review article

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REVIEW ARTICLE

Plasma insulin profiles after subcutaneous injection: how close can we get to physiology in people with diabetes?

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Many people with diabetes rely on insulin therapy to achieve optimal blood glucose control. A fundamental aim of such therapy is to mimic the pattern of 'normal' physiological insulin secretion, thereby controlling basal and meal-time plasma glucose and fatty acid turnover. In people without diabetes, insulin release is modulated on a time base of 3–10 min, something that is impossible to replicate without intravascular glucose sensing and insulin delivery. Overnight physiological insulin delivery by islet β cells is unchanging, in contrast to requirements once any degree of hyperglycaemia occurs, when diurnal influences are evident. Subcutaneous pumped insulin or injected insulin analogues can approach the physiological profile, but there remains the challenge of responding to day-to-day changes in insulin sensitivity. Physiologically, meal-time insulin release begins rapidly in response to reflex activity and incretins, continuing with the rise in glucose and amino acid concentrations. This rapid response reflects the need to fill the insulin space with maximum concentration as early as 30 min after starting the meal. Current meal-time insulins, by contrast, are associated with a delay after injection before absorption begins, and a delay to peak because of tissue diffusion. While decay from peak for monomeric analogues is not dissimilar to average physiological needs, changes in meal type and, again, in day-to-day insulin sensitivity, are difficult to match. Recent and current developments in insulin depot technology are moving towards establishing flatter basal and closer-to-average physiological meal-time plasma insulin profiles. The present article discusses the ideal physiological insulin profile, how this can be met by available and future insulin therapies and devices, and the challenges faced by healthcare professionals and people with diabetes in trying to achieve an optimum plasma insulin profile.

Keywords: analogue, basal, diabetes, insulin therapy, meal, physiology

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Introduction

The benefit of good blood glucose control in diabetes is irrefutable [1,2]. For everyone with type 1 diabetes, and many with type 2 diabetes, insulin therapy is the means to achieve such control. One fundamental aim of insulin therapy is to mimic the pattern of physiological insulin secretion to control both basal and meal-time plasma glucose levels. Attempts to mimic physiological profiles typically use long-acting basal insulin or continuous subcutaneous insulin infusion (CSII) to modulate endogenous hepatic glucose production and adipose tissue fatty acid release [3]. A meal-time insulin analogue is used to suppress adipose tissue fatty acid release and hepatic glucose production, and enhance peripheral glucose uptake after eating [4]. The major constraint to optimum control is hypoglycaemia, although high insulin doses and weight gain also contribute [5].

Since the 1920s, insulin therapy has evolved and our ability to mimic the average physiological profile, achieve good blood glucose control, minimize side effects and enhance user convenience has improved [6]; however, average glucose control in clinical practice and even in randomized controlled trials (RCTs) remains poor, and hypoglycaemia is still a problem to nearly everyone with type 1 diabetes and many with type 2 diabetes [7,8]. In a US database analysis of people with type 2 diabetes starting basal insulin, the rate of hypoglycaemia requiring assistance was 11.2 per 100 person-years [9]. The incidence and fear of hypoglycaemia (especially nocturnal) both contribute to sub-optimal adherence to insulin therapy. Other factors include the need for self-monitoring and patient education, and the complexity of insulin regimens [10,11].

The present review article discusses the ideal physiological insulin profile and the extent to which this can be met by available and future insulin therapies and devices.

Physiological Insulin Delivery: the Challenge

There is more to physiological insulin delivery than just achieving optimal average insulin profiles, and many of these issues are presently unapproachable. Most critically, individual insulin sensitivity varies from day to day with changes in lifestyle, both predictable and unpredictable (Table 1), while meal composition affects rates of gastric emptying and substrate absorption. Furthermore, there are underlying diurnal variations in insulin secretion and insulin action [12]. Hypoglycaemia can increase insulin sensitivity for up to 24 h, partly via changes in lipolysis and partly through upregulation of glucose transporters [13,14].

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Table 1. Factors determining acute insulin physiological need and effect.

