Circulating adiponectin levels and risk of type 2 diabetes in the Japanese

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INTRODUCTION

The number of diabetic patients has greatly increased in the past few decades in the world including Asia.1,2 Diabetes requires long-term medical care for glycemic control and decreases quality of life owing to complications such as retinopathy, neuropathy and nephropathy, leading to a large increase in medical expenditure.3 Additionally, diabetes increases risk of life-threatening diseases including cardiovascular disease and cancer.4 The prevention of diabetes is thus one of the priority issues.

Experimental and epidemiologic evidence has accumulated that supports a beneficial role of adiponectin, a major cytokine secreted from adipocyte, in glucose metabolism. Mechanistic studies show that adiponectin improves insulin sensitivity and inflammation,5,6 important mechanisms in the development of type 2 diabetes. In humans, several prospective studies have consistently shown a lower risk of type 2 diabetes among those with higher baseline levels of circulating adiponectin.7 However, some important issues remain to be solved. Data are conflicting as to the attenuation of adiponectin–type 2 diabetes association after adjusting for baseline levels of glucose8–10 and insulin resistance,11,12,13 and few studies adjusted for precisely measured visceral fat mass.14,15 Such information would be useful when inferring the major underlying conditions linking adiponectin to type 2 diabetes or selecting variables in the prediction of diabetes risk. Further, data are limited and conflicting whether the association between adiponectin and type 2 diabetes risk is modified by levels of obesity11,17,20 and insulin resistance;18,19 to our knowledge, no data are available for visceral fat.

To address these issues, we examined prospectively the association between serum adiponectin levels and risk of type 2 diabetes among employees of a large company in Japan while adjusting for a range of obesity and glucose metabolism markers, including visceral fat area (VFA), measured using a computed tomography (CT), and homeostasis model assessment of insulin resistance (HOMA-IR). We also assessed the above associations with stratification by these variables.

SUBJECTS AND METHODS

Study design and participants

The Hitachi Health Study is an ongoing study among employees and their spouses who participated in a comprehensive health examination at Hitachi Health Care Center (Hitachi, Japan).21 Of 17,606 screening examinees between April 2008 and March 2009 (baseline of the present analysis), 6996 participants underwent a CT and agreed to donate blood specimen for the study. Of these, 6612 subjects received health examination in fasting condition (fasted at least 12 h) and had data on biochemical data including serum adiponectin; were free of diabetes at baseline; and received health screening in 2011. Multiple logistic regression analysis was used to examine the association between adiponectin and incidence of diabetes among overall subjects, as well as subgroups. Stratified analyses were carried out according to variables including visceral fat area (VFA).

RESULTS: During 3 years of follow-up, 217 diabetic cases were newly identified. Of these, 87% had a prediabetes at baseline. Serum adiponectin level was significantly, inversely associated with incidence of diabetes, with odds ratios (95% confidence interval) adjusted for age, sex, family history, smoking, alcohol drinking, physical activity and body mass index (BMI) for the lowest through highest quartile of adiponectin of 1 (reference), 0.79 (0.55–1.12), 0.60 (0.41–0.88) and 0.40 (0.25–0.64), respectively (P-value for trend < 0.01). This association was materially unchanged with adjustment for VFA instead of BMI. Further after adjustment for both homeostasis model assessment of insulin resistance and hemoglobin A1c, however, the association became statistically nonsignificant (P-value for trend = 0.18). Risk reduction associated with higher adiponectin levels was observed in both participants with and without obesity or insulin resistance at baseline.

CONCLUSIONS: Results suggest that higher levels of circulating adiponectin are associated with a lower risk of type 2 diabetes, independently of overall and intra-abdominal fat deposition, and that adiponectin may confer a benefit in both persons with and without insulin resistance.

Received 8 April 2014; revised 22 June 2014; accepted 10 July 2014
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RESULTS

During the 3-year follow-up, a total of 214 patients were newly identified as having diabetes. Of these, 87% of patients were in a prediabetic condition at baseline (FPG \( \geq 110 \) mg dl\(^{-1}\) (6.1 mmol l\(^{-1}\)) and/or HbA1c \( \geq 6.0 \) (42 mmol mol\(^{-1}\)). Table 1 compares the baseline characteristics of study participants between those who developed diabetes and those who did not. Compared with participants who had been free of diabetes through the study period, patients who developed diabetes were older, had a higher mean of BMI, VFA, waist circumference, fasting plasma glucose, HbA1c, fasting insulin and HOMA-IR, but had a lower mean of serum adiponectin levels.

