Minimising hypoglycaemia in the real world: the challenge of insulin

Chantal Mathieu¹

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Abstract

Insulin therapy has been a life saver for people with type 1 diabetes and has been an essential tool in the therapy of people with type 2 diabetes, but the risk for hypoglycaemia has been a major hurdle to achieving good glycaemic control for most. Insulin analogues, the availability of novel technologies for the administration of insulin, like insulin pumps, and, in particular, tools to measure glucose levels, evolving from capillary measurements to continuous glucose monitoring, have revolutionised the way in which people living with diabetes use insulin. Novel insulin concepts, like once-weekly or oral insulin administration, will have to demonstrate safety on the side of hypoglycaemia before they will be able to move into the clinic.

Keywords Hypoglycaemia · Insulin · Insulin analogues · Real world · Review

Abbreviations

CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
GLP-1	Glucagon-like peptide-1
rtCGM	Real-time CGM
SGLT2	Sodium–glucose cotransporter 2
TIR	Time in range

Introduction

Since its first clinical application in 1921, insulin has become a widely prescribed glucose-lowering agent in people with diabetes. The purpose of using insulin is quite different depending on the situation: in people with type 1 diabetes or those who have lost pancreatic beta cells due to other causes, insulin is a life-saving therapy, where the goal is to mimic the physiological profile of insulin secretion of the original beta cells. Typically, beta cells would provide a variable basal insulin secretion, with the goal of keeping the body in an anabolic state. Intricate glucose sensing in the beta cells and neural mechanisms continuously feed back to the beta cell, thus allowing adaptation of basal insulin

secretion to the body's needs. Thus, in periods of low glucose supply or increased peripheral glucose use, insulin secretion would shut down, eventually being accompanied by increased counter-regulatory hormone (e.g. glucagon) secretion to prevent blood glucose levels from falling and to avoid hypoglycaemia. In addition, feedback signals from the brain and gut, together with rising blood glucose levels, would stimulate insulin secretion at mealtimes, leading to disposal of glucose in the liver, muscle and adipose tissue [1].

In type 2 diabetes, insulin therapy can also be given to replace failing insulin secretion by the beta cell, but often it is given as a supplement in severely insulin-resistant individuals where non-insulin therapies do not suffice to achieve tight glycaemic control [2].

The needs of the insulin formulations used in these different situations will, thus, differ. However, a major challenge common to all people using insulin is the fact that, to date, insulin is administered peripherally, whereas endogenous insulin is secreted directly in the portal system, ideally for targeting the liver, the primary target organ of insulin action. In most patients, this leads to over-insulinisation of peripheral organs (muscle and adipose tissue) while trying to achieve the desired hepatic insulin effect. Typically, this leads to undesired weight gain, both in people with type 1 diabetes and type 2 diabetes. The biggest challenge of present-day insulin formulations is, however, the risk of hypoglycaemia due to lack of feedback of ambient glucose levels for the amount of insulin released from the site of injection into the blood.

✉ Chantal Mathieu
chantal.mathieu@uzleuven.be

¹ Department of Endocrinology, UZ Gasthuisberg, KU Leuven, Leuven, Belgium

Hypoglycaemia: what it means

Defining hypoglycaemia proved to be a challenge, with learned societies issuing different descriptions, some using absolute glucose values, others symptoms to define levels of hypoglycaemia. In 2017, the International Hypoglycaemia Study Group proposed a workable definition, with three different levels of hypoglycaemia [3]. Levels 1 and 2 are linked to specific blood glucose cut offs, whereas level 3, severe hypoglycaemia, is defined just by clinical presentation and not linked to a blood glucose level. Level 1 (<3.9 mmol/l glucose) is to be considered an alert value for patients and clinicians and can prompt action, eventually including alterations in insulin dose or type. In contrast to level 1, where symptoms may not be present, level 2 (<3 mmol/l glucose) denotes impaired cognitive function and is considered serious, requiring immediate action to resolve the hypoglycaemic event. Level 3, or severe hypoglycaemia, is a severe event characterised by altered mental and/or physical functioning, coma or seizure that requires assistance from another person for recovery. These cut offs and definitions have been incorporated since their publication in clinical guidance documents worldwide. They have been used for defining the time(s) below range(s) in the metrics for continuous glucose monitoring (CGM) and have appeared, for instance, in the ADA standards of care since 2019 [4].

