

Higher circulating adiponectin and lower orosomucoid were associated with postload glucose ≤ 70 mg/dL, a possible inverse marker for dysglycemia, in young Japanese women

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ABSTRACT

Objective To examine whether serum adiponectin and orosomucoid were associated with postload glucose ≤ 70 mg/dL during an oral glucose tolerance test (OGTT), termed as postload low glycemia, a possible inverse marker for dysglycemia.

Research design and methods 75 g OGTTs were performed with multiple postload glucose and insulin measurements over a 30–120 min period in 168 normal-weight Japanese women (18–24 years). Insulin resistance (IR) and β -cell function inferred from serum insulin kinetics during OGTT, fat mass and distribution by dual-energy X-ray absorptiometry (DXA), serum adiponectin and inflammatory markers were compared cross-sectionally between 39 women with and 129 women without postload low glycemia.

Results Of 168 women, 161 had normal glucose tolerance. Women with as compared with those without postload low glycemia had lower fasting and postload glycemia despite similar fasting and postload insulinemia. They had higher insulinogenic index ($p=0.03$) and lower adipose IR (a product of fasting free fatty acid and insulin, $p=0.01$), although DXA-derived general and central adiposity, the Matsuda Index and homeostasis model assessment-IR did not differ. In addition, they had higher adiponectin and lower orosomucoid (both $p<0.001$). Multivariate logistic regression analyses revealed that adiponectin (OR: 1.14, 95% CI 1.03 to 1.26, $p=0.009$) and orosomucoid (0.96, 0.93 to 0.97, $p=0.008$) were associated with postload low glycemia independently of adipose IR and insulinogenic index.

Conclusions Higher adiponectin and lower orosomucoid were associated with 70 or lower mg/dL of postload glucose, a possible inverse marker for dysglycemia, in young women independently of DXA-derived fat mass and distribution, insulin secretion and IR.

INTRODUCTION

Measurements of fasting and 2-hour plasma glucose (PG) during a 75 g oral glucose tolerance test (OGTT) enable us to identify individuals at high risk for type 2 diabetes,

Significance of this study

What is already known about this subject?

- ▶ Postload glucose concentrations during an oral glucose tolerance test are related to insulin resistance and/or impaired insulin secretion, both of which are associated with obesity.

What are the new findings?

- ▶ Postload glucose concentrations in non-obese young women are related to higher circulating adiponectin and lower orosomucoid, and are not related to fat mass and distribution, insulin resistance and impaired insulin secretion.

How might these results change the focus of research or clinical practice?

- ▶ The association of postload glycemia with orosomucoid independent of insulin resistance and impaired insulin secretion suggests an opportunity to discover insights into the mechanisms of glucose dysmetabolism within normal glucose tolerance, although further research is needed.

that is, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), pre-diabetes.^{1–3} However, persons with IGT or IFG develop type 2 diabetes at an annual rate of approximately 10%.⁴ In contrast, it is reported that about 40% of subjects who had normal glucose tolerance (NGT) at baseline developed type 2 diabetes in prospective epidemiologic studies.^{1–3} Therefore, additional information other than fasting and 2-hour PG might help us identify a group of subjects who might benefit from early lifestyle intervention.

In this context, it seems reasonable to identify individuals at low risk for type 2 diabetes. Individuals with NGT whose postload PG



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returned to fasting PG (FPG) within 2 hours following an oral glucose load had greater insulin sensitivity, a higher early-phase insulin secretion, and a lower risk of developing type 2 diabetes than subjects with NGT whose postload PG did not return to FPG.⁵ We have shown that more than one in five young Japanese women who underwent 75 g OGTT had postload PG fell to a level less than or equal to 70 mg/dL at any time point within 2 hours following an oral glucose load (termed as postload low glycemia).⁶ Because their FPG exceeded 70 mg/dL, postload low glycemia is a simple way to identify individuals whose postload PG returned to FPG within 2 hours following an oral glucose load and therefore may represent a low risk for dysglycemia.

