Decreased Serum Levels of Adiponectin Are a Risk Factor for the Progression to Type 2 Diabetes in the Japanese Population

The Funagata study

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OBJECTIVE — To examine whether decreased serum levels of adiponectin are an independent risk factor for the progression to type 2 diabetes in a Japanese population.

RESEARCH DESIGN AND METHODS — The serum levels of adiponectin and tumor necrosis factor-α (TNF-α) at baseline (from 1995 to 1997) were evaluated in 1,792 individuals (1,023 women and 769 men, aged 58.5 ± 12.5 years) from a cohort population (n = 3,706) of the Funagata study. Glucose tolerance was evaluated at baseline and also at 5-year follow-up examinations (n = 978, follow-up rate, 54.6%) according to the 1985 World Health Organization criteria. The correlation of clinical traits with serum levels of adiponectin was examined. The association of the traits with the progression to type 2 diabetes at the 5-year follow-up was also examined.

RESULTS — Among the traits examined, the correlation with aging was highest (r = 0.312, $P < 0.001$). Eighteen subjects with normal glucose tolerance (NGT) developed diabetes, and 709 remained NGT at the 5-year follow-up examinations. The subjects who became diabetic had decreased serum levels of adiponectin (7.29 ± 2.35 vs. 9.13 ± 2.35 10 × log μg/ml, P = 0.009). Multiple logistic regression analysis with age, sex, waist-to-hip ratio, and 2-h plasma glucose as the variables revealed that serum adiponectin level (odds ratio [per 0.1 log μg/ml] 0.766, P = 0.029) was an independent risk factor for the progression to type 2 diabetes. The subjects whose serum levels of adiponectin were in the lowest tertile were 9.320 times (95% CI 1.046–83.1) more likely to develop diabetes than those in the highest tertile (P = 0.046).

CONCLUSIONS — Decreased serum adiponectin level is an independent risk factor for progression to type 2 diabetes.

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Adipose tissue, in addition to its function as the major storage depot for lipids, plays active roles in normal metabolic homeostasis and in the development of several diseases, such as type 2 diabetes, dyslipidemia, and atherosclerosis (1,2). These roles are mediated by factors known as adipocytokines, which are secreted from adipose tissue (3). Among those factors, tumor necrosis factor-α (TNF-α), leptin, and plasminogen-activator inhibitor type 1 (PAI-1) are well annotated, and the association of the dysregulated production of these factors with the pathophysiology of obesity-related insulin resistance and thrombosis is well established (3–6).

Adiponectin/ACRP30 is another adipocytokine, first identified in 1995 (7). The association of decreased plasma adiponectin levels with the presence of coronary artery disease (8) indicated the pathophysiological roles of adiponectin in the development of coronary artery disease. On the other hand, adiponectin's roles in stimulating β-oxidation in muscle and decreasing insulin resistance in the liver (9) indicated its possible involvement in the development of type 2 diabetes. Indeed, its involvement was shown in many animal studies. Administration of adiponectin improved diabetes in mice (10,11), and adiponectin-knockout mice exhibited diet-induced insulin resistance (12). The involvement of adiponectin has also been examined in clinical settings. After 1999, when the measurement of circulating (plasma and/or serum) levels of adiponectin using an enzyme-linked immunosorbent assay (ELISA) became available (13), several epidemiological studies revealed that the circulating levels of adiponectin were lower in obese and diabetic than in lean and nondiabetic humans, respectively (8,13). Later, another human study showed that decreased circulating levels of adiponectin were more closely related to the degree of insulin resistance and hyperinsulinemia than to the degree of adiposity and glucose intolerance (14). A recent study (15) that focused on the plasma levels of adiponectin during the progression to type 2 diabetes in rhesus monkeys genetically predisposed to insulin resistance showed that

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Abbreviations: ELISA, enzyme-linked immunosorbent assay; HOMA-IR, homeostasis model assessment of insulin resistance; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; PAI-1, plasminogen-activator inhibitor type 1; TNF-α, tumor necrosis factor-α; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

circulating levels of adiponectin decreased in parallel with the progression of insulin resistance. Altogether, it seems to be clear at this point that the prediabetic development of insulin resistance correlates with a decrease in the circulating levels of adiponectin, although it has not been well established whether the decreased levels are a cause or an effect of the dysregulated metabolic state.

