Insulin analogues in type 1 diabetes mellitus: getting better all the time

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Abstract | The treatment of type 1 diabetes mellitus consists of external replacement of the functions of β cells in an attempt to achieve blood levels of glucose as close to the normal range as possible. This approach means that glucose sensing needs to be replaced and levels of insulin need to mimic physiological insulin-action profiles, including basal coverage and changes around meals. Training and educating patients are crucial for the achievement of good glycaemic control, but having insulin preparations with action profiles that provide stable basal insulin coverage and appropriate mealtime insulin peaks helps people with type 1 diabetes mellitus to live active lives without sacrificing tight glycaemic control. Insulin analogues enable patients to achieve this goal, as some have fast action profiles, and some have very slow action profiles, which gives people with type 1 diabetes mellitus the tools to achieve dynamic insulin-action profiles that enable tight glycaemic control with a risk of hypoglycaemia that is lower than that with human short-acting and long-acting insulins. This Review discusses the established and novel insulin analogues that are used to treat patients with type 1 diabetes mellitus and provides insights into the future development of insulin analogues.

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder in which insulin-producing β cells are destroyed by the immune system. Secretion of insulin (which controls the metabolism of carbohydrates, proteins and lipids) is tightly regulated by feedback systems that enable stable control of metabolism, thus preventing hypoglycaemia, hyperglycaemia, protein catabolism, lipolysis and the formation of ketone bodies[1,2].

Basal insulin secretion maintains metabolism in an anabolic state. Upon food intake, β cells, driven by direct sensing of glucose through glucose transporter type 2 (GLUT2) receptors on their surface (as well as by neural signals and incretin signalling), release insulin into the blood to promote the uptake of carbohydrates, proteins, peptides and lipids into other cells. The effect of insulin on peripheral glucose uptake in muscle and the rapid inhibition of gluconeogenesis and glycogenolysis in the liver result in a decrease in blood levels of glucose, which causes β cells to stop synthesizing and secreting insulin[1,2].

A major challenge of insulin replacement in patients with T1DM is mimicking the insulin-action profiles of β cells — maintaining basal levels and achieving peak levels at mealtimes. The two major weaknesses of external insulin replacement are that insulin is administered peripherally, whereas β cells secrete insulin in the portal system (primarily targeting the liver), and that no feedback or suppression of insulin release is possible when levels of glucose fall, which increases the risk of hypoglycaemia[1,2].

Insulin preparations have come a long way since the discovery of insulin, from purified animal insulins to human insulins produced by genetically modified organisms to insulin analogues that enable an improved fit between insulin-action profiles and glucose excursions (that is, fluctuations in levels of glucose). In this Review, we detail the established and novel insulin analogues that are used to treat T1DM, and provide insights into future developments of insulin analogues.

From animal to human insulin

The human insulins come in different types: rapid-acting (regular) insulin, slow-acting neutral protamine Hagedorn (NPH) insulin or zinc-based insulin. Most patients in the 1980s were treated with mixtures of regular and NPH or zinc-based insulin (mixed by the patients or in a premix form) that were administered twice daily (before breakfast and dinner)[2].

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive insulin therapy resulting in tight glycaemic control prevented the microvascular complications that are associated with T1DM[3,4].

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Key points

- Established rapid-acting and long-acting insulin analogues have enabled more patients with type 1 diabetes mellitus to reach better glucose targets, with lower hypoglycaemia rates and a better quality of life than was possible with short-acting and long-acting human insulin
- In patients who are prone to severe hypoglycaemia, using a full analogue regimen is rapidly cost saving and should therefore be the standard of care in all patients with type 1 diabetes mellitus
- The new long-acting insulin analogues insulin glargine U300 and insulin degludec have shown increased stability, which translates to a reduced risk of nocturnal hypoglycaemia and increased flexibility in timing of administration
- Faster and shorter acting insulin analogues are needed for use in insulin pumps and future 'artificial pancreas' systems; fast-acting insulin aspart, a new formulation of aspart, is well advanced in clinical development

These findings established intensive insulin therapy, using regular insulin administered before each meal and basal insulin administered at bedtime, as the gold standard in the treatment of people with T1DM[3,4].

The DCCT also highlighted the limitations of insulin replacement therapy in T1DM, in particular when using 'human' insulins: patients who underwent intensive insulin therapy had a threefold increase in the risk of hypoglycaemia, particularly of severe hypoglycaemia. Moreover, intensively treated patients had a 30% higher risk of becoming overweight than non-intensively treated patients. These adverse effects are probably due to the absence of negative feedback on insulin release from subcutaneous depots once insulin is injected but could also be attributable to the mismatch between insulin-action profiles of the human preparations and mealtime or basal levels, which does not occur with the action profile of functioning β cells in a healthy person[3] (BOX 1).

Regular insulin

Regular insulin has the same structure as insulin produced by β cells: six monomers of insulin, each of which consists of an A chain and a B chain linked by two disulfide bridges (with an additional disulfide bridge between two amino acids in the A chain) that are positioned around a zinc ion and form a hexamer. When injected into the bloodstream, these hexamers immediately dissociate into monomers and are able to interact with the insulin receptor on target tissues, which means that the glucose-lowering effect of intravenous regular insulin is almost immediate. However, when regular insulin is injected into subcutaneous tissue, the hexamers must dissociate into monomers before resorption into the bloodstream can happen (FIG. 1). Thus, a delay in onset of action of the glucose-lowering effect occurs with subcutaneous injection of regular insulin (depending on several factors, such as the site of injection, blood flow and temperature), which causes variability in action and a mismatch between the insulin-action profile that results from injecting regular insulin immediately before a meal and the glucose excursion caused by the meal (FIG. 2). On the basis of this mismatch, patients who use regular insulin as their mealtime insulin are advised to allow 15–30 min between the injection and the start of the meal, which is inconvenient in daily life[2,5]. Of note, the concentration of regular insulin also influences the onset and duration of action of the preparation. As such, hyperconcentrated U500 regular insulin has an action profile that is right-shifted compared with that of regular insulin, with a delayed onset of action and a duration of action of 6–10 h (REF. 6).

Zinc and NPH insulins

Zinc and NPH insulins are formed by the addition of zinc or protamine, respectively, to regular insulin, which results in 'lumps' where the insulin molecules are linked to these substances (resulting in an inhomogeneous suspension in vials of the substances), which causes their action profile to be prolonged. The major drawback of these insulins is the variability in their action profile, which is partially attributable to the need for resuspension of the insulin in the vial before it is injected; however, variability is still present under fully controlled laboratory conditions of resuspension[7]. In subcutaneous tissue, regular insulin hexamers are released from the zinc or NPH depots in a stochastic way over several hours, which causes a highly variable insulin-release action profile, with durations of action ranging from a few hours to more than 24 h (REF. 8) (FIGS 1,3). Variation in duration of action is seen in these insulins, as well as variation in the strength of the insulin action and their action profiles, with peak levels of release sometimes happening soon after injection (causing early nocturnal hypoglycaemia and necessitating snacks before bedtime). Another major limitation of these insulins is that they do not cover the basal insulin needs for the full 24 h in many patients[8,9] (FIG. 3).

First-generation insulin analogues

In the past 20 years, rapid-acting and long-acting insulin analogues have been designed to mimic the action profiles in insulin secretion of pancreatic β cells more closely than previous preparations[1,2] (BOX 2).

Rapid-acting insulin analogues

The first rapid-acting insulin analogues were designed to create less-stable insulin hexamers, creating insulins that would more readily become monomeric or would even be monomeric in solution, thus moving into the bloodstream more rapidly after subcutaneous injection than human regular insulin. This action profile enables a shortening of the time between injection and start of the meal, and thus provides a better match than human regular insulin between the insulin-action profile and the glucose excursion that is caused by the meal[10]. Three rapid-acting insulin analogues are available for clinical use in Europe and the USA: insulin lispro, insulin aspart and insulin glulisine.