Factor	Impact or effect
Nutritional	
	Rate of gut absorption of nutrients (fasting = zero)
	Meal composition effects:
	Gastric emptying
	Nutrient absorption rate
	Incretin secretion
	Carbohydrate and fatty acid supply to liver
	Hepatic autoregulation of glucose production
	Glucose and amino-acid effects at the islet β cell
	Portion size
	Alcohol inhibition of gluconeogenesis
Physiological state	
	Physical activity
	Acute exercise
	Previous activity affecting insulin sensitivity
	Diurnal metabolic state
	Meal glucose tolerance
	Night-time changes in hepatic glucose production
	Hormonal cycles and state
	Female monthly
	Puberty-related
	Pregnancy
	Emotional state affecting adrenergic nervous system
Pathophysiological and disruptive	
	Insulin insensitivity secondary to calorie excess, long-term ('obesity')
	Previous (within 24 h) hypoglycaemia
	Metabolic stress (illness; trauma, including surgery)
	Hormonal disturbance (adrenal axis; growth hormone)
	Drug therapy
	Glucose-lowering
	Non-diabetes therapies (including hormonal, antipsychotics, retroviral)
	Recreational
	Travel and changes in time zones

Physiologically, changes in these factors are modulated by the islet β-cell response, increasing or reducing insulin secretion to match lower or higher plasma glucose concentrations, or in response to other hormonal changes or exercise [15–17]. None of these responses can be replicated through the delivery of subcutaneous exogenous insulins with improved plasma profiles, although avoidance of hyperinsulinaemia (e.g. postprandially or in the middle of the night) can ameliorate the risk of low glucose levels. Future solutions will depend on feedback control of insulin delivery ('closed-loop') [18], glucose-sensitive insulins [19], or engineering of cells to mimic islet β cells [20].

Subcutaneously delivered insulin is absorbed into the peripheral rather than the portal circulation. Whether or not this is important will not be further discussed in the present review, but again it is not addressed by absorption profile. There are likely to be consequences, however, for nocturnal versus daytime hypoglycaemia and peripheral versus central fat deposition (and thus body weight) [21,22].

Accordingly, average plasma glucose and insulin profiles are not typical of any individual, with further variance occurring in the same individual on different days; however, in trying to design an insulin delivery profile to give the best glucose control, it is appropriate to aim for average physiological profiles, while also aiming to minimize the variability of insulin absorption.

Average Physiological Basal Insulin Profile

In a lean person with a healthy pancreas, insulin is released continually at a near constant rate (ignoring pulsatility) during the basal state after food absorption ceases, often 3–5 h after a meal [23]; thus, nocturnally, and before breakfast, plasma insulin concentrations remain constant in young adults, as do C-peptide concentrations, suggesting unchanging insulin secretion (Figure 1) [23,24]. These individuals do not show any tendency towards reduced insulin secretion in the middle of the night, or increased insulin secretion or plasma glucose at the end of the night [23].

This contrasts with pumped insulin delivery, where insulin requirements often change between the middle of the night and breakfast, with hepatic glucose production rising before breakfast [25]; however, this only occurs when hepatic glucose production and plasma non-esterified fatty acid levels are above normal, and if these are strictly normal, this 'dawn phenomenon' is not evident [25]. In a study of night-time open- and closed-loop insulin delivery, there was no trend for change in insulin requirement overnight, although some individuals became hyperglycaemic on open-loop insulin later in the night [18].

Clinically, most people are hypoinsulinized, as evidenced by hyperglycaemia [26,27], so their ideal insulin profile is not the flat profile found physiologically. As changes in hormones, notably cortisol, could stress metabolism towards breakfast, any tendency for clinical insulin delivery to wane, as with neutral protamine Hagedorn (NPH) insulin, is likely to show exaggerated hyperglycaemia before breakfast [28,29].

During meals, pumped insulin and injected depot insulin delivery differ. For a pumped insulin, the basal rate can be subsumed into the meal insulin delivery profile (in effect, switched off), while an injected basal insulin will continue to be absorbed. Physiologically, however, this should not matter, as a primary action of meal-time insulin is to suppress hepatic glucose production, either directly or through suppression of peripheral fatty acid release; both basal and meal-time injection can contribute to this [30]. If this continuing basal insulin is included in any calculation, then it accounts for around half of total daily insulin secretion, consistent with modern insulin pump and injection studies [23].