In this report, we first examined the correlation of serum levels of adiponectin with traits related to type 2 diabetes, obesity, dyslipidemia, and hypertension in a large population-based Japanese sample. Then we examined whether decreased serum levels of adiponectin can be considered an independent risk factor for the progression to type 2 diabetes. We also measured the serum levels of TNF-α to examine the correlation between serum levels of adiponectin and TNF-α, since these adipocytokines have been reported to suppress each other's production locally in adipose tissue and each other's function remotely in muscle (12).

RESEARCH DESIGN AND METHODS

The Funagata study is a population-based study designed to clarify the risk factors, related conditions, and consequences of type 2 diabetes from an epidemiological point of view (16). In Funagata, an agricultural area ~400 km north of Tokyo, the population >35 years of age was 4,183 in 1995. Only residents >35 years of age participated in the study. Individuals (n = 377) with cerebrovascular diseases or other disabilities were unable to participate in the study and excluded. One-hundred residents, who had been identified by public health nurses and through contacts in outpatient clinics and were receiving medication for type 2 diabetes, were also excluded. Therefore, the number of residents registered for the study was 3,706. From 1995 to 1997, 2,013 residents attended the study. Among them, 1,792 were enrolled for this study (participation rate 48.4%).

This study was approved by the Ethical Committee of Yamagata University School of Medicine, and informed consent to participate was obtained from the participants. The following traits were analyzed: height, body weight, results of a 75-g oral glucose tolerance test, HbA_{1c}, waist circumference, hip circumference, waist-to-hip ratio (WHR), BMI, percent body fat, homeostasis model assessment of insulin resistance (HOMA-IR), systolic blood pressure, diastolic blood pressure, total serum cholesterol, serum triglyceride, and serum HDL cholesterol. Percent body fat was assessed on the principles of bioelectrical impedance (17). The participant's physical conditions were assessed with questionnaires. None replied that they were pregnant, lactating, on estrogen hormone replacement treatment, or on calorie restriction. The sera of the participants were kept at –20° C for future use. The mean age ± SD and the sex ratio (female/male) of the study group were 58.5 ± 12.5 years and 1,023/769, respectively. Glucose tolerance was diagnosed according to the 1985 World Health Organization criteria (18). The numbers of subjects with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and type 2 diabetes were 1,458, 246, and 88, respectively. Five years later (from 2000 to 2002), the glucose tolerance of the subjects was reexamined. At the 5-year follow-up examination, 978 subjects attended (follow-up rate 54.6%). In 2002, the levels of adiponectin (13) and TNF-α (Medgenix Diagnostics SA, Fleurus, Belgium) of the sera retained (namely, the serum levels at baseline) were measured by ELISA, as previously reported, in a commercial laboratory (Biomedical Laboratory, Tokyo, Japan).

Statistical analysis

Data are given as means ± SD. The statistical significance of the differences in the trait values between any two groups was assessed by ANOVA. Scheffe's test was used for post hoc analysis. The differences in the serum levels of adiponectin and TNF-α between the groups were also evaluated after the adjustment for clinical traits by ANCOVA. The statistical significance of the difference of the sex ratio was analyzed by χ^2 tests. Simple and stepwise linear regression analyses with the traits as covariates were performed to examine the correlation of the traits with the serum levels of adiponectin and TNF-α. Multiple logistic regression analyses determined the independent association of age, sex, WHR, 2-h plasma glucose, and serum levels of adiponectin and TNF-α with the progression to type 2 diabetes by the 5-year follow-up examinations. The subjects were divided into tertiles and quartiles based on serum levels of adiponectin. This information was used for multiple logistic regression analysis. For the analyses, the serum levels of adiponectin and TNF-α were log transformed ($\log_{10}$) to approximate a normal distribution. A value of $P < 0.05$ was accepted as statistically significant.

