A review of insulin and insulin regimens in type 2 diabetes

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Keywords: type 2 diabetes mellitus, insulin, hyperglycaemia

Abstract

We have reviewed the various insulins available in the South African market, together with the modes of action of each of the formulations. The insulin groups discussed include the Basal insulins, the bolus or prandial insulins, and the premixed insulins. Furthermore, an approach to the designing of an insulin regimen is discussed, and comments made on how to further intensify therapy depending on the response experienced. Oral hypoglycaemic agent failure is defined by an HbA_{1C} measurement that exceeds 7%, which is a definitive call for further therapy with insulin in type 2 diabetes.

SA Fam Pract 2009;51(2):97-102

The pathophysiology of type 2 diabetes, discussed in a previous article,[1] is characterised by progressive decrease in peripheral tissue sensitivity to insulin action, and progressive pancreatic ß-cell dysfunction. These aberrations result in hyperglycaemia, a situation that is further compounded by the observed hyperglucagonaemia from pancreatic α-cell dysfunction.

The United Kingdom Diabetes Prospective Study (UKPDS)[2] has demonstrated that there is a progressive loss of pancreatic ß-cell function over time, regardless of type of oral hypoglycaemic pharmacologic therapy used, at a rate of about 6% per annum.

In view of this, it could be predicted that most type 2 diabetics would require insulin replacement for diabetes control about 10–12 years after diagnosis. The UKPDS showed that about 30% of patients taking sulphonylureas and 22% of those taking metformin required insulin within 6 years because oral agents failed to maintain control.[5] Factors such as poor glycaemic control even whilst on oral hypoglycaemic agents could lead to glucotoxicity, where high glycaemic levels suppress ß-cell function, and this could hasten exogenous insulin requirement even in a shorter period of time.

Early in type 2 diabetes, there is postprandial hyperglycaemia due to the loss of early insulin secretion. As the disease progresses there is fasting hyperglycaemia, due to decreased insulin production. These represent two different mechanisms, one at the liver for increased hepatic glucose output and the fasting hyperglycaemia, and the other, decreased glucose utilisation in muscle leading to postprandial hyperglycaemia, which is why postprandial glucose goes up early in type 2 diabetes.[16]

The discovery of insulin in 1921 by Banting and Best from Canada was a quantum leap in terms of therapy for patients with type 1 diabetes initially, and then for other types of diabetes. The use of insulin has proved life saving for many patients with diabetes. From the early attempts at isolating insulin from animal pancreatic extracts, great strides have been taken in terms of purification of insulin to the development of human short-acting soluble insulins, intermediate- and long-acting insulins, human premix insulins, and now analogue insulins in a variety of formulations including rapid-acting, long-acting and premixed insulins.

Despite having these varieties of insulin formulations available for use, insulin therapy is very often started too late, with patients running HbA_{1C} values of > 7% for over 10 years, and HbA_{1C} values of > 8% for over 5 years,[6] which contributes to ongoing poor control and the development of numerous complications. The reasons for this are multifactorial, inter alia:

- 'Psychological' insulin resistance: a challenge that faces both doctors and patients alike is the resistance to taking insulin injection therapy. Busy doctors not too familiar with the use of insulin are gripped with a fear that their patients might develop frequent episodes of hypoglycaemia, with its attendant problems to the practitioner. There are also concerns (usually wrong) regarding the time that will be needed to train patients.
- The patient has needle phobia and is unwilling to initiate injection-based therapy. For attaining adequate control, most patients will require more than one insulin injection daily.
- The patient is inadequately educated about the use of insulin in diabetes care, and the patient perceives the change to insulin as 'a last resort', implying to them a poor prognosis.
- The patient thinks that this is 'drug-taking' equivalent, and habit forming. The patient often asks: *Won't we become dependent on it?*
- Type 2 diabetic patients should be informed that the introduction of insulin therapy is not punitive, but restorative. Further, that all type 2 diabetics, if they live long enough, will eventually need insulin therapy based on the pathophysiology of the disease.
- There are concerns regarding weight gain and hypoglycaemia.
- There may be a poor or non-availability of insulin in a particular area.