Even a perfectly flat and unvarying basal insulin profile can cause hypoglycaemia, notably if hepatic insulin sensitivity is changed by previous exercise, or if previous hypoglycaemia blunts counter-regulatory responses [31,32]. If a basal insulin profile is not flat, then either it will not control hepatic glucose production adequately – notably before breakfast – or it will oversuppress glucose production in the basal period. If, in any individual, insulin requirements are lower in the middle of the night and higher at the end of night, then a non-flat insulin profile may be harnessed to good effect by timing the injection

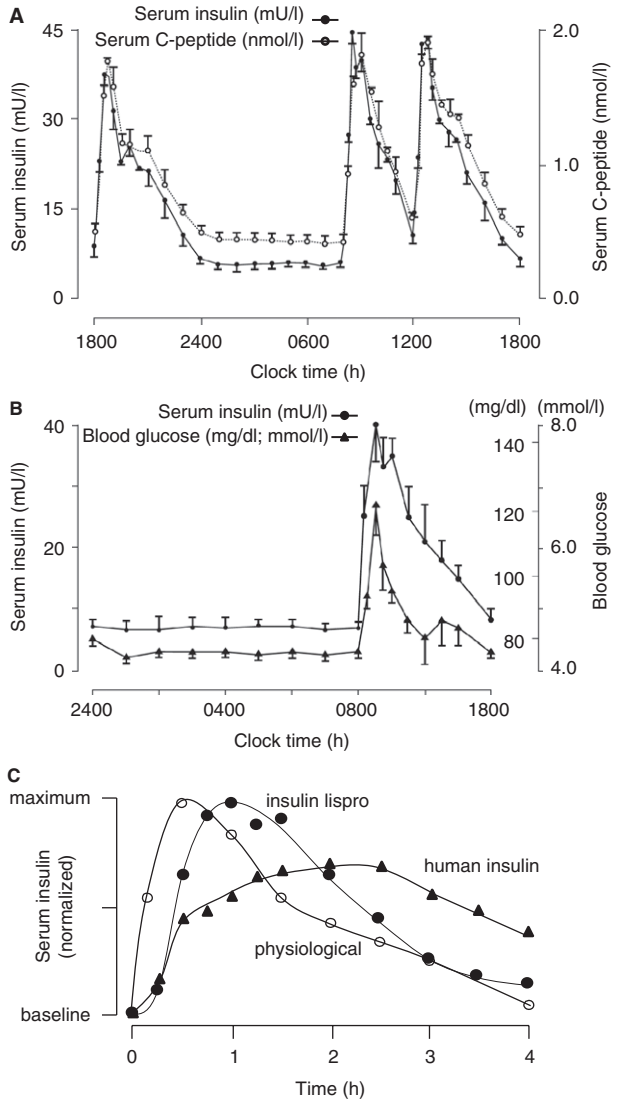

Figure 1. (A) 24-h serum insulin and C-peptide profiles in healthy people and (B) overnight and peri-breakfast serum insulin and blood glucose profiles in the same group of people (after Ref. [23], with permission). (C) 4-h physiological plasma insulin profiles plotted together with pharmacokinetic profiles for insulin lispro and human insulin in type 1 diabetes; the insulin lispro profile is normalized for excursion to the physiological profile to allow direct comparison of shape (after Ref. [24], with permission).

appropriately, e.g. by giving insulin glargine 100 U/ml during the evening [28,33]. Demonstrating this effect with insulin detemir, however, has been unsuccessful in type 2 diabetes [34]. Pump regimens often adopt non-flat profiles in type 1 diabetes to improve end-of-night control [35].

Average Meal-Time Insulin Profile

As with basal insulin secretion, meal-time insulin secretion is pulsatile, and regulated on a timescale of 3–10 min [36]. Ingestion of an oral glucose load, or administration of intravenous (i.v.) glucose as a bolus or square wave, cannot imitate physiological insulin delivery at meal times [36]. Glucose loads lack other nutrients, which may also affect stomach emptying (fat) or insulin secretion (amino acids) (Table 1). Food taken orally will result in 'anticipatory' insulin secretion through learnt reflexes, and notably by incretins secreted from the gut wall [37]. It is estimated that as much as 70% of postprandial insulin secretion can be accounted for by the incretin effect [38]; however, a primed i.v. dose of glucose will elicit a very rapid 'first-phase' secretion of insulin, showing that the islet β cells contain a depot of presynthesized insulin ready for immediate secretion into the bloodstream [39].

Figure 1A shows a mean 24-h insulin/C-peptide profile in healthy individuals after high-carbohydrate meals; Figure 1B focuses on the insulin/glucose profile during the overnight and breakfast period [23]. These results will not necessarily apply to an individual's meal intake in the real-world setting, where the composition and size of meals vary. Meal size might only affect the magnitude of the response, while meal composition, including the nature of the carbohydrate ingested [40], may affect the duration of the profile. Furthermore, insulin responses to meals may vary within individuals, with relative glucose intolerance in the afternoon [12,41] and after other lifestyle changes, as well as between individuals (Table 1).