RESULTS

Factors correlated with the serum levels of adiponectin and TNF-α

Baseline characteristics are shown in Table 1. As expected, the individuals in the type 2 diabetic and IGT groups were more obese, more insulin-resistant, and more dyslipidemic. Those who were known to be receiving medication for diabetes at the baseline were excluded from the current study. Therefore, subjects of the diabetic group were expected to be in an early stage of type 2 diabetes. Indeed, their HbA_{1c} levels were significantly, though not greatly, higher than those of the NGT group. The serum levels of adiponectin were significantly lower in the type 2 diabetic group than in the NGT group, while serum levels of TNF-α were significantly higher in the diabetic and IGT groups than in the NGT group. These significant differences were observed even after adjustment for age, BMI, systolic blood pressure, 2-h plasma glucose, and HOMA-IR (adiponectin: type 2 diabetes versus NGT, $P < 0.001$, IGT versus NGT, $P = 0.008$; TNF-α: type 2 diabetes versus NGT and IGT versus NGT, $P < 0.001$). These results seemed to indicate a negative correlation between the serum levels of adiponectin and TNF-α. However, simple regression analysis revealed only a weak correlation between them ($r = -0.074$, $P = 0.002$). The serum levels of adiponectin and TNF-α in women were significantly higher and lower, respectively, than in men (adiponectin: 9.72 ± 2.12 vs. 7.91 ± 2.43 10 × log μg/ml, $P < 0.001$; TNF-α: 11.3 ± 1.40 vs. 11.6 ± 1.29 10 × log pg/ml, $P < 0.001$).

As shown in Table 2, simple regression analyses revealed that the serum levels of adiponectin were positively correlated with age, systolic blood pressure, and serum levels of HDL cholesterol and negatively correlated with WHR, BMI, percent body fat, 2-h plasma glucose, HOMA-IR, and serum levels of triglyceride in the NGT group. Stepwise multiple regression analysis further confirmed the correlation of most of the traits indepen-

Table 1—*Baseline characteristics of the study groups*

Trait	Diabetes Mean ± SD	Diabetes *P*	IGT Mean ± SD	IGT *P*	NGT Mean ± SD
Sex (F/M)	45/43	0.249	141/105	0.979	837/621
Age (years)	64.9 ± 11.1	<0.001*	64.2 ± 10.5	<0.001*	57.1 ± 12.4
Height (cm)	151.9 ± 7.6	0.002*	152.3 ± 8.0	<0.001*	155.7 ± 8.8
Body weight (kg)	59.0 ± 10.2	0.330	57.7 ± 10.3	0.837	57.1 ± 9.8
Waist circumference (cm)	83.6 ± 9.0	<0.001*	82.1 ± 9.2	<0.001*	77.9 ± 8.83
Hip circumference (cm)	94.3 ± 6.7	0.014*	93.0 ± 6.4	0.070*	91.9 ± 5.8
WHR	0.887 ± 0.064	<0.001*	0.882 ± 0.067	<0.001*	0.847 ± 0.071
BMI (kg/m^2)	25.5 ± 3.9	<0.001*	24.8 ± 3.5	<0.001*	23.5 ± 3.2
Percent body fat	29.6 ± 8.2	<0.001*	28.2 ± 8.1	<0.001*	26.1 ± 6.8
Fasting plasma glucose (mg/dl)	126.6 ± 24.8	<0.001*	100.2 ± 11.1	<0.001*	92.0 ± 9.2
2-h plasma glucose (mg/dl)	256.3 ± 58.7	<0.001*	159.8 ± 16.6	<0.001*	99.3 ± 21.7
HbA_{1c} (%)	6.70 ± 1.10	<0.001*	5.73 ± 0.47	<0.001*	5.33 ± 0.36
Fasting serum insulin (μU/ml)	6.31 ± 5.46	<0.001*	5.36 ± 3.61	<0.001*	4.25 ± 2.99
HOMA-IR	1.98 ± 1.76	<0.001*	1.35 ± 0.91	<0.001*	0.98 ± 0.75
Systolic blood pressure (mmHg)	136.9 ± 20.5	<0.001*	133.4 ± 16.9	<0.001*	124.2 ± 17.2
Diastolic blood pressure (mmHg)	77.0 ± 11.9	0.006*	76.1 ± 9.2	0.003*	73.3 ± 9.9
Total cholesterol (mg/dl)	209.4 ± 29.1	0.339	215.2 ± 34.0	<0.001*	203.8 ± 36.4
Triglyceride (mg/dl)	169.5 ± 211.4	<0.001*	120.9 ± 65.6	0.469	112.6 ± 88.8
HDL cholesterol (mg/dl)	52.3 ± 15.2	0.013*	55.1 ± 14.4	0.103	57.3 ± 14.3
Adiponectin (10 × log μg/ml)	8.01 ± 2.55	<0.001*	8.60 ± 2.43	0.064	9.06 ± 2.41
TNF-α (10 × log pg/ml)	11.8 ± 1.27	0.006*	11.8 ± 1.37	<0.001*	11.4 ± 1.35

