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How well do rapid-acting insulins work in obese individuals?

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Diabetes has reached epidemic proportions worldwide and most individuals with type 2 diabetes are obese. Therefore, there is a pressing need to carefully evaluate the impact of obesity on the efficacy of all diabetes therapies. Previously, obesity has been shown to adversely affect the efficacy of oral antidiabetic drugs; however, less is known about the impact of obesity on the properties of insulin and its analogues. As patients near target HbA_{1c}, the more postprandial hyperglycaemia contributes to overall glycaemic control; thus, mealtime insulin, often supplied by a rapid-acting insulin analogue (RAI), becomes of increasing importance. As glycaemic targets set by professional bodies become lower and poor glycaemic control becomes increasingly less acceptable, earlier addition of RAIs to patients' treatment regimens may be required to meet these targets. However, in clinical practice, multiple barriers have challenged the acceptance and effective use of insulin therapy, including concern that it may cause weight gain. RAIs should ideally maintain their rapid-acting pharmacokinetic (PK) and pharmacodynamic (PD) profiles, irrespective of subcutaneous body fat, skin thickness and body mass index, in order to effectively meet intensive treatment goals. For example, initial PK/PD data with insulin glulisine in obese individuals suggest that this RAI may maintain its rapid-acting profile better than insulin lispro in the first 2 hours post-injection. However, data are preliminary and a thorough analysis of the impact of obesity on all RAIs in type 2 diabetes is warranted. This review focuses on the potential impact of obesity on RAIs and presents an overview of investigations in this area.

Keywords: diabetes mellitus, obesity, rapid-acting insulin

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Introduction

The Diabetes Control and Complications Trial and the UK Prospective Diabetes Study (UKPDS) have both clearly demonstrated the benefits of achieving good glycaemic control in patients with type 1 and type 2 diabetes (figure 1) [1–3]. Type 1 diabetes constitutes only 5–10% of the diabetes population, and its management commonly involves using a combination of rapid- and long/intermediate-acting insulins (basal–bolus therapy) [4]. Most patients have type 2 diabetes (90–95%) and are insulin resistant with varying degrees of insulin deficiency [4]. While patients with type 1 diabetes tend to be on the lean side, those with type 2 diabetes tend to be overweight (25–30 kg/m^2) to obese (>30 kg/m^2) at diagnosis, which in itself is associated with insulin resistance [5].

Insulin therapy is not usually the first-line therapeutic intervention in patients with type 2 diabetes, as these patients have the potential to initially be relatively well maintained with diet and exercise, normally with the addition of oral antidiabetic drugs (OADs). Type 2 diabetes is a progressive disease, however, resulting in the steady decline in β-cell function so that ultimately insulin therapy is required in the majority of patients to maintain adequate glycaemic control (figure 2) [4]. Many patients with type 2 diabetes remain suboptimally controlled for many years, either through diagnosis late

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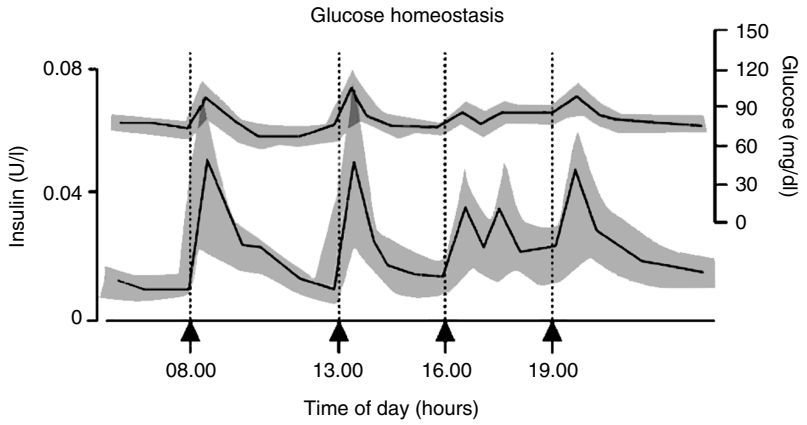

Fig. 1 Plasma blood glucose and insulin profiles (24 h) in healthy individuals (n = 12; mean values with 95% confidence intervals) [1]. Reprinted with permission from Elsevier (The Lancet 2001; **358**: 739–746).

in the course of the disease or because of the reluctance of patients and/or health professionals to initiate insulin therapy. With HbA_{1c} targets now approximately 7%, and the American Association of Clinical Endocrinologists and International Diabetes Federation (IDF) reducing targets to 6.5%, it is becoming increasingly important to initiate insulin therapy earlier in the course of the disease to achieve this and reduce the risk of long-term complications.