A major clinical problem is the phenomenon of ‘hypoglycaemia unawareness’, whereby the person experiencing the hypoglycaemic attack does not feel that hypoglycaemia is happening. This brings the person treated with insulin into a dangerous situation, in particular into level 2, where cognitive function is impaired and impacts, for instance, driving skills or other intellectual capacities, without the person being aware of the limitations, thus endangering the patient and even others. The frequency of these asymptomatic hypoglycaemic periods has been revealed by the use of CGM [5].

The impact of hypoglycaemia on the life of people living with diabetes is not to be underestimated. In both type 1 and type 2 diabetes, severe hypoglycaemia is linked to increased risk of mortality and morbidity [6] and is associated with an increased societal cost due to hospital and emergency room (ER) admissions, but also due to work absenteeism [7]. However, minor hypoglycaemia and, in particular, hypoglycaemia unawareness also has an impact on quality of life of people with diabetes [8], leads to fear of hypoglycaemia and contributes to insufficient glucose control by defensive down-titration of insulin doses [9, 10].

Striking the right balance between tight glycaemic control and hypoglycaemia prevention

During the past decades, insulin preparations have evolved from purified animal insulins to human insulins (produced by genetically modified organisms) and then insulin analogues, with each approach being better than the last with regard to the desired physiological profile of insulin secretion by the beta cell. However, the ideal insulin preparation that caters for all remains elusive [11].

Therefore, people treated with insulin have had to learn to live with the limitations of the resulting insulin profiles, which do not completely fit mealtime glucose curves or fail to cover basal insulin needs in a stable way. Thus, education and motivation through patient empowerment have been central to diabetes care for those on insulin. The advent of novel insulin analogues or new formulations of existing ones, with profiles better suited for the clinical demands, as well as novel technologies for insulin delivery, have improved the lives of those treated with insulin. In particular, the use of insulin analogues has allowed better personalisation of insulin therapy and more flexibility in lifestyle for many living with diabetes. Still, the ideal insulin replacement strategy has not been realised yet, and searches for adjunct therapies, added on to insulin, to limit side effects of our present insulin administration regimens, are being tested.

Education and motivation

Central to avoidance of insulin-induced hypoglycaemia in day-to-day life is education and motivation in those using insulin. Education for those using mealtime insulins should cover, for instance, a clear representation of the profile of the insulin, so that the person using the insulin can understand the need for proper timing of injection and the need to wait in between successive injections. Basal or premix insulin users should understand the duration of action of their insulin and learn how to adapt the dose to changing insulin needs, for example, when exercising. Also, emphasis on the need to collect information on glucose profiles is essential in people using insulin, and use of capillary blood glucose measurements or CGM is crucial, but it is only of value when it is linked to education on what to do with the collected glucose values. Intensive education on how to adapt mealtime insulin doses to glucose values, meal content, exercise or to changing day-to-day life should be available to all people using mealtime insulin. Also, practical tips and tricks are essential, like frequent injection needle change, avoidance of lipodystrophy and correct preservation of insulin preparations. These educational interventions are essential both in people with type 2 and type 1 diabetes, from young to old age [12, 13].

In people using insulin pumps (continuous subcutaneous insulin infusion [CSII]), specific attention should be given to the use of different bolus and basal profiles to allow adaptation of the insulin profile to the content or style of the meal (e.g., rich in protein and fat vs pure refined carbohydrates) or to the planned exercise (e.g., temporary basal rates) [14].