Pathophysiological Plasma Insulin Profile in People with Diabetes

Type 1 Diabetes

Destruction of pancreatic β cells in individuals with type 1 diabetes will generally progress to a state of near total insulin deficiency, although perhaps not at the rates previously believed [42–44]. Consequently, exogenous insulin must attempt to fulfil all of the need for the absent endogenous insulin, while avoiding any significant risk of hypoglycaemia. This is currently an impossible challenge because of the multiple factors that influence insulin requirements (Table 1). The difficulty of achieving glucose control with exogenous insulin, even in the clinical laboratory, is highlighted by noting that both open- and closed-loop insulin delivery can maintain average glucose control through the night, but with a much greater variance (high and low) for open-loop control towards morning, and high hour-to-hour variation of closed-loop insulin delivery [18].

Type 2 Diabetes

In type 2 diabetes, assessment of defects in insulin secretion is complicated by the marked degree of insulin insensitivity, both basally and after meals. Accordingly, plasma insulin concentrations are a poor guide to islet β-cell dysfunction; indeed, plasma insulin concentrations may be high basally, when allowance for insulin insensitivity shows gross deficiency in insulin secretion [45] (Figure 2). Published insulin profiles after meals or glucose lead to the obvious conclusion that meal-time insulin secretion is slow in rising, leading some to mistakenly conclude that this is the earliest observable defect in people progressing to type 2 diabetes [46]. Studies using an i.v. glucose challenge show an absent initial response once fasting plasma glucose has increased to as little as 6.4 mmol/l [47,48].

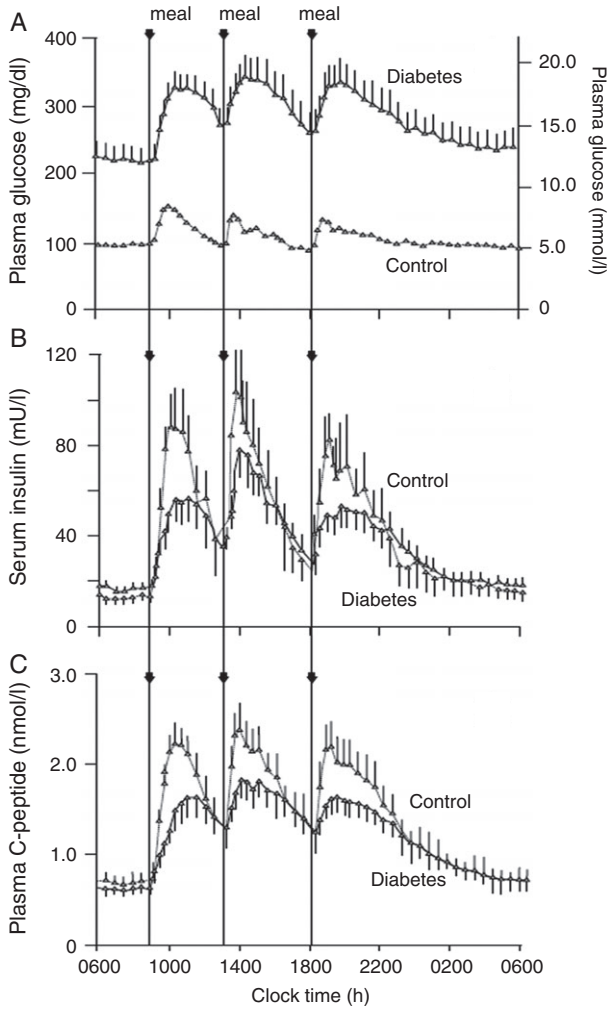

Figure 2. (A) 24-h plasma glucose, (B) serum insulin, and (C) plasma C-peptide profiles in people with type 2 diabetes and controls without diabetes. After Ref. [52], with permission.

