Rationale and Methods for the Estimation of Insulin Secretion in a Given Patient

From Research to Clinical Practice

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Although the plasma insulin assay is now 40 years old, it is not widely used in clinical practice. However, simple methods (such as the various indexes relating fasting insulin to fasting glucose), the increase in plasma insulin at the 30th minute of an oral glucose tolerance test, and the increase in insulin or C-peptide after stimulation by glucagon are relatively reliable compared with more sophisticated approaches to assess β-cell sensitivity to glucose, kinetics of insulin secretion, residual insulin secretion, or insulin sensitivity. But these measures are of no decisive help in distinguishing between the various forms of impaired fasting glucose or non-insulin-dependent diabetes, such as type 2 diabetes, slow type 1 diabetes, the various forms of maturity-onset diabetes of the young, or the mitochondrial genome defects. No data are available to show that the measurement of plasma insulin may be of help to adapt the treatment of a diabetic patient, except for the need of insulin therapy. There are some suggestions that fasting plasma insulin and, more precisely, the homeostasis model assessment indexes may help to predict the progression toward diabetes or the progressive deterioration of β-cell function in diabetic patients.

Diabetes 51 (Suppl. 1):S240–S244, 2001

Forty years ago, Yalow and Berson (1) developed a sensitive and specific immunoassay of plasma insulin. Based on this assay, thousands of studies have been undertaken and thousands of papers published that have tremendously helped the understanding of the physiology of insulin secretion and its disturbances in type 2 diabetes. However, contrary to the determination of “younger” protein hormones, such as thyroid-stimulating hormone, gonadotrophins, thyrocalcitonin, parathormone, growth hormone, etc, and various steroid hormones, which are routinely used and unavoidable in clinical practice, the assay of insulin or of its surrogate C-peptide is not part of routine clinical chemistry.

This brief review intends to investigate whether, on the basis of current knowledge, we may use insulin and C-peptide assays to improve the care of a given diabetic patient.

I. Among the various methods used to analyze the abnormalities of insulin secretion among diabetic patients, many of them are highly sophisticated and cannot be used for clinical purpose. Which of the simplest ones are sufficiently informative to be of interest?

The sensitivity of β-cells to prevailing glucose levels may be estimated by a hyperglycemic clamp at various glucose levels, a continuous infusion of glucose with model assessment (CIGMA) (2), and different indexes taking into account fasting plasma insulin in relation to fasting blood glucose. Among the simple indexes, the homeostasis model assessment (HOMA) index (3) is the best known and validated.

The magnitude and kinetics of insulin secretion after a glucose stimulus may be determined during a hyperglycemnic clamp (4,5), after rapid injection of glucose by the minimal model analysis (6), or during an oral glucose tolerance test (OGTT).

The β-cell responses to a nonglucose stimulus, such as tolbutamine, glucagon (7), arginine, or isopropylnorepinephrine (8), give an estimation of the insulin reserve of the β-cell.

Finally, the insulin-mediated glucose disposal may be appreciated by the hyperinsulinemic-euglycemic clamp (4), the minimal model (6), the intravenous insulin tolerance test, and various indexes relating the fasting plasma insulin and glucose levels, such as the HOMA model (3), the quantitative insulin sensitivity index (QUICKI) (9), and the Sib index (10).

It must be remembered that the validity of simple indexes may be low in some circumstances. Variations in insulin clearance, mainly in obese patients, particularly those with an excess of abdominal fat (11), may modify the relation between plasma insulin values and insulin secretion. The contamination of “insulin values” by the presence of insulin precursors is no longer a problem thanks to the specificity of the new insulin assays. The use of C-peptide as a surrogate of insulin is justified in some cases, as it allows the assessment of insulin secretion in insulin-treated patients, but its long half-life precludes any study of the kinetics of insulin secretion.

In fact, in clinical practice, only fasting samples or simple stimulation tests, such as the OGTT or the glucagon
stimulatory test, which are the most widely spread and validated, may be used. Are their results significant enough from a clinical point of view?

To estimate the β-cell sensitivity to glucose, it has been shown that the HOMA model offers good β-cell function estimation compared with CIGMA, the frequently sampled intravenous glucose tolerance test, or the hyperglycemic clamp (3,12).

The kinetics of insulin response to glucose, i.e., the possible delay in insulin secretion, may be appreciated by the ratio of the 30-min increment in insulin concentration to the 30-min increment in glucose concentration following oral glucose loading, which correlates well with the first-phase insulin secretion following intravenous glucose injection in subjects with normal or impaired glucose tolerance (13,4).

To appreciate insulin reserves, the most widely used test is the glucagon stimulatory test. The validity and the methodological aspects of its interpretation have been discussed (7). The standard breakfast test could be an alternative to the glucagon stimulatory test; a good correlation in C-peptide increments in these two tests have been observed (14). Few data are available in different clinical situations on the results of arginine or isopropyl-nephrine stimulation (8).

