Contribution of visceral adiposity and insulin resistance to metabolic risk factors in Japanese men

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Abstract

We investigated the relative impacts of visceral adiposity and insulin resistance on the metabolic risk profile in middle-aged Japanese men. A cross-sectional study was conducted in 636 nondiabetic Japanese men with a mean age of 51.6 years. Visceral adipose tissue (AT) was assessed using computed tomography and insulin resistance was determined by the homeostasis model assessment insulin resistance (HOMA-IR). Metabolic risk factors were diagnosed according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III metabolic syndrome criteria: (1) hypertriglyceridemia, 2) low high-density-lipoprotein cholesterol, 3) hypertension, 4) impaired fasting glucose (IFG), and 5) impaired glucose tolerance (IGT). Visceral AT and HOMA-IR were significantly and positively correlated with each other ($r=0.41$, $p<0.001$). Using the 75th percentile value as a cut-point, those with isolated large visceral AT showed significantly greater odds ratios for each of the five risk factors measured except IFG, while those with isolated high HOMA-IR showed significantly greater odds ratios for each of the five risk factors except hypertriglyceridemia and IGT compared to the control group. The combined group (increased visceral AT and HOMA-IR) had the highest odds ratios for all studied risk factors. On logistic regression analysis using visceral AT and HOMA-IR as continuous independent variables, they were each independently associated with most of the metabolic risk factors and their clustering. In conclusion, neither visceral AT nor HOMA-IR stands out as the sole driving force of the risk profile; each makes a significant contribution to metabolic abnormalities in Japanese men.

1. Introduction

Although there have been some controversies regarding the use of the term metabolic syndrome [1], even detractors agree that metabolic risk factors tend to cluster together in individuals [2]. Two main factors have been proposed to underlie this clustering: insulin resistance [3-6] and abdominal obesity [6-8]. Because insulin resistance is not easily measured in the outpatient setting and is significantly interrelated with abdominal obesity [9], a large waist girth has been adopted in recent criteria of metabolic syndrome [10, 11]. However, it has not been determined which of these is more fundamental for the clustering or how each contributes to specific metabolic risk factors.

Asians, including the Japanese, develop metabolic disorders at a lower level of obesity than their Western counterparts [12]. This finding may be partly explained by the greater amounts of visceral adipose tissue (AT) in Asians than Europeans at any given level of body mass index [13, 14]. Visceral AT is supposed to play a unique role in the metabolic complications of obesity [15-18]. We recently reported that visceral AT, but not subcutaneous AT, was significantly associated with risk factor variations even after adjustments for body mass index and waist girth [19]. Thus, a direct measure of visceral AT would improve the accuracy of the associations between metabolic risk factors and obesity above anthropometric indices in the Japanese population.

The aim of the present study was to investigate the relative contributions of visceral adiposity and insulin resistance to the metabolic risk profile in a relatively lean Japanese population. For that purpose, we cross-sectionally measured visceral AT using computed tomography (CT), and the

homeostasis model assessment insulin resistance (HOMA-IR), a widely used indicator for insulin resistance [20], in a large number of nondiabetic Japanese men.

2. Methods

2. 1. Study population

Hokuriku Central Hospital has a special department where public school employees can receive routine medical checkups. Annual medical checkups are mandated by law and are sponsored by their mutual aid association. Of the 7,261 Japanese male employees who received a regular medical checkup between April 2006 and December 2008, 658 individuals voluntarily underwent both CT scanning to evaluate abdominal fat distribution and oral glucose tolerance test (OGTT). Of the 658 participants, 22 were excluded due to elevated fasting plasma glucose (≥126mg/dl). The remaining 636 participants were enrolled in the study. Each patient completed a questionnaire regarding current diseases and medications, alcohol consumption and smoking status. Participants were considered smokers if they smoked at least one cigarette per day. Alcohol use was assessed by the number of days per week of drinking regardless of quantity. Signed informed consent was obtained from all participants, and the hospital review board approved the study protocol.

2. 2. Anthropometric measurements and blood sampling

Anthropometric measurements were conducted according to published methods [21]. Blood

pressure was measured twice in the sitting position with an automatic device (Colin Model BP-203RV, Colin, Tokyo, Japan) after at least five minutes of rest. The average of the two readings was used for the blood pressure value.