It has been suggested that postprandial hyperglycaemia is more marked than basal hyperglycaemia in early type 2 diabetes, although this has been disputed [49,50]; however, by the time insulin is started in clinical practice, the major defect is usually in basal blood glucose control [51]. Figure 2 neatly illustrates the dilemma of interpretation here [52]. The C-peptide curves could be interpreted as showing a mostly meal-time insulin secretory deficiency, of up to ~50% of normal, with a slow rise to peak [52]; however, it is clear from the plasma glucose curves that these individuals have a marked defect in basal blood glucose control, which accounts for most of the area under the curve above the normal glucose profile [52]. Hyperglycaemic clamp data would suggest that raising plasma glucose in people without diabetes to these basal levels (16–17 mmol/l) would raise insulin secretion more than threefold in the steady state [53], in contrast to C-peptide levels, which are essentially normal or barely raised. The same group reported elevated 24-h insulin secretion rates compared with people without diabetes, but <60% of levels in an obese group with no diabetes [54].

Table 2. Factors determining the effects of subcutaneously administered insulin.

Variations in insulin requirement*
Minute-to-minute
Day-to-day
Longer-term
Insulin dose
Insulin absorption profile
Basal
Activity through to 24–30 h
Peak to 24 h ratio
Inappropriate timing of peak
Meal-time
Delay before absorption commences
Rate of rise to peak
Rate of fall back to basal levels (too long or short)
Overlap issues between basal and meal-time insulins
Buffering ability of endogenous insulin supply
Islet β-cell function
Progression of dysfunction
Variability of absorption (day-to-day or meal-to-meal)
Circulating pool (albumin-bound insulins)
Injection site
Region
Injection-site damage
Injection-site blood flow
Insulin organ specificity

*See Table 1.

Challenges in Mimicking the Physiological Insulin Profile

A goal of insulin therapy should then be to provide as close to possible optimal glycaemic control, in the absence of feedback control, by mimicking the physiological pattern of insulin secretion, in terms of both basal and prandial insulin profiles. It is not known to what extent perfect average glucose profiles would achieve near-normal glucose control or reduce hypoglycaemia, and this would in any case vary by individual, but it is probably unrealistic to expect hypoglycaemia reductions of even 50% from current rates. Exogenous insulin delivery should perhaps reflect the continuous release of basal insulin by the pancreas, with allowance for diurnal requirements, and approximate both the rapid rise in secretion in anticipation of or during gut intake of food, and also the appropriate fall-off in insulin secretion after meals (Figure 1, Table 2). The latter is important because insulin has a half-time of action of ~20 min, despite a plasma clearance of 4–5 min [24], so the meal-time surge can result in hypoglycaemia after meals, even in people without diabetes (reactive hypoglycaemia) if gut absorption of foods is relatively brief [55].

In addition to physiological changes in insulin sensitivity, diurnal variations, effect of meal composition, and effect of previous hypoglycaemia (discussed above), gastric emptying can also be disturbed in people with diabetes [56]. In practice, however, all these issues can be difficult to address prospectively (Table 2). Hence, in type 1 diabetes, many clinicians advise an initial goal of a flat basal insulin profile, with rapid-acting meal-time insulin, and then develop the insulin regimen iteratively, according to glucose-monitoring patterns.

The challenges of erratic insulin absorption or erratic control of unexplained cause both require a similar approach. Apart from feedback delivery by pancreas or islet transplantation, even a 'perfect' insulin profile will not resolve either issue, but clearly minimizing the deviation from such a profile will reduce the risk that other factors will raise or lower insulin levels to a degree that might result in hyper- or hypoglycaemia. Addressing conventional factors, such as avoiding scarred injection sites, injecting within one region of skin, reaching a consistent injection depth, avoiding leakage, and minimizing temperature fluctuations at injection sites remains appropriate (Table 2) [57,58].

Achieving a Physiological Plasma Insulin Profile

Matching changing day-to-day requirements can then only be met by innovative approaches that restore feedback control and by providing the food reflex and incretin signals. Closed-loop glucose control has a 40-year history, but the delays involved with subcutaneous sensing and insulin delivery will continue to cause difficulties with meal-time insulin delivery and acute exercise, i.v. sensing and insulin delivery still being impossible. Little published information yet exists in people with diabetes on the glucose-sensitive insulins, or for engineered islet β cells [20].

Nevertheless, there have been notable improvements in available insulins for subcutaneous injection and infusion therapy, improvements that mostly address the issue of average plasma insulin profile, and to a lesser extent, variability of absorption (Table 3).

