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Dysregulation of glucose, insulin, triglyceride, blood pressure, and oxidative stress after an oral glucose tolerance test in men with abdominal obesity

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Abstract

Postprandial metabolic dysregulation plays a role in the development of atherosclerosis. Visceral fat accumulation is an important component of various metabolic disorders including glucose intolerance, dyslipidemia, and hypertension, which correlate with atherosclerotic cardiovascular disease. The aim of the present study was to compare the postprandial response of various metabolic parameters, blood pressure, adiponectin, and oxidative stress to 75-g oral glucose tolerance test (OGTT) in men with (n = 23) and without (n = 7) abdominal obesity based on waist circumference (WC) cutoff value of 85 cm (based on the Japanese criteria for the metabolic syndrome). The cross-sectional prospective study included 30 male subjects who were on no medications and newly diagnosed with mild hypertension and/or dyslipidemia. The percentage change in each parameter ([each parameter at 120 minutes after an OGTT − that before an OGTT]/that before an OGTT × 100) was calculated. The percentage systolic blood pressure, percentage diastolic blood pressure, and percentage triglyceride were −6.3% ± 3.5%, −9.4% ± 3.0%, and −10.2% ± 2.1%, respectively, in the WC less than 85 group (vs baseline: $P = .10$, $P < .01$, and $P < .001$) and 2.0% ± 1.7%, 0.9% ± 2.4%, and 2.8% ± 3.3%, respectively, in the WC at least 85 group (vs WC <85 group: $P < .05$, each). However, there were no significant differences in percentage total cholesterol and percentage high-density lipoprotein cholesterol between the 2 groups. The percentage thiobarbituric acid–reacting substances tended to be lower in the WC less than 85 group (vs baseline: $P = .07$), but not in the WC at least 85 group, albeit statistically insignificant (WC <85 vs ≥85 group: $P = .057$). The maximum carotid intima-media thickness was larger in the WC at least 85 group than the WC less than 85 group ($P < .05$). Evaluation of postprandial changes in obesity-related parameters may be important in preventing atherosclerotic diseases.
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1. Introduction

The postprandial phenomenon is a key factor in the development of atherosclerosis [1]. Postprandial hyperglycemia, hyperinsulinemia, and dyslipidemia with hypertriglyceridemia (also referred to as *postprandial dysmetabolism*) are individually and collectively recognizable cardiovascular risk factors [2-5]. The cardiovascular toxicity of postprandial dysmetabolism is mediated by oxidative stress, which is directly proportional to the levels of glucose and triglycerides (TGs) after high-caloric meals [2-5]. These transient spikes acutely trigger inflammation, sympathetic hyperactivity, endothelial dysfunction, and a cascade of other atherogenic changes, leading to future cardiovascular events [6-8].

Several studies analyzed the relationship between severity of cardiovascular diseases (CVDs) and postprandial hyperinsulinemia using an oral glucose tolerance test (OGTT) challenge [9-11]. Moreover, there are several reports that high levels of nonfasting serum TGs could predict the risk of CVDs, independent of total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) [12-14]. Postprandial dysregulated metabolism is a major contributor to the pathogenesis of atherosclerosis and

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CVD events [3]. Usually, glucose and lipids are systematically measured in the fasting state. Most studies on the characterization of blood pressure, glucose, and TG levels in obese subjects, especially those with accumulation of abdominal adipose tissue, that is, abdominal obesity, were conducted by measuring visceral fat accumulation or greater waist circumference (WC) during the fasting state, with postprandial changes in these metabolic parameters being barely investigated.

Visceral fat accumulation is an important component of the metabolic syndrome, which encompasses various metabolic disorders such as glucose intolerance, dyslipidemia, and hypertension, and is associated with atherosclerotic CVDs [15]. Adipose tissue is not only a passive reservoir for energy storage but also an important endocrine organ, secreting a variety of bioactive molecules collectively known as *adipocytokines*. We identified adiponectin as an adipocytokine in the human adipose tissue complementary DNA library [16], which exhibits direct antiatherosclerotic and antidiabetic properties in experimental studies [17]. The blood levels of adiponectin are low in obesity [18]. There is increased oxidative stress in subjects with obesity [19,20]. Recent studies confirmed the inverse relationship between oxidative stress and blood levels of adiponectin in human [19,21]. It has been reported that enhanced oxidative stress in the adipose tissue causes dysregulation in the production of adipocytokines, for example, low expression of adiponectin [19].

