%) was estimated as an National Glycoheaemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the following formula: HbA1c (%) = HbA1c (JDS)(%) + 0.4% (18). The plasma glucose level was measured by the glucose oxidase method and the serum level of lipids, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) by automated enzymatic methods. Renal function was assessed by the estimated glomerular filtration rate (eGFR) (19). Blood was sampled before glucose loading (fasting) and after 30 and 120 min; the plasma glucose and serum insulin levels were measured at these time points together with the profile of fasting lipids. Serum insulin levels were measured using a commercial EIA kit (E-test, TOSHO II, Tosho. Tokyo, Japan).

The values of homeostasis model assessment (HOMA-IR) (20) and the Matsuda index (21,22) were calculated to assess insulin sensitivity. The Matsuda index was calculated as follows: Matsuda index =10000/sqrt {0 min (before loading) plasma glucose (mg/dl) x 0 min serum insulin (μU/ml) x120 min plasma glucose x 120 min serum insulin}(22). The capacity to secrete insulin in response to oral glucose stimulation was estimated by the ratio of I_{30} to G_{30} (insulinogenic index)

as follows: increment of serum insulin from 0 to 30 min/increment of plasma glucose from 0 to 30 min) (23). We also estimated the homeostasis model assessment for β cell function (HOMA-β) as previously described (16) and the disposition index (24). The disposition index was calculated as follows: Insulinogenic index x Matsuda index. The serum level of total adiponectin was measured by using a commercial ELISA Kit **(**R&D Systems Inc**.,** Minneapolis, USA).

Statistical analysis

Data are expressed as the mean ± SD. Statistical difference between normally distributed variables was calculated using parametric tests. Comparison of continuous variables among three groups was performed by one-way analysis of variance with *post hoc* analysis by the Scheffe method. The distribution of triglyceride, insulinogenic index, disposition index and Matsuda index data was skewed and expressed as median and interquartile ranges (25 th and 75 th percentile). Statistical difference between skewed variables was evaluated by a non-parametric analysis of variance (Kruskal-Wallis test). Univariate and multivariate regression analyses were performed to evaluate the relationship of HOMA-IR or log–transformed Matsuda index (Log-Matsuda index) with clinical parameters in all subjects. The independent variables included in the multivariate regression analysis were age, body mass index, waist circumference, hip circumference, body fat weight, systolic blood pressure, diastolic blood pressure, aspartate aminotransferase, alanine aminotransferase, total cholesterol, triglyceride, HDL-cholesterol, eGFR,

adiponectin, HbA1c and family history of diabetes (no:0, yes:1). In a separate multivariate analysis, the relation of markers of insulin resistance with anthropometric variables (age, body mass index, waist circumference, hip circumference and body fat weight) was also evaluated. The serum level of triglyceride was log-transformed before using in the regression analysis. The difference in frequency was assessed by χ^2 test complemented by adjusted residual analysis. $P<0.05$ was considered as statistically significant. Statistical analyses were performed using the StatView 5.0 software package (Abacus Concepts, Berkeley, CA, USA) for the Macintosh and the SPSS version 22.0 for Windows (Statistical Package for the Social Science; SPSS, Chicago, IL, USA).

Results

The clinical characteristics of the patients of each group are described in Table 1. There was no significant difference in BMI between the normal-BMI/high-WC and normal-BMI/normal-WC groups. The body fat weight of normal-BMI/high-WC group was significantly increased compared with that of low normal-BMI/normal-WC groups ($p<0.001$). The serum level of ALT was increased in the normal-BMI/high-WC groups as compared to the low normal-BMI/normal-WC group ($p<0.05$). The serum level of triglycerides was significantly increased in the normal-BMI/high-WC groups as compared to the low normal-BMI/normal-WC group ($p<0.001$). In addition, the HDL cholesterol level was significantly increased in the low normal-BMI/normal-WC group compared with the normal-BMI/high-WC ($p<0.01$) or normal-BMI/normal-WC groups ($p<0.05$). The total adiponectin levels in the normal-BMI/high-WC ($p<0.001$) or normal-BMI/normal-WC ($p<0.001$) groups were significantly decreased compared with the low normal-BMI/normal-WC group. Dyslipidemia was more significantly frequent in the normal-BMI/high-WC than in the low normal-BMI/normal-WC group ($p<0.05$).

