Classification of Newly Diagnosed Diabetic Patients as Insulin-Requiring or Non–Insulin-Requiring Based on Clinical and Biochemical Variables

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In a prospective study of 41 consecutively referred newly diagnosed diabetic patients, we evaluated the predictive value of fasting and glucagon-stimulated C-peptide values, ketonuria, age, and body weight in the classification of subjects as insulin-requiring (IR) or non–insulin-requiring (NIR). The patients were followed up for ≥12 mo and classified as NIR if adequate glycemic control could be achieved without insulin (i.e., fasting plasma glucose <8 mM and no glycosuria). Patients who needed insulin to obtain this status were classified as IR. We found that all subjects with plasma C-peptide values >0.60 nM 6 min after intravenous glucagon were NIR, whereas all IR subjects together with 3 NIR subjects had C-peptide values below this limit. All NIR subjects but 1 had fasting C-peptide values >0.30 nM, and all IR subjects but 1 had C-peptide values below this limit. Seventy-five percent of the subjects could be correctly classified by use of age and percent desirable body weight. Thus, all subjects >40 yr old and >100% ideal body weight were NIR, and all subjects below both these limits were IR. Ketonuria was found in 10 of 12 IR subjects and in 10 of 29 NIR subjects. We conclude that *1*) 75% of the subjects could be correctly classified by use of age and percent desirable body weight only and *2*) C-peptide measurements are useful in the classification of newly diagnosed diabetes, whereas presence of ketonuria is of limited value. *Diabetes Care* 11:531–37, 1988

Correct classification of diabetic subjects at the time of diagnosis is often difficult but clearly of importance in clinical practice in the decision of correct treatment and in scientific studies of the pathogenesis and natural history of the disease. In the reclassification of diabetes in 1979 by the National Diabetes Data Group (NDDG) type I, or insulin-dependent diabetes mellitus (IDDM), was defined as "usually characterized clinically by abrupt onset of symptoms, insulinopenia and dependence on injected insulin to sustain life, and proneness to ketosis," whereas type II, or non-insulin-dependent diabetes mellitus (NIDDM), was defined as "not ketosis prone, commonly associated with obesity, and often with its onset after the age of 40" (1). These guidelines, however, may be difficult to apply in practice (2–4) and have been criticized as quantitative and imprecise (5–7). "A tendency to ketosis in the basal state" is vague, and where diabetes services are well organized, IDDM patients may be referred early and started on insulin before significant ketosis develops. On the other hand, patients with NIDDM may experience complete remission from decompensated diabetes and, in fact, even after episodes of ketoacidosis (8). However, because insulin dependency may depend on residual β-cell function, it has been proposed that measurements of β-cell function may be of value in classification. Recently, several reports have confirmed that C-peptide determinations in selected subgroups of patients are of value in the choice of treatment (9–17).

In a sample of 41 newly diagnosed diabetic subjects, clinical characteristics and C-peptide response to glucagon were determined. Based on clinical evaluation, patients were classified as IDDM and NIDDM and treated accordingly with and without insulin. During the following year, we evaluated whether these patients could be adequately controlled without insulin treatment or

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whether insulin was required. Finally, we evaluated the ability of clinical parameters and C-peptide determined at the time of diagnosis to predict the classification of patients as insulin-requiring (IR) or non–insulin-requiring (NIR).

MATERIALS AND METHODS

Patients. All untreated patients with newly diagnosed diabetes mellitus admitted to the medical department in Aarhus, Amtssygehus, during an 18-mo period were consecutively included in the study. Diabetes was defined as fasting hyperglycemia according to NDDG criteria (1).