All participants were asked to visit our hospital between 8:00 a.m. and 9:00 a.m. after an overnight fast. Blood samples were drawn from the antecubital vein to measure total cholesterol, triglycerides, and high-density lipoprotein (HDL)-cholesterol. Then, OGTT (75 g dextrose monohydrate in 250 ml water) was performed with 0, 30, 60, and 120 min sampling to establish plasma glucose and insulin levels. Plasma glucose was assessed using the glucose oxidase method (Automatic Glucose Analyzer ADAMS Glucose GA-1160, Arkray, Kyoto). Triglycerides, total cholesterol, and HDL-cholesterol were measured using enzymatic analytical chemistry (Autoanalyzer BioMajesty JCA-BM1650, JEOL Ltd., Tokyo, Japan) at the hospital laboratory. Insulin concentration assays were performed by the chemiluminescence immunoassay method at a commercial laboratory (BML. Inc. Tokyo, Japan).

2. 3. Assessment of HOMA-IR and metabolic risk factors

Metabolic risk factors were defined according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III definition of metabolic syndrome [10]: 1) hypertriglyceridemia: ≥150 mg/dl (1.69 mmol/l) or taking lipid-lowering medications; 2) low HDL-cholesterol: <40mg/dl (1.04mmol/l) or taking lipid-lowering medications; 3) high blood pressure: ≥130/85 mmHg or taking

anti-hypertensive medications; and 4) impaired fasting plasma glucose (IFG): ≥100mg/dl (5.6 mmol/l) In addition, 5) impaired glucose tolerance (IGT) was defined as 2-hour post-challenge plasma glucose ≥140mg/dl (7.0 mmol/l). The HOMA-IR was calculated as follows: fasting plasma glucose (mmol/l) x fasting plasma insulin (μ U/ml) / 22.5 [22].

2. 4. Measurement of abdominal adipose tissue by CT

AT measurements were conducted using previously published methods [21]. Briefly, an axial CT scan at the level of the umbilicus was performed on each participant using an electron beam CT scanner (Aquilion Toshiba Medical Systems, Tokyo, Japan). Planimetric measurements at the level of the umbilicus have been well-correlated with volumetric quantifications of visceral AT (r=0.81, p<0.001) [23]. The images generated were analyzed using commercial software designed for the quantification of visceral AT (Fat Scan version 3.0, N2 System, Osaka, Japan). Correlation coefficients between two observers analyzing the same visceral AT image (n=30) were r=0.98 (p<0.001).

2. 5. Statistical analysis

All analyses were conducted using SPSS software version 11.0 for Windows (SPSS Inc. Chicago, IL). Risk factor prevalence was plotted according to deciles of visceral AT and HOMA-IR. Tests for linear trends across deciles were performed by assigning the median value within each

category and treating the categories as a continuous variable. The participants were classified into four subgroups according to their visceral AT and HOMA-IR values using the 75th percentile as the cut-point. The control group consisted of those with both visceral AT and HOMA-IR below the 75th percentile. The isolated large visceral AT group was those with visceral AT above the 75th percentile but HOMA-IR below the 75th percentile. The isolated high HOMA-IR group was those with HOMA-IR above the 75th percentile but visceral AT below the 75th percentile. The combined group was those with both visceral AT and HOMA-IR above the 75th percentile values. Adjusted odds ratios for each metabolic risk factor in each group relative to the control group were calculated using binary logistic regression. The following variables were used as covariates in the regression analyses: age, alcohol use (<1 day per week, 1-6 days per week, or daily use), and cigarette smoking (currently smoking or not). The independent associations of visceral AT and HOMA-IR as continuous variables were also assessed using logistic regression analysis. Visceral AT and HOMA-IR were first standardized to a mean of 0 and standard deviation of 1, and then included in the models with the covariates mentioned above. The significance of the interactions were examined using interaction terms (visceral AT * HOMA-IR) in the logistic regression model. The triglyceride and HOMA-IR values were log-transformed prior to analysis due to their skewed distribution. A *p* value of <0.05 was considered statistically significant.

