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Advances in Diabetes Mellitus: A Contemporary Review

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ABSTRACT

Diabetes mellitus is a group of metabolic disorder in which a person has high blood sugar either because the body does not produce enough insulin or because cells do not respond to the insulin. There are three main types of diabetes, Type I, Type II and Gestational, insulin therapy is used for the treatment of diabetes by administration of exogenous insulin. Several classes of oral hypoglycemic agents like sulfonylureas, biguanides and alpha-glucosidase inhibitors are available for the treatment of type II diabetes. Tremendous advances have occurred in past few decades. New technologies include a variety of alternatives to needle injection for insulin delivery, advances in blood glucose (BG) monitoring devices and novel treatment technologies. The overall goal of DM technology to improve BG control, avoid long term complications and improve patient quality of life. Although these new technologies interesting to use, they must improve outcomes such as BG control and prevent long term complications to be effective and receive widespread acceptance.

Keywords: Diabetes Mellitus, Insulin, Oral Hypoglycemic Agents, Advance Therapies.

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INTRODUCTION

Glucose is a simple sugar found in food. It is an essential nutrient that provides energy for the proper functioning of the body cells. After meals, food is digested in the stomach and the intestines into glucose and other nutrients. The glucose in digested food is absorbed by the intestinal cells into the bloodstream, and is carried by blood to all the cells in the body. However, glucose cannot enter the cells alone. It needs assistance from insulin in order to penetrate the cell walls. Insulin therefore acts as a regulator of glucose metabolism in the body. Insulin (Figure 1) is called the "hunger hormone**".** As the blood sugar level increases following a carbohydrate rich meal, the corresponding insulin level rises with the eventual lowering of the blood sugar level and glucose is transported from the blood into the cell for energy[1-3]. When the blood glucose levels are lowered, the insulin release from the pancreas is turned off. When the blood sugar level drops below a certain level, hunger is felt. This often occurs a few hours after the meal. In normal individuals, such a regulatory system helps to keep blood glucose levels in a tightly controlled range. Cravings for sweets frequently form part of this cycle, which can lead to snacking, often for more carbohydrates. If the cravings are not fulfilled, sensations such as hunger, dizziness, moodiness, and a state of "collapse" can result. This system of auto regulation and homeostasis is the function of the pancreas and it works around the clock. Dysfunction of this auto regulation system - either inability of the pancreas to secrete any or insufficient insulin, or pancreas overload from too much sugar ingested over a long period of time, or over compensatory mechanism, or a combination of these, results in the lack of insulin, and hence high blood sugar. This is the hallmark of diabetes mellitus (commonly called diabetes).

- Impaired fasting glucose (100 to 125 mg/dL).
- Impaired glucose tolerance (fasting glucose less than 126 mg/dL and a glucose level between 140 and 199 mg/dL two hours after taking an oral glucose tolerance test)[4,5].

INSULIN, CHEMICAL STRUCTURE AND METABOLISM

Insulin is a polypeptide hormone formed, after elimination of C peptide by hydrolysis, of two chains of 21 and 30 amino acids, connected by two disulfide bridges. It is secreted by the ß cells of the islets of Langerhans of the pancreas and exerts hypoglycemic action. It belongs to the group of peptides called IGF (insulin like growth factors) or somatomedins.

Biosynthesis of Insulin

Insulin is produced in beta cells which constitute 75% of the islets of Langerhans of the pancreas. Alpha cells secrete glucagon, delta cells somatostatin. Insulin is synthesized in the

form of a single polypeptide chain, preproinsulin which is transformed into proinsulin which, itself, catalyzed by proteases called furines, gives insulin and C peptide (C for connecting, because connecting the two chains A and B). Bound to two zinc atoms, insulin is stored in granules as a polymer, probably a hexamer[6].