In the present study, we investigated postprandial metabolic parameters, blood pressure, adiponectin, and oxidative stress using OGTT in Japanese men with abdominal obesity.

2. Subjects and methods

2.1. Study populations

Thirty consecutive Japanese middle-aged men on no medications, who visited the clinic and were newly diagnosed with mild hypertension and/or dyslipidemia between February 2008 and March 2009, were enrolled in the present study (age mean ± SD, 54.7 ± 14.0 years). *Hypertension* was defined as systolic blood pressure (SBP) of at least 130 mm Hg and/or diastolic blood pressure (DBP) of at least 85 mm Hg. Dyslipidemia represented high fasting TG levels of at least 1.69 mmol/L and/or low HDL-C levels of less than 1.04 mmol/L, according to the Japanese criteria of the metabolic syndrome [22,23]. We divided the subjects into those with WC less than 85 cm (WC <85, n = 7) and those with WC at least 85 cm (WC ≥85, n = 23), according to the Japanese criteria of the metabolic syndrome [22,23]. All individuals underwent a standardized 75-g OGTT (Trelan G 75; Shimizu, Shizuoka, Japan) in the clinic after overnight fast. To investigate the OGTT overloading, the subjects with overt diabetes (fasting glucose levels ≥7.8 mmol/L) were excluded. The study was approved by the human ethics committee of Osaka University, and a written informed consent was obtained from each participant. This trial (called *The Hokusetsu Trial*) is registered with University hospital Medical Information Network (no. UMIN 000001454).

2.2. Anthropometry and laboratory measurements

Each subject was asked to complete a questionnaire on family history, medical history, current medication, and smoking history. Height and body weight were measured in standing position. Body mass index was calculated as weight (in kilograms) divided by the square of height in meters (square meters). Waist circumference was measured at the umbilical level using a nonstretchable tape in late expiration while standing (in centimeters). Blood pressure was measured with a standard mercury sphygmomanometer on the right arm after the subjects had rested in the supine position for at least 10 minutes in the clinic. Mean values were determined from 2 independent measurements made at 3-minute intervals. In the fasting state before an OGTT after overnight fasting, venous blood samples were collected for measurements of blood glucose, hemoglobin A_{1c} (HbA_{1c}), immunoreactive insulin (IRI), TC, HDL-C, TG, adiponectin, tumor necrosis factor–α (TNF-α), high-sensitivity C-reactive protein (hCRP), and thiobarbituric acid–reacting substances (TBARS), as an oxidative stress marker, while the subject was in the supine position.

Next, an OGTT was performed after overnight fasting. Venous blood samples were obtained from the forearm while the subject was in the supine position and were collected in the fasting state and at 30, 60, and 120 minutes after an OGTT to evaluate blood glucose and IRI concentrations. Each parameter, such as TC, TG, HDL-C, adiponectin, and TBARS, and blood pressures were measured both in the fasting state and at 120 minutes after the ingestion of 75-g OGTT. The plasma glucose and the IRI area under the concentration-time curve values (AUC glucose and AUC IRI, respectively) during the OGTT were calculated. The summation values of glucose and IRI (Σglucose and ΣIRI) were calculated. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: HOMA-IR (milliunits per liter × milligrams per deciliter) = [(fasting IRI × fasting glucose)/405]. The homeostasis model assessment of pancreatic β-cell function (HOMA-Iβ) was calculated using the following formula: HOMA-Iβ [(milliunits per liter)/(milligrams per deciliter)] = [(fasting IRI × 360)/(fasting glucose − 63)]. The *insulinogenic index* was defined as the ratio of IRI to glucose at 30 minutes after glucose loading. Insulin sensitivity index was calculated using the following formula: 10 000/square root of [(fasting glucose × fasting IRI) × (mean glucose × mean IRI during an OGTT)] [24]. The percentage changes in SBP, DBP, TC, TG, and HDL-C (%SBP, %DBP, %TC, %TG, and %HDL-C, respectively) were calculated using the following

