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Inverse correlation between serum high-molecular-weight adiponectin and proinsulin level in a Japanese population: The Dynamics of Lifestyle and Neighborhood Community on Health Study

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Keywords

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ABSTRACT

Serum high-molecular-weight adiponectin (HMWA) has a positive correlation with insulin secretion in the Japanese population. To validate this correlation, we investigated the correlation between serum HMWA and proinsulin, a marker of β -cell dysfunction, in this population. A total of 488 participants (53.9% women) aged 35–79 years not taking oral hypoglycemic agents and/or insulin were enrolled. HMWA was significantly and inversely correlated with proinsulin adjusted for age and sex (partial regression coefficient $\beta = -0.37$; 95% confidence interval -0.46 to -0.28). When the participants were divided into two groups by median values of body mass index (23.2 kg/m^2), serum insulin ($4.3 \mu\text{U/mL}$) or homeostasis model assessment of insulin resistance (1.0), similar inverse correlations were observed adjusted for age and sex in both groups. Our results showed that the HMWA level was inversely correlated with the proinsulin level in a general Japanese population.

INTRODUCTION

Adiponectin is an adipocyte-derived secreted protein that acts like a hormone with insulin-sensitizing properties¹. Many previous studies have consistently reported that there is an inverse association between serum adiponectin levels and the presence of type 2 diabetes². Although the nature of the association between serum adiponectin levels and pancreatic β -cell function is controversial^{3–9}, our previous study in a Japanese population showed that serum high-molecular-weight adiponectin (HMWA) has a positive correlation with insulin secretion¹⁰.

Proinsulin is synthesized in pancreatic β -cells, and it is a precursor molecule for insulin and C-peptide¹¹. Increased proinsulin secretion could be a marker for β -cell dysfunction, although the exact mechanism behind this increase is

unknown¹². In fact, evidence has suggested that fasting proinsulin is the most sensitive marker that reflects glucose tolerance among the five estimation methods evaluating β -cell function in our previous study¹³.

In the current community-based study, to validate the positive correlation between serum HMWA and β -cell function, we examined the correlation between serum HMWA and proinsulin levels in a Japanese population.

METHODS

Study participants and data collection

In this cross-sectional study, the data from part of the Dynamics of Lifestyle and Neighborhood Community on Health Study (DOSANCO Health Study) were analyzed. Details regarding the DOSANCO Health Study have been described in our previous reports^{10,13}. A total 488 participants (53.9% women) aged

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35–79 years without oral hypoglycemic agents and/or insulin were enrolled¹⁰. This research design was approved by the Research Ethics Committee of the Faculty of Medicine, Hokkaido University (15-002 and 17-015), and written informed consent was obtained from each participant. Venous blood samples were collected at rest in the morning after overnight fasting, and some of them were shipped to a single laboratory to measure fasting plasma glucose (FPG) and glycated hemoglobin levels. Serum samples were stored at -80°C until insulin, C-peptide, HMWA and proinsulin levels were measured. FPG, glycated hemoglobin, insulin and C-peptide levels were measured using standard techniques, whereas HMWA and proinsulin levels were measured using a chemiluminescent enzyme immunoassay (Fujirebio Inc., Tokyo, Japan) and a radioimmunoassay (Millipore Corporation Inc., Burlington, MA, USA), respectively^{10,13}. The homeostasis model assessment of insulin resistance (HOMA-IR) was used as an indicator of insulin resistance¹⁴.

Statistical analysis

Anthropometric and biochemical parameters were compared among participants stratified according to HMWA quartiles. The significance of differences in anthropometric and biochemical characteristics was tested using one-way analysis of variance, χ^2 -test or Kruskal–Wallis test, as appropriate. Because the serum HMWA and proinsulin data represented skewed distributions, these values were normalized by natural logarithmic transformation. To examine the correlation between logarithmic transformed serum HMWA and logarithmic transformed proinsulin levels, univariate and multivariable linear regression analysis was carried out. Estimates included partial regression

