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***published in***

Journal of Clinical Endocrinology and Metabolism  
2008

***DOI (link to publisher)***

[10.1210/jc.2007-2837](https://doi.org/10.1210/jc.2007-2837)

***document version***

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

***citation for published version (APA)***

Nijpels, G., Boorsma, W., Dekker, J. M., Hoeksema, F., Kostense, P. J., Bouter, L. M., & Heine, R. J. (2008). Absence of an acute insulin response predicts onset of type 2 diabetes in a Caucasian population with impaired glucose tolerance. *Journal of Clinical Endocrinology and Metabolism*, 93(7), 2633-2638. <https://doi.org/10.1210/jc.2007-2837>

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## Absence of an Acute Insulin Response Predicts Onset of Type 2 Diabetes in a Caucasian Population with Impaired Glucose Tolerance

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**Context:** In persons with impaired glucose tolerance (IGT), both impaired insulin secretion and insulin resistance contribute to the conversion to type 2 diabetes mellitus (T2DM). However, few studies have used criterion standard measures to assess the predictive value of impaired insulin secretion and insulin resistance for the conversion to T2DM in a Caucasian IGT population.

**Objectives:** The objective of the study was to determine the predictive value of measures of insulin secretion and insulin resistance derived from a hyperglycemic clamp, including the disposition index, for the development of T2DM in a Caucasian IGT population.

**Design, Setting, and Participants:** The population-based Hoorn IGT study consisted of 101 Dutch IGT subjects (aged < 75 yr), with mean 2-h plasma glucose values, of two separate oral glucose tolerance tests, between 8.6 and 11.1 mmol/liter. A hyperglycemic clamp at baseline was performed to assess first-phase and second-phase insulin secretion and insulin sensitivity. During follow-up, conversion to T2DM was assessed by means of 6-monthly fasting glucose levels and yearly oral glucose tolerance tests.

**Results:** The cumulative incidence of T2DM was 34.7%. Hazard ratio for T2DM development adjusted for age, sex, and body mass index was 5.74 [95% confidence interval (CI) 2.60–12.67] for absence of first insulin peak, 1.58 (95% CI 0.60–4.17) for lowest vs. highest tertile of insulin sensitivity, and 1.78 (95% CI 0.65–4.88) for lowest vs. highest tertile of the disposition index.

**Conclusions:** In these Caucasian persons with IGT, the absence of the first insulin peak was the strongest predictor of T2DM. (*J Clin Endocrinol Metab* 93: 2633–2638, 2008)

Impaired glucose tolerance (IGT) is a strong risk factor for developing type 2 diabetes mellitus (T2DM). About one third of people with IGT develops T2DM in 5–10 yr time (1, 2). The general idea is that insulin resistance precedes  $\beta$ -cell dysfunction in the process of conversion to T2DM (3–7). Most evidence for the predictive value of insulin resistance and  $\beta$ -cell function for T2DM was based on estimates derived from oral glucose tolerance tests (OGTTs), like fasting and 2-h postload insulin levels, fasting proinsulin levels, and the ratio between fasting proinsulin and fasting insulin levels. However, the agreement between these estimates and the criterion standards for insulin sensitivity and  $\beta$ -cell function are far from perfect (8, 9). The criterion standards

for assessing  $\beta$ -cell function and insulin sensitivity are, respectively, the first (and second) insulin secretion phase of the hyperglycemic clamp and the M-value of the euglycemic hyperinsulinemic clamp (10).

Because of the strong correlation between the M-value to insulin (M/I) ratio of the hyperglycemic clamp and the M-value (10–12), the M/I ratio can also be used to assess insulin sensitivity. Clamp studies are time consuming, invasive, and labor intensive and therefore difficult to use in large epidemiological studies. Therefore, only few clamp studies have been performed. Only in populations with a high risk for developing T2DM, such as in Pima Indians, or in populations with IGT, have iv glucose

0021-972X/08/\$15.00/0

Printed in U.S.A.