formula: [(each parameter at 120 minutes after an OGTT − that in the fasting state before an OGTT)/that before an OGTT × 100]. Plasma glucose concentrations were determined by the glucose oxidase method. Serum IRI concentrations were determined by an immunochemiluminometric assay (ADVIA Centaur IRI; Siemens Healthcare Diagnostics, Tarrytown, NY). The value of HbA_{1c} was determined by high-performance liquid chromatography. Serum concentrations of TC, TG, and HDL-C were determined by enzymatic methods. The serum concentration of adiponectin was measured by a sandwich enzyme-linked immunosorbent assay system (Adiponectin ELISA Kit; Otsuka Pharmaceutical, Tokushima, Japan). Serum concentration of TNF-α was measured by a quantitative sandwich enzyme immunoassay technique (Quantikine HS Immunoassay kit; R&D Systems, Minneapolis, MN). Serum concentration of hCRP was measured with hCRP assay (N-Latex CRP II; Dade Behring, Marburg, Germany). Serum concentration of TBARS, reflecting serum lipid peroxidation products, was determined by the method of Yagi (Japan Institute for the Control of Aging, Nikken SEIL, Shizuoka, Japan) [25].

The maximum (max) carotid intima-media thickness (IMT) and mean IMT of the common carotid artery were also measured in supine position (LOGIQ S6; GE Healthcare, Waukesha, WI). The max IMT was measured on both the right and left sides in the observation-possible areas of the common carotid artery, bulbus, and internal carotid artery, except the external carotid artery.

2.3. Statistical analysis

Data are presented as mean ± SEM and were compared by unpaired Student *t* test or Mann-Whitney *U* test for experiments with only 2 groups. Differences in frequencies were examined by the χ^2 test. In all cases, *P* values <.05 were considered statistically significant. All analyses were performed with the StatView software version 5.0 (HULINKS, Tokyo, Japan).

Table 1
Characteristics of enrolled subjects

	WC <85 cm (n = 7)	WC ≥85 cm (n = 23)	*P* value
Age (y)	57.1 ± 7.1	53.9 ± 2.6	NS
BMI (kg/m^2)	22.6 ± 0.6	29.1 ± 1.1	<.01
WC (cm)	80.7 ± 2.1	99.7 ± 2.6	<.001
SBP (mm Hg)	131.4 ± 9.7	137.3 ± 3.6	NS
DBP (mm Hg)	71.1 ± 5.1	79.2 ± 2.7	NS
Fasting glucose (mmol/L)	5.24 ± 0.28	5.66 ± 0.14	NS
Fasting IRI (mU/L)	4.3 ± 0.4	16.2 ± 3.2	<.05
HbA_{1c} (%)	4.8 ± 0.1	5.3 ± 0.1	<.05
Fasting TC (mmol/L)	5.45 ± 0.25	6.03 ± 0.15	NS
Fasting TG (mmol/L)	1.43 ± 0.21	2.30 ± 0.26	NS
Fasting HDL-C (mmol/L)	1.47 ± 0.21	1.26 ± 0.07	NS
Adiponectin (μg/mL)	10.3 ± 1.4	5.8 ± .04	<.001
TNF-α (pg/mL)	1.0 ± 0.3	1.3 ± 0.1	NS
hCRP (mg/dL)	0.04 ± 0.01	0.16 ± 0.04	.114
TBARS (nmol/L)	3.17 ± 0.18	3.76 ± 0.18	.101
Mean IMT (mm)	0.8 ± 0.1	0.9 ± 0.1	NS
Max IMT (mm)	0.9 ± 0.1	1.3 ± 0.1	<.05
Smoking (%)	57.1 (n = 4)	78.3 (n = 18)	NS

Data are mean ± SEM. NS indicates not significant.

Table 2
Changes in metabolic parameters measured during 75-g OGTT in subjects with and without *abdominal obesity*, defined based on WC cutoff value of 85 cm

	WC <85 cm (n = 7)	WC ≥85 cm (n = 23)	*P* value
2-h glucose (mmol/L)	5.1 ± 0.9	8.0 ± 0.5	<.05
2-h IRI (mU/L)	25.1 ± 4.4	95.8 ± 14.3	<.05
Peak glucose (mmol/L)	8.2 ± 0.9	10.9 ± 0.5	<.05
Peak IRI (mU/L)	55.3 ± 8.4	120.6 ± 18.3	.064
AUC glucose (mmol/L per 2 h)	13.1 ± 1.5	17.9 ± 0.8	<.01
AUC IRI (mU/L per 2 h)	67.0 ± 7.8	170.0 ± 27.3	<.05
Σglucose (mmol/L)	25.2 ± 2.5	33.5 ± 1.4	<.01
ΣIRI (mU/L)	111.9 ± 11.6	299.2 ± 49.2	<.05
HOMA-IR	1.0 ± 0.2	4.1 ± 0.8	.052
HOMA-I*β*	54.6 ± 8.3	135.0 ± 20.2	<.05
Insulin sensitivity index	9.6 ± 1.0	3.5 ± 0.4	<.001
Insulinogenic index	0.3 ± 0.5	1.3 ± 0.4	NS

