Review Article

Insulin Therapy

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Optimal glycemic control in type 1 diabetes mellitus (T1DM) requires Intensive Insulin Therapy. Implementation of intensive therapy should be early and prolonged as suggested by the results of Diabetes control and complications trial and Epidemiology of Diabetes Interventions and Complications (EDIC) study. Proper implementation of intensive therapy requires a course teaching flexible intensive insulin treatment combining dietary freedom and insulin adjustment as shown by the Dose adjustment for normal eating (DAFNE) randomized controlled trial. Pen injectors appear to be feasible for routine use although pumps may be required in special situations. Various types of insulin are available in the market, including newer analogs (Iispro, aspart, glargine). Although insulin analogs seem to be more physiological, controlled studies suggested either similar efficacy to regular insulin or only a minor benefit in favor of insulin analogs. The primary concern in developing countries like India is the cost-benefit ratio of short acting insulin analogs in the treatment of diabetic children but this still remains unclear. It would be premature to recommend switching patients to newer analogs especially those who are well controlled, especially when the long-term data is still awaited. The choice of post-meal short acting insulin in toddlers may be decided by the care provider if deemed appropriate. Noninvasive insulin deliveries are now in development. It does appear that the most clinically viable non-invasive system to date may be pulmonary delivery.

Key words: *Intensive insulin therapy, Insulin analogs, Noninvasive insulin delivery.*

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Children with type 1 diabetes mellitus (T1 DM) require proper insulin therapy, regular monitoring of blood glucose (including HbA 1c) and an optimal diet. Insulin therapy began with beef/pork insulin, followed by an era of recombinant human insulin and now we are in the third phase of insulin therapy where insulin analogs are used. This review focuses on details of insulin therapy with special emphasis on newer analogs and noninvasive insulin delivery.

A. Conventional insulin therapy

Conventional therapy, the most commonly used, refers to 1-2 daily insulin injections. The total daily dose is divided into 2/3 pre-breakfast and 1/3 pre-dinner. Ratio of short acting (human regular): intermediate acting (NPH, Lente) = 30:70. Insulin is started at 60-70% of the full replacement dose. Further adjustments are made as per pre-meal sugars (usually 10-15% of dose or approximately 0.5 U for toddlers and 1U for an older child). After initial stabilization of blood glucose the patient does not alter the daily dose of insulin as per pre-meal sugars, exercise and expected diet.

B. Intensive insulin therapy (IIT)

Intensive therapy includes the administration of insulin ≥3 times daily by multiple daily injections (MDI) or pen, or an external pump. Every dose of insulin is adjusted according to the pre-meal blood glucose performed at least four times daily, dietary intake, and anticipated exercise. It does

not refer to the type of insulin(1). Total daily dose is divided as follows:

- *Basal dose:* 25-30% of the total dose in toddlers and 40-50% in older children, given at bedtime. This suppresses the glucose production between meals and overnight.
- *Bolus doses:* Remaining dose is divided into 3 pre-meal doses. The meal time (prandial) doses limit post-prandial hyperglycemia. Every bolus dose of insulin is adjusted as per the scale in *Table I*(2).

Sliding scale refers to basing an insulin dose as per the premeal sugars. Thinking scales are replacing this concept, where the amount of exercise (recent and expected) and the expected diet intake are also taken into consideration along with the pre meal sugars. The pre-meal blood glucose should never be the only factor considered. The inherent advantage is that sugar monitoring has to be done 3-4 times a day to follow the scale. IIT imposes extra demand on the family in terms of number of injections per day, blood glucose monitoring and financial costs.

Diabetes control and complications trial (DCCT) has conclusively proven that intensive therapy improves long-term glycemic control (HbA 1c) and reduces the risk of development and progression of microvascular complications(1); the major drawback being 2-3 fold increase in severe hypoglycemic episodes.