3. Results

Table 1 shows the clinical characteristics of the participants. The mean age was approximately 50 years and the mean body mass index was approximately 25 kg/m^2. Although all participants were apparently healthy and engaging in full-time work, approximately half were hypertensive, more than one quarter had either IFG or IGT, and 39.0% had hypertriglyceridemia.

Figure 1 shows the prevalence of hypertension, IFG, IGT, hypertriglyceridemia, low HDL-cholesterol, and the clustering of two or more risk factors across deciles of visceral AT (A) and HOMA-IR (B). Increased levels of both visceral AT and HOMA-IR were significantly associated with increases in all risk factors (p<0.05).

Visceral AT and HOMA-IR were significantly and positively correlated with each other (r=0.41, p<0.001). The participants were classified into four groups according to the 75th percentile values, and the odds ratios for individual risk factors in each group compared to the control group were calculated (Table 2). Those with isolated large visceral AT had significantly greater odds ratios for each of the five risk factors measured except IFG, while those with isolated high HOMA-IR had significantly greater odds ratios for each of the five risk factors except hypertriglyceridemia and IGT compared to the control group. Both those with isolated large visceral AT and high HOMA-IR showed greater odds ratios for the clustering of two or more risk factors compared to the control group. The combined group (both large visceral AT and high HOMA-IR) had the highest odds ratios for all the five risk factors and their clustering.

Table 3 shows the results of logistic regression analysis using visceral AT and HOMA-IR as continuous independent variables for each metabolic risk factor. Increased visceral AT, independent of HOMA-IR, was significantly associated with each of the five risk factors except IFG, while increased HOMA-IR was independently associated with each of the five risk factors except low-HDL-cholesterol and IGT. Both visceral AT and HOMA-IR were independently associated with the clustering of two or more risk factors. There was a significant negative interaction between visceral AT and HOMA-IR for hypertriglyceridemia (p=0.003), indicating that its odds ratio associated with increasing visceral AT and HOMA-IR was attenuated at higher levels.

The same analyses were conducted after substituting fasting insulin levels for HOMA-IR (supplementary data). When participants were classified by fasting insulin levels, group comparisons showed similar patterns of association with metabolic risk factors as HOMA-IR. In the logistic regression analysis, the association of fasting insulin with IFG was attenuated compared to that of HOMA-IR, but was still significant (p<0.001).

4. Discussion

This cross-sectional study demonstrated that increased visceral AT and HOMA-IR were each independently associated with most metabolic risk factors and their clustering, although their respective contributions varied among risk factors. Visceral AT and HOMA-IR were indeed correlated with each other in this relatively lean Japanese population, but the large sample size of

this study allowed to evaluate the independent relationships of these intersected conditions with metabolic risk factors.

Visceral AT and HOMA-IR showed a significant correlation with each other, which is in agreement with prior studies in other populations. Previously reported correlation coefficients between directly measured visceral AT and HOMA-IR were 0.40 in Japanese men with normal glucose tolerance [15]; 0.34 in black and 0.44 in white men [24]; and 0.28 in healthy Koreans [25]. **However,** when using the top quartile of visceral AT and HOMA-IR in group comparisons, the overlap between these two conditions was about 50%; the remaining half had each condition in isolation. Obesity can be dissociated from HOMA-IR even when evaluated by visceral AT.

Hypertriglyceridemia was associated independently both with visceral AT and HOMA-IR by logistic regression analysis. Prior studies using a more sophisticated method to assess insulin resistance revealed a major contribution of visceral AT but an additional independent contribution of insulin resistance to triglyceride concentrations in nondiabetic subjects [26] [27]. Conversely, Piche *et al*. reported that women with large visceral AT but low insulin resistance showed similar triglyceride concentrations to control subjects, and visceral AT accumulation was associated with hypertriglyceridemia only in the presence of insulin resistance [28]. This inconsistency may be attributed to the inclusion of diabetic subjects in the latter study. In this study, the odds ratio of hypertriglyceridemia was not significantly different between the isolated high HOMA-IR group and the control group. Theoretically, the reduced anti-lipolytic action of insulin generates an increase in

circulating free fatty acids (FFAs) which can flux to the liver and stimulate triglyceride formation [29, 30].