P values compared subjects with diabetes or IGT with subjects with NGT. *$P < 0.05$.

dently from each other ($r^2 = 0.404$). However, in the type 2 diabetic group, age and WHR were the only traits that were correlated with the serum levels of adiponectin independently from the other traits ($r^2 = 0.472$). These results indicate that the traits related to diabetes, obesity, insulin resistance, and dyslipidemia contribute substantially to the serum levels of adiponectin in subjects with NGT but not in subjects with diabetes. A correlation of the serum levels of TNF-α with most of the traits mentioned above was also observed in the NGT group by simple regression analysis (Table 2). However,

Table 2—*Factors correlated with the serum levels of adiponectin and TNF-α determined by regression analysis*

	Diabetes				IGT				NGT			
	Adiponectin		TNF-α		Adiponectin		TNF-α		Adiponectin		TNF-α	
Trait	Simple	Stepwise	Simple	Stepwise	Simple	Stepwise	Simple	Stepwise	Simple	Stepwise	Simple	Stepwise
r^2 of the test	—	0.472	—	0.070	—	0.377	—	0.080	—	0.404	—	0.065
Age (years)	0.629†	0.612†	−0.092	NA	0.375†	0.305†	0.209†	0.231†	0.327†	0.372†	0.136†	0.136†
WHR	−0.315†	−0.277†	0.265*	0.265*	−0.307†	−0.283†	0.184†	NA	−0.350†	−0.305†	0.088†	NA
BMI (kg/m^2)	−0.221*	NA	0.134	NA	−0.256†	NA	0.089	NA	−0.259†	−0.120†	0.131†	0.069*
Percent body fat	−0.077	NA	−0.059	NA	−0.140*	NA	0.082	NA	−0.090†	0.198†	0.074†	NA
2-h plasma glucose (mg/dl)	−0.038	NA	−0.176	NA	−0.083	NA	0.054	NA	−0.061*	−0.046*	0.028	NA
HOMA-IR	−0.333†	NA	0.064	NA	−0.327†	−0.137*	0.065	NA	−0.274†	−0.129†	0.111†	NA
Systolic blood pressure (mmHg)	0.170	NA	0.083	NA	0.058	NA	0.136*	NA	0.080†	NA	0.127†	NA
Diastolic blood pressure (mmHg)	−0.061	NA	0.072	NA	−0.114	NA	0.121	NA	−0.034	NA	0.117†	0.076†
Total cholesterol (mg/dl)	−0.156	NA	0.198	NA	0.067	NA	0.051	NA	0.010	NA	0.005	NA
Triglyceride (mg/dl)	−0.365†	NA	0.149	NA	−0.339†	NA	0.094	NA	−0.333†	−0.128†	0.082†	NA
HDL cholesterol (mg/dl)	0.364†	NA	−0.149	NA	0.423†	0.285†	−0.166*	−0.193†	0.371†	0.187†	−0.176†	−0.163†

Correlation coefficients (*r*) are shown. ($r > 0.3$ and < -0.3 are underlined). *$P < 0.05$, †$P < 0.01$. Parameters indicated by NA are those not accepted as significant for stepwise multiple regression analysis.