Design of study. All patients were observed untreated for the first 4 days, except four patients who needed immediate insulin therapy and therefore were started on a low-dose insulin regimen. All patients consumed a common everyday diet for the first 4 days. Height, weight, and total CO_2 were determined on the day of admission. Urine was collected during the first 3 days for determination of ketone bodies. The glucagon/C-peptide test was performed in the morning on day 3 or 4 after an overnight fast. In patients already started on insulin therapy the glucagon/C-peptide test was performed before the morning insulin dose. Thereafter, patients were classified as IDDM or NIDDM based on assessment of overall clinical presentation, including knowledge of age, percent desirable body weight (DW), total CO_2, plasma glucose concentrations, and ketonuria during the first 3–4 days. All patients were thereafter treated with an individualized diabetes diet according to percent DW (20% protein, 35% fat, 45% carbohydrate) and followed up by a trained dietitian. Patients classified as IDDM were started on insulin treatment. In patients classified as NIDDM, dietary treatment was supplemented with oral hypoglycemic agents if necessary. The patients were followed in the outpatient clinic at regular intervals for ≥12 mo. Tapering of the insulin dose was tried in all insulin-treated patients, and insulin was withdrawn if possible. Patients were seen in the outpatient clinic every 2 wk during change of treatment. If treatment and control were stable, 2- to 3-mo intervals were allowed between visits. Patients were classified as NIR if acceptable glycemic control could be achieved during a period of ≥12 mo without insulin treatment. Patients who did not achieve acceptable control were treated with insulin and classified as IR.

The criteria for acceptable glycemic control were fasting plasma glucose concentrations <8 mM and/or postprandial plasma glucose concentrations <10 mM combined with no glycosuria during at least 12 mo of observation.

Glucagon/C-peptide test. After an overnight fast a catheter was placed in an antecubital vein for blood sampling and glucagon injection. Blood samples were obtained before and 6 min after an intravenous bolus injection of 1 mg glucagon (Novo, Bagsvaerd, Denmark) (18). Blood was collected in plastic tubes containing 250 KIU aprotinin and 50 U heparin per milliliter of blood. Plasma was obtained after 10 min centrifugation at 4°C and stored at a temperature below −25°C until assay.

Methods. Plasma C-peptide concentration was measured as described by Heding (19) with antibody M1230 (20). Glucose in plasma and urine was analyzed with a glucose dehydrogenase method (Merck enzymatic kit). Urine was collected for 12- and 24-h periods and urine ketone body concentration analyzed photometrically as acetoacetate (21). Plasma total CO_2 was measured on the day of admission with an autoanalyzer method. Height without shoes and weight in light clothing were recorded. Body mass index (BMI) was calculated as body weight (kg) divided by height^2 (m). For adults, BMI is linearly related to the index of percent DW. Percent DW is derived from the medium frame ideal body weight estimates of the Society of Actuaries. Thus, percent DW was calculated as BMI × 4.76 for women and BMI × 4.39 for men (1). Predictive values of positive and negative test results were calculated as follows: predictive value of a positive test = (number of NIR subjects with a positive test)/(total number of subjects with a positive test); predictive value of a negative test = (number of IR subjects with a negative test)/(total number of subjects with a negative test). In correlation analysis, Spearman's rank correlation was used.

