Higher circulating orosomucoid and lower early-phase insulin secretion in midlife Japanese with slower glucose disposal during oral glucose tolerance tests

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Abstract

Objective We examined whether serum orosomucoid, an acute phase protein as with C-reactive protein, in addition to insulin resistance and beta-cell dysfunction, was involved in glucose disposal during oral glucose tolerance tests.

Research design and methods 124 midlife Japanese (65 women, 66% with normal glucose tolerance) received dual-energy X-ray absorptiometry and 75 g oral glucose tolerance tests with multiple postload glucose and insulin measurements. Subjects were divided based on the relationship between postload and fasting glucose. Obesity measures, insulin resistance, insulin secretion, serum orosomucoid and adiponectin were cross-sectionally analyzed by analysis of variance and then Bonferroni's multiple comparison procedure.

Results In 10 subjects (group A) and 19 subjects (group B), postload glucose fell below fasting glucose at 1 h and 2 h, respectively. In the remaining 95 subjects (group C), postload glucose never fell below fasting glucose. The insulinogenic index was lower and area under the glucose curve was higher in groups B and C as compared to group A (both $p < 0.05$), whereas the Matsuda index, the homeostasis model assessment of insulin resistance, adipose insulin resistance (the product of fasting free fatty acid and insulin) and area under the insulin curve did not differ. Although there was no difference in fat mass index, trunk/leg fat ratio and adiponectin, orosomucoid was higher in group C as compared to group A ($p < 0.05$).

Conclusions Lower early-phase insulin secretion and low-grade inflammation were associated with slower glucose disposal during an oral glucose tolerance test in midlife Japanese. The rate of glucose disposal was not related to adiposity and insulin resistance.

Keywords Orosomucoid · Inflammation · Glucose tolerance test · Glucose disposal · Insulin secretion

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Introduction

The number of people with type 2 diabetes has rapidly and remarkably increased throughout the world, especially in Asia [1]. Obesity in general, abdominal obesity in particular, and ethnicity are known determinants for development of type 2 diabetes [2], which is characterized by insulin resistance and impaired insulin secretion. It has been proposed, based mainly on studies of Caucasians, that type 2 diabetes is triggered by obesity-associated insulin resistance, which is compensated initially by increased β cell response that eventually leads to diabetes due to exhaustion of pancreatic β cells [3, 4]. It is reported that in East Asians, prediabetes and early-stage diabetes are characterized primarily by reduced insulin secretion and lower degree of insulin resistance and obesity [5, 6]. In addition to obesity, it was reported that lower muscle mass was associated with increases in insulin resistance and prediabetes [7].

The San Antonio Heart Study examined the relationship between postload plasma glucose (PG) and fasting PG to assess the risk of progression to type 2 diabetes [8]. Individuals with normal glucose tolerance (NGT), whose postload PG never fell to fasting PG within 2 h following an oral glucose load (termed as group IV), had higher BMI and waist, greater insulin resistance, a lower early-phase insulin secretion and a higher risk of developing type 2 diabetes than subjects with NGT whose postload PG returned to fasting PG more quickly [8]. In other words, group IV was less efficient in disposing of the glucose load. As far as we know, no study has examined the relationship between postload PG and fasting PG in Asian populations. In the present study, therefore, we examined whether the relationship between postload PG and fasting PG was associated with body fat and distribution, insulin resistance and lower early-phase insulin secretion in Japanese midlife adults.

Orosomucoid (ORM), an acute phase protein, is one of the most abundant plasma proteins, accounting for about 1% of all plasma proteins [9]. Many biological activities of ORM have been identified including acting as a disease marker, modulating immunity, binding and carrying drugs, maintaining the barrier function of the capillary and regulating metabolism [9]. Higher circulating levels of ORM have been reported to be associated with an increased risk of type 2 diabetes [10]. We have recently shown that elevated circulating ORM was associated with glucose excursion during OGTT without changes in insulin secretion and insulin resistance in young Japanese women with NGT [11]. Therefore, we examined whether serum orosomucoid, in addition to insulin resistance and β -cell dysfunction, was involved in glucose disposal during oral

glucose tolerance tests in Japanese midlife adults, in whom 66% had NGT. We further tested whether the relationship between postload PG and fasting PG was associated with lower muscle mass.

