JOE DOUPE AWARD LECTURE

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Emerging Strategies for the Preservation of Pancreatic Beta-cell Function in early Type 2 Diabetes

Abstract

A fundamental problem in the clinical management of type 2 diabetes is the inability to prevent the ongoing deterioration of pancreatic beta-cell function over time that underlies the chronic progressive nature of this condition. Importantly, beta-cell dysfunction has both reversible and irreversible components. Furthermore, the amelioration of reversible beta-cell dysfunction through the early institution of short-term insulin-based therapy has emerged as a strategy that can yield temporary remission of type 2 diabetes. In this context, we have forwarded a novel therapeutic paradigm consisting of initial induction therapy to improve beta-cell function early in the course of diabetes followed by maintenance therapy aimed at preserving this beneficial beta-cell effect. Ultimately, this approach may yield an optimized therapeutic strategy for the durable preservation of beta-cell function and consequent modification of the natural history of type 2 diabetes.

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The Natural History of Type 2 Diabetes

Type 2 diabetes mellitus (T2DM) is a chronic progressive disorder characterized by worsening glycemia over time, the long-term exposure to which confers risks of vascular complications including cardiovascular disease, nephropathy, retinopathy and neuropathy. Although multiple metabolic abnormalities are present in affected patients, the pathophysiology of T2DM can be characterized as reflecting two main metabolic defects: (i) target cell resistance to the activity of insulin (*insulin resistance*) and (ii) insufficient secretion of insulin by the pancreatic beta-cells to compensate for this peripheral tissue resistance (*beta-cell dysfunction*) [1,2]. The relative importance of these defects to the pathophysiology of T2DM has been long debated, partly owing to the undeniable clinical heterogeneity of this condition. Nevertheless, several insights in recent years have led to current thinking that the central pathophysiologic feature of T2DM is ultimately beta-cell dysfunction [3].

Firstly, it has been clearly established that, in patients with T2DM, beta-cell function progressively declines over time [4]. Moreover, this deterioration precedes the development of T2DM. Notably, worsening of beta-cell function over time can be demonstrated in patients with pre-diabetes [5] and even in individuals with normal glucose tolerance who are at high-risk for the future development of diabetes (such as women with a history of gestational diabetes)[6-8]. The insight provided by the genetics of T2DM has further supported this understanding. Indeed, of the >60 genetic loci that have been linked to T2DM in recent years, almost all are associated with insulin secretion by the beta-cells (rather than insulin resistance)[9], supporting the central role of beta-cell dysfunction in the pathophysiology of diabetes.

This pathophysiology is relevant to the clinical course of T2DM. In patients, the ongoing decline of beta-cell function over time leads to worsening glycemic control, resulting in progressively increased requirements for glucose-lowering therapy [4,10]. Importantly, however, no current anti-diabetic medication has yet been conclusively shown to prevent the deterioration of beta-cell function in patients with T2DM [2,11]. Consequently, the typical clinical course of T2DM involves the sequential addition of anti-diabetic medications over time, followed ultimately by permanent insulin therapy (when beta-cell function has declined to the point where endogenous insulin secretion is insufficient for the maintenance of glycemic control in the absence of exogenous insulin). Thus, a fundamental problem in the clinical management of T2DM is the inability to prevent the deterioration of beta-cell function that underlies the progressive natural history of this condition.

Beta-cell Dysfunction and its Potential for Reversibility

At autopsy, it has been shown that patients with T2DM have a lower beta-cell mass, as compared to those with pre-diabetes or normal glucose tolerance, and evidence of beta-cell apoptosis [12,13]. Accordingly, while the predominant determinant in the relationship between beta-cell mass and function is not clear, it is believed that death of beta-cells (i.e., leading to loss of mass) is a contributor to the deterioration of insulin secretory capacity over time [11-13]. Many pathologic processes have been implicated as contributing to this deterioration, including inflammation, dysregulation of adipokines/cytokines and chronic exposure to high levels of islet cell amyloid, glucose and free fatty acids, ultimately leading to cellular stress and apoptosis [3,11]. Despite the presumed irreversibility of beta-cell death and the apparent inexorable nature of the decline in beta-cell function over time in patients, it is important to recognize that some of these factors are reversible early in the course of T2DM. Indeed, foremost amongst these reversible factors are the deleterious effects on insulin secretion of chronic exposure to high levels of blood glucose and free fatty acids, known as glucotoxicity and lipotoxicity, respectively [14-16]. Notably, the impact of glucotoxicity is apparent in the observation that the first-phase of the normal biphasic secretion of insulin by the beta-cells is completely abolished at a blood glucose concentration of 6.4 mmol/L [15]. Furthermore, even at a blood glucose level of 5.6 mmol/L, abnormalities in first-phase secretion can start to arise [15].

