Review: The importance of residual endogenous beta-cell preservation in type 1 diabetes
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British Journal of Diabetes & Vascular Disease 2009 9: 248
DOI: 10.1177/1474651409351881

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What is This?
The importance of residual endogenous beta-cell preservation in type 1 diabetes

MOHAMMAD ALHADJ ALI, COLIN M DAYAN

Abstract

Achieving tight glycaemic control in type 1 diabetes remains very challenging for patients. However, some individuals retain a degree of endogenous beta-cell function for 5 or more years after diagnosis, and prospective studies confirm that this is associated not only with lower glycated haemoglobin A1c levels, and less hypoglycaemia, but also a reduced incidence of long-term complications. An independent effect of insulin C-peptide may contribute to this beneficial effect. Retention of even small amounts of endogenous beta-cell function for as long as possible should therefore be a key therapeutic goal in type 1 diabetes. Tight glycaemic control from diagnosis has already been shown to help in this regard, and we argue that the introduction of novel immunotherapies which achieve this important goal should be strongly encouraged, even if they fall short of an insulin-free ‘cure’. Br J Diabetes Vasc Dis 2009;9:248–253

Key words: type 1 diabetes, beta-cell preservation, C-peptide, immunotherapy

Introduction

Type 1 diabetes usually presents in childhood and early adulthood, providing the individual with a lifelong challenge to maintain metabolic control to avoid acute emergencies and the longer term sequelae of vascular complications. Preservation of endogenous beta-cell function, even at sub-optimal capacity improves metabolic control, and mechanisms to facilitate preservation are being investigated.

The challenge of achieving good metabolic control in type 1 diabetes

Type 1 diabetes is defined as a condition in which progressive beta-cell destruction leads to absolute insulin deficiency. Most commonly, this destruction is due to autoimmunity. Although the autoimmune process is now appreciated to be present for 5 or more years prior to clinical diagnosis, at the time of clinical presentation, it is estimated that 50–80% of beta-cell function has been lost. Following diagnosis, treatment is with insulin replacement therapy. However, despite improvements in blood glucose monitoring, insulin pharmacokinetics, matching subcutaneous insulin dosing to blood glucose levels, carbohydrate ingestion and physical activity levels, achieving good glycaemic control remains very challenging. Multiple capillary blood glucose tests, repeated meal content assessments and insulin dose adjustments every day for 50 or more years are required. Not surprisingly, in clinical practice a minority of individuals (< 20%) achieve levels of glycaemic control associated with major reductions in long-term complications (HbA1c < 7%) and attainment of HbA1c levels within the normal reference range are almost always accompanied by frequent episodes of hypoglycaemia (figure 1). As a result, a high toll of microvascular complications persists among patients with type 1 diabetes.

It has long been appreciated that persistence of endogenous insulin secretion is associated with improved metabolic control (HbA1c 1% lower), less risk of ketosis and of hypoglycaemia. Martin et al. noted that individuals with a glucagon stimulated c-peptide level > 400 pmol/L at diagnosis (a value that is still less than 25% of stimulated levels in healthy individuals) had a 10 times increased likelihood of a spontaneous insulin-free remission (‘honeymoon’) over the following year. However, with the development of newer immunotherapies aimed at slowing the autoimmune process, the importance of even minor degrees of beta-cell preservation has received renewed attention.

Measuring residual beta-cell function: physiology of C-peptide

The insulin gene is transcribed to produce preproinsulin. Microsomal enzymes then cleave this to proinsulin, which comprises the alpha and beta chains of insulin linked by the 31 amino...
Proinsulin is packaged into clathrin-coated secretory granules in the Golgi apparatus and the presence of the C-peptide in the sequence is important to allow correct folding of the molecule and hence formation of two disulphide bridges between the cysteine residues of the alpha and beta chains. Further maturation of the granules results in loss of the clathrin coat, cleavage of proinsulin first into two alternative split proinsulin products (split-32,33 proinsulin and split-65,66 proinsulin), and subsequently into insulin and free C-peptide with the loss of two pairs of amino acids removed by carboxypeptidases (figure 2). As a result, C-peptide is stored and released in equimolar amounts with insulin. On secretion into the portal circulation, up to 50% of insulin is removed in the first pass through the liver. However, C-peptide is not removed in this way and is predominantly metabolised in the kidney, with small but significant amounts passing into the urine. Overall, C-peptide has a half-life around six times longer than insulin (20–30 min versus 3–5 min for insulin) allowing it to circulate at around five times the concentration of insulin. Hence, it can be readily measured in both the plasma and urine. Currently, accurate measurement of beta-cell mass is not possible, but studies in islet cell autotransplantation suggest that stimulated insulin C-peptide secretion rates do correlate with islet cell numbers. C-peptide production can be estimated in a number of ways (table 1). Fasting C-peptide is the