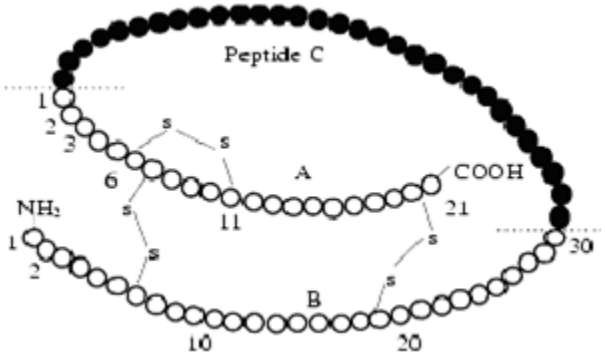

Figure 1: Structure of Insulin[2, 3]

Secretion Of Insulin

Insulin, as well as C peptide, is released by exocytosis into the portal venous system which leads it directly to the liver, which takes up nearly 50%. The remainder of insulin is distributed throughout the body. With a basal secretion of approximately 40 microgram/h under fasting conditions, there are increases of secretion linked to meals. To these slow variations are superimposed peaks of pulsatile secretion. The aim of the treatments by exogenous insulin is to approach the physiological curve of secretion. The principal stimulant of insulin secretion is glucose; it elicits a biphasic release: an immediate effect of short duration and a sustained effect. The cells of the islets are connected by tight junctions, which allow the transfer of ions, of metabolites, secondary messengers from one cell to another, and thus play an important part in synchronizing the secretions[7].

The Stimulation of Insulin Occur In Following Circumstances

1. Penetration of glucose into beta cells, by Glutathion 2 carriers, independently of the presence of insulin.

2. Phosphorylation of glucose by glucokinase, then its metabolisation with synthesis of Adenosine Triphosphate (ATP) whose intracellular concentration increases (Figure 2). This increase in ATP induces the closing of ATP-dependant potassium channels and the cessation of potassium exit, with as a consequence depolarization and opening of the voltage-dependant calcium channels. The entry of calcium elicits the activation of A_2 and C phospholipases and the secretion of insulin[8].

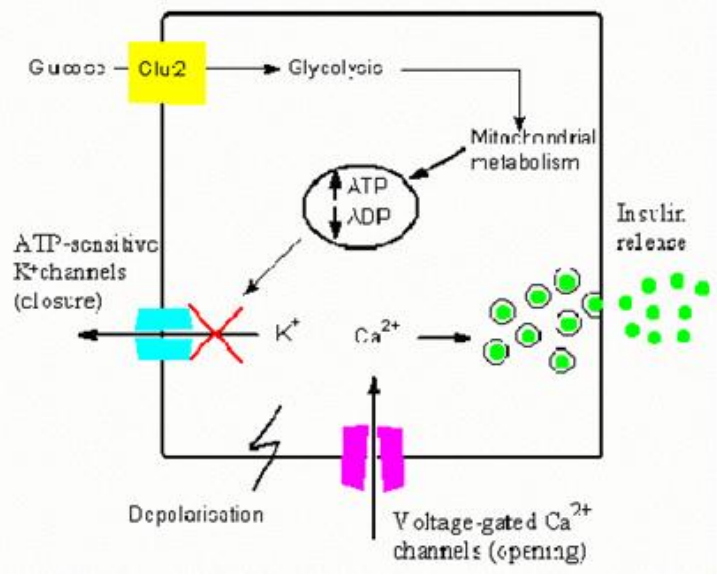

Figure 2: Metabolic Regulation of Insulin Secretion[6, 7]

Diabetes Mellitus

Diabetes mellitus (madhumeha) has been known for ages and sweetness of diabetic urine was mentioned by Sushruta in Ayurveda. Its pharmacotherapy, however, is just over 80 years old. The word Diabetes (to flow through) was coined by Greek physician Aeretaeus in the 1st centuary A.D. In the 17th century, Willis observed that the urine of diabetics was "wonderfully sweet as if imbued with honey or sugar." The presence of sugar in urine was demonstrated by Dobson in 1755. Insulin is ineffective orally. Hence, the search was continuing for an orally effective agent. Synthalin A, a biguanide, was the earliest oral hypoglacemic agent (OHA), to be used in therapy but was found to be too toxic. A chance observation by Janbon (1942) led to the action of sulfonamides. This was confirmed by Frank and Fuchs in 1955, who observed the blood sugar lowering action of carbutamide, a sulfonamide, during its trial in infectious diseases. Since then, many sulfonylurea compounds have been introduced as oral anti-diabetic agents[9-11].

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to a deficiency of insulin. The main cause of this beta cell loss is a T-cell mediated autoimmune attack. There is no known preventive measure which can be taken against type 1 diabetes; it is about 10% of diabetes mellitus cases in North America and Europe (though this varies by geographical location), and is a higher percentage in some other areas.