The results of the 75g OGTT and values of several parameters are described in Table 2. There was no significant difference in the plasma glucose levels among the three groups before loading 、after 30 min and 120 min. The serum insulin levels were significantly increased in the

normal-BMI/high-WC group as compared to the normal-BMI/normal-WC group before loading ($p<0.05$) and 120 min ($p<0.01$). Subjects from the normal-BMI/high-WC group showed significantly increased HOMA-IR compared with the normal-BMI/normal-WC ($p<0.01$) and the low normal-BMI/normal-WC groups ($p<0.0001$). Matsuda index in the normal-BMI/high-WC group was significantly decreased compared with the normal-BMI/normal-WC ($p<0.05$) and low normal-BMI/normal-WC groups ($p<0.0001$). HOMA-β in the normal-BMI/high-WC group was significantly increased compared with the low normal-BMI/normal-WC group ($p<0.0001$). No significant difference in the values of HOMA-β was observed between the normal-BMI/high-WC and normal-BMI/normal-WC groups. There was no significant difference in insulinogenic index and disposition index among the three groups (Table 2).

The univariate regression analyses of HOMA-IR or Matsuda index with clinical parameters were performed in all subjects (Table 3). HOMA-IR was significantly correlated with the waist circumference ($r=0.39$, $p<0.0001$, Figure.1), BMI ($r=0.42$, $p<0.0001$), body fat weight ($r=0.37$ $p<0.0001$). Matsuda index was significantly correlated with the waist circumference ($r=-0.39$, $p<0.0001$, Figure.2), BMI ($r=-0.40$, $p<0.0001$) and body fat weight ($r=-0.47$, $p<0.0001$). Moreover, HOMA-IR were significantly correlated with serum ALT ($r=-0.27$, $p<0.001$) and adiponectin ($r=-0.22$, $p<0.01$). Masuda index were significantly correlated with serum ALT ($r=-0.25$, $p<0.005$) and adiponectin ($r=-0.22$, $p<0.005$). The multiple regression analysis showed

that the HOMA-IR ($p<0.05$) and Masuda index ($p<0.005$) are significantly correlated with the body fat weight among several clinical variables (Table 4). Moreover, HOMA-IR ($p<0.05$) and Masuda index ($p<0.0001$) were significantly correlated with the body fat weight among several anthropometric variables (Table 5). However, waist circumference is not associated with HOMA-IR and Matsuda index in either analysis (Table 4,5).

Discussion

A population of subjects with normal body weight but with a cluster of obesity-related characteristics has been reported. This group is characterized by excess visceral fat, insulin resistance and hyperinsulinemia and has been categorized as metabolically obese but normal weight (MONW) subjects (4). In the Japanese population, non-obese (BMI <25 kg/m^2) subjects with increased visceral fat areas (100 cm^2) fulfill the criteria for including them in the MONW group. In this study, we compared several clinical parameters and indexes of insulin resistance and insulin secretion between normal-BMI/high-WC and normal-BMI/normal-WC subjects to clarify the effect of visceral accumulation assessed by the waist circumference on clinical parameters in subjects with normal BMI and normal glucose tolerance.

