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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 postabsorbtive / interprandial periods. They are known as basal-bolus therapy because they

attempt to replicate the normal insulin secretion by combining basal and meal-time insulin replacements (58).

The "gold-standard" of insulin replacement is CSII by means of a pump, which delivers short-acting insulin in a continuous manner at determined rates and assures a peakless insulin profile between meals and insulin surges at meal-time (56, 58). The short-acting insulin analogues are better suited for CSII because of their faster absorption from subcutaneous tissue (59). The basal insulin rates can be adjusted on an hourly basis according to blood glucose oscillations to meet the 24-hour requirements of each individual and should provide about half of the total daily dose. The prandial doses are calculated by the patients and delivered according to blood glucose monitoring results, target glucose levels, carbohydrate content of the meal, physical activity, insulin sensitivity and other factors (58). Several studies have shown that CSII offers more flexibility and provides better glycemic control with improved HbA1c levels and fewer hypoglycemic events due to lower variability and better reproducibility of insulin absorption (probably resulting from the fact that the subcutaneous insulin depot is smaller) (60, 61). However, the cost of such therapy is too high to be widely available and it also requires significant patient involvement, education and motivation.

Alternatively the basal/bolus replacement can be supplied in the form of multiple daily injections. Traditionally, the regimens consisted of two injections of NPH (in the morning and at bedtime) plus 2-3 injections of regular insulin with meals. The problem with the intermediate-acting insulin preparations like NPH is that their pharmacokinetic profile does not provide a physiologic basal replacement: they have a peak at about 4-6 hours post subcutaneous injection and the action wanes rapidly at about 5-6 hours after the peak (56, 58). This profile increases the risk of nocturnal hypoglycemia (even with a bedtime snack intake), because at the time of their highest concentration (which usually occurs between midnight and 2-3 a.m.) the insulin sensitivity is higher and patients would require less basal insulin (56). Nocturnal hypoglycemia is a serious concern because it causes morning hyperglycemia through the release of counter-regulatory hormones (glucagon, epinephrine, growth hormone, cortisol) and prolonged insulin resistance and influences different physical and psychological functions during the following day. In addition, undetected nocturnal hypoglycemic episodes contribute to hypoglycemia counter-regulatory failure and unawareness, which in turn predisposes to severe hypoglycemia and profoundly impacts on patients' quality of life (62). On the other hand, the time-action profile of the intermediate-acting insulin poses another problem: during the morning hours (after 4 a.m.) the requirement for basal insulin is greater due to increased release of counter-regulatory hormones and by then the insulin action is waning, which results in morning hyperglycemia. An attempt to correct this by increasing the bedtime insulin dose may result in higher risk of nocturnal hypoglycemia.

A different approach of multiple daily injections which attempts to alleviate these problems uses short-acting insulin analogues at meal-time with one or two injections of long-acting insulin analogues (glargine or detemir) and it is the preferred regimen in recent years (58). The long-acting analogues afford less glycemic fluctuations, less variability, reduced risk of hypoglycemic events and a significantly prolonged duration of action (17-24 hours) due to a steady absorption into the circulation and more stable serum concentrations (63, 64). Studies have indicated fewer overall, nocturnal and severe hypoglycemic episodes in both types of diabetes (especially in type 1), while providing similar or slightly improved metabolic control compared with NPH insulin (65-67).

5. The limitations of current prandial insulin treatment for type 1 and type 2 diabetes

Multiple daily insulin injections are the mainstay of insulin delivery for many patients with type 1 diabetes and patients with type 2 diabetes that cannot be controlled with other regimens, especially those with longer duration of the disease and severe insulin deficiency. Despite the evidence and increased awareness of the necessity to achieve strict glycemic control, current insulin therapy has some limitations that preclude reaching the goal of maintaining near-normal glycemia in the long-term, even in compliant patients. The major challenges are related to avoiding postprandial hyperglycemia and late hypoglycemia, which are mainly caused by the mismatch between the time-action profile of the administered insulin and postprandial glucose excursions.