Basal Insulin Therapy

Extensive attempts were made in the 1930s and 1940s to extend the action of unmodified insulin, but only protamine- (NPH insulin) and zinc-based products stayed the course (Table 3). Zinc insulins have since largely been withdrawn because of incompatibility with fine-bore injection needles; however, neither NPH nor the zinc (Lente) series achieve anything like a flat insulin delivery profile, typically with peak plasma insulin concentrations at ~5 h after administration, and declining to ineffectual levels even by 10–12 h, although with high inter-patient variation [59,60]. Such a profile is a bad mismatch with high insulin sensitivity during the night, or rising requirements at dawn, and the consequences are nocturnal hypoglycaemia and pre-breakfast hyperglycaemia. Difficulties in resuspension of a complexed insulin may contribute to erratic insulin delivery. Nevertheless, the NPH approach has, until very recently, remained the standard for newer premixed insulins, albeit with the insulin in the complex being an insulin analogue.

Many attempts were made from 1970 to 2000 to develop new basal insulins with longer – and thus flatter – profiles, but these largely floundered because of erratic absorption and poor bioavailability [61]. Some success was gained around 1995 by the approaches used for insulin glargine (soluble *in vitro* at acidic pH, microprecipitation at neutral pH in tissues) and insulin detemir (derivatization with a fatty acid moiety to promote albumin binding, thus delaying absorption), both having flatter profiles than NPH insulin (Table 3) [60,62]. While neither is a true 24-h insulin in people with type 1 diabetes [63], both will ensure night-time coverage if given in the evening, and the shorter absorption profile of insulin detemir may be compensated for by the intravascular albumin binding that will buffer erratic changes in insulin absorption [60,64].

A problem with long-acting analogues is assessment of duration of action. Logically, it might seem that glucose-clamp glucose requirement at 24 h or beyond is the appropriate measure; however, by that time, the study participant's metabolism is abnormal because of prolonged fasting (apart from clamp glucose infusions). As a result, while comparative studies may show differences between insulins, absolute duration (ability to control glucose levels to normal at 24 h in normal life) is not measurable, although could be achieved by injecting in the morning, feeding as normal during the day and clamping

Table 3. Approaches to achieving a more physiological profile from subcutaneous insulin delivery.

Product	Mode of action
Basal insulins	
NPH insulin	Protamine crystal suspension
Lente insulin series	Zinc complexes, amorphous and crystalline
Pumped insulin	Continuously pumped insulin delivery
Insulin glargine 100 U/ml	Basic amino acid derivatization, microprecipitation on injection
Insulin glargine 300 U/ml	Basic amino acid derivatization, compact precipitation on injection
Insulin detemir	Fatty acid derivatization, tissue albumin binding
Insulin degludec	Fatty acid derivatization, tissue multihexamer formation
Pegylated lispro	PEG derivatization, tissue diffusion limited
Meal-time insulins	
Insulin lispro	Amino acid substitutions, monomeric in tissues
Insulin aspart	Amino acid substitutions, monomeric in tissues
Insulin glulisine	Amino acid substitutions and reformulation, rapidly monomeric in tissues
EDTA/citrate human insulin	Chelation of metal ions, rapid dissociation of insulin hexamers
Insulin with hyaluronidase	Increased permeability of tissue injection site
Faster-acting insulin aspart	Amino acid substitutions plus reformulation; rapid dissociation in tissues and possibly enhanced absorption into circulation
Controlled action insulin	
Smart insulins	Compete with glucose for lectin clearance from circulation, thus higher plasma concentration with hyperglycaemia
Closed-loop pumped delivery	Glucose sensor-controlled insulin pumps
Bioengineered islets	Restoration of feedback control of insulin secretion and synthesis

only overnight. Researchers often report time to inability to maintain plasma glucose using a level well above target levels, thus biasing the study in favour of the insulin [60,65]. An additional problem is that, while the ideal platform might seem to be totally insulin-deficient type 1 diabetes, reported clamp glucose requirements in this population are often rather erratic [66]. Indeed, European regulators suggest that clinically unacceptable 95% confidence intervals of 80–125% are pragmatically acceptable as showing similarity between insulin products [67]. Accordingly, better judgement might be based on pre-breakfast plasma glucose control 24 h from the last injection.

