Fasting Insulin Levels and Metabolic Risk Factors in Type 2 Diabetic Patients at the First Visit in Japan

A 10-year, nationwide, observational study (JDDM 28)

IKURO MATSUBA, MD, PHD[1]
KAZUMI SAITO, MD, PHD[2]
MASAHIKO TAKAI, MD, PHD[3]
KOICHI HIRAO, MD[4]
HIROHITO SONE, MD, PHD, FACP[2]
ON BEHALF OF THE JAPAN DIABETES CLINICAL DATA MANAGEMENT STUDY GROUP

OBJECTIVE—To investigate the relationship between fasting insulin levels and metabolic risk factors (MRFs) in type 2 diabetic patients at the first clinic/hospital visit in Japan over the years 2000 to 2009.

RESEARCH DESIGN AND METHODS—In total, 4,798 drug-naive Japanese patients with type 2 diabetes were registered on their first clinic/hospital visits. Conventional clinical factors and fasting insulin levels were observed at baseline within the Japan Diabetes Clinical Data Management (JDDM) study between consecutive 2-year groups. Multiple linear regression analysis was performed using a model in which the dependent variable was fasting insulin values using various clinical explanatory variables.

RESULTS—Fasting insulin levels were found to be decreasing from 2000 to 2009. Multiple linear regression analysis with the fasting insulin levels as the dependent variable showed that waist circumference (WC), BMI, mean blood pressure, triglycerides, and HDL cholesterol were significant, with WC and BMI as the main factors. ANCOVA after adjustment for age and fasting plasma glucose clearly shows the decreasing trend in fasting insulin levels and the increasing trend in BMI.

CONCLUSIONS—During the 10-year observation period, the decreasing trend in fasting insulin was related to the slight increase in WC/BMI in type 2 diabetes. Low pancreatic β-cell reserve on top of a lifestyle background might be dependent on an increase in MRFs.

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Diabetes is a major global health concern (1). Particularly in Asian countries, the prevalence of diabetes has increased rapidly in recent decades with economic development and accompanying changes in food supply and dietary patterns, technology transfer, and cultural admixtures (2). In Japan, it is estimated that there are 8.9 million diabetic patients (population-adjusted prevalence, 7.3%) and an additional 13.2 million individuals with impaired glucose tolerance (3). In total, one in six Japanese individuals suffers from hyperglycemia, which represents a 1.6-fold increase from 10 years ago. With respect to diabetes complications, estimates show that there are ~14,000 patients starting hemodialysis due to diabetic nephropathy, 3,500 patients losing their eyesight, and 3,000 lower limb amputees every year (3). There is no doubt that the cluster of clinical and metabolic features associated with insulin resistance predicts the risk of developing type 2 diabetes and cardiovascular disease (4). Previous cross-sectional studies have shown that both high homeostasis model assessment of insulin resistance and low homeostasis model assessment of β-cell function were associated with increased prevalences of impaired glucose tolerance and type 2 diabetes in Japanese (5–7), Mexican American (8), and non-Hispanic white individuals (4). However, whether the relationship between fasting insulin levels and the character of type 2 diabetes at the onset differs according to metabolic risk factors (MRFs) is unknown. The purpose of the current study was to determine whether fasting insulin levels and metabolic profiles differed at the first clinic/hospital visit over the last 10 years in Japan.

RESEARCH DESIGN AND METHODS

A cross-sectional and longitudinal study was conducted that included 22 medical clinics (i.e., general practitioners) or general/university-affiliated hospitals from different areas in Japan, using the same software (CoDiC) to compile electronic medical records, as a working study group, the Japan Diabetes Clinical Data Management (JDDM) study (9). A detailed description of the study has been published previously (9,10). The study was performed in primary care settings. All consecutive patients with type 2 diabetes who visited each clinic/hospital between 2000 and 2009 and whose diabetes was diagnosed before 2009 were included (n = 45,876). In total, 4,798 drug-naive patients were recruited on their first visits between 2000 and 2009 from across Japan. The 10-year period was divided into five consecutive 2-year periods. All patients met the Japan Diabetes Association criteria for type 2 diabetes (11). All case participants had their height, weight, HbA_{1c}, blood pressure (BP), and lipids measured. BMI was calculated as weight (kg) divided by height squared (m^2). BP was measured with a standard mercury sphygmomanometer. Mean BP values were determined from the measurements. Waist circumference (WC) was assessed at the

From the [1]Matsuba Medical Clinic, Kawasaki, Kanagawa, Japan; the [2]Department of Endocrinology and Metabolism, Mito Medical Center, University of Tsukuba, Tsukuba, Ibaraki, Japan; the [3]Takai Internal Medicine Clinic, Kamakura, Kanagawa, Japan; and the [4]H.E.C. Science Clinic, Yokohama, Kanagawa, Japan.
Corresponding author: Ikuro Matsuba, ikuro@matsuba-web.com.
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top of the iliac crest at the end of a normal expiration (12). The JDDM protocol, which is in accordance with the Declaration of Helsinki, received ethical approval from the institutional review boards of all of the participating institutions and was undertaken in accordance with the Ethical Guidelines for Clinical Studies of the Japanese Ministry of Health, Labor, and Welfare.

