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Insulin Therapy and Hypoglycemia - Present and Future

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1. Introduction

Over the last few decades the prevalence of diabetes has dramatically grown in most regions of the world. In 2010, 285 million people had diabetes and it is estimated that the number will increase to 438 million in 2030 (1). About 5-10% of them have type 1 diabetes. Both types of diabetes are characterized by a progressive decline of pancreatic beta cell function and mass. In type 1 diabetes, the chronic autoimmune process causes the selective destruction of insulin-producing beta cells by the auto-reactive T cells in genetically predisposed individuals. There is a continuous loss of functional C-peptide responses and at the time of clinical presentation the beta cell mass is reduced by 70–90 %, as suggested by anatomic studies (2, 3). This results in an inability to secrete sufficient amounts of insulin and loss of metabolic control. As a consequence, exogenous insulin replacement in the form of multiple subcutaneous injections or continuous subcutaneous insulin infusions (CSII) is essential for patients with type 1 diabetes. It prevents death from acute metabolic complications and assures normal growth and development, maintenance of normoglycemia and prevention of end-organ complications.

Type 2 diabetes results from an entirely different pathophysiological process. It is characterized by an increased resistance to insulin action in the peripheral tissues with decreased glucose uptake and enhanced hepatic glucose output associated with impaired insulin-secretory capacity caused by a progressive decline of beta cell function over time. Studies indicate a substantial loss of beta cell mass (of about 25-60 %) by the time of diagnosis, mainly secondary to increased apoptosis and impaired augmentation of cell mass through neogenesis (4, 5). The clinical onset is due to the reduction of beta cell mass per se and to a concomitant dysfunction of residual beta cells (6, 7). The beta cell failure, which seems to occur much earlier during the natural history of the disease than previously thought, results in significant insulin deficiency and by then, insulin administration is required in order to achieve glycemic control (8, 9).
2. Intensive insulin regimens: Evidence for benefit

It is well established that in patients with both types of diabetes obtaining a good metabolic control is of paramount importance because the risk of developing chronic micro- and macrovascular complications is dependent on the degree of glycemic control (10). Current guidelines from professional organizations recommend achieving glycated hemoglobin (HbA1c) levels lower than 7% (and closer to normal values in selected individuals, if this could be achieved without significant increase in hypoglycemic events or other side effects) (11). Several landmark studies emphasize the importance of more physiologic insulin profiles in reaching these goals.

The Diabetes Control and Complications Trial (DCCT) proved that tighter glycemic control after onset obtained with intensive insulin regimens can prevent / delay microvascular complications in patients with type 1 diabetes compared with conventional insulin regimens (12). The follow-up of the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) study provided evidence for the sustained benefit in subjects with prior intensive treatment, even if during the follow-up period the glycemic control was similar to that of subjects previously receiving conventional therapy (13-16). These studies demonstrated that the risk of developing long-term complications is determined both by the degree and the total duration of glycemic exposure. In addition, the DCCT established the relationship between glucose control and residual beta cell function as subjects with stimulated C-peptide concentrations > 0.2 pmol/ml had better outcomes (17, 18). The maintenance of endogenous beta cell function was associated with diminished disease progression, improved long term metabolic control and reduced chronic complications. These studies highlighted the role of insulin therapy over long-term.

In patients with type 2 diabetes similar benefits of intensive insulin regimens have been shown. In the Kumamoto study, which included a smaller patient population, intensive glycemic control obtained by multiple insulin injection therapy delayed the onset and progression of the early stages of diabetic microvascular complications (19, 20). Likewise, the United Kingdom Prospective Diabetes Study (UKPDS) emphasized the role of glycemic control in reducing the incidence of chronic complications in patients with type 2 diabetes, although in this study the intensive treatments were not limited to insulin regimens (21-23). Similar to EDIC, the follow-up of the UKPDS cohort showed the persistence of microvascular benefits in patients formerly treated with intensive regimens (24). A more recent study in subjects with newly diagnosed type 2 diabetes demonstrated that transient intensive insulin therapy (with continuous subcutaneous insulin infusion or multiple daily insulin injections) resulted in favorable outcomes on glycemic control and beta cell function compared to oral hypoglycemic agents (25). Trials in patients with type 2 diabetes of longer duration have also supported the benefits (even if more modest) on the onset / progression of chronic complications (26-28).