coefficient (β) and 95% confidence interval (CI). To determine whether obesity, hyperinsulinemia and insulin resistance affected the correlation of interest, we carried out the analysis after the study participants were divided into two groups by the median values of body mass index, fasting serum insulin and HOMA-IR, respectively. In addition, a similar analysis was carried out after these participants were divided by the presence or absence of diabetes, defined as having a history of diabetes, FPG $\geq 126 \text{ mg/dL}$ and/or glycated hemoglobin $\geq 6.5\%$ ¹⁵. P -values <0.05 were considered to show statistical significance, and statistical analysis was carried out using JMP 10 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Table 1 shows anthropometric and biochemical characteristics of 488 study participants stratified according to HMWA quartiles. Body mass index, waist circumference, FPG, HOMA-IR, insulin, C-peptide and proinsulin were lower in higher HMWA groups.

The correlation between serum HMWA and proinsulin is shown in Table 2. In a univariate linear regression analysis, HMWA was significantly and inversely correlated with proinsulin. Furthermore, a multiple linear regression analysis showed that HMWA was inversely correlated with proinsulin after adjusted for age and sex. When these participants were divided into two groups by median values of body mass index (23.2 kg/m^2), serum insulin ($4.3 \mu\text{U/mL}$) or HOMA-IR (1.0), similar inverse correlations were observed adjusted for age and sex in both strata. Also, these inverse correlations were observed in both non-diabetic participants and diabetes patients.

Table 1 | Anthropometric and biochemical characteristics of 488 study participants

	Total participants	Serum HMWA				P -value
		1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	
<i>n</i>	488	122	121	123	122	
HMWA ($\mu\text{g/mL}$)	3.6 (2.3–5.5)	1.6 (1.2–2.0)	2.8 (2.6–3.2)	4.5 (4.0–4.8)	7.5 (6.2–9.6)	
Age (years)	57.9 \pm 12.5	55.3 \pm 11.7	57.0 \pm 12.6	57.7 \pm 13.0	61.8 \pm 11.8	<0.01
Sex (male/female)	225/263	96/26	69/52	41/82	19/103	<0.01
BMI (kg/m^2)	23.7 \pm 3.6	25.0 \pm 3.7	24.0 \pm 3.5	23.8 \pm 3.7	22.0 \pm 2.9	<0.01
Waist circumference (cm)	81.6 \pm 10.4	86.8 \pm 9.4	83.5 \pm 9.8	80.6 \pm 10.3	75.3 \pm 8.9	<0.01
FPG (mg/dL)	93 (86–100)	96 (89–109)	95 (86–101)	90 (85–99)	91 (84–98)	<0.01
HbA1c (%)	5.4 (5.2–5.7)	5.4 (5.2–6.0)	5.4 (5.3–5.7)	5.4 (5.1–5.7)	5.4 (5.2–5.7)	0.25
HOMA-IR	1.0 (0.6–1.6)	1.7 (1.0–2.6)	1.0 (0.7–1.5)	1.0 (0.6–1.4)	0.7 (0.5–1.0)	<0.01
Insulin ($\mu\text{U/mL}$)	4.3 (2.8–6.5)	6.6 (4.2–10.1)	4.4 (3.1–6.4)	4.1 (2.9–5.9)	3.0 (2.1–4.2)	<0.01
C-peptide (ng/mL)	1.2 (0.9–1.7)	1.7 (1.2–2.2)	1.2 (1.0–1.7)	1.1 (0.9–1.5)	1.0 (0.8–1.2)	<0.01
Proinsulin (pmol/L)	9.0 (6.7–14.1)	13.7 (8.8–19.9)	9.2 (7.2–14.0)	8.4 (6.4–12.9)	7.5 (5.4–9.5)	<0.01

Values are expressed as the mean \pm standard deviation or median (interquartile range). Data are presented for the entire group and for participants grouped according to their serum high-molecular-weight adiponectin (HMWA) levels. One-way analysis of variance, Kruskal–Wallis test or χ^2 -test were used to compare each parameter among the serum HMWA groups. BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HMWA, high-molecular-weight adiponectin; HOMA-IR, homeostasis model assessment of insulin resistance.