Finally, insulin sensitivity may be appreciated by indexes derived from fasting plasma insulin and glucose values. The correlation with more sophisticated methods is good for the Sib index (r = 0.83 with the minimal model) (10), the QUICKI index (r = 0.78 with the glucose clamp) (9), and the HOMA index (r = 0.88 with the clamp and the minimal model index) (3). In nondiabetic individuals, fasting plasma insulin levels are also well correlated with insulin sensitivity determined by minimal model analysis (10) or the hyperinsulinemic-euglycemic clamp (3,15).

II. Are these indexes that can be obtained with relative ease in clinical practice of some help to the physician?

Faced with a diabetic or a glucose-intolerant patient, the physician may want to determine the diabetic etiological type, decide the best therapeutic approach (especially the need for insulin therapy), and predict the progressive deterioration of β-cell function. The help given by simple determinations of insulin secretion and insulin sensitivity to these questions will now be analyzed.

Classification of diabetes. The etiological classification of patients with “impaired fasting glucose” or “non-insulin-requiring diabetes” of the current classification of diabetes (16) is not always evident, especially in the absence of frankly excessive body weight. Apart from type 2 diabetes, slowly evolving type 1 diabetes, the various forms of maturity-onset diabetes of the young (MODY), and mitochondrial genome defects, calcifying fibrocalkidous pancreatitis should be mentioned. Does the estimation of insulin secretion facilitate this etiological classification? Apart from type 2 diabetes, the other etiological types are directly related to impaired insulin release. However, in type 2 diabetes, where insulin resistance and defective insulin secretion both concur to produce glucose intolerance, the defect in insulin secretion is more prominent in patients with relatively normal body weight, i.e., in those for whom the etiological classification may be difficult. Therefore, one cannot expect to distinguish clearly between the various types of type 2 diabetes by the simple study of insulin secretion.

Approximately 10% of patients with non–insulin-requiring diabetes are probably affected by slowly evolving type 1 diabetes (17). Among three studies comparing patients at diagnosis according to the presence or absence of anti-GAD antibodies, it has been observed that those with slow type 1 diabetes had, on average, a lower BMI and a slightly higher fasting plasma glucose and that their fasting plasma insulin or C-peptide or β-cell function in the HOMA model were, on average, two times lower than in the group without anti-GAD antibodies (17–19). However, in a recent study (20), 11 patients with slow type 1 diabetes were carefully matched in terms of age, sex, and BMI with 11 type 2 diabetic patients. Fasting C-peptide and HOMA model parameters did not differ in these two groups, which share the same degree of insulin resistance. From a practical point of view, the demonstration of the presence of anti-GAD antibodies is the best discriminating way of establishing the presence of slow type 1 diabetes (21).

The so-called MODY types of diabetes are related to three main genetic defects in the β-cells. MODY 2 is related to mutations of the glucokinase gene on chromosome 7, MODY 1 with mutations of HNF4α gene on chromosome 20, and MODY 3 with mutations of HNF1α on chromosome 12.

If one considers that the various glucokinase mutations render the β-cell relatively blind to glucose, one could expect a lower insulin release for a given degree of mild hyperglycemia in the affected patients. A recent study showed (22) that diabetic patients with a glucokinase mutation had lower fasting plasma insulin values than patients with type 2 diabetes, but the difference was not significant, and a wide overlap existed between the two groups. When comparing diabetic and nondiabetic glucokinase-deficient subjects, it has been observed that the presence of hyperglycemia was not related to a decrease in insulin secretion but to a decrease in insulin sensitivity assessed by a euglycemic-hyperinsulinemic clamp or by the HOMA model (23). The sensitivity index was 37% for the diabetic patients and 54% for the nondiabetic glucokinase-deficient subjects.

Insulin secretion has been extensively studied among patients with the HNF4α mutation (MODY 1), but no comparison has been made with type 2 diabetes. In recent studies (24–27) where nonaffected subjects, affected but normo-tolerant subjects, and affected diabetic individuals were compared, fasting insulin and/or C-peptide were lower in diabetic individuals in two studies, and similar to nondiabetic individuals in two other studies.

Diabetic subjects with the HNF1α mutation (MODY 3) had lower fasting plasma insulin and lower insulin responsiveness to increasing hyperglycemia than nonaffected individuals, but no comparison has been made with type 2 diabetic patients (28).

In summary, although the evaluation of insulin secretion has been extensively studied in the various MODY types of diabetes, the abnormalities are too subtle in the mildly hyperglycemic subjects to be characterized by simple routine exploration and to discriminate with type 2 diabetes.

In a few subjects with mild hyperglycemia secondary to defects in the mitochondrial genome (29), the insulin
response to glucose was low, but the response to arginine was preserved. Fasting C-peptide or insulin were variable but did not differ from the nondiabetic subjects. On the contrary, in a larger Japanese study (30), C-peptide response to glucagon was diminished among the patients who were diabetic.

In glucose-intolerant subjects with fibrocalculous pancreatitis, it has been shown that the β-cells did not respond better to a nonglucose stimulus such as tolbutamide than to glucose, contrary to subjects whose fasting hyperglycemia is related to type 2 diabetes (31,32). However, there are no recent data on the study of insulin secretion in fibrocalculous pancreatitis or calcifying pancreatitis and its potential usefulness for the diagnosis or the treatment of this disease (33).