The "conventional" prandial insulin therapy with regular human insulin has its shortcomings in terms of the pharmacokinetic properties which limit their clinical efficacy: the onset of action is slow, the peak is reached in about 2-3 hours and the total duration of action lasts 5-8 hours (68). This is caused by the fact that the dissociation rate of human insulin from hexamers into monomers in the subcutaneous tissues is slow and the absorption into the bloodstream is gradual. Thus, the maximal insulin concentrations do not occur at the time when glucose levels are the highest, and so the short-acting insulin has to be administered 30-45 minutes before meals in order to minimize postprandial hyperglycemia. This is quite inconvenient for patients (and poses a risk of pre-meal hypoglycemia if the food intake is inadvertently delayed) and even so, the time-action profile is not optimal. Glycemic excursions are not properly covered and 4-5 hours post-injection, after the food absorption is completed, there is still some insulin absorption from subcutaneous depot (58). This results in relative hyperinsulinemia, which increases the risk of late postprandial hypoglycemia and would require a snack intake to prevent it. Moreover, the regular human insulin preparations have important intra- and inter-individual variations that result in unpredictable effects and makes it even more difficult to avoid hyper- and hypoglycemia (69).

In order to overcome the problems of non-physiologic pharmacokinetics, the regular human insulins have been largely substituted with the newer insulin analogues that were developed by means of protein engineering and recombinant DNA technology to enable better glycemic control by faster action (70). The insulin analogues have been obtained by substitution or minimal alterations in the amino acid sequence in regions of the molecule not essential for binding to the insulin receptor but pivotal for dimer formation in order to diminish the tendency of self-association between insulin molecules and allow a faster absorption from injection site (70). There are three rapid-acting insulin analogues available at the moment: insulin lispro (based on amino-acid substitution of proline at position B28 and lysine at position B29), insulin aspart (with aspartic acid substituted for proline at position B28) and insulin glulisine (that has an asparagine to lysine substitution at position B3, and a lysine to glutamine acid substitution at position B29) (71). Despite the differences in structure, the three analogues have similar pharmacokinetic and pharmacodynamic properties (70). Their onset of action is more rapid, which permits an administration within 10-15 minutes before meals, the peak is greater and occurs at about 1-2 hours and the total duration of action is shorter (4-5 hours) compared to regular human insulin (Table 1) (58, 68). This allows an improved replacement of mealtime insulin needs with regards to postprandial plasma glucose control and more flexibility than regular insulin. In addition,

the insulin analogues have a smaller intra- and inter-individual variability compared to regular insulin which could provide a somewhat improved glycemic control and potentially reduced risk of hypoglycemia (69).

Insulin	Onset of action	Peak action	Total duration of action
Short-acting			
Regular	30-45 min	2-3 h	5-8 h
Rapid-acting			
Lispro Aspart Glulisine	5-15 min	1-2 h	4 h

Table 1. The pharmacodynamic profiles of currently available prandial insulin formulations (68)

However, even with the insulin analogues the synchronization between insulin action and glucose absorption from a meal is still less than ideal, as they do not replicate normal physiology, and many patients still have suboptimal glucose control. Several meta-analyses have suggested that insulin analogues offer rather modest or inconsistent clinical advantages over conventional insulin in terms of lowering HbA1c and reducing hypoglycemia, in children and adults with type 1 diabetes (72-76). Data on the influence on hypoglycemia is particularly inconsistent. Some studies have shown that in fact the overall frequency of hypoglycemic episodes were similar with analogue insulin and regular insulin use in adults with type 1 diabetes and were modestly decreased in children (72-77). Moreover, some reports indicated that the frequency of severe and nocturnal hypoglycemia seemed to be reduced with analogues in adults, but not in prepubertal children, while others found no difference in the frequency of severe or nocturnal hypoglycemia and no evidence for reduction in patient awareness for hypoglycemia with insulin analogues (72-78). It should be noted that hypoglycemia occurrence is not fully attributable to the pharmacokinetic profile of the insulin preparations, but may also result from a mismatch between insulin dose and the carbohydrate content of the meal, delayed food intake or other factors (79).