The 75g OGTT showed that the serum insulin levels before loading were significantly increased in the normal-BMI/high-WC group compared to the normal-BMI/normal-WC group with no difference in the plasma glucose level. Moreover, the serum insulin levels at 120 min were significantly increased in the normal-BMI/high-WC group compared to the normal-BMI/normal-WC group. It is known that the post-challenge serum insulin levels at 120 min are negatively correlated with insulin sensitivity as measured by the glucose clamp method in non-diabetic subjects (25). The Matsuda index significantly decreased in the normal-BMI/high-WC group compared with the normal-BMI/normal-WC group. The Matsuda

index is a good indicator of insulin sensitivity including insulin-mediated peripheral glucose uptake because this index is calculated using post-challenge insulin and glucose levels (21,22). Therefore, the increased post-challenge serum levels of insulin at 120 min and decreased Matsuda index indicate that the insulin sensitivity is reduced in subjects of the normal-BMI/high-WC group compared to those of the normal-BMI/normal-WC group. The univariate regression analyses showed that the Matsuda index is significantly correlated with waist circumference in all subjects, suggesting that insulin sensitivity is influenced by the increase of the waist circumference in subjects with normal glucose tolerance and normal BMI. The Matsuda index is an indicator of muscle insulin resistance as measured by the euglycemic-hyperinsulinemic clamp test (26). Visceral fat accumulation may induce insulin resistance leading to low post-challenge peripheral glucose uptake and affect insulin sensitivity measured by the Matsuda index in obese subjects (2,26). Therefore, visceral fat accumulation may affect the muscle insulin sensitivity causing reduced Matsuda index in normal-BMI/high-WC subjects.

HOMA-IR in the normal-BMI/high-WC group was significantly increased compared with the normal-BMI/normal-WC group. Moreover, univariate regression analyses showed that HOMA-IR is significantly correlated with waist circumference and BMI. HOMA-IR is a useful marker of insulin sensitivity and it is calculated based on the basal glucose and insulin levels (17). HOMA-IR mainly reflects hepatic insulin resistance and it is a different from the Matsuda index

(27). It was reported that accumulation of visceral fat is correlated with HOMA-IR (28). The significant correlation between the waist circumference and HOMA-IR suggests that visceral fat accumulation may affect fasting glucose homeostasis by hepatic and extrahepatic actions (29,30). These observations suggest that the waist circumference may be related with Matsuda index and HOMA-IR in subjects with normal BMI and normal glucose tolerance. Future studies using these markers are needed to identify changes in insulin resistance.

In this study, there was no significant difference in the serum ALT levels between the normal-BMI/high-WC and normal-BMI/normal-WC groups. Moreover, the serum ALT levels were significantly correlated with the HOMA-IR by multiple regression analysis (Table 4). These observations suggest that the serum ALT levels are correlated with HOMA-IR independently of the west circumference. The serum ALT was associated with insulin resistance in non-obese subjects (31). Excessive accumulation of fat in the liver called non-alcoholic fatty liver disease (NAFLD) may be the cause of ALT elevation (32). Abnormalities in lipid metabolism and fat accumulation in the liver accelerate glucose overproduction from the liver leading to hepatic insulin resistance (32). Another report has shown the presence of peripheral insulin resistance without hepatic glucose overproduction in non-obese patients with NAFLD, suggesting that peripheral insulin resistance is an important factor for inducing liver fat accumulation (33). Both mechanisms may explain the correlation of ALT elevation with HOMA-IR. Further studies are needed to clarify the

process of hepatic insulin resistance in non-obese subjects

Adiponectin produced by adipocytes is a marker of visceral fat accumulation (34,35). The production of adiponectin is decreased due to functional changes following excessive accumulation of visceral fat (34-36). The present study showed that the circulating levels of serum total adiponectin are significantly and inversely correlated with the waist circumference in all subjects ($r=-0.17$, $p<0.05$), suggesting that excessive accumulation of visceral fat is associated with adiponectin production in these subjects. However, there was no significant difference between normal-BMI/high-WC and normal-BMI/normal-WC groups. In addition to fat accumulation, genetic factors, physical activity and smoking may also influence the adiponectin metabolism, and this may explain the lack of significant difference between the two groups (36,37).