Even as progress in systems for automated insulin delivery through a combination of CSII with CGM reduce the burden of these insulin dose calculations, education, as well as motivation and support of the person needing treatment of insulin by a member of the medical team, will remain important.

Successful examples of educational programmes are the US blood glucose awareness training (BGAT) and the UK-originated Dose Adjustment for Normal Eating-Hypoglycaemia Awareness Restoration Training (DAFNE-HART) programme. These have demonstrated that hypoglycaemia rates in the real world can be reduced, even in those in whom hypoglycaemia awareness is impaired [15, 16].

Mastering the match between insulin profiles and insulin needs requires an enormous effort from the person treated with insulin and a complex set of skills for guessing the changes in insulin needs as a consequence of food intake, exercise, stress and many other factors, which has been mastered by few. Any minor error, such as failing to anticipate physical activity or miscounting carbohydrate intake, can lead to hypoglycaemic episodes, which are distressing to the person involved and, occasionally, dangerous. The margin for error is small, particularly if those affected are aiming for tight glucose targets and/or are affected by hypoglycaemia unawareness.

Insulin analogues

The purpose of manufacturing insulin analogues was to create insulin formulations that would better mimic the insulin profiles of the beta cell in normal physiology while administering the insulin preparations subcutaneously. The primary clinical aim of analogues was, thus, the avoidance of hyperglycaemia and to allow more people to achieve lower HbA_{1c} levels. However, the major benefit of the introduction of insulin analogues actually lies in the reduction of hypoglycaemic events and greater flexibility in lifestyle for people treated with insulin [11].

Sadly, these insulin analogues come at a higher price than human insulins and are not affordable to all. Biosimilar insulin analogues have been manufactured, somewhat reducing the price. For each individual patient, the advantages (more stable glycaemic profiles, lower risk of hypoglycaemia, more flexibility, often higher quality of life) will have to be weighed against the higher cost of these analogues. Clinicians should discuss value in terms of benefits with their patients, rather than pure cost of therapy.

Rapid-acting insulin analogues With the advent of lispro, aspart and glulisin insulin, a revolution happened in the life of people with type 1 diabetes [17]. Until then, clinicians urged them to take in-between meal snacks and, in particular, bedtime snacks to avoid late hypoglycaemic attacks, which occurred due to the action of subcutaneously administered human regular (conventional) insulin being too long (more than 4 h). When using the more rapid- and shorter acting analogues, these snacks became redundant. The biggest benefit of using rapid- and shorter acting insulin analogues both in trials and in the real world was the reduction in night-time hypoglycaemia. The problem, however, with the present-day rapid-acting insulin analogues is that clinicians and patients have overestimated their rapidity of onset and underestimated their variability and duration of action. Many people are, thus, injecting just before meals, or even after meals, leading to inadequate postprandial glucose control, with mealtime glucose peaks and post-meal hypoglycaemic attacks. In addition, use of CGM, with which people are now continuously seeing glucose swings, has led to the phenomenon of repetitive administration of rapid-acting insulin, particularly in pump users, with accumulation of insulin again ensuing in increased hypoglycaemia risk. Education to provide insight into the profile of the insulin used by the patient and guidance on how to use the particular insulin preparation are as important as the profile of the preparation itself.

Still, newer and ‘better’ preparations of insulin analogues are being proposed, resulting in insulins with an even faster onset and shorter duration of action, like the faster acting insulin aspart and the ultra-rapid-acting insulin lispro [18, 19]. These insulin preparations now provide a profile of mealtime insulin that has an onset of action just 5 min after the subcutaneous injection, peaking at 90 min and completely disappearing after 5 h [18, 19]. The impact of these even faster and shorter acting insulins on hypoglycaemia is limited and will depend on how they are used by the patient. In those using CSII, in particular (hybrid) closed-loop systems, these analogues may help to more closely mimic physiological insulin secretion of the beta cell, with more time in target blood glucose range and less time in hypoglycaemia [20, 21]. However, this will most probably depend on the performance of the algorithm in the system more than on the type of analogue used.