On the other hand, postprandial hyperglycemia still occurs with the new insulin analogues (80, 81). Hyperglycemic postprandial glucose excursions were found to reach levels over 300 mg/dl in about 50% and over 180 mg/dl in almost 90% of children with type 1 diabetes with good overall metabolic control (82). The findings were confirmed by other studies that indicated postprandial glucose levels higher than 300 mg/dl in subjects with type 1 diabetes receiving multiple insulin injection therapy (83). Targeting postprandial hyperglycemia is important in order to improve HbA1c levels and this has also been recently highlighted by the International Diabetes Federation guidelines (84, 85).

In everyday life the control of postprandial hyperglycemia poses even more challenges due to variations in dietary intake and physical exercise or insulin dosage and timing changes (patients may modify the timing of insulin administration in the sense of dosing immediately before or even after meals in order to fit their lifestyle / daily activity requirements) (86). In addition, lack of predictable insulin response may occur with insulin analogues because their absorption can be affected by various factors such as: mechanics of injection, the injection site, and metabolic factors, similar to regular human insulin (87).

Two meta-analyses indicated that regular human insulin and rapid-acting analogues have comparable frequencies and types of adverse events (other than hypoglycemia), i.e. local site reactions, ketoacidosis and the discontinuation rates during the clinical studies were similar for the two types of insulin preparations (75, 77).

6. Current ultrafast insulin formulations

Thus, the limitations of current insulin formulations and the need for proper postprandial glycemic control have led to research of novel, ultrafast insulin formulations /delivery systems that could eventually better match post-prandial glucose excursions (by speeding the onset of insulin absorption and action coupled with a faster offset of action) and that would offer improved flexibility in terms of injection time relative to a meal (Table 2). By a closer approximation of the normal insulin release, several outcomes could be obtained, i.e. improvement of HbA1c through a better control of postprandial blood glucose, reduced incidence of late-phase hypoglycemia, lower intra-subject variability, and less weight gain. Recently, stainless steel microneedle syringe devices have been under investigation for intradermal delivery of insulin and their potential to improve postprandial glycemia has been evaluated. The microneedles (34-gauge; an external diameter of approximately 260 μm, 1.25-1.75-mm long) penetrate the stratum corneum and epidermis to reach the dense beds of capillaries and lymphatic vessels of the dermis (88). The dermis layer can facilitate a faster insulin absorption compared to injection into the subcutaneous layer by an increased lymphatic absorption and reach blood circulation.

Insulin	Onset (early T50%)	Peak (T GIRmax)	Offset (late T50%)
Intradermal[90]	28-35 min	105-110 min	271-287 min
rHUPH20+insulin[93]	43-44 min	72-114 min	119-275 min
VIAject[95]	31-35 min	111-136 min	270-297 min
InsuPatch[101]	NA	95 min	NA
Technosphere[105,106]	NA	42-79 min	NA
Oral-lyn[119-121]	23-35 min	40-50 min	56-101 min

Table 2. The pharmacodynamic profiles of ultrafast insulin formulations / delivery systems under development

In animal models the intradermal delivery of insulin by microneedles provided a unique pharmacokinetic profile more closely resembling the intravenous rather than the subcutaneous administration (89). The profile is characterized by an extremely rapid uptake and systemic distribution from the injection site: the time to maximum concentration was significantly reduced (with 64%) for insulin lispro administered intradermaly vs. subcutaneously. In addition, the maximum circulating peak concentrations were elevated several fold (349% for insulin lispro) compared to subcutaneous delivery. Moreover, both regular and analogue insulins, despite their differences in molecular weight, when delivered by microneedles showed a more rapid onset of action than subcutaneous delivery of insulin analogue (lispro) (89).

A clinical study in healthy volunteers that evaluated the pharmacokinetics and pharmacodynamics of intradermal administration of insulin lispro compared to subcutaneous injections under euglycemic clamp conditions, has basically confirmed these findings (90). Delivery via microneedles resulted in faster insulin uptake with decreased time to maximal insulin concentration (by approximately 24 minutes), higher relative bioavailability at early post-injection times and a more physiologic metabolic effect, with faster onset of action (shorter times to maximal and early half-maximal glucose infusion rates) and more rapid offset of action (shorter time to late half-maximal glucose infusion rates) (90). Another clinical study was conducted in patients with type 1 diabetes in order to determine if the more rapid absorption of insulin resulting from microneedle administration translates into a significant reduction in postprandial glucose levels under standardized meal conditions (91). The results indicated that postprandial glucose levels were improved when regular human insulin was delivered intradermaly vs. subcutaneously, but were similar for analogue insulin. In clinical studies the intradermal delivery was generally well tolerated (although some transient, localized wheal formation and redness were noticed at injection sites), but the potential effects of high level or repetitive exposure of protein drugs such as insulin on the lymphatics and immune system need full investigation (90, 91).