The disposition index represents the balance between insulin secretion and insulin resistance (24). HOMA-β is an indicator of the baseline insulin secretion. There was no significant difference in these parameters between normal-BMI/high-WC and normal-BMI/normal-WC groups. These findings are consistent with previous studies (26) and indicate that insulin secretion is not impaired and compensated for the increase of insulin resistance in the normal-BMI/high-WC group.

The serum triglyceride and HDL cholesterol levels in the normal-BMI/high-WC group were not significantly difference compared with the normal-BMI/normal-WC group. Abnormalities in the levels of triglycerides and HDL cholesterol occur in metabolic syndrome. We previously reported

that insulin resistance and visceral fat accumulation influence the serum triglyceride levels in MONW with normal glucose tolerance (38). Visceral fat accumulation also influences both triglyceride and cholesterol metabolism (30). Current data indicate that increased waist circumference may exert weak effect on lipid metabolism in subjects with same BMI and normal glucose tolerance.

In the current study, the multivariate analysis showed that the total fat weight is significantly correlated with HOMA-IR and Matsuda index. Recently, the body fat weight was found to be a better indicator of cardiovascular mortality than the waist circumference (14). Another report has shown that BMI-based lean men with similar waist circumference and with prediabetes or type 2 diabetes have increased body fat weight and HOMA-IR compared to subjects with normal glucose tolerance (39). These observations suggest that the total fat weight is more related with insulin resistance than with BMI or waist circumference (15, 39). Therefore, the significant correlation of the body fat weight with insulin resistance suggests that the body fat weight is a more accurate indicator of insulin sensitivity than the waist circumference in normal BMI subjects.

There was no significant correlation between the Matsuda index and HOMA-IR and waist circumference by multivariate analysis. The waist circumference reflects the grade of visceral and subcutaneous fat accumulation as assessed by CT and visceral fat decreased in subjects with reduced waist circumference (40). The results of the present study suggest that low waist

circumference is associated with decreased visceral fat accumulation and effect of insulin resistance may be reduced. By contrast, deposition of fats at different sites such as intramuscular fat deposition correlates and influences insulin sensitivity in normal BMI subjects (41). Extra-abdominal fat accumulation may exert strong effect in subjects with normal BMI and normal waist circumference (15). These may explain why HOMA-IR and Matsuda index were correlated with the total fat weight but not with the waist circumference.

HOMA-IR and Matsuda index are surrogate indexes of insulin sensitivity measured by the glucose clamp technique. Correlation of HOMA-IR and Matsuda index with insulin sensitivity by euglycemic-hyperinsulinemic technique was influenced by ß cell function and BMI (42,43) in non-diabetic subjects. Moreover, basic and follow-up studies have shown different correlations of HOMA-IR and Matsuda index with insulin resistance as estimated by the minimal model in the same subjects (44). This report suggests that some factors of insulin sensitivity that influence both HOMA-IR and Matsuda indexes may be different from those affecting the minimal model. Waist circumference reflects both visceral and subcutaneous fat accumulation (40). However, it is not possible to estimate the accurate ratio of visceral and subcutaneous fat by the waist circumference. Body fat weight is indirectly measured by impedance method (45). Impedance for whole body is influenced by several factors. Thus, measurement of body fat weight should be carefully assessed (45). Overall, evaluation of insulin sensitivity by HOMA-IR and Matsuda index is useful, less

invasive and has more cost-benefit than the conventional method; but both indexes require careful assessment. Further studies are needed to clarify the association of body fat accumulation and its distribution with insulin resistance in non-obese subjects by several markers with longitudinal study.

In the present study, we found that the body fat weight is a useful marker to identify subjects with insulin resistance as shown by the Masuda index and HOMA-IR in subjects with normal BMI and normal glucose tolerance in the general population. In general, medical check-up of both waist circumference and body fat weight would be useful for identifying insulin resistance in normal BMI subjects.

