INSULIN THERAPY IN DIABETES MANAGEMENT

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ABSTRACT

Insulin the core molecule in diabetes remains the best treatment for the disease even after eighty five years of use. Although associated with several myths and apprehensions, insulin therapy has no specification contraindication. The goal is to design and implement insulin regimen that mimic physiologic insulin secretion. Because individuals with type-1 diabetes mellitus lack exogenous insulin production, administration of basal, exogenous insulin is essential for regulating glycogen breakdown, gluconeogenesis, lipolysis, ketogenesis. Insulin regimen includes multi component insulin regimens, multiple daily injections (MDI) or insulin infusion devices[1]. The species and dosage of insulin used should be consistent and the patient's injection technique should be reviewed periodically with the diabetes care team. The effective use of insulin to obtain the best metabolic control requires a understanding of the duration of action of the various types of insulin and the relationship of blood glucose levels to exercise, food intake, intercurrent illness, certain medications, and stress; SMBG; and learning to adjust insulin dosage to achieve the individualized target goals established between the patient, family, and diabetes care team[2].

Keywords: Type-1 Diabetes Mellitus, Insulin Therapy, Human Insulins, Delivery Modes, Combination Therapy and SMBG.

INTRODUCTION

Insulin is the mainstay of treatment for patients with type 1 diabetes. Insulin is also important in type 2 diabetes when blood glucose levels cannot be controlled by diet, weight loss, exercise, and oral medications. Ideally, insulin should be administered in a manner that mimics the natural pattern of insulin secretion by a healthy pancreas; however, the complex pattern of insulin secretion by the pancreas is difficult to duplicate. Still, adequate blood glucose control can be achieved with careful attention to diet, regular exercise, home blood glucose monitoring, and multiple insulin injections throughout the day. With the acceleration of scientific research in the latter half of the twentieth century, beef and pork insulin were replaced by human insulin[3]. In 1977, the gene for human insulin was cloned, and through modern Recombinant technology, human insulin is being manufactured in huge amounts and is freely available Human insulin is now widely used. Insulin now comes in a variety of preparations that differ in the amount of time following injection until they begin to work and the duration of their action. Because of these differences, combinations of insulin are often used to allow for a more tailored regimen of blood sugar control[4,5].

Patients Who Should Receive Insulin:

- Patients manifesting OHA failure.
- Insulin should be considered in diabetics with significant complications like ischemic heart disease, CVA, peripheral artery disease, significant retinopathy, nephropathy and neuropathy, hepatic complications such as viral hepatitis.
- Any diabetic with an acute problem like several infection, injury, etc., should receive insulin.
- Diabetics with tuberculosis often do better with insulin.
- Any Type II patient who manifests ketosis for whatever reason.
- Diabetics undergoing most surgical procedures, especially those requiring general anesthesia, and where the patient will be on intravenous fluids for any significant period of time should be stabilised on insulin.
- Pregnant diabetics, if not "tightly" controlled with diet alone, must be managed with insulin.
- Any patient, even if optimally controlled with OHA's who shows evidence that may contraindicate the use of these oral agents, must be shifted to insulin.
- Many underweight patients and those with significant symptoms would do better with insulin therapy, possibly in combination with small doses of sulfonylureas[6]

Patients Who Should Preferably Use Human Insulins:

- All patients who are on beef or porcine insulins and manifest resistance due to the presence of antibodies;
- Patients requiring intermittent therapy, i.e. patients with gestational diabetes, those undergoing major surgery, patients with acute infections, etc., who otherwise may be controlled on diet, with or with out OHA's, should use Human insulins.
- Patients who require very large doses of beef or porcine insulins (>80 units/day), may benefit with changeover to human insulins.[8]

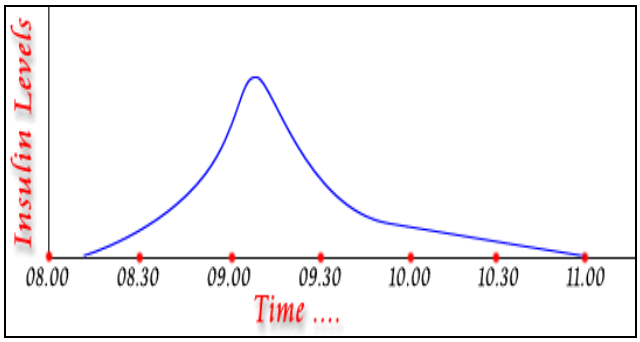
TYPES OF INSULIN[3,5]