The finding that even mild hyperglycemia is deleterious to insulin secretion serves as a reminder of how tightly the body normally regulates blood glucose levels in the absence of diabetes. Furthermore, these data suggest that glucotoxicity is likely contributing to beta-cell dysfunction in the vast majority of patients with T2DM, even when meeting clinical targets for glycemic control. Most importantly, these data highlight the concept that there is a reversible component to the progressive loss of beta-cell function over time in T2DM [17]. This concept is often overlooked because current measures of beta-cell function cannot differentiate between reversible and irreversible dysfunction. Accordingly, two patients with the same apparent level of beta-cell function by conventional measures can be very different in their respective relative

contributions of reversible and irreversible dysfunction [18]; for example, a patient with primarily reversible dysfunction, superimposed on an otherwise relatively conserved islet mass, can be expected to experience a greater clinical response to glucose-lowering therapy than a patient with a smaller reversible component and comparatively greater irreversible dysfunction [18].

Besides explaining some of the clinical heterogeneity of T2DM, this concept holds important implications for the natural history of beta-cell dysfunction and therapeutic strategies for its modification. Notably, it is believed that the relative contributions of reversible and irreversible dysfunction change over time. Indeed, as shown in Figure 1, the relative proportion of reversible *versus* irreversible dysfunction likely declines with longer duration of T2DM. Accordingly, it follows that amelioration of reversible beta-cell dysfunction should be particularly beneficial early in the course of T2DM. This recognition is important because exogenous insulin therapy is an established anti-diabetic treatment that could reduce exposure of the beta-cells to both excessive glycemia and free fatty acids [18]. If it were to be used for the purpose of ameliorating reversible beta-cell dysfunction, however, insulin therapy would need to be introduced in early

T2DM [18]. In current clinical practice, insulin therapy is typically introduced late in the course of disease (when beta-cell dysfunction is primarily irreversible) and then continued on a permanent basis. In contrast, if insulin were to be used to address reversible dysfunction in early T2DM, this pathophysiologic perspective suggests that a short course of therapy should be sufficient for this purpose. In other words, could we use short-term treatment insulin as a *biologic therapy* for the purpose of disease modification?

Short-term Intensive Insulin Therapy in Early Type 2 Diabetes

The strategy of providing short-term intensive insulin therapy (IIT) early in the course of T2DM has been tested in previous clinical studies [18-32]. In most of these studies, the goal of this treatment strategy was the induction of “remission” of diabetes, defined variably as the subsequent maintenance of normoglycemia without any anti-diabetic therapy after cessation of the initial IIT. Most of these studies have been performed in patients with newly-diagnosed T2DM, with short-term IIT provided for 2-5 weeks by either continuous subcutaneous insulin infusion or multiple daily subcutaneous injections

FIGURE 1. Model showing the relative contributions of the reversible and irreversible components of beta-cell dysfunction over the course of type 2 diabetes. The contribution of the reversible component is greatest early in the course of diabetes and declines over time.

targeting both fasting and post-prandial glycemic control. With this therapeutic strategy, remission of T2DM was achieved in the vast majority of newly-diagnosed patients. Indeed, in these studies, the overall proportion of participants in medication-free glycemic remission has been ~66.2% at 3 months after stopping IIT, ~58.9% after 6 months and ~46.3% at 1 year, with remission continuing for up to 2 years or longer in some cases [33]. As recently demonstrated in a meta-analysis of these studies, short-term IIT consistently induces robust improvement of both beta-cell function and insulin resistance when administered to patients who are early in the course of T2DM [33]. Furthermore, consistent with the model of reversible dysfunction described earlier, the persistence of this improved beta-cell function post-IIT has been associated with an increased likelihood of remission at 1 year [23].

This improvement in beta-cell function induced by short-term IIT is accompanied by features indicative of enhanced endogenous islet function. Specifically, the improvement in beta-cell function with IIT is associated with a marked reduction in glycemic variability and a normalizing shift of the delayed postprandial glycemic peak typically observed in patients with T2DM [34,35]. Moreover, this effect can be achieved with sub-physiologic doses of exogenous insulin [17]. Third, the rates of hypoglycemia seen with this therapy are very low, in stark contrast to the usual increased risk of hypoglycemia that arises as one approaches normoglycemia when administering insulin therapy late in the course of disease in clinical practice (i.e., when there is limited beta-cell reserve) [17,36]. As only the beta-cells can finely regulate insulin secretion to achieve euglycemia without hypoglycemia, the limited hypoglycemia that has been observed in response to IIT in early T2DM likely reflects the recovery of residual beta-cell function [17,36].

Overall, the studies of short-term IIT to date have yielded the following important insights. First, in early T2DM, short-term IIT can improve both insulin resistance and beta-cell function [33]. The improvement in insulin resistance is a key determinant of the reversibility of beta-cell dysfunction [17], and this recovery of beta-cell function appears to play a central role in the long-term beneficial effect of this short-term therapy [18]. Second, this long-term benefit is reflected in the observation

that, after stopping IIT, patients can have a prolonged glycemic remission, off anti-diabetic medications; however, this effect is not permanent, as the rate of remission clearly wanes over time [33]. Thus, taken together, these data suggest the need for therapeutic strategies aimed at maintaining the beneficial beta-cell effects of initial short-term IIT.