Dose adjustment for normal eating (DAFNE). The intensive approach used in the DCCT trial involved frequent outpatient visits with close supervision of insulin dose adjustment and has not been incorporated into general diabetes practice. Current treatment of T1DM fails to engage many patients in intensive self-management, which is essential to successful treatment of T1DM. DAFNE trial has shown that, a course teaching flexible IIT combining dietary freedom and insulin adjustment, significantly improves glycemic control at 6 months (mean HbA1c 8.4% vs 9.4%, P <0.0001), however severe hypoglycemia, weight, and lipids remained unchanged. Despite an increase in the number of insulin injections and blood glucose monitoring there was sustained positive effects on quality of life, satisfaction with treatment, and psychological well-being. The DAFNE approach has the potential to reduce the incidence of microvascular complications(3). Patients need to fit diabetes into their life and not their life into diabetes. It requires huge

TABLE I–*Subcutaneous Basal-Bolus Insulin Dosing and Glycemic Targets*

Age group (years)	Target pre-meal blood sugar*	Target HbA 1c (mg%)	Dose** (U/kg/d)
0-6	100-180	7.5-8.5%+	0.6-0.7
6-12	90-180	<8%	0.7-1.0
13-19	80-130	<7.5%	1.0-1.2

* These are only target values. If 50-60% of the values are in the target range then the HbA 1c will be in the target range.

\+ To minimize the risk of hypoglycemia as well as excessive hyperglycemia, both lower and upper targets for this age group are provided(3).

** The dose also varies with pubertal status–Pre-pubertal–0.7-0.8 μ/kg/day, Mid-pubertal–1-1.5 μ/kg/day, Post-pubertal–1-1.1 μ/kg/day, Honeymoon period–0.2-0.5 /kg/day.

commitment from the individual and family to check blood glucose several times daily and adjust insulin dose accordingly. Dietary flexibility and DAFNE approach can only be offered if the family is committed to an intensive monitoring regime, which is psychologically, and financially demanding.

C. Types of insulin

The pharmocokinetic details of available insulins are shown in *Table II*. Conventional insulins were beef/pork pancreas extract. Intermediate/long acting preparations were prepared by adding zinc (Lente, ultralente) or other proteins *e.g.,* protamine (NPH). Recombinant human insulin has lesser antigenic reactions and side effects, better subcutaneous absorption, earlier and a more defined peak, and have replaced older insulins. Modifying the amino acid sequence of insulin molecule has developed newer analogs.

Short acting insulin analogs (SAI)

Insulin lispro and aspart are the available SAI analogs. They have a faster rate of absorption because of the reduced tendency to self-associate into dimers and hexamers. Peak plasma concentrations about twice as high and within approximately half the time compared to regular insulin. Both are identical pharmacokinetically.

Cochrane meta-analysis comparing the effect of SAI analogs with regular insulin concluded that use of a SAI analog in continuous subcutaneous insulin therapy (CSII) provides a small, but statistically significant improvement in glycemic control [weighted mean difference (WMD) –0.19% (95% CI: –0.27 to –0.12)]. The effect on glycemic control was even smaller with the use of MDl [WMD –0.08% (95% CI: –0.15 to –0.02)]. The rates of overall hypoglycemic episodes were not significantly reduced with SAI analogs in either injection regimen. No study was however designed to investigate possible long-term effects (*e.g.,* mortality, diabetic complications)(4). Other meta-analysis and reviews have also shown similar results(5-9). In one meta-analysis and one systematic review no differences were observed in children between treatments, while others have not separately evaluated the data in children(4,5). Studies have demonstrated that lispro can be administered even after meals in toddlers(9), hence allowing more accurate titration of doses for an erratic eater and can minimizing the potential for hypoglycemia.