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doi: 10.1210/jc.2007-2837 Received December 26, 2007. Accepted April 25, 2008.

First Published Online May 6, 2008

Abbreviations: AUC, Area under the curve; BMI, body mass index; DAISI, Dutch Acarbose Intervention Study in IGT Persons; IGT, impaired glucose tolerance; M/I, M-value to insulin; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus; WHO, World Health Organization.

tolerance tests or clamp tests been used (6, 7, 13, 14). In these studies, the first insulin secretion phase was the strongest predictor for developing T2DM (3). However, insulin resistance and  $\beta$ -cell function have a close interrelationship, and this has not been taken into account in most of these studies. In general, insulin resistance is compensated for by an increase in insulin secretion (15). Thus, high insulin production may be regarded as good  $\beta$ -cell function, whereas in reality the insulin production may already be impaired (16, 17). This compensatory insulin secretion in the presence of insulin resistance is taken into account in the disposition index, the product of insulin sensitivity, and insulin secretion. In this study, we analyzed the predictive value of measures, derived from a hyperglycemic clamp, of insulin resistance and insulin secretion, including the disposition index, for the development of T2DM in a Caucasian IGT population.

## Subjects and Methods

### Study population

The participants in our analysis came from two existing studies. The population-based cohort Hoorn Study, conducted in 1989–1991, analyzed the glucose metabolism of 2484 men and women of the municipality of Hoorn (18). During the 1996–1998 follow-up, we identified 55 patients with IGT, all of whom were under 75 yr of age and had mean fasting plasma glucose levels of 6–7 mmol/liter and mean 2-h postload plasma glucose levels of 7.8–11.1 mmol/liter. For the Dutch Acarbose Intervention Study in IGT Persons (DAISI) study, conducted in 1994–1995, a random sample of 12,093 men and women was also taken from the population register of Hoorn (19). From that sample, 6651 participants underwent two OGTTs within 2 wk. Of those, we included the 108 participants who were under 70 yr of age and had mean fasting plasma glucose levels of 5.5–7.8 and mean 2-h postload plasma glucose levels of 8.6–11.1 mmol/liter. The coefficient of variation was 6.5% for fasting plasma glucose and 16.7% for 2-h postload plasma glucose (18). These 108 persons together with the 55 IGT persons from the Hoorn study ( $n = 163$ ) were randomized in the DAISI study (19). The intervention group (acarbose,  $n = 54$ ) was excluded from the present analysis. Finally, the study population for the present analysis consisted of 109 subjects.

All participants signed written informed consents, and the study was approved by the Ethical Review Committee of the VU University Medical Center.

### Measurements

#### OGTT

Blood samples were taken from all patients in a fasting state and 2 h after a 75-g oral glucose load. We used a glucose hexokinase-method (Roche Diagnostics GmbH, Mannheim, Germany) to determine fasting and 2-h postload plasma glucose levels. We determined insulin levels using a two-site immunoradiometric test (Medgenix Diagnostics, Fleurus, Belgium). This insulin-specific test does not show cross-reactivity with proinsulin and split products. Intact proinsulin was determined by immunoradiometric method based on antibodies (Dako, Cambridgeshire, UK).

#### Hyperglycemic clamp

Participants underwent a hyperglycemic clamp after at least 12 h of fasting. Lying supine, patients received a priming infusion of saline (0.9%) and glucose (20%) in one arm. To sample blood, we cannulated

a vein on the back of the hand of the opposite arm. The hand was placed in a thermo-regulated box at 45°C to arterialize the venous blood. After infusing the patients with a bolus of glucose (150 mg/kg), we took immediate blood glucose measurements every 2.5 min with a glucose analyzer (Yellow Springs Instrument, Inc., Yellow Springs, OH); we maintained blood glucose levels at a hyperglycemic level of 10 mmol/liter for 180 min. We obtained insulin samples every 2.5 min during the first 10 min and at 5- to 10-min intervals for the remaining 170 min.