The contribution of visceral AT and HOMA-IR varied between IFG and IGT. Because fasting plasma glucose is part of HOMA-IR, the analysis was repeated substituting HOMA-IR with fasting insulin concentrations. The results were similar, showing a dominant association between IFG and fasting insulin and between IGT and visceral AT. These results confirm the notion that IFG and IGT may have different pathophysiological origins. IFG is primarily caused by hepatic insulin resistance in a fasted state, whereas IGT is caused by peripheral (muscle) insulin resistance followed by a decline in beta-cell function in a fed state [31, 32].

For almost all risk factors, the odds ratios were highest in those with both visceral AT and HOMA-IR above the 75th percentile. This was particularly pronounced for clustering of two or more risk factors. However, even in this instance, the interaction between visceral AT and HOMA-IR was not significant, indicating that their effects are additive, not multiplicative. Notably, a negative interaction between visceral AT and HOMA-IR was found with respect to hypertriglyceridemia. This may be due to a threshold effect, whereby hypertriglyceridemia prevalence is already so high that increased HOMA-IR is not associated with further increases in its prevalence.

Metabolic responses to fat accumulation have been reported to differ by ethnicity. African-Americans have higher HOMA-IR or fasting insulin values and lower serum triglyceride concentrations than Caucasians even after controlling for visceral AT [33, 34]. Conversely, Asians

reportedly have significantly lower HOMA-IR values compared to Caucasians even after accounting for body mass index [35] and for liver fat content [36]. In the present study, HOMA-IR independently contributed to metabolic risk factors, although it should be noted that the absolute level of HOMA-IR in Japanese populations would be much lower compared to Western populations.

Several limitations of this study should be considered. First, HOMA-IR is an indirect measure of insulin resistance, which is assumed to reflect mainly hepatic insulin resistance in the basal state [37]. However, studies using a direct measure such as euglycemic-hyperinsulinemic clamp [38] or intravenous glucose tolerance [39] have reported that metabolic syndrome risk factor patterns were similar when HOMA-IR was used in place of these direct measures. Second, participants were recruited from a population engaging in a specific profession, not from a community-based sample. The role of the "healthy worker effect" should also be considered when generalizing these results to other populations. Third, the reproducibility of the measurements of visceral AT by CT scanning still seems to be incomplete due to the effects of respiratory and peristaltic movements of the patients. Nonetheless, a single planimetric measurement of visceral AT has shown good correlation with volumetric quantifications [23]. Fourth, we did not measure sex hormones, which have been proposed to underlie the expression of the metabolic abnormalities and might have confounded the associations of visceral AT and HOMA-IR with risk factors [40, 41]. Finally, the cross-sectional design is unable to determine the causal or temporal sequence among visceral AT, HOMA-IR, and metabolic risk factors.

In conclusion, neither visceral AT nor HOMA-IR stands out as the sole driving force of the metabolic syndrome profile, as each contributed significantly to various metabolic abnormalities. Those with a combination of large visceral AT and high HOMA-IR had the highest odds ratios for the individual risk factors and their clustering. Further longitudinal studies are needed to investigate the time sequence from the emergence of underlying factors to the expression of metabolic aberrations.

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Disclosure

The authors declared no conflict of interest.

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Figure 1. The prevalence of metabolic abnormalities across deciles of visceral AT (A) and HOMA-IR (B)