Treatment

Diabetes mellitus is currently a chronic disease, without a cure, and medical emphasis must

necessarily be on managing/avoiding possible short-term as well as long-term diabetes-related problems. There is an exceptionally important role for patient education, dietetic support, sensible exercise, self monitoring of blood glucose, with the goal of keeping both short-term blood glucose levels, and long term levels as well, within acceptable bounds. Careful control is needed to reduce the risk of long term complications. This is theoretically achievable with combinations of diet, exercise and weight loss (type 2), various oral diabetic drugs (type 2 only), and insulin use (type 1 and for type 2 not responding to oral medications, mostly those with extended duration diabetes) [12-15].

Type 2 Diabetes Mellitus

There is no loss or moderate reduction in β cell mass, insulin in circulation is low, normal or even high degree, no anti β cell antibody is demonstrated; has a high degree of genetic predisposition, generally has a late onset (past middle age) over 90% cases are type 2 diabetes mellitus causes may be,

- Abnormality in gluco receptor of β cells so that they respond at higher glucose concentration or relative β cells deficiency. Reduced sensitivity of peripheral tissues to insulin; reduction in no. of insulin receptors.
- Excess of hyperglycemic hormones (glucagon) obesity, cause relative insulin deficiency.

Gestational Diabetes

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2%–5% of all pregnancies and may improve or disappear after delivery. Gestational diabetes is fully treatable but requires careful medical supervision throughout the pregnancy. About 20%–50% of affected women develop type 2 diabetes later in life[16, 17].

Treatment

It's important to control blood sugar level if the woman has been diagnosed with gestational diabetes. This means regular testing of your blood sugar (glucose) levels, a carefully planned diet and keeping active (Table 1).

Glipizide

Glipizide is an oral medium-to-long acting anti-diabetic drug from the sulfonylurea class. It is classified as a second generation sulfonylurea, which means that it undergoes enterohepatic circulation. Mechanism of action is produced by blocking potassium channels in the beta cells of the islets of langerhans. By partially blocking the potassium channels, it will increase the time

the cell spends in the calcium release stage of cell signaling leading to an increase in calcium. The increase in calcium will initiate more insulin release from each beta cell.

Table.1. Comparative Study of Type 1 and Type 2 Diabetes Mellitus[18]

Sr.no.	Feature	Type 1	Type 2
1	Frequency	10-20%	80-90%
2	Age of onset	Early below 40 years	Late after 40 years
3	Type of onset	Abrupt and severe	Gradual and insidious
4	Weight	Normal	Obese
5	HLA	HLA-D linked	No HLA association
6	Family history	<20%	About 60%
7	Genetic locus	Unknown	Chromosome 6
8	Identical twins	50% chances in them	60-80% chances in them
9	Pathogenesis	Autoimmune	Insulin resistance
10	Islet cells changes	Insulin, beta cell depletion	No insulitis, mild beta cell depletion
11	Islet cell antibodies	Yes	No
12	Blood insulin level	Decreased insulin	No
13	Amyloidosis	Infrequent	Common in chronic cases
14	Acute complications	Ketoacidosis	Hyperosmolar coma
15	Clinical management	Insulin and diet	Diet and drugs

Metformin HCl

Metformin (dimethylbiguanide) is an orally administered drug used to lower blood glucose concentrations in patients with non-insulin-dependent diabetes mellitus (NIDDM). It improves insulin sensitivity and thus decreases the insulin resistance that is prevalent in NIDDM. The efficacy of glycemic control achieved with metformin is similar to that achieved with sulfonylureas, although their modes of action differ. Metformin can be used either as initial therapy or as an additional drug when sulfonylurea therapy alone is inadequate[18].

Repaglinide

Repaglinide increases the amount of insulin released in a natural and physiological pulsatile pattern. The activity of repaglinide is dose-dependent. Mean insulin levels begin to rise approximately 1.5 hours after the pre-prandial dose of repaglinide and declines towards baseline levels between meal-time. The rapid onset of action and the short duration of hypoglycemic effect of repaglinide make this agent suitable for pre-prandial administration. The main advantage of pre-prandial administration is that patients can miss or postpone a meal (and the corresponding repaglinide dose) without increasing the risk of hypoglycemia or compromising glycemic control[19].

Troglitazone

Troglitazone is a new oral antidiabetic drug that increases the sensitivity of peripheral tissues to insulin. It may therefore increase the efficacy of exogenous insulin in patients with insulin-

resistant diabetes mellitus.

