

DIABETES CARE
THE ADVANTAGES OF NATURAL INSULIN

Arthur Teuscher, MD
University of Bern, Medical School
Switzerland

Written in collaboration with
Philip Corfman, MD
Formerly associated with the NIH and the FDA
USA

Principal author's address

Prof. Dr. Arthur Teuscher
Diabetes Centre Lindenhof
Bremgartenstr. 119
CH-3012 Bern

Fax +41313028210
Email info@insulin.ch
Internet www.Insulin.ch

**Banting and Best, the discoverers of insulin in 1922,
donated their patent to Toronto University so that
"no diabetic patient in the world would suffer from lack of insulin**

Professor Teuscher and his colleague, Dr. Corfman, prepared this brochure for a series of postgraduate lectures to be given in India in December 2002. They dedicate the brochure to all diabetics in need of adequate care.

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1. Introduction

1.1 Definition

Diabetes mellitus is characterized by too much sugar in the blood. Indeed, "mellitus" is derived from the Latin word for honey. With the condition, the body can not process glucose in the life sustaining energy-producing and storage organs, mainly the liver and muscles. Glucose is derived from the digestion of starch from bread, potatoes, pasta, rice, fruit, sugar containing products, sweet drinks and so on. In addition, the liver independently produces glucose when blood sugar is falling or is too low.

Insulin is produced in the islet cells of the pancreas. It is a peptide hormone and is responsible for the transfer of blood sugar into the cells through receptors in the cell walls. Besides producing insulin, the pancreas also produces digestives that drain from the pancreas into the intestine and break down starches into sugars, proteins into amino acids, and fats into fatty acids.

1.2 Two types of diabetes

Type 1 diabetes, also called insulin dependent diabetes, develops characteristically in children and young people but also may occur in middle age and in seniors. In this type of diabetes, most insulin cells are destroyed, probably immunologically, thus producing a severe insulin deficiency. Type I diabetes must be treated by insulin injections and individually adjusted nutrition. Such a diet is not sugar free, but one that is rich in fibers, with moderate amounts of meat and fat, and liberal with olive, sunflower, and rapessed oils, which contain mono - unsaturated fatty acids. The major complications of type I diabetes are long-term problems with the eyes, nerves and the kidneys.

Type 2 diabetes, also known as non-insulin dependent diabetes, develops when the body produces less insulin or insulin, which is less active; this occurs primarily in individuals who are overweight. This type of diabetes develops at increasing rates after age 40. Initial treatment may be effective simply by controlling weight, and undertaking more physical activity. In many cases oral anti-diabetic drugs are required, and in about 30% of cases insulin may be necessary. The aim of good control is to maintain the blood sugar at 5-7 mmol/l before eating and less than 8-10 mmol/l after food. It is possible in this way to prevent the long-term complications of diabetes.

1.3 The regulatory system

Blood glucose is the important source of energy for the brain. In fact it is the only fuel, which can be directly metabolized by brain and nerve cells. Nevertheless, nerve cells store only a little glucose and thus depend on a continuous flow of blood glucose. The body has a complicated system of controls to maintain blood glucose levels by means of the production of glucose by the liver, activated by adrenaline and/or by carbohydrate intake resulting from hunger. Two hormones, insulin and glucagon, produced in different pancreatic cell nets play a key role in maintaining this balance. Insulin transports glucose into the muscles where it serves as a source of energy or into the liver where glycogen is produced. If the blood sugar is too low because of poor

nutrition, excessive use of oral drugs, or too much insulin, the glucose-controlling hormone, glucagon, is activated to liberate glucose from the liver in order to raise the blood sugar back to a normal level of 4-8mmol/l (70-140mg/dl).

1.4 The insulin, glucagon interaction

Normally insulin and glucagon cooperate so well that in non-diabetics blood remains essentially stable. The body is not fine-tuned in this way in diabetics; insulin injected subcutaneously doesn't mimic insulin produced normally and glucagons aren't produced on demand in the same way. Indeed, the injection of insulin can easily disturb the equilibrium and lead to hypoglycemia. At the beginning of a fall in glucose the autonomous nervous system is activated and stimulates the suprarenal gland to eject adrenaline. Adrenaline in turn creates warning signals as mentioned above. At the same time glucose is liberated and is transported to the brain and the heart.

