6 Treatment of Diabetes

27 Insulin and Insulin Treatment

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Keypoints

- Insulin is a potent anabolic hormone essential for life. Insulin has a circulating concentration of 15–20 mU/L in the fasting state, and 60–80 mU/L post-prandially.
- Early insulins were extracted from the pancreata of pigs and cows but good glycemic control was difficult to achieve because of residual impurities after the purification process. The newer and purer animal insulins are better tolerated and can potentially achieve a level of glycemic control similar to synthetic human insulins. Clinically significant hypoglycemia rates between the human and animal insulins also appear to be similar.
- The challenge of insulin replacement therapy is to reproduce a normal physiologic insulin profile without incurring significant hypoglycemia. A range of insulin preparations with differing durations of actions are available to achieve this: rapid-acting insulin analogs (about 3 hours), soluble insulin (about 6–8 hours), neutral protamine Hagedorn (NPH) insulin (12–18 hours), lente insulins (about 12–24 hours), long-acting insulin analogs (about 24 hours).
- Current recommendations for the injection of insulin are that the skin is pinched to reduce the risk of injecting into muscle, and to inject at a right angle to the skin after which the fold should be held for 5–10 seconds before removing the needle. Injection needle lengths of 5–12 mm are available to ensure that the insulin is delivered deep enough into the subcutaneous tissue to prevent back-leakage, but not so deep that it is intramuscular. Alternative modes of insulin administration such as continuous subcutaneous insulin infusion can also be highly effective.
- Multiple-dose insulin therapy is an appropriate initial approach to reproducing the physiologic insulin profile in patients with absolute insulin deficiency such as those with type 1 diabetes. This consists of a long-acting insulin preparation administered once or twice a day to meet the basal insulin requirement, with the injection of a short-acting insulin preparation with each meal.
- A number of different insulin injection regimens are available for patients with type 2 diabetes who may already be treated with non-insulin-based therapies. These include a once daily injection of a long-acting insulin, a once daily injection of a long-acting insulin with an injection of a short-acting insulin with the main meal, twice a day injections of insulin mixtures, and multiple dose injections.

Life (and death) before insulin

Insulin is a potent anabolic hormone, and its absence induces a profound catabolic state that affects fat, carbohydrate and protein stores. Absolute insulin deficiency, such as that characterized by type 1 diabetes (T1DM), will result in death if left untreated (Figure 27.1). What the study of patients with diabetes in the pre-insulin era teaches us is the surprisingly long period that can be survived without insulin. Leonard Thompson was the first patient to have effective insulin treatment. He was 12 years old when he was diagnosed with diabetes in 1919 and had survived over 2 years when at 11AM on January 22, 1922 he received his first injection of insulin. This said, it was a miserable existence without insulin. Other than the weight loss, constant tiredness, thirst, urination and frequent infections, there was the certain knowledge that a death sentence had been passed, and that death would be an agonizing and slow process. The most effective therapy available at that time appeared to be severe nutritional restriction, perhaps most popularly expounded by Allen [1] from the Rockefeller Institute in New York. However, this was a difficult regimen which did not appear to prolong life expectancy significantly, and when death came it was not clear whether it was the result of diabetes or starvation.

The discovery of insulin

Although there had been previous attempts to identify a pancreatic agent that could control blood sugar, most notably by the

Textbook of Diabetes, 4th edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

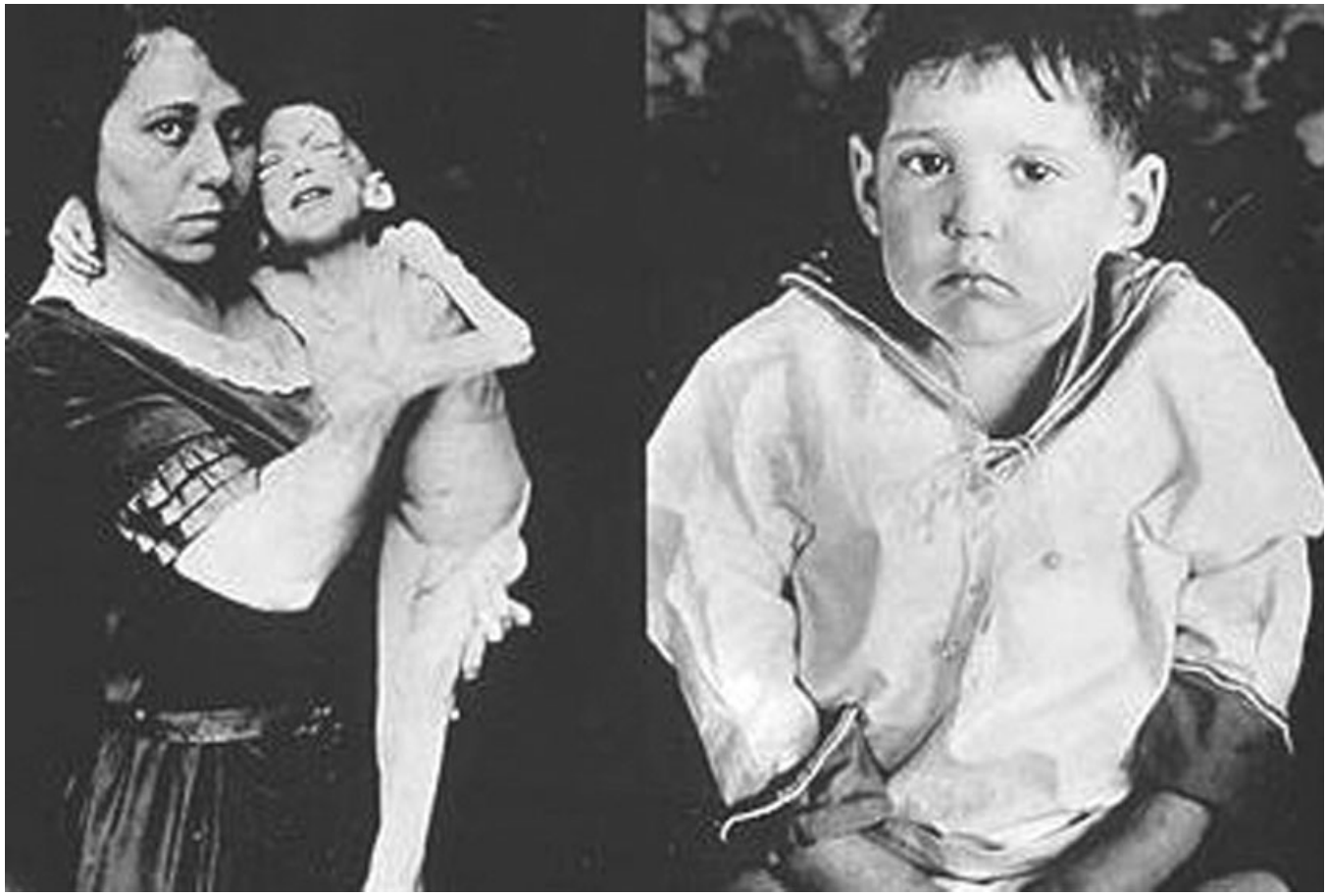

Figure 27.1 A patient with diabetes before and after insulin therapy.