3. Results

3.1. Baseline characteristics according to WC

The baseline characteristics of the WC <85 and WC ≥85 groups are summarized in Table 1. The WC ≥85 group had a higher body mass index, IRI, and HbA_{1c} and lower adiponectin than the WC <85 group. The blood levels of hCRP and TBARS tended to be higher in the WC ≥85 group, although the difference was not significant. There were no differences between the 2 groups with regard to SBP, DBP, fasting glucose, TC, TG, and HDL-C concentrations. The max IMT was larger in the WC ≥85 group (1.3 ± 0.1 mm) compared with the WC <85 group (0.9 ± 0.1 mm, $P < .05$).

3.2. Changes in metabolic parameters and blood pressure after an OGTT

First, we evaluated the postprandial glucose, insulin, lipid, and blood pressure using OGTT in both WC groups. The results of glucose and insulin metabolism are shown in Table 2 and in Fig. 1A, B. Six patients had impaired glucose tolerance, 3 had type 2 diabetes mellitus, and 14 had normal glucose tolerance. Both blood glucose and IRI levels after OGTT were higher in the WC ≥85 group than the WC <85 group (Fig. 1A, B). Two-hour glucose, 2-hour IRI, peak glucose, AUC glucose, AUC IRI, Σglucose, and ΣIRI were also significantly higher in the WC ≥85 group than in the WC <85 group. The HOMA-I*β*, a marker of pancreatic *β*-cell function, was higher in the WC ≥85 group than in the WC <85 group. In addition, HOMA-IR, a marker of insulin

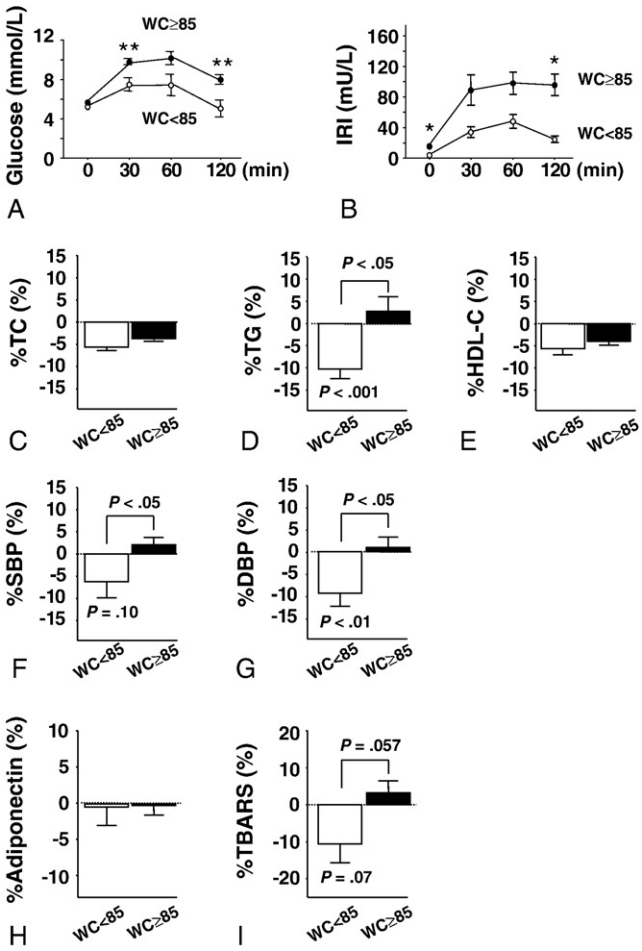

Fig. 1. Differences in plasma glucose (A) and serum IRI (B) levels during 75-g OGTT in subjects with (WC ≥85) and without (WC <85) abdominal obesity. *P < .05, **P < .01; between the WC ≥85 and WC <85 groups. Percentage changes in TC (C), TG (D), HDL-C (E), SBP (F), DBP (G), serum adiponectin (H), and serum TBARS (I) in response to glucose loading in the WC ≥85 and WC <85 groups. [(TC, TG, HDL-C, SBP, DBP, adiponectin, or TBARS at 120 minutes after an OGTT − that in the fasting state before an OGTT)/that before an OGTT (%)]. The OGTT was performed as described in "Subjects and methods." P values: vs baseline in the WC <85 group; between WC ≥85 and WC <85 groups. Data are mean ± SEM; error bars represent 95% confidence intervals.

resistance, was also higher in the WC ≥85 group, albeit statistically insignificant; and insulin sensitivity index, a marker of insulin sensitivity, was significantly lower in the WC ≥85 group than in the WC <85 group. There was no difference in insulinogenic index, a marker of initial insulin response to glucose, between the 2 groups.