1.5 Hyperglycemia, ketoacidosis, and diabetic coma

In both known and occult type I diabetics, ketoacidosis may develop from the excessive production of blood sugar and fatty acids. Some individuals may end in hyperglycemic diabetic coma with or without acetone in the urine. The symptoms of such as an episode are extreme fatigue, increasing sleepiness, thirst, passing large amounts of urine, nausea, vomiting, abdominal pains (appendicitis may be a false diagnosis but may indeed precipitate diabetic coma), deep respiration, dry mouth, and disturbed consciousness. Ketoacidosis results from the severe insulin deficiency and increased fatty acids in the blood are characteristic. Elderly people may face a special risk in that they underestimate the symptoms and do not recognize them as an incipient diabetic coma. Emergency hospitalization is obligatory. Intravenous hourly insulin doses of about 6 units are life saving. Most important is the infusion of several liters of saline.

Marked dehydration of the body because of fever and profuse sweating may develop into a non-ketotic, coma with unusually high blood-glucose values. In this situation intravenous fluids are most important than insulin.

2. Types of Insulins and their actions

There are 4 types of insulins, classified according to their duration (kinetics) and peak action (dynamics):

- Short-acting : regular, about 6-8 hours, increasing with the dose
- Intermediate-acting : isophane NPH or insulin zinc suspension, about 12-24 hours
- Long-acting: more than 24 hours
- Mixed 70/30 (70% isophane / 30% regular) : About 6-24 hours

When taking care of diabetics, it is best to concentrate in the beginning but also throughout their life on just a few insulin products, namely

- A short-acting insulin,
- An intermediate -acting insulin,
- A long-acting insulin, and
- A 70/30-mixed insulin.

Today's diabetologists and family physicians have two major types of insulins to offer their patients (assuming that they are available) :

- Natural insulin - obtained from beef or pork, or
- Synthetic insulin - called " human" insulin by the manufacturers, despite the fact that it is not the same as the body's natural and truly human insulin

Insulin may be extracted from beef or pork pancreas and purified by crystallization. Beef insulin is now rarely used in industrialized countries because of perceived risk of BSE viral contamination, even though such contamination has never proven to be a problem. Synthetic insulin may be produced semi-synthetically by enzymatic modification of porcine insulin or by recombinant DNA technology using E-coli bacilli or yeast cells. In long-term studies no real advantage of synthetic insulin has been demonstrated and shorter kinetics and earlier peaks necessitate 3-4-6 injections per day.

All insulin preparations are to a greater or lesser extent immunogenic (sero-antibodies) in man but immunological resistance to insulin action is rare with highly purified beef and porcine insulin. Preparations of synthetic insulin should theoretically be less immunogenic, but no real advantage has been shown in practice. Indeed there are studies showing elevated synthetic insulin antibodies in pregnancy and pregnant diabetics.

Insulin extract, used for the first time by Banting and Best in 1921, was the only drug available for 20-30 years and became a favorite for several generations of diabetic patients. Today it is rarely used. An advantage of beef insulin is its "softer" insulin curve. Therefore its duration (its pharmacokinetics) is prolonged and its flatter peak (its pharmacodynamics) occurs later compared to the same type of porcine insulin. In contrast, synthetic insulin is faster and shorter acting. Beef insulin has the advantage in

diabetics with gastro-paresis and delayed emptying of the stomach into the intestine after a meal. This may be caused by autonomous diabetic neuropathy, high fiber food or other reasons for delayed gastric transport.

Insulin is inactivated by gastro- intestinal enzymes so must be given by injection. The subcutaneous route is ideal in most circumstances. It is usually injected into the upper quadrants of the abdomen (short-acting insulin) or into the thighs or buttocks (intermediate- and long-acting insulins). Injection into the legs or upper arm may give faster absorption and thus may result in hypoglycemia, especially if the patient exercises following the injection. Generally subcutaneous insulin injections cause fewer problems since rotating the injection sites can minimize fat hypertrophy. Injection of synthetic insulin such as glargine (Lantus) may be more painful because of its acidic nature. Typical skin allergy is no longer seen with purified or highly purified insulins. It may occasionally occur with synthetic insulin. Local allergic reactions are rarely seen with present types of animal and synthetic insulins.