TIME-ACTIVITY CHARACTERISTICS:[7]

Rapid acting:

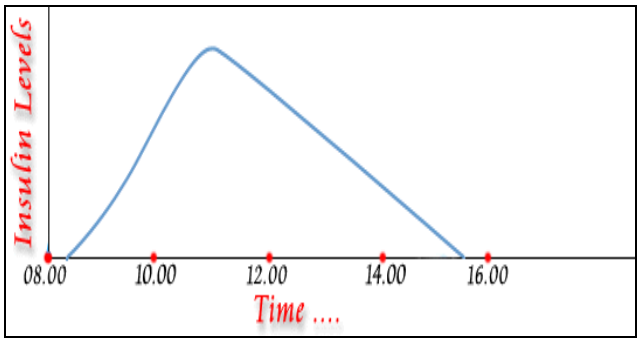
Insulin analogs have been developed by modifying the amino acid sequence of the insulin molecule. This modification alters the time characterisitics of activity. The only insulin analog available in India is the rapid acting Lispro. It reaches the blood within 15 minutes after

injection. It peaks 30 to 90 minutes later and may last as long as 4-5 hours.



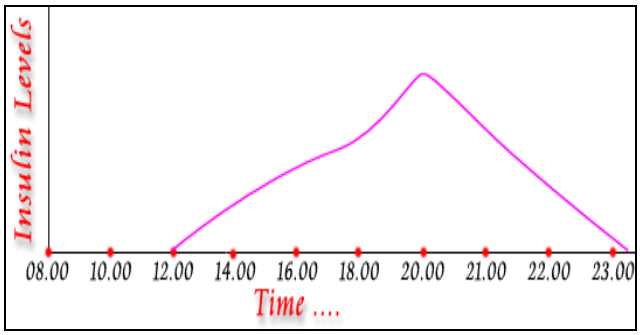
Short acting:

Short-acting (regular) insulin usually reaches the blood within 30 minutes after injection. It peaks 2 to 4 hours later and stays in the blood for about 4 to 8 hours.



Intermediate acting:

Intermediate-acting (NPH and lente) insulins reach the blood 2 to 6 hours after injection. They peak 4 to 14 hours later and stay in the blood for about 14 to 20 hours.



Long acting:

Long-acting (ultralente) insulin takes 6 to 14 hours to start working. It has no peak or a very small peak 10 to 16 hours after injection. It stays in the blood between 20 and 24 hours.

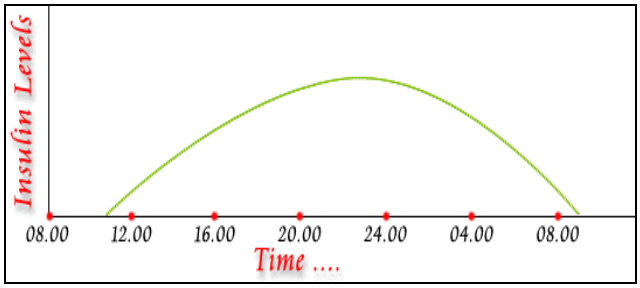


Table 1: Types of insulin

Type	Onset (hr)	Peak (hr)	Duration	Can be mixed
Rapid acting:				
Insulin lispro	0.2-0.4	1-2	3-5	Regular, NPH
Insulin aspart	0.2-0.4	1-1.5	3-5	Regular, NPH
Insulin glulisine	0.3-0.5	1-2	2-4	Regular, NPH
Short acting: Regular (soluble) insulin	0.5-1	2-4	6-8	All preparations (except glargine)
Intermediate acting:				
Insulin zinc suspension or Lente	1-2	8-10	20-24	Regular
Neutral protamine hagedorn(NPH) or isophane insulin.	1-2	8-10	20-24	Regular
Long acting:				
Protamine zinc insulin(PZI)	4-6	14-20	24-36	Regular
Insulin glargine	2-4	5-12	24	None
Premixed insulin:				
70/30 - 70% of protamine aspart and 30% aspart	0.2 –0.4	1-1.5	10-16	----
50/50 - 50% of protamine lispro and 50% of lispro	0.2-.4	1-1.5	10-16	----
70/30- 70% of NPH and 30% regular insulin	0.5-1	Dual	10-16	----
50/50 - 50% of NPH and 50% of regular insulin	0.5-1	Dual	10-16	----

Table 2 : Insulin analog formulation

(Insulin Analog Formulations available in Pen and Doser Devices[1].)