Table 3—*Baseline characteristics of the subjects who progressed to diabetes and who remained nondiabetic at the 5-year follow-up examination*

Trait	IGT to diabetes	*P*	IGT to nondiabetic	NGT to diabetic	*P*	NGT to IGT	*P*	NGT to NGT
Sex (F/M)	14/22	0.085	46/36	4/14	0.001†	53/57	0.0184*	426/283
Age (years)	66.2 ± 9.9	0.049*	61.4 ± 9.1	60.8 ± 10.4	0.165	62.4 ± 9.5	<0.001†	56.0 ± 11.3
Height (cm)	153.9 ± 7.8	0.788	153.4 ± 7.6	156.8 ± 6.0	0.991	153.7 ± 8.2	0.039*	156.0 ± 8.6
Body weight (kg)	59.0 ± 9.6	0.715	59.3 ± 9.9	59.0 ± 8.9	0.785	57.2 ± 9.3	0.975	57.4 ± 9.6
Waist circumference (cm)	84.7 ± 7.7	0.259	82.1 ± 8.4	81.3 ± 6.6	0.218	79.7 ± 8.9	0.069	77.6 ± 8.9
Hip circumference (cm)	94.0 ± 5.5	0.624	93.2 ± 5.8	91.3 ± 4.2	0.837	92.1 ± 5.3	0.996	92.1 ± 5.9
WHR	0.901 ± 0.061	0.228	0.880 ± 0.064	0.891 ± 0.068	0.015*	0.865 ± 0.072	0.007†	0.841 ± 0.071
BMI (kg/m^2)	24.8 ± 2.8	0.507	25.2 ± 3.4	23.9 ± 2.5	0.886	24.2 ± 3.2	0.155	23.6 ± 3.1
Percent body fat	27.4 ± 6.6	0.319	28.4 ± 8.2	23.4 ± 7.1	0.189	26.7 ± 6.5	0.631	26.3 ± 6.7
Fasting plasma glucose (mg/dl)	105.3 ± 9.2	<0.001*	98.4 ± 9.0	102.2 ± 13.9	<0.001†	96.4 ± 9.4	<0.001†	91.0 ± 8.0
2-h plasma glucose (mg/dl)	164.0 ± 17.1	<0.001*	154.3 ± 12.4	114.9 ± 19.5	0.002†	111.1 ± 19.9	<0.001†	98.2 ± 20.6
HbA_{1c} (%)	5.95 ± 0.50	<0.001*	5.61 ± 0.37	5.63 ± 0.50	0.003†	5.50 ± 0.36	<0.001†	5.30 ± 0.34
Fasting serum insulin (μU/ml)	4.70 ± 2.58	0.169	5.75 ± 3.92	4.30 ± 4.03	0.995	4.51 ± 2.52	0.605	4.29 ± 2.96
HOMA-IR	1.23 ± 0.69	0.368	1.41 ± 0.93	1.09 ± 1.08	0.811	1.08 ± 0.62	0.327	0.98 ± 0.73
Systolic blood pressure (mmHg)	136.7 ± 17.2	0.563	133.3 ± 16.8	129.0 ± 20.5	0.377	128.3 ± 14.6	0.019*	123.5 ± 16.6
Diastolic blood pressure (mmHg)	76.6 ± 9.8	0.307	77.9 ± 9.7	74.2 ± 13.1	0.921	75.7 ± 10.2	0.099	73.3 ± 9.6
Total cholesterol (mg/dl)	217.5 ± 33.8	0.943	216.4 ± 35.4	205.2 ± 37.9	0.980	213.4 ± 37.0	0.072	203.4 ± 36.7
Triglyceride (mg/dl)	120.0 ± 80.8	0.886	120.8 ± 53.8	136.6 ± 117.6	0.317	114.1 ± 57.4	0.637	106.6 ± 74.3
HDL cholesterol (mg/dl)	56.0 ± 15.3	0.933	55.1 ± 14.2	58.8 ± 16.3	0.835	56.4 ± 15.4	0.449	58.0 ± 13.9
Adiponectin (10 × log μg/ml)	8.27 ± 2.19	0.912	8.32 ± 2.35	7.29 ± 2.35	0.009†	8.98 ± 2.32	0.672	9.13 ± 2.35
TNF-α (10 × log pg/ml)	11.6 ± 1.4	0.448	11.8 ± 1.4	11.6 ± 1.2	0.718	11.5 ± 1.5	0.283	11.3 ± 1.3

