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Letters

Insulin resistance facilitates the development of coronary artery disease in Japanese Type II diabetic patients: a single hospital-based follow-up study

Dear Sir,

Insulin resistance and hyperinsulinaemia are often associated with many cardiovascular risk factors. Whether or not insulin resistance or hyperinsulinaemia or both are risk factors for cardiovascular disease is, however, controversial [1]. Even if these conditions are risk factors, their mechanisms may vary among different ethnic populations. This study, in Japanese diabetic patients, has directly tested the hypothesis that insulin resistance in itself is a cardiovascular risk factor. We conducted a 4–8 (average 5.8) year prospective study on patients with Type II (non-insulin-dependent) diabetes mellitus who were regularly examined at our hospital to accurately assess their outcome.

The subjects were 89 Type II diabetic patients who underwent evaluation of whole-body insulin sensitivity using the euglycaemic hyperinsulinaemic clamp method described previously [2]. All subjects met the following criteria: 1) older than 40 years of age at the time of the clamp test (baseline), 2) absence of macrovascular disease and 3) observation for at least 4 years in our diabetes centre. During the follow-up period, ten patients (11.2%, 5 men) developed coronary artery disease, three patients (3.4%, 1 man) cerebrovascular disease and one patient (1.1%, woman) peripheral artery disease (two patients developed two diseases). Coronary artery disease was diagnosed by cardiologists: seven patients (including six non-fatal myocardial infarction) by angiography and three by electrocardiogram on the tread-mill test and ^{201}Thallium scintigraphy. We compared the following variables between the macrovascular disease-negative group ($n = 77$, 43 men) and coronary artery disease group ($n = 10$, 5 men): age (55 ± 9 vs 58 ± 7 years, means ± SD, respectively), sex (55.8 vs 50.0% for men), body mass index (23.2 ± 3.8 vs 24.1 ± 3.1), duration of diabetes (7.5 ± 4.3 vs 8.8 ± 3.8 years), smoking (24.7 vs 30.0%), treatment modality (19 : 41 : 40% vs 40 : 40 : 20% for diet : oral hypoglycaemic agents : insulin), association of retinopathy (47.4 vs 60.0%) and nephropathy (38.2 vs 70.0%, not statistically significant, $p = 0.0865$ by Fisher's exact probability test) at baseline, and haemoglobin A_{1c} (7.7 ± 1.7 vs 7.6 ± 1.3%) and mean arterial blood pressure (98.2 ± 9.3 vs 95.6 ± 8.9 mm Hg) wherein three determinations a year were used, and serum concentration of total cholesterol (5.53 ± 0.91 vs 5.51 ± 0.67 mmol/l), high-density-lipoprotein cholesterol (1.42 ± 0.41 vs 1.16 ± 0.28 mmol/l) and triglyceride (1.86 ± 1.31 vs 2.60 ± 1.19 mmol/l) using all data available. There were no statisti-

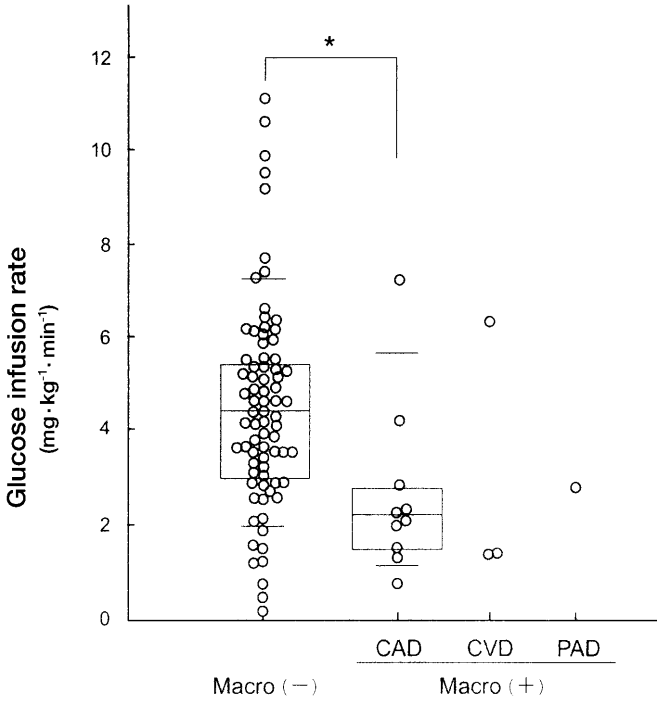

Fig. 1. Raw values with box plot presentation of glucose infusion rate in Type II diabetic subjects with or without macrovascular diseases (Macro). CAD = coronary artery disease, CVD = cerebrovascular disease, PAD = peripheral artery disease. * $p = 0.004$

