Abstract
The modern goals of insulin replacement in type 1 diabetes mellitus are glycated haemoglobin (HbA1c) <7.0% and prevention of hypoglycaemia, as well as hypoglycaemia unawareness. In addition to appropriate education and motivation of diabetic subjects, the use of insulin analogues, both rapid- and long-acting, is critical to achieve the above goal more easily and safely, and with greater compliance on the part of diabetic subjects. The benefits of the rapid-acting analogues lispro, aspart and glulisine, which have superimposable pharmacodynamic effects, as compared to unmodified human regular insulin are lower postprandial blood glucose, lower risk of postprandial hypoglycaemia, and better quality of life. However, rapid-acting analogues improve HbA1c only to the extent to which replacement of basal insulin is optimized by either multiple daily NPH insulin, continuous subcutaneous insulin infusion (CSII), or the long-acting insulin analogues glargine or detemir. The benefits of long-acting insulin analogues, as compared to the traditional NPH insulin, are lower risk of hypoglycaemia in the interprandial state, especially at night, and lower variability of blood glucose. When optimally combined, rapid- and long-acting insulin analogues are more effective in maintaining HbA1c <7.0% over the long term than human insulin, with less hypoglycaemia and better quality of life. This regimen based on insulin analogues is not inferior to CSII in terms of goals for HbA1c and prevention of hypoglycaemia.

Keywords: type 1 diabetes, insulin analogues, multiple daily injections, hypoglycaemia.

Introduction
More than 85 years after the discovery of insulin by Nicolae Paulescu in 1921, and its successful extraction and use in humans for the first time in Toronto in 1922, the replacement of insulin in type 1 diabetes mellitus (T1DM) remains one of the major challenges in medicine. Insulin-treated subjects with T1DM continuously drift between hyper- and hypoglycaemia. If the former prevails and the percentage of glycated haemoglobin (HbA1c) remains elevated over the years, devastating long-term complications are likely to appear and unavoidably progress. On the other hand, the condition of frequent, recurrent hypoglycaemia is not only dangerous and unpleasant for the patient, but it may lead over time to the syndrome of hypoglycaemia unawareness. In turn, hypoglycaemia unawareness is the major risk factor for subsequent episodes of severe hypoglycaemia.

There are several reasons why it has been (and still is!) so difficult to replace insulin in T1DM. First, insulin is replaced in the wrong place, i.e. in the subcutaneous (s.c.) tissue, instead of the intravascular space, which drains into the peripheral rather than into portal circulation. This is responsible for slow insulin absorption at mealtime, with an excessive increase in the postprandial plasma glucose concentration (figure 1). In addition, s.c. insulin delivery induces systemic hyperinsulinaemia in order to match the physiological portal plasma insulin concentrations. The resulting hyperinsulinaemia in the peripheral plasma concentration is, in itself, a risk factor for hypoglycaemia, despite peripheral insulin resistance. Moreover, insulin is injected at a time prior to a meal and at a dose that cannot be ideal in terms of calculating of insulin absorption/peak and insulin sensitivity, despite optimal knowledge of the pharmacokinetics and pharmacodynamics of insulin preparations and the use of carbohydrate counting. Taking together the above observations, it is no surprise that current insulin replacement in T1DM is far from being perfect. Rather, it
is surprising that with such a “primitive” replacement of insulin, after all, not so different from the approach introduced in the early 20’s, it is indeed possible to maintain HbA1c below the value of 7.0%, which protects from the onset and/or progression of long-term complications. At present, insulin analogues contribute to improving the outcome of the still imperfect method of s.c. insulin replacement by minimizing hypoglycaemia, and preventing and/or reversing unawareness of hypoglycaemia, while still maintaining good glycaemic control. This contrasts with the early message from the DCCT in 1993, in which lowering HbA1c was associated with ~3-fold increase in risk for severe hypoglycaemia. In order to be successful, insulin replacement in T1DM should be based on the following criteria: a) education of subjects by educated physicians; b) use of modern insulin replacement regimens and insulin analogues; and c) awareness of treatment goals on the part of diabetic subjects and physicians. In the present article, the importance of the use of insulin analogues as a key tool for achieving good glycaemic control and prevent hypoglycaemia is emphasized.

