Insulin Therapy for Patients with Type 1 Diabetes
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Abstract
The incidence of type 1 diabetes is increasing world wide, especially in younger children. Unfortunately, there is little information on the incidence of type 1 diabetes or its management from India. Recent studies have emphasized the importance of strict glycemic control in the prevention and delay of chronic microvascular complications of diabetes mellitus. This has lead to increasing efforts in devising means of physiological insulin delivery, in which basal insulin and meal related boluses of insulin are separately given and insulin doses are appropriately altered based on frequent blood glucose testing, meal size and exercise. Newer insulin analogues, which better mimic basal and meal related increments of insulin secretion, have been marketed. Regimes for physiological insulin delivery, such as multiple subcutaneous insulin injections and continuous subcutaneous insulin infusion are becoming increasingly popular. However, the high frequency of hypoglycemia is an important constraint to achieving normal glycemic control. In developing countries such as India, other obstacles include the high cost of insulin and blood glucose monitoring strips, social barriers to accepting insulin injections and lack of trained teams for management of type 1 diabetes.

Introduction
The purification of insulin by Banting, Best, Collip and Macleod in 1921 was one of the most important scientific achievements of the twentieth century. When first used in the treatment of a patient with type 1 diabetes in 1922, it led to disappearance of ketones and glucose in the urine and a remarkable improvement in his clinical features. It gave hope to thousands of patients with type 1 diabetes, prolonged their life span by decades, and allowed them to lead a highly improved quality of life. However, the early hopes that insulin replacement would prevent chronic complications of long-term diabetes have not been fulfilled. This is because it has been exceedingly difficult to design means for physiological replacement of insulin, such that glucose is maintained within a normal range over the long-term while avoiding disabling hypoglycemia.

The results of the many recent studies have conclusively proven that strict glycemic control can prevent or delay chronic microvascular complications of this disease. Hence, the aim of treatment of type 1 diabetes should be to achieve glycemic control within, or close to the normal. However, there are many impediments to the physiological replacement of insulin. Even the most intensive insulin regimes only imperfectly mimic insulin secretion by the beta-cell. Until recently, the commonly available insulins had an action profile which made it difficult to mimic exactly the way insulin is secreted in the body i.e. to provide true basal insulin levels and short prandial peaks. Furthermore, as with any other chronic illness, numerous social and psychological factors hinder appropriate insulin replacement, even when resources are available. Finally, and more so in developing countries, there are constraints of finances and knowledge which stand in the way of optimal use of insulin.

Physiology of insulin secretion
The secretion of insulin is tightly linked to plasma glucose levels by a closed loop feedback, which allows glucose levels to remain tightly controlled within a narrow range (70-120 mg%). In its most simple form (Figure 1), insulin secretion can be divided into basal secretion and meal-related increments. In the basal state, beta-cells of the pancreatic islets secrete adequate insulin to utilize the glucose produced in the body, especially by the liver. Appropriate levels of basal insulin are required to ensure that blood glucose levels are maintained between meals. Each meal leads to a sharp increase in insulin secretion, the amount of insulin secreted being proportional to the meal. Plasma glucose increases to a maximum in 30-60 minutes, and then returns to basal within 2 hours (Figure 1). Insulin levels rise and then decrease to basal levels in a similar time frame. The sharp rise in insulin ensures appropriate utilization of ingested nutrients, while the rapid fall of insulin to basal levels prevents hypoglycemia in the period between meals.

Insulins and newer analogues
Conventional insulins
Commonly available conventional insulins are derived from animal sources (bovine, porcine), while human insulin is manufactured by recombinant DNA technology. Until the recent synthesis of insulin analogues, these were main types of insulins available for the last 80 years. Since the advent of recombinant human insulin this has become the preferred method for commercial production. There are only minor differences in the action profile of insulins from different
sources, and since all insulins are nowadays highly purified, they have similar adverse effects.\textsuperscript{13, 14} In general, the source of insulin has far less effect on glycemic control compared to other factors such as the dose, timing, site and depth of injection, proper mixing of cloudy insulins etc.\textsuperscript{15,16} In view of the higher cost of human insulin we often prescribe bovine insulin. However, bovine insulin is not easily available in India anymore.