One thing remains clear: we have a problem. The disease is progressive with serious chronic complications and yet, despite having the tools, we delay timeous intervention.

Most of the above problems can be overcome by educating the patients and their families. In many type 2 patients with reasonably regular lifestyles, use of premixed insulins reduce the need for too many injections. Currently available ultra-fine needles are relatively painless, and the use of pen devices has further added great convenience to patients. Most patients are on regular Self Blood Glucose Monitoring (SBGM), and the discomfort caused by injection administration is far less than performing SBGM.

Once we are confronted with a situation in which a diabetic patient's HbA_{1c} exceeds 7% despite maximal lifestyle modifications (correct diet and minimum prescribed exercise) and oral hypoglycaemic agents as discussed previously,[1] it becomes necessary for the next level of therapeutic intervention. The prompt control of postprandial hyperglycaemia would go a long way towards preventing chronic complications of diabetes, of which macrovascular disease accounts for most of the morbidity and mortality in type 2 diabetes. Also, type 2 diabetics who become pregnant, and who are not optimally controlled for pregnancy on either diet or metformin, will need to commence an appropriate insulin regimen.[4]

Insulin Therapy

Various representative bodies have recommended target guidelines at which glycaemic control should be maintained (see Table I)

Table I: Current recommendations for glycaemic control in adults with type 2 diabetes mellitus

Glycaemic parameter	AACE and ACE	ADA
HbA1C (%)	≤ 6.5	< 7.0
Preprandial glucose (mmol/l)	< 6.1	5.0–7.2
2-hr postprandial† glucose (mmol/l)	< 7.7	< 10.0

AACE – American Association of Clinical Endocrinologists
ACE – American College of Endocrinology
ADA – American Diabetes Association
† Postprandial glucose measurements should be made 1 to 2 hours after the beginning of a meal, when peak glucose levels generally occur in patients with diabetes.

There are a variety of insulins available commercially, and a thorough understanding of their formulations, their pharmacokinetics and their pharmacodynamics is essential in order to choose the appropriate one for a particular patient in order to achieve glycaemic targets. Insulin therapy is also selected on the patient's blood glucose profile (or glucose trend, derived from their SBGM) to assess which insulin would provide the best match for the patient's profile.

Insulins are traditionally grouped into BASAL and BOLUS insulins, based on their pharmacokinetic profiles.

Basal Insulin

So what pharmacological properties constitute ideal basal insulin? Its action should be protracted to ensure glycaemic control over long time periods with few injections (i.e. have a long duration of action). The kinetic profile should be flat and smooth (i.e. peakless) with minimal variability between patients and within each patient from day to day to ensure predictability of control and to lower the risk of hypoglycaemia.

The ideal exogenous insulin regimen should fit the physiological profile of insulin secretion seen in healthy non-diabetic individuals. Here, a relatively constant low range of basal insulin output is periodically supplemented by intervals of increased insulin secretion in response to food intake. The goal of attempting to recreate this profile in patients with diabetes is to maintain blood glucose as close to euglycaemia as possible at all times.

Basal insulin is meant to provide a constant 'background' level of insulin that controls hepatic plasma glucose production on a diurnal basis. It mimics the continuous pancreatic insulin secretion that controls the fasting and the pre-prandial glycaemic secretion.