Basal insulin analogues The most dramatic impact of the introduction of basal insulin analogues for people with diabetes using insulin was the decrease in nocturnal hypoglycaemia as compared with when using human NPH insulin. This decrease was seen both in people with type 1 and type 2 diabetes and was attributed to the flatter insulin profile in the blood, resulting from more regular release of insulin from the depot injection site due to innovative prolongation techniques (e.g., shifting of isoelectric point and, thus, solubility at

different pH values for glargine, and di-heximerisation and albumin binding due to the presence of a free fatty acid link in detemir). However, perhaps even more important than the flatter insulin profile was the decrease in variability of release [9]. Pharmacokinetic studies showed a clear relationship between decreased variability in insulin release, more reliable insulin profiles and risk of hypoglycaemia, with an advantage of glargine over NPH insulin and, in turn, an advantage of detemir over glargine [22]. In particular, nocturnal hypoglycaemia risk is decreased with basal insulin analogues, with randomised trials reporting a 30% reduction in nocturnal hypoglycaemia in individuals with type 1 diabetes using glargine or detemir compared with NPH users [23, 24]. In people with type 2 diabetes using basal insulin only (a popular way to initiate insulin therapy in this population), considering the fact that mainly nocturnal hepatic glucose output is targeted, the reductions in hypoglycaemia risk with these therapies also stand on the forefront, with the historic Treat-to-Target Trial also reporting 30% reductions in (nocturnal) hypoglycaemia in individuals with type 2 diabetes taking basal insulin analogues vs those on NPH insulin [25]. Real-world studies confirmed these observations, showing that the less variable the insulin profile, the lesser hypoglycaemia risk, with the lower nocturnal hypoglycaemia risk particularly contributing to the rise in status of the basal insulin analogues to the preferred basal insulins [26, 27].

The latest generation of basal insulins, the more concentrated form of glargine (glargine U300) and insulin degludec, with even flatter, less variable and longer duration profiles, have again moved the needle forward with regard to nocturnal hypoglycaemia risk, with further reductions of 30% risk as compared with the first generation analogues being observed in head-to-head studies, and similar observations being reported in real-world studies [28, 29, 30, 31]. Another advantage of these very-long-acting insulin analogues, in particular insulin degludec, is the increased flexibility in the time of injection, again contributing to improved quality of life [32].

Novel technologies for glucose monitoring and insulin administration

The availability of capillary blood glucose measurement techniques was the prerequisite for use of intensive insulin therapy, but it has been the arrival of CGM, under the form of intermittent scanning CGM (isCGM) or real-time CGM (rtCGM), that has revealed the real impact of insulin therapy on glucose profiles in day-to-day life. As demonstrated in a real-world study in Belgium, the biggest impact of the introduction of rtCGM in the country was the reduction in hypoglycaemic events, accompanied by a reduction in hospital admissions and absence from work or school in people with type 1 diabetes using rtCGM vs those not using this system [33]. A worry with the novel technologies, however,

is the false reporting of low blood glucose levels due to underestimation of glucose levels in the lower range, leading to down-titration of insulin doses or defensive snacking. The ‘flat lines’ reported by sensors during the night are also notorious; these are induced, in part, by sleeping on the arm where the sensor is applied, leading to hypoxia at the sensor site and, thus, false reporting of hypoglycaemia. Again, education and instruction of patients using these technologies is of the essence. Still, despite these shortcomings, the availability of CGM systems, in particular the availability of alarm-equipped technologies, have altered the way clinicians and insulin-treated patients are titrating insulin. Presence of alarms and long-distance monitoring systems have, in most patients, installed a confidence to bring glucose levels down and up-titrate insulin, as the systems reduce the fear of hypoglycaemia in the majority of users [33]. Moreover, use of CGM allows prevention of severe hypoglycaemic attacks in people with type 1 diabetes, even in those with hypoglycaemia unawareness [34]. In addition, these technologies have highlighted to patients the shortcomings of even the modern insulins when it comes to covering glucose excursions during meals, and have motivated many patients to adapt the time of injection at meal-times to deal with postprandial hyperglycaemia and late hypoglycaemia risk.

