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Risk factors for worsening to diabetes in subjects with impaired glucose tolerance

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Summary. In a 5–12 year follow-up study of 288 subjects with impaired glucose tolerance after a 100-g glucose load, 48 worsened to overt Type 2 (non-insulin-dependent) diabetes with the elevation of fasting blood glucose. The initial level of blood glucose was a major predictor of subsequent worsening to diabetes. In addition, subjects with a lower insulin response to glucose showed a higher incidence of worsening to the disease, irrespective of blood glucose levels. Multivariate analysis indicated that a diminished insulin response and a high maximal body weight index, as well as a high level of fasting and 2-h glucose values at the initial 100-g oral glucose tolerance test were significant independent risk factors for the development of diabetes in Japanese subjects.

Key words: Impaired glucose tolerance, Type 2 diabetes, worsening to diabetes, multivariate analysis, diminished insulin response, obesity.

A prospective follow-up study of subjects with impaired glucose tolerance is a useful way to study the aetiology and pathogenesis of diabetes mellitus. There have been several follow-up studies of subjects with impaired glucose tolerance reported in the literature [1–8]. These studies agree that the initial degree of hyperglycaemia is an important index predictive of subsequent worsening to diabetes, but the roles of obesity and low insulin response as predictive factors remain controversial.

Recently, based on the Second Report of the WHO Expert Committee on Diabetes Mellitus [9], the Japan Diabetic Society proposed a new set of diagnostic criteria for oral glucose tolerance tests [10]. In this proposal, a 'borderline type' was established between normality and diabetes. This prompted us to define a high risk group for worsening to diabetes in the 'borderline type'.

It is the purpose of the present study to report the results of a 5–12 year follow-up of 288 subjects of the 'borderline type' and to elucidate the risk factors for worsening to diabetes with special reference to diminished insulin response and obesity.

Subjects and methods

Subjects

The subjects were selected from the out-patient clinic of the Institute for Adult Diseases, Asahi Life Foundation, whose first visit was between 1 January 1969 and 31 December 1976. A total of 288 subjects was observed for 5–12 years (8.7 ± 2.6 years, mean ± SD). They presented with intermediate glucose levels at the initial 100-g oral glucose tolerance test corresponding with the 'borderline type' of the Japan Diabetic Society, as defined below.

Blood glucose was determined by a glucose oxidase method using a glucose-autoanalyser (Hitachi, Tokyo, Japan) from capillary whole blood. Samples were taken before and 30, 60, 120 and 180 min after a 100-g glucose load. Plasma immunoreactive insulin (IRI) was measured by a double-antibody technique [11] in venous blood samples withdrawn at the same time, the intra-assay variance being 8.1% and the interassay variance 11.4%. The glucose tolerance test results were divided as follows: (a) *diabetic type:* fasting blood glucose ≥ 6.7 mmol/l (120 mg/100 ml) and/or 2-h blood glucose ≥ 13.3 mmol/l (240 mg/100 ml); (b) *'borderline type':* fasting blood glucose between 5.6–6.7 mmol/l (100–120 mg/100 ml), and/or 1-h blood glucose ≥ 8.9 mmol/l (160 mg/100 ml), and/or 2-h blood glucose between 7.2–13.3 mmol/l (130–240 mg/100 ml); (c) *normal type:* fasting blood glucose < 5.6 mmol/l (100 mg/100 ml), and 1-h blood glucose < 8.9 mmol/l (160 mg/100 ml), and 2-h blood glucose < 7.2 mmol/l (130 mg/100 ml).

According to the comparison of 75-g and 100-g oral glucose tolerance tests made by Hagura [12], 2-h blood glucose values of 7.2–13.3 mmol/l (130–240 mg/100 ml) after a 100-g glucose load correspond with values of 6.7–11.1 mmol/l (120–200 mg/100 ml) after a 75-g glucose load. Therefore, the range of blood glucose values of the 'borderline type', as defined by the Japan Diabetic Society, has a similar upper limit to 'impaired glucose tolerance' in the diagnostic criteria of the WHO Expert Committee on Diabetes Mellitus [9], but a lower limit that is 1.1 mmol/l (20 mg/100 ml) lower.

