

B-CELL FUNCTION IN TYPE 1 DIABETES

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Patients with diabetes are subdivided into at least two subgroups: those with insulin-dependent diabetes mellitus (Type I) and those with non-insulin-dependent diabetes mellitus (Type II). Both groups of patients have abnormalities in the sensitivity of their tissue to insulin, as well as abnormalities in beta (B)-cell function. In type I diabetes, a marked decrease in the number of B-cells is the predominant feature.

Type I patients are characterized by an abrupt onset of symptoms, proneness to ketosis, and dependency on exogenous insulin. Prior to the diagnosis a period of B-cell destruction lasting months to years seems to have taken place (1).

After the initiation of insulin treatment, a temporary clinical remission occurs in most patients with stabilization of the intermediate metabolism. The degree and duration of this remission varies widely, from only a small reduction in the daily insulin requirement to nearly complete normalization of glucose tolerance without insulin therapy for a period of weeks to months. Thereafter, progressive increase in the requirement for exogenous insulin is observed until a relatively stable state is established, with absolute dependency on exogenous insulin throughout life.

Studies of insulin secretion in type I patients have always been attempted, but until recently impossible to complete because the insulin assay is unable to discriminate between endogenous secreted and exogenous injected insulin. Furthermore, after the start of insulin

therapy, the development of insulin-binding antibodies will interfere with the insulin assay and render estimation of insulin secretion impossible.

The discovery of the biosynthetic pathway of insulin from preproinsulin to proinsulin and then to insulin and C-peptide was a major breakthrough in diabetic research. C-peptide is secreted from the B-cell in equimolar amounts with insulin and, in contrast to insulin, is not metabolized by the liver, or only to a small extent. Therefore, C-peptide measurements can be used to estimate endogenous insulin secretion once insulin therapy has been initiated. During the past 10 years C-peptide measurements have been one of the most important research tools in diabetes (2).

This article will focus on the prevalence of residual B-cell function in diabetic individuals, as well as its metabolic consequences. The effect of residual B-cell function on the development of late diabetic complications will be summarized, and the practical use of C-peptide measurements in allocating patients with diabetes mellitus to different treatment regimens will be discussed.

Evaluation of B-Cell Function

Fasting plasma C-peptide concentrations seem to be a simple parameter for expressing B-cell function. It should be realized, however, that fasting blood glucose differs from day to day in diabetic patients, and, thus, the concomitant C-peptide concentration also varies.

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Hence, a fasting C-peptide level gives only limited information about the quantitative B-cell function. If the magnitude of B-cell function must be estimated, some load must be used. We recommend evaluation of B-cell function from C-peptide values obtained 60 to 120 minutes after breakfast or, alternatively, six minutes after 1 mg of glucagon has been administered intravenously. The two values correlate closely, and the glucagon test thus can predict well how the B-cells will respond to a mixed meal under daily living conditions.

About 5 percent of the total C-peptide secreted each day is found in the urine, and this amount correlates well with the plasma C-peptide concentration. Urine C-peptide is largely dependent on the ambient degree of glycemic control and therefore may vary widely from day to day in some patients. A patient may have a high C-peptide excretion on days when blood glucose levels are high and the B-cells are highly stimulated, and a low urine C-peptide excretion on days when glycemic control is good and B-cells are less stimulated. Therefore, if the aim is to estimate whether B-cell function is preserved, measurements of fasting C-peptide or urinary C-peptide may be sufficient, although some patients will be classified as having no B-cell function because of a corresponding low fasting blood glucose level. If more reliable information about the actual degree of B-cell function is needed, plasma C-peptide should be determined after some kind of stimulation.

Prevalence and Magnitude of Residual B-cell Function in Type I Patients

Most type I patients have residual B-cell function at diagnosis, and nearly all continue to display some B-cell function during the first two years of disease. There

after, the prevalence of residual B-cell function declines to about 10 to 15 percent after approximately five years and remains at this level in patients with disease of up to 40 years' duration (2).

The magnitude of residual B-cell function in patients with endogenous insulin secretion declines from a mean of 0.39 nmol/L in patients who have had diabetes for less than one year (normal range : 0.86 to 1.88 nmol/L; mean: 1.20 nmol/L) to about 0.15 nmol/L in patients with more than one year of diabetes duration. Surprisingly, the magnitude of B-cell function remains relatively constant in patients who have such function after one to two years of diabetes.