Basal insulins currently available are:

- Neutral Protamine Hagedorn (NPH) *(Protophane®, Humulin N®)*
- Glargine *(Lantus®)*
- Detemir *(Levemir®)*

The salient features of each are summarised in Table II[7] below:

Table II: Basal insulin pharmakokinetics

Insulin	Generic name	Brand name	Time of onset	Time to peak	Duration of action
Long-acting	Glargine Detemir	Lantus® Levemir®	2–4 hr 2 hr	No pronounced peak	20–24 hr 6–24 hr
Intermediate-acting	NPH	Protophane® Humulin N®	2–4 hr	4–10 hr	12–18 hr

Adapted from Goldstein & Miller

1. Neutral Protamine Hagedorn (NPH) insulin

In practice the varying insulin needs of the patient and the pharmacological limitations of exogenous basal insulins such as variable absorption means that it is impossible to maintain diurnal blood glucose control within the ideal range at all times. There are inevitably periods of hyperglycaemia and episodes of hypoglycaemia. The variable absorption rate and the peaked kinetic profile of traditional basal insulins like NPH means that an evening or bedtime injection can be followed by episodes of hypoglycaemia during the middle of the night yet high fasting plasma glucose levels in the morning.

NPH or isophane insulin is a crystalline suspension of insulin with protamine and zinc. This enhances its aggregation into dimers and hexamers after subcutaneous injection. A depot is formed after injection and insulin is released slowly, providing intermediate-acting insulin with a slow onset of action and a longer duration of action than regular insulin. The duration of action of NPH insulins is variable. Some patients use one injection daily, whereas others may require injecting two, or even three times daily, to maintain the basal insulin requirements of the body. Due to the variable absorption and peaks of NPH, side-effects such as early morning hypoglycaemia and fasting hyperglycaemic episodes are more likely, especially with higher doses. These limitations have been largely reduced by the introduction of basal insulin analogues like glargine and detemir.

2. Insulin glargine

Glargine is a recombinant human insulin analogue. It differs from human insulin in that it is soluble in an acidic environment and forms a stable hexamer precipitate in subcutaneous tissue following administration.

This allows for a delay in the onset of action as well as a steady release of insulin over a 24-hour period *without* any pronounced peak.[8] Thus, one injection per 24-hour period is sufficient to maintain basal insulin requirements for the day.

Glargine cannot be mixed with other forms of insulin as it is in an acid solution, and would alter the absorption kinetics of those insulins. A bedtime injection of insulin glargine produces a much lower frequency of nocturnal hypoglycaemia, but similar glycaemic control (as judged by the HbA_{1C}). Furthermore, there is less weight gain than when using bedtime NPH.[9] For similar HbA_{1C} reduction, glargine allowed significantly less weight gain than NPH Insulin ($p = 0.0007$).[12] In one study, the combination of glargine and oral agents resulted in a 56% reduction of nocturnal hypoglycaemia and lower post-dinner plasma glucose levels than NPH plus oral agents.[10]

3. Insulin detemir

This too is a recombinant human insulin analogue. Detemir is a normal analogue of human insulin in which a 14-carbon fatty acid is acylated to the B chain. This modification enables reversible albumin binding, delays and protracts the action of detemir, and buffers against changes in absorption rate from the subcutaneous injection site. Fatty acid acylation enhances detemir insulin's affinity to albumin, enabling a longer duration of action via delayed absorption from the subcutaneous adipose tissue depot.[11] The duration of action of detemir is dose-dependent, increasing from 5.7 hours at a low dose (0.1 µ/kg) to 23.2 hours at a high dose (1.6 µ/kg).

Following injection, the detemir forms a liquid depot in subcutaneous tissue. The molecules are assembled as hexamers. Where the injected detemir complex comes into contact with the interstitial fluid, dilution of the solvent causes some hexamers to aggregate reversibly, forming di-hexamers, or small chains. These are formed through contact between the fatty acid side-chains.

Further dilution results in some hexamers disassembling into three dimers. These in turn may separate into the detemir monomers. As the molecules enter the fluid medium between adipose cells they encounter albumin molecules, to which their fatty acid side-chains are able to bind. This is a dynamic process where detemir molecules spontaneously dissociate from one albumin only to reattach themselves to another. The albumin molecules may carry hexamers and dimers as well as monomers of detemir.

When bound to albumin detemir cannot penetrate the capillary but free or dissociated detemir penetrates the capillary wall into the blood stream. Hexamers and dimers penetrate the capillary wall only slowly but any free detemir monomers pass rapidly into the circulation.