The closed-loop systems, now available in their early stages as sensor-augmented pumps or hybrid closed-loop systems, will be yet another step towards better adaptation of insulin levels to the individual patient’s demands. Clinical trials and, in particular, real-world experience again show an important impact of these systems on the risk of hypoglycaemia, without compromising overall glucose control [35].

Alternative routes of insulin administration have been tested and, in particular, inhaled insulin was brought to market. However, issues of cost, uncertainty of long-term safety and hassle of use have led to most development programmes being stopped. One inhaled preparation (Technosphere insulin) remains available in some areas, with an interestingly rapid onset of action [36].

Reducing insulin needs

An alternative path that has been taken in type 1 diabetes, as well as in type 2 diabetes, is trying to reduce insulin needs or replace insulin altogether. In type 2 diabetes, the availability of other glucose-lowering agents, some of which have proven to go beyond glucose lowering and also have a direct impact on comorbidities, like cardiovascular disease (particularly heart failure) and chronic kidney disease, has changed the place of insulin in treatment algorithms. As such, insulin has been pushed back in priority, with drug classes like glucagon-like peptide-1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors moving to the front. Still,

the most recent ADA/EASD consensus highlights the importance of introducing insulin early on in the therapy of people with type 2 diabetes in specific circumstances, such as when in doubt on the diagnosis of type 2 diabetes, when symptoms of hyperglycaemia or catabolism are present or in pregnancy [37]. For the treatment of people with type 2 diabetes, combination preparations of insulin and GLP-1 receptor agonists are now available, allowing combination of these newer agents and insulin, resulting in improved glycaemic control, reduced weight gain and reduced hypoglycaemia risk compared with the use of basal insulin alone [38].

In type 1 diabetes, insulin is the mainstay of therapy, but adjunct therapies have been tested. The purpose of these adjunct therapies is not to replace insulin but to achieve equal or better overall glycaemic control (reduced HbA_{1c}), with more stable glucose curves (higher time in range [TIR]), less weight gain or less risk of hypoglycaemia. In particular, pramlintide, metformin and SGLT2 inhibitors have progressed to acceptance as adjunct therapies for type 1 diabetes by regulators or found their way into guidelines [39]. In particular, SGLT2 inhibitors have shown a clear effect on HbA_{1c} lowering and increased TIR (3.9–10.0 mmol/l [70–180 mg/dl]), while being insulin-dose sparing and resulting in reduced weight and systolic blood pressure in individuals with type 1 diabetes. The European Medicines Agency has approved use of dapagliflozin at low dose (5 mg) in people with type 1 diabetes and a BMI ≥ 27 kg/m² [40].

A major limitation with adjunct therapies is the increased risk of inducing ketosis through their insulin-sparing effect, reaching insulin doses that are insufficient to suppress peripheral lipolysis. This phenomenon, combined with the increase in ketosis directly induced by SGLT2 inhibitors, has hampered widespread use of SGLT2 inhibitors in people with type 1 diabetes, as these agents increase the risk for overt diabetic ketoacidosis by two- to fourfold [41].

Finally, GLP-1 receptor agonists have also been studied and are being used in clinic as adjunct therapies, primarily to induce weight loss. Studies show clear benefits, particularly in overweight type 1 diabetes patients but, to date, no label for use of these agents in type 1 diabetes is available [42].