In conclusion, the results of the present study, suggest that insulin resistance is associated with the waist circumference and body fat weight in male subjects with normal BMI and normal glucose tolerance. Screening of the body fat weight may be useful to identify individuals with insulin resistance in this group of subjects during a general medical check-up.

Acknowledgments

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Legends for the Figure

Figure. 1 Relationship between HOMA-IR and waist circumference in all subjects. The HOMA-IR was significantly correlated with waist circumference in all subjects (n=167, r=0.39, $p<0.0001$).

Figure. 2 Relationship between Log-Matsuda index and waist circumference in all subjects. The Log-Matsuda index was significantly and inversely correlated with waist circumference in all subjects (n=167, r=-0.39, $p<0.0001$).

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Table 1 Clinical characteristic of the subjects

	Normal-BMI/ high-WC	Normal-BMI/ normal-WC	Low normal-BMI / normal-WC	P value
	22≦BMI<25 kg/m^2	22≦BMI<25 kg/m^2	18.5≦BMI<22kg/m^2	
	Waist≧85 cm	Waist <85 cm	Waist <85 cm	
N	31	68	68	
Age (y.o.)	51.3 ± 7.1	52.4 ± 7.8	52.3 ± 7.7	0.795
Body mass index (kg/m^2)	23.6 ± 0.8*	23.3 ± 0.9*	20.6 ± 1.1	< 0.0001
Waist circumference (cm)	86.9 ± 2.0* #	79.9 ± 3.2*	75.3 ± 4.6	< 0.0001
Hip circumference (cm)	95.3 ± 4.2* $	92.6 ± 4.0*	89.4 ± 4.6	< 0.0001
Body fat weight (%)	24.0 ± 4.7*	22.0 ± 4.0*	18.9 ± 3.7	< 0.0001
Systolic blood pressure (mmHg)	137.2 ± 15.4	130.9 ± 17.1	131.1 ± 18.6	0.212
Diastolic blood pressure (mmHg)	83.3 ± 10.8	79.6 ± 11.3	80.8 ± 10.0	0.274
HbA1c (%)	5.4 ± 0.30	5.4 ± 0.30	5.4 ± 0.29	0.238
Aspartate aminotransferase (U/L)	29.3 ± 10.6	26.7 ± 9.4	27.4 ± 8.2	0.421
Alanine aminotransferase (U/L)	31.2 ± 13.7**	28.2 ± 13.5	24.1 ± 10.7	0.024
Total cholesterol (mg/dL)	209.0 ± 36.0	204.8 ± 37.3	194.6 ± 38.2	0.135
Triglyceride (mg/dL)	128.0 (97.0-181.0)*	110.0 (92.0-160.0)**	77.0 (62.5-123.0)	< 0.0001
HDL-cholesterol (mg/dL)	52.9 ± 10.9**	54.5 ± 10.0**	61.3 ± 14.0	0.0006
eGFR (mL/min/1.73m^2)	65.6 ± 11.2	64.9 ± 10.0**	70.0 ± 11.8	0.021
Adiponectin (μg/mL)	4.0 ± 2.2*	4.1 ± 2.2*	6.9 ± 4.0	< 0.0001
Family history of diabetes (%)	38.7	39.7	23.5	0.100
Current smoker (%)	19.3	36.7	36.7	0.180
Hypertension (%)	45.2	32.3	41.1	0.392
Dyslipidemia (%)	45.2**	33.8	20.6	0.036

Data are mean ± SD or median (25 th,75 th percentaile). #p<0.001 compared to normal-BMI/normal-WC, $p <0.05 compared to normal-BMI/normal-WC group, *p <0.001 compared to low normal-BMI/normal-WC group, **p <0.05 compared to low normal-BMI/normal-WC group, BMI, body mass index; WC, waist circumference; eGFR, estimated glomerular filtration rate.