A major reason behind the reluctance to initiate insulin therapy is its association with weight gain and nocturnal hypoglycaemia. In particular, this can deter health professionals from initiating insulin in already obese patients with type 2 diabetes [6,7]. Evidence from the UKPDS 57 study (glucose study 2), however, supports the early addition of insulin to maximize sulfonylurea therapy for the improvement of glycaemic control in patients with type 2 diabetes, without an increase in hypoglycaemia or weight [8]. In addition, the combination of metformin and insulin therapy has been showed to reduce insulin resistance and minimize weight gain [6]. There is some experimental evidence to suggest that thiazolidinediones (TZDs) may preserve β-cell function and hence potentially facilitate glycaemic control in patients with type 2 diabetes [9]. However, few studies have evaluated insulin therapy in combination with TZDs, and this is currently controversial due to the potential for weight gain and fluid retention [10].

As patients get closer to target HbA_{1c}, the more postprandial hyperglycaemia contributes to overall glycaemic control; thus, mealtime (prandial) insulin becomes of increasing importance [11]. Clearly, there is a role for the addition of prandial insulin to improve long-term diabetes care in patients with type 2 disease. Although this need can be met in some cases by twice-daily premixed 70/30 neutral protamine hagedorn insulin/regular human insulin (RHI), an alternative approach that is now often considered is the addition of a rapid-acting insulin analogue. These have a more physiological profile than RHI and indeed have been developed to try to overcome the problems of unphysiological insulin replacement associated with the traditional short-acting insulin preparations, particularly to address mealtime blood glucose excursions. Several widely used premixed insulin formulations using rapid-acting insulin analogues are currently available:

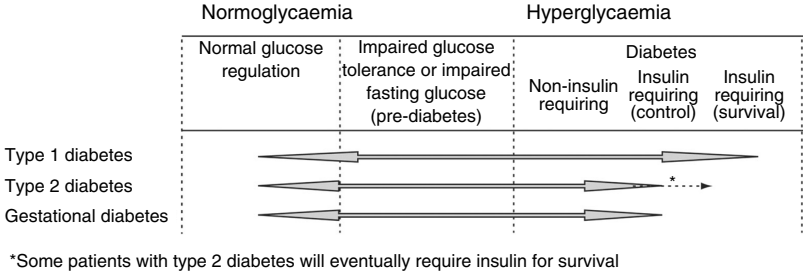

Fig. 2 Disorders of glycaemia [4]. Copyright © 2004 American Diabetes Association. Adapted from Diabetes Care, Vol. 27 Supplement 1, 2004; S5–S10. Reprinted with permission from *The American Diabetes Association*.

70/30 neutral protamine aspart/insulin aspart and 75/25 protamine insulin lispro (NPL)/insulin lispro [12]. Although these formulations eliminate the need for patients to mix their own insulins, they lack flexibility for specific insulin adjustments (especially with pens) as the dose of one insulin cannot be altered without the other, limiting the ability to treat-to-target for optimum glycaemic control [6].

Obesity in Type 2 Diabetes

Obesity is a major issue in the management of type 2 diabetes. The majority of individuals will be obese, and will generally have had this problem for some time prior to diagnosis [13]. Indeed, diabetes has now reached epidemic proportions in most of the world [14]. One-third of all Americans born today are predicted to develop diabetes as a consequence of obesity. In 1995, there were an estimated 200 million obese adults worldwide and another 18 million children under the age of 5 were classified as overweight; by 2000, the number of obese adults had increased to more than 300 million [15]. This obesity epidemic is not restricted to Western society; it is estimated that more than 115 million people suffer from obesity-related problems in the developing world [15]. The degree and duration of obesity is a defining risk factor for type 2 diabetes with 57% of cases directly attributable to obesity [16]. Glycaemic control may be particularly poor in patients who have experienced severe obesity for a prolonged period.