Romanian physiologist Nicolas Paulesco, the story of insulin may be considered to start in the autumn of 1920 when Frederick Grant Banting who, while preparing a lecture on carbohydrate metabolism, considered a way to isolate the internal secretion of the pancreas. By the summer of the next year he had arranged with John Macleod, Professor of Physiology at the University of Toronto, for facilities and the support of a science student Charles Best to start experimentation (Figure 27.2). They showed that tying off the pancreatic ducts induced atrophy of the exocrine glands of the pancreas, thus allowing the "internal" secretions to be isolated. They tested the effect of this internal secretion on blood sugar by injecting it into dogs rendered diabetic through pancreatectomy. With the help of a biochemist, James Collip, they were able to purify this abstract sufficiently for the early experiments on patients. For this work, Banting and Macleod shared the Nobel Prize for Medicine in 1923.

By no means was this discovery a straightforward process, and according to one particularly harsh commentator, "the production of insulin … originated in wrongly conceived, wrongly conducted and wrongly interpreted series of experiments" [2]. The discovery of insulin nevertheless was a defining moment in the history of diabetes and the molecule has gone on to be well studied, with work contributing to three further Nobel Prizes: Frederick Sanger in 1958 for determining its primary amino acid sequence; Dorothy Hodgkin in 1964 for X-crystallographic studies; and Rosalyn Yalow *et al.* in 1977 for contributing to the development of radioimmunoassays.

The first insulins

Commercially available insulin was initially extracted from porcine and bovine pancreata. The organs would be freshly collected from abattoirs and frozen immediately to prevent the enzymatic degradation of the insulin protein. The tissue would undergo acid-ethanol treatment to solubilize insulin, which would then be salted out with sodium chloride, precipitated and then crystallized [3]. This procedure resulted in insulin with a purity of 80–90%, the contaminants largely being pancreatic polypeptides and glucagon. Although this insulin was effective, it was often complicated by immune-mediated side effects, in particular lipoatrophy and antibody-mediated insulin resistance [4], both of which that can profoundly influence the kinetics of insulin action. These impurities also contributed to an allergic

Figure 27.2 Charles Best and Frederick Banting on the roof of the medical building at the University of Toronto, summer 1921.

reaction which sometimes resulted in swelling and pain at the site of injection.

Animal and human insulins

Animal insulin continues to be porcine and bovine derived. The amino acid structure of bovine insulin differs from that of human by three amino acids (position 30 of the B chain, and 8 and 10 of the A chain) and that of porcine from human by just one amino acid (position 30 of the B chain) [5,6]. These differences aside, it was the purity of the insulin preparation that appeared to influence its immunogenicity.

In the 1970s, additional purification steps using gel filtration and ion exchange chromatography resulted in an insulin, called mono-component or single component insulin, with fewer side effects and which was better tolerated (Table 27.1). The incidence of lipoatrophy and allergy decreased as these purer insulins became more widely available. It was a logical step therefore to move on to treatment with human insulin in an effort to further reduce immune-mediated complications and improve glucose control.

Table 27.1 Insulin therapy milestones.

1922	Isolation of insulin and treatment of the first patient
1936	Protamine insulin
1946	NPH isophane insulin
1951	Zinc lente insulin
1959	Biphasic insulin
1977	Continuous subcutaneous insulin infusion
1980	rDNA human insulin in humans
1981	Insulin pens
1987	Monomeric short-acting insulins
1987	Soluble prolonged-action insulin
1996	Rapid-acting insulin analog
2001	Long-acting insulin analogs

Human insulin has been obtained using three techniques. The earliest attempts were to isolate and purify it directly from human cadaveric pancreata. The supply of human tissue, however, was never sufficient to enable this technique to provide sufficient quantities. The technique of "semi-synthesis" chemically converts porcine insulin to the human sequence through the substitution of the one amino acid difference in the primary sequence. It was only in 1980 with the introduction of recombinant DNA technology that human insulin therapy became widely available. The technique involves the insertion of the human DNA sequence into a host cell, usually bakers' yeast or the bacteria *Escherichia coli*, allowing it to synthesize the insulin molecule [7]. The protein would then be purified usually via chromatography columns to achieve a 99.5–99.9% insulin purity. The quality of the human insulin preparation achieved with this technique, as indeed with the purified porcine insulin, has virtually eliminated problems associated with immune-mediated side effects.

Counter to expectations, rigorous and well-designed studies comparing purified animal insulin with recombinant human insulin have yet to demonstrate a significant benefit in glycemic control. A recent meta-analysis of 45 randomized controlled trials involving a total of 2156 participants comparing animal and human insulin failed to show a significant difference between these two therapies [8]. Most (36 of the 45) studies used highly purified porcine insulin, which many believe to be less immunogenic than bovine insulin and this may explain the favorable results for animal insulins. Overall, there is a marked absence of good studies demonstrating a superiority of human over animal insulin with regard to glycemic control. Bovine insulin was associated with a higher titer of anti-insulin antibodies, but these titers did not appear to influence the dose of insulin required, or the level of glycemic control achieved.

The move from animal to human insulin was associated in some patients with reports of greater hypoglycemia, anecdotally

brought about by changes in hypoglycemia warnings [9,10], but systematic reviews have failed to substantiate this finding in population studies [8,11].