Another area of research focuses on the combination of available insulin products with a human recombinant hyaluronidase, which facilitates the local dispersion and absorption of co-administered molecules (92, 93). The human recombinant hyaluronidase is a highly purified neutral pH-active enzyme that depolymerizes hyaluronan in the hypodermis under physiologic conditions. Thus, it decreases the resistance to fluid flow and further contributes to the drug dispersion for better exposure to a larger capillary network (92). Following this, concomitant injection with proteins / drugs such as insulin, is expected to lead to an enhanced absorption and improved bioavailability. Recombinant human hyaluronidase (rHuPH20) is a genetically engineered soluble hyaluronidase approved by the Food and Drug Administration as an adjuvant to enhance permeation of other injected drugs (94). Since rHuPH20 is rapidly metabolized locally, without systemic exposure and because hyaluronan has a fast turn-over, the permeation effects are transient (94).

A phase 1 glucose clamp study in healthy volunteers evaluated the insulin time-concentration curve and pharmacodynamic profiles of insulin analogue (lispro) and of regular human insulin combined with rHuPH20 and reported significantly faster systemic absorption, enhanced insulin plasma concentrations and faster metabolic effects compared with either insulin formulation alone (95). A rise in insulin concentration was observed within 3 minutes following the injection and the enhanced pharmacokinetic and glucodynamic effects early after injection were accompanied by reduced late effects. A second study in healthy subjects also reported a lower intra-subject variability with rHuPH20 coadministration (94). A phase 2 standardized meal-test study in patients with type 1 diabetes examined whether the accelerated insulin absorption has favorable consequences on the control of postprandial glycemic excursions (94). As in the phase 1 studies, the coadministration of rHuPH20 with regular insulin or lispro yielded an accelerated insulin concentration profile that was accompanied by a significant reduction in both mean peak and total post-meal glucose concentrations compared to either insulin alone. Post-meal hypoglycemia was reported to be generally mild and the overall hypoglycemic risk comparable for lispro with or without rHuPH20 and reduced for regular insulin with rHuPH20 compared with regular insulin alone (94). Clinical studies reported a

good tolerability profile without severe adverse effects, but there is no safety data so far regarding the repeated or long term exposure to recombinant hyaluronidase.

A third novel ultrafast insulin formulation, VIAjectTM, is currently under clinical development. The main concept of the approach is that instead of altering the structure of insulin molecule, the zinc ions are pulled away from human insulin hexamers and simultaneously charges on the surface of the insulin molecule are masked by the addition of ethylene diamine tetraacetic acid and citric acid (96). This results in destabilization and dissociation of the insulin hexamer and prevents re-association to the hexameric state after subcutaneous injection.

A glucose clamp study in healthy volunteers evaluated the pharmacodynamic, pharmacokinetic and the dose-response properties of the VIAject in comparison with regular human insulin and insulin lispro (96). The results indicated a more rapid increase and decline in serum insulin concentrations after VIAject injection compared to regular human insulin and insulin lispro, but the difference between the later and VIAject failed to reach statistical significance (96). The three dose of ultrafast insulin used in the study showed a linear dose-response relationship. The time-action profile induced by VIAject was faster than either subcutaneously injected human insulin or lispro, with a more rapid onset of action and maximal metabolic activity, while the activity in the first 2 hours after injection was higher. A second glucose clamp study in patients with type 1 diabetes confirmed the faster absorption kinetics and the more rapid onset of insulin action compared to regular human insulin and showed that upon repeated administration, the within-subject variability is lower than that of human insulin (97). Moreover, a more recent meal-test study conducted in patients with type 2 diabetes indicated that treatment with VIAject determined a significant decrease of postprandial oxidative stress and improved endothelial function compared with regular insulin or insulin lispro, while all insulin formulations resulted in comparable improvements in central arterial elasticity (98).