Once in the bloodstream hexamers or dimers of detemir rapidly dissociate into monomers. This is a dynamic process. Detemir monomers sporadically disassociate only to reattach to other albumin. Albumin binding further protracts the action of detemir, and in addition, it may buffer against oscillations in the absorption rate from the injected site.

Free detemir monomers can, of course, pass back through the capillary wall and in this way they reach their target tissues. Here interstitial albumin binding will again take place and this further delays and protracts the action of detemir.

Within the target tissue the detemir binds to the insulin receptor expressed by the target cells. Once internalised the signalling process begins. Detemir monomers continue to arrive at the target tissue with a slow and steady rate. The retarded absorption of detemir into blood and its subsequent albumin binding ensures that the insulin action is maintained for many hours after injection. Albumin binding will also buffer the effect of any change in absorption rate to ensure the steady signalling rate added to its kinetic variability for one injection to another.

Bolus Insulin (pre-meal or prandial insulin)

The use of basal/bolus therapy attempts to provide a delicate balance between tight glycaemic control and avoidance of hypoglycaemia by combining insulins with different kinetic properties (intermediate- or long-acting, with short- or rapid-acting). Rapid- or short-acting insulin is injected at mealtimes to eliminate postprandial hyperglycaemia, while long-acting slowly absorbed insulin is taken once or twice daily to ensure that a basal level of insulin is maintained, regulating hepatic glucose output. Ideally these injections should be combined to produce an optimal plasma insulin profile.

Bolus insulin is given as one of the short-acting insulins or rapid-acting insulin analogues. Some of the insulins that are available (Table III)7 include:

1. Short-acting regular insulin

Short-acting regular insulin consists of zinc insulin crystals in monomeric form in a clear solution.[13] After subcutaneous injection it tends to self-associate into dimers and then into hexamers, which then have to dissociate before absorption as monomers and dimers. This results in a 30–60 minute delay in onset of action, and has to be taken at least 30–45 minutes before meals to allow adequate absorption of the soluble insulin to peak in time with the anticipated glycaemic rise post meals. This limits its flexibility and convenience of time of administration in relation to meals. Furthermore, because the peak glycaemic response to a mixed meal is between 2–4 hours after ingestion, regular insulin may peak too late to allow targeted control of postprandial hyperglycaemia, especially if not taken 30–45 minute premeal. There is also a potential for hypoglycaemia to develop as a late sequelae several hours after a meal has been absorbed because of regular insulins' longer duration of action. This may limit insulin titrations to tight postprandial plasma glucose goals.

In some patients, the longer duration of action of the short-acting insulins can be used to advantage in those who have high pre-lunch values. They are available to us as Actrapid® and as Humulin R®, and the injections are currently presented in vials or prefilled disposable pens.

2. Rapid-acting insulin analogues

Because of the dual advantages of rapid action and rapid clearance, rapid-acting insulin analogues are generally preferred as prandial injections.[14,15] In view of the rapid action, the insulin may be administered before meals, or even immediately after meals. Formulations available include lispro (Humalog®), aspart (NovoRapid®) and glulisine (Apidra®).

The capacity of the insulin to self-aggregate in subcutaneous tissue is a function of the formulation of insulin lispro, which allows rapid absorption from the injection site. Insulin lispro was the first available rapid-acting insulin analogue to closely match circulating insulin levels seen physiologically after a carbohydrate rich meal. The rapidity of action is also of benefit in situations where rapid reduction of glycaemia is required, as, for example, in diabetic keto-acidosis, or post acute myocardial infarction.

Insulin aspart and glulisine too have formulations that allow for a more rapid onset and duration of action analogous to those seen with lispro, as compared to regular insulin.

They are provided in injectable forms both as vials and as reusable or disposable pens. Prandial (or meal-related) insulins cover glucose excursions that occur following meal. Doses are usually adjusted to match anticipated carbohydrate intake. The advantage of individual bolus injections is one of greater flexibility in that adjustments can be made to accommodate varying meal times, and also varying meal proportions.