Table 1 summarizes the abnormalities of insulin secretion and insulin sensitivity observed in type 2 diabetes and the consequences in terms of therapeutic approaches.

## Table 1

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To conclude at this point, a simple, routinely used study of insulin secretion appears to be of no help in the etiological classification of a patient with fasting hyperglycemia or non–insulin-requiring diabetes, whereas detection of anti-GAD antibodies or, when substantiated by clinical characteristics, the search for nuclear or mitochondrial DNA mutations are highly discriminating.

**Treatment adaptation.** Table 1 summarizes the abnormalities of insulin secretion and insulin sensitivity observed in type 2 diabetes and their consequences in terms of pathophysiological therapeutic approaches. The simplest way to detect delayed insulin secretion could be to assay plasma insulin during an OGTT; an insufficient insulin secretion with respect to the prevailing blood glucose could be estimated with the HOMA model, which may also allow the assessment of the degree of insulin resistance. An insufficient insulin reserve is simply assessed by the glucagon stimulatory test (7). Can these measures help to adapt the treatment?

Very few studies have analyzed the response to an oral hypoglycemic agent in relation to the insulin secretory status of the patients. One study (34) showed that the responders and nonresponders to acarbose or gliclazide did not differ in terms of insulin secretion, whereas another showed (35) that efficacy of the addition of metformin to gliclazide was not correlated with any of the measured variables at baseline.

Patients with uncontrolled type 2 diabetes and a relatively normal body weight have lower plasma insulin or C-peptide levels in the postprandial state or after a glucagon stimulatory test than well-controlled diabetic patients matched for weight (7,36). The situation is different among uncontrolled obese diabetic subjects in whom C-peptide levels may be lower than those of well-controlled obese patients, but are higher than those of normal-weight diabetic subjects and are often in the range of normal subjects with normal body weight (7).

Pontiroli et al. (36) observed similar C-peptide values among obese diabetic patients either controlled by oral agents or insulin-requiring. Similarly, Groop et al. (37) ascribed the secondary failure to oral hypoglycemic agents (OHAs) in moderately overweight individuals (mean BMI 27.7 kg/m²) to an increase in insulin resistance and hepatic neoglycogenesis rather than to a failure of insulin secretion. It is therefore mandatory to take into account the relative body weight of uncontrolled type 2 diabetic patients when estimating insulin secretion in order to decide the usefulness of insulin treatment.

In normal-weight individuals, increase in C-peptide after glucagon is the most useful test. An increment of <0.35 nmol/l is almost always associated with OHA failure (38). Scionti et al. (39) have shown that among 25 uncontrolled normal-weight patients with apparent secondary OHA failure, the 10 who normalized their blood glucose after 8 days in a metabolic ward and who had an adapted weight-maintaining diet had a baseline fasting and postglucagon C-peptide value >0.45 and 0.75 nmol/l, respectively. The other 15 who were in true failure had lower values. It may be concluded that, among normal-weight uncontrolled diabetic patients, frankly impaired insulin secretion as shown by fasting or stimulated C-peptide values are indicative of OHA failure and the need for insulin treatment.

Among obese type 2 diabetic patients, definition of OHA failure is more operational. Incidentally, if body weight is dramatically reduced, for example with the help of bariatric surgery (40), insulin treatment is no longer necessary.

**Prediction of the progressive deterioration of β-cell function?** From an epidemiological point of view, progressive β-cell failure occurs with time in type 2 diabetes and is responsible for the increase in blood glucose (41). However, its occurrence varies from subject to subject. The Belfast study (42) has shown that the worsening of diabetes could be predicted by a β-cell function <50% at the time of diagnosis of diabetes. In the patients with β-cell function above this value, diet alone was sufficient to control diabetes for at least 10 years (43).

In the same way, the efficacy of short-term normalization of blood glucose by 3 days of intensive treatment on the restoration of β-cell function is associated with a high fasting C-peptide level (44).

Finally, among high-risk subjects (45,46), high fasting plasma insulin levels or insulin resistance assessed by the HOMA model are predictive of the occurrence of diabetes, whereas impaired β-cell function is not.

The abnormalities of insulin secretion and insulin sensitivity occurring in patients with type 2 diabetes are relatively well known. Simple measures to estimate these
parameters are available. However, they are of little help in clinical practice for characterizing the patient or for adapting the treatment. There are two main reasons for this. Defective insulin secretion and insulin action are so frequently associated and interrelated that their interaction makes difficult the interpretation of plasma insulin values, except in some classic situations, such as a major impairment in residual insulin secretion. The second point is that so many factors are involved in the control of blood glucose—environmental (e.g., diet, exercise, stress), somatic at various tissue levels, and probably genetic—that we cannot expect to obtain an overview of the phenomenon from the measurement of simple variables, and, in fact, the literature supports this conclusion.

REFERENCES


DIABETES, VOL. 51, SUPPLEMENT 1, FEBRUARY 2001