Thiazolidinedione

Thiazolidinediones (TZDs) are a new class of oral antidiabetic agents. They selectively enhance or partially mimic certain actions of insulin, causing a slowly generated antihyperglycaemic effect in Type 2 (noninsulin dependent) diabetic patients. This is often accompanied by a reduction in circulating concentrations of insulin, triglycerides and nonesterified fatty acids. TZDs act additively with other types of oral antidiabetic agents (suphonylureas, metformin and acarbose) and reduce the insulin dosage required in insulin-treated patients. The glucose-lowering effect of TZDs is attributed to increased peripheral glucose disposal and decreased hepatic glucose output.

Sulfonylureas

The first insulin secretagogues used as drugs were sulfonylureas. Sulfonylureas stimulate insulin secretion by beta cells of the pancreas by sensitizing them to the action of glucose. They bind to a receptor located on the plasma membrane adjacent to potassium channels, called SUR (sulfonylurea receptor) Sulfonylureas can, moreover, inhibit glucagon secretion and sensitize target tissues to the action of insulin. Sulfonylureas are administered by oral route, bind to plasma proteins (Table 2)[20-22].

Table.2 Drugs Used in Diabetes Mellitus[20-22]

SULPHONYLUREAS	Dose(mg)	T½ (hr)	Duration of action (hr)
Tolbutamide	250-300	4.5-6.5	6-12
Chlorpropamide	100-750	36	60
Gibenclamide	1.25-20	4-10	16-24
Glipizide	2.5-40	2-4	12-24
Gliclazide	40-320	10-12	--
Gimepiride	1-8	9	16-24
Acetohexamide	250-1500	0.8-2.4	12-18
Tofazamide	100-1000	7	12-24
BIGUANIDES			
Metformin	1500-2550	6.2	>3-4 wk
MEGLITINIDE			
Repaglinide	0.5-4	1-1.4	4-6
Nateglinide	120	1.5	--
THIAZOLIDINEDIONES			
Rosiglitazone	4-8	3-4	>3-4 wk
Pioglitazone	15-45	3-7	>3-4 wk

Advances in diabetes mellitus

Diabetes is one of the most serious challenges to health care worldwide; according to recent projections, it will affect 239 million people by 2010 a doubling in prevalence since 1994 the

incidence of insulin dependent diabetes is increasing in small children, who will be more prone to late complications of diabetes insulin dependent and non-insulin dependent diabetes are pathogenetically heterogeneous disorders caused by the interaction of several genetic and environmental factors. Although it is now shown that strict metabolic control prevents late micro vascular complications, it increases the risk of hypoglycaemia, demands high motivation from patients, and is costly.

New Delivery Systems

Pump Therapy

The effectiveness of continuous subcutaneous insulin infusion (pump therapy) has been rediscovered. First used in the 1970s and 1980s, pump therapy has been reintroduced with improved technology. Small amounts of a rapid-acting insulin analogue are infused, usually into the abdomen or buttocks, at a basal rate, which can be varied, with extra boluses calculated for each meal and snack. The major advantages are less variable absorption and improved insulin pharmacokinetics. Varying the basal rate can help regulate overnight blood glucose levels. Pump therapy is suitable for motivated patients, particularly those with frequent hypoglycaemic episodes or hypoglycaemic unawareness, as most studies show reduced hypoglycaemia. Because the infused insulin is rapid-acting, mechanical interruption of the pump can rapidly lead to ketosis, which is of particular concern in pregnancy. Pump therapy must therefore be accompanied by frequent blood glucose monitoring. Private health insurance companies now subsidise the cost of the pump and some consumables, but there is no government funding. As for all therapies, it is essential that the patient is central to the choice of pump therapy. This is also important when the patient is a child or adolescent, whose views may differ from those of their parents.

Aerosols

Aerosolized insulin for delivery by inhalation are under active investigation, with Phase III studies completed. These insulin provide effective cover for meals in combination with once-daily, long-acting, subcutaneous insulin. However, aerosol delivery requires six times as much insulin for the same effective dose as subcutaneous injection, which may create a cost barrier to widespread use. Also, the long-term safety of delivering large amounts of insulin to the alveolae is not known. At present, all systems deliver insulin to the systemic circulation rather than the enteroportal circulation. Systemic delivery contributes to the insulin resistance associated with obesity and adolescence and is a major barrier to physiological insulin replacement[23-26].