A recent meta-analysis has shown that a lower risk for type 2 diabetes is associated with higher adiponectin levels.⁷ Further, it is reported that higher adiponectin levels have been related to the lower risk of incident pre-diabetes among healthy African-Americans and European Americans with parental history of type 2 diabetes.⁸

Prospective studies have demonstrated that higher orosomucoid (ORM), a biomarker for inflammation and also referred to as α 1 acid glycoprotein, is associated with an increased risk of type 2 diabetes.^{9–11} Serum levels of glycoprotein acetyls (GlycA) have been found to be associated with dysglycemia in middle-aged and elderly Finnish men.¹² We have recently demonstrated that serum ORM was related to postload glucose and glucose excursion during OGTT in non-obese young Japanese women.¹³ However, associations between ORM and postload low glycemia were not evaluated in that study.¹³ Therefore, we aimed to examine whether serum adiponectin and ORM were associated with postload low glycemia, a possible inverse marker for dysglycemia, in 168 young Japanese women recruited from our previous cross-sectional study,^{6,13} and whether these associations, if any, depend on fat mass and distribution, insulin secretion and insulin resistance (IR) of muscle and adipose tissue, the latter of which was evaluated using fasting free fatty acid (FFA).¹⁴

METHODS

We cross-sectionally studied 168 young women (50 collegiate athletes and 118 untrained students of the university), aged 18–24 years, whose details have been reported elsewhere.^{6,13–15} The athletes were students of the Department of Health and Sports Sciences and had been training regularly for 2 years or longer prior to the study, 5 hours a day, 6 days a week. Non-athletes were students of the Department of Food Sciences and Nutrition and were not engaged in any regular sport activity. However, they had 9367 \pm 1971 steps/day (mean \pm SD of 77 non-athletes, who used a pedometer for 14 days, and the mean steps a day were calculated for each participant). Subjects who reported to be under treatment for clinically diagnosed acute or chronic inflammatory diseases,

endocrine, cardiovascular, hepatic, renal diseases, hormonal contraception, and unusual dietary habits were excluded. Nobody reported receiving any medications or having regular supplements.

After a 12-hour overnight fast, a standard 75 g OGTT with glucose and insulin measurements at 0 (fasting), 30 min, 1 hour, and 2 hours was performed in the morning. PG was determined by the hexokinase/glucose-6-phosphate dehydrogenase method (interassay coefficient of variation [CV] <2%). Serum insulin was measured by an ELISA method with a narrow specificity excluding des-31, des-32, and intact proinsulin (interassay CV <6%). FFA was measured using enzymatic colorimetric methods (Wako, Tokyo, Japan). The area under the response curve of glucose (AUC_g) and insulin (AUC_i) was calculated by the trapezoidal method. Homeostasis model assessment-IR (HOMA-IR) and the Matsuda Index were calculated as a more reflective surrogate of hepatic and muscle IR, respectively.^{16,17} The insulinogenic index (IGI), a measure of early-phase insulin secretion, was calculated as previously reported.¹⁸ Adipose IR was calculated as a product of fasting FFA and insulin.¹⁹

Leptin, adiponectin, high-sensitivity C reactive protein (hsCRP) and plasminogen activator inhibitor-1 (PAI-1) were measured in fasted samples as previously reported.^{13–15} ORM concentrations were measured in fasted samples by an immunoturbidimetric method using a commercially available kit (N Antiserum to Human α 1-acid Glycoprotein, Siemens Healthcare Diagnostics, Tokyo, Japan) and an autoanalyzer (JCA-BM6010, JEOL, Tokyo, Japan). Intra-assay and interassay CV at 87 mg/dL were 1.4% and 1.7%, respectively.

Fat and lean mass for arms, legs, trunk and the total body were measured using whole-body dual-energy X-ray absorptiometry (DXA, Hologic QDR-2000, V.7.20D, Waltham, Massachusetts) as previously reported.^{14,15} The leg region included the entire hip, thigh and leg. General adiposity was assessed using height-adjusted and weight-adjusted body fat, fat mass index (FMI) and percentage body fat, respectively. Abdominal fat accumulation was assessed by the ratio of the trunk fat to the leg fat.²⁰

Data were presented as mean \pm SD unless otherwise stated. Due to deviation from normal distribution, IGI and hsCRP were logarithmically transformed for analyses. Comparisons between young women with and without postload low glycemia were made with t-test and ² test when appropriate. Multivariate logistic regression analyses were performed for postchallenge low glycemia as a dependent variable. Independent variables included were those which displayed significant difference between women with and without postload low glycemia. A two-tailed value of $p < 0.05$ was considered significant. Statistics were performed with the SPSS V.17.0 system.