**Table 1. Ways of measuring residual endogenous insulin secretion**

<table>
<thead>
<tr>
<th>Method</th>
<th>Fasting C-peptide</th>
<th>Peak stimulated C-peptide (glucagon-stimulated, post-mixed meal)</th>
<th>AUC C-peptide (following stimulation), ± glucose clamp</th>
<th>Urinary C-peptide (fasting, post-prandial, 24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key: AUC = area under the curve</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Fasting C-peptide levels in healthy adolescents, newly-diagnosed and longstanding diabetes (subjects aged 12-19)**

<table>
<thead>
<tr>
<th>Group</th>
<th>&gt; 76 pmol/L¹</th>
<th>&gt; 333 pmol/L²</th>
<th>&gt; 633 pmol/L³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects</td>
<td>Not stated</td>
<td>95%</td>
<td>50%</td>
</tr>
<tr>
<td>Newly diagnosed diabetes (&lt; 1year)</td>
<td>83%</td>
<td>31%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Longstanding diabetes (≥ 5 years)</td>
<td>10%</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Data from Greenbaum et al. Cut-off levels are shown for ‘C-peptide positivity’ in DCCT study. 5th percentile and 50th percentile in healthy subjects. Figures represent the percentage of individuals from each subject group above each cut-off level. Conversion factor for c-peptide: 100 pmol/L = 0.3 ng/mL
most convenient measure in epidemiological studies, but appears relatively insensitive to the decline in stimulated insulin reserve around the time of diagnosis of type 1 diabetes. Values for stimulated C-peptide levels vary according to the stimulus used, and while results correlate well, values following meal stimulation (‘mixed meal tolerance test’) are generally higher and more reproducible than glucagon-stimulated levels. Although glucagon stimulation is less time consuming for patients (around 20 min, versus 150 min), it is associated with more nausea. Area under the curve rather than peak C-peptide levels following meal stimulation are generally considered the standard for monitoring beta-cell function in clinical trials, but the longer half-life of C-peptide (versus insulin) means that C-peptide levels may overestimate insulin secretion rates and more complex dynamic models or a clamped technique may be more accurate. C-peptide levels can be measured less invasively in urine and 24-h C-peptide excretion correlates well with plasma levels. However, for the reasons stated above, urine measurements are less accurate in determining the small changes in insulin secretion rates that can be of great importance in the early diagnostic period in type 1 diabetes.

**Table 3. Factors associated with preservation of beta-cell function (see text for references)**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect of increase in factor on retention of beta-cell function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>Increased</td>
</tr>
<tr>
<td>Number of different autoantibodies present</td>
<td>Reduced</td>
</tr>
<tr>
<td>BMI</td>
<td>Reduced (to be confirmed)</td>
</tr>
<tr>
<td>PTPN C1858T variant</td>
<td>Reduced</td>
</tr>
<tr>
<td>High risk HLA DR3/DR4</td>
<td>Reduced</td>
</tr>
<tr>
<td>HbA1c (glycaemic control)</td>
<td>Reduced</td>
</tr>
<tr>
<td>Baseline C-peptide</td>
<td>Increased</td>
</tr>
<tr>
<td>Immunological parameters:</td>
<td>Increased</td>
</tr>
<tr>
<td>increased</td>
<td></td>
</tr>
<tr>
<td>IL-1ra, reduced IL-1 beta</td>
<td></td>
</tr>
</tbody>
</table>

**Key:** BMI = body mass index; HbA1c = glycated haemoglobin A1c.

Benefits of preserved beta-cell function

While less than 1% of subjects with type 1 diabetes have levels of endogenous beta-cell function above the fifth percentile for healthy individuals after 5 years, multiple cross-sectional studies and retrospective analysis of the DCCT cohort has repeatedly demonstrated the benefits of preservation of even minor levels of beta-cell function.

**Improved HbA1c**

C-peptide levels 90 min following Sustacal (mixed meal) stimulation of < 500 pmol/L was an entry criterion for the DCCT study. Of the 1,441 subjects randomised, 855 had been diagnosed for 1–5 years and of these 303 had a peak C-peptide levels of 200–500 pmol/L, while 552 had a level < 200 pmol/L.
In the intensively treated group, preservation of C-peptide production (i.e. stimulated level > 200 pmo/L) was associated with a significantly lower HbA1c for the first 4 years (p < 0.01).9 A similar effect was seen for the first 3 years in the conventional treatment arm of the study. Similar findings have been reported in some3 but not all35 observational studies.

**Less hypoglycaemia**
In addition to a lower HbA1c, individuals with preserved beta-cell function had a striking reduction in severe hypoglycaemia in the DCCT study, 65% reduction, compared with the group with very modest levels of stimulated C-peptide levels, < 200 pmo/L.7 These data are consistent with data from islet cell transplantation studies indicating that transplants associated with detectable C-peptide markedly reduced the frequency of hypoglycaemia14 and improved quality of life,39 even if they did not produce sufficient insulin to result in insulin independence.

The improvement of HbA1c with less hypoglycaemia emphasises that metabolic control is easier to achieve in the presence of preserved beta-cell function. Such benefits are likely to be of particular value in teenagers and others who find it difficult to give their diabetes the level of attention required for tight metabolic control in the absence of beta-cell function.