Table III: Bolus insulin pharmakokinetics

Category	Generic name	Brand name	Time of onset	Time to peak	Duration of action
Rapid-acting	Lispro Aspart Glulisine	Humalog® NovoRapid® Apidra®	5–15 min	30–90 min	4–6 hr
Short-acting (regular)	Regular insulin	Humulin R® Actrapid®	30–60 min	2–4 hr	6–8 hr

Adapted from Goldstein & Miller

Premixed Insulins

Many type 2 diabetics, who have well-regulated lifestyles, benefit from the convenient use of premixed insulins. These insulins have been made available in a variety of fixed-dose combinations of short- or rapid-acting insulins with intermediate-acting insulins (see Table IV).[7] The most commonly used premixes are the 30/70 mixtures (a ratio of short-/rapid-acting 30 to intermediate acting 70). Premixes increase the convenience of insulin dosing, which may improve compliance, long-term control and outcome.[16]

Table IV: Premixed fixed-combination insulins6

Premixed insulin	Mixture components
Humulin 30/70®	30% regular/70% NPH
Actraphane 30/70®	30% regular/70% NPH
Humulin 50/50®	50% regular/50% NPH
Insuman Comb 30/70®	30% regular/70% isophane
Humalog Mix 50®	50% lispro/50% lispro protamine
Humalog Mix 25®	25% lispro/75% lispro protamine
Novomix 30®	30% aspart/70% aspart protamine

NPH = Neutral Protamine Hagedorn

Designing An Insulin Therapeutic Programme

It is important to balance the individual's need for glycaemic control with his/her willingness to take injections. For some, starting an insulin regimen with a single daily injection may be the best approach. Also, the use of basal insulin either alone or in combination with oral antidiabetic agents such as metformin, with or without sulphonylureas, provides acceptable glycaemic control until such time that glycaemic control starts deteriorating once again. Because of the 24-hour action of long-acting basal insulins, they can be taken at the same time, at any convenient pre-selected time of the day.

Regimens involving two daily injections of premixed insulin (regular human insulin plus NPH insulin) are useful in patients who do not require as much flexibility and who take meals at consistent intervals.

- Because of the slower absorption rate of the short-acting insulin, the dose has to be administered at least 30–60 minutes before meals. Also,
- Injections have to be taken at fixed times in the mornings and evenings everyday.
- Meal times also have to be rigidly adhered to in order to minimise hypoglycaemic events.

Use of premixed insulin analogues, because of the rapid action of the insulin analogue, allows their administration more conveniently *just before* meals. However, *fixed times* for their administration in the mornings and evenings have to be adhered to.

The type of regimen that most closely mimics physiologic insulin delivery involves basal insulin combined with bolus (prandial, or mealtime) rapid-acting insulin. This regimen also allows the greatest amount of flexibility:

- The basal insulin has to be injected at a fixed predetermined time daily;
- Boluses may be taken before meals *whenever* a meal is taken. Also,
- Doses of the rapid-acting insulin analogue may be adjusted to suit the meal size and content.

Insulin pens simplify self-injection, make it more convenient and provide increased dosing accuracy. Patient acceptance plays a pivotal role in compliance and improved control.

Insulin therapy requires a good understanding of the patient's lifestyle to choose the appropriate insulin regimen. Business executives who require flexibility in terms of timing their injections with their meals, their travel, etc will benefit from a different choice of insulin to one who has a more regular lifestyle. Executives cannot often predict eating times, and one has to select an insulin formulation that has the widest flexibility.