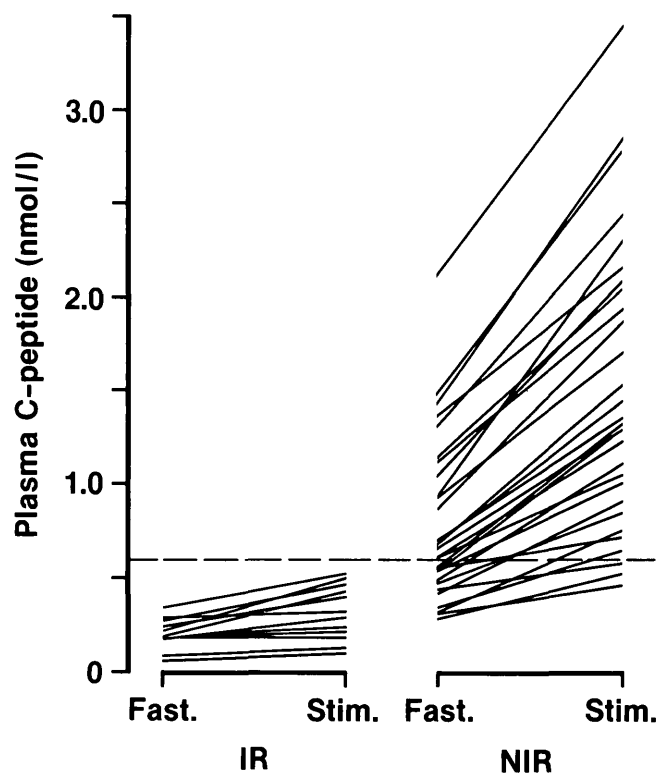

FIG. 1. Plasma C-peptide concentration before (Fast) and 6 min after (Stim) intravenous bolus injection of 1 mg glucagon in patients with insulin-requiring (IR) and non-insulin-requiring (NIR) diabetes.

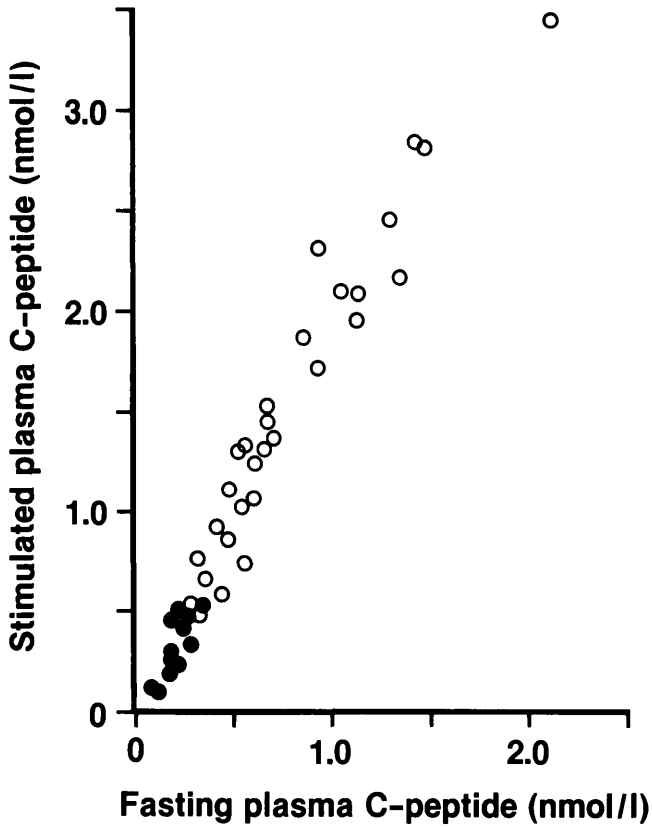

FIG. 2. Correlation between fasting and glucagon-stimulated plasma C-peptide concentrations in newly diagnosed diabetic patients with insulin-requiring (●) and non-insulin-requiring (○) diabetes.

RESULTS

Forty-one patients were included in the study: 17 women and 24 men. Four patients were started on insulin treatment immediately after admission on the basis of severe metabolic decompensation. Their plasma glucose concentration ranged from 28.4 to 40.4 mM, and total CO_2 ranged from 26.4 to 11.6 mM. Eighteen patients were initially classified as IDDM and started on insulin treatment. After controlled evaluation, 7 of these patients could later be treated without insulin, whereas 11 patients needed insulin for acceptable control. Twenty-three patients were initially classified as NIDDM and treated without insulin. After evaluation, 1 of these patients required insulin to achieve acceptable control. Thus, after 12 mo of evaluation, 12 patients were IR, and 29 patients were NIR. Of these, 15 were treated with diet only, 12 with diet combined with glyburide (1.75–14 mg/day), and 2 with metformin (1.5 g/day).

Glucagon/C-peptide test. Fasting and stimulated (6 min postglucagon) plasma C-peptide concentrations in IR and NIR patients are shown in Fig. 1. All patients in the IR group had stimulated C-peptide values below a limit of 0.60 nM, and all patients with a stimulated value above this limit belonged to the NIR group. Three patients from the NIR group had values below the limit.