RESULTS

Of 168 women studied, 161 had NGT, and 3, 22, and 21 women had postload low glycemia at 30 min, 1 hour and

2 hours after glucose loading, respectively. As 7 women had postload low glycemia at two different time points, 39 women had postload low glycemia at any time points during OGTT. Because there was no difference between athletes and non-athletes in serum ORM (126 ± 28 and 127 ± 26 mg/dL, respectively),¹³ adiponectin (11.6 ± 4.3 and 11.5 ± 4.3 mg/L, respectively)¹⁴ and the proportion of women with postload low glycemia (24.0% [12/50] and 22.9% [27/118], respectively),⁶ both groups were combined to be analyzed to obtain a wider range of adiposity. As shown in tables 1 and 2, young women studied were of normal weight, had normal waist circumference and hence were insulin-sensitive as indicated by normal fasting insulin levels.

Women with as compared with those without postload low glycemia had lower FPG and postload PG despite similar fasting and postload insulinemia (figure 1 and table 1). Consequently, they had lower AUC_g despite similar AUC_i (table 1). Increases in glucose during the first 30 min during OGTT were lower and those in insulin were higher in women with as compared with those without postload low glycemia (table 1). Hence, women with postload low glycemia had higher IGI (figure 2). In addition, they had lower adipose IR (figure 2), although the Matsuda Index and HOMA-IR did not differ (table 1).

Further, postload low glycemia was characterized by higher adiponectin and lower ORM (table 1), although serum leptin, hsCRP and PAI-1 did not differ (table 2). Age, anthropometric measurements and DXA-derived body composition did not differ, including fat and lean mass, FMI and trunk to leg fat ratio. There was also no difference in serum triglycerides and HDL cholesterol, although FFA tended to be lower in women with compared with those without postload low glycemia.

Multivariate logistic regression analysis (table 3) revealed that adiponectin (OR: 1.14, 95% CI 1.03 to 1.26, $p=0.009$) and ORM (OR: 0.96, 95% CI 0.93 to 0.97, $p=0.008$) were associated with postload low glycemia independently of adipose IR and IGI. Scatter plots between ORM and adiponectin and 120 min glucose are shown in figure 2.

DISCUSSION

In the present study, young women with postload low glycemia had higher early-phase insulin response to glucose (higher IGI) and higher insulin sensitivity in adipose tissue (lower adipose IR). In addition, they had higher adiponectin, an insulin sensitizing adipokine, and lower ORM, a marker of low-grade inflammation. Among them, higher adiponectin and lower ORM were independently associated with postload low glycemia, a possible inverse marker for dysglycemia, in normal-weight, young Japanese women. These associations were not related to sophisticated measures of general and abdominal adiposity, early-phase insulin secretion (IGI), IR of the liver (HOMA-IR), adipose tissue (adipose IR)

Table 1 Features of 75 g oral glucose tolerance tests of 168 young Japanese women in the presence and absence of postload low glycemia (≤ 70 mg/dL)

	Postload low glycemia		P value
	Absent (n=129)	Present (n=39)	
Fasting glucose (mg/dL)	85±6	81±7	0.001
30 min glucose (mg/dL)	129±23	103±21	<0.001
1-hour glucose (mg/dL)	112±30	76±22	<0.001
2-hour glucose (mg/dL)	97±19	76±16	<0.001
Fasting insulin (μU/mL)	5.8±2.9	5.8±3.7	0.895
30 min insulin (μU/mL)	50±28	63±39	0.052
1-hour insulin (μU/mL)	45±26	33±20	0.007
2-hour insulin (μU/mL)	38±22	30±26	0.054
Δglucose ₃₀ (mg/dL)	44±22	23±21	<0.001
Δinsulin ₃₀ (μU/mL)	45±27	57±38	0.049
Insulinogenic index	2.2±6.0	10.2±22.9	0.038
AUC _g	218±37	167±24	0.000
AUC _i	80±37	73±33	0.307
HOMA-IR	1.22±0.67	1.17±0.71	0.656
Adipose IR	3.07±2.31	2.37±1.11	0.010
Matsuda Index	9.3±4.3	10.4±4.0	0.114
Orosomucoid (mg/dL)	133±25	107±19	<0.001
Adiponectin (mg/L)	11.7±4.3	14.5±4.8	<0.001

Mean±SD.

AUC_g, area under the response curve of glucose; AUC_i, area under the response curve of serum insulin; HOMA-IR, homeostasis model assessment-IR; IR, insulin resistance; Δglucose₃₀, incremental glucose during the first 30 min during oral glucose tolerance tests; Δinsulin₃₀, incremental insulin during the first 30 min during oral glucose tolerance tests.

and skeletal muscle (Matsuda Index), and other markers of inflammation which were studied.