On the basis of their action profile, insulins can be divided into short, intermediate and long acting.\textsuperscript{15} Short acting insulin (regular or plain) is used to cover for meals, since it has a quick onset (30 minutes), peaks 2-3 hours after injection and has a short duration of action (4-6 hours, Table 1). Intermediate acting insulins consist of regular insulin modified by adding zinc (lente) or basic protein (NPH). These are used primarily to provide basal insulin replacement. These insulins have duration of action of 12-14 hours and usually need to be given twice in a day to provide cover for the entire 24 hours. Human long-acting insulin (ultra-lente) has duration of action of approximately 18-20 hours, but its absorption is highly variable.

Used in proper manner these insulins can provide insulin cover in a physiological manner. However, certain shortcomings make them less than ideal for this purpose (9-11). Regular insulin forms hexamers in solution and is released slowly from the subcutaneous tissue. Therefore, it has a relatively delayed peak and long duration of action to qualify as the ideal insulin for meal-related glucose rise. Since it reaches a peak relatively slowly, there is often hyperglycemia shortly after a meal; its relatively long duration of action however predisposes to hypoglycemia 3-4 hours after the meal. Intermediate acting insulins, when used to provide basal insulin replacement, have the disadvantage of definite peak 6-10 hours after injection and can therefore lead to hypoglycemia in-between meals and at night. By taking the intermediate acting insulin at bedtime, rather than before dinner, nocturnal hypoglycemia can be minimized and the problem of fasting hyperglycemia reduced.\textsuperscript{17} Since their duration of action is only 12-14 hours, these insulins need to be taken at least twice daily. Improper re-suspension of cloudy insulin (lente, NPH) is an important source of variability of insulin absorption.

Despite the above-mentioned disadvantages, if used in a proper manner, these conventional insulins can be used in regimens to provide physiological replacement.

### Insulin analogues

To provide insulins with distinct properties which are suitable for basal and bolus action, the insulin molecule has been genetically modified. Such insulin analogues are now commercially available. They can be divided into two types: rapid and long-acting (basal) insulins. Rapid-acting insulin analogues (insulin lispro, insulin aspart) have the property of not aggregating when injected subcutaneously under the skin, and are therefore absorbed quickly.\textsuperscript{9-11, 18-20} Lispro insulin results from an exchange of amino acid lysine and proline at position B28 and 29 while in aspart insulin, proline is substituted with aspartic acid at position 28 of the beta-chain. In comparison with regular insulin, they have an onset of action within few minutes, an earlier and higher peak and shorter duration of action (Table 1, Figure 2). Thus, they are ideally suited to provide insulin bolus for meal-related glucose increments. Studies using these analogues have shown that they may provide improved post-prandial glucose control, lower frequency of late post-meal hypoglycemia and slightly improved hemoglobin A1c, when compared to regular insulin.\textsuperscript{9-11, 21-23} They are especially useful in physiological insulin regimens where basal and bolus insulins are separately administered,\textsuperscript{9,11} in young children, where they can be given after meal is started,\textsuperscript{24, 25} and in insulin pumps.\textsuperscript{26, 27}

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**Table 1: Insulins available in India and their action profile**

<table>
<thead>
<tr>
<th>Insulins</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting</td>
<td>5-15 min</td>
<td>30-90 min</td>
<td>4 hrs</td>
</tr>
<tr>
<td>Lispro</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td>30-60 min</td>
<td>2-3 hrs</td>
<td>6-8 hrs</td>
</tr>
<tr>
<td>Regular</td>
<td>1-2 hrs</td>
<td>4-6 hrs</td>
<td>10-16 hrs</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting</td>
<td>2-4 hrs</td>
<td>No peak</td>
<td>20-24 hrs</td>
</tr>
<tr>
<td>Glargine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detemir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-mixed</td>
<td>30-60 min</td>
<td>Dual</td>
<td>10-16 hrs</td>
</tr>
</tbody>
</table>