Table 2 | Correlation of serum high-molecular-weight adiponectin (logarithmic transformed) with proinsulin (logarithmic transformed)

	Crude		Age and sex-adjusted	
	β (95% CI)	P-value	β (95% CI)	P-value
Total participants (<i>n</i> = 488)	-0.36 (-0.44, -0.29)	<0.01	-0.37 (-0.46, -0.28)	<0.01
Below median value of BMI (<i>n</i> = 244)	-0.19 (-0.29, -0.10)	<0.01	-0.24 (-0.35, -0.13)	<0.01
Median value of BMI, ≥ 23.2 kg/m ² (<i>n</i> = 244)	-0.37 (-0.49, -0.25)	<0.01	-0.33 (-0.47, -0.19)	<0.01
Below median value of insulin (<i>n</i> = 242)	-0.10 (-0.19, -0.02)	0.02	-0.14 (-0.24, -0.03)	<0.01
Median value of insulin, ≥ 4.3 kg/m ² (<i>n</i> = 246)	-0.33 (-0.45, -0.20)	<0.01	-0.26 (-0.40, -0.12)	<0.01
Below median value of HOMA-IR (<i>n</i> = 244)	-0.07 (-0.15, 0.02)	0.12	-0.11 (-0.20, -0.02)	0.02
Median value of HOMA-IR, ≥ 1.0 (<i>n</i> = 244)	-0.35 (-0.46, -0.23)	<0.01	-0.26 (-0.40, -0.13)	<0.01
Without diabetes (<i>n</i> = 441)	-0.30 (-0.37, -0.23)	<0.01	-0.32 (-0.41, -0.24)	<0.01
With diabetes (<i>n</i> = 47)	-0.52 (-0.80, -0.24)	<0.01	-0.36 (-0.68, -0.04)	0.03

A linear regression model was used to test the association between serum high-molecular-weight adiponectin (logarithmic transformed) and proinsulin (logarithmic transformed). β , partial regression coefficient; BMI, body mass index; CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance.

DISCUSSION

The present study showed that HMWA levels were inversely correlated with those of proinsulin in a general Japanese population. Given that fasting proinsulin is a marker of β -cell dysfunction, the inverse correlation we observed was consistent with the positive correlation between the HMWA and disposition index, as shown in our previous study¹⁰. Those results suggest that HMWA has a favorable effect on pancreatic β -cells, presumably supported by the data using adiponectin knockout mice and globular domain adiponectin transgenic *ob/ob* mice^{16,17}. Furthermore, it has been reported that treatment with adiponectin enhanced glucose-stimulated insulin secretion, and increased the expression levels of genes involved in β -cell function and maintenance of β -cell viability, including *Pdx1* and *Mafa*¹⁸.

In human studies, adiponectin was positively correlated with the insulin secretion-sensitivity index that represents pancreatic β -cell function in gestational diabetes⁴. A similar correlation was observed in young people with type 2 diabetes⁵. Additionally, adiponectin levels inversely correlated with fasting proinsulin in adolescents⁶. These studies support the present results. In contrast, a significant correlation was not observed between adiponectin and β -cell function^{7–9}. These inconsistent results could be due to limited or biased characteristics of participants, a relatively small sample size, or use of total adiponectin.

Some reports have proposed that the proinsulin : C-peptide ratio is a sensitive biomarker of β -cell dysfunction^{19,20}. Therefore, we investigated the correlation between HMWA level and this ratio. A significant inverse correlation was observed between HMWA level and the proinsulin : C-peptide ratio (β = -0.08; *P* = 0.03). This result provides further support for the present results, showing that HMWA level is inversely associated with β -cell dysfunction.

The strengths of the present study were that this was a population-based study and the sample size was larger than

that in the abovementioned reports. Another strength was that we measured the HMWA levels, because HMWA is considered to be the most active form of adiponectin²¹. In contrast, the limitation of the present study was its cross-sectional design, necessitating cautious interpretation of causality. Another limitation was that all participants in the present study were Japanese. The pathophysiological mechanisms of diabetes, including insulin secretion and insulin resistance, differ between Japanese and white individuals²². Therefore, whether the present results are applicable to non-Japanese patients remains unclear.

In conclusion, the HMWA level was inversely correlated with the proinsulin level in a general Japanese population.

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DISCLOSURE

The authors declare no conflict of interest.

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