Insulin lispro. The molecular structure of insulin lispro differs from that of regular human insulin by a switch in the order of proline and lysine at residues 28 and 29 of the B chain[5,11] (FIG. 4a). This change destabilizes hexamerization, and dissociation into dimers and monomers occurs swiftly, which enables an uptake through the blood vessels that is more rapid than that of human

regular insulin[5] (FIG. 1). Pharmacokinetic studies show that the peak plasma concentration of insulin lispro in the first hour after injection is twofold higher than that of human regular insulin and that the time to maximum concentration of insulin lispro is less than half that of human regular insulin[5,11] (FIG. 2). The concentration of insulin lispro decreases to levels <20% of peak concentrations 4 h after injection, whereas absorption of human regular insulin is still ongoing at this point[5,11]. Taken together, these pharmacokinetic data show that regular insulin and insulin lispro have a similar area under the curve, but the curve is shifted to the left for insulin lispro. Pharmacodynamic data show that, compared with the administration of human regular insulin at the same time, insulin lispro leads to a lower postprandial glycaemic peak, shorter time to peak and lower total glucose excursion for the 0–4 h period. These characteristics enable insulin lispro to be injected within 15 min of starting a meal[5,11]. In contrast to human regular insulin, the site of injection of insulin lispro is less important with regard to speed of onset of action. However, for rapid-acting insulin analogues, abdominal wall injections are advised, as the absorption from deltoid and femoral administrations is slower than that from abdominal administration and results in an increased duration of action for both regular insulin and insulin lispro according to pharmacokinetic and pharmacodynamic data[5,12]. The faster absorption and faster onset of the glucose-lowering effect of rapid-acting insulin analogues lead to postprandial levels of glucose that are considerably lower than those triggered by mealtime administration of human regular insulin[5,12–14].

Insulin aspart. The molecular structure of insulin aspart differs from that of human regular insulin by the replacement of proline with aspartic acid at residue 28 of the B chain[5,15,16] (FIG. 4a). The pharmaceutical formulation of insulin aspart — similar to that of insulin lispro — contains glycerine, metacresol, zinc and phenol, and has disodium hydrogen phosphate as the buffer[5]. The pharmacokinetic–pharmacodynamic action profile of insulin aspart is similar to that of insulin lispro[15], and most studies show that insulin lispro and insulin aspart have similar effects on lowering levels of glucose without a difference in the time to maximum concentration of insulin[5,17,18]; thus, insulin aspart can also be injected ≤15 min before the start of a meal[5,15]. The clinical action profile of insulin aspart is also similar to that of insulin lispro, with postprandial levels of glucose that are notably lower than those achieved with regular human insulin[19–23].

Insulin glulisine. The molecular structure of insulin glulisine differs from that of human regular insulin by the replacement of asparagine with lysine and of lysine with glutamic acid at residue 3 and residue 29 of the B chain, respectively[5,24] (FIG. 4a). In contrast to insulin lispro and insulin aspart, the formulation of insulin glulisine contains polysorbate 20 instead of zinc[24]. Whereas insulin lispro and insulin aspart are stable in subcutaneous pump catheters, issues of clotting and catheter obstructions are more frequent with insulin glulisine, which makes insulin lispro and insulin aspart the preferred insulin analogues for use in pumps[25]. In most pharmacokinetic–pharmacodynamic studies that compared insulin glulisine with insulin lispro or insulin aspart, insulin glulisine had a slightly faster onset of action than the other analogues[24,26,27]. The faster onset of action of insulin glulisine was particularly noticeable in patients with obesity[28,29]. The zinc-free formulation of insulin glulisine might be the reason behind the faster onset of action[24,26], as zinc might delay the absorption and action of insulin lispro and insulin aspart by slowing down the dissociation into monomers after injection[5] (FIG. 1).

Rapid-acting insulin analogues in clinical trials and real life. Overall, clinical studies in patients with T1DM that have compared first-generation rapid-acting insulin analogues with human regular insulin at mealtimes show minor improvements in levels of HbA_{1c}, with a reduced risk of hypoglycaemia, particularly severe nocturnal hypoglycaemia[5,13,14,30,31]. However, a major issue with these trials is the fact that they were carried out in the absence of good basal insulin optimization, mostly because basal insulin analogues were not available when the trials were carried out. This weakness points to the importance of having both good mealtime and basal coverage in T1DM. Later studies of novel insulin analogues have taken more care in optimizing basal insulin therapy before introducing the new mealtime analogue[32].

Using the Diabetes Treatment Satisfaction Questionnaire, patients with T1DM considered treatment with a rapid-acting insulin analogue at mealtime to enable more flexibility and noted the reduced risk of hypoglycaemia as an asset[13] (BOX 3).

A Cochrane Database systematic review published in 2016 considered only a few of the clinical studies that were carried out using these analogues as 'valuable' and showed that rapid-acting insulin analogues induced only a minor reduction of 0.15% in levels of HbA_{1c} compared with regular human insulin in patients with T1DM[31]. No differences in the frequency of hypoglycaemia were seen with insulin lispro or insulin glulisine compared with human regular insulin[31]. The Cochrane review also found no clear evidence for a substantial effect of these rapid-acting insulin analogues on health-related quality of life or weight gain[31]. In the few head-to-head clinical trials that compared the different rapid-acting insulin analogues, no clinically significant differences were seen in

Box 1 | **The need for tight glucose control in type 1 diabetes mellitus**

Intensive insulin therapy that results in tight glucose control can prevent the microvascular complications of diabetes in people with type 1 diabetes mellitus (T1DM). Studies such as the Diabetes Control and Complications Trial have established intensive insulin therapy as the gold standard in the treatment of patients with T1DM but also demonstrated the most important shortcomings of using exogenous insulin in striving for strict glucose control: that is, the risk of hypoglycaemia (particularly severe and nocturnal hypoglycaemia) and weight gain. The advent of insulin analogues has had a major effect on patient care, mainly on reducing the risk of hypoglycaemia. However, achieving normoglycaemia in a safe way remains a challenge in patients with T1DM, even with the newest insulin analogues.