As obesity, particularly centralized distribution of body fat (central obesity), has been implicated as a primary risk factor for type 2 diabetes and cardiovascular disease, there is a need to carefully evaluate the impact of obesity on the efficacy of all diabetes therapies [17–20]. Obesity has not been showed to affect the efficacy of OADs adversely; however, less is known about the impact of obesity and the thickness of the subcutaneous fat layer on the properties of insulin and its analogues. While long-acting insulin analogues have been studied in both type 1 and type 2 patients, rapid-acting insulin analogues are far less well characterized in individuals with type 2 diabetes, particularly those who are obese. In this review, I will discuss the potential impact of obesity on rapid-acting insulin analogues and will present an overview of investigations in this area.

Table 1 Pharmacokinetic properties of insulin preparations [21].

Insulin	Onset of action	Peak in activity (hours)	Duration of action (hours)
Analogues			
Lispro	5–15 min	1	4–5
Aspart	5–15 min	1	4–5
Glulisine*	5–15 min	1	4–5
Human insulin			
Regular	0.5–1 h	2–4	6–10

*This analogue was recently approved in the USA and EU. Adapted from Rosenstock J, Wyne K. Insulin treatment in type 2 diabetes. In: Goldstein B, Müller-Wieland D, editors. Textbook of Type 2 Diabetes. London: Martin Dunitz; 2003. pp. 131–154.

Pharmacological Experience with Rapid-Acting Insulin Analogues

The pharmacological [pharmacokinetic (PK)/pharmacodynamic (PD)] advantages of marketed rapid-acting insulin analogues (insulin lispro and aspart) over RHI have already been established (table 1) [21–23]. Modern rapid-acting insulin analogues have been developed to address the inadequacies of RHI and provide a more physiological mealtime insulin supply. Using these analogues, patients with type 1 diabetes benefit clinically from their improved time–action profiles, with better postprandial blood glucose control compared with RHI, and the potential to further reduce HbA_{1c} levels with a reduced risk of hypoglycaemia. Clinical experience with these analogues, however, has been largely confined to patients with type 1 diabetes, the majority of whom are lean; the use of basal (prandial) insulin in patients with type 2 diabetes, especially those in the higher body mass index (BMI) range, requires further investigation [24–33]. It is therefore important to evaluate whether rapid-acting insulin analogues maintain their efficacy in obese individuals with type 2 diabetes, specifically to determine whether the rapid-acting profiles of these insulins are influenced by BMI or distribution of body fat/total body fat levels. In this context, each of the current rapid-acting analogues is considered in turn.

Insulin Lispro

Several studies have demonstrated the clinical benefits of insulin lispro over RHI in patients with type 1 and type 2 diabetes [34–40]. However, few have been performed in obese patients to evaluate any potential differences in the time–action profile of insulin lispro compared with lean patients, and no studies have evaluated the use of premixed 75/25 NPL/insulin lispro in obese patients.

One study compared two patients with type 2 diabetes – one obese and the other non-obese [41]. Patient 1 had a BMI of 33 kg/m^2 and was insulin resistant with poor glycaemic control (HbA_{1c} 12.9%); patient 2 had a BMI of 24.7 kg/m^2 with good glycaemic control (HbA_{1c}

6.3%). Insulin binding improved in patient 1 after receiving insulin lispro, and a decrease in both serum glucose and insulin dose was observed post-treatment in a meal study. Patient 2 showed similar time courses for serum glucose, serum insulin and insulin binding after a meal to those obtained in healthy controls. These results suggest similar improvements in glycaemia, insulin receptor binding and insulin resistance in obese and non-obese subjects with type 2 diabetes. Only two patients were evaluated, however, and they were not matched for age, duration of diabetes, insulin usage or insulin sensitivity. In addition, the assessments performed differed markedly between the two patients; hence, the results cannot be reliably interpreted as a comparison of the insulin lispro profile in obese vs. non-obese individuals.