Another innovative approach developed in order to accelerate insulin absorption into the bloodstream is using a technology (InsuPatchTM) that heats the tissue locally around the injection site (99). Changes in temperature at injection site are partially responsible for variability in insulin absorption (87). Increased skin temperature results in vasodilatation and improved local perfusion, which enables accelerated and enhanced insulin absorption (100). The InsuPatchTM device is an add-on to the insulin pump and is comprised of a heating pad attached to an insulin infusion set and a controller that monitors the temperature of the pad (99). The heating pad warms in a controlled manner the tissue surrounding the injection site for 30 minutes after insulin delivery, without heating the insulin itself.

A study using a meal tolerance test in subjects with type 1 diabetes treated by CSII tested the effect of InsuPatchTM on rapid-acting insulin absorption and post-challenge glucose excursions. The study found a significant effect of the heating device on the pharmacokinetic parameters: the maximum insulin concentrations increased (by 38%), as well as the total insulin absorption during the first 30, 60 and 90 minutes, (by 57%, 45% and 27%, respectively) as measured by area under the curve (AUC). The time to maximal concentration and time to half maximal concentration significantly decreased, indicating an accelerated insulin absorption. The changes were accompanied by significant reductions in post-challenge glucose levels (both 90 minutes post-meal glucose excursion and AUC 0-120

minutes of glucose concentrations were lowered" before by 39%) (99). The InsuPatchTM was also tested in youth with type 1 diabetes using a euglycemic clamp procedure. The use of the InsuPatchTM was found to decrease time to peak action by more than 40 minutes, whereas the bioavailability and peak responses remained unchanged (101, 102). Such improvements in time-action responses may provide a better control of post-meal glucose excursions (101). Another study that evaluated the effect of the InsuPatchTM heating device on postprandial blood glucose levels after different standardized meals in patients with type 1 diabetes on CSII has confirmed that local heating of the skin around the infusion site significantly increases early post-delivery insulin levels (AUC 0-60 minutes for insulin concentrations above baseline) as well as significantly reduces post-prandial blood glucose (blood glucose at 90 minutes and AUC 0-120 minutes of blood glucose levels) without causing more hypoglycemia (103). Current efforts are being employed in order to optimize the effect of the device on the pharmacokinetic and pharmacodynamic parameters by improving the heating process. The InsuPatch™ device was well tolerated and no serious adverse effects were reported with its use to date (99).

A different strategy that attempts to overcome the barriers and limitations of subcutaneous insulin administration is engaging a diverse route of delivery (i.e. pulmonary). After the discontinuation of the first inhaled insulin product (Exubera), the development of most of the pulmonary administration systems has ceased. One of them though, Technosphere™ insulin, is still being developed and it appears to overcome some of the barriers that contributed to the withdrawal of Exubera (104, 105). Technosphere™ insulin is an ordered lattice array containing recombinant human insulin, formulated as a crystalline dry powder. The Technosphere™ carrier is created with microcrystallized plates of fumaryl diketopiperazine that undergo self-assembly into microparticles with a very large surface area and a high internal porosity which are then lyophilized into a dry powder (104). Insulin is absorbed onto the surface of the particles and is delivered by a high-impedance, low-flow, breath-powered inhaler with a powder de-agglomeration mechanism that allows for a high percentage of the administered insulin to be absorbed. At the neutral pH environment of the lungs, the microparticles dissolve rapidly and insulin is absorbed across the pulmonary epithelium into the systemic circulation, while the carrier is cleared unmetabolized (104, 106).