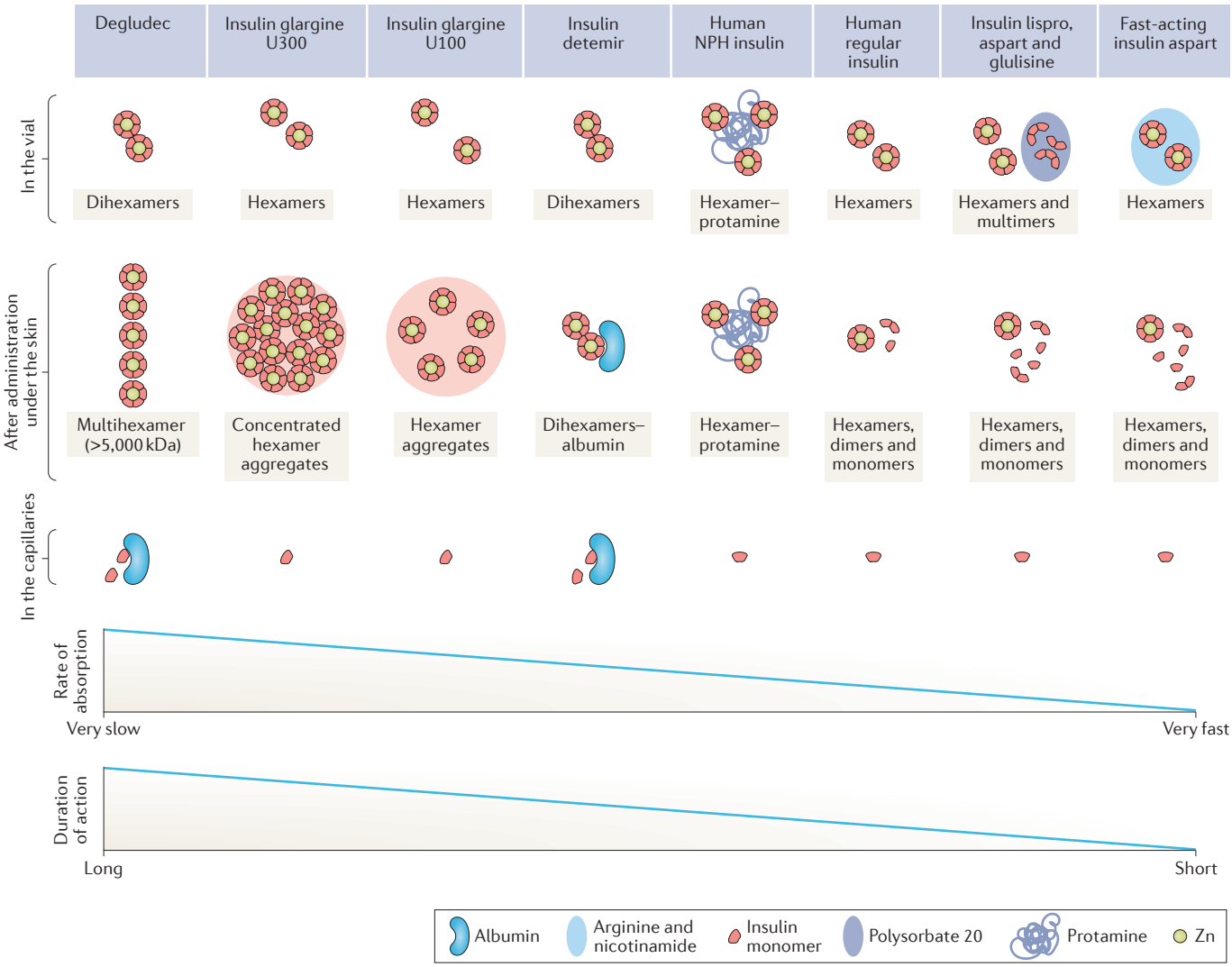


Figure 1 | **Different determinants of absorption and duration of action of human and analogue insulins.** Degludec forms weak hexamers in solution in the vial and stable multihexamers after administration at the injection depot, thereby slowing its absorption. Reversible binding to albumin in the circulation further prolongs its action. Insulin glargine U300 precipitates at physiological pH, forming compact aggregates at the injection depot, leading to a reduced surface area from which absorption can occur, causing slow absorption and prolonged duration of action. Insulin glargine U100 also precipitates at physiological pH but is less compact than insulin glargine U300. Insulin detemir forms weak dihexamers in the vial and strong dihexamers at the injection depot. Reversible binding to albumin, both at the injection depot and in circulation, further slows the absorption rate and prolongs the duration of action. Neutral protamine Hagedorn (NPH) insulin co-crystalizes with protamine, both in the pharmaceutical preparation and at the injection site, slowing absorption and action. The classic rapid-acting insulin analogues (lispro, aspart and glulisine) dissociate into dimers and monomers more rapidly than does human regular insulin, causing a more rapid absorption and shorter duration of action. For glulisine, polysorbate 20 is used as a stabilizing agent, and formation of hexamers is prevented by absence of zinc (Zn). More rapid absorption and earlier action of fast-acting insulin aspart is caused by addition of arginine and nicotinamide to the formulation, thereby increasing the rate of formation of monomers at the injection depot and increasing the rate of absorption.

glycaemic control or in the frequency of hypoglycaemia between these analogues[19–21]. In particular, despite the somewhat faster onset of activity of insulin glulisine, no differences in clinical efficacy have been seen between insulin glulisine and the other insulin analogues[24,26–28].

Despite the sometimes disappointing data coming from individual trials and meta-analyses, the clinical impact of these rapid-acting insulin analogues in real life has been dramatic, mainly because they prevent postprandial hyperglycaemia and late hypoglycaemia (especially hypoglycaemia in the early night period, which is caused by taking human regular insulin at the evening meal). Translation into lowering levels of HbA_{1c} was not spectacular, but quality of life of patients with T1DM improved with the use of rapid-acting insulins that enabled injections closer to meals and were less disruptive in daily life[13,22,33]. Studies have shown that patients have a personal preference for rapid-acting insulin analogues over human regular insulin[22,33]. Responses to the Diabetes Treatment Satisfaction Questionnaire showed that patients with T1DM perceived therapy with insulin analogues to be more flexible and reduced the

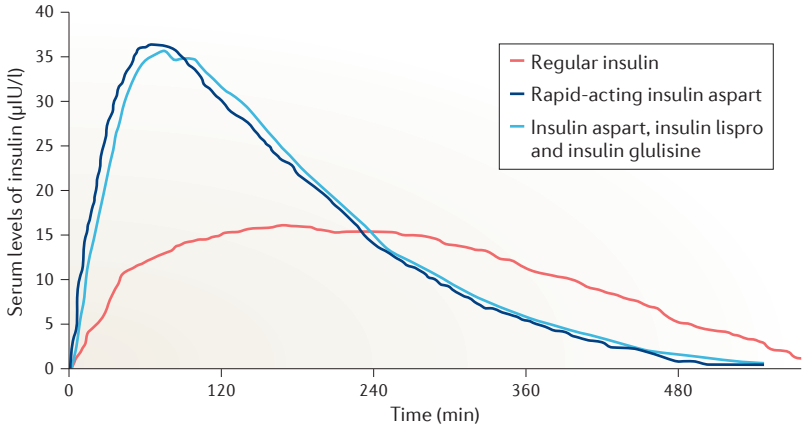


Figure 2 | **Pharmacokinetic action profiles of rapid-acting insulins.** The schematic shows the pharmacokinetic action profiles of rapid-acting insulins[7,102]. Compared with human regular insulin, insulin aspart, insulin lispro and insulin glulisine have a faster onset of action, a higher peak level and a shorter duration of action. Compared with the other rapid-acting insulin analogues, the curve for rapid-acting insulin aspart is shifted to the left, with a similar area under the curve, but a faster onset and earlier peak. Care must be taken when interpreting the curves, as experimental settings in which the data were gathered differed between studies. IU, international units.

perceived risk of hypoglycaemia compared with therapy with human regular insulin[13]. In addition, the use of rapid-acting insulin analogues in patients with T1DM is cost-effective[34,35]. Thus, these rapid-acting insulin analogues have become the standard of care in people with T1DM[36]. In the clinic, choices of one analogue over another are mostly driven by the characteristics of the tools they come with (for example, ease of use of pen or the availability of concentrated forms), their compatibility with continuous subcutaneous insulin infusion (CSII) or approval in special populations.

Rapid-acting insulin analogues in special populations. Insulin lispro and insulin aspart have similar effects on metabolic control and pregnancy outcomes as human regular insulin and are approved for use in pregnancy[37,38]. A large randomized controlled trial that included 322 patients has shown that insulin aspart is at least as safe and effective as human regular insulin when used in basal-bolus therapy with NPH insulin in pregnant women with T1DM and provides benefits in terms of postprandial glucose control and prevention of severe hypoglycaemia[38]. The safety and efficacy of insulin glulisine in pregnancy have not been investigated in large clinical trials; therefore, insulin glulisine is not approved for use in pregnancy.

All rapid-acting insulin analogues are approved for use in children, but the minimum age limits vary depending on available data from studies and regulatory approval. Insulin lispro has no minimum age limit, whereas the minimum age limit is 2 years for insulin aspart and 6 years for insulin glulisine[39].

All three rapid-acting insulin analogues are approved for use in CSII. However, studies using insulin glulisine indicate that this analogue is less stable and has a higher occlusion rate of catheters than the other two rapid-acting analogues[25,40]. In a laboratory setting that involved patients carrying pumps administering insulin lispro, insulin aspart and insulin glulisine, occlusions were rare, and the incidence was similar for the three rapid-acting insulin analogues in the first 72 h; however, after this time, the incidence of occlusions increased substantially, particularly with insulin glulisine[40]. This result might be due to the fact that insulin glulisine has lower physicochemical stability than the other two rapid-acting analogues. A systematic review published in 2013 that aimed to determine the stability and performance of rapid-acting insulin analogues in CSII in outpatients also concluded that the risk of occlusion is higher with insulin glulisine than with the two other rapid-acting insulin analogues when the infusion duration extends beyond approximately 3 days[25], which means that insulin aspart and insulin lispro are currently the preferred rapid-acting insulin analogues for use in people with T1DM using CSII.