30%/70% regular/NPH
50%/50% regular/NPH

NPH- Neutral Protamine Hagedorn

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**Fig. 1**: Glucose and insulin homeostasis in normal, non-diabetic people (n=8) Mean±2SD (Adapted from reference 9, with permission)
Studies using glargine insulin have shown that it provides similar or slightly improved fasting glucose level, similar hemoglobin A1c levels but significantly lower frequency of nocturnal hypoglycemia. 28, 29 In contrast to conventional intermediate acting insulins, glargine is peakless, and needs to be given only once daily. 9-11, 20, 29, 30 Another basal insulin analogue, insulin detemir, binds to albumin via a fatty acid chain, leading to its slow release and prolonged action.31 In comparison to NPH insulin, detemir has reduced variability of basal insulin requirements and decreased chances of nocturnal hypoglycemia.32, 33

The above advantages of insulin analogues are balanced by the disadvantage of high costs and scant data about long-term safety and teratogenicity.

Insulin delivery

Insulin is delivered most commonly by subcutaneous injection using insulin syringes. Insulin pens form a convenient alternative means for dispensing insulin accurately, but are more expensive than syringes. Subcutaneous infusion of rapid or short-acting insulin using an electromechanical pump has the advantage of controlling insulin absorption more accurately.24, 28 However, since the subcutaneous depot of insulin is small, the chance of resulting ketoacidosis if infusion is interrupted is high. More recently, pulmonary inhalation of short-acting insulin has shown promising results of providing bolus doses of insulin through this route.26-38 Inhaled insulin has recently received FDA approval.

Insulin regimens

Any form of insulin replacement which provides separately for basal insulin requirements and meal-related increments of insulin, and which allows for adjustment of insulin dosages in relation to ambient blood glucose, meals, exercise etc. is known as “physiological” replacement.7, 8

Non-physiologic regimens

Regimens that do not mimic the normal insulin secretion pattern are known as non-physiological. The use of intermediate (basal) insulin or short acting insulin alone are examples of such regimens. Fixed combinations of short acting and NPH insulin in ratios of 30:70 and 50:50 are the most popular forms of insulin sold worldwide (and in India). These combinations may be useful in patients with type 2 diabetes. While such combinations provide ease of use, they have no role in the management of type 1 diabetes, in view of the large variability of insulin requirements and frequent changes in daily insulin requirements. Such combinations result in poor glycemic control or lead to frequent hypoglycemia if strict control is attempted.
Physiologic insulin regimens

Such regimens mimic insulin secretion by the beta-cell and provide separate basal insulin and meal-related increments.

A. Conventional

Conventional insulin regimens consist of two injections of short and long-acting insulin, “split and mixed” regimen. The timing and dose of short and intermediate acting insulin can be altered depending on the blood glucose, meals or other factors. The intermediate acting insulin given before breakfast acts as both basal insulin during daytime, as well as prandial insulin for lunch. In general, with this regime the timings and amounts of meals and snacks and exercise have to be fixed and remain relatively constant. Glycemic control achieved is reasonably good, but attempts to normalize blood glucose may result in unacceptably high risk of hypoglycemia in between meals and at night. Hence, it is important to prescribe snacks in between meals. By taking the intermediate acting insulin later i.e. at bedtime rather than pre-dinner, both nocturnal hypoglycemia as well as fasting hyperglycemia can be reduced. Conventional insulin regimens are relatively easy to explain and require lesser resources from the diabetes management team. It also places a smaller financial burden on patients and their families. Such regimes are presently most suitable for vast majority of patients in our country, since the resources required for more intensive regimens are not affordable nor are diabetes education teams available to provide the necessary support.