Device	Insulin	Manufacturer
Disposable (prefilled) pens:		
Flexpen	Levemir, NovoLog Mix 70/30	Novo Nordisk
Lilly pen	Prefilled Humalog Mix 70/30, Humalog Mix 75/25, Humalog Mix 50/50, Humulin N	Eli Lilly
SoloSTAR	Lantus, Apidra	Sanofi –Aventis
Durable (cartridge) pens:		
NovoPen 3	Levemir, Novolg, Novolg Mix 70/30	Novo Nordisk
NovoPen Junior	Levemir, Novolog, Novolog 70/30.	Novo Nordisk
HumaPen LUXURA	Humalog, Humulin.	Eli Lilly
HumaPen MEMOIR	Humalog	Eli Lilly
Dosers InnoLet	Novolin N, Novolin R, Novolin 70/30.	Novo Nordisk

MODES OF ADMINISTRATION:

Unlike many medicines, insulin cannot be taken orally at the present time. Like nearly all other proteins introduced into the gastrointestinal tract, it is reduced to fragments (even single amino acid components), where upon all 'insulin activity' is lost. There has been some research into ways to protect insulin from the digestive tract, so that it can be administered in a pill. So far this is entirely experimental.

Subcutaneous

Insulin is usually taken as subcutaneous injections by single-use syringes with needles, an insulin pump, or by repeated-use insulin pens[9] with needles. Patients who wish to reduce repeated skin puncture of insulin injections often use an injection port in conjunction with syringes. Figure 1 indicates insulin injections and vials and figure 2 indicates different types of insulin pens.

Insulin pump

Insulin pumps are a reasonable solution for some. Advantages to the patient are better control over background or 'basal' insulin dosage, bolus doses calculated to fractions of a unit, and calculators in the pump that may help with determining 'bolus' infusion dosages. The limitations are cost, the potential for hypoglycemic and hyperglycemic episodes, catheter problems, and no "closed loop" means of controlling insulin delivery based on current blood glucose levels.[10]

How Does an Insulin Pump Works:

The pump is attached to a thin plastic tube (an infusion set) that has a soft cannula (or plastic needle) at the end through which insulin passes. This cannula is inserted under the skin, usually on the abdomen. The cannula is changed every two days. The tubing can be disconnected from the pump while showering or swimming. The pump is used for continuous insulin delivery, 24 hours a day. The amount of insulin is programmed and is administered at a constant rate (basal rate). Often, the amount of insulin needed over the course of 24 hours varies depending on factors like exercise, activity level, and sleep. The insulin pump allows the user to program many different basal rates to allow for variation in lifestyle. In addition, the user can program the pump to deliver a bolus (large dose of insulin) during meals to cover the excess demands of carbohydrate ingestion. Figure 3 indicates insulin pump.

Figure 1: Insulin injections and vials

Figure 2: Insulin pens

Figure 3: Insulin pump

Inhalation

In 2006 the U.S. Food and Drug Administration approved the use of Exubera, the first inhalable insulin. It has been withdrawn from the market by its maker as of 3Q 2007, due to lack of acceptance. Inhaled insulin claimed to have similar efficacy to injected insulin, both in terms of controlling glucose levels and blood half-life. Currently, inhaled insulin is short acting and is typically taken before meals; an injection of long-acting insulin at night is often still required. When patients were switched from injected to inhaled insulin.[11,12,13.] Figure 4 shows the insulin inhaler.

Figure 4: Insulin inhaler

Transdermal

There are several methods for transdermal delivery of insulin. Pulsatile insulin uses microjets to pulse insulin into the patient, mimicking the physiological secretions of insulin by the pancreas. Researchers have produced a watch-like device that tests for blood glucose levels through the skin and administers corrective doses of insulin through pores in the skin.[14.] Figure 5 indicates insulin jet injector.