Subjects previously known to be hyperglycaemic or who were receiving treatment were excluded.

Baseline variables

At the initial examination, the following nine baseline variables were recorded whose relationships to the deterioration of glucose tolerance were investigated: (a) age; (b) sex; (c) family history (judged as posi-

tive when either parents, siblings or children had diabetes); (d) past maximal body weight index (%) = [past maximal body weight (kg)/(body height (cm) -100) $\times 0.9$ (kg)] $\times 100$ [13] (when a subject had a highest body weight index before the initial visit, this value was used and when the highest body weight index was recorded at the initial visit, this value was used); (e) body weight index at the first visit; (f) fasting blood glucose at the initial 100-g oral glucose tolerance test; (g) 2-h blood glucose at the initial 100-g oral glucose tolerance test; (h) increments of insulin 30 min after a 100-g glucose load above the fasting values at the initial examination ($\Delta IRI_{(30)}$); (i) the ratio of increments of insulin to that of blood glucose 30 min after a 100-g glucose load at the initial examination ($\Delta IRI/\Delta BG_{(30)}$). First, since the absolute rise in blood insulin depends upon the glycaemic stimulus, it is necessary to estimate insulin response taking blood glucose rise into consideration [14, 15]. Second, impairment of 'early-phase' insulin response to glucose is characteristic of diabetic metabolism [14, 16]. In these respects, the ratio of increment of insulin to that of blood glucose at 30 min after a 100-g glucose load provides a simple measure of B cell function and this parameter has been regarded as one of the clinically useful indicies of insulin response [14, 17–19]. The value of 9.0 mU/mmol or 0.05 mU/mg for $\Delta IRI/\Delta BG_{(30)}$ serves as a meaningful point for insulin response based on the following observations: the majority of $\Delta IRI/\Delta BG_{(30)}$ values in healthy subjects are higher than 9.0 mU/mmol or 0.05 mU/mg, while $\Delta IRI/\Delta BG_{(30)}$ values are almost invariably lower than 9.0 mU/mmol or 0.05 mU/mg in subjects with definite diabetes who had presented with a fasting blood glucose $\geq$ 7.8 mmol/l (140 mg/100 ml) [17, 19]. Thus, in the present report we define a low insulin response as $\Delta IRI/\Delta BG_{(30)} < 9.0$ mU/mmol or 0.05 mU/mg and a normal-high insulin response as $\Delta IRI/\Delta BG_{(30)} \geq$ 9.0 mU/mmol or 0.05 mU/mg.

Worsening to overt diabetes

After the initial visit, the patients were reviewed at 1–4 month intervals for 5–12 years. Baseline variables were examined repeatedly at predetermined intervals; fasting blood glucose was examined approximately 4 monthly and ophthalmoscopy was performed yearly. They received no medication for diabetes during the observation period and were treated by diet alone; total calorie intake was restricted to 30 kcal · day^{-1} · kg^{-1} ideal body weight.

Subjects were diagnosed as having definite or unequivocal diabetes when they fulfilled at least one of the following criteria: (1) fasting blood glucose $\geq$ 7.8 mmol/l (140 mg/100 ml) (capillary whole blood); (2) development of clear diabetic retinopathy; scattered microaneurysms plus fasting blood glucose $\geq$ 6.7 mmol/l (120 mg/100 ml).

Statistical analysis

Proportional hazard function analysis [20], which takes varying follow-up times into account, was used to determine the roles of variables at the first examination in relation to worsening to diabetes. Coefficients were calculated from the linear discriminant function of the variables. Selection of variables was done in a stepwise fashion by use of a backward selection method. In practice, the variable with the lowest t-value was discarded one by one until each t-value of the variables reached the level of over $\sqrt{2}$.

