HOKKAIDO UNIVERSITY

Title	Serum adiponectin and insulin secretion : A direct or inverse association?
Author(s)	Nakamura, Akinobu; Miyoshi, Hideaki; Ukawa, Shigekazu et al.
Citation	Journal of diabetes investigation, 9(5), 1106-1109 https://doi.org/10.1111/jdi.12821
Issue Date	2018-09
Doc URL	https://hdl.handle.net/2115/71862
Rights(URL)	https://creativecommons.org/licenses/by-nc/4.0/
Type	journal article
File Information	Nakamura_et_al-2018-Journal_of_Diabetes_Investigation.pdf

Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
SHORT REPORT

Serum adiponectin and insulin secretion: A direct or inverse association?

Akinobu Nakamura[1]*, Hideaki Miyoshi[1], Shigekazu Ukawa[2], Koshi Nakamura[2], Takafumi Nakagawa[3], Yasuo Terauchi[4], Akiko Tamakoshi[2], Tatsuya Atsumi[1]

[1]Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine, [2]Department of Public Health, Hokkaido University Graduate School of Medicine, [3]The Hokkaido Centre for Family Medicine, Sapporo, and [4]Department of Endocrinology and Metabolism, Graduate School of Medicine, Yokohama City University, Yokohama, Japan

Keywords
Adiponectin, Disposition index, Insulin secretion

***Correspondence**
Akinobu Nakamura
Tel.: +81-11-706-5915
Fax: +81-11-706-7710
E-mail address:
akinbo@tim.hi-ho.ne.jp

J Diabetes Investig 2018; 9: 1106–1109

doi: 10.1111/jdi.12821

ABSTRACT

We investigated the association between serum high molecular weight (HMW) adiponectin and insulin secretion in a population-based study, with or without adjustment for insulin sensitivity. A total of 488 participants (263 women) were included in the present study. Insulin secretion was estimated using the homeostasis model assessment of β-cell function ± adjustment for insulin resistance using the disposition index. Multivariate analysis showed that HMW adiponectin was significantly and inversely associated with homeostasis model assessment of β-cell function (partial regression coefficient –0.19, 95% confidence interval –0.28, –0.10, $P < 0.0001$). However, HMW adiponectin was significantly and positively associated with disposition index (partial regression coefficient 0.15, 95% confidence interval 0.06, 0.24, $P = 0.0016$). The present study showed that a positive association between HMW adiponectin levels and insulin secretion evaluated using an index incorporating adjustment for insulin resistance was identified, and vice versa using an index that did not adjust for insulin resistance.

INTRODUCTION

Human type 2 diabetes is characterized by two major features: peripheral insulin resistance (IR) and impaired insulin secretion by pancreatic β-cells. With regard to IR, a Mendelian randomization study showed that genetically determined adiponectin levels were positively associated with insulin sensitivity evaluated by euglycemic hyperinsulinemic clamp[1], and it has been reported that associations with IR are slightly stronger for the high molecular weight (HMW) adiponectin than total adiponectin[2]. However, it has not been clarified whether adiponectin levels are directly or inversely associated with insulin secretion. In the present study, we investigated the association between HMW adiponectin levels and insulin secretion in a Japanese population-based study, with a specific focus on the effect of using indices of insulin secretion with or without adjustment for IR.

METHODS

Study design and participants

In the present cross-sectional study, we analyzed data from the Dynamics of Lifestyle and Neighborhood Community on Health Study. This was a community-based survey carried out in Suttu, Hokkaido, Japan, during 2015. A total of 2,100 participants (977 men and 1,123 women; 79.6% of all residents) completed the survey in the form of a questionnaire. Of the participants, 729, aged between 35 and 79 years, were also asked to provide blood samples and 545 participants (300 women) complied. Of these 545 participants, 57 were excluded due to missing data on HMW adiponectin or insulin levels ($n = 4$), or their use of insulin and/or oral hypoglycemic agents ($n = 53$). Consequently, data from 488 participants (263 women) were analyzed in the present study. The study design was approved by the Ethical Board of Hokkaido University School of Medicine (15-002), and signed informed consent was obtained from all participants.

Study definition and data collection

Venous blood samples were collected after overnight fasting and shipped to a single laboratory to measure fasting plasma glucose (FPG), insulin, C-peptide and glycated hemoglobin levels using standard techniques. HMW adiponectin levels were measured using a chemiluminescent enzyme immunoassay (Fujirebio Inc., Tokyo, Japan). Participants were considered to be diabetic if they had a previous history of diabetes, FPG ≥7.0 mmol/L or glycated hemoglobin ≥6.5% (47.5 mmol/mol).