Laboratory data

The morning after an overnight fast, venous blood was sampled for the baseline measurements of the HbA_{1c} level and plasma concentrations of glucose, LDL cholesterol, HDL cholesterol, triglycerides (TGs), creatinine, and insulin. Plasma glucose was measured by a glucose-oxidase method. HbA_{1c}, expressed in National Glycohemoglobin Standardization Program units, was measured by high-performance liquid chromatography. Plasma total cholesterol, HDL cholesterol, and TGs were assessed with standard enzymatic spectrophotometric techniques. Plasma LDL cholesterol was calculated with the equation of Friedewald et al. (13), except when TGs exceeded 400 mg/dL (in that case, data were treated as missing). Albumin concentrations in random spot urine samples were determined by turbidimetric immunoassay, and creatinine levels were determined by the enzymatic method. The Abbott IMx insulin assay (Dainabot; Abbott Laboratories, Tokyo, Japan) is used to quantitatively measure insulin at BML, Inc. (Tokyo, Japan). This assay shows no cross-reactivity with proinsulin (<0.005%). Within the assay, for every year, the coefficients of variation at mean values of 59.6 and 873.8 pmol/L were 4 and 2.5%, respectively. Between assays, the coefficients of variation at mean values of 59.6 and 872.4 pmol/L were 4.5 and 3.6%, respectively.

MRFs

The following three MRFs were evaluated as defined by the revised National Cholesterol Education Program criteria (14) and the World Health Organization criteria for Asia (15): *1*) WC ≥80 cm (men) or ≥75 cm (women); *2*) systolic BP ≥130 mmHg, diastolic BP ≥85 mmHg, or antihypertensive medications; and *3*) HDL cholesterol <1.04 mmol/L, TGs ≥1.68 mmol/L, or lipid medications.

Statistical analysis

All analyses were performed using SPSS version 18 for Windows. Sex, age, BMI, WC, mean BP, HbA_{1c}, fasting insulin, TGs, LDL cholesterol, HDL cholesterol, and microalbuminuria were compared by five consecutive 2-year periods from 2000 to 2009 using one-way ANOVA and the Bonferroni post hoc test. Statistical analyses included the unpaired Student *t* test, one-way ANOVA, the χ^2 test for categorical variables, univariate linear correlations, and ANCOVA. Multiple linear regression analysis was used to assess variables that were independently associated with variations in fasting insulin levels. Both fasting insulin and BMI differences over this 10-year term were assessed using ANCOVA to adjust for potential confounders (sex, age, and fasting plasma glucose [FPG]). Data are presented as means ± SD. Statistical significance was defined as a two-tailed *P* value ≤0.05.

RESULTS—Each clinical variable was compared for each 2-year period (Table 1). Comparisons between groups were analyzed for five consecutive 2-year periods versus each variable value in 2000–2001, when observation began. Sex, age, mean BP, and the prevalence of MRFs (%WC, hypertension, and dyslipidemia) did not differ significantly among year groups. Waist circumference (cm) and BMI were significantly different in the 2006–2007 and 2008–2009 groups. FPG, HbA_{1c}, fasting insulin, and TGs were significantly different in each group in 2002 and thereafter. Overall, differences on ANOVA are shown as the ANOVA *P* value. Compared with 2000–2001, the BMI increased significantly in 2006 and later, but the difference was slight. Blood pressure did not

