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Review Article

ADVANCEMENT IN THE TREATMENT OF DIABETES MELLITUS: AN OVERVIEW

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ABSTRACT

Diabetes mellitus is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. There is an increase in the prevalence of type 1diabetes also, but main cause of diabetic epidemic is type2 diabetes mellitus, which accounts for more than 90 percent of all diabetes cases. Future drug therapy of T1DM will depend on the success of ongoing and planned intervention trials. Immunomodulation alone, or possibly combined with immunosuppressive therapy. Also the treatment for type 2 diabetes mellitus is improved as the conventional treatments have many risk factors associated with cardiac and renal systems. So there is need to develop the advances in the treatment of T1DM and T2DM. So here some of the modern aspects of treatment discussed. Which are advantageous over the conventional methods.
KEYWORDS: Continuous glucose Monitoring, Intranasal, Pancreatic Transplantation, Type 2 Diabetes

INTRODUCTION

Diabetes mellitus, a major lifestyle disease is undoubtedly the most challenging public health problem of 21st century. The International Diabetes Federation (IDF) estimates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025. The majority of cases of diabetes fall into two broad etiopathogenetic categories now called T1 DM and T2 DM[**1].**

Indians have a peculiar genetic composition and Asian Indian phenotype that predisposes them to have higher propensity to metabolic syndrome, diabetes mellitus and coronary artery disease. Indians characteristically have increased insulin resistance, greater abdominal adiposity higher prevalence of impaired glucose tolerance. The current scenario of diabetes in India is likely to worsen in the coming decade. The greatest numbers of people with diabetes are between 40 and 59 years of age. High prevalence of obesity in Indian adolescents may aggravate the situation. The most disturbing trend is the shift in age of onset of diabetes to a younger age in the recent years. The recent trend of rising diabetes among rural Indians and women is also alarming. People of Indian origin who live in the United States have a lower prevalence of diabetes than those who live in India.India has seen many economic and nutritional changes in recent years, along with a rapid rise in diabetes cases.

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Main challenges posed by type 2 diabetes mellitus

- Rising prevalence in urban and rural areas
- High prevalence of prediabetes
- Genetic and environmental risk factors
- Rising prevalence among young people
- Delayed diagnosis
- Low disease awareness among the public
- Limited health care facilities
- High cost of disease management
- Suboptimal diabetes control
- Rising rate of diabetes complications[2]

ADVANCES IN MANAGEMENT OF T1DM

Intranasal*:*

Soluble insulin administered intranasaly is rapidly absorbed when given along with a detergent sub-stance to facilitate adsorption. Preliminaryclinical trials have demonstrated its efficacy in reducing post-prandialhyperglycemia in subjects with type 1 diabetes. However, its absorption islimited to less than 10% of the administered nasal dose. This reduces its costeffectiveness,and most manufacturers have dis-continued clinical trialsuntil more progress is made in improving its bioavailability. Inhalers that canprovide more precise delivery of drugs have been developed, and inhaledinsulin is currently in phase III trials [3].

Insulin pumps and continuous subcutaneous insulin infusion:

Insulin pumpdevices have become smaller and increasingly more sophisticated in theirfunctionality. Insulin is delivered through a cannula placed subcutaneouslyand replaced with a 72 h frequency. A continuous basal rate is programmedinto the pump and additional boluses of insulin can be administered ‘at thepush of a button. Smart pumps’ have a more sophisticated computerincorporated into the insulin pump. The delivery of CSII through insulinpumps has been extensively investigated in the paediatric and young adult population [3].

Continuous glucose monitoring (CGM) systems:

This system, throughwhich a subcutaneous, glucose oxidase coated sensor measures interstitial fluid glucose concentrations and converts them to a plasma glucose estimate, provides a promising modality for future management of type 1 diabetes. Aplot of plasma glucose concentrations over a 24-h period are produced andcan enable insulin adjustment to identify episodes of hyper or hypoglycaemiathat may not have been identified using conventional capillary glucosemonitoring. More recently, real-time CGM and CSII technologies havebeen combined in a single device and this exciting technology may representa step towards an ‘artificialpancreas’. However, despite advances, thistechnology is in its infancy and its current role in the management of type1diabetes is unclear[3].

Other modes of therapy in T1DM:

- Amylin analogues: Pramlintide is asynthetic analogue of amylin, a polypeptide hormone, co-secreted withinsulin from pancreatic b cells. It is injected pre-prandially in addition toinsulin and has shown modest improvements in post-prandial hyperglycaemiawith20-30% decrease of insulin dose. Treatment of type 1 diabetes withpramlintide is associated

with fewer hypoglycaemic episodes and significantweight loss. Its use is limited by nausea and additional prick required besidesinsulin[3].

