

Lecture

NEWER TREATMENT OF DIABETES MELLITUS

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The aim of the present communication is to high-light the recent methods of treatment of diabetes relating to diet, newer insulins, its newly devised delivery systems, transplantation of insulin producing tissue and newer oral hypoglycaemic agents.

Objectives

The objectives of optimal treatment of diabetes are as follows :

- i) Abolition of symptoms due to high blood sugar level and to provide a sense of wellbeing.
- ii) Prevention of acute metabolic complications both due to hyper and hypoglycaemia.
- iii) Maintenance of ideal body weight.
- iv) To prevent or minimise long term neurogenic and vascular complications and complications due to hyperlipoproteinaemia.
- v) To ensure optimal growth in children and normal sexual and reproductive function in the young.

Treatment with Diet

No other modes of treatment of diabetes has undergone so much of changes over the years than diet alone. Though it is very difficult to prescribe a rigid dietetic norm for all types of diabetics, yet a restricted calorie intake remains the mainstay of treatment. In the west, diabetics were advised to restrict carbohydrate so as to provide only 33 percent of total calories and fat up to 50 percent. This possibly, has shown a rising incidence of vascular complications and hence a modification of this practice appear desirable particularly in view of lower incidence of cardiovascular complication in India and other oriental countries where carbohydrate constitutes 60-65 percent of the calorie requirement of a diabetics. Further this proportion of carbohydrate in the diet does not impose any additional demand for insulin or oral hypoglycaemic agents.

For an average Indian diabetic man of 60 Kg weight (desirable weight) with moderate physical activity, a total of 1800 Kcal may be recommended out of which 60 percent should preferably be from carbohydrate, 22 percent from fat, a 18 percent from protein. The diabetics should be encouraged to divide their provision of calories almost equally among two major meals (lunch and supper) and a substantial breakfast. Tea time snack and bed time glass of milk are essential as supplements. Mid-morning snack may be required for those on regular insulin whole mill wheat flour is the most preferred form of cereal. Rice eating people may be allowed measured amounts of parboiled rice for the

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mid day meal. Legummes (Pulses) have to provide substantial protein of the diet in Indians particularly in vegetarians.

In the last few years fibre has become widely accepted as an essential dietary factor for regulating blood sugar level in diabetics. Evidences are also accumulating that fibre has important effect on metabolism. Dietary fibre constitutes of a mixture of carbohydrate polymers or polysaccharides (Cellulose or hemicellulose and pectin) together with small amount of lignin. Fibre has no nutrient value but form a packaging around nutrient.

Recent work suggest that dietary fibre has an insulin sparing effect due to slower absorption of glucose. Reports have shown that use of high fibre as added to high carbohydrate diet prevents rise of post prandial blood glucose level and may allow withdrawal of insulin when the daily insulin requirement is less than 20 units. Use of natural food such as whole cereals, pulses and leafy vegetables increases the fibre content of the diet but when one does not like these, use of medicinal fibres such as ispagoola husk, guar gum or pectin along with the diet is considered essential.

A very recent development is the use of “Acarbose” which effectively restricts the absorption of polysaccharides from G. I. tract by inhibiting digestive enzymes both in the lumen and in the wall of the gut. More of research is warranted to assess the long term effect of this useful enzyme (alpha glucosidase) inhibitor.

Artificial Sweetening Agent

Sachharin, Sodium cyclamate, fructose and sorbitol have been in use for this purpose. Sodium cyclamate which is pleasantly sweet has been banned from use due to its carcinogenic potentials. Sachharin need be used in very small quantity and hence chances of bladder cancer in human are practically eliminated. It is not to be used in unlimited quantity and should be avoided during pregnancy.

Insulin

Increased incidence of insulin allergy, resistance and long term vascular complications created an world wide problem and thus initiated the need for further purifying the insulin and make it humanised as much as possible.

Given below is a list of the newer insulins in use in developed countries.

Table- 1

A list of newer insulins

Type of insulin	Wellcome	Novo, Denmark	Nord, Denmark	Eli Lilly USA
Rapid acting.	Neusolin (Beef)	Actrapid (purified pork insulin).	Velosulin purified pork	Iletin I (beef and pork insulin mixture, single peak)

Short acting	-	Semitard purified pork (Insulin zinc suspension)	-	Iletin II (purified pork or purified beef insulin single component)
Intermediate acting	Neulente (bovine)	Monotard (purified pork & beef insulin zinc suspension)	(a) Insulin NPH purified (microcrys- taline pork insulin suspension) (b) Insulatard (porcine)	-
Long acting	Ultratard (Izs beef)	Ultratard (Izs beef)	Mixtard (30% volosulin +70% Insulatard)	-
Human insulin	-	Actrapid HM Monotard HM	-	Humilin

Chemically and biologically identical to human insulin, now available commercially, are obtained in one of the two ways. (a) Semisynthetic human insulin where amino-acid residue at B 30 position (alanine) of pork insulin is replaced by threonine, thus changing it to human insulin. (b) Biosynthetic human insulin by recombinant DNA technique.