Data are means ± SD. *P* values compared the IGT to diabetes group with the IGT to nondiabetic group, and the NGT to diabetes or the NGT to IGT groups with the NGT to NGT group. *$P < 0.05$; †$P < 0.01$.

only four traits (age, BMI, diastolic blood pressure, and serum levels of HDL cholesterol) were shown by stepwise multiple regression analysis to be independently correlated, and the r^2 of the test was low (0.063). Furthermore, in the type 2 diabetic group, only WHR was shown to be independently correlated ($r^2 = 0.070$). These results indicated that the traits related to diabetes, obesity, insulin resistance, hypertension, and dyslipidemia contributed little to the serum levels of TNF-α.

Risk factors for the progression to type 2 diabetes

We reevaluated the glucose tolerance of 978 subjects 5 years later at the follow-up examinations. The subjects were divided based on the changes in their glucose tolerance. The divisions are as follows (change, *n*): NGT to NGT 709, NGT to IGT 110, NGT to diabetes 18, IGT to NGT 27, IGT to IGT 47, IGT to diabetes 36, diabetes to NGT 5, diabetes to IGT 5, and diabetes to diabetes 21. To examine the risk factors for the progression to diabetes, these subjects were also grouped as follows: subjects whose glucose tolerances were IGT at baseline and who had not progressed to diabetes by the 5-year follow-up examinations (IGT to nondiabetic: IGT to NGT and IGT to IGT), subjects who were not diabetic at baseline and who either remained nondiabetic or became diabetic by the 5-year follow-up examinations (remained nondiabetic [NGT to NGT, NGT to IGT, IGT to NGT, and IGT to IGT] or progressed to type 2 diabetes [NGT to diabetes and IGT to diabetes], respectively). The baseline characteristics of NGT to NGT, NGT to IGT, NGT to diabetes, IGT to nondiabetes, and IGT to diabetes are shown in Table 3. The ratios of male sex, glycemic levels, and WHR were significantly higher in the NGT to diabetes group than in the NGT to NGT group. HOMA-IR and the traits related to dyslipidemia were not significantly different among the groups. The serum levels of adiponectin were significantly lower in the NGT to diabetes group than in the NGT to NGT group, while levels of TNF-α were not significantly different among the groups. The traits that varied significantly among the groups were expected to be the risk factors for the progression to type 2 diabetes from NGT by the 5-year follow-up examinations. In addition, the serum levels of adiponectin were not different between the IGT to diabetes and IGT to nondiabetes groups, indicating that the levels may not be considered a risk factor for the progression to diabetes from IGT.

Multiple logistic regression analysis was then used to examine whether these risk factors were independent of each other and to determine the extent of the contribution (odds ratio [OR]) of the factors to the progression to type 2 diabetes from NGT. Sex, age, WHR, 2-h plasma glucose, and the serum levels of adiponectin and TNF-α were used as the covariates in this analysis. WHR and 2-h plasma glucose were chosen as the representatives of the traits related to obesity and glycemic levels, respectively. As shown in Fig. 1, this analysis revealed that an increase in 2-h plasma glucose, a decrease in serum levels of adiponectin, and male sex were independent risk factors for the progression to diabetes, whereas age, WHR, and serum levels of TNF-α were not. WHR was not shown to be an independent risk factor in this analysis. However, simple logistic regression analysis showed that WHR was a significant risk factor with an OR of 1.106 (95% CI 1.032–1.185, $P = 0.004$). Serum levels of TNF-α were not shown to be a risk factor, even in simple logistic regression analysis (1.166, 0.815–1.670, $P = 0.400$).