Received 4 September 2017; revised 11 January 2018; accepted 12 February 2018

© 2018 The Authors. Journal of Diabetes Investigation published by Asian Association for the Study of Diabetes (AASD) and John Wiley & Sons Australia, Ltd
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

IR and insulin secretion were estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) and homeostasis model assessment of β-cell function (HOMA-β%), respectively[3]. For one set of analyses, insulin secretion was adjusted for IR using the disposition index (DI), defined as the ratio of HOMA-β% to HOMA-IR[4].

Statistical analysis

Because the serum HMW adiponectin, HOMA-β, insulin, C-peptide and DI data showed skewed distributions, the values for these parameters were normalized by natural logarithmic transformation. Univariate linear regression analysis was carried out to examine the association between serum HMW adiponectin (ln-transformed) and HOMA-β% (ln-transformed), insulin (ln-transformed), C-peptide (ln-transformed) and DI (ln-transformed). Multivariable linear regression analysis was used to calculate coefficients after adjustment for age, sex and body mass index (BMI). Estimates included partial regression coefficient (β), 95% confidence interval (CI) and corresponding *P*-values. All tests were two-sided, and $P < 0.05$ was considered to be statistically significant. Statistical analysis was carried out using JMP 10 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The profile and biochemical parameters of participants according to the HMW adiponectin quartiles are shown in Table 1. Age and the proportion of women were positively associated with HMW adiponectin quartile, whereas BMI, waist circumference, FPG and HOMA-IR showed significant inverse associations. HOMA-β%, insulin and C-peptide were inversely associated with HMW adiponectin quartile. Unexpectedly, DI, an index of insulin secretion with adjustment for IR, showed a significant positive association.

Table 2 shows the association between HMW adiponectin and indices of insulin secretion. Serum HMW adiponectin was significantly and inversely associated with HOMA-β% in a univariate linear regression analysis. Additionally, a multiple linear regression analysis showed that HMW adiponectin was inversely associated with HOMA-β% adjusted for age, sex and BMI. When the participants were classified into younger (<65 years-of-age) and elderly groups (≥65-years-of-age), HMW adiponectin was inversely associated with HOMA-β% adjusted for age, sex and BMI in both groups. Furthermore, in participants without diabetes, HMW adiponectin level was inversely associated with HOMA-β% adjusted for age, sex and BMI. When insulin secretion was estimated using fasting insulin or C-peptide levels, similar results were obtained. Conversely, HMW adiponectin was significantly and positively associated with DI both in univariate and multiple linear regression analyses. These positive associations were observed in all the above subgroups (younger, elderly and non-diabetic groups).

DISCUSSION

In the current study, we found that serum HMW adiponectin was inversely associated with HOMA-β%, being consistent with previous reports[5,6]. However, it would not be appropriate to evaluate insulin secretion without taking variability in IR into consideration, because circulating insulin levels are influenced not only by the capacity for insulin secretion, but also by IR. DI is thought to reflect the capacity for insulin secretion

Table 1 | Clinical and biochemical characteristics of 488 study participants

	Total participants	Serum HMW adiponectin				*P*-value
		1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	
n	488	122	121	123	122	
HMW adiponectin (μg/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 ± 12.5	55.3 ± 11.7	57.0 ± 12.6	57.7 ± 13.0	61.8 ± 11.8	0.0005
Sex (male/female)	225/263	96/26	69/52	41/82	19/103	<0.0001
BMI (kg/m^2)	23.7 ± 3.6	25.0 ± 3.7	24.0 ± 3.5	23.8 ± 3.7	22.0 ± 2.9	<0.0001
Waist circumference (cm)	81.6 ± 10.4	86.8 ± 9.4	83.5 ± 9.8	80.6 ± 10.3	75.3 ± 8.9	<0.0001
FPG (mmol/L)	5.2 (4.8–5.6)	5.3 (5.0–6.1)	5.3 (4.8–5.6)	5.0 (4.7–5.5)	5.1 (4.7–5.4)	0.0001
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)	0.2479
HbA1c (mmol/mol)	36 (33–39)	36 (33–42)	36 (34, 39)	36 (32–39)	36 (33–39)	0.2479
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)	<0.0001
HOMA-β%	52 (34–78)	63 (46–107)	53 (35–75)	53 (38–78)	37 (27–54)	<0.0001
Insulin (pmol/L)	30 (19–45)	46 (29–70)	31 (22–44)	28 (20–41)	21 (15–29)	<0.0001
C-peptide (nmol/L)	0.4 (0.3–0.6)	0.6 (0.4–0.7)	0.4 (0.3–0.6)	0.4 (0.3–0.5)	0.3 (0.3–0.4)	<0.0001
Disposition index	52 (39–74)	47 (29–62)	48 (38–74)	60 (41–78)	57 (43–83)	0.0001

