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The Evolution of Insulin

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Abstract

Patients with diabetes mellitus have been injecting insulin for the past 80 years, but the long-term complications of diabetes continue to cause significant morbidity and mortality. Good 'diabetes control', with near normal blood glucose levels, reduces the risk of long-term complications, but also increases the rate of hypoglycaemia and weight gain. This review looks at the normal physiology of endogenous insulin and how modifications have been made to manufactured insulin in order to mimic normal physiology. The properties of newer insulin products are examined to see where they might be advantageous for individual patients.

Key words: Insulin-dependent diabetes mellitus – Multiple injection regimens – Insulin analogues – Hypoglycaemia

Introduction

The incidence of insulin-dependent diabetes mellitus is increasing during childhood, particularly in children under the age of five years[1]. This provides new challenges in therapy for affected children.

The Diabetes Control and Complications Trial (DCCT), published in 1993, proved that improving blood glucose control reduced the incidence of long-term complications such as retinopathy, neuropathy and nephropathy[2,3]. The study included 15% adolescents from a total of 1441 patients, selected by their clinicians if they were considered sufficiently motivated to comply with the rigours of the trial. No children under the age of 13 were included and the selected population chosen means that it may not be possible to replicate the findings of the trial in the typical clinic population[4,5].

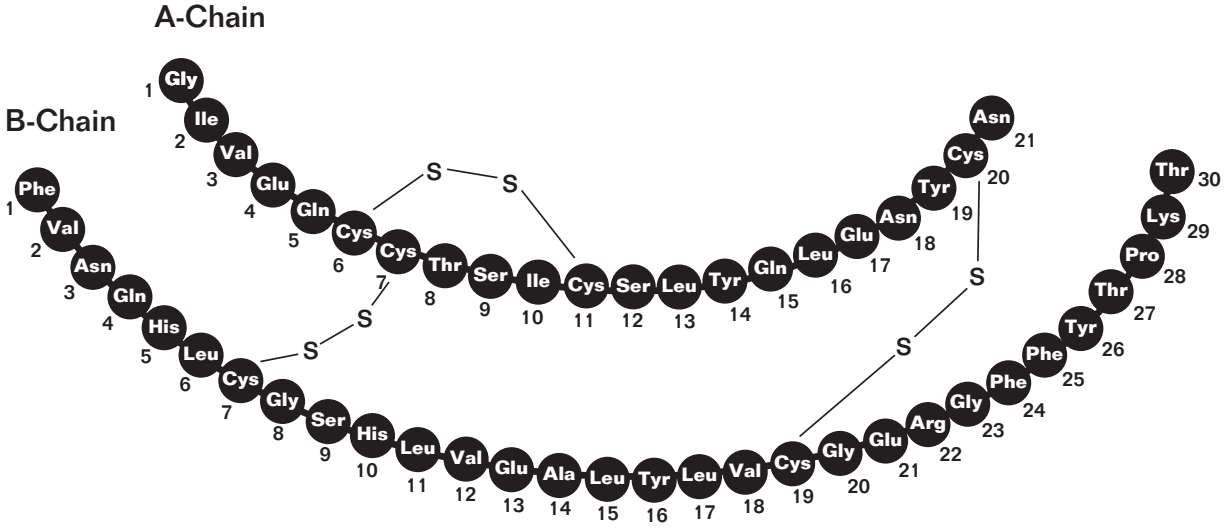

Figure 1. The structure of human insulin

However, the results showed clearly that an intensive insulin regimen, with support from a committed diabetes team, reduced the incidence of microvascular complications. It also demonstrated a slowing in progression of the pathological process when complications had already developed. The 'price' of this improved control was a three-fold increase in moderate and severe hypoglycaemia, as well as twice the incidence of obesity in the intensive treatment group of adolescents[4]. These are immediate complications greatly feared by adolescents, to whom long-term complications seem distant.

Clinicians should be aiming for good blood glucose control in older children, while considering ways of reducing the incidence of hypoglycaemia and excessive weight gain. Increasing hypoglycaemia in younger children, particularly those under the age of five years, is undesirable due to the risk of significant neurological and developmental impairment[4,6]. These are the patients with the longest duration of disease, and who consequently are at greatest risk of developing complications, so we need to find treatment that allows reasonable blood glucose control with few acute complications.

This review describes progressive changes in insulin therapy with respect to current aims of management of diabetes mellitus.

The Physiology of Normal Insulin Secretion

In order to understand the aims of insulin therapy, we need to consider the physiology of insulin secretion in a healthy individual.