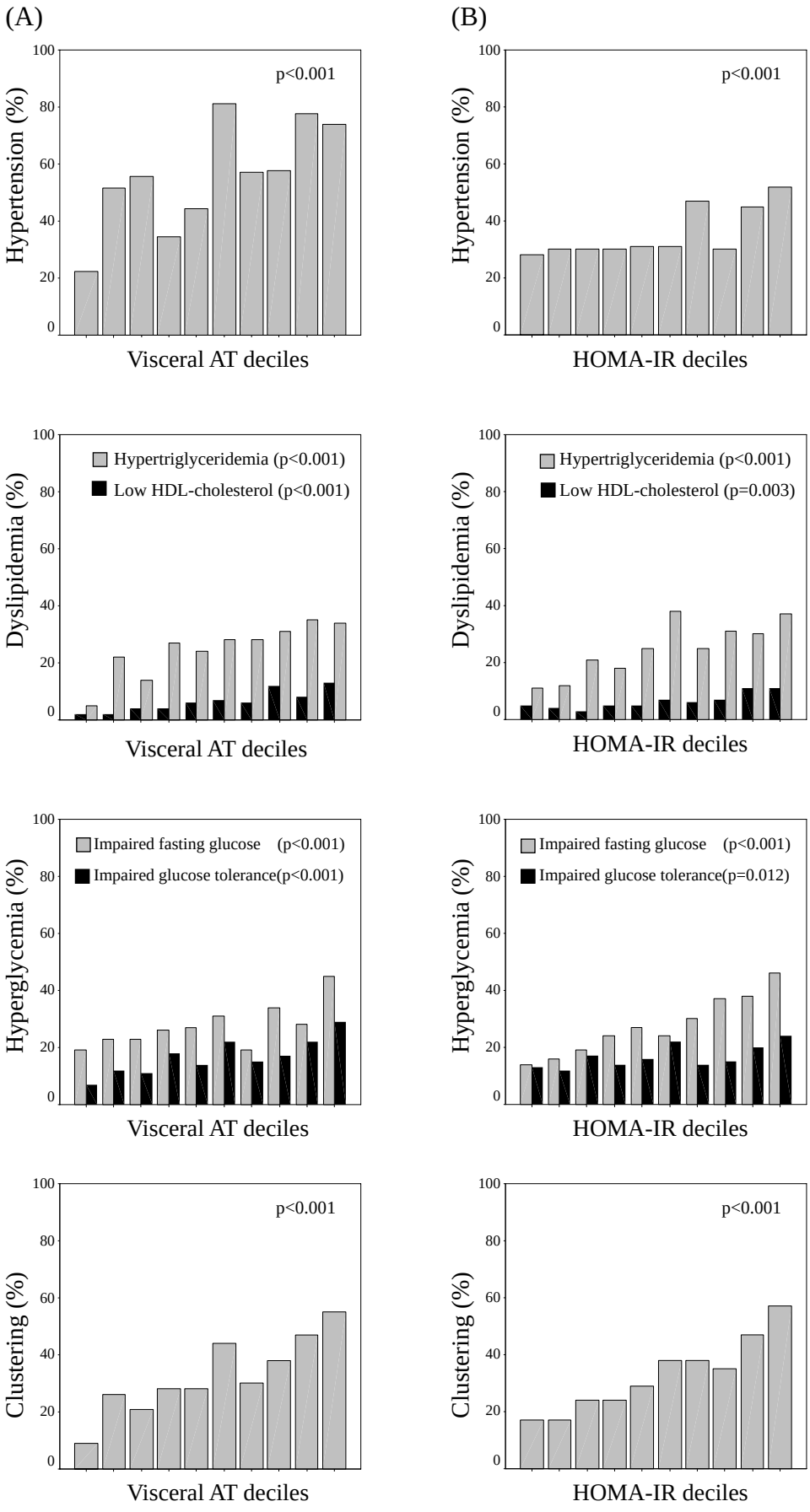

Table 1 Clinical characteristics of the study participants

Characteristics	Men (n=636)
Age (years)	51.6 ± 7.1
Height (cm)	170.0 ± 5.8
Weight (kg)	73.3 ± 10.2
Body mass index (kg/m^2)	25.3 ± 2.9
Waist circumference (cm)	87.9 ± 7.5
Systolic BP (mmHg)	130.5 ± 15.2
Diastolic BP (mmHg)	81.5 ± 9.5
Total-cholesterol (mg/dl)	212.3 ± 36.4
Triglycerides (mg/dl)	91/122/174
HDL-cholesterol (mg/dl)	54.3 ± 12.0
Fasting plasma gulcose (mg/dl)	99.2 ± 9.2
2-hour plasma gulcose (mg/dl)	123.5 ± 32.4
Fasting insulin (mg/dl)	3.2/4.4/6.1
HOMA-IR	0.79/1.07/1.51
Visceral AT (cm^2)	140.9 ± 50.7
Hypertension[a] (%)	55.7
Hypertriglyceridemia[b] (%)	39.0
Low HDL-cholesterol[c] (%)	10.1
Impaired fasting glucose[d] (%)	43.2
Impaired glucose tolerance[e] (%)	26.3
Two or more risk factors (%)	51.3
Current cigarette smoker (%)	22.3
Alcohol use (%)	
drinking everyday	33.8
drinking 1-6 days per week	39.6