### Clamp-derived estimates of insulin sensitivity

Under stable conditions of constant hyperglycemia, the amount of glucose infused (milligrams per kilogram per minute) equals the amount of metabolized glucose. The amount of glucose infused was calculated by the area under the curve of the glucose infusion rate during the last 20 min of the clamp using the trapezoidal rule. The M value divided by the average plasma insulin concentration during the same interval, the M/I ratio, provides a measurement of tissue sensitivity to insulin (milligrams per kilogram per minute per milliunit per liter).

### Clamp-derived estimates of $\beta$ -cell function

Several measures of  $\beta$ -cell function were obtained from the hyperglycemic clamp (20). The first insulin secretion phase was assessed in the first 15 min of the clamp. For the definition of the presence of a first insulin peak, we used the following procedure. By visual inspection, we selected 23 flat insulin curves. For each separate curve, we calculated the SD of the insulin values. Next, from these 23 SDs, we calculated the pooled estimate of the typical SD of these flat curves. We considered an insulin peak present if the difference between two subsequent insulin levels exceeded  $1.96 \cdot \sqrt{2} \cdot$  pooled estimate (Fig. 1).

Another measure for the first insulin secretion phase was the area under the curve ( $AUC_{ins0-10}$ ) of the insulin levels of the first 10 min of the clamp, which were calculated using the trapezoidal rule. The second insulin secretion phase (160–180 min) was calculated by the mean insulin level of that period ( $ins_{160-180}$ ).

### Other measurements

During the baseline medical examination, we measured weight, height, and waist and hip circumferences and calculated body mass index (BMI) and waist to hip ratio. We measured blood pressure twice on the right arm with a random-zero sphygmomanometer (Hawksley-Gelman Ltd., Lancing, UK) and used the mean in our analyses.

### Disposition index

The disposition index was calculated as the product of M/I ratio (micrograms per kilogram per minute per milliunits per liter) and the  $AUC_{ins0-10}$  (milliunits per liter).

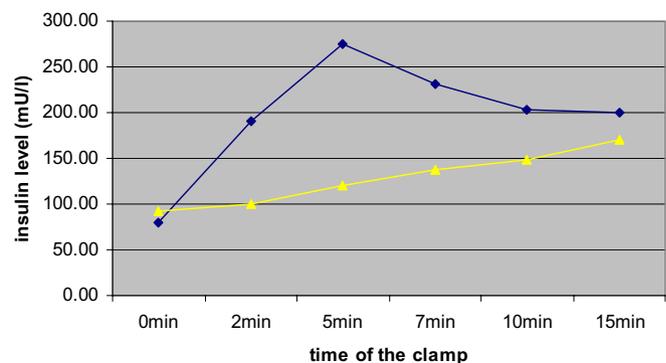


FIG. 1. Difference between persons with and without a peak of insulin levels in the first 15 min of the hyperglycemic clamp.

## Conversion to diabetes

When the study started, the World Health Organization (WHO) had in 1985 defined T2DM as a fasting plasma glucose value of 7.8 mmol/liter or greater and/or a 2-h plasma glucose value of 11.1 mmol/liter or greater (21). In 1999, during the study, the WHO lowered the fasting plasma glucose value criterion to 7.0 or greater (the 2 h plasma glucose value remained  $\geq$  11.1 mmol/liter) (22). We used both sets of WHO criteria in separate analyses (not all WHO 1985 analyses are shown). For the analysis with the WHO 1999 criteria, participants with a fasting plasma glucose of 7.0 mmol/liter or greater at the start of the study were excluded.

In the participants of the DAISI study, fasting plasma glucose levels were measured every 3 months for 3 yr and once a year thereafter. In the participants of the Hoorn Study, fasting plasma glucose was measured yearly. Participants underwent an OGTT if the fasting plasma glucose level reached a value of 6.0 mmol/liter or greater or at the end of the study. For subjects not developing T2DM, the follow-up time was calculated as years from the date of the baseline clamp to the end of the study, with a maximum of 8 yr.