3. The importance of controlling postprandial hyperglycemia and hypoglycemic events

To date, the therapeutic interventions have mainly been focused on lowering HbA1c with emphasis on fasting blood glucose levels. However, in order to obtain optimal glycemic control with HbA1c levels < 7%, controlling both fasting and post-meal glycemia is necessary (29, 30).
It is well established that poorly controlled diabetes is associated with development of chronic micro- and macrovascular complications. Experimental studies demonstrated the atherogenic role of postprandial glycemic peaks and the link between the post-meal or post-challenge hyperglycemia (2hPG) and cardiovascular morbidity and mortality. Two meta-analyses have shown an exponential relationship between incidence of cardiovascular events and fasting glucose or 2hPG (31, 32). The relationship was stronger and highly significant for 2hPG and there seemed to be no threshold for 2hPG. Several population-based studies have basically confirmed this finding indicating an increased relative risk (in the range of 1.18 to 3.3) of cardiovascular or coronary heart disease mortality in patients with increased 2hPG (33). It has been reported that in individuals with type 2 diabetes, especially women, postprandial plasma glucose is a stronger predictor of cardiovascular events than fasting glucose levels (34). Another study indicated that both fasting and post-meal glycemia were predictive for cardiovascular events after adjusting for other risk factors in type 2 diabetic subjects (35).

A growing body of evidence shows that there is a relationship between postprandial hyperglycemia and markers of cardiovascular disease such as oxidative stress, carotid IMT and endothelial dysfunction. Oxidative stress has been implicated as a cause of both macro- and microvascular complications of diabetes. The proposed mechanism is that hyperglycemia, insulin resistance and free fatty acids feed into oxidative stress, activation of RAGE and PKC, which leads to vascular inflammation, thrombosis and vasoconstriction (36). Furthermore, increased risk of retinopathy, certain cancers and cognitive dysfunction in elderly was shown to be associated with postprandial hyperglycemia in type 2 diabetic patients (37-39).

The Kumamoto study demonstrated that postprandial glycemia was strongly associated with onset of retinopathy and nephropathy (as were fasting blood glucose and HbA1c) and that control of both fasting glucose levels < 110 mg/dl and post-meal glucose levels < 180 mg/dl prevented the onset and progression of diabetic microvascular complications (19, 20). On the other hand, the cost of strict glycemic control and intensive therapy is an increased risk of hypoglycemia, which per-se is a limiting factor in achieving long-term near-normal glucose control in patients with diabetes (40). Depending on its degree, hypoglycemia can affect physical and cognitive functions and can induce negative psychological and social consequences (41). Studies have consistently indicated a higher rate of hypoglycemia in patients with type 1 diabetes treated to lower HbA1c targets (40, 42). In the DCCT, the frequency of severe hypoglycemia was three times higher in subjects treated with intensive insulin therapy compared with those on conventional therapy, while in the Stockholm Diabetes Intervention Study - severe hypoglycemia occurred 2.5 times more frequently in the intensively treated group (43, 44). Insulin-treated subjects with type 2 diabetes experience severe hypoglycemia less frequently than patients with type 1 diabetes. This fact is explainable in part by the maintenance of some beta cell function (which allows a decrease of insulin secretion when blood glucose falls) and by insulin resistance (41). However, data from UKPDS provide evidence that the risk of hypoglycemia increases with longer duration of insulin treatment. Another study reported similar frequencies of severe hypoglycemia in patients with type 2 and type 1 diabetes after matching for duration of insulin therapy (45, 46). It is plausible that in real life patients on intensive insulin regimens experience higher rates of hypoglycemia, but since there is relatively limited data on the actual frequency of asymptomatic and mild hypoglycemia, episodes of mild hypoglycemia may be underestimated and/or underreported (41).
Hypoglycemia, even mild (especially if it occurs recurrently), can be associated with negative effects, such as impaired autonomic counter-regulation, compromised behavioral defenses against subsequent decreasing glucose concentrations and hypoglycemia unawareness, which causes a vicious cycle of recurrent hypoglycemia (41, 47). Severe hypoglycemia may exert even more serious side effects, such as seizures, unconsciousness (which may be particularly debilitating in the elderly), coma and even death (48). In older patients with type 2 diabetes and a history of severe hypoglycemia, an increased risk of dementia has been reported, particularly for patients who have a history of multiple episodes (49). In the UKPDS, recurrent hypoglycemia was associated with decreased quality of life in patients treated with insulin (50). Moreover, the unpleasant symptoms and negative consequences of hypoglycemia may result in fear and anxiety, lower treatment satisfaction, which in turn may negatively impact the diabetes management and adherence to therapy, precluding a full attainment of the benefits offered by improved glycemic control (48).