There has been a large-scale uptake of recombinant human insulin such that less than 7% of global insulin sales are now animal insulin. This shift has probably resulted at least in part, because of the phasing out of animal insulins by the leading insulin manufacturers. Several companies continue to provide this alternate source, and both bovine and porcine-derived insulin remain available. Although cheaper to produce, the price of animal insulins in the UK is structured at a cost comparable to that of recombinant human insulin (£17–18 per 10 mL vial; BNF 2009). This pricing strategy is not the same worldwide; in the developing world for example, the cost of animal insulin is about half that of recombinant human insulin, a factor that may influence the choice of insulin preparation [12].

Soluble and long-acting insulin preparations

The biologic action of soluble insulin lasts about 5–6 hours and the early preparations were often also associated with pain and swelling at the site of injection. Attempts were therefore made in the 1920s and 1930s to provide the patient's daily insulin requirement in just one injection. To this end, modifying agents such as lecithin, oil and cholesterol were used [13]; however, their duration of action varied significantly from injection to injection which made their clinical use very difficult.

In 1936 a method for incorporating insulin into a poorly soluble complex, thus slowing its absorption, was reported [14]. This technique involved the addition of a highly basic protein, protamine, derived from the sperm of salmon or trout. The complex was further stabilized by the addition of a small amount of zinc such that it lasted about 24 hours, and this insulin was called protamine-zinc insulin. It was difficult to make consistent batches and absorption again tended to be erratic. In 1946, the technique was further refined such that protamine and zinc were added in stoichiometric proportions (so that there was no free protamine or zinc), which resulted in a preparation that was absorbed at a more consistent rate and lasted 12–24 hours. This insulin was called isophane or neutral protamine Hagedorn (NPH), and became available clinically in 1940.

In 1951, a development that prolonged the action of insulin without the need for protamine was reported; this required zinc to be added in excess and in acetate buffer, resulting in crystals of relatively insoluble zinc-insulin complexes, called the lente insulins [15]. The size of the crystals could be adjusted by changing the pH such that larger crystals, which were more slowly absorbed (ultralente), and smaller crystals (semilente) could be produced. A preparation containing a 70:30 ratio of the ultralente and semilente insulins (lente insulin) was the most popular form of the zinc insulins and was used widely in clinical practice.

Rapid and long-acting insulin analogs

Insulin circulates as single molecules in the blood at concentrations of approximately 10^{-9} mol/L. At higher concentrations, such as in commercial preparations, insulin molecules tend to associate non-covalently into dimers, tetramers and hexamers [16]. The presence of zinc further stabilizes the hexamer association. Following injection, fluid is drawn into the injected insulin depot through osmosis. This leads to dilution of the insulin and dissociation of the insulin molecules, a spontaneous but gradual process that must occur before insulin can cross the capillary walls as monomers into the blood circulation [17,18]. Patients are therefore advised to inject their soluble insulin 15–20 minutes before a meal so that circulating insulin levels are optimal at the time their meal is being absorbed (Figure 27.3). A significant

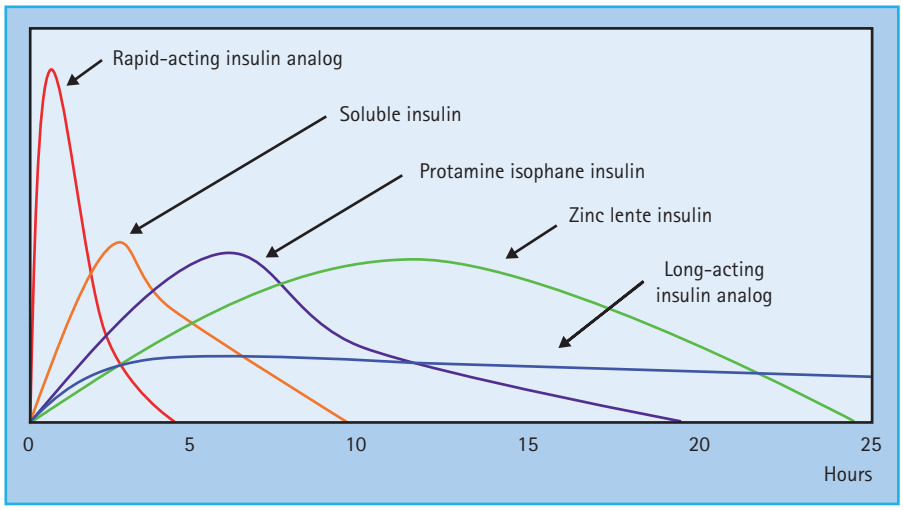

Figure 27.3 Time–action profiles of the different insulin formulations.

proportion of patients find it hard to follow this advice because of the planning required. Even when they do, the calculated doses may be inaccurate, particularly when the preparation of the meal is not under the patient's control.

The association between insulin molecules can be reduced by specific changes to the amino acid sequence of insulin [19]. These changes result in faster absorption of the insulin into the bloodstream, and allow it to be injected just before, or even immediately after eating a meal [20]. To date, three such rapid-acting analogs (RAIs) have become available: insulin lispro (Humalog®, Lilly), insulin aspart (Novorapid®, Novo Nordisk) and insulin glulisine (Apidra®, Sanofi-Aventis). These analogs act more quickly (within 10–20 minutes) and have a shorter duration of action (3–5 hours) than soluble insulin (30–60 minutes, and 6–8 hours, respectively) (Figure 27.3) [21]. A number of studies have now demonstrated the safety of RAIs in both T1DM and type 2 diabetes (T2DM), as part of a "basal bolus" insulin injection regimen combined with intermediate-acting insulins, and in continuous subcutaneous insulin infusion (CSII) [22]. The time–action profile of RAIs is well suited to mimicking the requirement at meal times, and therefore they probably control post-prandial hyperglycemia more effectively than soluble insulin. As a result, patients can achieve better glycemic control with fewer episodes of hypoglycemia with RAIs than with soluble insulin. The benefits of RAI over soluble insulin appears to be clearer in studies involving patients with T1DM than T2DM, and using CSII than for multiple dose injections [21].