## Statistical methods

Quantitative data are expressed as means with SDs (skewed variables as medians with interquartile ranges) and categorical data as percentages. ANOVA was performed to test for statistically significant differences between continuous variables, the skewed variables were log transformed first. When variances were unequal among the groups to test (Levene's test), differences were evaluated by Mann-Whitney *U* test.  $\chi^2$  test was used to test for categorical variables. We calculated the cumulative incidence of T2DM using the 1999 WHO definition. The incidence was also calculated in tertiles of the clamp-derived measures of insulin resistance and  $\beta$ -cell function and in tertiles of the disposition index, after which Kaplan-Meier survival curves were plotted. Multivariate analyses were performed, adjusted for sex and age, using Cox proportional hazard analysis. Insulin resistance and  $\beta$ -cell function were first analyzed separately and subsequently combined in one model. The relative risk of the incidence of T2DM was calculated as a hazard ratio with a 95% confidence interval. All statistical analyses were performed with SPSS

12.0.1 (SPSS Inc., Chicago, IL).  $P < 0.05$  was considered to be statistically significant.

## Results

The cumulative incidence of T2DM according to 1999 WHO criteria was 34.7% (mean follow-up 4.2 yr; range 0.5–8.0 yr). Table 1 presents the baseline characteristics for participants who did and did not develop T2DM.

The mean glucose level during the clamp was 10.2 mmol/liter (SD 1.07), the coefficient of variation of the glucose level during the clamp was 10.5%. The mean glucose level during the last 20 min of the clamp was 9.9 (SD 0.6), the coefficient of variation 6.6%.

Figure 2 shows Kaplan-Meier survival curves for the presence or absence of the first insulin peak and tertiles of the M/I ratio, disposition index, and first insulin secretion phase. The absence of the first insulin peak was the strongest predictor for the development of T2DM.

Table 2 shows the results of Cox proportional hazards analyses of OGTT and clamp-derived measures for the incidence of T2DM for both the 1985 and 1999 WHO criteria, adjusted for age, sex, and BMI. The highest hazard ratio was observed for the absence of the first insulin peak. The other variables were not as predictive of T2DM development (1999 WHO criteria). First-phase insulin secretion, insulin resistance, second-phase insulin secretion, and the disposition index were not significantly associated with the risk of developing T2DM. When we applied the WHO 1985 criteria, however, the first insulin secretion phase and the disposition index were both predictive of T2DM conversion.

**TABLE 1.** Baseline characteristics of participants developing and not developing diabetes

1999 WHO definition	No diabetes Mean (SD)	Diabetes Mean (SD)	<i>P</i> value
n	66	35	
Age (yr)	62.7 (8.9)	61.3 (9.1)	0.45
Sex (percent men)	50%	40%	0.23
Hemoglobin A <sub>1c</sub>	5.5 (0.5)	5.7 (0.6)	0.10
BMI (kg/m <sup>2</sup> )	27.3 (3.7)	29.0 (4.4)	0.04
Waist			
Women	92.2 (84.3–97.6)	98.0 (88.6–102.3)	0.14
Men	95.4 (92.0–99.0)	99.4 (95.7–106.3)	0.06
Waist to hip ratio			
Women	0.88 (0.80–0.95)	0.90 (0.80–0.92)	0.19
Men	0.94 (0.80–1.00)	0.90 (0.90–0.95)	0.43
OGTT measurements			
Fasting plasma glucose (mmol/liter)	5.9 (0.7)	6.5 (0.6)	0.001
Two-hour postload plasma glucose (mmol/liter)	7.8 (2.0)	9.3 (1.1)	0.001
Fasting specific insulin (mU/liter)	9.0 (7.2–12.3)	11.4 (8.5–15.8)	0.04
Fasting proinsulin (mU/liter)	2.3 (1.8–3.0)	2.8 (2.1–5.3)	0.06
Hyperglycemic clamp measurements			
Peak (percent present)	80%	52%	0.004
AUC, 0–10 min (mU/liter min <sup>-1</sup> )	24.6 (16.7–34.1)	21.9 (15.4–39.4)	0.95
Mean insulin, 160–180 min (mU/liter min <sup>-1</sup> )	48.1 (36.1–78.8)	47.9 (33.4–103.6)	0.75
MI ratio (mg/kg/min per mU/1)	11.2 (6.3–15.2)	9.8 (4.4–16.2)	0.29
Disposition index	226.4 (147.5–349.9)	176.8 (137.4–307.6)	0.14