Results

Baseline characteristics

After follow-up for 5–12 years, 48 of the 288 subjects developed frank diabetes. Among these 48 subjects, 34 had a fasting blood glucose $\geq$ 7.8 mmol/l (140 mg/100 ml) without retinopathy, seven subjects had clear diabetic retinopathy and the remaining seven had both a fasting blood glucose $\geq$ 7.8 mmol/l (140 mg/100 ml) and retinopathy. There was no difference in follow-up periods between those worsening to diabetes and those who did not worsen (8.4 ± 2.7 and 8.7 ± 2.5 years (mean ± SD), respectively).

We have compared those worsening to diabetes (n = 48) and those who did not worsen to diabetes (n = 240) with respect to their blood glucose curves (BG), plasma IRI values and IRI : BG ratio in incremental changes above the fasting values ($\Delta IRI/\Delta BG$) (Table 1) and also the nine baseline variables (Table 2).

Table 1. Blood glucose, plasma immunoreactive insulin and IRI : BG ratio in incremental changes above the fasting values ($\Delta IRI/\Delta BG$) at the initial 100-g oral glucose tolerance test

		Worsening to diabetes (n = 48)	Not worsening to diabetes (n = 240)
Blood glucose (mmol/l)	basal	5.7 ± 0.7[d]	5.2 ± 0.6
	30 min	10.6 ± 1.2[c]	10.0 ± 1.8
	60 min	13.0 ± 1.8[d]	10.9 ± 2.3
	120 min	10.6 ± 1.1[d]	8.7 ± 1.9
	180 min	7.2 ± 2.0[c]	6.4 ± 1.6
Plasma immunoreactive insulin (mU/l)	basal	14.2 ± 8.3	13.1 ± 8.6
	30 min	37.8 ± 22.9[d]	53.9 ± 30.9
	60 min	69.8 ± 46.8	75.8 ± 48.4
	120 min[a]	78.5 ± 62.4	70.2 ± 57.5
	180 min[b]	43.2 ± 29.8	42.4 ± 31.2
$\Delta IRI/\Delta BG$ (mU/mmol)	basal	–	–
	30 min	4.9 ± 4.3[d]	8.5 ± 6.6
	60 min	7.6 ± 5.4[c]	10.8 ± 8.1
	120 min[a]	13.1 ± 9.2	16.6 ± 11.7
	180 min[b]	19.3 ± 15.2	24.4 ± 18.8

Results expressed as mean ± SD. [a,b] n = 32 for those worsening to diabetes and n = 170 for those not worsening to diabetes; [c] $p < 0.05$, [d] $p < 0.01$: for the difference between those worsening to diabetes and those not worsening to diabetes

Table 2. Baseline variables in relation to worsening to diabetes

Variable	Worsening to diabetes (n = 48)	Not worsening to diabetes (n = 240)
Age (years)	49 ± 11	49 ± 10
Number of women (%)	17	28
Positive family history (%)	35	31
Maximal body weight index (%)	127 ± 20[c]	118 ± 16
Body weight index at the first visit (%)	114 ± 20[c]	107 ± 15
Fasting blood glucose (mmol/l)	5.7 ± 0.7[c]	5.2 ± 0.6
2-h blood glucose (mmol/l)	10.6 ± 1.1[c]	8.7 ± 1.9
$\Delta IRI_{(30)}$[a] (mU/l)	23.6 ± 17.7[c]	40.8 ± 30.5
$\Delta IRI/\Delta BG_{(30)}$[b] (mU/mmol)	4.9 ± 4.3[c]	8.5 ± 6.6

Results expressed as mean ± SD. [a] Increments of insulin 30 min after a 100-g glucose load above the fasting values; [b] the ratio of increments of insulin to that of blood glucose 30 min after a 100-g glucose load; [c] $p < 0.01$

Mean blood glucose values were higher in those worsening to diabetes. The incremental changes of blood glucose 30 min after a glucose load, however, were similar between the two groups. Plasma IRI after a glucose load was significantly lower both in the absolute value and in its incremental change above the fasting value in those worsening to diabetes at 30 min, although it was similar at other time points. The ΔIRI/ΔBG curve was lower in those worsening to diabetes; at 30 min this was almost entirely due to a lower ΔIRI value and at 60, 120 and 180 min this was mainly due to higher ΔBG values. Maximal body weight index and body weight index at the first visit were significantly greater in those worsening to diabetes. No significant differences were found between the two groups in mean age, sex or family history.