Insulin options

There are a few options one may exercise in the introduction of insulin to the therapeutic regimen:

- Addition of a single dose of basal insulin
- Addition of a single dose of premix insulin
- Use of twice daily premix insulin
- Use of a basal-bolus insulin regimen

1. Addition of basal insulin

As mentioned earlier, the pathophysiology of type 2 diabetes reveals that with the presence of hyperglucagonaemia, coupled with a steady reduction in insulin secretion there is increased hepatic glucose production, and consequent fasting hyperglycaemia. The use of basal insulin at night, together with concomitant use of current oral hypoglycaemic agents, would suppress the hepatic output of glucose and reduce the fasting hyperglycaemia. The use of a single dose of basal insulin, where appropriate, solves the problem. One could use NPH insulin provided it suppresses fasting hyperglycaemia without early morning hypoglycaemic episodes. Alternately, one could use detemir or glargine at a convenient time in the evening, starting with a dose of 10–14 units nocte, and can be gradually up-titrated at 2–4 units every third day until target fasting blood glucose of below 6 mmol/l is reached.

The additional value of adding basal insulin is that when the next level of intervention is required, usually the conversion to twice daily premix

insulin, the patient has already been introduced to insulin therapy. If post supper values are high, it may be better to initiate insulin therapy with an evening premeal dose of a premixed insulin analogue.

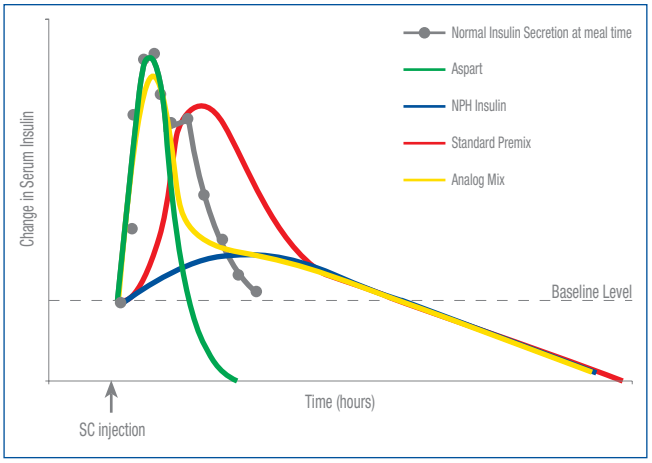
In order to get HbA_{1C} to less than 7%, with time, both fasting and postprandial glucose levels have to be lowered to target.

The key consideration is to balance the individual's need for glycaemic control with his or her tolerance for performing self-injection. The use of basal insulin either alone, or in combination with an oral antidiabetic agent such as metformin, provides considerable flexibility in the earlier stages of the disease. The long-acting basal insulins can be administered at the same time, any time of the day, at 24-hour intervals. However, it is usually taken at bedtime for convenience by most.

2. Addition of a single dose of premix insulin

The principle behind the use of premix insulin is to mimic the physiological action of basal insulin secretion with a meal-related peak of insulin, the so-called Dual-Release Insulin Concept. Using a rapid-acting analogue provides a rapid prandial peak, coupled with slow basal release, which regulates hepatic glucose production. See Figure 1.[16]

Figure 1: Biphasic insulin analogues



If the fasting glucose is within the desired range and yet the HbA_{1C} is not coming down, the problem is usually elevated postprandial glucose values. As HbA_{1C} comes down closer toward normal, there is a greater contribution to glycaemia from postprandial glucose. The patient may have a pattern of elevated fasting blood glucose, together with an elevated post-supper value (noting that often the supper is the largest meal of the day).

This defect is conveniently overcome by using premixed insulin (regular human insulin plus NPH insulin, or premixed insulin analogue). This controls both the post-supper and the fasting hyperglycaemia with a single injection. The oral hypoglycaemic agents must be continued to assure glycaemic control.