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

© 2018 The Authors. Journal of Diabetes Investigation published by AASD and John Wiley & Sons Australia, Ltd

Table 2 | Association of serum high molecular weight adiponectin (ln-transformed) with indices of insulin secretion (ln-transformed)

	Crude		Adjusted†	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value
All participants				
ln(HOMA-β%)	−0.27 (−0.35, −0.19)	<0.0001	−0.19 (−0.28, −0.10)	<0.0001
ln(Insulin)	−0.41 (−0.49, −0.33)	<0.0001	−0.29 (−0.38, −0.21)	<0.0001
ln(C-peptide)	−0.29 (−0.34, −0.24)	<0.0001	−0.20 (−0.25, −0.14)	<0.0001
ln(Disposition index)	0.19 (0.11, 0.27)	<0.0001	0.15 (0.06, 0.24)	0.0016
Participants aged <65 years‡				
ln(HOMA-β%)	−0.22 (−0.32, −0.12)	<0.0001	−0.16 (−0.27, −0.05)	0.0050
ln(Insulin)	−0.38 (−0.49, −0.27)	<0.0001	−0.24 (−0.35, −0.13)	<0.0001
ln(C-peptide)	−0.29 (−0.36, −0.23)	<0.0001	−0.19 (−0.26, −0.12)	<0.0001
ln(Disposition index)	0.22 (0.13, 0.31)	<0.0001	0.12 (0.02, 0.22)	0.0246
Participants aged ≥65 years§				
ln(HOMA-β%)	−0.31 (−0.46, −0.16)	<0.0001	−0.23 (−0.39, −0.06)	0.0081
ln(Insulin)	−0.49 (−0.62, −0.35)	<0.0001	−0.36 (−0.50, −0.22)	<0.0001
ln(C-peptide)	−0.31 (−0.40, −0.23)	<0.0001	−0.19 (−0.28, −0.10)	<0.0001
ln(Disposition index)	0.24 (0.10, 0.39)	0.0014	0.19 (0.01, 0.38)	0.0380
Subjects without diabetes¶				
ln(HOMA-β%)	−0.32 (−0.40, −0.23)	<0.0001	−0.24 (−0.33, −0.15)	<0.0001
ln(Insulin)	−0.41 (−0.49, −0.32)	<0.0001	−0.29 (−0.38, −0.20)	<0.0001
ln(C-peptide)	−0.28 (−0.34, −0.23)	<0.0001	−0.20 (−0.25, −0.14)	<0.0001
ln(Disposition index)	0.12 (0.06, 0.18)	0.0002	0.07 (0.00, 0.14)	0.0441

A linear regression model was used to test the association between serum high molecular weight (HMW) adiponectin (ln-transformed) and indices of insulin secretion (ln-transformed): †adjusted for age, sex and body mass index. ‡n = 321, §n = 167, ¶n = 441. β, partial regression coefficient; CI, confidence interval; HOMA-β%, homeostasis model assessment of β-cell function.

adjusted for IR and thus to provide a useful measure of pancreatic β-cell function. Therefore, we further investigated the association between HMW adiponectin level and DI, and found that these parameters were significantly and positively associated each other. When we examined the association between serum HMW adiponectin and insulin secretion in the participants classified the participants into younger and elderly groups, similar results were obtained. Thus, the above association was observed even in the elderly.

In vivo and *in vitro* experimental studies have suggested that the major effect of adiponectin on the pancreas includes the promotion of β-cell function and survival[7]. As one of the mechanisms, adiponectin induces activation of peroxisome proliferator-activated γ receptors, which enhances insulin content and has positive effects on glucose-stimulated insulin secretion[8]. Regarding HMW adiponectin, although it remains unknown how HMW adiponectin could increase insulin secretion capacity, it has been recently reported that HMW adiponectin positively correlated with β-cell function after adjustment for age, sex and BMI in the The Treatment Options for type 2 Diabetes in Adolescents and Youth study[9]. In the present study, when insulin secretion was evaluated using HOMA-β%, without adjustment by IR, the association between HMW adiponectin levels and insulin secretion was paradoxical with the results of the above experimental studies. However, if DI as an IR-adjusted insulin secretion index was utilized, the association was consistent with these results. Furthermore, the positive association shown in the present study is consistent with previous observations that low serum adiponectin is associated with the future development of type 2 diabetes[10,11], and the concept that hypoadiponectinemia might not only be a marker of IR, but also of β-cell dysfunction, both contributing to the pathophysiology of type 2 diabetes[12]. Therefore, when insulin secretion is evaluated in epidemiological studies, it is important to use indices that correct for the degree of IR.