Multivariate analysis

Baseline variables were examined further by proportional hazard function analysis (Table 3). Because of a close correlation ($r=0.77$, $p<0.001$) between $\Delta IRI_{(30)}$ and $\Delta IRI/\Delta BG_{(30)}$, the roles of these two variables were assessed separately. Initially, the eight baseline variables except $\Delta IRI_{(30)}$, were used and regression coefficients and t-values were calculated. Subsequently, variables, were discarded one by one in a backward stepwise fashion according to the lowest t-value. As a final result, four variables (maximal body weight index, fasting blood glucose, 2-h blood glucose and $\Delta IRI/\Delta BG_{(30)}$) were selected which reached conventional statistical significance (Table 3, Analysis 1). These variables are strongly predictive of subsequent worsening to diabetes; maximal body weight index, fasting blood glucose and 2-h blood glucose are positively related to worsening to diabetes, while $\Delta IRI/\Delta BG_{(30)}$ are inversely related to worsening. On the other hand, body weight index at the first visit was not adopted as a significant independent contributor in the final result of multivariate analysis, though it was significant in the univariate analysis. Next, the proportional hazard function analysis using $\Delta IRI_{(30)}$ instead of $\Delta IRI/\Delta BG_{(30)}$ was performed and this gave similar results (Table 3, Analysis 2).

Blood glucose level in relation to worsening to diabetes

Figure 1 shows the rate of worsening to diabetes in relation to fasting blood glucose and 2-h blood glucose. As fasting blood glucose and 2-h blood glucose values become higher, the rate of worsening clearly increases. Worsening to diabetes was not observed in those with 2-h blood glucose <6.7 mmol/l (120 mg/100 ml) and occurred 5.4 times more frequently in those with an initial 2-h blood glucose ≥ 10.0 mmol/l (180 mg/100 ml) than in those with a 2-h blood glucose between 6.7–10.0 mmol/l (120–180 mg/100 ml).

Table 3. Hazard function analysis relating worsening to diabetes

Variable	Coefficient	t-value
Analysis 1		
Initial step		
Age (years)	−0.38	0.88
Sex	−0.01	0.77
Family history	−0.02	0.09
Maximal body weight index (%)	0.03	2.20[c]
Body weight index at the first visit (%)	−0.00	0.03
Fasting blood glucose (mmol/l)	0.97	3.45[d]
2-h blood glucose (mmol/l)	0.11	2.49[c]
$\Delta IRI/\Delta BG^{a}_{(30)}$ (mU/mmol)	−0.07	1.85
Final step		
Maximal body weight index (%)	0.03	3.81[d]
Fasting blood glucose (mmol/l)	0.97	3.68[d]
2-h blood glucose (mmol/l)	0.13	3.00[d]
$\Delta IRI/\Delta BG^{a}_{(30)}$ (mU/mmol)	−0.07	2.03[c]
Analysis 2		
Initial step		
Age (years)	−0.35	0.81
Sex	−0.01	0.72
Family history	−0.02	0.10
Maximal body weight index (%)	0.03	3.80[d]
Body weight index at the first visit (%)	−0.00	0.03
Fasting blood glucose (mmol/l)	0.95	3.38[d]
2-h blood glucose (mmol/l)	0.13	3.03[d]
$\Delta IRI_{(30)}{}^{b}$ (mU/l)	−0.24	1.95
Final step		
Maximal body weight index (%)	0.03	3.74[d]
Fasting blood glucose (mmol/l)	0.97	3.60[d]
2-h blood glucose (mmol/l)	0.14	3.26[d]
$\Delta IRI_{(30)}{}^{b}$ (mU/l)	−0.24	2.01[c]