Values are means (SD) or medians (interquartile ranges) for skewed variables.

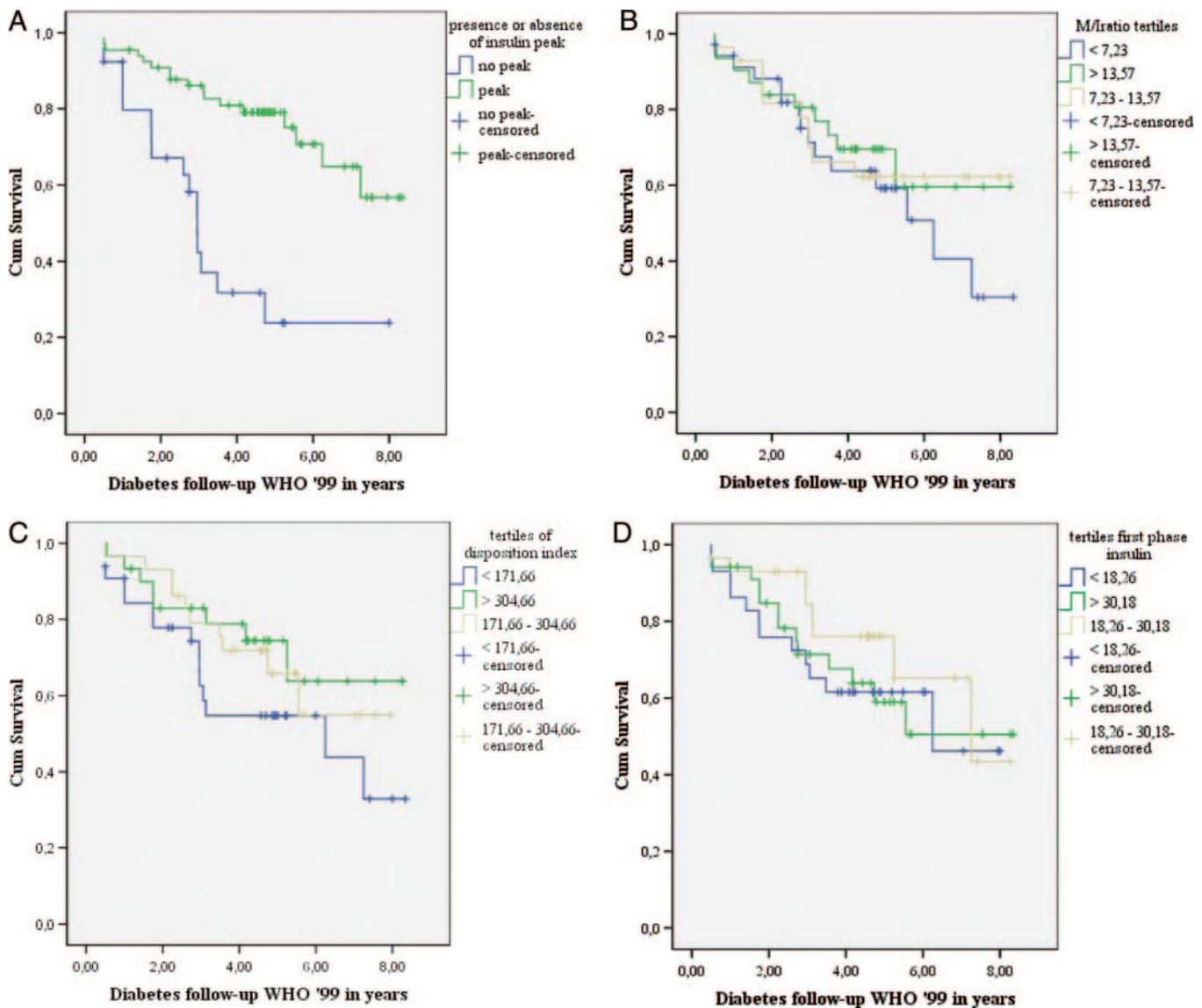


FIG. 2. Kaplan-Meier survival curves for either the presence of a first insulin secretion peak (A), insulin sensitivity (B), the disposition index (C), and first-phase insulin secretion (D).

Additional analyses in the eight persons with T2DM according to the WHO 1999 criteria, thus excluded at baseline, demonstrated that their fasting and 2-h plasma glucose values were higher at baseline than in those who developed T2DM at the follow-up (Table 3). They were younger and the percentage of women was higher among these eight persons than in the group of new T2DM. They also had a higher percentage of absence of first-insulin peak and a lower mean disposition index.

## Discussion

The incidence of T2DM in this confirmed IGT population was almost 35%, with a relatively short mean follow-up period of 4 yr. The absence of the first insulin peak was the strongest predictor of the development of T2DM. The second insulin secretion phase, insulin resistance, and the disposition index did not independently predict T2DM.

The participants were selected according to the 1985 WHO criteria, but during the study the WHO criteria for T2DM changed. For the 1999 WHO analyses, therefore, we excluded participants with a fasting plasma glucose greater than 7.0 mmol/liter. The true criterion standard measurement for insulin sensitivity is the M-value of the hyperinsulinemic euglycemic clamp (22, 23). Because, the M-value of the hyperinsulinemic clamp and the M/I value of the hyperglycemic clamp are highly correlated (11, 12), a hyperglycemic clamp was the most efficient