The pharmacokinetic clamp studies performed in healthy volunteers and patients with type 2 diabetes revealed a very rapid systemic insulin uptake (time to maximal insulin concentration around 15 minutes) with a subsequent fast onset of action (time to maximal metabolic effect of about 40-80 minutes) and a short duration of action (106-109). These characteristics had basically been confirmed by a meal-test study in patients with type 2 diabetes, which demonstrated a more rapid absorption and higher peak insulin levels as well as markedly improved postprandial glycemic control with the inhaled insulin compared with subcutaneous regular human insulin (110). A linear systemic insulin uptake profile was noted in studies employing healthy volunteers inhaling three doses of insulin (106-108). In addition, the within-subject variability of insulin exposure following inhalation of Technosphere™ insulin was lower compared to regular insulin (109). The relative bioavailability was reported to be 26-50% in the first 3 hours after administration (111). Given that other inhaled insulin preparations have been associated with reduced absorption in patients with chronic obstructive pulmonary disease, a study assessing the pharmacokinetic profile and safety of Technosphere™ insulin in nondiabetic patients with chronic obstructive pulmonary disease has shown that insulin absorption was not

significantly altered in this group (112). Similarly, the absorption of inhaled insulin appeared not to be altered in a clinically significant manner in smokers (105).

The clinical efficacy of Technosphere™ insulin was assessed in studies of 11 or 12 week-duration in patients with type 2 diabetes (either insulin-naive or treated with basal insulin glargine), which demonstrated significant reductions in postprandial glucose excursions as well as clinically meaningful improvement of glycemic control as evaluated by HbA1c (113, 114). Moreover, a study of longer duration (52 weeks) in subjects with type 2 diabetes compared the inhaled insulin plus insulin glargine with twice daily biaspart insulin and indicated that changes in HbA1c determined by the treatment with inhaled insulin were similar and non-inferior to that with biaspart insulin (115). In addition, the weight gain and the incidence of both mild-to-moderate and severe hypoglycemic events were lower with inhaled insulin therapy.

Considering the issues associated with Exubera in the past, patient satisfaction and acceptance has been evaluated with the new inhaled insulin product. Overall, significant improvements in attitudes toward insulin therapy, treatment satisfaction, and treatment preference were reported with Technosphere™ insulin (105, 116). The therapeutical approach using the new inhaled insulin was implemented without a negative impact on health-related quality of life (116).

To date, Technosphere™ insulin has demonstrated a favorable safety and tolerability profile in clinical studies that collected data in healthy volunteers and patients with diabetes (105). The most frequent treatment-emergent adverse events associated with inhaled insulin in clinical studies were cough and hypoglycemia. Weight gain is commonly associated with insulin therapy. However, data so far indicated that with Technosphere™ insulin the weight gain was actually less compared with subcutaneous prandial insulins (105). While there are no reports of lung cancer or other serious side effects associated with Technosphere™ insulin to date, longer-term safety follow-up and evaluation should be done in subjects treated with this inhaled insulin formulation, especially in smokers and in subjects with respiratory disorders.

Finally, another alternative approach of insulin delivery is through the oral (buccal) route, which offers some advantages: good accessibility, high level of vascularization, relatively large surface for absorption (100–200 cm²), avoidance of presystemic metabolism in the liver, robustness, direct contact of the drug with the mucosa, weak variations of pH (117, 118). Oral-lyn is a liquid formulation of human regular insulin with very small amounts of generally regarded as safe (GRAS) ingredients, which is delivered to the buccal mucosa with a metered-dose, slightly modified asthma-like spray and used for prandial insulin therapy (117). The device spray the uniform-sized insulin droplets with high speed (100 mph) into the mouth, which then penetrate the superficial layers of the mucosa and get absorbed into the bloodstream.

The pharmacokinetic and pharmacodynamic properties of Oral-lyn have been evaluated in a number of glucose clamp studies, which have demonstrated a significantly more rapid absorption (about 25 minutes) to higher levels than subcutaneous injection of regular human insulin and a rapid return to baseline values (90 minutes after application) (118-121). The profile was paralleled by the glucose infusion rates that reached maximal levels significantly earlier (at about 45 minutes) and then returned back to baseline concentrations after approximately 120 minutes. Increasing doses of Oral-lyn determined a linear dose-response relationship with respect to maximal insulin concentrations, while time to maximal insulin

levels was similar across doses (118-121). Additional meal-test studies indicated that the 30- and 60-min glucose levels were significantly lower with oral insulin spray treatment (122, 123). The metabolic effects of Oral-lyn were evaluated in subjects with type 2 diabetes suboptimally controlled with oral hypoglycemic agents and showed that oral insulin spray significantly decreased the 2-hour postprandial glucose increments in comparison with the oral agents alone and that the difference was more pronounced at the end of the 4-h period, due to the rapid onset and wane of action of oral insulin spray (124). In all of the studies Oral-lyn was generally well tolerated, although some individuals experienced transient (1–2 min), mild and self-limited dizziness during dosing with both the oral insulin and placebo spray (122-124). No other significant side effects (including severe hypoglycemia) were noted in studies involving subjects with type 2 diabetes (122).