3. Hypoglycemia

Hypoglycemia (called "hypo" by some patients) is the term for a blood sugar that is dangerously low. It may occur because of too much insulin or because of blood sugar lowering oral drugs. No matter how carefully clinicians observe their patients, they may not be able to prevent hypoglycemia in every situation. Usually it is easy to recognize and to correct it before a more dangerous blood glucose fall occurs. Every insulin treated diabetic should know his/her typical symptoms and should act to correct it before a more severe drop in blood sugar occurs. Nevertheless, it isn't always easy to recognize the warning signs, and, unfortunately, this is more often the case with synthetic ("human") insulin.

It's instructive to note that in 1953 Dr. Joslin recommended in his diabetic manual - 30 years before human insulin that "insulin reactions can be serious because they may occur in places where they are embarrassing or dangerous to the patient; they can be prevented by taking a little carbohydrate to raise the sugar in the blood to normal when the first warning signal appears or better still, by a little food between meals and upon retiring."

Hypoglycemia is characterized by

- Blood glucose levels below 2.8 mmol/l (50 mg/dl) - so-called "biochemical hypoglycemia"- and
- Clinical symptoms of hypoglycemia, which may occur even at a level of 4 mmol/l (70mg/dl).

There are three grades of hypoglycemia:

- Grade 1: light to moderate : no outside help required
- Grade 2: moderately severe : still conscious, needs assistance
- Grade 3: severe: unconscious, needs outside help

These are the main adrenal symptoms

- Sweating
- Trembling
- Hunger
- Increased heartbeat (palpitations)
- Tingling around lips

These are the main neuroglycopenic symptoms

- Disturbance of concentration
- Disturbance of coordination
- Disturbance of behavior
- Visual disturbance
- Anxiety
- Lack of concentration

Neuroglycopenic brain symptoms are seen in hypoglycemia resulting from the use of natural human insulin, and such signs are also found in diabetics treated with synthetic ("human") insulin.

These are symptoms of advanced brain hypoglycemia

- Depression
- Irrational behavior: aggressiveness, unmotivated laughing, yawning, becoming Silent, absent
- Paralysis
- Epileptic type of attack

3.1 Nocturnal hypoglycemia and the dead in bed syndrome

Many diabetics who take insulin are rightfully frightened about the prospect of nighttime hypoglycemia since more than 30-50% of severe hypoglycemia episodes occur during sleep. Personal observations indicate that the greatest risk occurs between 2-3 am more precisely, at 1.30 am. This occurs most often if intermediate or long acting insulins are injected before the evening meal, with the result that maximal insulin activity occurs after midnight. Changing the insulin injection to bedtime (10, 11 pm) may solve this problem because maximum activity will then occur later, in the early morning, and at this time the liver produces enough glucose to stabilize blood sugar levels.

The major problem with nocturnal hypoglycemia is if it occurs during sleep and therefore may not be noticed immediately by patients. In this instance, it may last for several hours until early morning when the patients is waking up. Sometimes there is marked unconscious unrest during sleep, which may be noticed by the partner or other members of the family and may lead to family disruptions.

Early morning hypoglycemia may be prevented if blood glucose is measured at 2 am. If the blood sugar is 4 or less mmol/l (70mg/dl) there is a risk that it may fall even farther and the patient may take preventative measures. Many patients try having a late night carbohydrate food source at bedtime to prevent hypoglycemia but, unfortunately, insulin activity may be so strong during the first 3-4 hours after midnight that even carbohydrate rich food at bedtime may not offer enough prevention. For less severe hypoglycemia a piece of bread, a glass of milk, a cereal bar with a low glycemic index may be a good idea.

One has to observe in addition that with a drop of blood sugar after midnight or later, the regulatory mechanism of glucagon release is so strong that early morning blood sugars may be too high. In blood glucose constellations " low after midnight - high in the morning" measurement at 2 am is an important cornerstone for establishing a correct night dose. In case of a high fasting glucose one should not increase the following night dose, but consider a counter-regulatory effect of the night dose as stable as possible if there are no unusual circumstances the day or evening before. This will result in stable fasting glucose values, enabling a smoother blood, sugar profile the following day.