**Physiology of plasma glucose homeostasis** (figure 2)

Normal, non-diabetic subjects maintain plasma glucose below 100 mg/dl during fasting, and below 135 mg/dl during the postprandial period. In the fasting state, this is possible because of the continuous release of insulin from the pancreas, which results in a steady-state plasma insulin concentration, thus restraining hepatic glucose production and thereby preventing fasting hyperglycaemia. At mealtime, the normal pancreas releases insulin early in response to meal ingestion, resulting in an early and elevated plasma peak. This prevents postprandial hyperglycaemia. Similarly important is the prompt decrease in plasma insulin 60-90 minutes after meal ingestion, which prevents hypoglycaemia in the postprandial state. Finally, between-meal plasma insulin is flat and peakless to prevent interprandial and fasting hypoglycaemia, especially during the nocturnal fasting hours.
Thus, nature’s model of insulin dynamics should be mimicked whenever insulin is replaced in the absence of endogenous insulin secretion, as in subjects with T1DM. In the fasting state, insulin should be replaced with a preparation of “basal” insulin that provides a flat, peakless concentration (figure 2). In contrast, any insulin preparation that resulted in a peak during the fasting state would be likely to induce hypoglycaemia. On the other hand, any insulin that would “wane” during fasting would result in hyperglycaemia. At mealtime, a bolus injection of a rapid-acting insulin is needed in order to reproduce the early, high peak plasma insulin in coincidence with carbohydrate ingestion. Ideally, the shorter the time-to-peak of the injected preparation, the lower the increase in postprandial hyperglycaemia. After meals, plasma insulin should return rapidly to baseline. If plasma insulin remained elevated at the time at which carbohydrate absorption was completed, hypoglycaemia would unavoidably develop.

Advantages of insulin analogues versus unmodified human insulin

In the early 80’s, human insulin was introduced with great impetus in place of animal insulin in the belief that diabetic subjects would thus be treated with the insulin secreted “naturally” by the human body. Paradoxically, a few years later, major efforts were made to modify the human insulin preparation for administration to diabetic subjects. Several insulin analogues were generated which are ultimately replacing human insulin in the treatment of diabetes mellitus. The easy explanation of the short-living popularity of human insulin is, of course, that human insulin works perfectly if delivered into the bloodstream as occurs in nature, but less so when injected into the s.c. tissue. In fact, soluble human insulin should be “rapid-acting” in its action, but in reality it is not so rapid (figure 3) because the slow dissociation of hexamers into monomers in the s.c. tissue (figure 4) delays the appearance of insulin in plasma after the absorption of carbohydrates has taken place. This causes hyperglycaemia early after meal ingestion, combined possibly with late postprandial hypoglycaemia due to continuing absorption of insulin beyond the meal absorption (figure 1).

Rapid-acting insulin analogues

At present, there are three different rapid-acting insulin analogues (lispro, aspart and glulisine). All these ana-
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Insulin analogues are obtained with a recombinant DNA technique by substituting or deleting one or more amino acids in regions of the insulin molecule not crucial for binding to the insulin receptor. These changes introduce repulsive electrical charges between monomer molecules, thus weakening the association forces within the hexamer, as compared to human insulin. As a consequence, at the diluted concentration in the s.c. tissue, the hexamers of rapid-acting analogues of insulin dissociate faster than those of human insulin and appear in plasma with an earlier and greater insulin peak (figures 3 and 4). Although lispro, aspart and glulisine are different molecules in terms of primary structure, they exhibit similar pharmacokinetic (PK) and pharmacodynamic (PD) properties as compared to human regular insulin. Upon s.c. injection, these rapid-acting analogues reach the status of monomeric insulin earlier than human regular insulin and, therefore, are absorbed faster. The earlier and greater plasma insulin peak achieved with the analogues controls postprandial plasma glucose better than human regular insulin (figure 5). The advantages of the rapid-acting analogues can be summarized as follows. First, despite the still “primitive” s.c. injection, it is nevertheless possible to mimic nature in terms of peak prandial insulin and, therefore, it is possible to reduce postprandial hyperglycaemia vs. human regular insulin. Second, because of the early waning, insulin analogues reduce the risk of postprandial hypoglycaemia vs. human regular insulin. Third, and perhaps the most important, insulin analogues improve quality of life since subjects with T1DM can now “inject and eat”. This is a great advantage as compared to the old days when subjects had to wait between 15-45 minutes between injection and meal ingestion, with the longest interval improving maximally postprandial blood glucose, but, of course, increasing the risk of hypoglycaemia (figure 1).