Intermediate acting insulin

Neutral protamine lispro (NPL) Insulin. This preparation is intended primarily as an

TABLE II–*Types of Insulin*

	Insulin	Onset of action	Peak (Hrs)	Duration (Hrs)
Short acting	Human Regular	30-60 min	2-4	6-10
	Lispro, Aspart	5-15 min	1-2	4-6
Intermediate	NPH, NPL	1-4 hrs	5-10	10-16
Acting	Lente	3-4 hrs	6-12	12-18
	Ultra Lente	2-4 hrs	8-16	16-20
Long acting	Glargine	1-2 hrs	Flat	24
	Detemir	1-2 hrs	Flat	18-24

alternative to human insulin 30/70. NPL was developed for use within insulin lispro mixtures because an exchange between insulin lispro and NPH insulin precludes prolonged storage of mixtures of these insulins. To avoid this problem, NPL insulin (intermediate -acting insulin), an insulin lispro formulation, was developed, which is an analog of the NPH insulin.

Compared with human insulin mixtures, twice-daily administration of insulin lispro mixtures resulted in similar overall glycemic control, improved postprandial glycemic control(10,11), and less nocturnal hypoglycemia, as well as offering the convenience of dosing closer to the meals(10).

Long acting insulin

Insulin glargine: It is less soluble at neutral pH because of shift in the isoelectric point from pH 5.4 to 6.7. It is supplied as a clear solution at acidic pH. After injection, the acid in the vehicle is neutralized and glargine precipitates, thereby delaying absorption and prolonging action.

Studies comparing insulin glargine versus NPH insulin have consistently shown significantly lower fasting plasma glucose(12-15) and a significant decrease in the variability of fasting blood glucose values in glargine-pooled groups(12). Some studies have shown no differences in the glycemic control (HbA1c)(12,13,16) while others have demonstrated a small statistically significant improvement with glargine(14). Symptomatic hypoglycemia was reduced in some(13,14,16), but similar in others(12). A RCT of glargine versus ultralente showed that glargine resulted in slightly but significantly lower HbA 1c, less nocturnal variability, and less hypoglycemia(17). RCT of insulin glargine plus lispro vs NPH plus regular insulin on IIT showed no significant difference in HbA1c levels (LIS/GLAR versus R/NPH: 8.7 vs 9.1%, P = 0.13) and rates of self-reported symptomatic hypoglycemia(18).

In an Indian study a novel combination of short acting and NPH insulin before breakfast and combination of short acting and glargine insulin before dinner was used. It helped to reduced the number of injections, avoid pre-lunch insulin, reduce cost while achieving better glycemic control. Mean HbA 1C reduced from 9.5 to 7.3%, incidence of hypoglycemias from 1.6 to 0.8 over a six-month observation period(19).

Insulin Detemir: Insulin detemir has a more predictable, protracted and consistent effect on blood glucose than NPH insulin(20-22). It is as effective as NPH insulin in maintaining overall glycemic control(23), with a similar/lower risk of hypoglycemia(21,22). Insulin detemir is, therefore, a promising new option for basal insulin therapy.

Insulin injection

(*a*) *Where to Inject?* Insulin is injected into the subcutaneous tissue of the upper arm, anterior and lateral aspects of the thigh, buttocks, and abdomen. Insulin is absorbed more rapidly from the abdomen> arm>thigh>buttock. Rotating within one area recommended (*e.g.* rotating injections systematically within the abdomen) rather than rotating to a different area with each injection because it decreases day-to-day variability in absorp-tion. Any two sites can be chosen as per preference and the areas, which are not liked, can be skipped. More consistency in insulin levels may be obtained by giving all shots in the same parts for a week at a time *e.g.*, in the arm area for a week and then in the leg sites for a week or choose one area for the morning and one for the evening. Exercise increases the rate of absorption from injection sites;

therefore, if one is playing tennis do not inject insulin in that arm(24).

(*b*) *How to draw?* Draw an amount of air equal to the dose of insulin required and inject into the vial to avoid creating a vacuum. Inject air into the long acting first keeping the vial upright. Then inject air into the short acting insulin. Turn the vial upside down and withdraw the short acting insulin, followed by long-acting insulin.