Table 2 Values of 75g OGTT and several parameters associated with insulin resistance

	Normal-BMI/ high-WC	Normal-BMI/ normal-WC	Low normal-BMI / normal-WC	P value
Glucose level (mg/dL)				
Before loading	91.3 ± 7.4	90.4 ± 7.7	89.6 ± 6.9	0.581
30 min	161.2 ± 24.2	154.0 ± 30.3	154.1 ± 32.0	0.490
120 min	102.4 ± 22.5	93.7 ± 19.7	92.9 ± 22.9	0.110
Insulin level (μU/mL)				
Before loading	5.4 ± 2.5*$	4.3 ± 1.6*	3.1 ± 1.2	< 0.0001
30 min	48.5 ± 32.3**	37.9 ± 21.3	30.2 ± 22.1	0.002
120 min	33.9 ± 25.6*$	23.9 ± 19.1**	16.3 ± 10.1	< 0.0001
HOMA-IR	1.23 ± 0.59*#	0.96 ± 0.36*	0.70 ± 0.28	< 0.0001
Matsuda index	8.19 (5.97-14.41)*$,	12.20 (9.09-17.08)**	15.93 (12.27-22.83)	< 0.0001
HOMA-β	70.8 ± 31.2*	61.2 ± 28.6**	45.0 ± 20.6	< 0.0001
Insulinogenic index (ΔI_{30} /ΔG_{30})	0.45 (0.26-0.93)	0.50 (0.39-0.67)	0.35 (0.20-0.69)	0.066
Disposition index	4.38 (2.50-6.69)	6.09 (3.57-9.30)	6.04 (2.92-13.28)	0.091

Data are mean ± SD or median (25 th,75 th percentaile). #p<0.01 compared to normal-BMI/normal-WC, $^{\$}$p <0.05 compared to normal-BMI/normal-WC group, *p <0.001 compared to low normal-BMI/normal-WC group, **p <0.05 compared to low normal-BMI/normal-WC group. HOMA-IR: homeostasis model assessment for insulin resistance. HOMA-β: homeostasis model assessment for β cell function

Table 3. Univariate analysis with HOMA-IR and Matsuda index as dependent variables in subjects with all subjects (n=167)

	HOMA-IR		Log-Matsuda index	
	r	p	r	p
Age	0.057	0.461	- 0.150	0.053
Body mass index	0.422	< 0.0001	- 0.401	< 0.0001
Waist circumference	0.386	< 0.0001	- 0.386	< 0.0001
Hip circumference	0.265	0.0005	- 0.238	0.0019
Body fat weight	0.369	< 0.0001	- 0.474	< 0.0001
Systolic blood pressure	0.145	0.061	- 0.145	0.062
Diastolic blood pressure	0.097	0.214	- 0.035	0.652
HbA1c	0.182	0.019	- 0.034	0.660
Aspartate aminotransferase	0.106	0.171	- 0.059	0.452
Alanine aminotransferase	0.265	0.0005	- 0.249	0.0012
Total cholesterol	0.072	0.354	- 0.131	0.091
Triglyceride	0.191	0.014	- 0.260	0.0007
HDL-cholesterol	- 0.154	0.046	0.308	< 0.0001
eGFR	- 0.271	0.0004	0.244	0.0015
Adiponectin	- 0.217	0.005	0.220	0.0042

HOMA-IR, homeostasis model assessment for insulin resistance; eGFR, estimated glomerular filtration rate.

Table 4. Multiple linear regression analysis with HOMA-IR and Matsuda index as dependent variables in all subjects (n=167)