3.2 Hypoglycemia from too much pancreatic insulin in type 2 diabetics

Approximately 90% of all diabetics are type 2 and most of them are given oral anti-diabetic drugs. Some of these are sulphonylureas, which stimulate pancreatic insulin secretion. Quite often if patients aren't started on low doses, they experience unwanted adverse events, even serious life endangering hypoglycemia from the body's own beta cells.

3.3 Spontaneous hypoglycemia in non-diabetics

The question also comes up whether healthy non-diabetics can also develop hypoglycemic episodes. Indeed, it's not unusual that after an early breakfast, which increases insulin secretion, the blood sugar will fall significantly after 2-3 hours. These people recover with a second breakfast. Heavy physical exercise may also induce hypoglycemia in normal individuals.

3.4 Insulinomas

Rare cases of insulin overproduction may occur from beta-cell tumors called-insulinomas. Blood glucose values of less than 2.8 mmol/l may be experienced in such individuals. Such tumors must be removed, in part because of their pre-cancerous nature.

4. Management of hypoglycemia

It is very important that diabetic hypoglycemia be treated at the first symptoms of low blood sugar. Three or four tablets of glucose or a spoonful of plain sugar or sweet drinks may be all that's needed.

At times, however, diabetics don't recognize that they are in trouble. Here are two examples of such a problem:

- "I saw sugar on the table that I knew I needed, but just couldn't raise my arm to reach it."
- "I heard my son, who was my passenger in the car, shout 'Father, keep straight!' but like a drunk I kept driving to the left and crashed into the central barrier".

The second example demonstrates how often persons with diabetics experiencing hypoglycemia often will observe unusual behaviour before the diabetic does. Such behavioural changes were observed very early in the use of insulin, but since the 80s more diabetic patients are on synthetic ("human") insulin and such "hypoglycemia unawareness" occurs much more frequently. In western countries, where synthetic insulin is widely used, the numbers of unexpected sudden hypoglycemic episodes is on the increase, and is seen at present in about 20% of all "human" insulin users.

4.1 Mild hypoglycemia

When blood-glucose levels are as low as 3,4mmol/l, the body's adrenaline is stimulated and should elicit the early adrenal warning symptoms, but, as noted, these classical symptoms may not be apparent in some patients on human insulin.

Patients should take sugar immediately in such form as:

- Glucose tablets, 3-4 pieces (10-12 grams)
- Sugar: 2,3 pieces (8-12 grams). Plain sugar is 50% glucose / 50% fructose. Fructose does not produce glucose.
- Sweet drinks containing sugar such as orange juice or Coke (1-3 dl = 10-30 grams of sugar) "Light" or "diet" drinks don't contain sugar.

Every diabetic on insulin and/or oral drugs should have sugar or glucose tablets in his or her pocket so they can react immediately.

4.2 Moderate hypoglycemia

In more serious hypoglycemic events the same warning signals develop as in light events but brain symptoms may occur as well as adrenal symptoms. This condition is

also treated with sugar orally. After such events it is advisable for the patient to consume snacks of bread or fruit in order to keep the blood sugar normal for 1-2 hours.

4.3 Severe hypoglycemia

Light or moderate hypoglycemia may develop into severe cases if not treated quickly. Severe hypoglycemia always requires outside help. Because unconscious people may aspirate fluids they should not be given food or drinks. Nevertheless it may be possible to get glucose tablets, honey or jam into the cheek pouch, because the swallowing reflex may still be present. If the patient remains unconscious despite such treatment, further help must be organized. At home it is important to have glucagon in the icebox, which may be injected subcutaneously, intramuscularly, or intravenously. The goal is to achieve a blood sugar rise within 5-10 minutes and then to provide light food by mouth. Ambulance personnel may also provide immediate help. Injecting glucagon is in principle a physician's responsibility but in cases of emergency, healthcare workers certainly may provide the needed treatment including intravenous glucose infusion.

