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)

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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, HbA1c, blood pressure (BP), and lipids measured. BMI was calculated as weight (kg) divided by height squared (m²). BP was measured with a standard mercury sphygmomanometer. Mean BP values were determined from the measurements. Waist circumference (WC) was assessed at the...
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 HbA1c level and plasma concentrations of glucose, LDL cholesterol, HDL cholesterol, triglycerides (TGs), creatinine, and insulin. Plasma glucose was measured by a glucose-oxidase method. HbA1c, 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 4.1 mmol/L (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, HbA1c, fasting insulin, TGs, LDL cholesterol, HDL cholesterol, and microalbuminuria were 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, HbA1c, 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**                                 |
| 2000–2001  | 2002–2003 | 2004–2005 | 2006–2007 | 2008–2009 | P value<sup>a</sup> |
| n (N = 4,798) | 957 | 1,131 | 1,311 | 941 | 458 | 0.612 |
| Sex (male/female) | 645/312 | 748/383 | 884/427 | 654/287 | 309/149 | 0.089 |
| Age (years) | 56.1 ± 11.3 | 56.6 ± 11.4 | 57.4 ± 11.8 | 56.8 ± 11.8 | 57.4 ± 12.4 | 0.283 |
| Mean BP (mmHg) | 106 ± 15 | 105 ± 15 | 105 ± 14 | 104 ± 14 | 104 ± 14 | 0.05 |
| WC (cm) | 85.6 ± 9.3 | 85.9 ± 10.3 | 86.2 ± 9.3 | 86.8 ± 8.9 | 87.6 ± 10.3 | <0.05 |
| %WC (cm) ≥80 (men) or ≥75 (women) | 69.1 | 70.3 | 66.2 | 69.2 | 72.1 | 0.674 |
| BMI (kg/m²) | 24.9 ± 4.0 | 24.8 ± 3.9 | 25.1 ± 4.1 | 25.5 ± 4.2 | 25.6 ± 4.4 | <0.001 |
| FPG (mmol/L) | 8.80 ± 2.56 | 9.28 ± 2.71<sup>b</sup> | 9.1 ± 2.75 | 9.21 ± 2.76<sup>b</sup> | 8.98 ± 2.58 | <0.01 |
| HbA₁c (% NGSP units) | 8.3 ± 1.7 | 8.6 ± 1.8<sup>c</sup> | 8.8 ± 2.0<sup>c</sup> | 8.9 ± 1.9<sup>c</sup> | 7.7 ± 1.9<sup>c</sup> | <0.001 |
| Fasting insulin (pmol/L) | 55.6 ± 46.3 | 52.9 ± 49.2<sup>c</sup> | 47.1 ± 43.4<sup>c</sup> | 43.4 ± 44.9<sup>c</sup> | 39.6 ± 34.0<sup>c</sup> | <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<sup>c</sup> | <0.001 |
| HDL (mmol/L) | 1.37 ± 0.37 | 1.38 ± 0.36 | 1.42 ± 0.38<sup>b</sup> | 1.41 ± 0.37 | 1.42 ± 0.37 | <0.01 |
| TGs (mmol/L) | 1.61 ± 1.19 | 1.80 ± 1.52<sup>b</sup> | 1.72 ± 1.31<sup>b</sup> | 1.85 ± 1.39<sup>b</sup> | 1.82 ± 1.32<sup>b</sup> | <0.01 |
| Microalbuminuria (mg/g Cr) | 74.5 ± 11.4 | 103.7 ± 11.7 | 129.1 ± 19.2 | 129.9 ± 16.2<sup>c</sup> | 139.8 ± 29.7<sup>c</sup> | <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 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. <sup>P</sup> values determined by ANOVA among the five consecutive 2-year groups or by the χ² test. <sup>B</sup>P < 0.05. <sup>C</sup>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 adjustment for sex, age, and HbA1c, 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 HbA1c. 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

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**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  | <0.001a | -0.117  | <0.001a |
| Mean BP (mmHg)   | NS      |          | 0.091   | <0.001a |
| BMI (kg/m²)      | NA      |          | 0.252   | <0.001a |
| WC (cm)          | 0.32    | <0.001a |          | NA      |
| LDL (mmol/L)     | -0.096  | <0.001a | -0.109   | <0.001a |
| HDL (mmol/L)     | -0.193  | <0.001a | -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 R² values were 0.38 and 0.42 for models 1 and 2, respectively. Data were adjusted for sex, age, and HbA1c. NA, not applicable. *Significant P values on the Wald F test for fasting insulin variables.
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