Although delayed-action insulin such as insulin lente and isophane can cover the 12–24-hour period, their absorption from subcutaneous tissue can vary significantly [23]. Therefore, attempts at stringent glucose control can be associated with an increased risk of hypoglycemia. The modification of the primary amino acid sequence of the insulin molecule can result in a shift in the isoelectric point towards neutrality (the isoelectric point is that at which the molecule is least soluble). This shift in the isoelectric point therefore encourages insulin to precipitate following injection into the subcutaneous tissue (which is at neutral pH), and results in a slower and, more importantly, a more reproducible absorption [24]. Early studies of the long-acting analog insulins, designed to demonstrate equivalence rather than superiority over the isophane NPH insulins, have failed to show a clear benefit in glycemic control [25]. However, what the studies do appear to show is that achieving glycemic control with the long-acting insulin analogs is associated with less symptomatic and nocturnal hypoglycemia [26].

Reproducing physiologic insulin delivery – the size of the problem

In health, the background insulin secretion is low and stable between meals, with significant prandial surges (Figure 27.4). The stimulus and pattern of insulin secretion is reviewed in Chapter 6, but suffice it to say that the background as well as the prandial

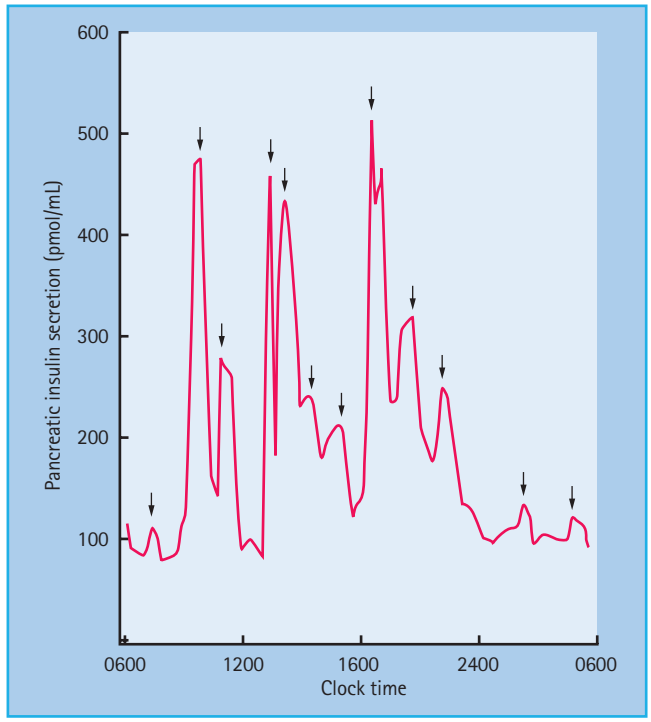

Figure 27.4 Pancreatic insulin secretion in a healthy non-obese individual. Meals were consumed at 0900, 1300 and 1800. Statistically significant pulses of secretion are shown by the arrows. Reproduced from Polonsky *et al.* [27], with permission from the American Society for Clinical Investigation.

insulin secretion can vary significantly within the same individual; the former according to the level of counter-regulatory hormones such as growth hormone and catecholamines, and the latter according to the carbohydrate and protein content of the meal [27].

Furthermore, the insulin is secreted into the portal circulation, with about 50% of the insulin removed in the first pass through the liver [28]. The continuous low levels (15–20 mU/L) of insulin secretion act to suppress hepatic glucose output. Peripheral tissues such as muscle also take up glucose but this is at higher insulin concentrations (60–80 mU/L) and tends to occur predominantly post-prandially.

The challenge of insulin replacement therapy is to reproduce the physiologic insulin profile without incurring significant risk of hypoglycemia.

Routes of insulin administration other than subcutaneous

The early experiments of Frederick Banting quickly revealed that the oral route of insulin administration was not an effective means of delivery, and subsequently that the insulin molecule was functionally degraded by gut peptides. Subcutaneous injection of

insulin has become the most popular route of insulin delivery because of its relatively reproducible kinetics of absorption, and the relative ease with which it can be administered, but it is worth visiting some of the other routes.

Intramuscular injection is more painful and absorption more rapid than the subcutaneous route [29] but is useful, for example, in the emergency situation when intravenous access is difficult. Inadvertent intramuscular administration should be considered in the slim patient with diabetes who complains of pain on insulin injection, and who may have erratic glucose control and hypoglycemia. The correct choice of insulin needles can help address this problem.

Intraperitoneal insulin administration is absorbed more quickly than the subcutaneous route and has gained some interest recently for use with implantable insulin pump therapy [30]. An advantage is that the major part of absorbed insulin is into the portal circulation [31], thus reducing the risks of high levels of peripheral insulin that may conceivably contribute to the vascular complications of diabetes and development of obesity [32,33]. Certainly, the early studies of implantable intraperitoneal pumps appear to achieve better glucose control and less hypoglycemia than the subcutaneous route. A longer experience of intraperitoneal insulin delivery has been obtained in patients requiring renal replacement therapy using continuous ambulatory peritoneal dialysis where the insulin is administered along with the dialysis fluid. There are some reports that this route is associated with more consistent absorption and lower peripheral insulin levels; however, there are no robust trials to show that any one route is superior to another [34,35].

The oral administration of insulin is a route by which this drug can enter the portal circulation, thus avoiding high levels of peripheral insulin. There are emerging reports that such an approach may be possible. Techniques such as insulin modification to engender resistance to degradation [36,37] have been reported to increase circulating insulin concentrations effectively and decrease blood glucose in early phase clinical trials.

Subcutaneous route of insulin administration

Subcutaneous insulin administration is the most popular route of insulin therapy and suggested sites for injection are the abdomen, thigh and deltoid. Despite a scarcity of clinical trials on this subject, the current recommendations are that the skin is pinched to reduce the risk of injecting into muscle, and to inject at right angles to the skin, after which the fold should be held for 5–10 seconds before removing the needle (Figure 27.5) [38].