[a] The ratio of increments of insulin to that of blood glucose 30 min after a 100-g glucose load at the initial examination; [b] Increments of insulin 30 min after a 100-g glucose load above the fasting values; [c] $p<0.05$; [d] $p<0.01$

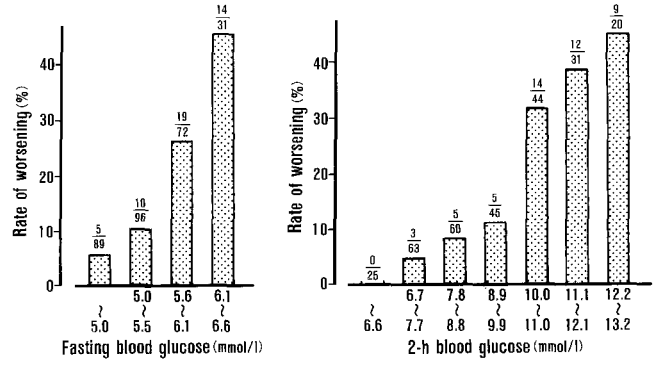

Fig. 1. Incidence of worsening to diabetes in relation to fasting and 2-h blood glucose after a 100-g glucose load at the initial examination. Fractions shown above each column indicate the number of subjects with worsening (numerator) in the total subjects who belong to each class of blood glucose level (denominator)

Table 4. Worsening to diabetes in relation to insulin response to glucose ($\Delta IRI/\Delta BG_{(30)}$)

2-h blood glucose (mmol/l)	Insulin response to glucose: $\Delta IRI/\Delta BG_{(30)}$ (mU/mmol)					
	Severely low (<4.0)		Mildly low (4.0–9.0)		Normal or high (>9.0)	
	Number	Worsening (%)	Number	Worsening (%)	Number	Worsening (%)
< 6.7	10	0 (0)	6	0 (0)	9	0 (0)
6.7–10.0	47	8 (17)[a]	62	4 (7)	59	1 (2)
⩾10.0	45	22 (49)[a]	30	9 (30)	20	4 (20)
Total	102	30 (26)[b]	98	13 (13)	88	5 (6)

The values in parentheses denote the percentage of those worsening to diabetes; [a] $p<0.05$ versus normal or high group; [b] $p<0.01$ versus normal or high group

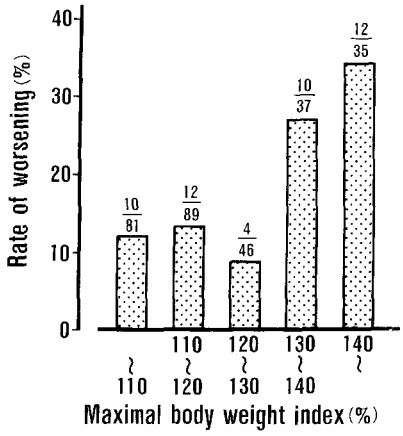

Fig. 2. Incidence of worsening to diabetes in relation to past maximal body weight index. Fractions shown on the top of each column indicate the number of worsening (numerator) in the total subjects who belong to each class of adiposity (denominator)

Maximal obesity in relation to worsening to diabetes

Figure 2 shows the rate of worsening to diabetes in relation to maximal body weight index. This figure indicates that severe obesity has a substantive impact on the subsequent development of diabetes. In fact, in 216 subjects with a maximal body weight index of <130%, only 26 (12%) worsened to diabetes, while in 72 subjects with a maximal body weight index ⩾130%, as many as 22 (31%) worsened to diabetes ($p<0.01$). The influence of obesity was further assessed in the mild glucose intolerance group (2-h blood glucose <10.0 mmol/l or 180 mg/100 ml) and in the severe glucose intolerance group (2-h blood glucose ⩾10.0 mmol/l or 180 mg/100 ml). In the mild glucose intolerance group, the rate of worsening to diabetes was not substantially different between the subjects with a maximal body weight index of <130% and those with a maximal body weight index of ⩾130%; that is, 9.1% in the former and 8.1% in the latter. On the other hand, in the severe glucose intolerance group, worsening to diabetes occurred significantly more frequently in subjects with a maximal body weight index ⩾130% than in those with a maximal body weight index of <130% (49% and 29%, respectively; $p<0.01$).