Methods

A total of 124 individuals whose details were reported elsewhere [12–14], 65 women and 59 men, who were parents of students of Mukogawa Women's University were included in the study. Among 148 women previously reported [12, 13], we report here results of 65 women who underwent an OGTT. There was no significant difference between the 65 women and remaining 83 women in anthropometric and biochemical variables (data not shown). Nobody reported receiving any medications or having regular supplements. The study was approved by the Mukogawa Women's University Ethical Committee (No. 07-28 on 19/02/2008) and was in accordance with the Helsinki Declaration. All subjects were recruited as volunteers and gave written consent after the experimental procedure had been explained.

At 8:30 A.M. after a 12-h overnight fast, they received a standard 75 g OGTT. Blood was withdrawn at 0 (fasting), 30 min, 1 h and 2 h after glucose ingestion. None of the blood samples showed hemolysis. Plasma glucose (PG) and serum insulin were measured as previously reported [12, 13]. Incremental glucose and insulin concentrations during the first 30 min of OGTT (Δ glucose₃₀ and Δ insulin₃₀, respectively) were the difference between respective fasting and 30 min concentrations. 'The area under the response curve of glucose (AUC_G) and insulin (AUC_I) was calculated by the trapezoidal method. Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated as a more reflective surrogate of hepatic IR [15, 16]. Matsuda index and the insulinogenic index (IGI) were calculated as a surrogate of muscle IR and early phase insulin secretion, respectively [17, 18]. To evaluate β -cell function, the insulin secretion $\times$ sensitivity index (disposition index) was calculated as the product of IGI and Matsuda index. Adipose insulin resistance (adipose IR) was calculated as a product of fasting insulin and free fatty acids (FFA) [19]. Prediabetes and diabetes, termed as dysglycemia, were diagnosed based on the criteria of the American Diabetes Association [20].

FFA, leptin, adiponectin, high-sensitivity C-reactive protein (hsCRP), tumor necrosis factor- α (TNF- α), ORM and plasminogen activator inhibitor-1 (PAI-1) were measured in fasted samples as previously reported [11–13].

Fat, bone and lean mass for extremities and trunk were measured using whole-body dual-energy X-ray absorptiometry (DXA) (Hologic QDR-2000, software version 7.20D, Waltham, MA) as previously reported [12, 13]. General adiposity was assessed using fat mass index (FMI) calculated

as body fat mass in kilogram divided by height in meter squared. Abdominal fat accumulation was assessed by the ratio of trunk to leg fat [21]. Because lean mass in arms and legs represents skeletal muscle mass, a sum of the two was used as appendicular skeletal muscle mass (ASM). Skeletal muscle mass was assessed by ASM index (ASMI) calculated as ASM in kilograms divided by squared height in meters.

Data were mean $\pm$ SD. IGI, disposition index and hsCRP were logarithmically transformed for analyses because of deviation from normal distribution. Differences among the three groups were analyzed using analysis of variance and then Bonferroni's multiple comparison procedure. A two-tailed value of $p < 0.05$ was considered significant. SPSS system 17.0 (SPSS Inc., Chicago, IL) was used for statistical analyses.

Results

ORM was elevated in 41 subjects with dysglycemia compared to 83 subjects with NGT (200 ± 44 vs. 141 ± 31 mg/dL, $p < 0.001$). In 10 subjects (group A) and in 19 subjects (group B), postload PG returned to levels below fasting PG at 1 h and 2 h, respectively. In the remaining 95 subjects

(group C), postload PG never fell below fasting PG. There was no subjects whose postload PG fell below fasting PG at 30 min.