- ***HbA*1c *measurement:***Measurement of glycosylated haemoglobin (HbA1c) remains the criterion standard to judge the outcome of diabetes management. Rapid measurement with a desktop device expedites assessment and education. Results of longitudinal studies now allow accurate prediction of the risk of vascular complications for a given HbA1c. This can be very useful when counselling patients. For example, a teenager can be advised that large trials show that reducing the HbA1c level from 9% to 8% and maintaining the reduction during adolescence reduces the risk of proliferative and severe non-proliferative retino-pathy in young adulthood by 70%–80%[3].

Pancreatic and islet transplantation:

Whole-organ pancreatic transplantationfor the treatment of type1 diabetes has largely been reserved for thoseundergoing renal transplantation for end-stage diabetic nephropathy. While normalization of glycaemic control is achieved following successfultransplantation, but this therapy carries the risk of pancreatic graft rejectionand side effects of immunosuppressant.Islet cell transplantation provides a promising treatment option for type 1diabetes. β-cellsisolated from a donor pancreas are injected into the portalvenous system where they then lodge within liver sinusoids. These b cells remain glucose sensitive and secrete insulin into the portal system, in thesame way as occur in the physiological situation. Variable β-cell yieldusing this isolation technique requires harvest from more than one pancreasto provide sufficient tissue for successful transplantation. Nonetheless, withthe future promise of engineered b cells using stem cell differentiationmethods, this technique of cell delivery/transplantation may provide asuccessful long-term treatment of glycaemia in type 1 diabetes [4].

Immunotherapy

Pancreatic β-cell preservation using immune suppression or immune tolerancehas been disappointing. When used as secondary prevention of type 1diabetes, ciclosporin and anti- CD3 antibodies reduce the required insulindose and prolong b-cell survival, as assessed by fasting and stimulated serum C-peptide concentrations. However, both of these treatment modalities have unacceptable side-effect, particularly given the age of thetarget population.GAD-alum immunization in an attempt to promoteimmune tolerance in subjects with diagnosed type 1 diabetes did not significantly reduce their requirement for insulin or improve fasting serum C peptide concentrations. The use of these therapies requires more researchbefore their introduction as mainstream approaches to prevention of type1 diabetes mellitus[3].

ADVANCES IN MANAGEMENT OF T2DM

Diabetes is one of the most common chronic diseases in the United States. With type 2 diabetes being the most common form of the disease, it’s a priority to make progress in its treatment. And researchers have done just that.

Insulin

Type 1 diabetes usually comes to mind with insulin. But most people with type 2 diabetes will eventually need to use it. People with type 2 diabetes account for most insulin use due to their sheer numbers. Approximately 30% of type 2 diabetes patients use insulin. So making advances in insulin treatment benefits many people with type 2 diabetes in the last 10 years, new types of insulin have come to market.

Rapid-acting analogues:

These are also known as rapid-onset and ultra-short-acting insulins and include insulin aspart and insulin lispro. They were created by modifying the amino acid sequence of the insulin B chain (substituting aspartic acid for proline at position 28 [aspart] and reversing proline and lysine at positions 28 and 29 [lispro].

These analogues have the advantages that:

- They follow better the rise in blood glucose level after eating than conventional short-acting insulins, thereby reducing postprandial hyperglycemia and between-meals hypoglycemia.
- Their very rapid onset of action allows them to be injected immediately before meals or even after eating, which is especially useful in young children with erratic eating patterns.

Their disadvantages are:

- Shorter duration of action than traditional short-acting human insulins, which could cause pre-prandial hyperglycemia.

The short-acting analogues are available on the Pharmaceutical Benefits Scheme.

Long-acting analogues:

These were created by substituting and adding amino acids to the insulin molecule (glargine) and by adding a fatty acid chain, which enhances binding to albumin.

The long-acting analogues have the advantages of:

- More reproducible absorption than conventional long-acting insulin.
- A flat dose profile with a low peak of action, which provides more predictable background control than the intermediate-acting insulins, without the unwanted peaks of action around lunchtime and during the night. Initial studies indicate that the long-acting analogues reduce the risk of nocturnal hypoglycemia and produce a modest reduction in fasting blood glucose levels compared with intermediate-acting preparations. Neither is as yet available on the Pharmaceutical Benefits Scheme (PBS). There are few data on the relative benefits of administration by pump versus multiple daily injections for glargine or detemir as the basal insulin, but better night-time blood glucose control with pump therapy has recently been described.