A fasting C-peptide concentration of 0.30 nM also appeared to discriminate between IR and NIR. All subjects except one in the IR group had fasting C-peptide concentrations below this limit, and all subjects except one in the NIR group had fasting C-peptide concentrations above this limit. Apart from one patient with a plasma glucose concentration of 6.7 mM after low-dose insulin regimen, the range of plasma glucose concentrations at the time of the glucagon test was 8.1–20.2 mM in the NIR group and 9.8–18.0 mM in the IR group. The stimulated C-peptide concentrations were correlated to the fasting C-peptide concentrations ($r = .978$, $P < .001$; Fig. 2) as well as to the increase over the fasting value ($r = .975$, $P < .001$; not shown).

Ketonuria. The relation between maximal urine ketone body concentration during the first 3 days of hospitalization and glucagon-stimulated C-peptide concentrations is shown in Fig. 3. It appears that 10 of 12 IR patients showed ketonuria, but 10 of 29 NIR patients also had ketonuria. It also appears that some NIR patients had rather high ketone body concentrations and that ketonuria in the NIR group was not limited to subjects with low or borderline values of stimulated C-peptide.

Acidosis. Total CO_2 concentration was (mean ± SD) 24.6 ± 3.6 mM in the NIR group and 24.6 ± 3.2 mM in the IR group (normal range 22.0–29.0 mM). Four patients had total CO_2 concentrations <20 mM. Two of these patients were classified as IR and two were NIR. None of these patients had evidence of renal, hepatic, or cardiopulmonary disease on clinical and standard routine laboratory examination and chest X ray.

Age and desirable body weight. Whereas most IR pa-

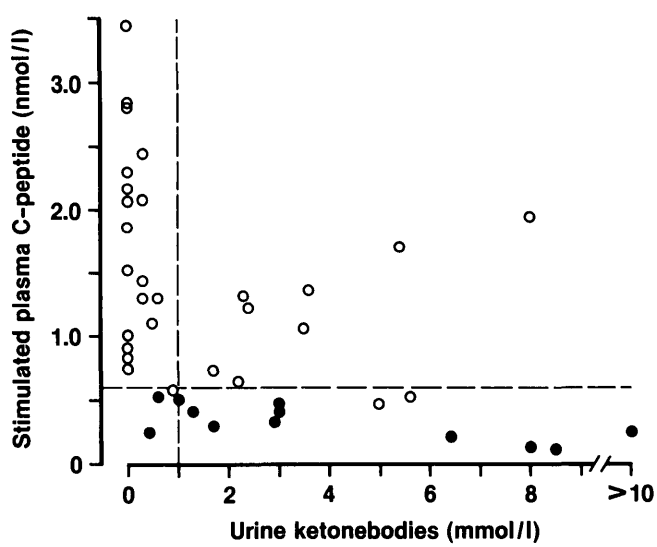

FIG. 3. Relation between maximal urine ketone body concentration during 1st 3 days after diagnosis and glucagon-stimulated C-peptide concentrations in patients with insulin-requiring (●) and non-insulin-requiring (○) diabetes.