4.4 Causes of hypoglycemia

- Too much insulin
- Not enough food
- Hypoglycemia (the same day or severe hypoglycemia up to several days before)
- Misuse of synthetic ("human") insulin
- Intensive physical activity
- Diabetes of long duration

5. Clinical pointers

Diabetes-Management of a new patient with adult type I diabetes with natural animal insulin:

First phase: A morning injection of 8-12 units of an insulin with intermediate activity, such as isophane or Lente insulin, increasing the dose by 2-4 units every two to three days and observing for a short period.

Second phase: Add isophane or Lente insulin at bedtime with half the morning dose (or less in thin people), e.g. 2/3 of the total 24 hours period in the morning, and 1/3 at bedtime (because of higher sensitivity to insulin after midnight).

Third phase: Add short acting insulin at breakfast, lunch, and evening to reduce the 2 hour post-prandial peak blood-glucose values, starting with about 4 units of regular insulin at breakfast, 2 units at lunch and 3 units at dinner, and only in rare instances 2-3 units of regular insulin at bedtime, when blood glucose is over 12 mmol/l (The greatest risk of hypoglycemia occurs around 2 am).

5.1 Insulin sensitivity

When adding regular insulin to such a regimen, it should be noted that sensitivity to insulin is lowest in the morning (and therefore a higher dose is required), increased in the afternoon (and therefore a lower dose is required), and low again in the evening (and therefore an intermediate dose is required).

Regular and intermediate isophane insulin can be mixed with regular insulin in the same syringe, but with Lente insulin it is better to use two injections because binding of regular to isophane insulin may decrease activity of regular insulin.

5.2 Intensified insulin therapy

For intensive insulin regimens, multiple injections (regular insulin 3-4 times a day) are usually recommended to be given before meals along with isophane insulin before breakfast, at dinner or bedtime. Best overnight glucose control can be achieved with Semilente insulin at bedtime.

5.3 Natural insulin in type 2 diabetics

Porcine or beef insulins are better tolerated than synthetic insulin in substantial number of patients. This is particularly true at night in diabetics over 65 years of age. Natural insulin has a "softer" and longer action than synthetic insulin as well as producing the type of hypoglycemia which is more easily recognized by the patient.

5.4 Risk of nocturnal hypoglycemia

If isophane or Lente insulin is given before dinner, it may produce serious hypoglycemia after midnight, between 2-3 am. An intermediate acting insulin at bedtime is preferable at this time when the liver activates glycogenolysis.

5.5 Risk of hypoglycemia when driving

Diabetics should always be aware of the possibility of hypoglycemia while driving. Such a risk is increased if the driver is on his/her way to a meal (and thus essentially fasting) or returning from heavy exercise. Such hypoglycemic episodes increase every year in Switzerland, in part because of the increased use of synthetic insulin (which is prone to inducing hypoglycemia unawareness) and the use of sulphonylureas by type 2) diabetics.

The UK Ministry of Transport states: "Drivers treated with insulin or oral anti-diabetic drugs are required to notify the Driver and Vehicle Licensing Agency of their condition. Drivers need to be particularly careful to avoid hypoglycemia and should be informed how to prevent it. They should normally check their blood-glucose concentration before driving and on long journeys at intervals of approximately two hours. They should ensure that the supply of sugar is always available in the car. If hypoglycemia occurs, a car driver should switch off the ignition until recovery is complete, which may take up to 15 minutes or longer. Driving is not permitted when awareness of hypoglycemia is lost."

6. Hypoglycemia unawareness with synthetic insulin

Severe hypoglycemic events with intensive insulin therapy have increased more than 3 times since the introduction of synthetic insulin in 1982. In the UKPDS study, published in 1988, a doubling of severe insulin hypoglycemia was reported in newly discovered diabetic patients; this finding supported a study from the late 80's, which drew the same conclusions in that it found a tripling of severe insulin hypoglycemia events after 7.5 years of careful diabetes control. Two reports from the Swiss Insulin Study Group from the university of Bern also confirmed these observations with both a double-blind crossover study and a case control study. Numerous other studies have also been published that substantiate the conclusion that hypoglycemia unawareness is increased in diabetics who use synthetic insulin.