**Reduced long-term complications**
Follow-up of the DCCT cohort, as well as cross-sectional cohorts, indicates a reduced frequency of microvascular complications. In the DCCT, stimulated C-peptide levels > 200pmol/L were associated with a 50% reduced risk of retinopathy progression over the duration of the study.26 A similar effect was seen in the observational study of Madsbad et al.37 In a more recent observational study, higher fasting C-peptide levels were associated with reduced risk of neuropathy and nephropathy as well as retinopathy.31

**Less diabetic ketoacidosis**
As discussed above, endogenous insulin secretion has been shown to slow the rate of development of ketoacidosis on insulin withdrawal,10 and is likely to reduce the risk of ketoacidosis in poorly compliant individuals.

**Improved response to immunotherapy**
In recent studies using anti-CD3 or glutamic acid decarboxylase, an improved response in terms of preservation of insulin production was seen in subjects who had preserved C-peptide levels at baseline.38 This is consistent with the view that suppression of the immune response does not result in beta-cell regeneration, but can only preserve what beta-cell function remains. However, it emphasises that the longer beta-cell function is preserved after diagnosis, the more likely it is that subjects can benefit from new developments in immunotherapy as these become available. Hence, if a given treatment preserves function for several years, such subjects might then be potential responders to a future novel therapy as and when it becomes available.

**Mechanism of the effect of preserved beta-cell function on long-term complications**
While it remains most likely that the effect of preserved beta-cell function on long-term complications relates to the improvement in HbA1c, not all studies have shown an effect on HbA1c.33 In addition, there is evidence, predominantly from animal studies, that the preservation of C-peptide secretion may itself have a direct benefit.35 In particular, C-peptide alone has been shown to signal via G-proteins, increase intracellular calcium and mitogen-activated protein kinase in endothelial cells and stimulate Na/K+ ATPase activity and endothelial nitric oxide levels.62 Administration of C-peptide to diabetic rats has shown improvements in nerve conduction velocity41 and changes of early diabetic nephropathy.62 In addition, clinical studies have shown a reduction in albumin excretion rates over 3 months of subcutaneous C-peptide administration,43 and beneficial effects on nerve conduction and autonomic neuropathic manifestations.46,43,44 However, these findings have yet to be widely replicated, and the failure to identify a specific receptor for C-peptide along with the occurrence of long-term complications in type 2 diabetes patients who still have circulating C-peptide has led some to doubt the central importance of C-peptide in this respect.45

**Regulatory approval for partial preservation of C-peptide production as a therapeutic goal in type 1 diabetes**
Among patients with type 1 diabetes and their relatives, it is often assumed that the only relevant therapeutic goal should be a ‘cure’, represented by insulin independence in type 1 diabetes. However, the foregoing discussion emphasises the important clinical benefits to be obtained from even partial preservation of beta-cell function both in terms of short (hypoglycaemia) and long-term (microvascular complications) benefits. Significant progress has recently been achieved in convincing the regulatory authorities, notably the US FDA and the EMEA, that partial preservation of beta-cell function is a sufficient basis for licensing of new therapies.46 Previously, improvement in HbA1c has been a requirement, but this is inappropriate in clinical trials as careful matching of HbA1c levels between control and intervention groups is required to exclude differences in metabolic control causing effects on beta-cell function as described above. Key to this change in approach was reaching agreement on appropriate and reliable estimates of beta-cell function which regulators could consider to be of clinical significance and appropriate for regulatory approval.46 The acceptance of this endpoint by regulators and its precise definition, is of particular importance in interesting major pharmaceutical companies to invest in this area.

**Conclusions**
A new diagnosis of type 1 diabetes is a traumatic event for patients and their relatives. Clinical teams have often consid-
Figure 3. Benefits of preservation of endogenous insulin secretion.

Key messages

- The rate of loss of endogenous insulin secretion after diagnosis of type 1 diabetes varies widely between individuals.
- Preservation of even minor endogenous insulin secretion reduces HbA1C, hypoglycaemia and long-term complications.
- At diagnosis there should be increased efforts to preserve endogenous insulin secretion and achieve tight glycaemic control.
- When they become available beta-cell preserving immunotherapies should be used at diagnosis.

The advent of new immunotherapies to preserve residual beta-cell function is particularly welcome in this concept, and since the demonstration of the very important short- and long-term benefits of preservation of even minor degrees of endogenous insulin, should inject a new degree of urgency in intensive management of early type 1 diabetes (figure 3). The advent of new immunotherapies to preserve residual beta-cell function is particularly welcome in this concept, and since they are most effective if initiated early, will add to the intensity of clinical activity in managing patients immediately after diagnosis. Early treatments may preserve function long enough for a second generation of more effective treatments to be introduced, with very marked long-term benefits for patients, especially those who find managing glycaemic control particularly challenging.

References


THE BRITISH JOURNAL OF DIABETES AND VASCULAR DISEASE