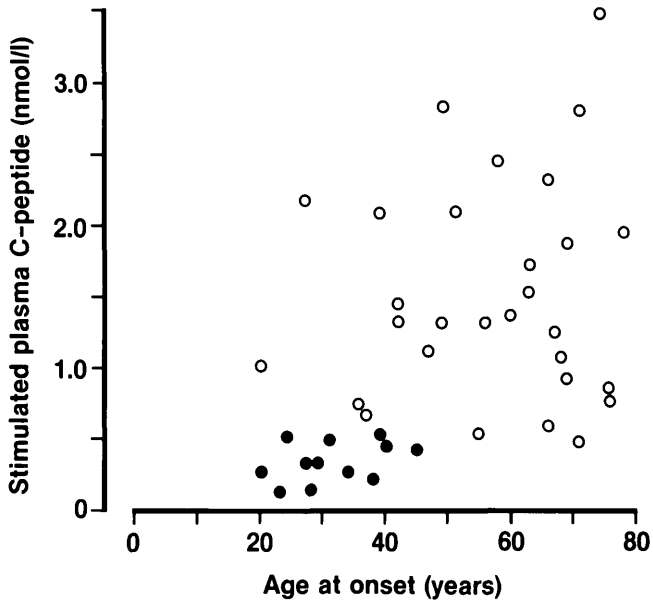

FIG. 4. Stimulated plasma C-peptide concentrations in relation to age at diagnosis in patients with insulin-requiring (●) and non-insulin-requiring (○) diabetes.

tients were <40 yr old and most NIR patients were >40 yr old, some NIR patients were <40 yr (Fig. 4). Similarly, most IR patients were <100% and most NIR patients were >100% DW (Fig. 5). However, several NIR patients were between 100 and 120% DW and therefore not severely obese. With a combination of age and percent DW, 75% of the patients were correctly classified (Fig. 6). All patients <40 yr of age and <100% DW were IR, and all patients above both these limits were NIR. Ten patients could not be classified by these criteria.

Predictive values of tests. The predictive values of single and combined parameters are shown in Table 1. The predictive value of a positive test indicates the chance of a diabetic patient being NIR provided that the patient's parameters fall into the identified class or classes. Similarly, the predictive value of a negative test indicates the chance of a patient being IR provided that the patient's parameters do not fall into either of the identified classes.

DISCUSSION

In this study, we evaluated the relative importance of different clinical parameters and C-peptide determination in the classification of diabetic patients at the time of diagnosis. In the revision of diabetes classification in 1979, the NDDG suggested that diabetes should be classified in two major groups as type I, or IDDM, and type II, or NIDDM, and a third group of secondary diabetes (1). It was emphasized that the ketosis-prone IDDM type may be diagnosed in a pre–ketosis-prone stage and that the usually non–ketosis-prone NIDDM type may develop ketosis under certain circumstances. Therefore, assessment of insulin dependence may be difficult at the time of diagnosis and may be best determined in retrospect. In insulin-treated patients, trials of insulin withdrawal may be necessary. In clinical practice, however, insulin dependence is seldom proved. If a patient is considered insulin dependent at diagnosis, insulin treatment is most often continued for the rest of his/her life. Usually, classification is based on assessment of the patient's overall clinical presentation. In this assessment, presence or absence of ketosis and ketonuria at the time of diagnosis is an important parameter, but several other parameters, i.e., percent DW, age at diagnosis, and severity of symptoms, may influence the decision. However, the relative importance of these parameters to predict insulin dependence and thereby the necessity to initiate insulin treatment has not previously been evaluated.

In this study, 41 newly diagnosed diabetic patients were classified by trained endocrinology specialists as IDDM or NIDDM. In this classification, we tried to apply the criteria of the NDDG (1). Thereafter, we evaluated whether the patients did or did not require insulin to achieve adequate control during a clinical follow-up of ≥12 mo. In 7 of 18 patients initially classified as IDDM, insulin treatment could be stopped and adequate control obtained without insulin during a period of ≥12 mo. Of 23 patients initially classified as NIDDM, it was necessary in 1 patient to give insulin to obtain adequate control.

Of course we cannot exclude the possibility that some of our NIR patients may at a later stage require insulin. However, the fact that they could achieve adequate glycemic control without insulin during a period of ≥12 mo indicates that they were not dependent on insulin. Because we used rather strict criteria for adequate con-