Long-acting insulin analogues

The first long-acting insulin analogues, insulin glargine and insulin detemir, were designed to provide more stable basal insulin-action profiles and longer, as well as better, 24 h coverage of the insulin needs of patients compared with human long-acting insulins. Although insulin glargine and insulin detemir are very different basal insulins, they show dramatic improvements in variability in their insulin-action profiles and duration of action compared with NPH insulin[7,41,42]. Clinically, this improvement in variability translates to an important reduction in the risk of nocturnal hypoglycaemia; however, no improvements in levels of HbA_{1c} have been consistently observed[43–47]. The introduction of these basal insulins has had an effect on the quality of life of patients with T1DM, particularly because of the reduction in the risk of nocturnal hypoglycaemia[1] (BOX 3).

Insulin glargine. Insulin glargine, currently the most frequently prescribed long-acting insulin analogue, was the first basal insulin analogue approved for clinical use and its mechanism of protracted action is precipitation in the subcutaneous tissue, which forms aggregates that lead to long term release[48]. This precipitation only happens at neutral pH, whereas, at acid pH (in the vial), insulin glargine is soluble[49,50]. This feature was achieved by shifting the isoelectric point to pH 6.7 through the addition of two arginine molecules to the amino terminus of the B chain. In addition, a substitution of asparagine with glycine at residue 21 of the A chain was introduced (FIG. 4b). Clinically, insulin glargine has a time-action profile that is not only longer but also flatter than that of NPH insulin[43,51] (FIG. 3). The mean duration of insulin glargine action is 22–24 h under single-dose conditions[7,49] and 24–25.6 h under steady-state conditions[50,52]. Consequently, once-daily dosing is effective in most, but not all, patients[8,44,53].

Insulin glargine has an action profile that is less variable than that of NPH insulin[7], which translates to a decrease in the risk of hypoglycaemia in clinical trials, in particular nocturnal hypoglycaemia[45], whereas head-to-head studies fail to demonstrate superiority in

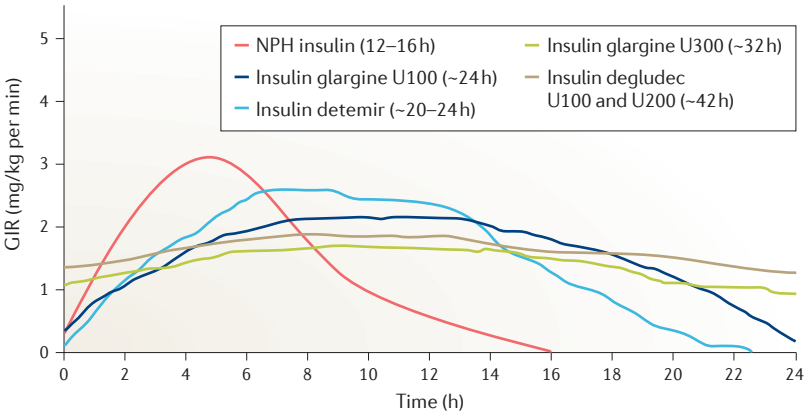


Figure 3 | **Pharmacodynamic action profiles of long-acting insulins.** The schematic shows the pharmacodynamic action profiles of long-acting insulins in steady state[9,75,78]. The pharmacokinetic action profiles of these insulins cannot be compared because the acylated insulins (insulin detemir and insulin degludec) are mostly bound to albumin and total concentrations of insulin do not yield helpful information on action profiles. Therefore, this figure shows the pharmacodynamic action profiles from studies that were carried out in steady state, as these yield the most useful information for the clinician using these insulins on a daily basis in patients with type 1 diabetes mellitus. The difference in action profile between a single injection and steady state is particularly important for those insulins with half-lives above 12 h (insulin glargine U300 and insulin degludec). Care must be taken when interpreting the curves, as experimental settings in which the data were gathered differed between studies. GIR, glucose infusion rate; NPH, neutral protamine Hagedorn.

lowering levels of HbA_{1c} (REF. 43,45). Insulin glargine and NPH insulin have similar effects on weight, generally resulting in weight gain[43,45].

Insulin detemir. Insulin detemir is a pH-neutral, soluble basal insulin analogue in which the threonine has been removed from residue 30 of the B chain of human regular insulin and a 14-carbon myristoyl fatty acid has been added to lysine at residue 29 of the B chain, which facilitates self-association of insulin detemir molecules into dihexamers at the injection site and reversible binding to albumin in tissue and the bloodstream (FIG. 4b). The formation of dihexamer and the binding to albumin are some of the mechanisms that are involved in the increased length of action of insulin detemir; however, we do not completely understand how insulin detemir has a long duration of action[54] (FIG. 1). The concentration of insulin in insulin detemir is four times higher than that of human regular insulin because its molar potency is lower than that of human regular insulin and other insulin analogues[41,55,56]. This feature has few clinical implications, as the required doses are only slightly higher than those of NPH insulin or insulin glargine[56,57].

The mean duration of action of insulin detemir is 21.5 h in patients with T1DM (which is slightly shorter than that of insulin glargine) on the basis of data obtained using a dose of 0.4 units per kg in a single-dose clamp study[8,58] (FIG. 3). The studies evaluating the duration of effect of basal insulins are heavily debated, and subtle differences in technique of clamping, as well as differences in single-dose versus steady-state studies, add to the confusion[42]. Even so, looking at the overall data, insulin detemir seems to have a duration of action that is shorter than that of insulin glargine (particularly under steady-state conditions); however, the duration of action of both insulins approaches 24 h in most, but not all, patients with T1DM[59]. In clinical studies in patients with T1DM[57], and in real-life settings, this shorter duration of action translates to a higher proportion of people using twice-daily insulin detemir compared with insulin glargine to maintain full basal coverage[46].

A large-scale, repeated-clamp study compared within-patient variability in the glucose-lowering response from injection to injection in adults with T1DM using NPH insulin, insulin glargine or insulin detemir as basal insulin[7]. The lowest variability was reported for insulin detemir, which was fourfold and twofold more stable than NPH insulin and insulin glargine, respectively[7]. Similar data were reported in children[60].

Clinically, studies that investigate insulin detemir in patients with T1DM report a notable decrease in overall and nocturnal hypoglycaemia but no minimal reduction in levels of HbA_{1c} compared with NPH insulin[57,61]. Meta-analyses show an overall small (about 0.2–0.4%) but notable reduction in levels of HbA_{1c} in patients treated with detemir compared with patients treated with NPH[62,63]. A 52-week study that compared insulin detemir and insulin glargine showed similar rates of hypoglycaemia[57], whereas a 26-week study showed less nocturnal and severe hypoglycaemia in patients using twice-daily insulin detemir than in patients using once-daily insulin glargine[56]. Therefore, in patients with T1DM who have a high risk of nocturnal hypoglycaemia, insulin detemir might be the preferred long-acting insulin analogue.

Intriguingly, in all studies that compared insulin detemir with NPH insulin, less weight gain and even a small weight loss were seen in patients treated with insulin detemir[62,63]. This difference was not observed in the head-to-head studies of insulin detemir and insulin glargine[56,57]. Of interest, the weight advantage was greatest in those patients who received insulin detemir once daily[64]. The reasons for this relative reduction in weight gain are not understood but might be related to a slight hepato-preferential effect[65] or satiety effects on the central nervous system[66].