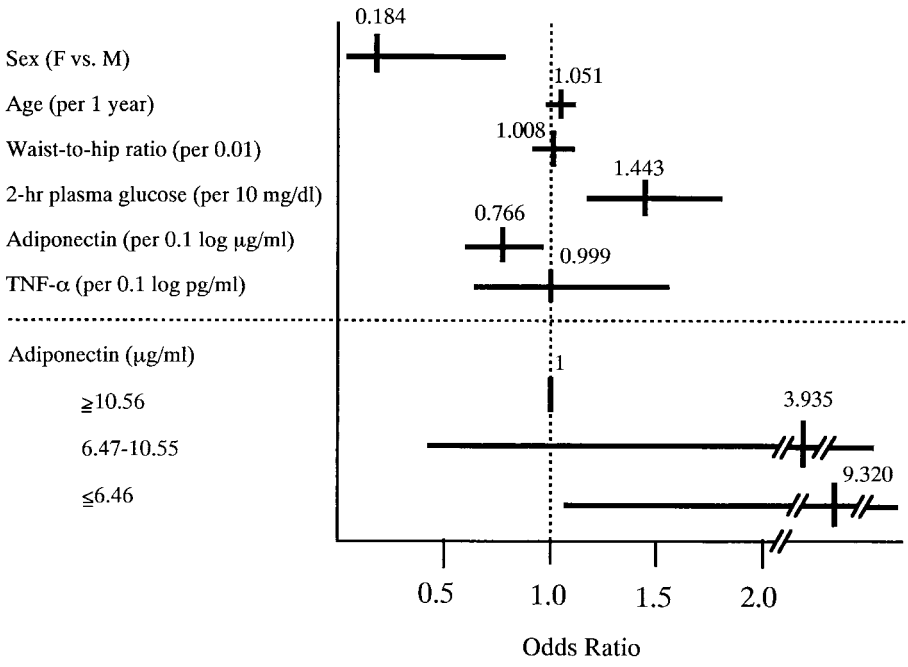

Figure 1—*Risk factors for the progression to type 2 diabetes by the 5-year follow-up examination. The results of the multiple logistic regression analyses are shown, including all variables. ORs are shown above the vertical bars. Horizontal bars are 95% CIs.*

The association of the serum levels of adiponectin with the progression to diabetes from NGT was analyzed in another way. The subjects were divided into tertiles based on serum levels of adiponectin. As shown in the lower part of Fig. 1, the subjects in the lowest tertile developed diabetes by the 5-year follow-up examinations 9.320 times more than those in the highest tertile ($P = 0.046$). Because the number of subjects in the NGT to diabetes group was not high, these analyses could lead to an overestimation. Thus, we performed the same analyses with the "progressed to type 2 diabetes" and "remained nondiabetic" groups, although performing these analyses could in turn lead to an underestimation. These analyses, however, also showed that the decrease in serum levels of adiponectin was an independent risk factor (OR 0.825, 95% CI 0.704–0.956, $P = 0.011$), and that the subjects in the lowest quartile (≤5.32 μg/ml) developed diabetes by the 5-year follow-up examinations 3.469 (1.106–10.884) times more than those in the highest quartile (≥11.72 μg/ml) ($P = 0.033$). Together, these results clearly indicate that decreased serum levels of adiponectin are a significant independent risk factor for the progression to type 2 diabetes by the 5-year follow-up examinations.