(*c*) *How to inject?* Grasp a fold of skin between the thumb and index finger and push the needle at 90° angle. Thin individuals or children can use short needles or may need to pinch the skin and inject at a 45º angle to avoid intramuscular injection, especially in the thigh area. Needle should go all the way into the skin. Release the pinch before injecting or else insulin would be squeezed out. The needle should be embedded within the skin for 5s after complete depression of the plunger to ensure complete delivery of the insulin dose. Insulin is available as 40 U/mL and 100 U/mL vials. Syringes of 40 U/mL and 100 U/mL marking are available making dose calculations easier and reducing errors.

(*d*) *How to store?* Vial should be refrigerated and warmed to room temperature to limit local irritation at the injection site. Extreme temperatures (<36 or >86ºF, <2 or >30ºC) and excess agitation should be avoided to prevent loss of potency, clumping, frosting, or precipitation. Specific storage guidelines provided by the manufacturer should be followed. Patients should always have available a spare bottle of each type of insulin used. Inspect before each use for changes like clumping, frosting, precipitation, or change in clarity or color that may signify a loss in potency. Rapid/short-acting/glargine insulin should be clear and all other insulin type uniformly cloudy.

D. Modalities of injectable insulin delivery

Continuous Subcutaneous Insulin Infusion (CSII)

The advantages of pumps are that multiple daily doses are not required, decreased nocturnal hypoglycemia and improved control of Dawn's phenomenon with the use of variable basal rate and better freedom in timings of meals and snacks.

Meta-analysis of 12 RCT's comparing CSII with MDI showed improved glycemic control with CSII [WMD HbA1c 0.44 (0.2-0.7)]. The relative frequencies of potential side effects, particularly severe hypoglycemia, keto-acidosis, and weight gain could not be assessed due to poor reporting and short duration of studies(25).

The position statement by the American diabetes association have suggested(26):

- Pumps are relatively costly, and special expertise and adequate educational facilities are needed by the medical team to initiate and supervise pump patients. If, then, patients are doing well on optimized multiple insulin injection regimens, CSII is not indicated.
- After a 2- to 3-month trial of modern optimized insulin injection therapy, a trial of CSII is appropriate if poor control persists because of (1) frequent unpredictable hypoglycemia or (2) a marked dawn blood glucose rise.
- Patients with erratic swings of blood glucose concentration or an erratic lifestyle with delayed or missed meals and unpredictable activity will fall into the first category when attempts to improve control with insulin injections lead to frequent hypoglycemia.

Insulin pen injectors

Premixed insulin preparations in pen

syringes maintain glycemic control(27). They are small and convenient, use smaller gauge needles and can facilitate compliance. They are preferred by patients(27,28), more discreet for use in public, overall easier to use, insulin dose scale on the pen is easier to read(28). The use of premixed insulin decreases the errors that occur while mixing the insulins and also the contamination if any(29).

E. Noninvasive insulin delivery

There is a long history of attempts to develop novel routes of insulin delivery that are both clinically effective and tolerable. However, despite significant research, the first effective noninvasive delivery systems for insulin are only now in development, marking a new milestone in effective management of diabetes. It does appear that the most clinically viable system to date may be pulmonary delivery .

Intradermal approach

Jets: These devices administer insulin without needles by delivering a high-pressure stream of insulin into subcutaneous tissue. The discomfort associated is the same as with insulin injections. Insulin is absorbed faster and hence glycemic control can be altered. It should not be viewed as a routine option but may benefit selected cases; such as those with severe insulin-induced lipoatrophy or phobia for needles. They are rather expensive.

Transferosomes: These are lipid vesicles made of soybean phosphatidylcholine loaded with insulin that are flexible enough to pass through pores much smaller than themselves, despite being much larger. Transferosomes transport the insulin with at least 50% of the bioefficiency of a subcutaneous injection. These are not rapid enough for bolus regimen but useful for basal regimen. The application of insulin-laden transferosomes over a skin area 40 cm^2 would provide the daily basal insulin needs(30).