Another small study of seven obese patients with type 2 diabetes measured fat mass and fat-free mass by using skinfold thickness measurements (BMI range: 28–38 kg/m^2) [42]. In this study, insulin lispro was associated with a faster increase in plasma insulin concentrations compared with RHI, thereby restoring a pseudo first-phase insulin secretion. Time to inhibition of glucose production and suppression of glycogenolysis was similar for insulin lispro and RHI. Insulin lispro more effectively stimulated glucose uptake and metabolism in insulin-sensitive tissues and had greater bioavailability than RHI, as would be expected based on the action profiles of these two insulins. Furthermore, the higher insulin concentrations reached in the immediate postprandial period overcame insulin resistance to a certain extent in obese patients with type 2 diabetes who were poorly controlled by diet and oral agents. Therefore, insulin lispro improved treatment outcomes compared with RHI; however, no evaluation by obesity class or comparison with leaner individuals was made, and in this study, only a small number of patients were evaluated. Moreover, RHI was only administered 20 min before the meal, rather than 30–45 min as recommended by the label.

Insulin Aspart

Absorption of insulin aspart has been showed to be slower in both obese and non-obese patients with type 2 diabetes [43] compared with those with type 1 diabetes [44,45]. In one study [43], of 10 obese (mean BMI: 31.4 kg/m^2) and 10 non-obese (mean BMI: 24.1 kg/m^2) patients with type 2 diabetes, all received rapid-acting insulin injections in the abdomen and the thigh. The disappearance half-life of radio-labelled insulin was 4–6 h for all injection sites, except for the upper abdominal area in non-obese subjects (approximately 3 h). The most rapid absorption of radio-labelled insulin was from the upper abdominal area and slowest from the thigh in non-obese subjects; absorption rates did not differ between sites in obese subjects, and there was no correlation between the depth of the fat layer and the amount of residual radioactivity for any injection site. The absorption rates of a similar dose of rapid-acting insulin from subcutaneous injection sites in the abdominal wall and in the thigh were significantly lower in patients with type 2 diabetes compared with those with type 1 diabetes studied under identical conditions.

On the positive side, this study showed no correlation between the depth of the fat layer and the insulin absorption rate. However, this does not necessarily mean that the PK and PD profile of insulin aspart is unaffected by subcutaneous fat levels, as no formal PK or PD parameters were evaluated. In the lean subjects, the absorption rate differed between the abdominal and femoral injection sites, whereas in the obese subjects these absorption rates were similar, which suggests that the PK profile of insulin aspart might be affected by subcutaneous fat thickness.

Another study of insulin aspart in 22 patients with a range of BMIs (21.9–35.0 kg/m^2) and type 2 diabetes (HbA_{1c} 6.8–10.0%) did not investigate correlations between BMI and efficacy [32]. Insulin aspart was showed to improve postprandial glucose control, as demonstrated by lower maximum serum glucose concentrations and smaller postprandial blood glucose excursions compared with RHI. Immediate pre-meal administration of insulin aspart improved postprandial glucose control compared with RHI, with similar control to RHI injected 30 min pre-meal. Given the number of patients in this study and the wide range of BMI, it would have been of interest to perform a subanalysis of efficacy by BMI to determine any correlations. Interestingly, Rosenfalck *et al.* also performed a post hoc analysis with a new insulin aspart-specific monoclonal assay, which showed that in these C-peptide-positive type 2 diabetes patients, the absorption of insulin aspart was slower with a t_{max} of 75.5 min, compared with 40–50 min typically seen in patients with type 1 diabetes [32]. This is in accordance with the findings of Clauson and Linde already discussed [43]. In the light of these findings, it would be of interest to perform a formal trial with insulin aspart comparing patients with type 1 and type 2 diabetes. In addition, studies evaluating the use of premixed aspart 70/30 in obese patients would also be of interest.

Insulin Glulisine

Insulin glulisine (Aventis Pharma Deutschland GmbH, Frankfurt, Germany), a new prandial insulin analogue

developed to have a more rapid onset and shorter duration of action than RHI [46,47], has recently received the approval of Food and Drug Administration and European Agency for the Evaluation of Medicinal Products. Of relevance to this review is an explorative study of obese individuals without diabetes, which compared the PK and PD properties of insulin glulisine with those of RHI and insulin lispro following subcutaneous administration in obese subjects [48]. The aim was to determine the dependence of the PK properties on the thickness of the subcutaneous fat layer. Preliminary results have been reported, but only in abstract form.

