Can J Diabetes 39 (2015) S142–S147

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Review

Novel Strategies for Inducing Glycemic Remission during the Honeymoon Phase of Type 2 Diabetes

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ARTICLE INFO

Article history:
Received 18 June 2015
Received in revised form
31 July 2015
Accepted 10 August 2015

Keywords:
beta-cell function
GLP-1
short-term intensive insulin therapy

ABSTRACT

A lofty goal in the management of type 2 diabetes is the achievement of glycemic remission. Glycemic remission can be defined as the sustained maintenance of normoglycemia without antidiabetic therapy for variable periods of time after stopping an initial disease-modifying intervention. Although this goal remains largely elusive at this time, growing recognition of the potential reversibility of pancreatic beta-cell dysfunction early in the course of type 2 diabetes has yielded a target for such disease modification. Furthermore, short-term intensive insulin therapy for 2 to 5 weeks has emerged as an intervention that could be applied as a biologic agent for this purpose during a window of opportunity that we have called the *honeymoon phase* of type 2 diabetes. This recognition has led to a novel therapeutic paradigm consisting of initial induction therapy to improve reversible beta-cell dysfunction during the honeymoon phase, followed by maintenance therapy aimed at preserving this beneficial beta-cell effect. This concept of induction and maintenance therapy is being applied in a series of recent and ongoing clinical trials, toward the goal of ultimately preserving beta-cell function and thereby modifying the natural history of type 2 diabetes.

Mots clés :
fonctionnement des cellules bêta
GLP–1 (sigle du *glucagon-like peptide–1*)
insulinothérapie intensive de courte durée

RÉSUMÉ

L'atteinte de la rémission glycémique constitue un objectif ambitieux de la prise en charge du diabète de type 2. La rémission glycémique peut être définie par le maintien prolongé de la normoglycémie sans thérapie antidiabétique au cours de périodes de temps variables après l'interruption d'une intervention initiale modificatrice de la maladie. Bien qu'actuellement cet objectif demeure en grande partie élusif, la reconnaissance accrue de la réversibilité potentielle du dysfonctionnement des cellules bêta du pancréas dès le début du diabète de type 2 a fourni une cible en matière de modification de l'évolution de la maladie. De plus, l'insulinothérapie intensive de courte durée, soit de 2 à 5 semaines, s'est révélée une intervention pouvant être appliquée comme un agent biologique à cette fin durant un créneau que nous avons appelé la « lune de miel » du diabète de type 2. Cette reconnaissance a mené à un nouveau paradigme de traitement qui consiste initialement dans le traitement d'induction pour améliorer le dysfonctionnement réversible des cellules bêta durant la lune de miel et, par la suite, dans le traitement d'entretien visant la préservation de cet effet bénéfique sur les cellules bêta. Ce concept de traitements d'induction et d'entretien est appliqué dans une série d'essais cliniques récents et en cours en vue d'atteindre l'objectif ultime de préservation du fonctionnement des cellules bêta et ainsi modifier l'évolution naturelle du diabète de type 2.

Introduction

The clinical course of type 2 diabetes is generally characterized by rising glycemia over time, leading to progressively greater requirements for antidiabetic therapy with longer duration of diabetes (1). Accordingly, with the passage of time, patients typically advance from lifestyle modification alone to metformin monotherapy

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http://dx.doi.org/10.1016/j.jcjd.2015.08.007

to a variety of more complex regimens consisting of multiple antidiabetic medications, which eventually may culminate in permanent insulin therapy. Patients with type 2 diabetes have multiple metabolic abnormalities, but the central pathophysiologic defect underlying the natural history of the disorder is ultimately pancreatic beta-cell dysfunction (2). Indeed, the observed need for increased antidiabetic therapy in practice is a reflection of the progressive worsening of beta-cell function over time, a chronic pathologic deterioration that current treatment regimens have been unable to halt. As such, though elusive to date, therapeutic strategies aimed at modifying the natural history of beta-cell dysfunction hold great potential for changing the clinical course of type 2 diabetes in patients (3,4). In this context, recent insights into this natural history, and particularly its under-appreciated potential for reversibility, have led to the development of novel strategies that ultimately may enable the preservation of beta-cell function early in the course of type 2 diabetes. It is this concept of reversibility and the resultant pharmacologic strategies that it has spawned that form the focus of this review.

Natural History of Beta-Cell Dysfunction

The familial nature of type 2 diabetes has long been recognized in clinical practice, but its genetic underpinnings have only recently begun to be unravelled. In this regard, it is notable that almost all of the genetic loci that have been linked to type 2 diabetes are associated with insulin secretion by the beta-cells, rather than insulin resistance (5). This observation supports not only the pathophysiologic importance of the beta cells but also speaks to a defect that long precedes the development of type 2 diabetes in at-risk individuals. This concept has been directly demonstrated in patient populations that are at risk for developing type 2 diabetes, such as women with a history of gestational diabetes mellitus (GDM). Indeed, in the years after delivery, beta-cell function generally declines in women with a history of GDM, even while they maintain normal glucose tolerance (6–9). Similarly, deterioration of beta-cell function over time is evident in patients with prediabetes (10), ultimately leading to the rising glycemia that determines their progression to type 2 diabetes. Finally, as shown in the United Kingdom Prospective Diabetes Study, beta-cell function continues to decline in the years after diagnosis of type 2 diabetes (11). From this perspective, the typical institution of insulin therapy late in the course of type 2 diabetes in clinical practice can be looked upon as reflecting a point in the natural history wherein endogenous insulin secretion by the beta cells is so severely diminished that glycemic control can no longer be maintained without the contribution of exogenous insulin supplementation.