Insulin is a small protein composed of two amino acid chains linked by di-sulphide bonds (Figure 1). It is synthesised in the beta cells of the pancreas, initially as pro-insulin, which is then cleaved to form insulin and the waste product C peptide. Insulin is then stored in secretory granules. Human insulin is monomeric and, once released into the blood stream, insulin that has not bound to receptors is rapidly degraded.

The main function of insulin is to allow storage of glucose as glycogen, so that it can be broken down for use as energy when blood glucose levels fall. Insulin is secreted at two levels – 'basal' and 'stimulated'.

Basal Insulin Secretion

Basal secretion of insulin occurs throughout the day when there is no excess of glucose in the blood. In the presence of this low level of insulin, the liver is unable to store glucose and glycogen is broken down producing sufficient glucose to provide energy for cerebral metabolism. Entry of glucose to the brain is not facilitated by insulin, but is dependent on extracellular levels. When insulin levels are low, growth hormone, glucocorticoids, adrenaline and glucagon are present, all of which increase blood glucose levels.

Stimulated Insulin Secretion

When carbohydrate is digested in the small intestine, the pancreas is stimulated to secrete insulin, which circulates in the blood attaching to receptors on liver, muscle and fat cells. Since glucose is absorbed into the portal circulation, the majority passes directly to the liver where insulin induces glucokinase, the first step in the production of glycogen for storage of energy. In the presence of insulin, glucose passing the liver is taken into muscle cells for glycogenesis and fat cells for storage as triglycerides.

Exercise

In a well person, there is a fall in insulin production during exercise, which reduces hepatic production of glucose by gluconeogenesis, increasing the risk of hypoglycaemia. Growth hormone, glucocorticoids and adrenaline are produced during exercise in an attempt to increase plasma glucose levels, for energy supply to muscle cells.

Puberty

Insulin resistance occurs during normal puberty, related to increasing pulses of growth hormone secretion[7–9]. There are reduced circulating levels of insulin-like growth factor 1 (IGF1) in the adolescent with diabetes, inducing positive feedback on growth hormone secretion. This growth hormone 'hypersecretion' leads to the exaggerated insulin resistance seen in diabetes during puberty.

IGF1 has metabolic effects similar to insulin, which have not previously been thought to have physiological significance due to high protein binding of IGF1[9]. However, infusion of recombinant human IGF1 has been shown to improve insulin sensitivity, suggesting that a deficiency of IGF1 may cause worsening diabetes control. Research is underway to examine whether giving IGF1 regularly will improve diabetes control.

History of Insulin Production

In 1922, Banting and Best gave insulin in the form of pancreatic extract to a 14-year-old boy with diabetes mellitus[10]. His blood sugar level

dropped and he survived. Since then attempts to manufacture insulin that works as well as endogenous insulin have continued.

When the extraction process improved and purified insulin became commercially available, it was recognised that in order to avoid frequent injections both day and night, it would be necessary to manufacture insulin that had a longer half-life. Peptides (such as protamine), or zinc, were added to prolong insulin activity[11,12].

In the 1980s, human insulins were produced by enzymatic modification of porcine insulin (Velosulin) or biosynthetically by recombinant DNA technology using *E. coli* (Actrapid, Humulin S, Insulatard and Humulin I). The majority of children are now using human insulins, with a combination of short- and medium-acting insulin.

The time profiles of commonly used insulins are shown in Tables 1 and 2[11,13].

Table 1. Time profiles of commonly used insulin products

Insulin	Onset	Peak action	Dura-tion
Humalog (lispro)	15 min	–	2–5 h
Novorapid (aspart)	10–20 min	1–3 h	3–5 h
Actrapid (soluble)	30–60 min	2–4 h	8 h
Velosulin (soluble)	30–60 min	2–4 h	8 h
Humulin S (soluble)	30–60 min	2–4 h	12 h
Insulatard (isophane)	1–2 h	4–12 h	24 h
Humulin I (isophane)	1–2 h	4–12 h	22 h
Ultratard (crystalline)	4 h	6–18 h	28 h

Table 2. Commonly used mixed insulin preparations

Propriety name	Short-acting insulin	Medium-acting insulin
Mixtard 10	10% soluble	90% isophane
Mixtard 20	20% soluble	80% isophane
Mixtard 30	30% soluble	70% isophane
Humulin M2	20% soluble	80% isophane
Humulin M3	30% soluble	70% isophane

Current Insulin Regimens

Twice-daily Regimen

At present, the majority of children in the United Kingdom use a mixture of short- and medium-acting insulins, injected subcutaneously twice daily. The mixture can be adjusted either by mixing the required combination or by varying the proportions of pre-mixed insulins. Children of school age are generally started on a mixture of 30% short-acting and 70% medium-acting insulin, which is given before breakfast and before the evening meal. The proportion of short-acting insulin can be altered according to blood glucose trends and life-style. For example, a younger child who has small meals, but frequent snacks, might need less short-acting insulin, while a child who eats a large evening meal with a tendency to nocturnal hypoglycaemia needs more short-acting insulin. A twice-daily regimen has the advantage of minimising the number of injections required.