To counteract such findings, Novo-Nordisk supported two short-term prospective studies, which were published in 1992 with a company director as co-author. These studies suggested that synthetic insulins do not present the hazard noted by others. The work was faulty, however, in that no HbA1c levels were provided in one of the studies, the other had an unspecified number of drop-outs. In a comparable study by Clark et al. in 1984, 6 out of 94 type I diabetics dropped out because of hypoglycemia and one patient who experienced unconsciousness had to be retransferred to natural insulin.

It is most important to conduct a definitive large-scale study on the issue, but neither industry nor regulatory agencies are willing to do so. The three main insulin producers (Lilly in the USA, Novo-Nordisk in Denmark, and Aventis in Germany), which, astoundingly, control 94% of the worldwide insulin market, refuse to sponsor a long-term, double blind study. They even refuse to conduct a post-marketing study, as do regulatory agencies, which recently mandated such a study of the new long-acting glargine insulin Lantus because of possible mitogenic and proliferative retinopathy effects. A definitive study would require about 2800 type I diabetics in order to spot a 50% increase in one year of severe hypoglycemia episodes or about half that number to detect a doubling.

The companies "blame the victim", by suggesting that diabetics who experience difficulties with synthetic insulins don't follow instructions on proper insulin use. They say it's the patient's fault because of inadequate nutrition, inappropriate physical activity, too much insulin, etc. Nevertheless, it is both instructive and intriguing to note that the labelling for "Humulin" when it was approved by the US FDA in 1982 included the following statement at the request of the company: "A few patients who have experienced hypoglycemic reactions after transfer from animal-source insulin to human insulin have reported that the early warning symptoms of hypoglycemia were less pronounced or different from those experienced with their previous insulin." This is certainly a clear recognition by the company that there may be problems with their product. It is intriguing in that the company essentially denies this warning in its heavy promotion of its synthetic insulin.

Similarly, the British National formulary now states: "Since 1991 some patients have reported loss of hypoglycemia warning after transfer to human insulin. If a patient believes that human insulin is responsible for the loss of warning it is reasonable to transfer him to animal insulin and to educate the patient about avoiding hypoglycemia. Great care should be taken to specify whether a human or an animal preparation is required."

7. A comparison of natural with synthetic ("human") insulin

7.1 Allergy/Antibodies

The early expectation that human insulin would produce fewer antibodies and allergies has not been fulfilled. Instead high levels of antibodies to synthetic insulin have been observed in pregnant women. Since animal insulin is now highly purified, the prevalence of allergic reaction and antibodies is no greater than with synthetics.

7.2 Hypoglycemia

As to note there's higher incidence of neuroglycopenic symptoms, such as lack of concentration and disturbances of coordination and cognitive functions, in patients using synthetic insulin. Such symptoms may be recognized late and at a more dangerous stage than adrenal symptoms such as the trembling, sweating, hunger, and tingling around the lips, seen with users of natural insulin.

7.3 Therapeutic and health claims

Since the introduction of synthetic insulin no relevant health advantages compared to natural insulin have been presented. Animal insulin has a long-standing reputation as a dependable treatment with good results and low rates of unwanted adverse effects.

7.4 Action profile

Synthetic insulin peaks earlier and has a shorter duration than natural insulin. This is of particular importance during the night since synthetics express critical activity after midnight and thereby increase the risk of hypoglycemia at the time of the highest Insulin sensitivity around 2 am. Natural insulin acts less abruptly and "smoother" and longer. It presents a flatter profile with less severe nighttime hypoglycemia. Best results are seen with Semilente Insulin, which has shorter to intermediate activity during the night and during the day when given before breakfast.

8. Summary: Natural insulin should remain freely available

It's clear that some patients using synthetic insulin may experience alarming drops in blood sugar fall, at times like a flash of lightning without warning symptoms. In 1987, our Swiss Insulin Study Group named this phenomenon as "human insulin hypoglycemia unawareness" (The Lancet, 1987). That was at the time that insulin producers intensified efforts to switch patients to their new and more expensive product, even though it is less expensive to make than natural insulin.