At present, the rapid-acting analogues are the gold standard for mealtime insulin replacement in T1DM. They should substitute for human regular insulin in all diabetic subjects, provided they are combined with optimal replacement of basal insulin (see below). Under these conditions, rapid-acting analogues lower HbA1c and reduce the risk of hypoglycaemia. The former goal reduces risk for long-term complications, whereas the latter improves awareness of hypoglycaemia. The same question can be rephrased in different terms. At present, is there any role left for using soluble (rapid-acting) human insulin in T1DM? The answer is “no”, as long as the administration is s.c. The sole indication to use soluble (rapid-acting) human insulin remains i.v. administration, in which clearly rapid-acting analogues are not superior to human insulin.

Finally, a mention should be made of the recently expressed view that rapid-acting insulin analogues should not be used in place of human regular insulin, since they would not “improve glycaemic control”. This concept has been reiterated in three different publications by the same group of authors. The reason why those papers are misleading and should be ignored by diabetologists who care about their diabetic patients, is that the authors confuse “better glycaemic control” with “lower HbA1c”. The reality is that rapid-acting insulin analogues, on the one hand, reduce the frequency of hypoglycaemia and, on the other, reduce HbA1c provided that basal insulin is optimally replaced. If basal insulin is not optimized, HbA1c does not decrease, but hypoglycaemia is still prevented.

Thus, first, rapid-acting insulin analogues always improve glycaemic control even in the absence of changes in HbA1c. Second, when rapid-acting insulin analogues were introduced into the market in the year 1996, long-acting insulin analogues were not available. Although it was immediately demonstrated that rapid-acting analogues decrease HbA1c when combined with continuous s.c. insulin infusion (CSII), or multiple daily NPH insulin administrations, it has only been recently, with
the introduction of insulin glargine, that the important beneficial effect of the analogues on HbA1c has been proven.24,25 Nobody nowadays would use a rapid-acting insulin analogue in the absence of its long-acting partner! Thus, a claim that rapid-acting analogues are not superior to human regular insulin18-20 is simply not true.

**Long-acting insulin analogues**

NPH insulin, the first prolonged-acting insulin preparation, invented by Hans Hagedorn in 1936,26 reached the market in 1946. Ever since, NPH insulin has been the bestseller in the “basal” insulin market. However, when NPH insulin is analyzed with the glucose clamp technique27 (figure 6), it appears to be far from mimicking the flat, peakless, physiological basal insulin (figure 2). NPH insulin has a peak 5-6 hours after injection and wanes a few hours later (figure 6). Thus, when injected during the evening, the peak action of NPH insulin increases the risk of hypoglycaemia after midnight. On the other hand, the relatively short duration of the action of NPH insulin makes it very difficult to achieve near-normal glycaemia in the fasting state without increasing the risk for nocturnal hypoglycaemia. Finally, since NPH insulin is an insoluble preparation that needs to be resuspended prior to s.c. injection, its absorption is quite variable, resulting in different fasting blood glucose from day to day. For these reasons, NPH insulin should no longer be used in T1DM. Only long-acting insulin analogues (glargine, detemir) or CSII should be used to replace basal insulin in T1DM.