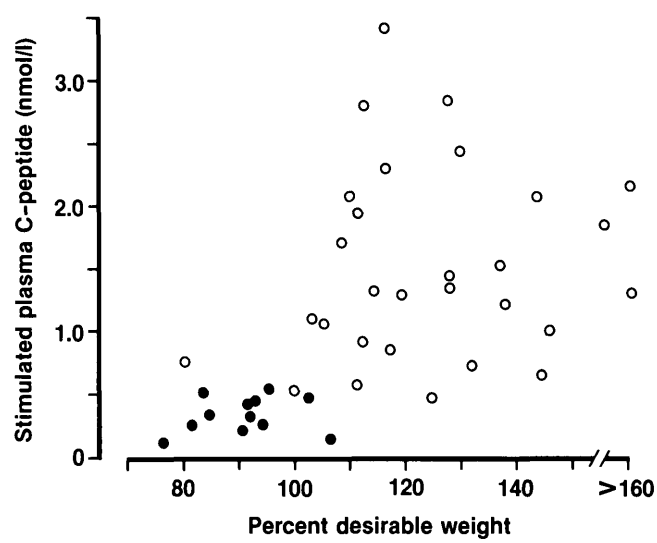

FIG. 5. Stimulated plasma C-peptide concentrations in relation to percent desirable body weight in patients with insulin-requiring (●) and non-insulin-requiring (○) diabetes.

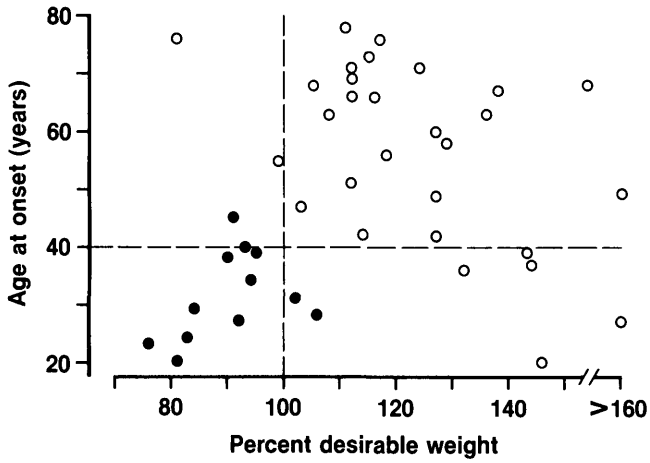

FIG. 6. Distribution of age and percent desirable weight in newly diagnosed diabetic patients with insulin-requiring (●) and non-insulin-requiring (○) diabetes.

trol without insulin, it is possible that some of our IR patients, too, could have survived without insulin treatment and therefore may not be truly insulin dependent. Although our classification of patients as IR and NIR is not entirely identical to the NDDG classification of IDDM and NIDDM, it is of value to be able to predict at the time of diagnosis whether a given patient will require insulin or can be treated without insulin during the 1st yr after diagnosis.

Looking at initial parameters, we found that 75% of the patients could be classified as IR and NIR on the basis of age at onset and percent DW. Thus, subjects with age at onset <40 yr and percent DW <100% were all correctly classified as IR, whereas patients >40 yr old and >100% DW were all NIR. This is in accordance with the statement by the NDDG that IDDM often has its onset before age 40 yr, and NIDDM often after age 40 yr, and that in Western societies 60–90% of NIDDM patients are obese (1). However, as emphasized by the NDDG, both types of diabetes may become symptomatic for the first time at any age, and obesity does not exclude insulin dependency.

Ketosis and ketonuria at diagnosis are often assumed in epidemiologic research to indicate insulin deficiency and, thereby, insulin dependence (22–23). Of four patients presenting with acidosis, two required and two did not require insulin during the following year. Although most IR subjects had ketonuria, a comparable number of NIR subjects also had ketonuria. Therefore, in this study, ketonuria was of questionable value as a predictive marker. Furthermore, in several of the NIR subjects, ketonuria was of considerable magnitude and was present in subjects with stimulated C-peptide values well above the discriminatory C-peptide level. Thus, although ketonuria may indicate insufficient insulin action, it does not equal insulin dependence. Insufficient insulin action may be due to either absolute insulin deficiency or severe insulin resistance.