Long-acting insulin analogues in special populations and real-life settings. Most studies of insulin glargine in pregnancy are small and retrospective, and include women with T1DM, T2DM and gestational diabetes; however, a systematic review and meta-analysis of these studies found no safety issues[67]. Therefore, regulatory bodies allow continuation of insulin glargine during pregnancy if required to achieve desired glycaemic control[36,68]. A head-to-head study of insulin detemir versus NPH insulin has reported on the safety of insulin detemir in pregnant women with T1DM[69]. The study was too small to enable conclusions on fetal outcomes, but fasting plasma levels of glucose improved with insulin detemir without an increased incidence of hypoglycaemia, which supports the use of insulin detemir as the long-acting insulin analogue of choice in pregnancy[69]. Considering the importance of tight glycaemic

control in women with T1DM from the first days of pregnancy to the moment of delivery, the insulin analogue with the action profile that best fits the insulin needs of the patient has to be chosen by the clinician in charge. Insulin glargine is approved by the FDA for use in children from 6 years of age and by the European Medicines Agency (EMA) from 2 years of age, and insulin detemir is approved for use in children from 2 years of age (these age limits are the result of clinical study data and regulatory approval)[70,71].

The choice of which long-acting insulin analogue to use in patients with T1DM in special populations is driven by the action profile and the regulatory approval in that particular group of patients but also by the tools it comes with (such as the pen it comes with or the availability of more concentrated forms). As most patients with T1DM will require twice-daily insulin detemir when it is used as the basal insulin, most individuals will prefer once-daily insulin glargine. However, some guidelines, such as the UK NICE guideline, advocate the use of insulin detemir in patients with T1DM on the basis of its superior action profile with respect to the risk of hypoglycaemia, particularly during the night, compared with using insulin glargine[72].

The need for more insulin analogues

The introduction of the rapid-acting and long-acting insulin analogues described so far has changed the lives of patients with T1DM; more patients are reaching better glucose targets, with hypoglycaemia rates decreasing and quality of life improving compared with previous regimens, particularly when full analogue regimens are used[5,47,73]. In a head-to-head study, a mean of 22.1 fewer episodes of hypoglycaemia per patient-year were recorded, and the frequency of nocturnal hypoglycaemia was also statistically significantly reduced in patients treated with the full analogue compared with patients using human insulins[47].

In our opinion, the use of full analogue regimens should be standard of care in all patients with T1DM. In a small but elegant study (HypoAna trial) that was carried out in Denmark in people with T1DM who experienced recurrent severe hypoglycaemia, it was demonstrated that people treated with the full analogue regimen (insulin detemir and insulin aspart) had a 29% reduction in the rate of severe hypoglycaemia episodes (absolute reduction of 0.5 episodes per year) compared with people receiving human insulins (NPH and regular insulin)[74]. Of note, using a full analogue regimen in this vulnerable population of people who are prone to severe hypoglycaemia is cost saving[35].

Box 2 | **The need to achieve a physiological insulin-action profile**

Insulin analogues enable people with type 1 diabetes mellitus to live more flexible lives than do previous regimens, as using rapid-acting insulin analogues reduces the time needed between the injection of a mealtime insulin and a meal, and obviates the need for inter-meal snacking. The long-acting insulin analogues have enabled improved stability of replacement of basal insulin needs, reducing the risk of nocturnal hypoglycaemia compared with human insulin preparations. The major remaining challenge is the absence of physiological feedback on insulin supply.

As rapid-acting insulins have a start of action that is too slow, particularly for patients who use pumps, improvements are still needed. This shortcoming has become obvious with the introduction of algorithms for dose adaptation by smart insulin pumps and with the development of closed-loop or semi-closed-loop systems. In contrast to early suggestions from pharmacokinetic–pharmacodynamic studies, the current rapid-acting insulins still take at least 10 min to start their glucose-lowering action, thus still forcing patients to wait at least a few minutes between injections and starting the meal for full matching of the insulin-action profile to meal-induced glucose excursions[75,76]. The use of sensor technology has been particularly helpful in uncovering this shortcoming[75,76], which has created a demand for faster-acting and shorter-acting insulin analogues, especially for use in artificial pancreas systems. In addition, the first-generation long-acting insulin analogues (insulin glargine and insulin detemir) do not achieve full 24 h basal insulin coverage in all patients with T1DM, which has resulted in the need for twice-daily administration in some patients[42]. Another, more important, problem is the variability in insulin-action profile that is still an issue for the current long-acting insulin analogues, especially insulin glargine, which can contribute to hypoglycaemia (particularly nocturnal hypoglycaemia).

In 2014 and 2015, a biosimilar insulin glargine was approved by the EMA and the FDA, respectively, for use in people with T1DM[77,78]. Pharmacokinetic-pharmacodynamic studies confirmed full similarity of the action profile to the original insulin glargine[79,80]. A limited clinical trial programme has confirmed identical clinical efficacy and safety of the biosimilar and the original insulin[81–83]. As this 'new' long-acting insulin is identical in clinical effect to the original insulin, the biosimilar will not be discussed in more detail here.

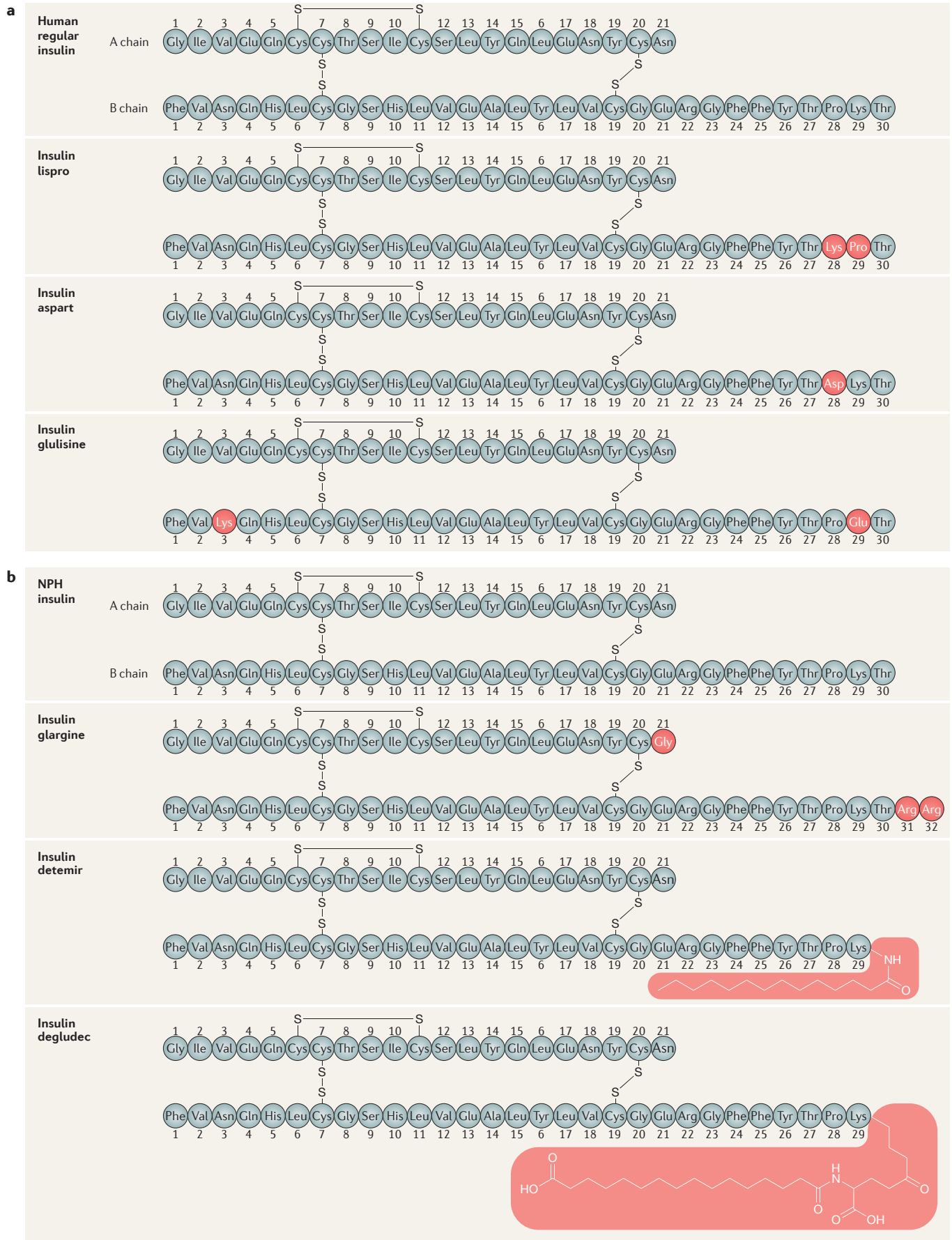
New basal insulins

At present, two new basal insulins are available for clinical use in Europe and the USA: insulin glargine U300 and insulin degludec (U100 and U200).