Companies have not only discouraged patients who prefer natural insulin, but have also implied that the controversy is related to doubts about the safety of gene technology. Actually, the real issues are economic (the need for companies to satisfy their stockholders) and their unfortunate lack of respect for the needs of patients who experience dangerous hypoglycemic events without being given appropriate information by the producers or, at times, their physicians.

Unfortunately, synthetic insulins are by now so well entrenched in clinical practice, that the younger generation of diabetologists don't recognize that a real problem exists. It is disturbing that many scientific papers on insulin in referred journals don't specify whether the insulin used was natural or synthetic.

It is accepted that many diabetics have no problems with synthetic insulin, but it is also true that patients and their health care providers should have the right to choose the best insulin for the patient, both for reasons of safety and cost.

9. Immunogenicity of Natural Insulins

Prof Dr. **N Kochupillai, Delhi**

A poor young diabetic, 20 yrs of age was admitted (duration of diabetes about 8 yrs). He came with ketoacidosis, several complications of diabetes, cataract, both limbs paralysed, and almost comatose. On dwelling into the history, it was revealed that the patient could not take the mandatory insulin due to its high cost.

This incidence forced us to think on the problems of young insulin requiring diabetics in our country.

The human insulin which first entered in the Indian market in the early 80's was aggressively promoted by two companies on the plea that Bovine and the other animal insulins are much more immunogenic than human insulin and therefore human insulin is the best. Natural Animal Insulins were substituted with human insulin without being aware as to what is the under current of the politics and the commercial dimensions of this shift in prescription preferences.

It was very clear that human insulin was introduced aggressively into the Indian market by an overt and covert submersion of market forces, violating at least three laws of the country by interested companies and very safely working on the rather superficial understanding of the profession on the problem of immunogenicity of insulin.

These days we advocate aggressive glycemic control especially after the DCCT and UKPDS which clearly showed if blood glucose is tightly controlled, one can avoid getting most of the complications and particularly the small vessel disease and therefore all these new approaches to Insulin Therapy has come about during the last 6-8 yrs

To my great sadness I realized that much of what is touted through this very scientific approach in the western clinical horizon is largely irrelevant even to our upper middle class, I do not know whether it is relevant to rich class.

If that is so with regard to type II diabetes and other those who can well manage diabetes in an affordable manner, what about the poor conditions of those majority of young diabetics whose life depends on insulin and the socio-economic conditions do not allow them to practice the diabetes control the way the DCCT advocate. What can we provide as a nation to protect their life and their limb and prevent their complications and ensure a desirable longevity in them?

These are all important questions, which we can't afford to ignore if we are a free society with our own constitutional rights. Therefore the plight of the 2.5 laces young diabetics of our country is left to the fore winds of International Market Forces. We have 60% of them very poor, with a monthly income of less than Rs. 2000/-.

They also face the mounting cost of Insulin, with the prohibitive cost of human insulin, 220 rupees for 400 units in open market where as the cheaper forms of Insulin are available at a much lower price but which is also expensive (65-70 rupees.)

The human insulin costs Rs.220. Is the price differential justifiable to the advantages; or the so called touted advantages of human insulin offers?, have you looked at it scientifically for a moment?

How about the immunogenicity of insulin. Bovine insulin is three amino acids different from human insulin. Two of these amino acids will be in alpha chain and the third amino acid is the thirty-third residue of Beta Chain. The biologically active configuration, which logs on or docks on to a receptor of human being, initiates the biological action and is the same in all species. Therefore biological action of different forms of insulin cannot be different. We have over 5-6 decades of experience with various insulins, specially the natural insulins.

So the molecular configuration are different between animal insulin and human insulin, those configuration account only for the immunogenicity to some extent but that immunogenicity truly doesn't affect the function of insulin as a molecule because that segment or that epitope of the molecule which is responsible for docking on to the insulin receptor and initiating its action is not different and it is well known fact to all of us. The immunogenicity of most Insulin preparations is because of consideration of purity, a problem which has been resolved late in the 70's and these days we have only pure monocomponent and highly purified Insulins available whether it is human, Bovine or porcine. So the purity of a contamination which caused major problem of Immunogenicity is already resolved whether it is Human, Bovine or Porcine.