INSULIN DELIVERY DEVICES

Needle and Syringe

A common way of administering insulin is with a needle and syringe. Syringes come in a range of capacities (1 mL, 0.5 mL or 0.3 mL) and with a range of needle types (different gauges — that are thicknesses and lengths) attached. The needles have very fine points and special coatings to make injections relatively pain-free. Select a syringe that suits the size of the insulin dose you take and that has your preferred needle type and needle size attached. One of the main advantages of the syringe system is the variety of products available. Needles and syringes also make it easy to use a mixture of different types of insulin ('mixed insulin'), and to draw up a week's supply in advance, to be stored in the refrigerator. However, some people find syringes daunting and not very convenient. For this reason a number of other delivery devices have been developed, including insulin pens, jet injectors and pumps.

Insulin Pens

Insulin pen injectors are a convenient and discreet way of administering insulin. They have a built-in dial that allows you to determine the amount of insulin to be injected, a short needle at one end, and a plunger at the other. Some are disposable, and don't need to be assembled before use, while others have a replaceable insulin cartridge that needs to be inserted (much like a fountain pen cartridge). Insulin pens are particularly useful if you need to take premixed insulin. They have become popular for use by people with both type 1 and type 2 diabetes[27-29].

Insulin Jet Injectors

Jet injectors offer an alternative to needles, and work by sending a fine spray of insulin into the skin using a pressurized jet of air instead of a needle. However, jet injection isn’t any less painful than administering insulin with a needle, and may cause bruising or altered absorption levels. Jet injectors also require frequent cleaning and maintenance.

Insulin Patches

Insulin patches are also currently under development, but it is difficult for insulin to be absorbed through the skin. The patch is designed to release insulin slowly and continuously. Additional doses can be administered by pulling off a tab on the patch[30].

Insulin Inhalers

Insulin inhalers are a new way of delivering pre-mealtime insulin. Insulin inhalers work like an asthma inhaler, but deliver dry powdered insulin into the bloodstream via the lungs. However, because the system can only be used to deliver fast-acting insulin, long-acting insulin must still be injected. Large doses are needed because only around 10 per cent of the dose actually reaches

the bloodstream and that amount may vary, for instance, if you have a cold or asthma. The inhalers are not yet commercially available in Australia, but have been approved for use in the USA.

Other Delivery Devices

Insulin sprays, either for the nose or mouth, and oral insulin (insulin pills) are methods of insulin delivery that continue to be investigated. These options represent long-term possibilities for insulin delivery, as difficulties in obtaining adequate amounts of insulin in the bloodstream are yet to be overcome[31, 32].

Insulin Pills

The discovery of a new polymer that may allow development of an effective insulin pill was reported at a recent meeting of the American Chemical Society. When the polymer is used as a pill coating, it allows insulin to get into the bloodstream without being destroyed by the digestive system. So far it has only been tested in animals. Some experts question whether insulin in pill form will prove useful, since dosing is so critical and often variable.

NEWER INSULINS

In the past few years, three new formulations of insulin have become available which have been designed to offer the advantages of simpler regimens and better glucose control for people whose diabetes must be treated with insulin. All are human insulin analogs derived from recombinant DNA technology.

Glargine (Aventis Co.) is basal insulin, offering a more continuous activity with much less of a peak than NPH insulin. It can be used with a very-rapid-acting insulin such as lispro or aspart, and should provide a flatter basal amount of insulin. Until now this has only been possible with twice daily injections of ultralente or by the basal rate of an insulin pump. This approach tries to permit more normal mealtime patterns individualized to a person's own habits.

Aspart (from Novo Nordisk) is a very-rapid-acting insulin that can be injected 15 minutes prior to eating. Its fast action also allows more freedom in the timing of meals and the amount of food eaten. A 75/25 lispro mixture is the first of the analog mixtures available (from Eli Lilly); it contains Lilly's very-rapid-acting lispro and a novel human insulin analog called NPL. It is designed for those who need better control after meals and want to use an insulin pen[33-35].

NEW TREATMENT

Islet Cell Transplant

A new islet cell transplant technique has shown promise in people with Type 1 Diabetes. Called the 'Edmonton' technique, the transplants have resulted in seven patients becoming insulin free

for up to 14 months after treatment. Clinical trials are now underway at 10 national diabetes centers to see if the insulin reversal can be successful with more patients. The Edmonton technique uses islet cells (cells from the pancreas) from two or more donor pancreases. The cells are transplanted into a person with diabetes and then special medications are given to prevent rejection of the new cells. One difficulty with the transplants is that even though a person may become free of the need to take insulin, the medications to prevent rejection of new tissue must be taken for a lifetime. These medications have side effects[36].