Insulin glargine U300

When human regular insulin is concentrated, its pharmacokinetic–pharmacodynamic action profile is altered. Compared with the non-concentrated form, concentrated insulin has a similar time to onset of action, but the glucose-lowering effect is longer than that of the non-concentrated form, as a result of protracted release from the injection site. At high doses, the blood glucose-lowering effect of human regular insulin U500 is extended to up to 21 h, whereas it is 18 h for human regular insulin U100 (REF. 6). A probable explanation for this phenomenon is that, compared with the non-concentrated form, more-compact conglomerates of insulin are formed under the skin, which decreases the surface area from which dissociation of insulin molecules can occur and increases the distance to capillaries[84].

A similar effect has been achieved by concentrating insulin glargine from the usual U100 to a U300 formulation (FIG. 1). Compared with insulin glargine



◀ Figure 4 | **Amino acid structure of short-acting and long-acting insulins.** All insulin analogues are created from the basic structure of human regular insulin. **a** | Rapid-acting insulins are designed to decrease the formation of hexamers and are typically constructed through amino acid exchanges. **b** | Long-acting insulins are created through exchange of amino acids to shift the isoelectric point (insulin glargine) or through addition of free fatty acid moieties that enhance formation of dihexamers and multihexamers, as well as binding to albumin (insulin detemir and insulin degludec). NPH, neutral protamine Hagedorn.

U100, insulin glargine U300 has an extended glucose-lowering action profile (FIG. 3). After 1 week at steady state (0.4 units per kg per day), the half-life of insulin glargine U300 was 19.0 h compared with 13.5 h for insulin glargine U100 (REF. 85). In these pharmacokinetic–pharmacodynamic studies in patients with T1DM, the duration of action even extended to over 32 h (from ~24 h with the U100 formulation) with a pharmacokinetic–pharmacodynamic action profile for insulin glargine U300 that is flatter than that for insulin glargine U100 (REF. 86). However, this study also showed a decrease in the biopotency of insulin glargine U300 at steady state (27% less than insulin glargine U100)[86], which suggests that the dose needs to be adjusted when switching patients from insulin glargine U100 to insulin glargine U300. The observed variability for insulin glargine U300 is lower than that for insulin glargine U100 (REF. 87). A lower increase in levels of glucose (based on continuous glucose monitoring) in the last 4 h of the 24 h injection interval, smoother average 24 h glucose profiles irrespective of injection time and reduced nocturnal hypoglycaemia were observed in the group who received insulin glargine U300 compared with the changes seen in patients who received insulin glargine U100 (REF. 87).

Clinical studies that use insulin glargine U300 in patients with T1DM are limited in number, with only two studies available, one of which was exclusively in Japanese patients[88,89]. This limited development programme of insulin glargine U300 is due to the fact that regulatory bodies allowed a shorter programme, as the insulin molecule was the same as the one that had already been extensively studied with insulin glargine U100. In EDITION 4, patients with T1DM treated with basal-bolus therapy were randomly assigned to receive insulin glargine U100 or insulin glargine U300 as basal insulin[89]. No differences in levels of HbA_{1c} were observed, and the study only showed a benefit of the U300 formulation in decreasing the incidence of nocturnal hypoglycaemia during the first 8 weeks of the study (the titration phase) and not during the maintenance phase; this finding is in contrast to reports on insulin degludec[90–92]. No firm conclusions on severe hypoglycaemia could be drawn as too few events were recorded. The increase in body weight was 0.6 kg lower in patients who were given insulin glargine U300 than in those given insulin glargine U100 ($P < 0.4$). Basal doses of insulin at the end of the study were higher in patients who were given insulin glargine U300 than in those on insulin glargine U100 (0.47 units per kg per day versus 0.40 units per kg per day). No difference in efficacy or safety was present between morning and evening injections of insulin glargine U300 (REF. 89). Flexibility was also increased with insulin glargine U300 compared with insulin glargine U100, but the study only included a window of ± 3 h around the usual injection time.

There is no clinical experience with the use of insulin glargine U300 in pregnant women or children. However, considering the fact that glargine U300 is the same molecule as insulin glargine U100, no specific safety issues for this formulation are to be expected, and clinicians should use the insulin analogue with the action profile most suitable for the individual patient.

Overall, insulin glargine U300 is an important step forward in basal insulin coverage in patients with T1DM. Now, full 24 h coverage can be reached in all patients, with increased stability translating to a reduced risk of nocturnal hypoglycaemia and increased flexibility in timing of administration. In addition, insulin glargine is administered with a disposable pen, which is a major asset for ease of use and should avoid all confusion around dosing of this concentrated insulin. Patients and health-care professionals should be aware and cautioned against using regular insulin syringes (labelled for dosing U100 insulins) for this concentrated insulin.

Insulin degludec

Insulin degludec is long acting owing to a novel method, as it relies on the formation of multihexamer chains following injection in the subcutaneous tissue (FIG. 1). This formation is achieved through the manipulation of the human regular insulin molecule, with the removal of threonine at residue 30 of the B chain and the addition of a 16-carbon fatty acid at residue 29 of the B chain through a glutamic acid spacer (FIG. 4b) This change also enables albumin to bind to the insulin molecule, which contributes to its ultra-long and stable action profile[93] (FIG. 3).

In a head-to-head 42 h glucose-clamp study in patients with T1DM, the mean half-life of insulin degludec action was 25.4 h (versus 12.1 h for insulin glargine) with a duration of insulin degludec action at steady state using once-daily administration of 0.4 units per kg of at least 42 h (REF. 93) (FIG. 3). The coefficient of variation of the glucose-lowering effect of insulin degludec was four times lower than that of insulin glargine at the same dose (20% versus 82%), with a more even distribution of the glucose-lowering effect over 24 h for insulin degludec[94,95]. As demonstrated through modelling and later confirmed in clinical studies, a once-daily administration of such a long-acting insulin does not result in the accumulation of active insulin but leads to the build-up of a stable 'reserve' of insulin, resulting in a stable basal insulin-action profile[96]. Clinically, however, this feature means that patience is required when adapting doses, as 3 days are required for insulin degludec to reach the stable plateau after the first injection[96].

Clinically, the long and stable action profile of insulin degludec translates to fewer episodes of nocturnal hypoglycaemia with insulin degludec than with insulin glargine in patients with T1DM[90,91,97]. Use of either drug can result in similar levels of HbA_{1c}, but with a 25% lower rate of confirmed nocturnal hypoglycaemic events in patients receiving insulin degludec than in those on insulin glargine. However, the trend for the rate of

Box 3 | **Pros and cons of insulin preparations in type 1 diabetes mellitus**

Rapid-acting insulins

- Rapid onset of action — favours insulin analogues
- Postprandial glucose control — favours insulin analogues
- Short action profile — favours insulin analogues
- Risk of diurnal hypoglycaemia — favours insulin analogues
- Need for snacks — favours insulin analogues
- Risk of nocturnal hypoglycaemia — favours insulin analogues
- Flexibility (injection with meal) — favours insulin analogues
- Cost — favours human insulin
- Experience — favours human insulin
- Availability — favours human insulin
- Availability of concentrated forms — favours both forms
- Use of continuous subcutaneous insulin infusion — favours insulin analogues