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cally significant differences in any of the above conventional variables. The average glucose infusion rate (an index for insulin resistance) of 2.68 ± 1.86 mg $\cdot$ kg^{-1} $\cdot$ min^{-1} for the coronary artery disease group was, however, lower than 4.55 ± 2.2 mg $\cdot$ kg^{-1} $\cdot$ min^{-1} for the non-macrovascular disease group ($p = 0.004$ by Mann-Whitney test) (Fig. 1). One patient with a normal glucose infusion rate (7.28 mg $\cdot$ kg^{-1} $\cdot$ min^{-1}) developed unstable angina. This patient smoked and had hypertension and incipient nephropathy but obesity, hyperinsulinaemia, and dyslipidaemia were not observed. Risk ratio analysis by quartile showed that patients whose glucose infusion rate fell in the lowest quartile had a relative risk of developing cardiovascular disease approximately seven times higher than patients with higher infusion rates. This result was the same whether the comparison was to an individual higher quartile or the combined quartiles above the lowest. We did not measure the serum insulin concentration in all cases because about one third of the subjects used variable doses of daily insulin. The clinical features common to ten coronary artery disease patients were that they were non-obese and had a higher prevalence of nephropathy, although they were not statistically significantly different from those for the non-macrovascular disease group. Based on these results we concluded that insulin resistance either alone or in combination with some undetermined risk factors, contributes to the development of coronary artery disease in Japanese Type II diabetic subjects. Type II diabetic subjects showing lower insulin sensitivity should therefore be considered as a high-risk group for coronary artery disease and their coronary management should be closely monitored.

Yours sincerely,
T. Wasada, K. Katsumori, H. Kuroki, Y. Iwamoto

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Absence of glutamic acid decarboxylase antibodies in Pima Indian children with diabetes mellitus

Dear Sir,
The Pima Indians of Arizona have the world's highest incidence and prevalence of Type II (non-insulin-dependent) diabetes mellitus and the disease is now common in Pima Indian children [1]. Based on clinical characteristics and lack of islet cell antibodies in a previous sample of 46 diabetic Pimas aged 17–47 years, their disease was described as being exclusively Type II (i. e. not immune mediated and not insulin-dependent) diabetes [2]. There is no evidence for linkage to known MODY loci in the Pimas [3]. To characterize diabetes further in Pima children, we determined the presence of glutamic acid decarboxylase antibodies (GAD65Ab) which are positive in 75–80 % of patients with the autoimmune form of Type I (insulin-dependent) diabetes mellitus [4] and rarely found in children without diabetes [5].

This report includes the 125 diabetic Pima subjects aged 5 to 19 years, reported in our recent paper [1]. Diabetes was diagnosed by the World Health Organisation WHO criteria and obesity was estimated according to relative weight. Sera frozen at the time of each subject's first examination with diabetes (the date of diagnosis for 78 % of the subjects) were used for the antibody test. We measured GAD65Ab in a radiobinding immunoassay on coded serum samples [5]. The levels were expressed as relative index (GAD65 index); the assay considers a positive at 0.07, the 97.5 centile based on 200 normal controls (unpublished data).

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Table 1. Characteristics of 125 children with Type II diabetes

	Age group[a] (years)		
	5–9	10–14	15–19
Number	3	44	78
% in upper tertile of relative weight[b]	33	84	74
% GAD65Ab 0.07–0.14	0	11.3	2.6
% GAD65Ab > 0.14	0	0	0

[a] Age group at first exam with diabetes
[b] Age-specific

The characteristics of the 125 children with diabetes, at the first examination at or after the time of diagnosis, are shown in the Table 1. Their clinical features indicate Type II diabetes and include a family history of Type II diabetes in 92 % of the subjects, obesity (relative weight in the upper tertile, ≥ 110 %) in 68 %, lack of symptoms at diagnosis (78 % were diagnosed at a research examination, following a 75-g oral glucose tolerance test, OGTT) and infrequent subsequent insulin treatment (17 %). The levels of GAD65Ab, expressed as GAD65 indices, were similar in Pima Indian children with diabetes (median = 0.027; range = –0.06, 0.14), and in 85 non-diabetic Swedish children (median = –0.007; range = –0.03, 0.82). By contrast, they were substantially lower than in 155 Swedish children with newly diagnosed Type I diabetes (median = 0.29; range = –0.02, 2.4) [5].

Of the 125 Pima children with diabetes only seven (5.6 %) had GAD indices of 0.07 or more. The expected rate of indices ≥ 0.07 was 2.5 %; therefore, the excess over a non-diabetic cohort was only 3.1 %. The weakly GAD65Ab positive children were of full Indian heritage, obese and had at least one parent with Type II diabetes. One was subsequently treated with insulin. This subject was born to a mother with Type II diabetes. At age 3.5 years he had an OGTT diagnostic of diabetes (2-h glucose 12.2 mmol/l), but several normal tests during subsequent years. At age 11 years he had a GAD65Ab index of 0.09 and a 2-h glucose concentration of 10.8 mmol/l. At age 13 years he developed symptoms of diabetes (polyuria and enuresis) and had