The increasing availability of insulin pens, which are easier to use than the traditional needle and syringe, has seen a shift towards this mode of delivery. A selection of the pen types available from the major insulin manufacturers is shown in Figure 27.6. Currently available needle lengths are 12.7, 8, 6 and 5 mm. There are few if any indications for prescribing the 12.7 mm

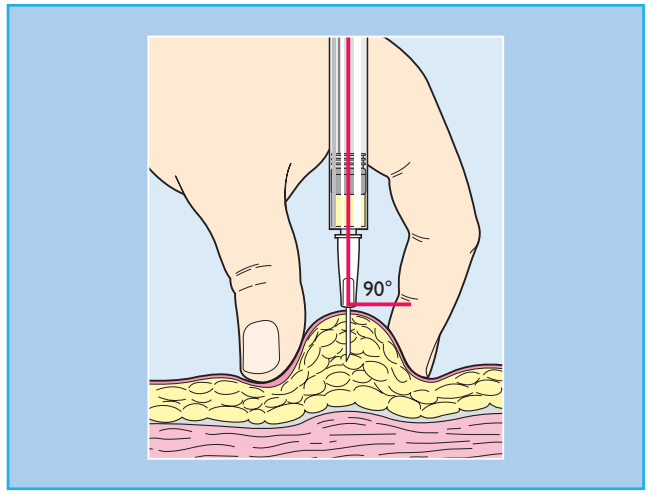

Figure 27.5 The recommended technique for the subcutaneous injection of insulin.

Figure 27.6 A selection of the available insulin injection devices. These are the most commonly used injection devices, although others are also available. Most are available on prescription.

needle, and shorter needles are associated with a lower risk of intramuscular injection and may well be perceived to be less traumatic. Nevertheless, there is some evidence that unless the injection technique is good, the shorter needles are associated with a greater risk of back-leakage of insulin. For a non-obese patient who uses the pinch technique on the abdomen, arm or legs, the 6–8 mm needle is usually the most appropriate.

Standard insulin preparations have a shelf life of 4–6 weeks when stored at under 25°C. Storage for longer periods will require that they be kept in a fridge (4°C), which then allows them to be stored till their expiry date. Exposure of insulin to high temperatures or to microwaves can render them inactive, a technique that may be employed by patients who wish to manipulate their treatment secretly.

Some preparations of delayed-action insulin exist in a two-phase solution which needs to be mixed adequately for complete suspension. It is important that patients are educated on the importance of this to ensure consistent amounts of insulin are drawn up on each occasion [39]. This mixing is not required for the long-acting insulin analogs.

Insulin preparations consist of insulin at or over 40 U/mL, which will exist largely as monomers, dimers or hexamers. Fluid drawn into the injected depot by osmosis following injection results in the dissociation of the oligomers into single molecules which are then able to traverse the capillary membrane and enter the circulation. Circulating insulin binds onto the insulin receptor on the target cell, is internalized and triggers a number of intracellular pathways. This internalization and degradation of insulin is the major route of insulin disposal, with less than 1% excreted by the kidney [40]. Overall, about 60–80% of insulin is degraded in the liver, 10–20% in the kidney and 10–20% in skeletal muscle and fat tissue [41]. Hence, failure of liver or renal function can and does result in the persistence of circulating insulin, with the risk of hypoglycemia.

Studies of absorption of subcutaneously administered insulin have used a variety of techniques including measuring the rate of loss of ^{125}I labeled insulin from the site of injection using a gamma counter [42]. Studies show that the rate can vary significantly between individuals, but also from one injection to another within the same individual [43]. Absorption rates in the obese patient are slower than in the non-obese patient, and there does not appear to be any clear differences in the rate of absorption between the different injection sites. In the non-obese patient, the absorption of soluble insulin from the abdomen appears to be faster than the arm or leg [44], and the upper abdomen faster than the lower abdomen [45]. These differences across injection sites appear to be less apparent with the insulin analogs than with soluble insulin [24,46].

Repeated injection of insulin at the same site results in local hypertrophy of adipose tissue, resulting in slower and more erratic insulin absorption. Patients should always be advised to rotate their insulin injection sites to avoid this complication, but the non-obese patient must also be warned that the rates may vary when they move from one part of the body to the other. Other local factors such as edema or local inflammation can influence rates of absorbtion. Exercise results in greater blood flow to the skin and can result in faster uptake of insulin, particularly when injected into an area close to the muscle groups being exercised; patients who are planning to run, for example, should be advised that injection into the leg may be less favorable than injecting into the arm or abdomen [47]. Similarly, temperature influences cutaneous blood flow and can influence insulin absorption [48]; hot climates or sitting in the sauna may result in a rapid surge in insulin levels whereas the converse, traveling to cooler climates, can result in a slower uptake. There are also reports that hypoglycemia and smoking can reduce the rate of insulin absorption [49,50].

Complications of subcutaneous insulin therapy

The most serious complication of insulin injection for most people is hypoglycemia. The causes, avoidance, consequences and management of hypoglycemia are discussed in Chapter 33. With respect to insulin treatment, the fear of hypoglycemia may be a major barrier to insulin initiation and achievement of tight glycemic control.

Insulin can not only restore fat and muscle mass in newly or suboptimally treated insulin-requiring patients, but can also lead to excessive weight gain [51,52]. This remains a major concern for many patients, particularly for the already overweight patient with T2DM who can no longer be controlled on oral hypoglycemic agents. Weight gain can be reduced by concomitant advice from the dietitian and an insulin regimen tailored to the individual needs of the patient, that wherever possible provides most insulin when needed (i.e. at meal times). Overaggressive insulin titration regimens leading to low blood glucose and stimulation in appetite can lead to excessive weight gain. Some patients, particularly but not exclusively young females, can pose a management challenge when they reduce their insulin dose to suboptimal levels to manipulate body weight (see Chapter 55).

Immune responses to the older animal insulins have been well reported but such responses to current human and analog insulins are extremely uncommon. Allergies may very rarely develop in response to both insulin and agents added to the insulin preparation. Most commonly, but again rarely, local acute urticarial reactions develop and are best treated by switching to an alternative insulin. Occasionally, the urticarial reaction may develop into a subcutaneous nodule. Antihistamines may be of benefit in such patients as too may be the use of high dose steroids in exceptional circumstances.

With the introduction of increasingly purified animal insulins, human insulin and analog insulin, antibodies to exogenous insulin are rare but, when detected, are usually induced by animal insulin products [53], polyclonal in nature, and directed against various parts of the insulin molecule. Clinically, they may lead to local allergic reactions described above and may have a retardant effect on short-acting insulins by reducing peak and raising trough levels. Such effects are likely to be unpredictable. While many clinicians speculate, in difficult to manage patients, over

the potential effect of insulin antibodies on blood glucose levels and glycemic control, there is little evidence, outside anecdotal case reports, to substantiate any significant effect.