Evidence exist that hypoglycemic episodes, especially severe ones, are associated with adverse cardiovascular events (such as prolongation of the QT interval, cardiac arrhythmias, sudden cardiac arrest, and acute myocardial infarction), which are triggered by the stimulation of the sympathetic nervous system and the catecholamine surge (51, 52). Hypoglycemia also has proinflammatory consequences that may augment the risk of plaque inflammation and rupture, causing subsequent cardiovascular events (51). Hypoglycemia, mainly the recurrent and severe episodes, and the presumed ensuing cardiovascular toxicity may increase the susceptibility to poor cardiovascular outcomes, especially in subjects with significant atherosclerosis and functional / structural heart abnormalities. The cause of excess mortality during intensive therapy seen in the ACCORD study is not entirely clear, but it is thought that the most plausible cause is iatrogenic hypoglycemia (51). Thus, it is equally important to avoid both hyperglycemic surges and hypoglycemic events while striving to obtain a tight metabolic control.

4. Restoring physiological insulin secretory profiles

In the normal, physiologic conditions there is a low basal insulin output that suppresses endogenous hepatic glucose production (overnight and between meals) as well as incremental responses of insulin secretion following food ingestion. After a meal, blood glucose concentrations start rising within 15 minutes, reach a peak at about 30-45 minutes and within 1-2 hours return to basal levels and remain stable until the next food ingestion (53, 54). The maximal amplitude of glucose excursion depends on the amount and type of carbohydrates ingested (53). These dynamics are mirrored by the prandial insulin secretion profile: there is an initial (first) phase, which peaks in 2-3 minutes and lasts about 10 minutes, then there is a second phase of insulin release that becomes apparent after 10 minutes and continues as long as the glucose concentrations remain elevated and is concordant with the amount of carbohydrates absorbed (54-56). Once the blood glucose levels decrease, insulin secretion returns to baseline values, in order to prevent hypoglycemia in the post-absorptive phase (56).

It is believed that insulin regimens that best mimic the physiological pattern of insulin production are most likely to reach near-normal glycemic control by regulating both fasting and postprandial blood glucose levels (56, 57). These regimens require a sharp increase of insulin levels after meals and flat, nearly constant plasma insulin concentrations in the postabsorptive / interprandial periods. They are known as basal-bolus therapy because they


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Over the last few decades the prevalence of diabetes has dramatically grown in most regions of the world. In 2010, 285 million people were diagnosed with diabetes and it is estimated that the number will increase to 438 million in 2030. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the serum glucose concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. Hopefully, this book will be of help to many scientists, doctors, pharmacists, chemicals, and other experts in a variety of disciplines, both academic and industrial. In addition to supporting researcher and development, this book should be suitable for teaching.

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