Next, we evaluated the postprandial changes in lipid parameters and blood pressure during OGTT (Fig. 1C-G). The %SBP and %DBP of the WC <85 group were −6.3% ± 3.5% and −9.4% ± 3.0%, respectively (vs baseline: P = .10 and P < .01; Fig. 1F, G), whereas those of the WC ≥85 group were 2.0% ± 1.7% and 0.9% ± 2.4%, respectively (vs WC <85 group: P < .05, each; Fig. 1F, G). The %TG in the WC <85 group was −10.2% ± 2.1% (vs baseline: P < .001, Fig. 1D), whereas that in the WC ≥85 group was 2.8% ± 3.3% (vs WC < 85 group: P < .05, Fig. 1D). However, there were no differences in %TC and %HDL-C between the 2 groups (Fig. 1C, E).

3.3. Changes in serum adiponectin and oxidative stress level after OGTT

In addition, we investigated the changes in serum adiponectin and oxidative stress levels after OGTT. There was no significant difference in percentage adiponectin (% adiponectin) between the 2 groups (Fig. 1H). However, percentage TBARS (%TBARS) was −10.8% ± 5.3% in the WC <85 group (vs baseline: P =.07, Fig. 1I) and 3.3% ± 3.4% in the WC ≥85 group, albeit the difference was statistically insignificant (vs WC < 85 group: P = .057, Fig. 1I).

4. Discussion

The main findings of the present study were as follows: (1) postprandial %TG, %SBP, and %DBP were lower significantly in the WC <85 group (vs baseline: P = .10, P < .01, and P < .001, respectively), but not in the WC ≥85 group; and the differences between the 2 groups were significant (P < .05, each); (2) %TBARS tended to be lower in the WC <85 group (vs baseline: P = .07), but not in the WC ≥ 85 group, albeit statistically insignificant (the WC <85 vs WC ≥85 group, P = .057); and (3) the response of serum adiponectin to glucose loading was similar in the 2 WC groups.

Postprandial hyperglycemia, hypertriglyceridemia, and hyperinsulinemia are recognized predictors of cardiovascular pathology [9-14,26,27]. The present study demonstrated that glucose overload resulted in a significant fall in %SBP and %DBP in the WC <85 group vs baseline (Fig. 1). This finding is similar to another study in elderly subjects, which reported a fall in blood pressure after drinking simple sugar solution [28], and adds support to the notion that glucose affects the decrease in systemic postprandial blood pressure after an increase of splanchnic blood flow in healthy subjects [28].

The present study also showed a significant postprandial decrease in %TG in the WC <85 group vs baseline. This finding is also similar to those reported previously in healthy adults [29] and healthy volunteers [30] under similar glucose challenge. What is the mechanism of the decrease in %TG in the WC <85 group? It is possible that TG decreases gradually after insulin-induced activation of lipoprotein lipase, which generally increases in response to a rise in blood glucose level, as reported previously [29,30]. The present study also demonstrated for the first time postprandial dysregulation of blood pressure and TG in the WC ≥85 group (Fig. 1). This observation might be partly due to the fact that insulin resistance affects excess sodium reservoir and dysregulation of lipoprotein lipase activity. Another potential mechanism regarding postprandial

dysregulation of blood pressure is the following: Kawano et al [31] reported that hyperglycemia after OGTT suppresses flow-mediated endothelium-dependent vasodilation of brachial artery in the impaired–glucose tolerance group and the diabetic group. They also demonstrated that the endothelial function decreased in association with an increase in plasma levels of TBARS after OGTT [31]. The current study might result in dysregulated blood pressure through endothelial dysfunction in the group of WC ≥85 because of increased reactive oxygen species production after OGTT (Fig. 1I). These vasodilation responses of the brachial arteries in 1- and 2-hour post-OGTT need to be investigated in the further study.