Table 1—*Patients' characteristics for each 2-year group*

	Year group number					
	1	2	3	4	5	
	2000–2001	2002–2003	2004–2005	2006–2007	2008–2009	P value[a]
n (*N* = 4,798)	957	1,131	1,311	941	458	
Sex (male/female)	645/312	748/383	884/427	654/287	309/149	0.612
Age (years)	56.1 ± 11.3	56.6 ± 11.4	57.4 ± 11.8	56.8 ± 11.8	57.4 ± 12.4	0.089
Mean BP (mmHg)	106 ± 15	105 ± 15	105 ± 14	105 ± 14	104 ± 14	0.283
WC (cm)	85.6 ± 9.3	85.9 ± 10.3	86.2 ± 9.3	86.8 ± 8.8[b]	87.6 ± 10.3[b]	<0.05
%WC (cm) ≥80 (men) or ≥75 (women)	69.1	70.3	66.2	69.2	72.1	0.674
BMI (kg/m^2)	24.9 ± 4.0	24.8 ± 3.9	25.1 ± 4.1	25.5 ± 4.2[b]	25.6 ± 4.4[b]	<0.001
FPG (mmol/L)	8.80 ± 2.56	9.28 ± 2.71[b]	9.1 ± 2.75	9.21 ± 2.76[b]	8.98 ± 2.58	<0.01
HbA_{1c} (%, NGSP units)	8.3 ± 1.7	8.6 ± 1.8[c]	8.8 ± 2.0[c]	8.9 ± 1.9[c]	7.7 ± 1.9[c]	<0.001
Fasting insulin (pmol/L)	55.6 ± 46.3	52.9 ± 49.2[c]	47.1 ± 43.4[c]	43.4 ± 44.9[c]	39.6 ± 34.0[c]	<0.001
LDL (mmol/L)	3.06 ± 0.83	3.17 ± 0.87	3.16 ± 0.87	3.12 ± 0.86	3.43 ± 0.92[c]	<0.001
HDL (mmol/L)	1.37 ± 0.37	1.38 ± 0.36	1.42 ± 0.38[b]	1.41 ± 0.37	1.42 ± 0.37	<0.01
TGs (mmol/L)	1.61 ± 1.19	1.80 ± 1.52[b]	1.72 ± 1.31[b]	1.85 ± 1.39[c]	1.82 ± 1.32[c]	<0.01
Microalbuminuria (mg/g · Cr)	74.5 ± 11.4	103.7 ± 11.7	129.1 ± 19.2	129.9 ± 16.2[c]	139.8 ± 29.7	<0.001
Hypertension (%)*	72.7	70.7	71	69.5	69.7	0.591
Dyslipidemia (%)#	57.7	61.1	55.2	56.9	56.3	0.561
MRFs: no/1/2/3 (%)	8/21/35/36	8/22/36/34	9/25/41/25	7/26/34/33	6/20/45/29	0.095

Data are means ± SD. NGSP, National Glycohemoglobin Standardization Program. *Hypertension is defined as systolic BP ≥130, diastolic BP ≥85, or taking antihypertensives. #Dyslipidemia is defined as TGs ≥1.69 mmol/L, HDL cholesterol <1.04 mmol/L, or lipid medications. [a]*P* values determined by ANOVA among the five consecutive 2-year groups or by the χ^2 test. [b]$P < 0.05$. [c]$P < 0.01$ vs. type 2 diabetic group of 2000–2001 on a post hoc Bonferroni test.

change during the 10-year period. For lipids, compared with 2000–2001, TGs increased in 2002 and thereafter. Fasting insulin tended to decrease over the 10-year observation period. As a visual representation of this study, profile plots were created showing the estimated marginal means for the fasting insulin levels/BMI values in each of the 2-year groups (Fig. 1). Further analysis using ANCOVA adjusted for age and FPG showed differences among year groups, with an increase in BMI and a decrease in fasting insulin ($P < 0.001$). In each year group, BMI and fasting insulin values in females were higher than in males ($P < 0.001$). Multiple linear regression analysis was performed to identify factors affecting fasting insulin levels (Table 2). Factors that significantly affected the fasting insulin value, in order of greater β, were WC, BMI, year group, mean BP, HDL cholesterol, TGs, and microalbuminuria. As the year groups advanced, fasting insulin decreased. The factors most affecting fasting insulin were WC and BMI, but even after correction for sex, age, and HbA_{1c}, the values decreased during the 10-year period. There was also a highly linear relationship between WC and BMI ($R = 0.87$, $P < 0.001$).

CONCLUSIONS—In this 10-year study of drug-naive Japanese diabetic patients evaluated at their first clinic/hospital visit, fasting insulin levels were found to decrease over time, with WC and BMI being the most important factors after corrections. From 2000 to 2009, when the current study was conducted, a diabetes status survey in Japan also estimated an increase in the number of diabetic patients, from 6.9 to 12.5 million (3). It is clear that, in the last 10 years, the insulin secretion ability of Japanese individuals has gradually decreased each year. The reason for this is the following changes that were observed in MRFs that play a role in insulin resistance. As MRFs, in the current study, the relationships with WC, BMI, BP, lipids, and microalbuminuria were examined. The factors most involved with the decrease in fasting insulin levels were WC and BMI. Fasting insulin levels were affected by age, sex, and HbA_{1c}. Even after adjustment for these, based on our study, the role of MRFs (WC, BMI, BP, lipids, and microalbuminuria) seems important in the pathogenesis of type 2 diabetes in Japanese individuals.