Lipoatrophy, in which subcutaneous tissue at the site of injection disappears or atrophies, is an allergic response seen predominantly with the older animal insulins; it is rarely seen today. In contrast, lipohypertrophy is not uncommon, is not an allergic response at all but develops as an increase in adipose tissue as a trophic response to insulin. It is most commonly seen in patients with a poor injection technique and usually in patients who do not rotate their insulin injection sites. The patient usually finds the appearance unsightly and further injections into sites of hypertrophy can lead to poor and delayed insulin absorption with consequent effects on blood glucose levels [54]. Lipohypertrophy tends to settle if injections are avoided in that particular area. Occasionally, mild ulceration, pitting and, more commonly, bruising can occur at injection sites. Moving to another area for injection is advisable and, particularly when bruising occurs, a shorter needle may be preferable.

Insulin regimens

As insulin preparations have evolved from the early animal insulins to both human and analog insulins we have also seen the development of more versatile and flexible treatment regimens that enable the doctor and nurse to provide the patient requiring insulin with a bespoke treatment that fits in better with their individual needs and lifestyle.

In people without diabetes it is well known that the β-cells of the pancreas have the ability to produce insulin both between meals and at meal times to maintain blood glucose values within a narrow physiologic range. In people with T1DM, who are no longer producing endogenous insulin, the administration of exogenous insulin is required to try, as far as is possible, to mimic physiologic insulin release using a combination of both fast or rapid-acting insulin to deal with the glucose challenge presented at meal times and more longer acting or basal insulin to provide a background control of glucose between meals. In people with T2DM, the principle is the same although as the β-cells may still be producing some insulin, the addition of exogenous insulin to existing oral hypoglycemic agents can be used to try to achieve control of blood glucose levels.

We discuss how each of the individual insulins discussed above can be used, alone or more often in combination, in conjunction with lifestyle and diet to control blood glucose.

Basal only regimen

In excess of 50% of people with T2DM will require insulin injections at some point in their lives [55]. Often, as T2DM progresses, the transition from oral hypoglycemic agents to insulin injections can be a time of great stress and anxiety to many people for a number of related reasons [56]. While health care professionals employ a variety of skills and techniques to minimize what people see as a life-changing event, we remain very aware of the many anxieties insulin injections can induce. These can include a sense of personal failure in not being able to control blood glucose levels with lifestyle, diet and oral therapy; a feeling that the diabetes is now much more serious than it was, as it now requires injections rather than tablets; apprehensions, fears and, very occasionally, real phobias over the need to self-inject a treatment [56]; worries of hypoglycemia leading to coma and death; concerns over weight gain; and also that the use of insulin may impact severely on a patient's occupation and lifestyle activities.

One way in which insulin injections can be introduced to people no longer able to manage their blood glucose on diet, lifestyle and oral therapy alone is to start with only one injection a day. This is usually added on to existing oral therapies rather than as a replacement therapy. An increasing number of studies have now been published demonstrating that a once a day basal insulin can be used as an add-on therapy to metformin, a sulfonylurea, the thiazolidinedione pioglitazone and as an add-on to these agents when used as a dual or triple oral therapy [57]. National and international guidelines in the UK, Europe and the USA also recommend the use of a basal insulin with oral therapy as a way of initiating insulin in patients with T2DM [58–60]. At the time of writing, some of the newer agents including the dipeptidyl peptidase 4 (DPP-4) inhibitors and the glucagon-like peptide 1 (GLP-1) receptor agonists do not have a license for use with insulin therapy in people with T2DM although trials are ongoing and this may change.

The initiation of insulin therapy, whether in the hospital or, more commonly, in the community, should only take place within a structured program employing active insulin dose titration. The program should include appropriate education, ongoing telephone, text and/or email support, the use of blood glucose self-monitoring to help with dose titration to an agreed target, an understanding of diet, avoidance and management of hypoglycemia and support from appropriately trained and experienced health care professionals.

A number of guidelines continue to recommend initiation with a human NPH insulin taken once or twice a day according to need [60]. However, many health care professionals opt for long-acting insulin analogs particularly in people who require assistance with injections from a carer or health care professional and where the use of an analog would reduce the number of injections from twice to once a day. Long-acting analog insulins may also be preferred in people whose lifestyle is restricted by recurrent symptomatic hypoglycemia, those who would otherwise need twice daily insulin injections in combination with oral therapy and those who have difficulties with the device required for injection of NPH insulin [57]. Similarly, indications for switching from NPH insulin to a long-acting basal analog include failure to reach an agreed HbA_{1c} target because of hypoglycemia regardless of HbA_{1c}.

Once started on a basal insulin it is important to adjust insulin doses appropriately to achieve an agreed target. A number of algorithms have been developed to assist with this with almost all

based upon the fasting blood glucose measured in the patient's home and usually by patient themselves [57,61,62]. While self monitoring of blood glucose is important in the dose titration process, the ultimate measure that determines the success or otherwise of the basal insulin is the HbA_{1c} value. If this is proving difficult to control with satisfactory fasting plasma glucose values, the next step would be to add a prandial fast or rapid-acting insulin component.

Combinations of prandial and basal insulins

In patients with T2DM, a rising HbA_{1c} in the face of normal or near-normal fasting glucose values suggests significant postprandial glucose excursions and the need for a meal time insulin. This can be achieved by the addition of a prandial insulin with the main meal followed as needed by the addition of a prandial insulin before every meal [57]. Alternatively, patients can be switched from a basal insulin to a premixed insulin which traditionally has been given twice daily, at breakfast and the evening meal, but which increasingly is also given initially once a day with the main meal and increased up to three times a day [59,63].

Clearly, for patients with T1DM, a basal insulin alone is inadequate and either a complete basal bolus regimen is required with prandial insulin before each meal alongside a basal insulin or alternatively a twice or thrice daily insulin premix can be used.