	HOMA-IR		Log-Matsuda index	
Decision coefficient (R^2)	0.331		0.351	
P value	< 0.0001		< 0.0001	
Independent variables	Standard β	p	Standard β	p
Body fat weight	0.211	0.016	- 0.263	0.002
Waist circumference	0.147	0.176	- 0.083	0.439
Body mass index	0.112	0.294	- 0.040	0.705
Hip circumference	- 0.015	0.870	- 0.035	0.697
Age	- 0.106	0.218	- 0.016	0.851
Systolic blood pressure	0.117	0.265	- 0.114	0.269
Diastolic blood pressure	- 0.003	0.973	0.059	0.522
HbA1c	0.194	0.011	- 0.022	0.762
Aspartate aminotransferase	- 0.091	0.415	0.061	0.580
Alanine aminotransferase	0.226	0.043	- 0.153	0.162
Total cholesterol	- 0.122	0.160	- 0.020	0.813
Triglyceride	- 0.001	0.990	- 0.009	0.913
HDL-cholesterol	0.037	0.673	0.128	0.140
eGFR	- 0.226	0.003	0.148	0.049
Adiponectin	- 0.050	0.523	0.073	0.347
Family history of diabetes (no: 0, yes: 1)	- 0.008	0.910	- 0.086	0.229

HOMA-IR, homeostasis model assessment for insulin resistance; eGFR, estimated glomerular filtration rate.

Table 5. Multiple linear regression analysis with HOMA-IR and Matsuda index as dependent variables with anthropometric variables in all subjects (n=167)

	HOMA-IR		Log-Matsuda index	
Decision coefficient (R^2)	0.227		0.282	
P value	< 0.0001		< 0.0001	
Independent variables	Standard β	p	Standard β	p
Body fat weight	0.208	0.015	- 0.335	< 0.0001
Waist circumference	0.096	0.375	- 0.080	0.443
Body mass index	0.239	0.020	- 0.177	0.072
Hip circumference	0.046	0.614	- 0.040	0.646
Age	0.013	0.858	- 0.077	0.270

HOMA-IR, homeostasis model assessment for insulin resistance;.

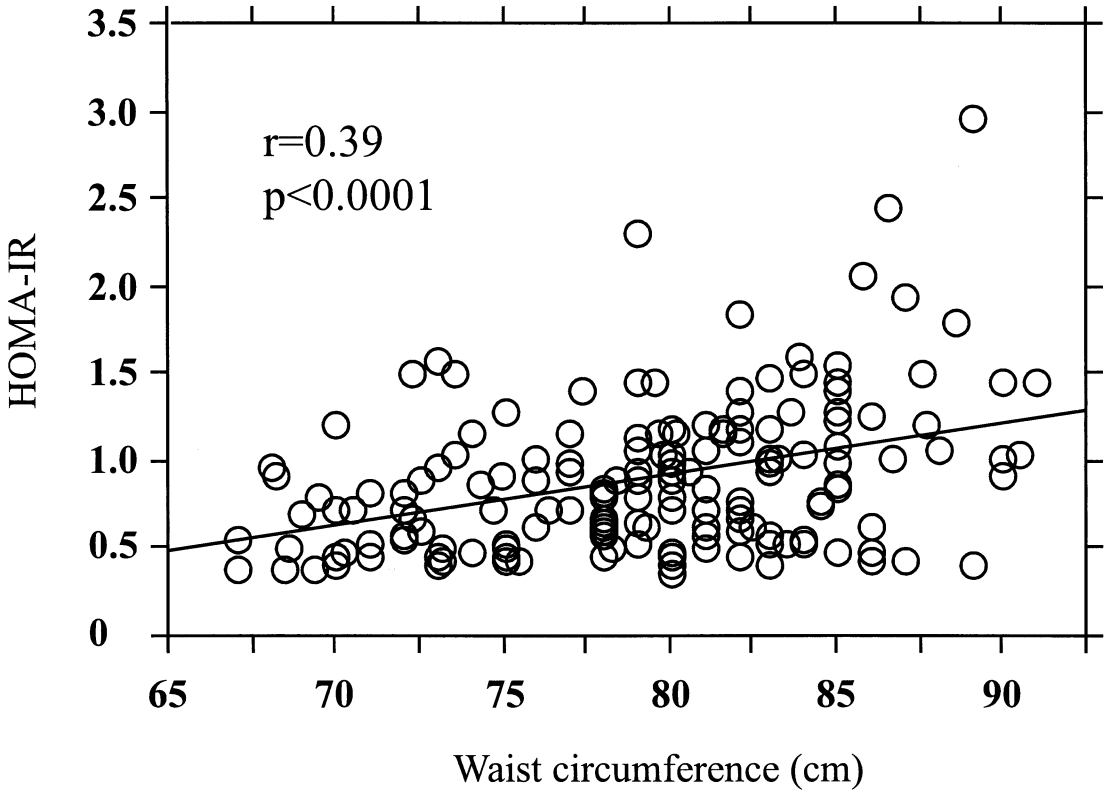
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
HOMA-IR
r=0.39
p<0.0001
65
70
75
80
85
90
Waist circumference (cm)