The Asia-Pacific region has been considered to be the major site of a rapidly emerging epidemic of diabetes (16), and with its large populations, it is of prime importance for the epidemiology of diabetes. Approximately 13.5% of the Japanese population now has either type 2 diabetes or impaired glucose tolerance (17). Insulin secretion ability is lower in Japanese than in Caucasians. Furthermore, it is thought that Westernization of the lifestyle and an increased percentage of fat in the diet play a role in increasing insulin resistance (18). In Asian populations, the β-cells may lose their ability to compensate for the decrease in insulin sensitivity seen with the development of central adiposity. Loss of β-cell function has been demonstrated to appear before the development of the obesity-induced decreased insulin sensitivity among subpopulations of Japanese and Japanese Americans who develop type 2 diabetes (19,20). The Japanese have a higher prevalence of polymorphisms for at least three genes that code for proteins thought to play key roles in lipid and glucose metabolism: the β3-adrenergic receptor, the peroxisome proliferator–activated receptor γ, and calpain-10 (18,21). The interaction between changes in lifestyle and the "thrifty" genotype characteristic of many Japanese people may play a significant role in the increasing prevalence of diabetes and associated cardiovascular risk in this population. Although this type of genetic background has not changed, compared with ~30 years ago, dietary habits have become Westernized with a high-fat diet. Surprisingly, the daily calorie intake has not changed over the last 50 years and remains at ~2,000 kcal. However, 50 years ago, when a traditional Japanese diet was consumed, the percentage of fat in the calorie intake was ~7%, but now it is >27%, a sudden, almost fourfold increase in only 50 years (3). Therefore, an imbalance with the characteristic Japanese insulin secretion ability has developed. As a result, the current state of obesity and poor insulin effectiveness has become very significant. Since Japanese people with

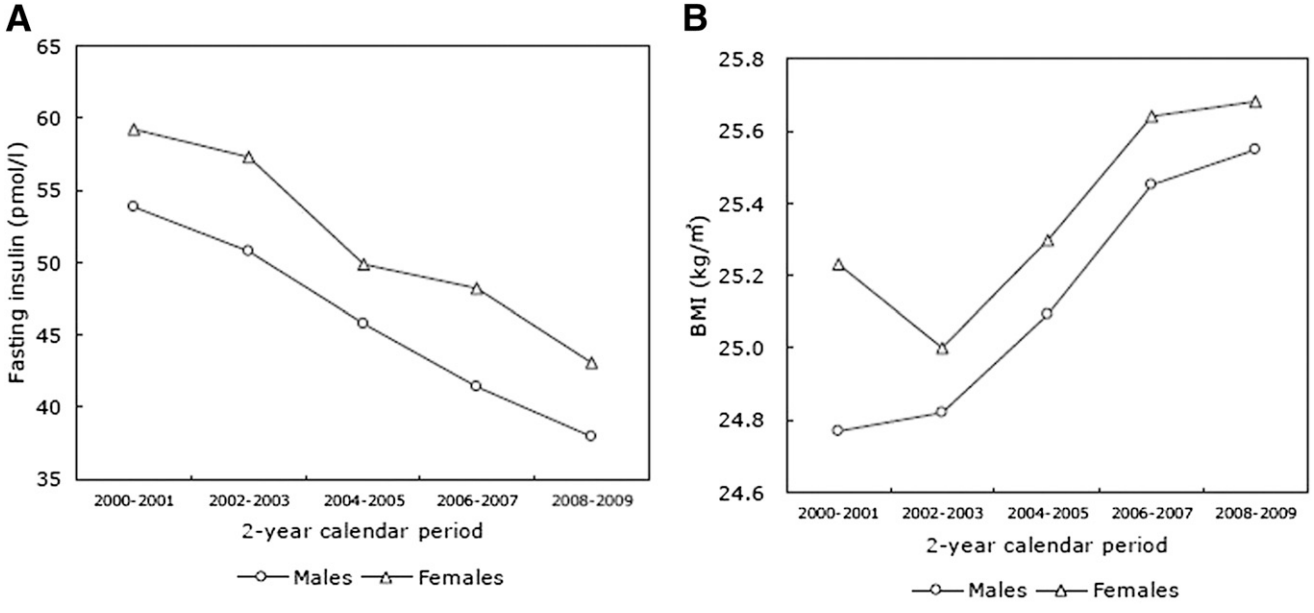

Figure 1—*Estimated marginal mean for ANCOVA results among year groups for fasting insulin* (A) *and BMI* (B). *Covariates in each model were evaluated based on age = 56.7 years and FPG = 9.1 pmol/L.*