Basal plus

The addition of a fast-acting human insulin or rapid-acting analog insulin prior to the main meal of the day can be a useful next step in intensification after starting a basal insulin in patients with T2DM [59,64]. Increasingly, health care professionals are using rapid-acting insulin analogs over fast-acting human insulins for convenience, as they can be given immediately before, during and even immediately after a meal [65–67]. The dietary intake of the individual will determine which the main meal of the day is and therefore with which meal the single injection of fast- or rapid-acting insulin will be given. Once again it is important to titrate the prandial insulin to a glucose target. The ideal time to test the impact of the prandial insulin, and certainly a rapid-acting insulin analog, is 90 minutes to 2 hours after the meal. As with basal insulin adjustment it is advisable not to make too frequent a change in insulin dosage and ideally no less than every 3 days or no more than twice a week. The patient may vary the amount of insulin administered based upon the size of the meal, although as the insulin is given with the main meal of the day, the dose is usually fairly stable from one day to another. As glycemic control becomes more difficult to achieve a second prandial insulin injection may be necessary, taken before the second main meal of the day using a similar dose titration procedure as that for the single prandial injection [64].

Basal bolus

The use of the basal bolus regimen in patients with T1DM and T2DM attempts to mimick, as closely as possible, the normal physiologic secretion of insulin by providing a background 24-hour coverage of insulin along with a bolus injection at each meal time (Figure 27.7). In most patients, with the development of long-acting analog insulins, the basal injection is administered once a day. However, based on the results of pre-meal self-monitored blood glucose values some patients may require two basal injections approximately 12 hours apart to achieve satisfactory before meal glucose values without hypoglycemia.

Traditionally, with animal and then human insulins, basal injections are given in the evening, often before bed. This is less important with the basal analog insulins and indeed many patients benefit from having their once a day basal injection at the same time each morning. It is important that insulin doses are adequately titrated to achieve target glucose and HbA_{1c} values and for the basal bolus regimen the dose of the basal insulin is determined by measurement of fasting (pre-meal) glucose values and the most appropriate fast human or rapid-acting analog insulin dose is best determined by 2 hour post-prandial glucose values.

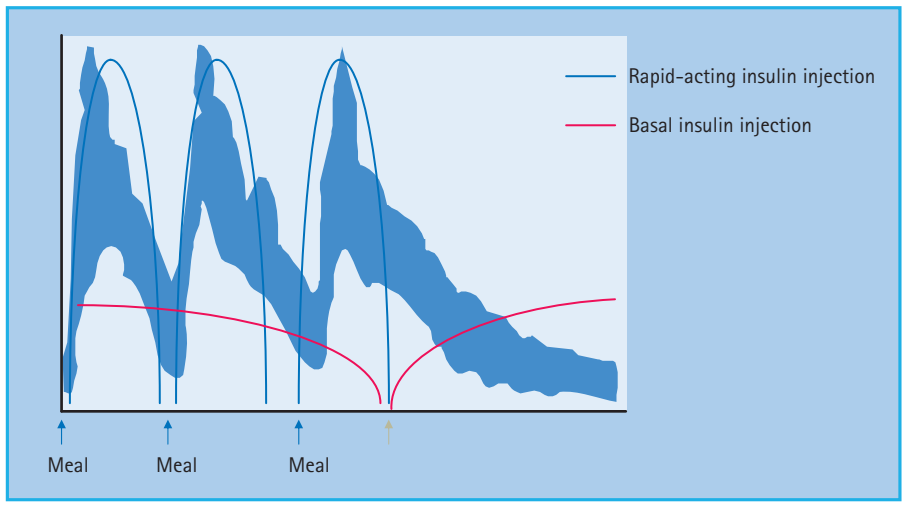

Figure 27.7 Schematic representation of the attempt to mimic physiologic insulin release following three main meals using a basal bolus regimen.

Insulin mixtures

While some patients still self-mix either animal or human fast-acting and long-acting insulins prior to injection, most people using insulin mixes inject premixed insulin preparations. In recent years, we have seen a whole spectrum of insulin premix insulins ranging from a 10:90 to 50:50 short:long-acting insulin ratios. In reality, many of these premixes were not required and consequently through lack of use the range of premixes has contracted down to 25:75, 30:70 and 50:50 mixes.

Most patients use premixed insulin twice a day, before breakfast and the evening meal. In people with T2DM, insulin initiation may start with a once a day premix insulin with the main meal, increasing up to two injections a day when needed based on self-monitored blood glucose values and the HbA_{1c} [59,64]. Some patients with T1DM, but more frequently patients with T2DM, move to three injections a day by also administering an injection before lunch. For patients moving up to three injections a day, the 50:50 mixture providing more rapid-acting insulin at meal times may be more appropriate than the more commonly used 25:75 or 30:70 mixture, usually given twice a day.

Selecting the most appropriate insulin regimen

Most people with T1DM and T2DM try a number of treatment regimens throughout their lives. There are many factors that influence the decision to opt for a specific regimen and ultimately the most important is patient choice rather than evidence from clinical trials.

Type 1 diabetes

All patients with T1DM, unless they have been fortunate enough to become insulin independent following a pancreas or islet cell transplant, will require exogenous insulin to provide 24-hour background and meal time coverage. For many patients this is provided by the basal bolus regimen. The advantages of such an approach are that it is generally better at providing a more physiologic insulin replacement with a greater degree of 24-hour flexibility than less frequent premixed insulin. While it has the disadvantage of more daily insulin injections and for many more frequent self blood glucose monitoring, which is not popular with some patients, particularly young and teenage children, it does provide a much greater degree of flexibility throughout the day. Importantly, it allows the patient to vary the meal time dose at up to three different time points during the day to accommodate different daily activities and meal sizes. For some, this "freedom" is less important and the administration of only two injections a day sways them towards an insulin premix.

Type 2 diabetes

While in some patients with T2DM insulin requirements are similar to those with T1DM, for many, insulin initiation and intensification is a more gradual process. Views differ on the insulin of choice for initiation, particularly as an add-on to oral hypoglycemic therapy. Prior to the introduction of the long-acting basal analogs, many patients requiring insulin were started on a twice a day premixed insulin often as an add-on to metformin. If patients were also on a sulfonylurea this was usually stopped. Supported by clinical trials, using long-acting basal analogs as an add-on to existing oral therapy and low rates of hypoglycemia compared to those seen with NPH insulin, once a day long-acting basal insulins are now recommended in T2DM treatment guidelines and have found significant popularity, particularly in the community as a means of introducing the patient to insulin [57,61]. Anecdotally, while this is a popular way of starting insulin, many health care professionals struggle to achieve satisfactory glycemic targets with this regimen and many patients will require a second insulin injection with a meal time component within 6–12 months.