Insulin response in relation to worsening to diabetes

Table 4 shows the rate of worsening to diabetes in relation to insulin response to glucose ($\Delta IRI/\Delta BG_{(30)}$), taking blood glucose level (2-h blood glucose) into account. It is clearly demonstrated that subjects with lower values of $\Delta IRI/\Delta BG_{(30)}$ showed a higher incidence of worsening to diabetes, irrespective of 2-h blood glucose levels.

In addition, because of the well-known effect of obesity on plasma IRI, subjects were classified into three groups according to their maximal body weight index; group 1 (maximal body weight index <110%, $n=81$), group 2 (maximal body weight index 110–140%, $n=172$), group 3 (maximal body weight index ⩾140%, $n=35$). Group 1 was regarded as a nonobese, group 2 as a mildly or moderately obese and group 3 as an extremely obese group. In each group, the values of $\Delta IRI/\Delta BG_{(30)}$ are shown in Figure 3 in relation to worsening to diabetes. For the sake of comparison, the values of $\Delta IRI/\Delta BG_{(30)}$ for 101 healthy subjects with normal glucose tolerance and 86 definite diabetics who had experienced fasting blood glucose ⩾7.8 mmol/l (140 mg/100 ml) are also plotted in this figure. In groups 1 and 2, deterioration to diabetes occurred almost exclusively in those with a low insulin response whose $\Delta IRI/\Delta BG_{(30)}$ values were below 4.5 mU/mmol and 9.0 mU/mmol, respectively. On the other hand, in group 3 there was no such discriminating point of $\Delta IRI/\Delta BG_{(30)}$ for the subsequent development of diabetes and a certain number of subjects with a normal or high insulin response ($\Delta IRI/\Delta BG_{(30)}$; 15.1–37.3 mU/mmol) did, in fact, develop diabetes. Moreover, as can be seen from Figure 3, in groups 1 and 2, the mean $\Delta IRI/\Delta BG_{(30)}$ values were significantly lower in those worsening to diabetes compared with those who did not worsen. However, in group 3, there was no substantial difference in mean $\Delta IRI/\Delta BG_{(30)}$ values between those who worsened and those who did not worsen to diabetes.

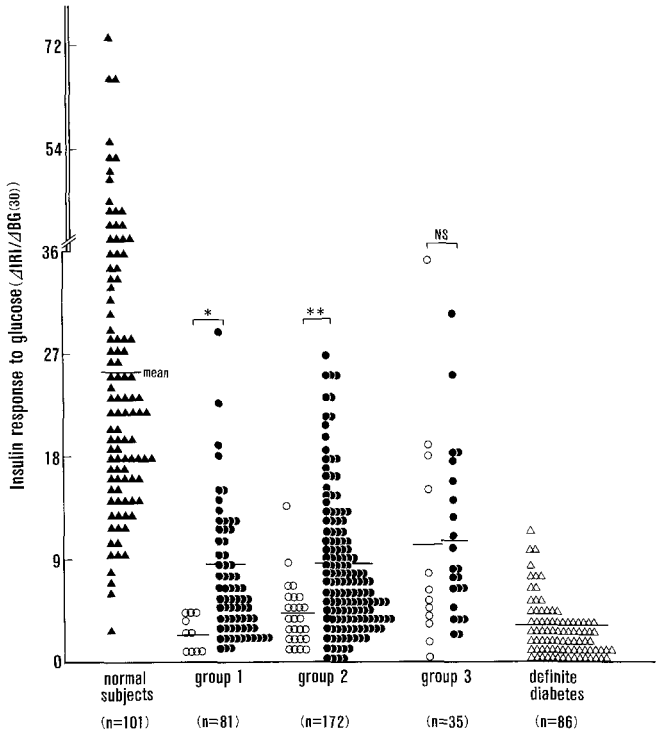

Fig. 3. Insulin response to glucose (ΔIRI/ΔBG(30)) in subjects with impaired glucose tolerance (○; those worsening to diabetes and ●; those not worsening), in normal subjects (▲) and in definite diabetes (△). Groups 1–3 denote subjects with impaired glucose tolerance with maximal body weight index (<110%, 110–140% and >140%, respectively). NS = not significant. $*p<0.05$; $**p<0.01$

Discussion

The present study indicates by multivariate analysis that high levels of both fasting and 2-h blood glucose, obesity and diminished insulin response were all significant independent risk factors for the development of diabetes.