Data are mean ± SD, 25/50/75th percentile values, or %. BP, blood pressure; AT, adipose tissue; HDL, high-density lipoprotein.
[a]defined by systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg; [b]defined by ≥150 mg/dl; [c]defined by <40 mg/dl.[d]Fasting glucose ≥ 100 mg/dl. [e]2-hour plasma glucose ≥140 mg/dl.

Table 2 Adjusted[a] odds ratios for the presence of metabolic risk factors according to viscear adipose tissue (AT) and HOMA-IR status

	Group 1 n=392	Group 2 n=85	Group 3 n=85	Group 4 n=74
	control	isolated large visceral AT	isolated high HOMA-IR	combined
Hypertension	1.00	**2.0 (1.2-3.3)**	**2.0 (1.2-3.2)**	**5.9 (3.0-11.3)**
Hypertriglyceridemia	1.00	**2.6 (1.6-4.3)**	1.5 (0.9-2.5)	**3.4 (2.0-5.7)**
Low HDL-C	1.00	**2.8 (1.4-5.8)**	**2.5 (1.2-5.2)**	**2.9 (1.4-6.2)**
Impaired fasting glucose	1.00	1.2 (0.7-1.9)	**3.4 (2.1-5.7)**	**5.9 (3.3-10.5)**
Impaired glucose toleran	1.00	**1.8 (1.0-3.0)**	1.2 (0.7-2.2)	**2.9 (1.7-4.9)**
Two or more risk factors	1.00	**3.2 (2.0-5.3)**	**3.8 (2.3-6.4)**	**14.0 (6.5-30.1)**

control, both visceral AT and HOMA-IR are below their 75th percentiles; isolated large visceral AT, visceral AT is above 75th percentile but HOMA-IR is below 75th percentile; isolated high HOMA-IR, HOMA-IR is above 75th percentile but visceral AT is below 75th percentile; combined, both visceral AT and HOMA-IR are above their 75th percentiles. [a]adjusted for age, smoking status, and alcohol consumption. Significantly higher odds ratios compared to the control group are shown in bold letters.

Table 3 Adjusted[a] odds ratios for having metabolic risk factors with 1 SD increase in visceral adipose tissue (AT) and HOMA-IR as continuous variables.

		Odds ratio	p value	p for interaction
Hypertension	visceral AT	1.69 (1.39-2.06)	<0.001	0.142
	HOMA-IR	1.26 (1.04-1.53)	0.017	
Hypertriglyceridemia	visceral AT	1.68 (1.37-2.05)	<0.001	0.003
	HOMA-IR	1.34 (1.10-1.63)	0.004	
Low HDL-C	visceral AT	1.68 (1.25-2.24)	<0.001	0.116
	HOMA-IR	1.17 (0.86-1.58)	0.327	
Impaired fasting glucose	visceral AT	1.07 (0.89-1.30)	0.463	0.096
	HOMA-IR	2.17 (1.74-2.71)	<0.001	
Impaired glucose tolerance	visceral AT	1.49 (1.21-1.83)	<0.001	0.999
	HOMA-IR	1.15 (0.93-1.42)	0.199	
Two or more risk factors	visceral AT	1.94 (1.57-2.41)	<0.001	0.128
	HOMA-IR	2.03 (1.62-2.55)	<0.001	

[a]adjusted for age, smoking status, and alcohol consumption. Data presented the change in odds of having the risk factor per 1 SD increase in visceral AT or HOMA-IR. HOMA-IR was analyzed after a logarithmic transformation.