Multiple Injection Regimen

A multiple injection regimen, also known as a 'basal bolus regimen', allows more intensive therapy and is used increasingly by adolescents with diabetes. It depends on blood glucose testing four times daily, and the insulin dose is adjusted according to the planned dietary intake, the timing of meals and the amount of exercise anticipated. This allows for more flexibility in life-style, for example late breakfasts and sports training, when the patient has a good understanding of the condition. It certainly improved blood glucose control in the selected patients participating in the DCCT[2]. However, the number of injections and blood sugar tests required mean that it is unlikely to be successful in children who are not well motivated, so it cannot be assumed that a teenager with poor diabetes control will improve on a multiple injection regimen.

Continuous Subcutaneous Insulin Infusion (CSII)

Advances in pump technology over the past 20 years mean that battery-operated insulin infusion pumps are now a viable option. The external pump uses short-acting insulin at a basal rate set by the user, with boluses given prior to eating. Lower basal rates can be set to cover night-time and exercise. This should allow a closer match to physiological insulin levels in patients who have a good understanding of their insulin requirements related to their life-styles. The injection site can be changed every few days, but

the pump can be disconnected after a bolus of insulin if the patient wants a break, e.g. for swimming.

There has been reluctance to use CSII in children for the following reasons:

- Pump failure, causing interruption of insulin flow, will lead to rapid decompensation and ketosis, as no medium-acting insulin is given.
- Although the pump itself is much smaller than previously (about the size of a pager), some adolescents may be self-conscious of the extra 'bulk'.
- Only 25% of adolescents in the DCCT chose to use insulin infusions subcutaneously, compared with 50% of adults. This suggests either a reluctance to wear an external device continuously or that adolescents are not committed to the same goals of intensive therapy as adults.

A group in Yale, where there is considerable experience in the use of CSII in adolescence, studied 75 adolescents on intensive therapy for a year, 25 of whom chose to use CSII, the rest being on a multiple injection regimen[14]. They found that the CSII group were able to maintain an improvement in glycosylated haemoglobin (HbA1c) – a measure of long-term blood glucose control – for longer than the multiple injection group. They also had a lower rate of severe hypoglycaemia. Those who chose CSII felt that the flexibility of the regimen compensated for the wearing of an external pump. They also noted that both groups had improved quality-of-life and self-efficacy scores at the end of the year, suggesting that both intensive regimens are acceptable to the adolescent.

Shortfalls of Exogenous Insulin

Despite the increased flexibility of insulin regimens, we still have continuing problems trying to match physiological secretion of insulin. Reasons for this mismatch include the following.

Peripheral Delivery

Subcutaneous injections provide peripheral delivery with less insulin delivered directly to the liver than in the normal physiological situation. This means that instead of storing glucose as hepatic glycogen, low levels of hepatic insulin allow glucose to be released from the liver to the blood stream. Raised blood glucose levels further increase the peripheral insulin requirement.

The site of injection influences absorption of insulin. There is faster absorption when injected subcutaneously in the abdomen, followed by the arm, followed by the buttocks. However, it is necessary to rotate injection sites in order to avoid lipohypertrophy. The rate of absorption will also vary depending on blood supply and body temperature, with much more rapid absorption when the patient is hot. There is also faster absorption if the injection site is rubbed; however, absorption is less predictable, so patients should be advised to avoid rubbing the injection site. Even when all of these factors are standardised, there is marked inter-patient variability of absorption of current insulins when injected subcutaneously.

Hexamer Formation

Unlike endogenous insulin, injected insulin forms hexamers, which are slow to dissociate once absorbed. Entry into plasma is determined by the rate of dissociation of the hexamers to monomers at the injection site, giving a peak action of regular short-acting insulin of 2–4 hours after injection. For this reason, patients are advised to give themselves insulin half an hour before meals. Many families find it difficult to maintain this routine and 70% of patients use intervals of less than 15 minutes between injections and meals[15].