When used with rapid-acting insulin analogues, both insulin glargine and insulin detemir provide improved glycated haemoglobin (HbA_{1c}) and less nocturnal hypoglycaemia in people with type 1 diabetes when compared with human insulin regimens [33,62,68]. A recent manufacturer-supported systematic review showed similar or better glycaemic control, reduced within-person variability, similar or reduced frequency of hypoglycaemia and less weight gain with insulin detemir compared with NPH insulin [69]. In type 2 diabetes, the situation is complicated by the buffering effect of endogenous insulin secretion, and some reimbursement authorities believe that basal analogues have no advantage over NPH insulin, despite treat-to-target studies showing less nocturnal hypoglycaemia. In a Cochrane analysis, no significant difference was found in glycaemic control between insulins glargine and detemir in people with type 2 diabetes, as measured by HbA_{1c}, between-day variability of fasting plasma glucose, or consistency of glucose concentrations over 24 h [70]. Detemir was associated with lower weight gain, whereas glargine was associated with a lower basal insulin dose [70].

Because neither insulin detemir nor insulin glargine 100 U/ml are true 24-h insulins in people with type 1 diabetes, a single injection may not provide full coverage in some individuals. Furthermore, they may not be suitable for morning injection or allow the injection-time interval to be beyond 24 h, as sometimes occurs in normal life; however, these insulins are better matched to diurnal changes in insulin sensitivity if given in the evening, perhaps even more so than would be the case with a perfectly flat insulin profile. Furthermore, it is still evident that within-individual variability is a problem from the average pre-breakfast glucose levels reported in clinical trials – still around two-thirds higher than the normal level [27,71,72]. Accordingly, attempts have been made to extend action further, for example, with the development of insulin degludec [27,71,73], insulin glargine 300 U/ml [65,72], and pegylated lispro [21,22].

The absorption profile of insulin degludec, an acylated analogue of human insulin, is convincingly longer than 24 h, with a half-life of ~25 h (vs 13 h for insulin glargine 100 U/ml) [74]. This is confirmed by studies of extreme flexibility of injection times, which show no major detriment [75]. Interestingly, the mechanism of delayed absorption is very different from that of insulin detemir, the cartridge/vial dihexamers self-associating subcutaneously into long-chain multihexamers, which slowly disassociate from their ends [76]. This provides essentially zero order kinetics, not changing with depletion of the injection depot until towards the end of the profile. The acylation should mean that, as with detemir, there is some albumin buffering of any erratic absorption. This may also be reflected in the results found in controlled trials versus insulin glargine 100 U/ml, where HbA_{1c} is unchanged (because of a treat-to-target approach) but nocturnal hypoglycaemia is reduced [27,71,73]. Insulin doses do not rise with insulin degludec despite the longer subcutaneous residence time [26,27]. Speculatively, this may be because the multihexamer structures pack tightly and consistently with fatty acid chains externally [76], perhaps protecting against tissue peptidases.

Insulin glargine 300 U/ml shows a much lower peak-to-trough ratio than glargine 100 U/ml in clamp studies and, thus, better 24-h efficacy in glucose control [65]. Published studies in very obese, high-dose-requiring people with type 2 diabetes show reduced nocturnal hypoglycaemia in the context of unchanged overall glucose control (HbA_{1c}) [72,77]. Further studies appear underpowered for any putative advantage for hypoglycaemia [78,79], although comparison of continuous glucose monitoring profiles in type 1 diabetes versus glargine 100 U/ml does suggest much more consistent 24-h action after one injection [80].

Pegylated insulin lispro is an ultra-long acting basal insulin, but is also designed to be hepato-selective (not discussed here, but not necessarily an advantage). Again, clamp data appear to confirm an advantage over insulin glargine 100 U/ml [81,82], with an apparently very long duration of action. Phase II and III trials show a reduction in nocturnal hypoglycaemia, but daytime events may be increased [21,83], presumably because of suppression of counter-regulatory hepatic glucose production.

Meal-Time Insulins

The kinetic properties of the rapid-acting insulin analogues have been reviewed elsewhere [24]. These insulins incorporate amino acid substitutions that result in a primarily monomeric form in subcutaneous tissue (Table 3). The pharmacokinetic profiles are much more similar in duration to the average meal-time endogenous insulin profile than for unmodified human insulin, although still with a lag after injection and delayed time to peak concentrations (Figure 1C) [24]. These properties have been used to promote administration closer to meal-times, provide better postprandial plasma glucose control and a lower risk of late-postprandial hypoglycaemia compared with unmodified human insulin [24]. Glulisine, because of formulation changes, shows faster onset of action in pharmacokinetic and pharmacodynamic studies than insulin aspart or insulin lispro, especially in obese people, but it has not been possible to show that these differences are clinically meaningful, such that the overall plasma glucose profile appears similar [24]. Currently, when used with the long-acting basal insulins and compared with human insulin (meal-time and NPH), aspart and lispro have been shown to be superior for both HbA_{1c} and nocturnal hypoglycaemia (in the same study) in RCTs in people with type 1 diabetes [33,62,68].