way to analyze both insulin resistance and  $\beta$ -cell function. We observed that  $AUC_{ins0-10}$  as a measure of first-phase insulin secretion did not predict the conversion to T2DM. Probably this can be explained by the close relationship between the  $AUC_{ins0-10}$ , the measure of insulin sensitivity. In our data  $AUC_{ins0-10}$  was strongly correlated with the M/I ratio derived from the hyperglycemic clamp (data not shown). Perhaps unexpected, insulin resistance did not emerge as a significant independent predictor of diabetes. This is likely to be due to the fact all participants had

**TABLE 2.** Cox proportional hazard analyses for diabetes, all models adjusted for age, sex, and BMI

Model	WHO, 1985 Hazard ratio (95% CI)	WHO, 1999 Hazard ratio (95% CI)
Absence of insulin peak		
Model 1	6.47 (2.76–15.19) <sup>a</sup>	5.74 (2.60–12.67) <sup>a</sup>
Model 2	7.26 (2.97–17.75) <sup>a</sup>	5.68 (2.55–12.64) <sup>a</sup>
AUC <sub>0–10</sub> (model 1)		
Tertile 1 vs. tertile 3	2.09 (0.78–5.70)	0.71 (0.26–1.93)
Tertile 2 vs. tertile 3	1.29 (0.46–3.61)	0.71 (0.30–1.69)
AUC <sub>0–10</sub> (model 2)		
Tertile 1 vs. tertile 3	4.10 (1.22–13.80) <sup>b</sup>	0.86 (0.29–2.57)
Tertile 2 vs. tertile 3	1.53 (0.54–4.30)	0.75 (0.25–1.67)
Ins <sub>160–180</sub> (model 1)		
Tertile 1 vs. tertile 3	1.05 (0.41–2.73)	0.64 (0.25–1.67)
Tertile 2 vs. tertile 3	0.80 (0.30–2.13)	0.72 (0.30–1.71)
M/I ratio (model 1)		
Tertile 1 vs. tertile 3	1.68 (0.55–5.10)	1.58 (0.60–4.17)
Tertile 2 vs. tertile 3	1.62 (0.52–5.06)	0.96 (0.34–2.70)
DI (model 1)		
Tertile 1 vs. tertile 3	4.95 (1.38–17.77) <sup>b</sup>	1.78 (0.65–4.88)
Tertile 2 vs. tertile 3	1.72 (0.43–6.85)	1.20 (0.44–3.24)