In the San Antonio Heart Study,⁵ NGT subjects whose postload PG fell below FPG within 2 hours during OGTT had higher IGI and lower IR, measured by HOMA-IR and Matsuda Index, compared with subjects whose postload PG never fell below FPG (designated as group IV). In the present study, there was no difference in HOMA-IR and Matsuda Index between NGT women with and without

Table 2 Characteristics of 168 young Japanese women in the presence and absence of postload low glycemia (≤ 70 mg/dL)

	Postload low glycemia		P value
	Absent (n=129)	Present (n=39)	
Age (year)	20.4 \pm 1.0	20.3 \pm 1.1	0.605
Height (cm)	161.4 \pm 6.3	162.0 \pm 7.3	0.561
Weight (kg)	54.4 \pm 7.9	54.1 \pm 9.1	0.832
Body mass index (kg/m ²)	20.9 \pm 2.5	20.5 \pm 2.2	0.396
Fat mass index (kg/m ²)	5.49 \pm 1.81	4.97 \pm 1.42	0.092
Percentage body fat (%)	26.2 \pm 6.3	24.4 \pm 5.5	0.104
Waist circumference (cm)	73.5 \pm 5.7	72.5 \pm 5.4	0.357
Trunk to leg fat ratio	1.24 \pm 0.25	1.20 \pm 0.23	0.442
Arm fat (kg)	1.1 \pm 0.6	1.0 \pm 0.5	0.090
Leg fat (kg)	5.6 \pm 1.6	5.3 \pm 1.6	0.308
Trunk fat (kg)	7.0 \pm 2.6	6.3 \pm 2.0	0.146
Body fat (kg)	14.3 \pm 4.7	13.1 \pm 4.0	0.155
Arm lean mass (kg)	3.5 \pm 0.7	3.5 \pm 0.7	0.739
Leg lean mass (kg)	12.9 \pm 2.3	13.0 \pm 2.8	0.816
Trunk lean mass (kg)	17.5 \pm 2.6	18.0 \pm 3.3	0.245
Body lean mass (kg)	37.2 \pm 5.6	37.8 \pm 6.9	0.557
Cholesterol (mg/dL)	183 \pm 28	191 \pm 30	0.093
Triglycerides (mg/dL)	54 \pm 20	68 \pm 64	0.170
HDL cholesterol (mg/dL)	73 \pm 12	77 \pm 13	0.083
Free fatty acid* (mEq/L)	0.47 (0.37–0.65)	0.44 (0.32–0.62)	0.064
Leptin (ng/mL)	7.8 \pm 3.9	6.8 \pm 2.8	0.076
PAI-1* (ng/mL)	23 (18–30)	23 (19–29)	0.644
hsCRP (μ g/dL)	32 \pm 45	37 \pm 106	0.657

Mean \pm SD.

*Median (IQR).

HDL, high-density lipoprotein; PAI-1, plasminogen activator inhibitor-1; hsCRP, high-sensitivity C reactive protein.

postload low glycemia, the latter are analogous to group IV.⁵ This may be explained by the big differences between young women without postload low glycemia and mid-life participants in group IV⁵ in fat mass and distribution

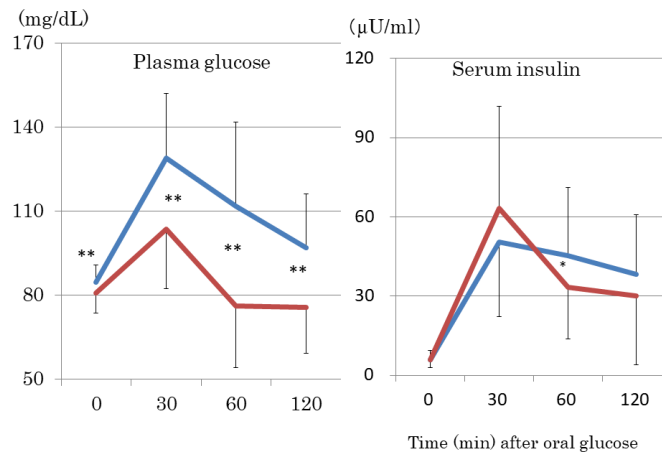


Figure 1 Glucose and insulin concentrations during 75 g oral glucose testing of young Japanese women with and without postchallenge low glycemia (red and blue lines, respectively). Mean \pm SD; * p <0.05, ** p <0.001.