Figure. 1

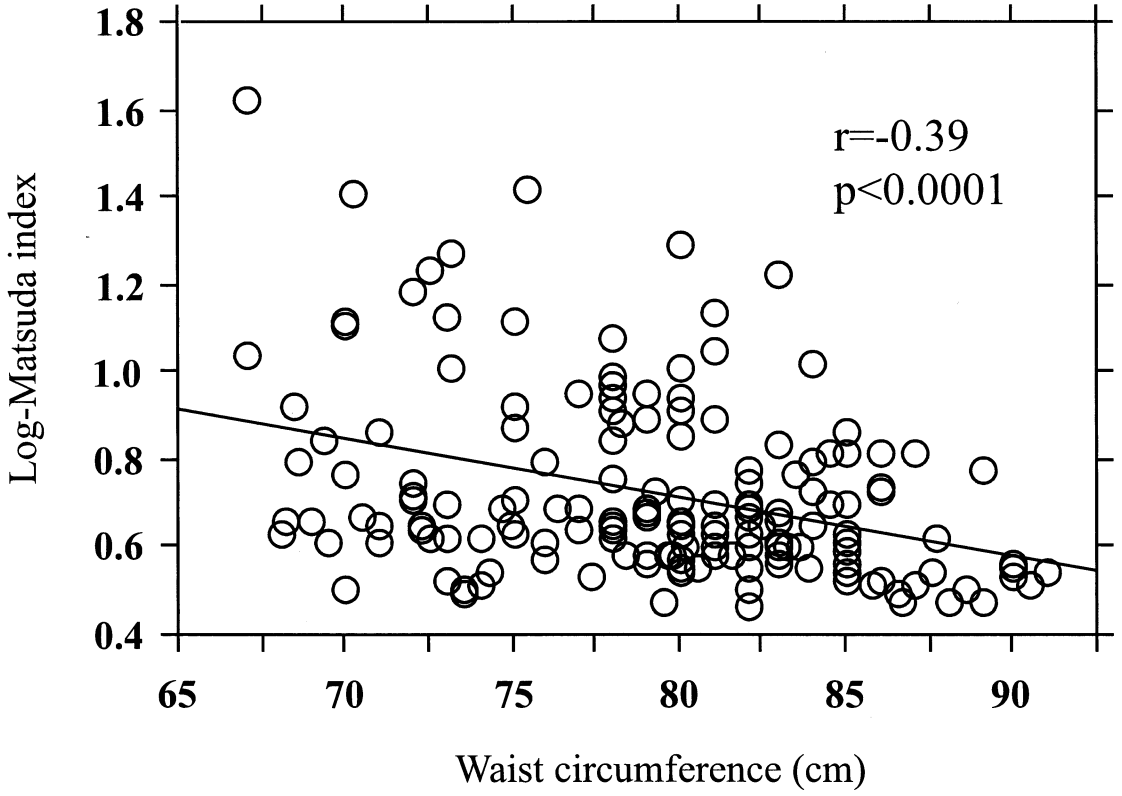
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
Log-Matsuda index
r=-0.39
p<0.0001
65
70
75
80
85
90
Waist circumference (cm)

Figure. 2