Following its implementation in late type 2 diabetes, exogenous insulin is generally a permanent lifelong therapy. One of the reasons that it cannot be stopped is that patients with type 2 diabetes experience a loss of beta cells over time (12,13). Indeed, at autopsy, patients with type 2 diabetes exhibit lower beta-cell mass than individuals with prediabetes or normal glucose tolerance and show evidence of beta-cell apoptosis (12,13). It is thus believed that death of beta cells (yielding a loss of mass) is a contributor to the deterioration of insulin secretory capacity over time (4,14). Although their respective independent contributions remain difficult to ascertain, many pathologic processes have been implicated in this deterioration. These pathologic factors include inflammation, dysregulation of adipokines/cytokines and chronic exposure of the beta cells to excessive amyloid, glucose and free fatty acids, ultimately leading to cellular stress and apoptosis (2,4,14). Thus, it is generally believed that the natural history of type 2 diabetes is characterized by an inexorable worsening of beta-cell function that is accompanied by the ongoing loss of insulin-secreting cells over time.

Potential reversibility of beta-cell dysfunction: the honeymoon phase

Despite the perceived inevitability of this natural history and its terminal outcome of presumably irreversible beta-cell death, it is important to recognize that there exists a reversible element to beta-cell dysfunction, particularly early in the course of type 2 diabetes (3,15). This reversibility is often overlooked because conventional measures of beta-cell function cannot distinguish between reversible and irreversible dysfunction, yielding, instead, an overall assessment of secretory capacity (to which both of these components contribute) (16). Furthermore, the relative contribution of these components is believed to change over time, with reversible dysfunction playing a predominant role early in the course of type 2 diabetes (3). In contrast, after long duration of diabetes, irreversible dysfunction (i.e. owing to the loss of beta cells) is the main determinant of beta-cell insufficiency. As such, addressing reversible dysfunction in early type 2 diabetes could provide a means of preserving beta-cell functional capacity, thereby modifying the clinical course of diabetes in patients. Toward this goal, then, we must first consider the factors contributing to reversible dysfunction and how they could be addressed.

Glucotoxicity and lipotoxicity are 2 such reversible factors, reflecting the deleterious effects of chronic exposure to excessive glycemia and free fatty acids, respectively (17). Indeed, glucotoxicity is relevant in most patients with type 2 diabetes, owing to the fact that even mild degrees of hyperglycemia have adverse effects on insulin secretion by the beta cells. Specifically, in normal physiology, insulin secretion by the beta cells is biphasic, consisting of a rapid first phase followed by a more prolonged second phase of secretion. However, first-phase insulin secretion is completely abolished at a blood glucose concentration of just 6.4 mmol/L, reflecting the deleterious effect of glucotoxicity (18). Moreover, abnormalities in first-phase secretion can start to arise even at blood glucose levels of 5.6 mmol/L (18). As such, it should be recognized that glucotoxicity impacts glucose homeostasis in most patients with diabetes.

Figure 1 is a schematic showing how this impact of glucotoxicity potentially may manifest. In patients at risk for diabetes (such as women with a history of GDM), beta-cell function declines over time,

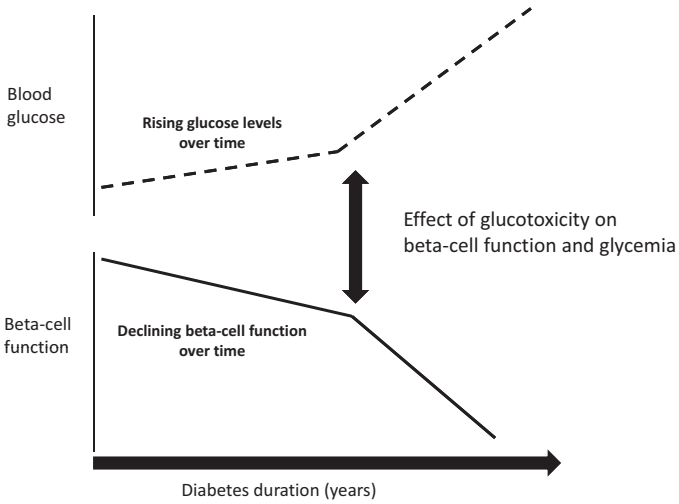

Figure 1. This schematic shows the anticipated effect of glucotoxicity on beta-cell function and glycemia over the course of type 2 diabetes. Early in the natural history of diabetes, the rising glycemia secondary to declining beta-cell function will reach a threshold (i.e. the point of inflection on the glucose curve above) at which glucose will further compromise beta-cell dysfunction (i.e. glucotoxicity). This glucotoxic insult to insulin secretory capacity will have the effect of then amplifying the rising glycemia.