Giving regular insulin immediately before meals leads to insufficient plasma levels at the time of carbohydrate absorption, but excess levels in the post-absorptive period, leading to high blood glucose excursions after meals with a risk of late hypoglycaemia. It is known that high blood glucose levels after breakfast cause an increase in markers of long-term control[15], so it is important to avoid post-prandial swings in blood glucose levels.

Dose Requirement

It is difficult to predict accurately how much insulin will be required to cover varying meal content. Even when carbohydrate 'exchanges' were used to regulate food intake, it was difficult to guarantee an appropriate insulin dose which could account for both food and activity levels.

While it is sometimes possible to accurately predict what a child of school age will eat during the day, toddlers and adolescents are much more difficult to anticipate. Toddlers may be 'grazers', eating small amounts throughout the day, or more worryingly, they may simply refuse to eat after having the insulin injection. Parents understandably fear hypoglycaemia and the toddler soon learns that refusing to eat a meal is rewarded with chocolate, biscuits or a milkshake.

The adolescent is gaining independence and parents have much less of an idea of what they eat outside the home. In common with their non-diabetic peers, they have more access to 'junk food' and a high rate of binge eating. They also get up late at weekends, meaning that insulin injections are given at more variable times.

Insulin Analogues

Insulin analogues were developed in order to tackle some of the problems of current insulin therapy. They are used in adult practice, but we are less familiar with their actions in children.

Insulin analogues were designed primarily to prevent hexamer formation, so that absorption is more rapid[12,16]. The structure of the insulin molecule has been altered to reduce the affinity of one molecule for another. There are currently two fast-acting insulin analogues in clinical use:

- Lispro has the amino acids proline and lysine at positions 28 and 29 on the beta chain exchanged.
- Aspart has aspartate instead of proline at B28.

This region of the beta chain was chosen to mimic the sequence of IGF1, which has a lower rate of association compared with insulin, and is thought to be critical for the high-affinity association between insulin molecules[16].

In normal adults, the serum concentration of these insulin analogues showed a rapid onset of action, within 20 minutes, with a peak action between 1 and 3 hours, twice as high as regular short-acting insulin. Pharmacokinetic studies show that the insulin analogues have the same half-life when given subcutaneously as intravenously, which confirms that absorption is not affected by hexamer formation[17]. The rapid onset has been confirmed by pharmacokinetic studies in children[18]. The duration of action is 3–5 hours and less intra-individual variability in absorption has been demonstrated. Insulin analogues are no more immunogenic than regular insulin.

Both insulin analogues are licensed for use in children over the age of 12 years; aspart is licensed in children over 6 years. However, there is little clinical experience so far in their clinical use in children.

Potential Advantages of Insulin Analogues

In theory, the analogues would be ideal for use in toddlers, when it could be given with, or even after, a meal[19,20]. This would make it possible to omit or reduce the dose of short-acting insulin if the child refuses to eat. A small trial[20] showed no disadvantage in giving Humalog after a meal compared with pre-prandial regular short-acting insulin. However, the insulin analogue was only used on one occasion in each patient.

Analogues would allow children to inject immediately before their meal, without risking post-prandial surges in blood glucose[19,21,22]. This would have substantial benefits on the busy routines of most families on a school day!

Insulin analogues should reduce the incidence of hypoglycaemia, particularly late morning and nocturnal hypoglycaemia, because the peak levels of insulin drop more quickly[21–23].

Insulin analogues could be useful for those patients undertaking regular exercise, depending on the timing of exercise related to insulin injection[19,24]. For example, there is an increased incidence of hypoglycaemia with exercise 40 minutes after injection, but a reduced incidence of hypoglycaemia with exercise 180 minutes after injection.

Lispro has been used for outpatient management of ketonuria in unwell children with diabetes, but showed no advantage, or disadvantage, when compared to regular short-acting insulin[25].

As yet, studies of adults have not shown a long-term improvement in markers of diabetes control, such as glycosylated haemoglobin (HbA1c). This may be because patients have only been studied for short periods, or, possibly, owing to the reduction in hypoglycaemia. Aspart has been shown to have a statistically significant reduction in HbA1c in adults after 6 and 12 months of use, but this was only of 0.15%, so may have little clinical significance.

Summary

Obviously, the management of diabetes mellitus in children is not as simple as the manipulation of insulin dose. Diabetes education, exercise, diet and adherence with insulin injections all have a major role to play. However, we should aim to find an individual regimen, which closely mimics normal physiology, for each child. The regimen should be easily adaptable to changes in life-style, but allow near normal blood glucose levels in order to avoid long-term complications. There should be minimal side-effects, particularly hypoglycaemia and weight gain. Not much to ask really!

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