B. Intensive

These regimens aim to provide glycemic control within, or close to the normal range, using all available resources for this purpose. They provide for completely separate basal insulin and insulin boluses for meals. To be successful, the regimes require frequent adjustment of insulin dosage taking into account the ambient blood glucose, food (especially carbohydrate) intake and exercise schedule. Thus, frequent monitoring of blood glucose 3-5 times per day is an important prerequisite of such regimens. Adjustment of basal insulin and meal-related bolus of insulin is done separately according to previously defined algorithms. The basal-bolus regime can provide excellent glycemic control, though risk of severe hypoglycemia is high as hemoglobin A1c reaches normal range. The regimen provides greater flexibility in meal timings and amounts, but it requires greater motivation and financial resources from the patient and family members. In addition, the availability of an experienced team (doctor, nurse educator and dietician) who can assist the patient is essential. Indications for intensive insulin management include adults and selected adolescents and children with type 1 diabetes, pregnant women with diabetes, labile diabetes and those with renal transplantation.

Intensive insulin replacement can be provided by regimens of multiple subcutaneous insulin injections (MSII) or by continuous subcutaneous insulin infusion (CSII). A comparison of conventional and intensive insulin regimens is shown in the Table 2.

MSII

This is by far the most popular regimen for intensive insulin therapy. In MSII, the basal insulin is provided by

| Table 2: Physiological insulin therapy: conventional vs. intensive insulin regimen |
|-----------------|------------------------|
|                  | Conventional regimen   | Intensive regimen |
| Principle        | • Attempt to provide    | • Separate basal and meal insulin |
|                  | • basal and meal related bolus of insulin | • Frequent HBGM |
|                  | • HBGM as far as possible | • Insulin dose adjustments |
| Goals            | • HbA1c < 8% | • HbA1c < 7% |
|                  | • Fasting glucose 80-160 mg% | • Pre-meal glucose 80-130 mg% |
|                  | • Post meal glucose <160 mg% | • Post meal glucose <160 mg% |
| Advantages       | • Easier for subject to manage | • More flexibility in life-style |
|                  | • Fewer resources required | • Lower risk of microvascular complications |
|                  | • Less risk of hypoglycemia | • More resources necessary |
| Disadvantages    | • Less flexibility | • Increased risk of hypoglycemia |
|                  | • Higher risk of microvascular complications | |
| Qualified        | • Not required | • Necessary |
| management       | | |
| team | | |
| Regimes | • Twice daily regular and NPH insulin | • MSII or CSII |
|          | • HBGM 2-3 times/day | • HBGM 4-5 times/day |
|          | • Insulin dose supplementation and adjustment | • Insulin dose supplementation and adjustment |

MSII: multiple subcutaneous insulin injections
CSII: continuous subcutaneous insulin infusion
HBGM: home blood glucose monitoring
Hemoglobin A1c: normal range 4-6%; goals of therapy will vary depending upon age, motivation and economic status and need to be individualized

2 injections of NPH insulin taken 12 hours apart or by a single injection of insulin glargine or detemir every 24 hours. In addition, injections of short acting (regular) or rapid-acting (insulin aspart or lispro) are used before each meal. Approximately half the insulin is provided as basal replacement and half as meal-related boluses. Home blood glucose monitoring (HMBG) is required between 3-5 times per day, especially before each meal. Changes of pre-meal insulin doses are made depending on the ambient blood glucose and amount of carbohydrates consumed in the meal. Insulin “pens” are a convenient means of taking multiple injections.

Continuous subcutaneous insulin infusion (CSII)

Also known as “insulin pump therapy”, insulin is delivered continuously into the subcutaneous tissue at selected rates through a portable electromechanical pump. Either regular or rapid-acting insulin is used for this purpose. The insulin is delivered at pre-selected rates of continuous basal output throughout 24 hours. The ability to
have multiple programmable infusion rates allows rates of infusion to be increased in the early morning to take care of the phenomenon of rise of blood glucose before breakfast (the “dawn phenomenon”). Patient-activated boluses of regular or rapid-acting insulin are delivered before meals.