As shown in Table 1 and Fig. 1, 2 h PG was higher in group C as compared to A and B, whereas there was no difference in fasting and 30-min PG. One-hour PG increased in a stepwise fashion from group A to C. Consequently, AUCg was higher in groups B and C as compared to A. In contrast, there was no or modest difference in fasting and postload insulinemia, and AUCi among the three groups. IGI (Fig. 2) and disposition index (Table 1) were lower in groups B and C as compared to A as Δ glucose30 increased and Δ insulin30 decreased in a stepwise fashion from group A through C. In contrast, fasting insulin and HOMA-IR did not differ among the three groups and differences in Matsuda index and adipose IR were not statistically significant.

As shown in Table 2, there was no difference in measures of fat mass and distribution (BMI, FMI, waist and trunk/leg fat ratio) and ASMI among the three groups. Serum triglycerides, HDL cholesterol and blood pressure did not differ as well. Serum ORM was higher in groups B and C as compared to A (Fig. 2). However, the difference between groups B and A was not significant. There was no group difference in serum leptin, adiponectin, PAI-1, hsCRP and TNF- α .

Table 1 Plasma glucose (PG) and serum insulin responses during a 75 g oral glucose tolerance test and measures of insulin resistance in Japanese midlife adults divided into three groups based on the relationship between fasting and postload PG

	Group A			Group B			Group C		
	<i>n</i> = 10			<i>n</i> = 19			<i>n</i> = 95		
Fasting PG (mg/dL)	87	$\pm$	3	96	$\pm$	3	93	$\pm$	1
30 min PG (mg/dL)	122	$\pm$	12	146	$\pm$	8	146	$\pm$	3
1 h PG (mg/dL)	76	$\pm$	5	149	$\pm$	11	156	$\pm$	5 ^{a,b,c}
2 h PG (mg/dL)	92	$\pm$	7	88	$\pm$	3	129	$\pm$	4 ^{b,c}
Fasting insulin (μ U/mL)	4.9	$\pm$	0.7	5.2	$\pm$	0.7	5.2	$\pm$	0.4
30 min insulin (μ U/mL)	57	$\pm$	10	41	$\pm$	6	35	$\pm$	3 ^b
1 h insulin (μ U/mL)	35	$\pm$	9	62	$\pm$	9	47	$\pm$	6
2 h insulin (μ U/mL)	26	$\pm$	5	29	$\pm$	5	42	$\pm$	3
Δ glucose30 (mg/dL)	35	$\pm$	11	50	$\pm$	6	54	$\pm$	3
Δ insulin30 (μ U/mL)	52	$\pm$	10	36	$\pm$	6	30	$\pm$	2 ^b
Disposition index	54	$\pm$	22	14	$\pm$	2.9	6.5	$\pm$	0.8 ^{a,b}
AUCg	185	$\pm$	11	253	$\pm$	14	278	$\pm$	7 ^{a,b}
AUCi	69	$\pm$	13	83	$\pm$	11	76	$\pm$	7
HOMA-IR	1.1	$\pm$	0.2	1.3	$\pm$	0.2	1.2	$\pm$	0.1
Matsuda index	14.1	$\pm$	2.5	12.9	$\pm$	2.1	10.2	$\pm$	0.6
FFA (mEq/L)	0.46	$\pm$	0.04	0.50	$\pm$	0.04	0.57	$\pm$	0.02
Adipose IR	2.2	$\pm$	0.4	2.8	$\pm$	0.5	3.1	$\pm$	0.4

Mean $\pm$ SD. In groups A and B, postload PG fell below fasting PG at 1 h and 2 h, respectively, after glucose loading. Postload PG never fell below fasting PG within 2 h in group C

AUCg and AUCi Area under the response curve of plasma glucose and serum insulin, respectively. Δ glucose30 and Δ insulin30 the incremental glucose and insulin during the first 30 min during oral glucose tolerance tests, respectively, HOMA Homeostasis model assessment, IR insulin resistance, FFA free fatty acids

Significantly different at $p < 0.05$ or less. a: A vs. B, b: A vs. C, c: B vs. C