Intranasal approach

Intranasal insulin have a low bioavailability and the dose needed for glycemic control is 20 times higher than that of subcutaneous administration(31). Permeability enhancers (lecithin, laureth-9) are incorporated in most nasal formulations to augment the low bioavailability(32). High rate of treatment failure and propensity to cause nasal irritation makes them a less feasible option(33).

Buccal

A buccal system delivering a liquid aerosol formulation of insulin via a metered dose inhaler has been developed by Generex Biotechnology (Toronto, Canada). The buccal insulin preparation is human recombinant insulin with added enhancers, stabilizers, and a non-chlorofluorocarbon propellant. Data on efficacy and adverse effects is still limited.

Inhaled insulin

Lung is an ideal route for the administration of insulin due to a vast and well-perfused absorptive surface(34). The lung lacks certain peptidases that are present in the gastrointestinal tract, and "first pass metabolism" is not a concern. Action after inhalation is 15 to 20 min(35). Exubera, AERx iDMS, Dura's Spiros, are some of the inhaled insulin delivery systems. Cochrane Review of 6 RCT's including 1191 participants concluded that inhaled insulin taken before meals, in conjunction with injected basal insulin, to maintains glycemic control comparable to that of MDI's with no difference in total hypoglycemic episodes between the groups. The key benefit appears to be patient satisfaction and quality of life, presumably due to the reduced number of daily injections

Key Messages

- Improved glycemic control requires early and prolonged implementation of intensive insulin therapy. Psychological and economic demand is the major constraint in the Indian perspective.
- Pen injectors appear to be a more feasible option to MDI, whereas CSII is useful only in some special situations.
- All diabetics would need a short course teaching flexible intensive insulin treatment.
- The cost -benefit ratio of short acting insulin analogs in the treatment of diabetic patients is still unclear.
- It would be premature to recommend switching patients to newer analogs especially those who are well controlled, especially when the long-term data is still awaited.

required. No adverse pulmonary effects were observed, but longer follow-up is required(36).

Gastrointestinal delivery:

Hexyl-insulin monoconjugate 2 (HIM2) is recombinant insulin with a small polyethylene glycol 7-hexyl group attached to protein 828 amino acid lysine. Theoretical advantage that it would mimic the enterohepatic circulation of endogenous insulin is limited by low bioavailability (<0.05%) and extensive degradation in the gut mucosa. The results of phase I/II clinical trials suggests that oral HIM2, when added to a basal insulin regimen, was safe and may prove effective in controlling postprandial hyperglycemia. Further clinical investigation is necessary(37).

Conclusions

Improved glycemic control can prevent or delay the progression of diabetes complications(1). This requires early and prolonged implementation of intensive insulin therapy [proper insulin therapy either by multiple daily subcutaneous injections, CSII or pen injectors, regular monitoring of blood sugar (including HbA 1c) and an optimal diet]. Pen injectors appear to be a more feasible option to MDI, whereas CSII is useful only in some special situations. Not everyone with T1DM will wish to undertake IIT, even without dietary restrictions; some will prefer a simpler regimen with routine meal timing and fewer injections. Such options will still be needed. Nevertheless, as the only way of reducing microvascular disease currently is by maintaining tight glycemic control, we need better ways of enabling patients to intensify their insulin treatment. All diabetics would need a short course teaching flexible intensive insulin treatment, as suggested by the DAFNE study for proper implementation of intensive insulin therapy.

Insulin analogs seem to offer more physiological management for our patients. Despite this theoretical superiority, the cost-benefit ratio of short acting insulin analogs in the treatment of diabetic patients is still unclear, which is the prime concern in developing countries, like India. Most of the controlled studies suggested either similar efficacy to regular insulin or only a minor benefit in favor of short acting insulin analogs. Whether this statistical significance would be clinically significant is unclear, especially when the long-term data is still awaited. It would be premature to recommend switching patients to newer analogs especially those who are well controlled.

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