The study enrolled 18 obese subjects without diabetes (age 19–47 years; weight 84–140 kg), who were split into two groups according to the extent of their obesity (class I: 30.0–34.9 kg/m^2; class II: 35.0–40.0 kg/m^2). Three treatment periods were included in this randomized, double-blind, three-way crossover design, and subjects received single doses of insulin glulisine, RHI or insulin lispro (0.3 IU/kg) administered subcutaneously in the abdominal area. Insulin glulisine and insulin lispro had more rapid and shorter PK profiles than RHI (figure 3) [48]. This was demonstrated by the higher fractional insulin area under the curves (AUCs), C_{max} (203, 133 and 77 μIU/ml, respectively) and shorter t_{max} (76, 99 and 144 min, respectively) and mean residence time (MRT) (149, 166 and 229 min, respectively) for both insulin analogues compared with RHI. The absorption profile of insulin lispro was slower than that of insulin glulisine as showed by a longer t_{max} (99 vs. 76 min for insulin glulisine) and MRT (166 vs. 149 min for insulin glulisine) (figure 3) [48]. This difference between the two rapid-acting analogues was statistically significant for the first 2-h post-injection. This is an important period, particularly in type 2 diabetes because, ideally, insulin levels should be maintained to compensate for the so-called second phase of physiologic insulin secretion [49].

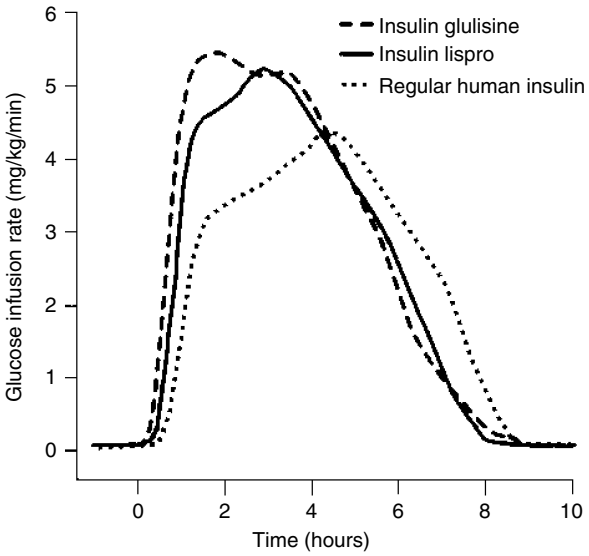

Fig. 3 Average glucose infusion rate profiles following subcutaneous (abdominal) injection of 0.3 IU/kg of insulin glulisine, insulin lispro or regular human insulin [48]. Copyright © 2004 American Diabetes Association. From Diabetes, 53, Supplement 2, 2004; 526-P. Reprinted with permission from *The American Diabetes Association*.

Insulin glulisine and insulin lispro had greater fractional glucose AUCs and GIR_{max} (glucose infusion rate) compared with RHI, although total glucose disposal was the same for all insulins. Interestingly, there was also a lack of relevant correlation between the anthropometric parameters within the BMI range studied and the PK or PD profile for insulin glulisine, suggesting that this insulin may maintain its rapid-acting properties irrespective of increased thickness in the subcutaneous fat layer that is associated with obesity. By contrast, there was a significant, positive correlation between skin thickness or BMI and t_{max} for insulin lispro and RHI. If insulin glulisine better maintains its rapid and short PK and PD profile in obese subjects, this could be relevant in patients with type 2 diabetes, because the time–action profile might be more physiological in these patients and more in line with the advantages of rapid-acting analogues observed in patients with type 1 diabetes. However, clearly this study needs to be repeated in patients with type 2 diabetes, over a range of BMI. In the study conducted with type 2 diabetic patients, most of them were overweight patients (mean BMI >34 kg/m^2), a slightly greater baseline to endpoint reduction in HbA_{1c} levels was seen with insulin glulisine vs. RHI (−0.46 vs.−0.30%; p = 0.0029) [50]. This may suggest that insulin glulisine maintains its rapid-acting properties in overweight patients, but further studies would certainly be required to confirm this. Additionally, a trial directly comparing obese vs. non-obese healthy volunteers would be of value.