There has been increased interest in utilising micro organism *E. coli* to produce insulin for commercial use. Colonies of *E. coli* are made to produce either A or B chain of insulin on insertion into the bacteria of plasmids impregnated with cDNA synthesised in vitro with help of m. RNA derived from B cells of human pancreas. The chains obtained from separate sets of colonies are purified and combined to form chemically identical human insulin.

Advantage of newer insulin

- (1) Dose per dose the purified insulins give better control of diabetic state than the conventional insulin.
- (2) Development of antibody and insulin resistance is much less common than the conventional insulin.
- (3) May delay the onset of long term vascular complications.

Disadvantage of newer insulins

- (1) Not easily available in India.

- (2) Cost factor is inappropriately high.
- (3) At present there are conclusive evidences that even these highly purified insulins do induce development of antibodies although of a low titre.

Insulin delivery system

It is now generally accepted that the incidence of vascular diseases increase almost in a linear fashion once the 2 hour post glucose plasma sugar level rises above 180 mg/dl. Though some diabetologist may not agree with the above finding, it may still be said that stricter the diabetes control better is the chance of delaying onset of vascular disease as animal studies have convincingly shown it to be true. In order to achieve the 24 hours euglycaemia or a blood sugar very close to physiological level, a changed outlook prevailed in the last decade regarding the insulin delivery system which includes :

- (i) Intensive conventional therapy of insulin (ICTI)
- (ii) Continuous subcutaneous of I.V. insulin infusion (CSII) by means of external pumps.
- (iii) Closed loop insulin delivery.

ICTI

Conventionally in many centres soluble insulin is being given in two doses or at the best in 3 doses subcutaneously to patients of I.D.D.M. which often results in fasting euglycaemia but estimation of blood sugar at random points may reveal high level, the ambient effect of which may be injurious to the fine blood vessels. Through ICTI usually 4 to 6 shots of insulin are given preferably by intramuscular route. It is also advisable to have a larger loading dose (about 10-15 units) and a subsequent smaller quantity of insulin (6-8 units).

CSII

The idea of using insulin pump (open loop) was to achieve normal blood sugar level and maintain it within acceptable limits by shortest possible time. Pumps both large and portable were brought into use. Insulin may be delivered by subcutaneous, intravenous and intraperitoneal routes. The metabolic effects from long term gluco-regulation with portable insulin infusion pumps are as follows :

- (a) Normal plasma glucose profile.
- (b) Normale levels of lactate, pyruvate, B-hydroxy-butarate and F.F.A.
- (c) Normal levels of alanin, valin, leucin and isoleucin.
- (d) Normalisation of counter regulatory hormones (Growth hormone, glucagon and catecholamines).

- (e) Eulipidaemia.
 - (i) Total cholesterol & LDL cholesterol.
 - (ii) Fall in total triglyceride.
 - (iii) Increase in HDL cholesterol.

In the open loop system, self monitoring of blood glucose level is mandatory.

Closed Loop Delivery System (Artificial B Cells)

This is a device where insulin infusion is regulated from minute to minute by changes in blood glucose concentration. The artificial pancreas is designed to create a physiological relationship between the insulin delivery and blood glucose concentration. This is most helpful in patients of brittle diabetes and patients of IDDM during labour, major surgery, patients of insulin resistance and in other emergency situations. This device has formed the basis of many investigative studies. Till date a portable closed loop pump is unavailable. The most commonly used closed loop pump is a Biostator.

Transplantation of Insulin Producing Tissue

This is most ideal form of treatment of IDDM. In animal studies there is convincing evidence that microvascular complications can be much delayed or reversed by islet transplantation. The optimal effect of transplantation without any rejection complication is achieved through use of human foetal pancreas embedded in the abdominal cavity.

Newer Oral Hypoglycaemic Agents

In India about 80% of diabetics can be managed with the oral hypoglycaemic agents and the compliance for such management is rather satisfactorily good. The U.G.D.P. report (1970) had very little impact on Indian physicians and the diabetic patients here. Tolbutamide was the most commonly used oral antidiabetic until the last decade. With the advent of more potent second generation of sulfonylureas (Glibenclamide, Glipizide and Gliclazide) and better control of diabetes, claims have been raised particularly in relation to prevention of vascular complications. It is so far difficult to accede to claims of specific advantages of gliclazide over other second generation sulfonyl-urea in this aspect.

Future Novel Approaches

Somatostatin (human growth hormone inhibiting hormone) which is known to be secreted from the G. cells of the pancreas and anterior hypothalamus has got inhibitory effect on secretion of anti insulin hormone like glucagon and growth hormone as well as of insulin. It is now thought that analogues and derivatives of somatostatin having no inhibitory effect on insulin secretion will be of immense use in uncontrolled diabetes in controlling the counter regulatory hormones.