Table 2 shows association between adiponectin concentrations and 3-year incidence of type 2 diabetes. In the basic model with adjustment for sex, age, family history of diabetes, smoking, alcohol use and physical activity (Model 1), higher adiponectin at baseline was significantly associated with lower risk of type 2 diabetes; OR (95% CI) of type 2 diabetes for the lowest through highest quartiles of adiponectin levels was 1 (reference), 0.76 (0.53–1.08), 0.54 (0.37–0.79) and 0.33 (0.21–0.52), respectively (P-values for trend < 0.01). The association was only slightly attenuated after further adjusting for BMI (Model 2) or VFA (Model 3); ORs for the highest quartile were around 0.4. The odds of diabetes in the highest quartile of adiponectin was somewhat elevated after additional adjustment for either baseline HOMA-IR (Model 4: OR = 0.53) or HbA1c (Model 5: OR = 0.56), but remained statistically significant. In the full model adjusting for all variables including HOMA-IR and HbA1c (Model 6), there was a sizable attenuation in association, which became statistically nonsignificant (OR for the highest quartile = 0.69; P-value for trend = 0.18). Table 3 shows results of analyses stratified by BMI, VFA, HOMA-IR and HOMA-β. A statistically significant, inverse association between adiponectin and type 2 diabetes risk was observed in all subgroups. The inverse association seems to be stronger in obese than non-obese participants (P-value for interaction by BMI

Table 1. Characteristics of study subjects at baseline

|                | Subjects without diabetes incidence | Subjects with diabetes incidence |
|----------------|-------------------------------------|---------------------------------|
| Number         | 4377                                | 214                             |
| Sex (% women)  | 53.4                                | 56.6                            |
| Age (years)    | 58.1 (8.9)                          | 62.8 (8.9)*                     |
| Family history of diabetes (%) | 16.7 | 22.9*                           |
| Smoking (%)    |                                     |                                 |
| Never          | 35.2                                | 32.2                            |
| Past           | 31.8                                | 35.0                            |
| Current        | 32.9                                | 32.7                            |
| Alcohol use (%)|                                     |                                 |
| Nondrinker     | 28.5                                | 26.6                            |
| Drinking < 1 go per day | 39.8 | 38.8                            |
| Drinking 1–9 go per day | 22.1 | 22.9                            |
| Drinking ≥ 2 go per day | 9.6 | 11.7                            |
| Physical activity, % >400 MET-min per week | 49.2 | 51.4 |
| Body mass index (kg m\(^{-2}\)) | 23.8 (2.9) | 24.8 (3.4)**                   |
| Waist circumference (cm) | 86.0 (12.9) | 88.4 (8.8)**                   |
| Visceral fat areas (cm\(^2\)) | 115 (52) | 137 (53)**                     |
| Fasting glucose (mg dl\(^{-1}\)) | 99.7 (7.9) | 112.5 (7.9)**                  |
| HOMA-β, homeostasis model assessment of insulin resistance | 0.48 (0.31) | 0.63 (0.41)**                  |
| Fasting insulin (μU ml\(^{-1}\)) | 5.8 (3.5) | 8.1 (6.1)**                    |
| HOMA-IR         | 1.46 (0.94)                         | 2.26 (1.71)**                   |
| HOMA-β          | 5.76 (3.26)                         | 5.93 (4.58)                     |
| Adiponectin (μg ml\(^{-1}\)) | 7.99 (4.09) | 6.82 (3.57)**                  |

Abbreviations: HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; MET, metabolic equivalent. Values are mean (s.d.), unless stated otherwise; *P < 0.05 and **P < 0.01. *Physical activity during leisure time and on commuting to work.
Percentage (%) Incidence Odds ratio (95% confidence interval)° P-value for trend P-value for interaction

Body mass index (kg m−2) % T1 b T2 T3
< 25 3.8 1 1.05 (0.68, 1.64) 0.53 (0.32, 0.88) 0.01
≥ 25 6.5 1 0.66 (0.41, 1.05) 0.30 (0.15, 0.62) < 0.01 0.03

Visceral fat area°
Low 3.4 1 0.99 (0.62, 1.59) 0.47 (0.28, 0.81) < 0.01
High 7.1 1 0.78 (0.51, 1.19) 0.43 (0.22, 0.83) 0.01 > 0.2