Trials comparing twice daily premixed insulins with a long-acting basal analog when added to metformin in insulin-naïve patients appear to show a benefit in favor of twice daily premixed insulin with respect to the numbers of patients achieving target HbA_{1c} values [68,69]. The relative merits of basal only, prandial only and premixed insulin are unclear [70] and are currently being further evaluated [71]. Clearly, there are advantages and disadvantages associated with each approach. A pragmatic response is to consider each patient individually and their lifestyle, social circumstances and co-morbidities and taking into account what their insulin needs are likely to be in the longer term to make a clinical judgment. If it seems likely that if started on a basal insulin they are likely to remain on this as a single injection or as part of a basal bolus regimen in the future, the basal insulin may be the best option. However, if it seems likely that the patient will be switched to a premixed insulin if a long-acting bolus does not achieve target, then initiating with a premixed insulin would seem sensible. Starting the premixed insulin as a once a day injection increasing to two and sometimes three injections is also an option with some clinical evidence to support it.

Starting insulin for the first time

In the past, insulin initiation, particularly for people with T1DM, was conducted either as an inpatient or as a day case in a hospital diabetes center. As confidence grows with the development of purer animal insulins and most recently with human and analog insulins and also with the introduction of disposable syringes, pen injectors and needles, more insulin initiations are performed on an outpatient basis. Most recently, with an increased emphasis on community-based diabetes care, insulin initiation, particularly in patients with T2DM, is taking place in health centers and GP surgeries [72]. While older algorithms for helping to decide when and where insulin should be initiated have been published, national and local guidelines now seem more appropriate as varying levels of expertise, infrastructure and service delivery are present in different health settings.

Table 27.2 Outpatient/community pathway for people starting insulin for the first time.

Session 1
- The need for insulin has already been discussed with the patient by a doctor or diabetes nurse specialist and patient has been seen by a dietitian
- A regimen will have been agreed upon and the first prescription has been obtained by the patient
- A review of "what is diabetes" including what insulin does and the need for insulin injections usually takes place
- Nurse demonstrates the basics and use of insulin injection device and patient gives first injection
- Further discussions including:
  (i) sites for injection/site rotation
  (ii) timing of injections
  (iii) where and how to obtain equipment (insulin, pens, needles, self blood glucose monitoring equipment, sharps disposal equipment)
  (iv) recognition and management hypoglycemia and hyperglycemia
  (v) self blood glucose monitoring
  (vi) driving and legal issues surrounding insulin
- 24-hour contact details provided

Session 2 (around 2 weeks after insulin initiation)
- Prior to session 2 patient and nurse will usually have had telephone contact over insulin injections and blood glucose readings
- Review of information provided in session 1
- Review of insulin injection technique

Session 3 (around 4 weeks after insulin initiation)
- Review of session 1 and 2
- Further information provided about:
  (i) insulin on holiday and when traveling
  (ii) insulin injections when traveling through time zones (e.g. transatlantic travel)
  (iii) insulin management during periods of acute sickness
  (iv) foot care, other diabetes-related complications and in females of childbearing age, pregnancy

Session 4 (around 10 weeks after insulin initiation)
- Review of previous sessions
- Assessment of glycemic control and need for further doctor/nurse follow-up
- Book follow-up clinic/surgery appointment

Wherever insulin is initiated it is vital that for it to be successful a good insulin initiation program is in place, with a qualified and competent diabetes nurse specialist. A number of programs are available, most with appropriate training courses for health care professionals. Insulin initiation involves much more than teaching a patient how to use a needle and syringe and the process of starting and successfully stabilizing a patient on insulin will require a number of structured contacts with the nurse and also a 24-hour emergency contact number for any urgent problems that may arise (Table 27.2).

For those patients presenting acutely ill with nausea and vomiting, with or without ketosis, admission to hospital for insulin initiation and, where needed, intravenous fluids, is a necessity.

Use of animal, human and analog insulins

The evolution from animal to human and then analog insulins has been discussed at the start of this chapter. We have subsequently outlined above some of the advice included in national guidelines regarding the use of human and analog insulin. In clinical practice all three types of insulin are in regular use. At the present time, patients wishing to stay on animal insulin should, wherever possible, be allowed to do so. There are also advantages associated with the use of the analog insulins although generally they are more expensive to prescribe than human insulin and concerns have been raised over cost–benefit when prescribed routinely. While some of the individual benefits appear small, collectively these benefits are likely to have an impact on many patients [65]. While those responsible for health care budgets seek persuasive clinical trial data it is most unlikely that we will ever see direct head to head studies that provide incontrovertible data one way or another. Ultimately, it will come down to clinical judgment and a decision involving the patient.

Assessments of glycemic control

While national and international guidelines have made recommendations on glycemic targets based predominantly on the HbA_{1c} [58–60,73], self-monitoring of blood glucose not only helps patients achieve HbA_{1c} targets by adjustment of insulin doses, but also helps patients better understand their own diabetes and blood sugar levels better. The timing of glucose tests and their role in determining the most appropriate insulin dose is discussed above and is disscussed in greater detail in Chapter 25. Generally speaking, patients should be advised to test at different times on different days including pre-meal and 2 hours post-prandial testing to obtain 24-hour glucose profiles over a number of days rather than performing a large number of tests every day. To achieve strict glycemic control, as seen in the T1DM DCCT [52], pre-meal blood sugar readings should fall between 4 and 7 mmol/L and post-meal levels from 4–10 mmol/L, with a value >7 mmol/L before bed. While individual specialists often follow their own dose adjustment algorithms, in general terms a change in dose of 2 units or 10% of a dose (whichever is the greater) is a sensible adjustment for most patients.

Similar targets may be sought for people with T2DM although recent trials based on achieving very tight HbA_{1c} values, with some aiming for <6%, serve to highlight the dangers of hypoglycemia [74]. The frequency of blood glucose testing is extremely variable, with patients being recommended to test anything from seven times a day to four or five tests a week. The most important aspect of regular self-monitoring by patients on insulin is that the test result should be used as part of a management plan to help decide prospectively on insulin dose. There are other points that should be considered when advising on the timing of self-testing, including intercurrent illness, symptoms and treatment of hypoglycemia, and foreign travel. While more frequent testing generally provides more information, it is also important to remember not to recommend unnecessary and costly testing as

pricking the finger is painful and for most patients is worse that injecting insulin.

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