In designing such strategies, we have suggested the following novel paradigm for pathophysiologically-based treatment early in the course of T2DM: the initial institution of “induction therapy” to improve reversible beta-cell dysfunction, followed by subsequent “maintenance therapy” to preserve this beneficial effect. The goal of this therapeutic approach is the preservation of beta-cell function over time and thereby modification of the natural history of T2DM. Short-term IIT can serve as one such induction therapy; hence, a current challenge is identification of the appropriate maintenance therapy. We are thus conducting clinical trials aimed at identifying the optimal delivery of this novel therapeutic approach to the treatment of T2DM.

Strategies for Maintaining the Beneficial Effect of Short-term IIT

The **B**eta-cell **E**valuation and **S**itagliptin **T**rial (BEST) was a double-blind randomized controlled trial designed to evaluate whether the dipeptidyl peptidase 4 (DPP-4) inhibitor sitagliptin could maintain the improvement in beta-cell function initially achieved with short-term IIT [37,38]. In this trial, patients with T2DM of mean 6 years duration underwent 4-8 weeks of IIT before randomization to either sitagliptin or placebo, both on a background of metformin, for 48 weeks. As expected, beta-cell function improved with the short course of pre-randomization IIT [26]; however, following cessation of the insulin therapy, this improvement in beta-cell function was lost in both the sitagliptin and placebo arms, such that the primary outcome of baseline-adjusted beta-cell function at 48 weeks was not different between the two arms [37]. Thus, in this study, sitagliptin was not able to maintain the initial beneficial effect of short-term IIT.

A similar study design was applied in the **L**iraglutide and **B**eta-cell **R**epAir (LIBRA) Trial, which addressed the research question of whether the glucagon-like peptide-1

(GLP-1) agonist liraglutide could be an effective maintenance therapy after short-term IIT. In this trial, patients with T2DM of mean 3 years duration underwent 4 weeks of IIT prior to randomization to either daily liraglutide or placebo injection for 48 weeks [39]. Following the initial improvement induced by IIT, the liraglutide arm experienced a further enhancement of beta-cell function that was maintained for the duration of the treatment [39]. Thus, the LIBRA Trial showed that ongoing treatment with liraglutide could preserve beta-cell function for 1 year after initial short-term IIT; however, this beneficial effect was completely lost within 2 weeks of stopping liraglutide, suggesting that this medication did not reverse the underlying pathology that drives beta-cell deterioration in T2DM [39].

In the LIBRA trial, both the liraglutide and placebo arms achieved excellent glycemic control throughout the 1 year of treatment. Indeed, at each quarterly assessment, >50% of participants in the liraglutide arm had A1c $\leq 6.0\%$ and glucose tolerance in the non-diabetic range on oral glucose tolerance test [39]. Even in the placebo arm, 56% of participants had A1c $< 6.5\%$ at 48 weeks, indicative of the long-term beneficial effect of short-term IIT almost 1 year earlier. These findings have helped inform the next set of trials aimed at preservation of beta-cell function.

The robust improvement in beta-cell function that has consistently been achieved with short-term IIT, and its long-term effects on remission, raise the possibility that IIT itself could be an ideal maintenance therapy [33]. This concept of intermittent IIT as both induction and maintenance therapy for the preservation of beta-cell function is currently being tested in the **RE**mission **S**tudies **E**valuating **T**ype 2 Diabetes – **I**ntermittent Insulin **T**herapy (RESET IT) Trial, a multi-centre randomized controlled trial funded by the Canadian Institutes of Health Research (CIHR).

An alternative strategy follows from the observation that, in the LIBRA Trial, liraglutide induced a further enhancement of beta-cell function beyond that achieved with IIT. Specifically, these data raise the possibility that combination therapy consisting of a GLP-1 agonist and basal insulin may be particularly beneficial to beta-cell function. This strategy is currently being tested in the **PRE**serVing Beta-cell Function with ExenA₁tide and In-

suLin (PREVAIL) Trial, a randomized control trial also funded by CIHR. The rationale for this study is further supported by a meta-analysis of recent trials demonstrating that, when administered late in the course of T2DM, combination therapy consisting of basal insulin and a GLP-1 agonist can achieve the ideal trifecta of excellent glycemic control, weight loss, and no increased risk of hypoglycemia [40].

In conclusion, recognition of the reversible component of beta-cell dysfunction in T2DM and its potential for amelioration with early insulin therapy has opened the door to an array of new strategies aimed at the preservation of beta-cell function. These concepts have yielded a novel therapeutic paradigm, wherein we first apply *induction therapy* to improve beta-cell function early in the course of disease and then *maintenance therapy* aimed at preserving this beneficial beta-cell effect. Clinical trials are currently evaluating specific strategies for applying this approach. Ultimately, this program of research may yield an optimized therapeutic strategy for preserving beta-cell function and thereby modifying the natural history of T2DM.

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