HOMA-IR°
Low 3.1 1 0.83 (0.51, 1.36) 0.56 (0.33, 0.96) 0.03
High 7.7 1 0.98 (0.65, 1.49) 0.43 (0.22, 0.81) 0.03 > 0.2

HOMA-β°
Low 5.4 1 0.74 (0.43, 1.29) 0.44 (0.25, 0.79) < 0.01
High 4.3 1 0.82 (0.56, 1.20) 0.27 (0.15, 0.49) < 0.01 0.12

Abbreviations: HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance. °Adjusted for sex, age, family history of diabetes, smoking, alcohol drinking and physical activity. bTertile of adiponectin (µg ml−1): T1, < 5.7; T2, 5.7–8.4; T3, ≥ 8.5. °Definition (cutoff) of ‘Low’ group: lower two-thirds for visceral fat area (138 cm2), HOMA-IR (1.61) and lower one-third for HOMA-β (40.1).

category = 0.03), although OR in the highest tertile of adiponectin was significantly decreased in both groups.

Incidence proportion of diabetes much differ according to baseline glucose level: 14.7% among those with an FPG ≥ 110 mg dl−1 (6.1 mmol l−1) and/or HbA1c ≥ 6.0% (42 mmol mol−1), a status strongly predictive of definite progression to diabetes,24 and 0.8% among those without prediabetes. Of patients who developed diabetes during the follow-up, 87% were in prediabetic state at baseline. Among subjects without prediabetes at baseline, OR (95% CI) of type 2 diabetes for the lowest through highest tertile of adiponectin levels was 1 (reference), 1.06 (0.41–2.78), 1.08 (0.41–2.89), respectively (P-value for trend > 0.2).

**DISCUSSION**

In this large, prospective study among a Japanese population, we found that baseline serum adiponectin concentrations were statistically significantly, inversely associated with risk of type 2 diabetes during 3 years. This association persisted even after adjusting for known risk factors of type 2 diabetes (age, sex, family history of diabetes, smoking, alcohol drinking, physical activity, BMI) or precise measure of abdominal obesity (CT-assessed VFA) instead of BMI. After additional adjustment for both HOMA-IR and HbA1c, however, the association was attenuated and became statistically nonsignificant.

Numerous studies to date have consistently reported a lower risk of type 2 diabetes in individuals with higher circulating adiponectin levels. In a meta-analysis of prospective studies on this issue,7 the inverse association was shown to be consistent across studies with diverse populations that varied in several methodologic aspects, including adiponectin measurement, diagnostic procedure of diabetes, length of follow-up and confounding variables considered, giving a strong credibility for a protective role of adiponectin against the development of type 2 diabetes. In the present study, nearly 90% of patients who developed diabetes during follow-up had in prediabetic condition...
an FPG $\geq 110$ mg dL$^{-1}$ (6.1 mmol L$^{-1}$) and/or HbA1c $\geq 6.0$ (42 mmol/mol$^{-1}$) at baseline. Thus, the present study provides data to support a protective role of adiponectin mainly in the progression from prediabetes to diabetes.

It is well known that circulating adiponectin concentrations decrease with increasing levels of obesity, which may largely account for the association between this adipokine and diabetes risk. In the present study, the association between adiponectin levels and diabetes risk was materially unchanged after adjustment for BMI, a finding compatible with those in most previous reports. Moreover, the adjustment for CT-assessed abdominal fat area, which is more closely associated with adiponectin levels than subcutaneous fat, had little impact on the association between adiponectin and diabetes risk, a finding compatible with those in a few previous studies that measured abdominal fat levels using CT.

These results suggest that neither systemic nor regional fat deposition can fully explain the inverse association between adiponectin and type 2 diabetes risk.

The major, hypothesized role of adiponectin against impairment of glucose metabolism is its favorable effect on insulin sensitivity. Mechanistic studies show that adiponectin improves insulin sensitivity by stimulating glucose utilization and fatty acid oxidation in the skeletal muscle and liver through improving AMP-activated protein kinase. In the present study, the odds of diabetes in the highest quartile of adiponectin was modestly changed after adjustment for either baseline HOMA-IR (Model 4: OR = 0.50, 95% CI 0.39–0.69) or glycemic marker (glucose or HbA1c). These findings are compatible with the hypothesized protective role of adiponectin against type 2 diabetes (i.e., lowering blood glucose through improving insulin sensitivity). Besides the etiologic importance of adiponectin, however, the measurement of this adipokine may not significantly improve predictive ability once data on traditional markers of glucose metabolism are available.