(body mass index: 20.9 \pm 2.5 kg/m² vs 26.6 \pm 4.4 kg/m²; and waist circumference: 73.5 \pm 5.7 cm vs 89.3 \pm 12.1 cm).

Higher adiponectin levels are associated with a lower risk of type 2 diabetes.^{7,21} In addition, higher adiponectin levels have been shown to be inversely related to the risk of incident pre-diabetes.^{8,22} The present result of association between higher adiponectin and postload low glycemia in young, healthy, normal-weight women suggests that the association of adiponectin with diabetes risk may be present at a much earlier stage in the pathogenesis of dysglycemia within the NGT range and that maintaining high adiponectin production might be protective of dysglycemia.

There are several explanations for the association between higher adiponectin and a lower risk of incident pre-diabetes/diabetes. It is well known that adiponectin is an adipokine that exerts a potent insulin-sensitizing effect.²³ However, the association between higher adiponectin and lower glycemia was not related to measures of insulin sensitivity/IR in young women of the present study. In mice, adiponectin mediates the metabolic effects of fibroblast growth factor 21,²⁴ which has recently been demonstrated to improve systemic insulin

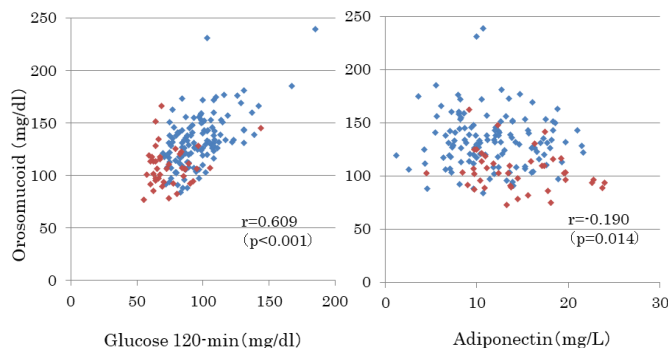


Figure 2 Scatter plots between orosomucoid and adiponectin and 120 min glucose. Red and blue circles: young Japanese women with and without postchallenge low glycemia, respectively.

Table 3 Multivariate logistic regression analyses for postload low glycemia as a dependent variable

Independent variables	OR	95% CI		P value
		Lower limit	Upper limit	
Orosomuroid	0.96	0.93	0.99	0.008
Adipose insulin resistance	0.85	0.63	1.16	0.305
Insulinogenic index	3.01	0.88	10.34	0.080
Adiponectin	1.14	1.03	1.26	0.009

Variables that showed significant difference between women with and without low glycemia were included as independent variables.

sensitivity by promoting the healthy expansion of subcutaneous adipose tissue.²⁵ In this context, it is noteworthy that subcutaneous fat evaluated by DXA-derived leg fat was positively associated with circulating adiponectin¹⁵ and inversely with postload glucose.²⁶ These findings may explain why lower glycemia was not related to measures of insulin sensitivity/IR in the present study. However, more work would need to be done for this issue to be clarified.

Studies have demonstrated that ORM and GlycA, in which ORM is one of the major acute phase proteins, were associated with higher PG during OGTT.^{12 13 27} In the present study, lower ORM was independently associated with postload low glycemia in young women. Therefore, the positive association of ORM with diabetes risk and vice versa may be present at a much earlier stage in the pathogenesis of dysglycemia within the NGT range. However, the biology underlying the association between serum ORM concentrations and postload glucose concentrations found in our previous¹³ and present study is not known.

The strength of the present study includes the homogeneous study population with few confounding factors, and the accurate and reliable measures of body composition by DXA. Several limitations of this study warrant consideration. The cross-sectional design complicates the drawing of causal inferences, and a single measurement of biochemical variables may be susceptible to short-term variation, which would bias the results toward the null. We used crude measures of insulin sensitivity/IR and insulin secretion, which may be less accurate. Statistical power was not calculated. As we studied young Japanese women only, the results may not be generalized to other gender, age populations, races or ethnicities.

In conclusion, higher adiponectin and lower ORM were associated with 70 or lower mg/dL of postload glucose, a possible inverse marker for dysglycemia, in young women independently of DXA-derived fat mass and distribution, insulin secretion and IR and other investigated markers of inflammation. Insulin-independent association of postload glycemia with ORM suggests an opportunity to discover insights into the mechanisms

of glucose dysmetabolism within NGT, although further research is needed.

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