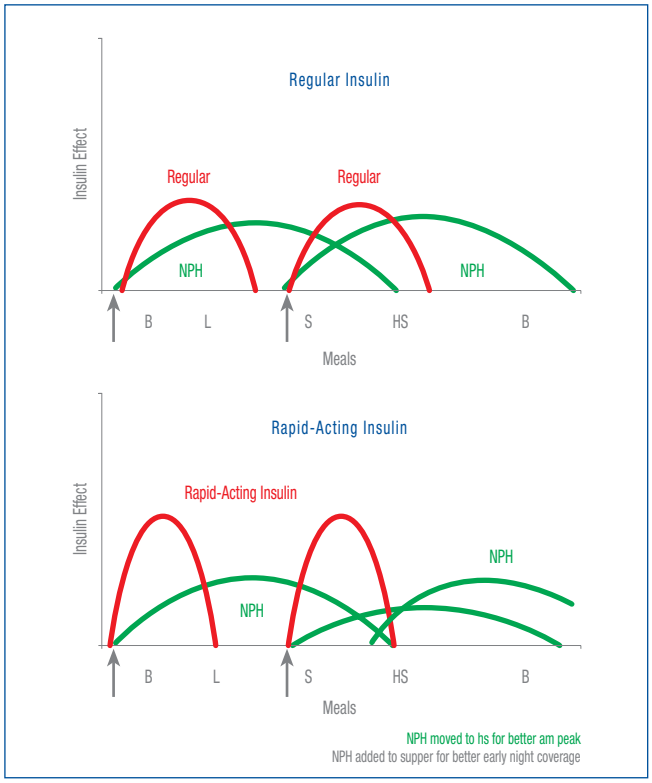
3. Use of twice daily premix insulin

When further deterioration of pancreatic ß-cell function results in postprandial hyperglycaemia after each of the meals taken daily, it is time to use the premixed insulin at least twice daily. At this stage the insulin secretagogues (sulphonylureas) are discontinued. For its utility in reducing insulin resistance, metformin is usually continued in the majority of patients, with or without thiazolidinediones. Regimens involving two daily injections of premixed insulin (regular human insulin plus NPH insulin, or premixed insulin analogue) are useful in patients *who do not require as much flexibility* and who take meals at consistent intervals.

It is important to remember that this regimen of insulin administration is not a physiological one. Insulin is injected in *anticipation* of daily activity, (which includes eating, physical activity, eating times, etc), and meal times should be regularly adhered to if hypoglycaemic episodes are to be minimised. It is important to administer the premixed insulin doses at *about the same time everyday* (inclusive of weekends): this is the price one pays (reduced flexibility) for opting for a two injections per day regimen versus a four injection per day regimen. Usually the total daily dose of insulin is split as two-thirds in the morning and one-third in the evening.

The injections may be given as a premix combination, or one could use short-acting regular, or rapid-acting analogues injections together with intermediate acting bolus injections. See Figure 2.[16]

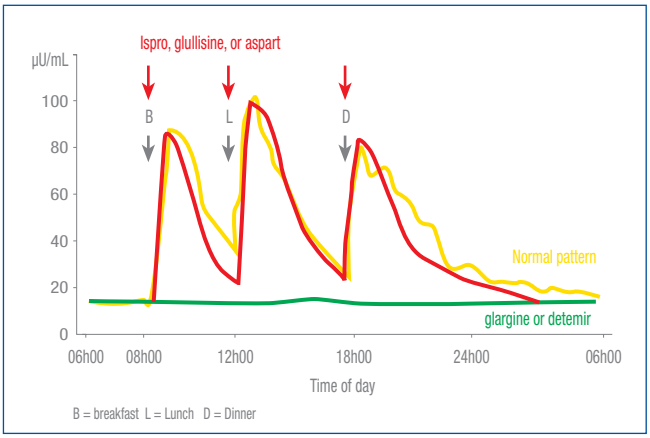
Figure 2: Multiple injection programme: NPH and pre-breakfast and supper short- or rapid-acting insulin