Using the C-peptide concentration 6 min after intravenous injection of 1 mg glucagon, we found a high predictive value for NIR of a C-peptide concentration >0.60 nM. Thus, all patients with C-peptide values exceeding this level were NIR. Although all IR patients had C-peptide values <0.60 nM, the predictive value of a negative test was less (0.80), because three NIR subjects also had C-peptide values below the limit. It is well established that the β-cell response to nonglucose secretagogues is dependent on the prevailing plasma glucose concentration (24). It was recently suggested that spuriously low C-peptide responses to glucagon may be obtained when patients with plasma glucose levels <7 mM are tested (25). However, among the patients with stimulated C-peptide values <0.60 nM, all had plasma glucose concentrations >8.9 mM. In this study, glucagon-stimulated C-peptide values were highly correlated to fasting C-peptide values. Therefore, fasting C-peptide concentrations could also be used to distinguish IR from NIR. By use of a fasting C-peptide concentration of 0.30 nM as the discriminatory level, only one IR patient and one NIR patient were misclassified. In previous studies a great overlap in fasting C-peptide values has been found (9–10,17). However, in these studies the subjects were of variable diabetes duration and received established treatment.

Ideally, classification of diabetes should be based on knowledge of etiology and pathogenesis. Pathogenetically, IDDM is characterized by progressive β-cell destruction and absolute deficiency of insulin secretion (26). In contrast, in NIDDM, β-cell secretion may be normal, slightly reduced, or above normal (1), but β-

TABLE 1
Predictive values of single and combined parameters

	Predictive value of positive test	Predictive value of negative test
Glucagon-stimulated plasma C-peptide >0.60 nM	1.00 (0.86–1.00)	0.80 (0.51–0.96)
Fasting C-peptide >0.30 nM	0.97 (0.82–1.00)	0.92 (0.61–1.00)
Urine ketone bodies <1 mM	0.90 (0.69–0.99)	0.50 (0.27–0.73)
Age at onset >40 yr	0.96 (0.79–1.00)	0.69 (0.41–0.89)
Age at onset >40 yr and urine ketone bodies <1 mM	1.00 (0.79–1.00)	0.82 (0.48–0.98)
Age at onset >40 yr and percent desirable body weight >100	1.00 (0.84–1.00)	1.00 (0.66–1.00)

95% confidence intervals are indicated in parentheses.

cell sensitivity to glucose is reduced (27,28). The disease is, however, almost invariably associated with reduced tissue sensitivity to the action of insulin (29). A long-standing controversy relates to the question of whether the primary lesion leading to NIDDM involves a defect in insulin secretion or in insulin action. In two prospective studies carried out in populations at high risk for diabetes (30,31), a high serum insulin concentration was found to be a risk factor for development of NIDDM among subjects who had normal glucose tolerance at baseline, suggesting that insulin resistance, but not impaired insulin secretion, preceded the development of NIDDM in these ethnic groups. Whether this observation can be generalized to other populations remains to be determined (32). In the meantime, although the precise etiology of the different types of diabetes is unknown, knowledge of insulin secretability and of insulin sensitivity may be important in the classification and choice of appropriate treatment.

Clinically, knowledge of the patient's β-cell capacity may provide the basis for a more rational approach toward treatment. In patients with absent or severely reduced β-cell secretion, insulin treatment is obviously necessary. In contrast, in patients displaying normal or elevated levels of β-cell secretion, insulin may not be the treatment of choice. In the clinical situation, C-peptide determination is obviously not necessary in all patients. Thin young patients with heavy ketonuria are probably insulin deficient, whereas obese elderly patients without ketonuria are probably insulin resistant. However, in several patients, clinical evaluation of the relative contribution of insulin deficiency and insulin resistance may be difficult. Whereas determination of insulin sensitivity may require rather sophisticated and resource-demanding methods, a measure of β-cell secretion can readily be obtained with the rather simple glucagon/C-peptide test.

In conclusion, at the time of diagnosis, measurement of β-cell function either as fasting or glucagon-stimulated C-peptide concentration has a high predictive value concerning future treatment and, thereby, in the classification of patients. Seventy-five percent of the patients could be classified on the basis of age and percent DW. Presence of ketonuria was of limited predictive value.

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