At present, it is unknown why patients with type I diabetes have different degrees of B-cell function after several years of disease. Age at onset is important in the first 5 to 10 years of disease (2). Patients with late onset have a longer survival of B-cell function than those with early onset (2, 3). In most studies, no association between HLA antigens and B-cell function has been observed. During the first year with diabetes patients displaying islet cell antibodies display lower B-cell function compared with patients without ICA. Nonetheless, it is impossible during the first year of disease to predict whether a patient will have some residual B-cell function throughout life (2).

Remission and B-cell Function

At the onset of disease, the magnitude of residual B-cell function (C-peptide concentration) is about 20 percent of the maximal value seen in normal individuals. After the initiation of insulin therapy, the B-cell function improves and on average doubles in magnitude after seven to 14 days of conventional insulin treatment. In most patients, maximum B-cell function is

seen after two to six months of insulin treatment. Thereafter, B-cell function declines, but, as already mentioned, most patients will display endogenous insulin secretion during the first one to two years of diabetes (2).

The best degree of glycemic control (remission) is observed in periods with maximal B-cell function (C-peptide concentrations), despite treatment with only a minimal daily dose of insulin (2). Several studies have also shown an inverse correlation between a fall in the daily insulin dose and the concomitant improvement in B-cell function. After remission, patients with the greatest increase in insulin dose will have the most pronounced decrease in B-cell function. Despite the increasing insulin dose, mean blood glucose and glucosuria increase with the decreasing B-cell function (2),

Another factor of importance in relation to remission is insulin resistance. Newly diagnosed ketotic diabetic patients show marked insulin resistance. This is ameliorated by initiating exogenous insulin, diet therapy, improvement in glycemic control, and continues to decrease during the following months. In a recent study, the patients with the highest C-peptide values also demonstrated the (relatively) most normal insulin sensitivity (4). Therefore, clinical remission in type I patients is a result of both an improvement in endogenous insulin secretion and an enhancement of insulin sensitivity, the former being the more important factor (2, 4).

Metabolic Importance of Residual B-cell Function in Patients with Long-Term Diabetes

After a long duration of diabetes, when the B-cell function in most patients is absent or minimal, the effect of B-cell function

on metabolic control is of minor importance (5). In most studies of patients with long-term diabetes, no major differences in the degree of metabolic control have been demonstrated between patients with and without B-cell function (5). An inverse correlation has been shown between residual B-cell function and glucosuria, but it is evident that the B-cell function must be considerable before it has any effect on glycemic control (5).

Most patients with residual B-cell function need a smaller daily dose of insulin than those without B-cell function require to obtain the same degree of control. An inverse correlation is seen between C-peptide concentration and daily dose of insulin, patients with the most preserved B-cell function requiring the smallest dose of insulin (5). This indicates that minimal B-cell function is not without effect on metabolic control. The influence of low endogenous insulin secretion can be overridden, however, by the quality of treatment and other factors of importance for regulation (e.g., adherence to diet).

The data also suggest that maintenance of B-cell function facilitates good metabolic control, and often only one daily dose of insulin is needed in patients with B-cell function, as compared with those without B-cell (5). Moreover, the tendency to severe ketoacidosis is reduced in patients with residual B-cell function (6). Thus, differences in B-cell function appear to partly explain the variability in lability and daily dose of insulin among type I patients.

A major advance in our understanding of glucose counterregulation was the recognition that glucagon and epinephrine are of foremost importance in the recovery of glucose levels. Type I patients generally fail to secrete glucagon in response to hypoglycemia. After many years of

diabetes, patients with residual B-cell function have a relatively more normal glucagon response than those without B-cell function, suggesting an interaction between the B-cells and the alpha cells (glucagon-producing cells) in the islets of Langerhans (7). Therefore, residual B-cell function may indirectly protect against severe hypoglycemia.

Therapeutic Attempts to Preserve B-cell Function

Two different methods have been used in attempts to preserve B-cell function—strict blood glucose control and immunotherapy. It has not been possible to preserve B-cell function by maintaining good metabolic control of diabetes in the first months after diagnosis through the use of multiple insulin injections or insulin-pump treatment (8-9). In some studies, a transient improvement in B-cell function has been observed (8). In a randomised prospective study we compared intensive insulin pump treatment versus conventional insulin treatment with regard to B-cell function. After three and six months and one and two years the two groups of patients displayed the same degree of B-cell function despite the pump treated group during the two years of follow-up displayed a significantly better degree of control. In both groups maximal B-cell function was observed after on the average three months of insulin therapy. The patients with the greatest B-cell function at diagnosis also demonstrate the greatest B-cell function after two years. The study strongly indicates that even year normalisation of glycemic control cannot change the natural history of B-cell destruction in Type I patients (9).