Gene Therapy

Two recent reports describe research into gene therapy for different aspects of diabetes. These reports are in the forefront of what will no doubt be ongoing and exciting research arising from the decoding of the human genome.

- Scientists have identified a gene called SHIP2 that appears to regulate insulin. Such findings make SHIP2 a potential gene therapy target for the treatment of type 2 diabetes aimed at improving the individual's insulin regulation.
- A protein that blocks the overgrowth of blood vessels in the eye is being studied as possible gene therapy for diabetic retinopathy. A recent study showed that treatment with the protein, called pigment epithelium-derived factor, or PEDF, prevented excessive new blood vessel formation in an animal model of retinopathy. It may also be used to treat macular degeneration.
- As scientists identify specific genes whose absence or improper functioning are associated with specific conditions, more possibilities for gene therapy are offered – for diabetes as well as all disease[37].

Vaccine Against Diabetes on the Horizon

Researchers have developed the world's first drug that stops the destruction of pancreatic beta cells in humans. It thereby offers the possibility of preventing type 1 diabetes in people at high risk and of halting its progress in people newly diagnosed with it. Israeli scientists have worked on this agent for more than a decade. To date, 200 patients in Israel, England, Hungary, Bulgaria and Germany have been successfully treated. Results published in a recent issue of The Lancet showed that three injections of the compound given within six months of diagnosis of type 1 diabetes successfully arrested the progression of the disease in newly diagnosed patients. After treatment, these patients produced insulin and required fewer insulin injections. They did not experience any harmful or major side effects. While this data looks promising, additional studies are under way to confirm its effectiveness and safety. The drug is a peptide, a type of protein. By

modifying a fragment of the protein, the developers created a drug that can selectively block the activity of immune cells that attack the pancreas. It thus deactivates the cells that attack the pancreas without interfering with the rest of the body's immune system[38].

A VIEW TOWARDS FUTURE

Methods of Insulin Delivery:

Inhaled Insulin

The large surface area of the lungs (more than 100 m^2) with its thin and highly vascularised epithelium provides an attractive site for rapid insulin absorption. Several aerosol devices have been developed for inhalation of insulin either as a dry powder or in solution and clinical trials are on-going. These are mainly focused on delivery of relatively small amounts of short-acting and rapid-acting insulins for mealtime 'top-up'. The main basal insulin dose in the trials is taken by conventional injection. Absorption via the pulmonary route is similar to or faster than subcutaneous injection of rapid-acting insulin, and the effect is longer lasting. Variability of absorption within an individual is small, but substantially affected by intercurrent respiratory conditions.

Oral Insulins

Many attempts to produce an oral insulin formulation have been reported over the last three decades, including liposome-encapsulated insulin and various polymer-wrapped insulins. None has provided both an adequate shield against proteolytic digestion and an effective aid to absorption to give reasonable bioavailability. A recent promising contribution is an alkyl-polyethylene-glycol conjugated hexyl-insulin (HIM2) in clinical trial with Nobex and GSK. Others include a particulate 'nanocubicle' emulsion and a polylactide microcapsule[39].

Buccal and Nasal Insulins

Buccal insulin delivery is under clinical development by Generex and Lilly under the names of Oralin® in Europe and Oralgen® in the USA. Administration is similar to an angina spray, with an aerosol (RapidMist®) delivering a fine spray directly onto the buccal mucosa. Nasal epithelium provides a very low bioavailability of insulin and is sensitive to intercurrent local infections and irritation. Surfactants and other absorption enhancers increase bioavailability, but have not led to a viable delivery system due to disturbances to the integrity of the the nasal epithelium.

Liver-Targeted Insulin

Subcutaneous injections of insulin do not replicate the normal physiological delivery of insulin into the portal circulation so that the liver is exposed to higher insulin concentrations than the

periphery. Preferential delivery to the liver is under investigation using insulin linked to thyroxine[40-41].

CONCLUSION:

The goal of this review paper is to give a general idea about the disease and the current status of diabetes mellitus in clinical research. Diabetes is a slow killer disease with no known curable treatments. Diabetes may occur at any age. However the risk of developing diabetes also increases as people grow older. Novel therapies are in various stages of development, and some are showing promising results in clinical trials. Adding new options with new mechanisms of action to the treatment armamentarium may eventually help improve outcomes and reduce the cost burden of this condition.

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