The future for insulin and hypoglycaemia

One hundred years after the first clinical application of insulin, insulin is still very much alive as a therapy for people with diabetes. No substitution therapy is available and it does not seem that one will be available in the near future. Still, major innovations are to be expected in the manufacturing of insulins in the following years. In the short term, ultra-long-acting, once-weekly insulins will be available [43]. Most patients applaud this evolution, while most clinicians are sceptical, in particular because of fear of hypoglycaemia. It is hard to

envision how a once-weekly administration of a basal insulin would be compatible with the demands of more flexibility of basal insulin delivery in type 1 diabetes, where CSII has clearly been proven to be the answer to avoiding hypoglycaemia, for example, when exercising. There may be a sweet spot in people with type 2 diabetes where this weekly basal insulin could be exploited as a ‘supplement’ to other glucose-lowering therapies. Still, robust clinical trials will be needed to convince clinicians to use this tool in the real world.

However, when an ultra-long-acting insulin could be combined with another pipeline concept, namely glucose-sensing technology, we could be facing a completely new paradigm. For several years, a number of industry players have already begun exploring the potential to apply one or other ‘glucose-sensing’ tool to insulin, making delivery or action of the injected insulin dependent on ambient glucose levels, thus eliminating the risk of hypoglycaemia, as insulin would only be delivered or active when glucose levels rise. The road to this concept has, however, been one with many disappointments to date [44].

Another development in insulin discovery is oral insulin. Here, again, several early reports were encouraging but there was subsequent silence and arrest of programmes. However, no particular benefit on reduction of hypoglycaemia risk is to be expected with this route of administration. In fact, experts even predict an increased risk of hypoglycaemia as the absorption of orally administered insulin in the presence of food could be more fluctuating than that achieved upon subcutaneous administration [44].

There have been attempts to produce liver-preferred insulins, which would preferentially target the liver, thus, not only reducing weight gain, but also reducing hypoglycaemia risk. One product, peglispro, was terminated during a late phase. This product had clear liver-preferred action, with less weight gain and a trend to reduced hypoglycaemia risk, in particular nocturnal hypoglycaemia, as compared with glargine U100. However, the development of this programme was halted due to liver enzyme rises, suggesting direct liver damage [45]. At present, several liver-preferred insulins are still in development.

In addition, combination insulins are currently being further developed. On top of the combinations at hand, such as combining a rapid-acting with a long-acting insulin, or a basal insulin with a GLP-1 receptor agonist for once-daily injection, novel formulations, such as once-weekly basal insulin formulations with once-weekly GLP-1 receptor agonists, are being considered. These could help mitigate the theoretical increased hypoglycaemia risk of using a once-weekly basal insulin in people with type 2 diabetes.

Finally, the future may lie in technology, with the development of connected pens that will reflect time of injection of insulin and link it to CGM reports, allowing both patients and medical teams to track insulin injections and learn from their

effect on glucose excursions. This may help prevent hypoglycaemic events, as suggested by study findings [35]. The biggest hopes, in particular for people living with type 1 diabetes, are placed on the realisation of closed-loop systems. As discussed, present-day smart pumps and hybrid closed-loop systems allow people to more frequently achieve TIR (3.9–10.0 mmol/l [70–180 mg/dl]) and have less time in hypoglycaemia, but they require a lot of work and input by the patients themselves and intensive guidance by the diabetes team. The advent of real full closed-loop systems, with algorithms that can cope with mealtimes and adapt to changing demands for insulin during the life of people living with diabetes, taking into account exercise, emotions, stress, etc., may be the final step to full avoidance of hypoglycaemic risk despite insulin therapy. Again, the discussion of cost and value of such systems will need to involve the person being treated with insulin.

Conclusions

One hundred years after its first clinical application, insulin therapy has come a long way, with novel insulin analogues, adjunct therapies and novel technologies for insulin administration and glucose monitoring all contributing to better glycaemic control. This better glycaemic control not only means avoidance of hyperglycaemia and, thus, in the long run, complications of diabetes, but also avoidance of hypoglycaemia, with its dramatic impact on healthcare budgets and the daily life of people living with diabetes.

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