Immunotherapy of Type I diabetes is based on the concept that autoimmune phenomena play a central role in the pathogenesis of B-cell damage. The

overall experience with immunosuppressive agents like corticosteroids and cyclosporine A is that it induced higher rates of remission than in control groups (10-11). After stop of cyclosporine relapse occurred within a few weeks (10-11). All studies have demonstrated that cyclosporine A protects the B-cells from destruction. The preservation of the B-cell mass was most pronounced in patients entering the study with short duration (< six weeks) of diabetes (10-11). Thus, lifelong treatment seems to be necessary to maintain the effect. The studies support the autoimmune hypothesis for the mechanism of B-cell damage. The adverse effects of cyclosporine, especially the nephrotoxic effect implicate that a risk-to-benefit ratio favors standard therapy with insulin compared to immunotherapy until safe immunotherapy is available (12).

B-cell Function and Late Diabetic Complications.

Many studies have examined the effect of B-cell function on the occurrence of retinopathy. When groups of patients with the same duration of diabetes were compared, however, no beneficial effect of residual B-cell function on late diabetic complications could be demonstrated (reviewed in 2).

Use of C-peptide Measurements to Discriminate Between Type I and Type II Diabetic Patients

Frequently, clinical problem exists when deciding whether symptomatic hyperglycemia in a Type II patient should be attributed to dietary noncompliance or to a need for insulin treatment. Another problem is that a Type II patient may have started insulin treatment several years earlier during a period of infection or perioperatively and has unnecessarily

continued it subsequently. This heterogeneity among Type II patients makes it difficult in the outpatient clinic to classify patients as insulin-dependent or non-insulin-dependent, and expensive evaluation of therapy in the hospital is often necessary. A practical clinical test that can assign a patient to a treatment regimen is therefore desirable. We have demonstrated that the glucagon/C-peptide test can markedly improve the process by which the best treatment is selected for individual patients (13).

In 215 patients treated with insulin and diet, 26 treated with diet alone, and 27 treated with diet plus hypoglycemic tablets, we measured, in the outpatient clinic, the C-peptide concentration six minutes after 1 mg of glucagon had been administered intravenously. Thereafter, glycemic control was reevaluated in the hospital. We defined a patient as well controlled without insulin when fasting blood glucose was below 8 mM/L. Among those whose diabetes was well controlled without insulin, the six-minute C-peptide value ranged from 0.58 to 3.36 nmol/L, compared with from 0 to 0.63 nmol/L in the insulin-treated group. Only three patients were found to have C-peptide values in the overlap range (0.58 to 0.63 nmol/L). Hence, a C-peptide value of 0.60 nmol/L six minutes after intravenous administration of 1 mg glucagon seems to have a high accuracy when used for selecting treatment. The fasting C-peptide level, however, was without value when used for choosing treatment, because 33 patients (14 of whom were insulin-dependent) had levels in the overlap range.

Several studies have confirmed the value of using the glucagon/C-peptide test in the choice of treatment.

The implication of our results is that the C-peptide level is a useful indicator of the

probability of success of various treatments. A low C-peptide level suggests true insulin dependency. A high C-peptide level in an insulin-treated patient suggests a possibility of stopping insulin without risk in the outpatient clinic. Furthermore, a high C-peptide response in a patient treated with diet indicates that the treatment will be successful. If such a patient displays unacceptable glycemic control, dietary instruction must be repeated. A blunted C-peptide response suggests failure of dietary treatment alone.

It should be borne in mind, however, that the predictive value of the C-peptide test is related to the actual function of the B-cells. In some Type II patients, deterioration of metabolic control may result from a decline in B-cell function and not to poor patient compliance ("pre-Type I patients"). The problem with classification of patients is further complicated by the fact that when metabolic decompensation (provoked by infection or other forms of stress) in a Type 2 patient is reversed by treatment a restoration of the insulin secretory capacity and a decrease in insulin resistance are observed, resulting in a less "severe" diabetes, which may be treated i.e. without insulin. Also in such patients measurements of C-peptide seems to be the primary investigation as an aid for the clinical management decision (13).

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