Figure 5: Insulin jet injectors

Intranasal insulin

Intranasal insulin is being investigated

Oral insulin

The basic appeal of oral hypoglycemic agents is that most people would prefer a pill to an injection. However, insulin is a protein, which is digested in the stomach and gut and in order to be effective at controlling blood sugar, cannot be taken orally in its current form. The potential market for an oral form of insulin is assumed to be enormous, thus many laboratories have attempted to devise ways of moving enough intact insulin from the gut to the portal vein to have a measurable effect on blood sugar. As of 2004, no products appear to be successful enough yet to bring to market.[15]

Biocon, Asia's largest biopharmaceutical company, based in Bangalore, India, is also developing an oral insulin product. It has recently entered phase III trials; the company hopes to launch their product, IN-105, in 2011.A Connecticut-based biopharmaceutical company called Biodel, Inc. is developing what it calls VIAtab, an oral formulation of insulin designed to be administered sublingually. This therapy is a tablet that dissolves in minutes when placed under the tongue. In a Phase I study, VIAtab delivered insulin to the blood stream quickly and resembled the first-phase insulin release spike found in healthy individuals. The company claims that an oral insulin therapy would be more convenient than currently available injectable or inhalable therapies, and they expect that convenience to result in increased insulin usage among the currently underserved early-stage patients with Type 2 diabetes, thus helping to create better long-term outcomes for that patient population.

Novo Nordisk announced on December 7, 2009, that it had initiated its first phase 1 trial with oral insulin analogue (NN1952). The aim of the trial is to investigate the safety, tolerance, pharmacokinetics (exposure to drug) and pharmacodynamics (effect) of NN1952 in healthy volunteers and people with type 1 and type 2 diabetes.Beta cell transplant may become practical in the near future. Additionally, some researchers have explored the possibility of transplanting genetically engineered non-beta cells to secrete insulin.[16.]

Pancreatic transplantation

Another improvement would be a transplantation of the pancreas or beta cell to avoid periodic insulin administration. This would result in a self-regulating insulin source. Transplantation of an entire pancreas (as an individual organ) is difficult and relatively uncommon. It is often performed in conjunction with liver or kidney transplant, although it can be done by itself. It is also possible to do a transplantation of only the pancreatic beta cells. Beta cell transplant may become practical in the near future. Additionally, some researchers have explored the possibility of transplanting genetically engineered non-beta cells to secrete insulin.[5.]

INITIATING INSULIN THERAPY

There are no precise formulae by which the initial dose can be calculated; start with a small dose of an

intermediate acting insulin (IAI), 8-12 units s.c. before breakfast; the therapy can be initiated with a mixture of a short acting insulin (SA) and IAI, in small doses.

PRACTICAL POINTS IN INSULIN THERAPY:

- Most of the short acting and the intermediate/long acting insulins available here may be mixed in the same syringe.
- Insulins are presently available in strengths of U-40, and U-100; one must ensure that the syringes used by the patient are compatible with the strength of insulin used.
- Insulin vials should be preferably stored at 4-80C. If possible they should be kept in the refrigerator, but NOT in the freezer section. The insulin vial should be brought down to body temperature by gently rubbing it between the palms before withdrawing the insulin into the syringes. If refrigeration facilities are unavailable, then the currently used vial can be stored at room temperature away from heat and direct sunlight. If vials have to be stored for longer periods, a simple method is for the unopened vials to be stored in the earthen pots which contain drinking water and are found in most homes where a refrigerator is not present.
- It is advisable to use disposable syringes which are now increasingly available; the cost of the syringe is often a limiting factor to the routine use of these syringes; patients can reuse the same disposable syringe and decrease the costs; it would seem prudent to use the syringe for around 6-8 injections, or less if the needle feels blunt; the same syringe should NEVER be used on different patients.
- Injections are usually given 20-30 minutes before the meal; this may need to be individualised.
- The needle is to be inserted at a slight angle so that the injection is in the **.**subcutaneous tissue; in patients with more subcutaneous fat, it would be correct to insert the needle vertically downwards.[5,17]

Sample regimen using insulin NPH and regular insulin:

Table 3: Sample regimen using insulin NPH and regular insulin[5,18].