Hivert et al. reported a decreased risk of type 2 diabetes associated with higher adiponectin in insulin-resistant but not in insulin-sensitive individuals in two cohorts, although the interaction was statistically significant in one of these cohorts. Similarly, in a 4-year follow-up study of older British men, Wannamethee et al. found that risk of type 2 diabetes associated with higher adiponectin levels was decreased among obese participants but not among non-obese participants. In the present study, although the association was slightly stronger among obese than non-obese participants, diabetes risk in the highest tertile group was decreased in both those with higher and lower HOMA-IR and in both obese and non-obese participants. The inconsistency between the previous and present studies may be ascribed, at least in part, to lower capacity of people of East Asian origin than non-Hispanic whites to secrete insulin. Even modest insulin resistance may confer diabetes risk in Japanese, who in turn might recognize greater benefit from improving insulin sensitivity by maintaining higher level of adiponectin. Alternatively, the differential association may be due to chance. In fact, two other reports did not find a significant difference in association by BMI level.

The strengths of the present study include a large number of participants, prospective design and the adjustment for known and potential confounders. As regards ascertainment of diabetes, most previous studies on this issue relied on fasting glucose and/or self-reported diabetes, whereas the present study additionally used HbA1c to exclude diabetes patients at baseline as well as to diagnose diabetes incidence at the follow-up. The present study also has some limitations. First, dietary information was not obtained. Some dietary factors including coffee and fish oil have been shown to be related to or influence circulating adiponectin levels, and thus the observed association in the present study might, at least in part, be ascribed to dietary factors. Second, follow-up period (3-year) of the present study was relatively short, and thus statistical power might not be sufficient to detect an association in a low-risk subgroup. Finally, the study participants were employees and their dependents of a large-scale company in Japan, and the majority were male (90%). Thus, caution should be exercised when generalizing the present finding.

In summary, higher levels of serum adiponectin were associated with decreased risk of type 2 diabetes in Japanese, and this association was independent of overall or abdominal fat deposition, supporting a significant protective role of adiponectin against the development of type 2 diabetes. Given that dietary and physical activity intervention, an established strategy of the prevention for type 2 diabetes, can increase circulating adiponectin levels, the present data may help understand the biologic mechanism whereby lifestyle modification prevents diabetes. Additional studies are warranted to examine whether increasing circulating levels of adiponectin can decrease risk of type 2 diabetes.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ACKNOWLEDGEMENTS
We thank the participants as well as the clinical and imaging staff at all of the investigator sites. This study was supported by a grant from the Ministry of Health, Labor and Welfare of Japan and Grant-in-Aid for Scientific Research (B) (25293146).

REFERENCES
1. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Pacioreck CJ et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet 2011; 378: 31–40.
2. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047–1053.
3. American Diabetes Association. Economic costs of diabetes in the US in 2012. Diabetes Care 2013; 36: 1033–1046.
4. Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011; 364: 829–841.
5. Kadowaki T, Yamauchi T, Kibuta N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest 2006; 116: 1784–1792.
6. Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, Walsh K. Obesity, adiponectin and vascular inflammatory disease. Curr Opin Lipidol 2003; 14: 561–566.
7. Li S, Shin HJ, Ding EL, van Dam RM. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 2009; 302: 179–188.
8. Spranger J, Kroke A, Mohlig M, Bergmann MM, Ristow M, Boeing H et al. Adiponectin and protection against type 2 diabetes mellitus. Lancet 2003; 361: 226–228.
9. Daimon M, Ozumi T, Satoh T, Kameda W, Hirata A, Yamaguichi H et al. Decreased serum levels of adiponectin are a risk factor for the progression to type 2 diabetes in the Japanese population: the Funagata study. Diabetes Care 2003; 26: 2015–2020.
10. Krakoff J, Funahashi T, Stehouwer CD, Schalkwijk CG, Tanaka S, Matsuzawa Y et al. Inflammatory markers, adiponectin, and risk of type 2 diabetes in the Pima Indian. Diabetes Care 2003; 26: 1745–1751.
11. Duncan BB, Schmidt MI, Pankow JS, Bang H, Couper D, Ballantyne CM et al. Adiponectin and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetologia 2004; 47: 2473–2478.
12. Nakashima R, Kamei N, Yamane K, Nakashima S, Nakashima A, Kohno N. 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.
13. Snijder MB, Heine RJ, Seidell JC, Bouter LM, Stehouwer CD, Nijpels G et al. Associations of adiponectin levels with incident impaired glucose metabolism...
and type 2 diabetes in older men and women: the Hoorn study. Diabetes Care 2006; 29: 2498–2503.