Evaluating More Thoroughly the PK and PD Profiles of Insulin Analogues in Obese Individuals

Comparative studies of rapid-acting insulin analogues in obese vs. non-obese individuals are needed to determine definitively how body fat, BMI and skin thickness affect PK and PD profiles. Differences in their profiles for rapid-acting analogues in obese subjects could relate to differences at injection sites or excipients used in formulation.

Injection Site

The injection site can have a profound effect on the activity of various insulin preparations [43]. Although a number of injection sites can be used for the subcutaneous administration of insulin, the abdominal area tends to be preferred, as there may be a degree of variability in the time–action profiles of insulins when administered at other sites, e.g. femoral and deltoid [51]. Increased amounts of subcutaneous fat may also slow the absorption of insulin from the injection site, thereby delaying and impeding its activity. This may be compromised in obese patients with type 2 diabetes with localized abdominal subcutaneous fat, although abdominal administration will still be the best injection site for those rapid-acting insulins whose time–action profiles are affected by obesity. Even if fat deposition is more generalized, a certain loss of the time–action profile would be expected due to the overall increased thickness of the subcutaneous fat layer.

Role of Excipients in PK/PD Profiles in Obese Individuals

Differences in time–action profiles observed between rapid-acting analogues may be attributable in part to the excipients used in different insulin formulations. For example, insulin lispro contains additional zinc to improve stability. This has been showed to retard the absorption of insulin post-injection [52]. It remains to be tested how important this is in explaining observed difference in PK and PD profiles between insulin glulisine (which does not contain additional zinc) and insulin lispro in obese individuals.

Conclusions

Obesity is increasing in modern society and is a particular issue in newly industrialized developing countries [13]. This increase is intrinsically linked to a similar increase in the incidence of type 2 diabetes [13]. Although lifestyle and diet changes are the most effective forms of first-line therapy, these regimens do not usually maintain glycaemic control in the long term, and pharmacological intervention is eventually required to achieve treatment targets and minimize the risk of developing complications.

Although the first-line pharmacologic intervention used in type 2 diabetes is generally OAD therapy, patients are often not optimally controlled on these regimens, and with associations such as the IDF now recommending reducing HbA_{1c} targets as low as 6.5%, earlier use of insulin in type 2 diabetes patients will become increasingly important. A recent expert opinion statement recommended that patients are initially administered basal insulin at bedtime and continue treatment with metformin, but discontinue treatment with other OADs (some authorities also recommend continuing sulfonylureas) [53]. Current practice is to initiate patients on insulin therapy either as twice-daily premixed insulin or by the addition of one or two injections of basal insulin per day to oral therapy.

As glycaemic targets set by professional bodies become lower and poor glycaemic control becomes increasingly less acceptable, earlier addition of rapid-acting insulin analogues to patients' current treatment regimens may be required to meet these targets. Assessing the profiles of rapid-acting insulins in patients with type 2 diabetes is becoming necessary. However, in clinical practice, multiple barriers have challenged the acceptance and the effective use of insulin replacement therapy in achieving target HbA_{1c} levels in patients with type 2 diabetes. These include fear of needles, complexity of insulin regimens, exaggerated concern that insulin therapy may cause significant weight gain and misconceptions relating to the significance of insulin with respect to complications [12].

As most patients with type 2 diabetes are overweight or obese, insulin analogue preparations should ideally maintain their rapid-acting PK and PD profiles, irrespective of subcutaneous body fat, skin thickness and BMI, in order to effectively meet intensive treatment goals. Few studies have been performed investigating the impact of obesity on the activity of rapid-acting insulin analogues, and it is clear that a thorough analysis of all RAIs in 'typical' patients with type 2 diabetes is warranted. For example, initial PK/PD data with insulin glulisine in obese individuals suggest that this rapid-acting analogue may maintain its rapid-acting profile better than insulin lispro in the first 2-h post-injection. This is a very preliminary work, and further, more detailed studies are needed to evaluate the potential impact of increasing BMI on established insulin treatment strategies for type 2 diabetes.

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