Table 2—*Multiple regression models for clinical background factors and fasting insulin levels*

	Model 1		Model 2	
	β-Coefficient	*P* values	β-Coefficient	*P* values
Year group number	−0.163	<0.001[a]	−0.117	<0.001[a]
Mean BP (mmHg)		NS	0.091	<0.001[a]
BMI (kg/m^2)		NA	0.252	<0.001[a]
WC (cm)	0.32	<0.001[a]		NA
LDL (mmol/L)		NS	0.09	<0.001[a]
HDL (mmol/L)	−0.096	<0.001[a]	−0.109	<0.001[a]
TGs (mmol/L)	−0.193	<0.001[a]	−0.045	0.013
Microalbuminuria (mg/g · Cr)		NS	0.041	0.009

The dependent variable was fasting insulin and the independent variables were year group number, mean BP, LDL cholesterol, HDL cholesterol, TGs, microalbuminuria, WC (model 1), and BMI (model 2). The R^2 values were 0.38 and 0.42 for models 1 and 2, respectively. Data were adjusted for sex, age, and HbA_{1c}. NA, not applicable. [a]Significant *P* values on the Wald *F* test for fasting insulin variables.

their lower insulin secretion ability cannot completely compensate for this, the prevalence of diabetes is increasing dramatically. In addition, it has been shown that Japanese Americans have experienced a higher prevalence of type 2 diabetes than in Japan. Research conducted in Seattle, WA, suggests that lifestyle factors associated with Westernization play a role in exacerbating this susceptibility to diabetes (22).

BMI is a strong determinant of insulin resistance, and it is concordant with the evidence that the mean BMIs of representative epidemiologic studies of Japanese diabetic patients are from 23 to 25 kg/m^2 lower than in the studies of other ethnic populations (23,24). BMI and WC thresholds vary among ethnicities, and values are lower for Asian populations.

Local and regional data have shown that the same level of BMI connotes a greater degree of obesity in Asians compared with Caucasians (25), and that Asians are prone to disorders such as diabetes, hypertension, and dyslipidemia at lower levels of BMI than Caucasian populations (25). The use of BMI as a measure of body proportion is a limitation because of its inability to provide information on body fat distribution and central adiposity. Asians have a higher percentage of body fat at a lower BMI than Caucasians. The current study also indicates that, for Japanese, a slight increase in WC/BMI may be as informative with regard to diabetes risk due to decreasing fasting insulin levels.

Decreased β-cell function and decreased insulin sensitivity are the two major risk factors for the development of type 2 diabetes. Insulin sensitivity varies widely among individuals who have normal glucose tolerance (26). The ability of β-cells to compensate for a decrease in insulin sensitivity enables these individuals to maintain normal glucose levels. The fundamental pathological sequence leading to type 2 diabetes is presumed to be the development of an obesity-induced decrease in insulin sensitivity followed by hyperglycemia when the β-cells can no longer compensate (27). However, it is still unknown whether β-cell dysfunction (28), decreased insulin sensitivity (29), or a combination of both defects is the primary abnormality leading to type 2 diabetes (30). Although the risk factors for type 2 diabetes are similar among ethnically diverse populations, there are ethnic differences in insulin sensitivity and β-cell function among groups at high risk for type 2 diabetes.

Since the study design was cross-sectional, causal relationships cannot be explored. Therefore, this analysis must be interpreted within the context of certain limitations. First, as our study included only type 2 diabetic patients in diabetes clinics/hospitals, our findings cannot be generalized to other patients in a typical practice or community population. Also, fasting insulin levels are limited measures of insulin sensitivity and β-cell function. Other environmental or lifestyle factors, including dietary fat or fiber, alcohol consumption, physical activity, smoking, and socioeconomic status might be related to the decreasing trend in fasting insulin over the 10-year period. Nevertheless, we have shown that fasting insulin levels in subjects with newly diagnosed diabetes have been decreasing progressively from 2000 to 2009, and this decrease has been associated with an increase in MRFs, particularly WC and BMI. In conclusion, the superimposition of low pancreatic β-cell reserve upon a lifestyle background of metabolic parameters appears to result in hyperglycemia and diabetes in Japan.

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I.M. designed the study, collected and interpreted data, and wrote the manuscript. K.S., M.T., and H.S. collected and interpreted data. K.H. collected and interpreted data and revised the manuscript for important intellectual content. All authors approved the final version of the manuscript. I.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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