It should be mentioned that although some of the ultrafast insulin formulations / insulin delivery systems are in early phases of development and/or have not specifically reported for hypoglycemic events, based on their pharmacokinetic properties it can be reasonably expected that they may benefit patients with diabetes by reducing post-meal hyperglycemia with decreasing (or at least without increasing) the risk of hypoglycemic events.

7. Conclusions

The main goal of insulin therapy is to obtain a near-normal glycemic control by mimicking the time-action profile of physiologic insulin secretion as close as possible and with minimal side effects. Management of both types of diabetes is continually evolving as new therapies, including new insulins / insulin delivery systems are still emerging. In real life, with all progress of the recent years, all the above mentioned objectives are difficult to be reached and successful implementation of intensive diabetes management poses true challenges.

Ideally, an insulin-replacement therapeutic approach would keep in check both the fasting and the postprandial glucose concentrations while attaining target HbA1c values, without high glycemic variations and without causing hypoglycemia. Current rapid-acting insulin analogues have a faster pharmacokinetics and action compared with regular human insulin following subcutaneous administration (Table 1). This allows improved control of the post-meal early hyperglycemic surge and late relative hyperinsulinemia, the cause of postprandial hypoglycemia. However, recent meta-analyses showed that in fact the use of insulin analogues had only a modest impact on overall glycemic control and on the rates of side effects, mainly hypoglycemia, compared to conventional insulins (72-76). This is because although improved, the time-action profile still does not exactly replicate normal insulin secretion and therefore there is a mismatch with the blood glucose concentrations curve. Both postprandial hyperglycemia and hypoglycemia have important health consequences as well as on quality of life and failure to address them both may compromise the success of treatment in the short- and long-term.

The extent to which these goals can be met depends on many factors, including the type of diabetes, the stage in the progression of the disease and the pharmacokinetic profile of insulin formulation. If some of these factors are unmodifiable, others are, and efforts are being employed to develop new, improved ultrafast insulin products / delivery systems. They provide even more rapid pharmacokinetic and pharmacodynamic properties compared with current prandial insulin products, which may offer some advantages. The short interval between insulin administration and the appearance of the maximal serum

insulin levels, and the rapid onset of action may have a beneficial effect on the control of post-meal glycemic excursions. Because their action wanes off more rapidly, the risk of postprandial hypoglycemia is decreased. Both requirements seem to be fulfilled by the ultrafast insulins, but their long-term safety and tolerability still remain a concern. Provided that larger clinical studies will confirm their positive safety and tolerability profile, these new technologies will become very attractive candidates for prandial insulin delivery.

However, it should always be kept in mind that the insulin regimens need to be customized to each individual's needs, in order to maximize compliance and optimize glycemic control, while reducing to a minimum the potential unwanted side effects like hypoglycemia and weight gain. Patients with diabetes need substantial psychosocial support, ongoing education and guidance from a diabetes team, in order to set and achieve appropriate, individualized management goals.

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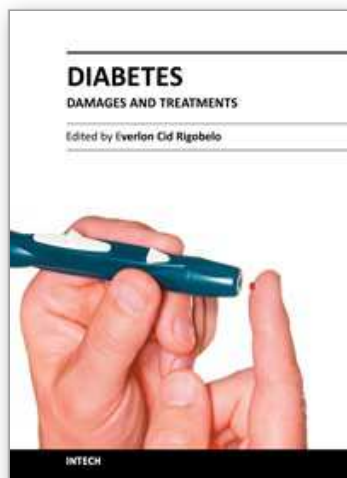
Diabetes - Damages and Treatments

Edited by Prof. Everlon Rigobelo

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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