The current guidelines of the World Health Organization stipulate a target 2-hour postprandial (postglucose challenge) plasma glucose level of less than 140 mg/dL [32]. The OGTT is helpful in screening for postprandial hyperinsulinemia, prediabetes, and diabetes. Standardized and validated protocols for assessment of postprandial dysregulated metabolism including blood pressure and TG levels are not yet available; and thus, normal values are not well defined at this stage. Ogita et al [30] reported that the changes in serum TG levels after OGTT are different from those after an oral fat tolerance test regarding the changes in plasma levels of insulin and apolipoprotein B. Sometimes, these tests are criticized as unrealistic methods for determination of postprandial metabolism because we scarcely consume glucose only or fat only. Therefore, analyses of the postprandial changes using various tolerance tests are required in the future.

Oxidative stress, defined as dysregulation of the cellular redox state, plays a pivotal role in the pathogenesis of vascular failure, especially vascular endothelial dysfunction [33,34]. Recent reports have demonstrated that the pathophysiology of postprandial dysregulated metabolism, especially hyperglycemia, was characterized by hyperglycemic spikes that induce oxidative stress [35,36]. To our knowledge, the effect of glucose loading on serum oxidative stress levels has not been firmly characterized previously. We therefore assessed the oxidative stress response to OGTT in both control subjects and subjects with abdominal obesity, that is, the WC ≥85 group. The present study showed that %TBARS after OGTT was −10.8% ± 5.3% in the WC <85 group (Fig. 1I), partly because the levels of TG and blood pressure, which are known to correlate with oxidative stress [37], decreased in the WC <85 group after the glucose load (vs baseline: $P = .07$, Fig. 1I). However, in the WC ≥85 group, the percentage change in TBARS was 3.3% ± 3.4%; that is, oxidative stress did not decrease but rather increased in subjects with abdominal obesity in response to glucose overload (Fig. 1I). This may be explained at least in part by overproduction of oxidative stress by accumulated visceral fat, as we reported previously [19]. The sustained increase in oxidative stress might accelerate vascular damage, that is, increased max IMT observed in the WC ≥85 group (Table 1).

Adiponectin is an adipocyte-specific secretory protein with antiatherosclerotic and antidiabetic properties in experimental studies [17]. Blood adiponectin levels are low in obesity [18]. In the present study, we found that subjects with abdominal obesity had lower blood levels of adiponectin in the fasting state before the OGTT compared with those without such obesity (Table 1), as reported previously [18]. Yildiz et al [38] reported no significant differences in 24-hour adiponectin patterns between lean and obese subjects. Furthermore, Yamauchi et al [39] reported that 75-g OGTT did not alter serum adiponectin levels in healthy subjects. It has been also shown that plasma adiponectin levels after a meal increase in obese subjects but not in lean subjects [40]. Experimental studies showed that adiponectin gene expression is reversibly down-regulated by insulin [41]. However, the present study demonstrated that there was no significant difference in %adiponectin during an OGTT between subjects with and without abdominal obesity (Fig. 1H). Differences in age, sex, body fat, disease, or the test among studies may account for the discrepant findings. This pathophysiologic relevance should be further investigated in a large number of subjects.

Treatment of postprandial metabolic dysregulation in subjects with abdominal obesity could include visceral fat reduction by diet and exercise, and various pharmacologic agents, which could probably lead to improvement of prognosis of atherosclerotic disease. Future prospective randomized controlled trials are needed to establish postprandial metabolism as an independent cardiovascular risk factor and confirm that intervention for postprandial metabolic dysregulation can improve cardiovascular prognosis.

In conclusion, the present study demonstrated a different response of blood pressure and glucose-lipid metabolism after an OGTT in WC ≥85 subjects relative to WC <85 subjects. Even if fasting metabolic parameters remain within the reference range, various loading tests for evaluating postprandial metabolism should be considered to prevent CVDs, especially in subjects with abdominal obesity.

4.1. Limitations of the study

Our study had several limitations. First, the cross-sectional design makes it difficult to establish a cause-effect relationship. Second, the results may not be valid in non-Japanese populations. Third, we used WC to evaluate abdominal obesity in the present study; and further research on both visceral and subcutaneous fat areas measured by computed tomography is needed to clarify the effects of visceral and subcutaneous adiposity on metabolic dysregulation. Fourth, serum lipid metabolism, adiponectin, and TBARS concentrations were measured in the fasting state before an OGTT and at 120 minutes after an OGTT, but not at 30 and 60 minutes after an OGTT. Measurement at each time point after an OGTT should be performed for a better assessment of the postprandial phenomenon. Finally, it was

difficult to recruit a sufficient number of control subjects; and thus, further multicenter studies of larger samples should be conducted in the future.

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