CSII is becoming increasingly popular as a means for providing intensified insulin therapy, with the greatest experience in USA. It allows for excellent glycemic control and good quality of life in selected patients. With careful attention to details, the frequency of hypoglycemia is not higher than with conventional therapy. However, the patients who opt for this form of therapy need to carefully chosen. Technical support for the pump and a diabetes care team trained in pump usage is also essential. Indications of CSII include patients unable to achieve glycemic targets despite being on MSII, recurrent hypoglycemia on MSII and motivated patients who indicate a preference for CSII over MSII. Patients who have “brittle” diabetes, with frequent episodes of ketoacidosis and hypoglycemia, may not be good candidates for CSII, since they often have psychological reasons for their poor control. Currently, insulin infusion pumps are available in India through Medtronic MiniMed.

Numerous studies have compared CSII with MSII regimens. In general, CSII achieves similar, or slightly improved, mean blood glucose and hemoglobin A1c values compared to MSII. The insulin dosage needed to achieve this glycemic control is often lower in CSII. In some, but not all studies, the frequency of hypoglycemia is lower in CSII compared to MSII. A few recent studies have shown that use of rapid acting insulin analogues in place of regular insulin in CSII regimens leads to a reduction in hypoglycemia. Earlier studies had shown an increased rate of ketoacidosis in patients on CSII. One reason for this is that patients on CSII have a far smaller subcutaneous depot of insulin than those on insulin injections, and ketosis can develop rapidly if insulin infusion gets interrupted. With more reliable pumps (with pump failure alarms), more experience with pump usage, insulin that do not aggregate, and better patient selection, the frequency of ketoacidosis is now reported to be similar to that in MSII. Infection at the catheter needle insertion site may complicate CSII therapy, but can be minimized with proper hygiene.

In summary, the level of glycemic control by MSII and CSII are similar, though some studies report a higher level of patient satisfaction with CSII. However, CSII is more expensive and requires greater patient involvement and support. If patients are doing well on MSII they need not be shifted to CSII.

Side effects of insulin therapy

The most frequent, and serious, side effect of insulin therapy is hypoglycemia. As the glycemic control reaches within, or close to, the normal range the frequency of severe hypoglycemia increases. Thus, in the Diabetes Control and Complications Trial study, the frequency of severe hypoglycemia was 3 times higher in the intensively treated group of patients compared with the conventionally treated group. However, with careful attention to education, blood glucose monitoring, and adjustment of insulin dosages, the rate of severe hypoglycemia may be as low as patients on conventional therapy.

Patients on insulin treatment often gain in weight at the start of treatment. This is related to a reversal of the catabolic state induced by insulin-deficiency. There may be further weight gain in intensive therapy regimens due to relaxation in dietary norms. Recurrent hypoglycemia may lead to increase in snacking and weight gain.

With the advent of highly purified insulin, local side effects such as insulin allergy and lipoatrophy are now rare. However, lipohypertrophy at the insulin injection sites is common if injection sites are not regularly rotated.

Special considerations: young children, adolescents

The management of diabetes in young children poses a special set of problems. Small children are more prone to develop hypoglycemia due to erratic feeding and activity, and due to their inability to express early symptoms of hypoglycemia. Severe hypoglycemia may lead to long-term cognitive impairment. Hence the goals of therapy in this age group are to achieve reasonable, but not strict, control. Most children are managed by conventional injection therapy, along with frequent HBGM. Short acting insulin analogues, given after feeds, are useful since the dose of insulin can be adjusted to the food intake. Recently, a few centers have published their experience with MSII and CSII regimens in very young children. Adolescence is associated with increasing insulin resistance. This leads to an increase in insulin requirements (1.2-1.6 U/kg/day) during this period. In addition, psychological factors can interfere with optimal diabetes care. Puberty has an adverse effect on glycemic control and is associated with an increased risk of microvascular complications. Therefore, depending upon the socio-economic condition and motivation of the patient and family, the aim of insulin therapy during this period should be to achieve as strict a glycemic control as feasible, using all resources available.