In the present study, DI was calculated using data obtained only from fasting samples. As previously stated, these results should be interpreted with caution[4], because DI should be calculated using glucose and insulin levels measured during intravenous or oral glucose tolerance tests[13]. This is one of the major limitations of the present study, and therefore further investigations are required to validate the identified association using the oral glucose tolerance test to calculate DIs. Another limitation of the present study was its cross-sectional design, necessitating that caution should be exercised with regard to any interpretation of causality. Furthermore, HOMA-IR and HOMA-β% are not reliable measurements in participants with moderate or severe diabetes. However, our sensitivity analysis also showed a significant association of interest in participants without diabetes based on only FPG or glycated hemoglobin levels; some participants with diabetes were grouped into the non-diabetes groups. Finally, the study participants were limited to residents of one rural

© 2018 The Authors. Journal of Diabetes Investigation published by AASD and John Wiley & Sons Australia, Ltd

community of Japan. The socioeconomic status and lifestyle of these participants might have influenced their health status including the parameters measured.

In conclusion, a positive association was observed between serum HMW adiponectin and insulin secretion, evaluated using an index that included adjustment for IR, in a Japanese population-based study. This finding implies that caution should be exercised in the interpretation of measures describing the insulin secretion of study participants, depending on whether or not this parameter has been adjusted for the degree of IR present.

ACKNOWLEDGMENTS

We express special gratitude to all the participants from Suttu, Hokkaido, Japan. This work was supported by Integration Research for Agriculture and Interdisciplinary Fields (No. 14538261) and the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number JP26670322.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Gao H, Fall T, van Dam RM, *et al*. Evidence of a causal relationship between adiponectin levels and insulin sensitivity: a Mendelian randomization study. *Diabetes* 2013; 62: 1338–1344.
2. Seino Y, Hirose H, Saito I, *et al*. High molecular weight multimer form of adiponectin as a useful marker to evaluate insulin resistance and metabolic syndrome in Japanese men. *Metabolism* 2007; 56: 1493–1499.
3. Matthews DR, Hosker JP, Rudenski AS, *et al*. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28: 412–419.
4. Ahuja V, Kadowaki T, Evans RW, *et al*. Comparison of HOMA-IR, HOMA-β% and disposition index between US white men and Japanese men in Japan: the ERA JUMP study. *Diabetologia* 2015; 58: 265–271.
5. Li Y, Yatsuya H, Iso H, *et al*. Inverse relationship of serum adiponectin concentration with type 2 diabetes mellitus incidence in middle-aged Japanese workers: six-year follow-up. *Diabetes Metab Res Rev* 2012; 28: 349–356.
6. Deichgræber P, Witte DR, Møller HJ, *et al*. Soluble CD163, adiponectin, C-reactive protein and progression of dysglycaemia in individuals at high risk of type 2 diabetes mellitus: the ADDITION-PRO cohort. *Diabetologia* 2016; 59: 2467–2476.
7. Turer AT, Scherer PE. Adiponectin: mechanistic insights and clinical implications. *Diabetologia* 2012; 55: 2319–2326.
8. Rao JR, Keating DJ, Chen C, *et al*. Adiponectin increases insulin content and cell proliferation in MIN6 cells via PPARγ-dependent and PPARγ-independent mechanisms. *Diabetes Obes Metab* 2012; 14: 983–989.
9. Arslanian S, El Ghormli L, Bacha F, *et al*. Adiponectin, insulin sensitivity, β-cell function, and racial/ethnic disparity in treatment failure rates in TODAY. *Diabetes Care* 2017; 40: 85–93.
10. Li S, Shin HJ, Ding EL, *et al*. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2009; 302: 179–188.
11. Nakashima R, Kamei N, Yamane K, *et al*. Decreased total and high molecular weight adiponectin are independent risk factors for the development of type 2 diabetes in Japanese–Americans. *J Clin Endocrinol Metab* 2006; 91: 3873–3877.
12. Bacha F, Saad R, Gungor N, *et al*. Adiponectin in youth: relationship to visceral adiposity, insulin sensitivity, and beta-cell function. *Diabetes Care* 2004; 27: 547–552.
13. Utzschneider KM, Prigeon RL, Faulenbach MV, *et al*. Oral disposition index predicts the development of future diabetes above and beyond fasting and 2-h glucose levels. *Diabetes Care* 2009; 32: 335–341.

© 2018 The Authors. Journal of Diabetes Investigation published by AASD and John Wiley & Sons Australia, Ltd