Cox regression models, all adjusted for age, sex, and BMI (model 1) and age, sex, BMI, and insulin sensitivity (model 2). CI, Confidence interval; Ins<sub>160–180</sub>, mean insulin level between 160 and 180 min of the hyperglycemic clamp; DI, disposition index.

<sup>a</sup>  $P < 0.001$ .

<sup>b</sup>  $P < 0.01$ .

IGT, itself an insulin-resistant state. Also, previous studies have demonstrated that insulin resistance is a predictor of conversion only in persons with normal glucose tolerance at baseline (3, 4).

In persons with an adequate  $\beta$ -cell function, the AUC<sub>0–10</sub> will be higher in insulin-resistant persons, compared with persons with a normal insulin sensitivity. The resulting disposition index and glucose tolerance will remain the same. In contrast, those who are not able to increase the (first) phase insulin secretion in response to insulin resistance, thus those with an absent first phase, will develop hyperglycemia. Insulin resistance itself stimulates insulin secretion, an adaptation of the  $\beta$ -cell for prevailing insulin resistance (26, 27). The disposition index, reflects the interrelationship between insulin secretion and insulin resistance. Alterations in the disposition index has been demonstrated to be predictive of changes in glucose tolerance status as reported by others (7, 19, 26–28). This study is one of the few prospective studies with measurements of the first insulin secretion phase in confirmed IGT persons and the first to report prospective analyses with the disposition index in a Caucasian IGT population (8). Impaired

first insulin secretion phase as an independent predictor for the development of T2DM, independent of obesity and insulin resistance, has also been described in a population in Sweden, in Pima Indians (29–34), and in Mexican-Americans (3). We found that the incidence of T2DM was predicted best by the absence of the peak of the first insulin secretion phase. In the prospective study in Pima Indians, the findings were very similar, although their estimate of  $\beta$ -cell function was acquired with an iv glucose tolerance test (38).

The disposition index, as an expression of the compensatory mechanism of insulin secretion on decreasing insulin sensitivity, appeared to be an independent predictor of the incidence of T2DM but only when we used the old WHO 1985 criteria. This is line with the notion that elevated fasting glucose (7.0–7.8 mmol/liter) clearly indicates defective insulin secretion and that fasting glucose levels less than 7.0 mmol/liter indicates sufficient compensatory insulin secretion (22).

In summary, the present study of Caucasian patients followed up prospectively over several years showed that the

**TABLE 3.** Comparison of the excluded T2DM (WHO, 1999) at baseline with the new T2DM at the follow-up

Variables	T2DM excluded	T2DM follow-up
n	8	35
Age	57.8 (6.9)	63.0 (8.8)
Sex (percent male)	37.0	45.0
BMI	30.7 (3.2)	28.6 (4.5)
Fasting plasma glucose (mmol/liter)	7.3 (0.2)	6.5 (0.6)
Two-hour postload plasma glucose (mmol/liter)	9.7 (0.6)	9.3 (1.1)
Peak (percent present)	37.5	52.0
Disposition index	128.4 (66.3–259.4)	176.8 (137.4–307.6)
M/I ratio	8.1 (2.5–18.1)	7.1 (3.8–10.0)

Values are means (sd) or medians (interquartile ranges) for skewed variables.

absence of the first insulin peak, as an expression of an impaired acute insulin response to glucose, was the strongest predictor of incident T2DM.

## Acknowledgments

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Disclosure Summary: The authors have nothing to declare.

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