Type 1 diabetes and insulin usage practices in India

There are very few clinical studies on the prevalence of type 1 diabetes or insulin usage and glycemic control in India. Available studies on the prevalence and incidence of type 1 diabetes in India do not allow us to get a good idea of the extent of the disease in this country. It is also unclear if the prevalence of type 1 diabetes is rising in this country, as is seen in other parts of the world.

The circumstances in which management of type 1 diabetes has to be carried out in India presents a unique set of problems. Patient related factors, which form an impediment to diabetes management, include a reluctance to take insulin injections and practice HBGM, poor economic resources leading to an inability to afford insulin, glucose strips and investigations, and lack of facilities for proper storage of insulin. The burden of a chronic disease is felt more acutely in the girl child with diabetes. In addition to these, lack of qualified health care professionals and poor availability of insulin and strips for blood glucose in smaller towns and villages lead to less than optimal care of
type 1 diabetes. There are few pediatricians and even fewer diabetes nurse educators trained in management of type 1 diabetes in India. In many instances, children are treated with a single injection of long acting insulin, or are treated with regular insulin without any basal insulin. Glucose monitoring is infrequent and often done in the laboratory. HMBG and adjustment of insulin doses is rarely carried out. Patient education is scanty or non-existent and little information is available to the patient for adjusting insulin or meal schedules or dealing with emergencies. However, patients may benefit from some positive factors that exist in traditional Indian families. These include high degree of family support and intact families, delayed autonomy for adolescents, and a staple diet (in north India) which includes chapatis, dals and vegetables with little variation in the meal pattern, timing and amounts.

In such circumstances, where economic and social considerations vary so widely from that in the western world, a pragmatic approach needs to be adopted. Resources for MSII/CSI are usually not available and in place of “tight” control of blood glucose a strategy needs to be adopted to achieve adequate control (A1c <8%) using the least amount of resources. Education of the patient and the family remains the key factor. Currently at our Institute we use a multi-disciplinary approach (including a teaching nurse and dietician) to manage children and adolescents with type 1 diabetes.56 We encourage patients to be admitted when they are first seen in our clinic for education and adjustment of insulin doses. The vast majority (>95%) of the children in our clinic are on twice daily short and intermediate acting insulin, while only 4% are on MSII. Home monitoring of blood glucose is encouraged 2-3 times a day, before meals and at bedtime, often using less expensive visually read strips. In case strips are not affordable, urine and blood sugar monitoring are combined. Using this approach, the mean hemoglobin A1c of our patients was 8.2% ±1.5% (euglycemic range 4.1-6%); 52% had an HbA1c of <8%, while it was > 10% in 10% of patients. This can be compared to a mean HbA1c of 8.6% ±1.7% (euglycemic range 4.1-6%) in healthy controls. 52% had an HbA1c between 8.2% +1.5% (euglycemic range 4.1-6%) and 8.6% +1.7% (euglycemic range 4.1-6%), while it was > 10% in 10% of patients. This can be compared to a mean HbA1c of 8.6% ±1.7% in a large population adequate glycemic control can be achieved by pragmatic use of insulin, testing and education. However, mortality remains unacceptably high.

Conclusions

The goal of insulin therapy in type 1 diabetes is to achieve near normal glycemic control so that microvascular complications of diabetes can be prevented. This needs to be done with the least risk of disabling hypoglycemia. Despite significant advances in the management of diabetes, this aim is still unattainable except for a minority of patients with type 1 diabetes. This is especially so in developing countries such as India. It should be the endeavor of diabetes care professionals and health authorities to provide suitable facilities and resources (insulin, glucose strips, testing for early diagnosis of complications) to all patients with type 1 diabetes. It is essential to educate patients and their families about the importance of strict glycemic control, and providing them with enough information and resources to achieve this aim to the best of their ability.

References