Fig. 1 Responses of glucose and insulin during 75 g oral glucose testing in middle-aged Japanese divided into 3 groups based on the relationship between postload plasma glucose (PG) and fasting PG. In 10 subjects (group A, blue lines) and 19 subjects (group B, yellow lines), postload PG returned to levels below fasting PG at 1 h and 2 h, respectively. In the remaining 95 subjects (group C, red lines), postload PG never fell below fasting PG. Mean $\pm$ SD. *: values were significantly higher in groups B and C as compared to group A. **: values were significantly higher in group C as compared to groups A and B. #: values were significantly higher in group C as compared to group A

Fig. 2 Insulinogenic index (IGI), a marker of early-phase insulin secretion, and serum orosomucoid (ORM), an acute phase protein, in groups A (blue columns), B (yellow columns) and C (red columns). Mean $\pm$ SD. a: $p < 0.05$ vs. group A. See the legend of Fig. 1 for groups A, B and C

Discussion

As far as we know, the present study is the first to examine the relationship between postload PG and fasting PG during OGTT in Asian populations. The time that is required for postload PG to fall below fasting PG during the OGTT is dependent on insulin response following

glucose ingestion and peripheral/hepatic insulin sensitivity [8]. The slower the postload PG drops below fasting PG, the less efficient is the disposal of the glucose load. We found in Japanese midlife adults, in whom 66% had NGT, that subjects with slower glucose disposal (group C) had a lower early-phase insulin secretion compared with subjects with faster glucose disposal. However, there was no difference among three groups in adiposity, insulin resistance and skeletal muscle mass. Instead, Japanese subjects with slower glucose disposal had higher circulating ORM, an acute phase protein. Our findings appears to be in line with the current understanding that prediabetes and early-stage diabetes in East Asians are characterized primarily by β -cell dysfunction and less adiposity compared to the conditions in Caucasians [22].

It is thought that East Asians have a limited innate capacity of insulin secretion [23]. This capacity may be decreased by aging or β -cell exhaustion due to continuous insulin resistance. Because subjects with slower glucose disposal (group B and C) had a lower IGI compared with those with faster glucose disposal (group A), a lower early-phase insulin secretion may explain slower glucose disposal in groups B and C in the present study. However, not only general adiposity (BMI and FMI), but also abdominal adiposity (waist circumference and trunk/leg fat ratio) in addition to age did not differ among the three groups. Further, hepatic and adipose tissue insulin resistance (HOMA-IR and adipose IR, respectively) as well as muscle insulin sensitivity (Matsuda index) did not differ among three groups.

Chronic low-grade systemic inflammation is often associated with insulin resistance and impaired insulin secretion, two core defects underlying the pathophysiology of type 2 diabetes [24]. ORM, a biomarker for inflammation and also known as α 1-acid glycoprotein [9], is one of the major acute phase proteins of glycoprotein acetyls (GlycA), which has been shown to be a composite nuclear magnetic resonance biomarker of systemic inflammation and a risk of incident type 2 diabetes [25]. Fizeleva et al. [26] investigated the association of hsCRP and GlycA with glucose levels and incident type 2 diabetes and found that GlycA was a stronger predictor of an increase in glycemia (FPG, 2 h PG, and glucose AUC) and incident type 2 diabetes in a large well-characterized cohort of nondiabetic Finnish men. These observations may be in line with the current finding that elevated circulating ORM was found in Japanese midlife adults with the slowest glucose disposal (group C) in the present study. Studies including ours have previously reported associations of higher ORM with higher PG during OGTT [11, 27, 28] and incident type 2 diabetes [10, 29–31].