14 Tabák AG, Brunner EJ, Miller MA, Karanam S, Mckernan PG, Cappuccio FP et al. Low serum adiponectin predicts 10-year risk of type 2 diabetes and HbA1c independently of obesity, lipids, and inflammation: Whitehall II study. Horm Metab Res 2009; 41: 626–629.

15 Zhu N, Pankow JS, Ballantyne CM, Couper D, Hoogeveen RC, Pereira M et al. Adiponectin and the risk of type 2 diabetes in the ARIC study. J Clin Endocrinol Metab 2010; 95: 5097–5104.

16 Marques-Vidal P, Schmid R, Bochud M, Bastardot F, von Känel R, Paccaud F et al. Adiponectin and visceral fat associate with cardiovascular risk factors. Obesity (Silver Spring, MD) 2009; 17: 2231–2236.

17 Wannamethee SG, Lowe GD, Rumley A, Cherry L, Whincup PH, Sattar N, Adipokines and risk of type 2 diabetes in older men. Diabetes Care 2007; 30: 1200–1205.

18 Hivert MF, Sullivan LM, Shrader P, Fox CS, Nathan DM, D'Agostino RB Sr et al. Insulin resistance influences the association of adiponectin levels with diabetes incidence in two population-based cohorts: the Cooperative Health Research in the Region of Augsburg (KORA) 54/F4 study and the Framingham Offspring Study. Diabetologia 2011; 54: 1019–1024.

19 Hanley AJ, Wagenknecht LE, Norris JM, Bergman R, Anderson A, Chen YI et al. Adiponectin and the incidence of type 2 diabetes in Hispanics and African Americans: the IRAS Family Study. Diabetes Care 2011; 34: 2231–2236.

20 Heidemann C, Sun Q, van Dam RM, Meigs JB, Zhang C, Tworoger SS et al. Total and high-molecular-weight adiponectin and resistin in relation to the risk for type 2 diabetes in women. Ann Intern Med 2008; 149: 307–316.

21 Matsushita Y, Nakagawa T, Yamamoto S, Kato T, Ouchi T, Kikuchi N et al. Adiponectin and visceral fat associate with cardiovascular risk factors. Obesity (Silver Spring, MD) 2014; 22: 287–291.

22 American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2012; 35 (Suppl. 1): 564–571.

23 Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, Araki E et al. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Invest 2010; 1: 212–228.

24 Heianza Y, Arase Y, Fujihara K, Tsuji H, Saito K, Hsieh SD et al. Screening for pre-diabetes to predict future diabetes using various cut-off points for HbA1c and impaired fasting glucose: the Toranomon Hospital Health Management Center Study 4 (TOPICS 4). Diabet Med 2012; 29: e279–e285.

25 Nakamura Y, Sekikawa A, Kadowaki T, Kadota A, Kadowaki S, Maegawa H et al. Visceral and subcutaneous adiposity and adiponectin in middle-aged Japanese men: the ERA JUMP study. Obesity (Silver Spring, MD) 2009; 17: 1269–1273.

26 Torrêns JI, Skurnick J, Davidow AL, Korenman SG, Santoro N, Soto-Greene M et al. Ethnic differences in insulin sensitivity and beta-cell function in premenopausal or early perimenopausal women without diabetes: the Study of Women's Health Across the Nation (SWAN). Diabetes Care 2004; 27: 354–361.

27 Pham NM, Nanni A, Yasuda K, Kurotani K, Kuwahara K, Akter S et al. Habitual consumption of coffee and green tea in relation to serum adipokines: a cross-sectional study. Eur J Nutr 2014; e-pub ahead of print 22 April 2014; doi:10.1007/s00394-014-0701-4.

28 Wu JH1, Cahill LE, Mozaffarian D. Effect of fish oil on circulating adiponectin: a systematic review and meta-analysis of randomized controlled trials. J Clin Endocrinol Metab 2013; 98: 2451–2459.

29 Esposito K, Giugliano D. Lifestyle and adiponectin level: four-year follow-up of controlled trials. Arch Intern Med 2010; 170: 1270–1271.