Long-acting insulins

- Duration of action — favours insulin analogues
- Flat profile — favours insulin analogues
- Variability — favours insulin analogues
- Risk of hypoglycaemia — favours insulin analogues
- Need for evening snacks — favours insulin analogues
- Risk of nocturnal hypoglycaemia — favours insulin analogues
- Flexibility — favours insulin analogues
- Cost — favours human insulin
- Experience — favours human insulin
- Availability — favours human insulin
- Availability of concentrated forms — favours insulin analogues

overall confirmed hypoglycaemia was higher in patients receiving insulin degludec but did not reach statistical significance. Importantly, a decrease (35%) in severe hypoglycaemia in the phase in which the dose of insulin was fully titrated was observed in those patients receiving insulin degludec[92]. These findings were confirmed in the SWITCH1 study, in which patients with T1DM who were using insulin degludec or insulin glargine as their basal long-acting insulin were compared in a double-blind manner, with a reduced overall risk of hypoglycaemia in those patients receiving insulin degludec[98]. Of interest, the very long action profile of insulin degludec enables extreme flexibility in administration of the basal insulin. Indeed, whereas insulin glargine and insulin detemir need to be injected at the same time every day to maintain appropriate basal insulin coverage in people with T1DM, insulin degludec can be injected with time intervals between two injections as small as 8 h to as long as 40 h, as long as it is administered once daily[91]. Importantly, this flexibility does not influence the effectiveness or safety of the basal insulin, as the glucose-lowering potency was similar and the nocturnal-hypoglycaemia advantage remained present[91]. This increased flexibility is important to patients with T1DM, as it enables them to live active lives[91]. A small observational study demonstrated that, in people with T1DM switching from twice-daily insulin glargine or insulin detemir to once-daily insulin degludec, levels of HbA_{1c}, risk of hypoglycaemia and treatment satisfaction improved, and doses of insulin decreased[99].

Insulin degludec is available commercially in two formulations: U100 and U200. In contrast to other insulins (human regular insulin U500 and insulin glargine U300), altering the concentration of insulin degludec has not altered its pharmacokinetic–pharmacodynamic action profile[100], which means that patients can switch between the formulations without dose adaptations. The reason why the concentration of insulin degludec has no effect on the action profile is unclear. However, protraction of the action profile relies on hexamer formation rather than on aggregation, which could be an explanation, as the release of zinc from multihexamer chains is the rate-limiting step for absorption of insulin degludec and this process is not dependent on concentration[101,102].

At present, insulin degludec is approved globally for use in children older than 1 year of age. A study in young children and adolescents (1–17 years of age) indicates that the metabolic advantages in children are similar to those in adults (that is, a reduced risk of nocturnal hypoglycaemia), with an intriguing observation of a decreased number of ketotic episodes in children treated with insulin degludec[103]. At present, no studies on the use of insulin degludec in pregnancy are available.

Overall, the very long-acting and stable action profile of insulin degludec, the extensive data from clinical trials and the ease of use of the disposable pen in which it comes make this insulin, in our opinion, the current preferred basal insulin analogue in patients with T1DM. However, a major challenge in many health-care systems is the price of insulin degludec, which prevents many people with T1DM from using this insulin. However, studies that include factors other than just the cost of the insulin have shown that insulin degludec can be a cost-effective alternative to other basal insulin analogues in patients with T1DM. The lower costs are mainly driven by the lower daily dose of insulin degludec and the reduced risk of severe hypoglycaemic events with insulin degludec[104,105].

Pegylated lispro

Despite promising metabolic results in the development programme of a new concept to prolong the duration of action of insulin analogues — pegylation — no pegylated basal insulin is available for clinical use at the moment, and it is doubtful whether this path is a viable method to develop novel insulin analogues. The concept of pegylation is built on the search for a 'liver-specific' insulin, which would hold the promise of enhanced glucose-lowering potential and reduced risk of hypoglycaemia and weight gain compared with currently available insulin analogues. This search is based on the fact that, when a large polyethylene glycol (PEG) polymer chain is attached to an insulin molecule, the hydrodynamic size of the molecule is substantially increased, thus leading to easy penetrance through the fenestrated capillaries of the liver but much less penetrance through the capillaries of other tissues, such as fat or muscle. This molecule would have a reduced rate of clearance, which would prolong its glucose-lowering action.

The pegylated insulin created by Eli Lilly, PEGLispro, fulfilled the promise of increased hepato-preferential effects[106] and was the first insulin of its kind to enter a

clinical development programme. Pharmacokinetic–pharmacodynamic studies showed a long half-life of 2–3 days[107,108], with PEGLispro having less within-patient variability in the glucose-lowering effect than insulin glargine U100 (REF. 109).

In the open-label IMAGINE 1 trial, patients with T1DM who received PEGLispro had better lowering of levels of HbA_{1c} but a higher rate of severe hypoglycaemic events compared with those who received insulin glargine U100 (REF. 110). The larger, blinded IMAGINE 3 trial confirmed the superior glucose-lowering effect, with less weight gain and a nonsignificant trend to lower rates of severe hypoglycaemic events, of PEGLispro compared with insulin glargine[111,112]. However, a major issue that arose in patients with T1DM, as well as in patients with T2DM, was abnormalities on liver function tests, which led to uncertainty about the safety of using pegylation as a protraction mechanism and termination of the programme[113,114]. To determine whether the safety issues were a direct toxic effect or a consequence of the liver-preferred insulin action (accumulation of fat in the liver that could lead to nonalcoholic steatohepatitis in the long term), long and extensive studies would have been needed, which was considered unachievable.

The story of PEGLispro opened the discussion on desirability of a 'liver-specific' insulin. Clearly, an essential part of insulin action is suppression of peripheral lipolysis. When suppression of glucose output by the liver is not accompanied by some suppression of lipolysis in fat tissue, the liver will be overwhelmed by free fatty acids coming in via that route, and thus liver steatosis, and even steatohepatitis, will inevitably ensue[114]. Achieving a 'liver-preferred' action, favouring the liver, but still affecting fat to some extent is the challenge for future analogue development.

Co-formulations

The structure of insulin degludec and the way it is formulated have made it possible to develop a combinatorial insulin in which insulin degludec and insulin aspart are co-formulated at a ratio of 70:30 (insulin degludec–aspart). Insulin degludec and insulin aspart remain separate entities in solution, and size-exclusion chromatography studies have found no evidence of physical or chemical interaction between the two insulins in co-formulation[115]. The glucose-lowering effect of once-daily insulin degludec–aspart is characterized by a peak action from the insulin aspart present in the solution and a separate basal action that lasts more than 30 h at steady state from the insulin degludec[116].

In our opinion, the need for this combinatorial insulin is limited in T1DM, as the basis of insulin therapy in T1DM is flexibility in dose adjustment of mealtime and basal components of the therapy dependent on variable factors such as meals, glycaemic levels and exercise. This flexibility is partially lost with a fixed-combination insulin such as insulin degludec–aspart. Even so, clinical trials in patients with T1DM have been carried out, and a 52-week study demonstrated that, when insulin degludec–aspart was administered at the main meal, combined with insulin aspart at the other meals, people with T1DM experienced fewer nocturnal hypoglycaemic attacks (relative risk: 0.62) and used less insulin than those using insulin detemir once or twice daily as basal insulin and insulin aspart at meals[117].

Future developments

Several projects on novel insulin analogues or at least novel concepts in insulin administration are under investigation and are close to being available to clinicians and patients[118].

Rapid-acting insulin analogues

A novel formulation of insulin lispro has been introduced (U200), which is primarily aimed at enabling injections of reduced volume in patients who need high doses of insulin (mainly patients with T2DM). Bioequivalence and comparative pharmacodynamics have been demonstrated, and the results are in contrast to the expectations that were based on experiences with more concentrated human regular insulin[119].

The pharmaceutical industry has taken several routes in the pursuit of the perfect match between insulin-action profiles and meal-induced glucose excursions, and in particular to find insulins that have a faster on/off action profile. Early on, Halozyme attempted to alter the injection site in such a manner that entry of the injected insulin into the draining blood vessels would be enhanced (for example, enzymatically by hyaluronidase). No clinical data are available, and the programme is not active. Several companies have altered the excipients in which existing rapid-acting insulin analogues are presented. For example, Biodel developed an ultra-fast-acting insulin on the basis of human regular insulin, now suspended in EDTA, citrate and magnesium sulfate, to increase the rapidity of onset of action, but this programme has also been halted[120–123].