Rapid-acting insulin analogues appear to be advantageous compared with human insulin in CSII. A meta-analysis of studies comparing these approaches concluded that analogues provide modest but significantly better reductions in HbA_{1c} and

are preferred by users [84]; however, the half-time of absorption of insulin analogues is not changed between pumps and injections (~45 min), meaning that it is still many times that of clearance of i.v. insulin (<5 min), and thus imposing limitations of the speed of response of closed-loop systems [85].

Unlike CSII, which when properly managed can give near-normal average pre-breakfast glucose levels, current injection therapy with basal analogues results in fasting hyperglycaemia in type 1 diabetes, indicating hypoinsulinaemia [27,71,72]. Accordingly, breakfast meal-time insulin has a dual task in dealing with the breakfast calorie load and correcting basal hypoinsulinaemia. In this situation, the failure of current rapid-acting insulin analogues to provide a physiologically rapid rise in plasma insulin concentrations is a double problem, even if the duration of action of ~4 h is appropriate (Figure 1C). Hyperglycaemia after breakfast is therefore usual, and can cause problems later in the day, as the breakfast insulin injection dose needs to be higher than otherwise necessary.

Current developmental approaches to the problem of faster onset of absorption include modified excipients and enabling of tissue diffusion (Table 3). Afrezza® human insulin inhalation powder is now marketed in the USA [86]. Absorption across the respiratory epithelium is ultra-rapid, but also of short duration, providing effective control of postprandial plasma glucose in some people with type 2 diabetes [87]. Issues remain over dose flexibility, administration of larger doses, use in type 1 diabetes, and safety concerns regarding the lung [88]. Another approach under investigation is the addition of hyaluronidase to insulin preparations. A clamp study examining the addition of recombinant human hyaluronidase to a rapid-acting analogue demonstrated a 13–25-min faster onset and 40–49-min shorter mean duration of insulin action [89]. Biodel insulins (such as BIOD-123 and BIOD-531) use EDTA/citrate to promote tissue dispersion of insulin monomers, and have been reported to have rapid absorption and decline from peak concentrations, or better post-meal glucose control, compared with insulin lispro [90,91].

Faster-acting insulin aspart is a new formulation that uses arginine as a pharmaceutical stabilizer and nicotinamide to enhance initial absorption after injection [92]. As well as earlier plasma insulin exposure after injection in people with type 1 diabetes, this insulin produces a significantly greater early glucose-lowering effect after a test meal than conventional insulin aspart [92]; clamp glucose infusion rates suggest that insulin action continues for ≥4 h. Very preliminary results from clinical trials appear encouraging [93].

Conclusions

The ideal insulin profile for any individual with diabetes will change from day to day and also within the day, due to lifestyle changes and metabolic influences, such as previous hypoglycaemia, and will only ever be attained using technologies sensitive to immediate changes in glucose concentration. In the meantime, it is logical to aim for average physiological profiles, with an awareness that hyperglycaemia can itself alter the diurnal pattern of insulin requirement. Current approaches include the accomplishment of basal insulins with completely flat insulin delivery over an extended day, and targeting of post-meal glucose control by faster-onset meal-time insulin analogues; however, other targets for insulin therapy, including minimizing day-to-day variation in absorption, potential to cause weight gain, and perhaps organ selectivity, also deserve consideration. New types and formulations of ultra-long-acting analogues and, for prandial control, fast-acting analogues based on more active dispersion of insulin monomers, enhanced absorption, or alternative delivery routes, exemplify such approaches. While these improvements are very welcome, glucose control in most people with type 1 diabetes still results in levels that are far from normal, emphasizing the need for continued investment in supporting activities to improve patient education and provide more informative glucose monitoring. The scope for continued technological innovation remains broad.

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Conflict of Interest

P. H., or institutions with which he is associated, receive funding from potential and actual insulin manufacturers Antriabio, Biocon/Mylan, Eli Lilly, Hanmi, Merck (MSD), Novo Nordisk and Sanofi, and competitor companies with non-insulin products, for his research, advisory and lecturing activities.

P. H. wrote most of the text of this manuscript, contributed the ideas and opinions that are guaranteed as his own or endorsed by him when referenced to others, has published some of the original research underpinning the topic, and directed choice of source materials and referencing.

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