Insulin glargine is a soluble long-acting insulin analogue, peakless as compared to NPH insulin, with a duration of action of 24 hours or more.27,28 The mechanism of action of insulin glargine is based on its modified isoelectric point (pH at which a protein is less soluble), which has been shifted from the acidic nature of human insulin to neutral. After s.c. injection, the change in pH from the acidic range within the vial (where insulin glargine is therefore soluble and “clear”) to the neutral value of s.c. tissue causes microprecipitation of insulin glargine into microcrystals with the subsequent slow absorption. Because it is soluble, it is, by definition, more reproducible than NPH.15,29 The more physiological PK/PD properties of insulin glargine vs. NPH translate into the clinical advantage of lower risk for nocturnal hyperglycaemia with similar or lower HbA1c.15

Insulin glargine should be given as a once daily evening injection (either before or after dinner). Some subjects with T1DM present an elevation in pre-dinner blood glucose despite optimal postprandial blood glucose.30 However, this phenomenon is not explained by the duration of action of insulin glargine of less than 24 hours, since steady-state insulin glargine generally has a duration of action of more than 24 hours.28,31 The pre-dinner hyperglycaemia is probably caused by the delayed absorption of the meal beyond the duration of the action of rapid-acting insulin given at lunch.30 Therefore, the administration of insulin glargine twice daily is not justified; rather, a double bolus of a rapid-acting insulin analogue should be given at lunch (be-
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breakfast and three hours later; the latter should consist of 1-3 units with no snack)32 (figure 7).

Insulin detemir is also a soluble, long-acting insulin analogue that is more reproducible than NPH insulin.29 When compared to therapeutic doses of insulin glargine, insulin detemir is similarly peakless, but exhibits a shorter duration of action, with an earlier increase in free fatty acids and plasma ketones during fasting.31 Thus, in the majority of subjects with T1DM, insulin detemir should be given every 12 hours. In theory, twice daily insulin detemir administration should achieve good glycaemic control, similar to that reported for insulin glargine once daily.24,25 However, in the only prospective study comparing insulin glargine and insulin detemir in T1DM, HbA1c did not reach the targets of intensive therapy with either of the two basal insulins.33 Thus, studies are needed to assess the proper tactics for the use of insulin detemir in T1DM to improve HbA1c, specifically to establish the titration of insulin detemir in the evening and in the morning, along with the titration of doses of the rapid-acting insulin analogue at meal-time. A peculiar characteristic of insulin detemir, not shared either by NPH insulin or by insulin glargine, is that its long-term use is associated with less weight gain (0.5-1.0 kg) as compared to the other basal insulin.24

Regimens of multiple daily injections and continuous subcutaneous insulin infusion

In the NPH insulin era, CSII has been shown to be superior to multiple daily injections (MDI)35 because the “basal” insulin delivered by CSII is soluble (either regular or rapid-acting insulin analogue), whereas that of MDI was NPH insulin (insoluble and, therefore, more variable).15 In the era of soluble long-acting analogues, MDI is no longer inferior to CSII in terms of HbA1c, and frequency of hypoglycaemia.36,37 CSII has the theoretical advantage of lower variability as compared to MDI,37 but, so far, this has been difficult to prove.36 Thus, in the “general” diabetic population, the choice between MDI and CSII is based on the individual preference of the type 1 diabetic subject, rather than on a real medical indication. However, in special sub-populations, such as subjects with long-standing diabetes and/or low daily insulin requirements, and/or hypoglycaemia unawareness, CSII might prove to be an easier tool for achieving the goal of HbA1c <7.0% while preventing hypoglycaemia. Needless to say, the insulin of choice to be used in CSII is a rapid-acting analogue, and there is no proven difference between insulin lispro, aspart and glulisine.

Conclusions

When combined with appropriate education and motivation of the subjects with T1DM, insulin regimens based on insulin analogues (either lispro, aspart or glulisine are used at mealtime; glargine once daily or detemir twice daily is given as basal insulin supplementation) successfully achieve the glycaemic targets of the DCCT, if the insulin dose is titrated to the target, thus protecting against the risk of the onset of long-term complications. At the same time, these regimens minimize the frequency of hypoglycaemia, prevent hypoglycaemia unawareness and improve quality of life.

Practical conclusions

- The modern goals of insulin replacement in type 1 diabetes mellitus are HbA1c <7.0% and prevention of hypoglycaemia as well as its unawareness.
- Rapid-acting analogues improve HbA1c when basal insulin is optimized by either multiple daily NPH insulin, or CSII, or the long-acting insulin analogues glargine or detemir.
- When compared to insulin glargine, insulin detemir is similarly peakless, but exhibits a less longer duration of action. Thus, in the majority of subjects with type 1 DM, insulin detemir should be given every 12 hours.
References