A novel rapid-acting insulin analogue with the most advanced clinical development is fast-acting insulin aspart, in which the excipients have been altered to enable a faster onset of action. Fast-acting insulin aspart includes the original molecule of insulin aspart set in a new formulation that contains two well-known excipients, nicotinamide and arginine. The addition of these excipients results in a stable formulation with an initial absorption after subcutaneous injection that is faster than that of standard insulin aspart[118]. In a pharmacokinetic study, fast-acting insulin aspart had a faster onset of action than insulin aspart (4.9 min versus 11.2 min) and reached the 50% maximum concentration more quickly (20.7 min versus 31.6 min)[118,124,125]. The greatest difference occurred during the first 15 min, when the area under the curve was 4.5-fold greater with fast-acting insulin aspart than with insulin aspart. Both insulins had similar time to maximum concentration, total exposure and maximum concentration. Pharmacodynamic analysis showed that fast-acting insulin aspart had a greater glucose-lowering effect within 90 min after dosing than insulin aspart. Both insulins had similar total and maximum glucose-lowering effects, which indicates that they have similar overall potency but that a shift of action to earlier time

points has occurred with fast-acting insulin aspart. These ultra-fast pharmacodynamic properties of fast-acting insulin aspart are similar in elderly patients (≥65 years of age) and children (6–17 years of age) with T1DM compared to the properties in young adults (18–35 years of age)[125,126].

A group of patients in whom fast-acting insulin aspart might be of most use is users of CSII. In a randomized, double-blind, crossover trial in users of CSII, the pharmacokinetic–pharmacodynamic action profiles for fast-acting insulin aspart were left shifted compared with those for insulin aspart, with onset of action 11.1 min earlier for fast-acting insulin aspart; however, the end of insulin action was also left shifted by 24 min[127]. In a double-blind, randomized, crossover trial in 43 patients with T1DM, CSII delivery of fast-acting insulin aspart had a greater glucose-lowering effect than insulin aspart after a meal test. In addition, continuous glucose-monitoring results showed that patients who received fast-acting insulin aspart spent less time with low levels of glucose (<70 mg/dl) than those who received insulin aspart[128].

The first clinical study results in patients with T1DM showed that 6 months of treatment with fast-acting insulin aspart enabled patients to achieve a level of HbA_{1c} that was significantly lower than the level in patients who used insulin aspart (a difference in HbA_{1c} levels of 0.15%), with lower postprandial glucose excursions[32]. No differences in the risk of hypoglycaemia were observed. In this study, postprandial administration of fast-acting insulin aspart showed similar glycaemic control to preprandial administration of standard insulin aspart, which suggests that postprandial administration of this rapid-acting insulin would become possible without compromising efficacy or safety[32]. This insulin was approved by the EMA in January 2017 (REF. 129).

Some researchers are underwhelmed by the gain of just a couple of minutes in speed of onset with this novel ultra-rapid-acting insulin. However, in our opinion, in real-life settings, these few minutes make a considerable difference to the lives of people with T1DM. From the introduction of the original rapid-acting insulin analogues, we have learned that a gain of a few minutes in onset of insulin action leads to improved prandial coverage of the meal-induced glucose excursions and enables patients to administer their insulin injection at mealtimes at a more convenient time. However, continuous glucose monitoring has shown that many patients now inject just at the start of the meal, or even during or after meals. Gaining another 4–5 min in speed of onset of insulin action will contribute to improved postprandial control and, as important, to more flexibility in people's lives without compromising efficacy or safety of the insulin regimens. In our opinion, particularly in patients with T1DM, the introduction of ultra-rapid-acting insulin analogues will make a difference. The group in which this difference of a couple of minutes is even more crucial is users of CSII, in particular those who use sensor-augmented pumps. With this technology, everything depends on the rapidity of onset and offset of the insulin in the pump[130]. Availability of these insulin analogues is also an important step in the development of workable algorithms for concepts to develop an artificial pancreas.

Other concepts

Intensive research is ongoing in the field of creating even longer-lasting insulin preparations[131], exploiting novel technologies such as antibody-linked insulins to achieve weekly administrable insulin preparations. These insulins have a protracted action profile as a result of decreased clearance. Data are preliminary, and research is still in the animal-model phase[132,133].

Another research avenue is the development of smart insulins, which are insulins that would be released from depots under the skin when levels of glucose rise. Currently, developments are happening based on resin-embedded insulins, as well as on lectin-bound insulins that would be released from lectin-binding areas when levels of glucose rise[134,135].

Finally, the goal of administering insulin through methods other than parenterally is still being pursued. Inhaled insulin is available but is used infrequently[136,137]. The first reports on the development of oral insulin preparations are beginning to appear[137,138].

Conclusions

Achieving normoglycaemia without hypoglycaemia and excessive weight gain in patients with T1DM remains an elusive goal, but the advent of insulin analogues has had a large effect, enabling intensive insulin therapy without being too disruptive to daily life. Rapid-acting insulin analogues, in particular the ultra-rapid-acting insulins, can be administered shortly before meals, giving better coverage of mealtime-induced glucose excursions than human regular insulin. In addition, basal insulin analogues are becoming more stable and provide better coverage of basal insulin needs for people with T1DM than human insulin. Clinical studies on individual agents show small advantages, mainly in prevention of hypoglycaemia, when treating patients to achieve similar glycaemic targets. In particular, studies comparing human regular insulin with full insulin analogue regimens clearly demonstrate the superiority of these agents in the treatment of patients with T1DM. Improvements in rapidity in onset of rapid-acting insulin analogues, stability of long-acting insulin analogues, mode of administration and glucose sensitivity for action would further contribute to improved glycaemic control in patients with T1DM.

The novel insulin analogues are an important step in the path to achieving tight glycaemic control without hypoglycaemia in patients with T1DM. However, even with the improved action profiles of the insulin analogues, insulin therapy in patients with T1DM remains a challenge, with the risk of hypoglycaemia and weight gain still present. In the treatment of patients with T1DM, education, improvements in glucose monitoring and devices that assist patients in insulin delivery and decision making have a crucial role for embedding T1DM in their lives until the ideal insulin preparation, able to fully mimic the physiological insulin secretion of β cells, is discovered.

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Author contributions

C.M. and K.B. researched data for the article, contributed to discussion of the content, wrote the article and reviewed and/or edited the manuscript before submission. P.G. contributed to discussion of the content and reviewed and/or edited the manuscript before submission.

Competing interests statement

C.M. serves or has served on the advisory panel for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, Intrexon, Janssen Pharmaceuticals, Hanmi Pharmaceuticals, Mannkind, Medtronic, Merck Sharp and Dohme Ltd., Novartis, Novo Nordisk, Pfizer, Sanofi, Roche Diagnostics and UCB. KU Leuven has received research support for C.M. from Abbott, Eli Lilly and Company, Intrexon, Merck Sharp and Dohme Ltd., Novartis, Novo Nordisk, Roche Diagnostics and Sanofi. C.M. serves or has served on the speakers bureau for AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Merck Sharp and Dohme, Novartis, Novo Nordisk and Sanofi. P.G. has served on the advisory panel for AstraZeneca, Lilly, Merck Sharp and Dohme Ltd., Novo Nordisk and Sanofi. P.G. has served on the speakers bureau for AstraZeneca, Bristol-Meyers Squibb, Boehringer Ingelheim, Janssen Pharmaceuticals, Lilly, Novartis, Novo Nordisk and Sanofi. K.B. has served on the advisory panel for AstraZeneca, Merck Sharp and Dohme Ltd. and Novo Nordisk. K.B. has served on the speakers bureau for AstraZeneca, Bristol-Meyers Squibb, Boehringer Ingelheim, Janssen Pharmaceuticals, Lilly, Novartis and Novo Nordisk. KU Leuven has received research grants for K.B. from AstraZeneca, Janssen Pharmaceuticals, Merck Sharp and Dohme Ltd., Novartis, Novo Nordisk and Sanofi.

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