Results of several follow-up studies are in agreement that the initial level of blood glucose is a powerful index for predicting 'worsening to diabetes' [1–7]. Keen et al. showed recently in the Bedford 10-year prospective study of 241 people with borderline diabetes, where 36 (15%) worsened to diabetes, that the major predictor for worsening to diabetes was the level of blood glucose [2]. O'Sullivan et al. demonstrated that an initial postprandial blood glucose level ⩾140 mg/100 ml proved valuable in defining a high risk group for diabetes in a 17-year follow-up study in Oxford, Massachusetts, USA [3]. In keeping up with these observations, our study confirmed again the importance of the initial level of blood glucose in predicting the subsequent development of diabetes.

In contrast with the predicting power of blood glucose level, that of obesity or low insulin response has remained controversial. Obesity is known to be the most common associated finding in Type 2 diabetes, but its predictive value for the development of diabetes has not been fully clarified. Keen et al. showed in the Bedford 10-year study that a large body mass index did not predict a worsening to diabetes during the first 5 years, although it was an independent and significant predictor of worsening during the second 5 years [2]. Hamman et al., in a 10-year follow-up study of Pima Indians, demonstrated that next to 2-h plasma glucose, obesity was the most significant independent predictor for decompensation of glucose tolerance [6]. Our data showed that previous maximal obesity could be regarded as a significant independent risk factor for worsening to diabetes by multivariate analysis and its influence was noticeable particularly in subjects with severe glucose intolerance. Obesity at the first visit had less predicting power for the development of diabetes than previous maximal obesity. This may be due partly to the loss of body weight by metabolic derangement at the time of the first visit even when they were obese in the past. In fact, the prevalence of obesity (body weight index ⩾130%) was 10% at the first visit, while it was 25% if the record of previous maximal body weight was included. The present data might support the idea of a 'delayed diabetogenic effect' of obesity described by Keen et al. [2].

It has been established that insulin response to glucose is decreased in definite diabetes [15–17], but the predictive value of a low insulin response for the development of diabetes remains controversial [19, 21–29]. A critical, yet still unresolved issue concerns whether those who progress to overt diabetes with fasting hyperglycaemia respond to glucose tolerance testing primarily with hypoinsulinaemia [19, 25, 26] or hyperinsulinaemia [22, 30]. Cerasi and Luft demonstrated that in a follow-up of non-diabetic subjects, those with low insulin response did indeed run a greater risk of developing diabetes than those with a normal insulin output [25]. Fajans et al. showed in a follow-up study of families of maturity-onset-type diabetes of the young and young non-obese mildly glucose intolerant patients that progression to insulin-requiring diabetes occurred only in individuals who had insulin responses which were delayed or low, or lower than the mean response of the control subjects [26]. The present report is the first to show that a low insulin response may be regarded as a significant independent risk factor for the development of diabetes in subjects with impaired glucose tolerance, even when one takes other risk factors into account. Thus, the idea that a diminished insulin response incurs a higher risk for the development of diabetes [19, 25, 26] was supported.

Finally, the present study of a large group of Japanese Type 2 diabetic subjects strongly suggests that low insulin secretion forms an essential basis and obesity plays a precipitating role among low-insulin responders for the development of diabetes. At the same time, it should not be disregarded that a certain number of severely obese subjects with apparently normal or high insulin secretion did develop diabetes, though they are a minority of diabetic subjects in Japan. It remains to be

resolved whether these two groups defined by their insulin response are truly distinct or if they belong to two extreme ends of a single spectrum.

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