The Recombinant insulin were touted and promoted as the panacea of the diabetic patients and the expectation was that the Recombinant insulin is produced and made available in plenty so that the cost of Insulin would go very low. Though it is more than 15 yrs since the patent rights of human insulin synthesis by Recombinant method has been lifted there is not even one single paisa of reduction of its price.

Instead it goes on escalating and its understandable on simple commercial terms in Lilly or Novo Nordisk sell human insulin at 20 dollars a vial in New York or in United States or in Europe, how will the same company sell the same insulin at Rs.20/- in India? its practically impossible!

Bovine or porcine Insulin were rejected on the plea that it is a different insulin therefore Immunogenic. However now the some multinationals are trying to bring in newer insulin, How are newer insulin different, they also have different amino acid structure like bovine Insulin or porcine Insulin. Aren't they immunogenic? Are they not different than the human insulin?

Are there any studies on immunogenicity of newer insulin ? What is the basis of immunogenicity of the newer insulin? Before they tout and sell it to you all of you prescribed LISPRO. Isn't it? or about to prescribe? What is the rational? you mean to say our intellect so badly damaged but we don't think about this, it is happening.

I would like to reiterate these facts from scientific literature and you are welcomed to go and scrutinize what I am saying. All insulins including human insulin are immunogenic and produce antibody particularly the long act, it may be a question of more or less antibodies. Bovine is more immunogenic than porcine which is more immunogenic than human.

But nobody today till now examined the functional significance of the antibody formed in terms of its ability to neutralize insulin functionally, which means that antibody should combine with the insulin with the same energy with which its receptors interact with the insulin and thus neutralize. Otherwise it cannot be functionally active and that is the question that we tried to ask. What is the titre of the insulin antibodies that is formed. What is the energy of the antibodies that is formed? What is its binding power and binding capacity? These are the data that we have generated.

Our study Cleary shows that the antibody has practically no pathogenic significance.

Allergic reactions caused by insulin therapy is so rare phenomenon that even if it occurs, one can conveniently know it. The current impression is that this lipoatrophy or lipodistropy is not caused by antibodies but by only impurities of insulin which has long since been removed as a result of purification technology and whatever that is causing residual immunogenicity or indeed to compound that add on to the human insulin or to the insulin molecule to make it long acting, say for example zinc or protamine.

There are of course data and it is scientifically also value to think that if you have antibody present in significant titers it can modify the pharmacokinetics of insulin. Indeed it is true, but how frequently do we experience this, I will come to my own 50-60 patients we have studied where we have demonstrated that antibody titers, their energy and their binding power, and their binding capacity are no different.

Youth Onset Diabetes in India (patients enrolled in the study):

Type I	Type 11	APS	FCP	KRT
36%	13%	8%	11%	32%

Antibody titers invariably occurred in all the patients who are treated with purified bovine insulin. However, the titers vary significantly from 5-42 standard deviation scores, which means only that type of titer will only bind into a small fraction of the therapeutically administered insulin.

Table I: Results

Parameters	Type 1	KRT
Affinity constant (X 10 ⁷ L/mmol)	7 ± 3.1	6 ± 33
Maximum binding capacity (mmol/L)	9.7 ± 7.8	4 ± 3.9
Insulin binding power	59 ± 29	29 ± 43
Daily insulin dose (U/Day)	36 ± 8	26 ± 11

The affinity constant of all antibodies that is formed is a level of affinity which is two orders or magnitude less than the affinity of the receptor for insulin that means all these antibodies invariably is functionally irrelevant. It cannot neutralize insulin or lead to increase in insulin requirement.

And as we observed in these 52 patients there was no insulin resistance caused by the insulin antibody that we demonstrated in them. There was no lipoatrophy or lipodystrophy demonstrated. There was no pharmacokinetic effects observed. There is no increase in the requirement of insulin; the maximum dose that we required was not more than 38 units of insulin. There were no allergic reactions observed and the glycemic control was smooth and easy despite presents of Insulin antibodies.

That much gentlemen for scientific facts which totally proves wrong the surmise with which we aggressively promoted human insulin all these years creating a situation where our poor 2/3rd diabetics have been deprived of their constitutionally provided right to life and health.