4. Use of a basal-bolus insulin regimen

The type of regimen that most closely mimics physiologic insulin delivery involves basal insulin combined with bolus or prandial rapid-acting insulin. This approach requires three or four daily injections. The major advantage of this regimen is the greater degrees of flexibility that are afforded to the patient. Meal times need not be adhered to strictly, and doses of bolus injections can be adjusted according to the content and quantity of meals taken. This is the ideal type of regimen for young adults requiring insulin, and also those with much variability in meal times due to business or other commitments. Active sportsmen would also benefit from this regimen, as would pregnant patients. See Figure 3.[16]

Figure 3: Basal-bolus insulin treatment with insulin analogues



The choice of using short-acting versus rapid-acting insulin devolves around the presence of premeal hyperglycaemia. The slower rate of absorption of a short-acting insulin with its relatively prolonged duration helps reduce the premeal glycaemia. Alternately, the dose of basal insulin may be increased to achieve the same result provided it does not increase hypoglycaemic episodes.

Insulin choices are made on glycaemic trends of patients that we aim to match with insulin pharmacokinetics. The best regimen is *one that controls the patient with a minimum of side effects.* All the currently available insulins are of value to the patients, allowing us the opportunity to 'mix-and-match'.

Studies have been conducted to compare the use of basal insulin vs. intermediate-acting insulin. This was the treat-to-target study, where glargine was compared with NPH in a group of patients not controlled on oral medicines.[12] *Both* insulins lowered HbA_{1c} from 8.6% to 7.1% over 3 to 4 months, and they required roughly equivalent doses. The difference in the study was that with glargine, there was a less nocturnal hypoglycaemia than with NPH.

Hypoglycaemic attacks with NPH are dose-dependent. If fasting glycaemic control can be achieved with NPH insulin *without* significant early morning hypoglycaemia, than its use is of value, as it is more cost-effective than the basal analogues. However, in view of the relatively shorter duration of NPH insulin compared to basal analogues, though fasting glycaemia may be achieved, often there may be a problem of pre-supper hyperglycaemia. Under these circumstances, one should consider the use of the long-acting basal analogues.

Once basal/bolus regimen is commenced, insulin secretagogues would be discontinued from the treatment programme, whilst still continuing metformin, which reduces insulin resistance and thus allows lower insulin doses to attain glycaemic targets. However, if the patient is very insulin resistant, then a thiazolidinedione[1] would remain part of the therapy for its insulin-sensitising effects.

Normally, 50% of the glucose in the body is exogenous (from ingestion of food) and 50% is derived from endogenous hepatic glucose production. Thus, it will be logical that about 50% of the total daily-injected insulin should be divided over three periods of the day, as prandial insulin, to control the three meals, whilst 50% will be taken as basal insulin to regulate hepatic glucose production. The three pre-prandial doses of insulin are adjusted according to the patient's eating habits, and appropriate dose are ascertained by measuring blood glucose values using a glucometer. Patients are asked to measure blood glucose values on waking (fasting value) followed by measures taken 2 hours after each of the meals. Insulin dose titrations are implemented according to the blood glucose values.

High premeal values can be brought under control by either increasing the basal insulin dose, or by using regular short-acting insulin at least 30 minutes premeal, in view of its longer duration of action, which would cover the premeal period.

Conclusion

The wide varieties of available insulin formulations allow us a large amount of latitude in making informed choices for selecting the best insulin to match the patient's profile. Appropriate selections can only be made if the practitioners familiarise themselves with each of the insulins.

The global problem in diabetes care has been the delay in initiating insulin therapy once oral hypoglycaemic agents are no longer effective in maintaining the HbA_{1c} values below 7%. Early on the addition of basal insulin, or premix insulin given at supper time often suffices.

The availability of pen devices has greatly facilitated the administration of insulin, both the basal and bolus varieties. Contrary to common expectation, patient acceptance has also been very good.

The art of insulin injection therapy can be mastered early, and confidence grows with further experience. Too often doctors call in nurse- or diabetes-educators to train patients: the doctor must be fully versant with the techniques as well. If the doctor lacks the confidence, patients should be referred to appropriate centres. It must be remembered that once the HbA_{1c} has risen above 7%, there is a call for immediate and urgent action.

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