A lower early-phase insulin secretion was evident in subjects with the slowest glucose disposal both in the present study (group C) and the San Antonio Heart Study (group IV) [8]. However, intra-study group differences in adiposity

Table 2 Anthropometric indices, serum lipids and lipoproteins, adipokines and blood pressure in groups A, B and C

	Group A			Group B			Group C		
	<i>n</i> = 10			<i>n</i> = 19			<i>n</i> = 95		
Age (years)	48.5	±	1.0	50.1	±	0.9	50.5	±	0.5
BMI (kg/m ²)	20.7	±	1.1	24.9	±	2.1	22.7	±	0.3 ^a
FMI (kg/m ²)	5.0	±	0.7	6.1	±	0.5	6.1	±	0.2
Percentage body fat (%)	23.3	±	2.4	26.6	±	1.7	26.6	±	0.8
Waist circumference (cm)	76.7	±	3.2	83.5	±	2.3	81.9	±	0.8
Trunk/leg fat ratio	1.68	±	0.21	2.00	±	0.14	2.05	±	0.07
ASMI (kg/m ²)	6.4	±	0.3	6.8	±	0.3	6.8	±	0.1
Total cholesterol (mg/dL)	221	±	10	224	±	8	215	±	4
LDL cholesterol (mg/dL)	126	±	7	137	±	8	125	±	4
HDL cholesterol (mg/dL)	73	±	7	69	±	4	66	±	2
Triglycerides (mg/dL)	110	±	23	91	±	11	116	±	13
SBP (mmHg)	125	±	7	132	±	5	128	±	2
DBP (mmHg)	77	±	5	81	±	2	81	±	1
Leptin (ng/mL)	4.0	±	0.6	5.5	±	0.9	5.3	±	0.4
Adiponectin (mg/L)	11.4	±	1.5	9.5	±	1.0	8.9	±	0.5
PAI-1 (ng/mL)	24	±	4	30	±	3	36	±	2
hsCRP (μg/dL)	13	±	6	16	±	4	33	±	8
TNF-α (pg/mL)	0.73	±	0.15	0.63	±	0.04	0.71	±	0.03
Men (n, %)	3	±	30.0	10	±	52.6	46	±	48.4

Mean ± SD. See Table 1 for groups A, B and C

ASMI Appendicular skeletal muscle mass index, FMI fat mass index, SBP and DBP systolic and diastolic blood pressure, respectively, PAI-1 plasminogen activator inhibitor-1, hsCRP high-sensitivity C-reactive protein, TNF-α tumor necrosis factor-α

Significantly different at $p < 0.05$ or less. a: A vs. B

and adiposity-associated insulin resistance were not significant in the present study, whereas they were evident in the San Antonio Heart Study [8]. This is because of lower values of mean BMI (22.7 vs. 27.6 kg/m²) and waist (81.9 vs. 88.4 cm) in group C subjects vs. group IV subjects. It is noteworthy that even sophisticated measures of fat mass and distribution (FMI and trunk/leg fat ratio) did not differ among the three groups in the present study.

Because skeletal muscle is a major site of insulin-mediated glucose disposal in the postprandial state [7], declines in skeletal muscle mass may be associated with a decrease in glucose disposal after an oral glucose load. Indeed, it is reported that declines in skeletal muscle mass, estimated by bioelectrical impedance, are associated with increases in insulin resistance and prediabetes [7]. However, there was no group difference in sophisticated measures of skeletal muscle mass (DXA-derived SMI) in the present study.

There were several strengths of this study. The study population was homogeneous as previously reported [13]. Fat and lean masses were estimated using DXA, a gold standard of measurement of body composition. There were several limitations that should be taken into account. The first is the small sample size. As we studied Japanese only, the results may not be generalized to other races or

ethnicities. The recruitment procedure may also have some potential impact on the results. As the participation was voluntary, parents who pay more attention to health may be more likely to participate. Because the present study was cross-sectional, causal inferences were not drawn. Biochemical parameters were measured only once. Crude measures of insulin resistance and insulin secretion were used, which may be less accurate. Statistical power was not calculated.

In conclusion, slower glucose disposal during OGTT was associated with higher circulating orosomucoid and lower early-phase insulin secretion, but comparable hepatic and peripheral insulin resistance in Japanese midlife adults, in whom 66% were normal glucose tolerant.

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Compliance with ethical standards

Conflict of interest None of the authors have any potential conflicts of interest to declare associated with this research.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimental-

tion (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions.

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