NPH dose	Before breakfast	Before lunch	Before dinner	At bedtime
Regular insulin dose if fingerstick glucose is (mg/dl) [mmol/L]:	12 units		6 units	
70-100 [3.9-5.5]	4units		4units	
101-150 [5.6-8.3]	5 units		5 units	
151-200 [8.4-11.1]	6 units		6 units	
201-250 [11.2-13.9]	7 units		7 units	
251-300 [14.0-16.7]	8 units	1 unit	8 units	1 unit
>300 [>16.7]	9 units	2 units	9 units	2 units

Carb counting and DAFNE:

A more complicated method that allows greater freedom with meal times and snacks is "carb counting." This approach is taught to diabetic patients in Europe as "Dose Adjustment For Normal Eating" or DAFNE.In Europe, patients that are not familiar with the DAFNE regime can take an educational course where the basic starting insulin dose guideline is "for every 10g of carbohydrates you eat, take 1 unit of insulin". DAFNE courses also cover topics that naturally work alongside this regime, such as blood glucose monitoring, exercise and carbohydrate estimation to help the patient work out their personal control requirements.

The patient also can use his or her total daily dose (TDD) of insulin to estimate how many grams of carbohydrates will be "covered" by 1 unit of insulin, and using this result, the patient can estimate how many units of insulin should be administered depending on the carbohydrate concentration of their meal. For example, if the patient determines that 1 unit of insulin will cover 15 grams of carbohydrates, then they must administer 5 units of insulin before consuming a meal that contains 75 grams of carbohydrates. Some alternative methods also consider the protein content of the meal (since excess dietary protein can be converted to glucose via gluconeogenesis).

With DAFNE, most dosages involve a fair degree of guesswork, especially with non-labelled foods, and will only work fairly consistently from one dosage to the next if the patient is aware of their body's requirements. For example, a patient finds they can take 1 unit to 10g of carbohydrates in the morning and the evening, but find that their body requires more insulin for a meal in the middle of the day so they have to adjust to 1 unit per 8.5g of carbohydrates.[18]

PARTS OF BODY WHERE INSULIN INJECTION CAN BE MADE:

Figure 6 shows the parts of the body where insulin injection can be made.

COMMONLY USED MULTIPLE DOSE REGIMENS (MDRs):

- Multiple dose regimens are not very commonly required for the routine management of most NIDDMs, but may be important in special cases.
- Most NIDDMs who require insulin for optimal management do well with judicious use of combination therapy (insulin with OHA).

- Twice daily mixture of short, acting and intermediate acting insulins; one given before breakfast and the other before dinner. Once the daily dose at a single injection reaches around 30 units, it would be preferable to divide the insulin requirements into twice daily injections. This is the most commonly used MDR regimen in NIDDMs.
- The same as above, but with the addition of a short acting insulin injection given before lunch.

Injections of short acting insulins given before breakfast and before lunch and a mixture of short acting and intermediate acting insulin given before dinner.[19]

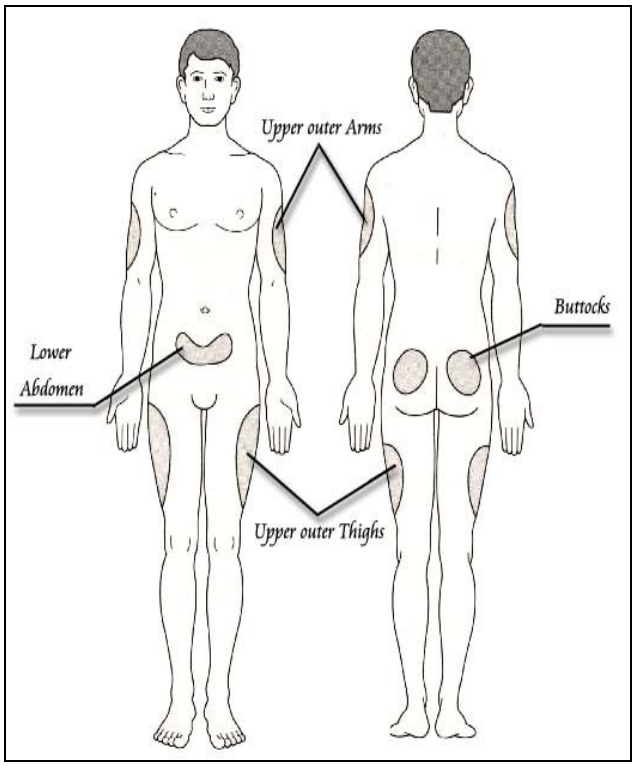


Figure 6: Parts of the body where insulin injection can be made

COMBINATION THERAPY:

Combination therapy is also very useful in the management of early stages of secondary OHA failure. A frequently advised regimen is the use of a long or very long acting insulin at bedtime along with the use of small amounts of an OHA at mealtimes. The rationale for this is that the insulin will lower the fasting blood glucose levels which is essential for glycemic control and will also maintain a basal insulin level. The OHAs will cause a bolus increase in the endogenous insulin to cover the mealtime rise in the blood glucose levels. A regimen which has also been found to be practical and effective is the use of combination of a small doses of SAI and IAI in the morning along with an OHA at mealtimes, especially with dinner.

COMMONLY SEEN SIDE EFFECTS:

1. *Hypoglycemia*: major side effect and to be guarded against stringently; start with small doses and adjust in small amounts; time activity characteristics should always be kept in mind when adjusting the doses.
2. *Allergy*: usually seen with the use of the older insulins insulins; beef insulin differs from human insulin in three amino acids and this difference can give rise to antibodies causing local, and systemic, allergy; porcine insulin differs from human insulin in one amino acid and this may give rise to allergy, but rare; human insulins have same amino acid composition as endogenous insulin.
3. *Resistance:* the impurities present in the older insulins insulins gave rise to antibodies which interfere with insulin action; newer insulins are purer and the chances of insulin resistance minimal.
4. *Edema*: insulin has salt retaining properties and may cause fluid retention; in some patients it may be necessary to adjust the dose of diuretics and/or salt intake.
5. *Lipodystrophy*: comprises, both, lipoatrophy and lipohypertrophy; lipoatrophy was seen with the use of older insulins; rare with the presently used insulins; best treated by changing over to the newer insulins and injecting the dose in the walls of the atrophic regions; Lipohypertrophy can be seen with the use of any insulin; no specific treatment, except to inject in parts of body which are usually covered.[20]

POINTS TO REMEMBER:

- Initiation of insulin therapy is invariably associated with apprehension on the part of the patient. Therefore, every patient or care giver should be taught techniques of insulin administration, and counseled.
- Regular insulin and premixed insulin should be administered at least 30 minutes before a meal to have optimum effect.
- Premixed, NPH and Lente insulin need to be; resuspended by tilting the vial several times or, gently rolling the vial between the palms.
- Insulin is administered in the subcutaneous tissue. At sites where the fatty layer is thick, needles may be inserted vertically; at places where the fat is thinner, needle angulation is necessary to negotiate the needle tip.
- Ideal site for insulin injection are the abdomen, about 2 inches away from the umbilicus, and the outer aspects of the upper thighs.
- All patients should be encouraged to do self monitoring of blood glucose (SMBG) at home and periodic check of HbA1c from standardized laboratory.(figure 7)
- All patients should be told that the adjustment of dose is necessary from time to time to achieve and maintain euglycemia. They should also be told about carbohydrate counts and carbohydrate to insulin ratio (C/I).
- Pen like injection devices are available, plate as also meters for self-testing of glucose.

All patients should be taught about sick day rules and not to stop insulin when sick. More frequent monitoring and urine ketone checks are necessary during illness.[5,21]

SMBG (Fig 7)

SUMMARY:

The injection of insulin is essential for management of patients with type I diabetes and may be needed by patients with type 2 diabetes for intermittent or continuous glycemic control. The species and dosage of insulin used should be consistent and the patient's injection technique should be revised periodically with the diabetes care team. The effective use of insulin to obtain the best metabolic control requires an understanding of the duration of action of the various types of insulin and the relationship of blood glucose levels to exercise, food intake, inter current illness, certain medications, and stress; SMBG; and learning to adjust insulin dosage to achieve the individualized target goals established between the patient, family and diabetes care team.[2,22]

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