CONCLUSIONS — The correlation of circulating levels of adiponectin with clinical traits has been examined extensively (8,14,19–21). We found decreased serum levels of adiponectin in the type 2 diabetes and IGT groups and in men. A negative correlation of serum levels of adiponectin with serum levels of triglyceride, fasting and postprandial plasma glucose levels, and traits related to obesity and insulin resistance, as well as a positive correlation of its serum levels with serum levels of HDL cholesterol, were also found. All of these results were in good agreement with previous reports (8,14, 19–21). The finding of a positive correlation of serum levels of adiponectin with age ($r = 0.312$, $P < 0.001$) was novel. Only one previous report examined the correlation between serum levels of adiponectin and age, and no correlation was found between them (22). However, in the study cited, the study population (45.1 ± 10.3 years, range 30–65) was much younger and less diverse than the one in our study (58.5 ± 12.5, 35–93). Furthermore, the number of subjects (967) was relatively small compared with our study (1,792). Very recently, Combs et al. (23) reported that adiponectin levels in mice increased abruptly by the third week of postnatal life but were relatively stable thereafter. TNF-α has been reported to suppress the production of adiponectin locally in adipose tissue (12), and the serum levels of TNF-α increased significantly with age ($r = 0.160$, $P < 0.001$). Therefore, a concomitant decrease in the serum levels of adiponectin was initially expected. However, as shown here, there was no concomitant decrease. Furthermore, the correlation coefficient between serum levels of adiponectin and TNF-α was very low (-0.074, $P = 0.002$). Therefore, serum levels of adiponectin might be induced by some factors strong enough to overcome its suppression by TNF-α.

The modulation of insulin sensitivity or insulin resistance by adiponectin has been examined extensively (14,19–21). Decreased serum levels of adiponectin are correlated with an increase in insulin resistance. Furthermore, a report (15) that focused on the serum levels of adiponectin during the progression to diabetes in rhesus monkeys revealed that the serum levels decreased in parallel with the progression of insulin resistance and thus preceded diabetes development. Therefore, the decreased serum levels of adiponectin were expected to be a risk factor for the progression to type 2 diabetes. Indeed, multiple logistic regression analysis showed that decreased serum levels of adiponectin were a risk factor for the progression to type 2 diabetes that was independent of age, sex, WHR, and 2-h plasma glucose. As shown in Table 3, the ratio of male sex in the NGT to diabetes group was much higher than in the NGT to NGT group, and serum levels of adiponectin were significantly lower in men than in women. Therefore, the decrease in the serum levels of adiponectin in the NGT to diabetes group could be attributed to the larger number of men in the group. However, as shown in Fig. 1, serum levels of adiponectin were shown to be a risk factor for the progression to diabetes even after adjustment for sex. Among the traits examined that were associated with progression to diabetes, WHR is of interest. An increase in WHR seemed to be a risk factor for diabetes progression. However, when serum levels of adiponectin were included as a covariate for the analysis, WHR was not a risk factor (Fig. 1). These findings indicated that the changes in WHR and serum levels of adiponectin were correlated and the change in serum levels of adiponectin contrib-

uted more to the progression to diabetes than WHR. Therefore, serum levels of adiponectin seem to be a more reliable trait to estimate the risk for diabetes progression than WHR.

Lindsay et al. (24) recently reported that decreased plasma levels of adiponectin were a risk factor for the development of type 2 diabetes (mean follow-up to diagnosis, 4–6 years) independent of age, fasting plasma glucose, 2-h plasma glucose, fasting insulin, and waist circumference. Their study was a nested case-control study ($n = 70$ each) in the Pima Indian population. The Pima Indians are prone to obesity and have the highest known prevalence of type 2 diabetes of any population. Our study was a population-based study of Japanese subjects, and the number of subjects was much larger. The incidence of type 2 diabetes in our study population in the follow-up period (5 years) was 5.7%, which was similar to that observed in other populations. Therefore, our study seemed to draw more universal findings. We noted the number of nondiabetic subjects at baseline but who developed diabetes at the 5-year follow-up examinations and determined the risk factors for the progression to type 2 diabetes. Our study was novel in this respect. In conclusion, a decrease in serum levels of adiponectin was a risk factor for the progression to type 2 diabetes in a Japanese population.

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