One very recent newcomer is a totally different form of insulin—Afrezza inhaled human insulin. We can take this type of insulin by breathing it in. It is a rapid-acting insulin and can be use it at mealtime and in combination with long-acting Injectable insulin [5].

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Other Injectable Drugs

Injectable drugs are medicines which are given with a needle and syringe. Insulin has been the only injectable medicine for diabetes until recently. But now there are new ones. They include medicines that mimic natural hormones other than insulin. These hormones have different roles in helping your body use blood sugar for energy.

The drugs in this category basically help regulate blood sugar and appetite. These medicines may also help you lose weight, which can be helpful in type 2 diabetes. Here are the two classes:

GLP-1 agonists are a group of drugs that are useful if you have type 2 diabetes.GLP-1 receptor agonists are an alternative treatment to pharmacologically enhance the release of insulin, with additional effects on reducing glucagon release, increasing satiety, and increasing gastric emptyingGLP-1 analogues mimic endogenous GLP-1 activity but are resistant to DPP-4 deactivation, resulting in prolonged activity. They cannot be administered orally, the current preparations being subcutaneous injections. Two GLP-1 agonists are currently available: exenatide, which has a half-life of four hours and requires twice-daily injection, and liraglutide, which has a half-life of 11–13 hours and requires once-daily injections. A long-acting, once-weekly formulation of exenatide has recently been granted marketing authorization by the licensing authority in Europe. Mild-to-moderate nausea is the most common side effect associated with the use of these drugs. This was reported by about 50% of subjects in studies but declined after the first eight weeks of treatment. Only 4% of patients withdrew from trials as a result of more severe gastrointestinal side effects, including vomiting [5].

Amylin analogs will help both type 1 and type 2 diabetes. That’s exciting because insulin was the primary treatment for type 1 diabetes until this new class. Amylin is a peptide hormone that is cosecreted with insulin from the pancreatic β-cell and is thus deficient in diabetic people. It inhibits glucagon secretion, delays gastric emptying, and acts as a satiety agent. Amylin replacement could therefore possibly improve glycemic control in some people with diabetesA stable analog, pramlintide, which has actions and pharmacokinetic and pharmacodynamic properties similar to the native peptide, has been developed. The efficacy and safety of pramlintide administration has been tested in a vast number of clinical trials [6].

Oral Drugs

Oral drugs are taken by mouth and they have been the mainstay of type 2 diabetes treatment. In the past, there were basically five classes of drugs in this category. In recent years, two more classes of oral drugs have come to market:

- DDP-4 inhibitors help trigger insulin release. But they work differently than other drugs that stimulate insulin release. As a result, they don’t cause low blood sugar the way other drugs can.DPP-4 inhibitors work by blocking the action of DPP-4, an enzyme which destroys the hormone incretin.Incretins help the body produce more insulin only when it is needed and reduce the amount of glucose being produced by the liver when it is not needed. These hormones are released throughout the day and levels are increased at meal times [7].

Examples of DDP-4 inhibitors are Alogliptin, Linagliptin, Sitagliptin, Saxagliptin, Vildagliptin.(Diabetes uk)In diabetic patients who also suffer from coronary heart disease, it was demonstrated that treatment with sitagliptin improved their heart function and coronary artery perfusion, as observed in echo-debutamin tests. Also risk associated with lowered blood pressure is overcome by administration of high dose ACE-inhibitor [8]

- SGLT inhibitors lower blood sugar by getting rid of extra sugar in the urine. This is a completely new way of working. The sodium glucose co-transporter 2 (SGLT2) inhibitors are the newest class of diabetes therapy and improve glycaemic control by increasing urinary glucose excretion through inhibition of SGLT2 receptors in the proximal renal tubule. SGLT2 receptors are responsible for reabsorption of approximately 90 per cent of filtered plasma glucose and SGLT1 receptors in the distal segment of the proximal tubule reabsorb the remaining 10 per cent. The renal threshold for glycosuria, which is increased from 10mmol/L in normal individuals to approximately 13.8mmol/L in those with type 2 diabetes, thus contributing to hyper glycaemia, is reduced to around 5mmol/L with SGLT2 inhibitors, resulting in increased glycosuria.But there is a downside to this group—they tend to cause urinary tract and yeast infections.

Old Drugs With New Diabetes Uses

Researchers started thinking outside the box. They looked at some existing drugs that treat other diseases to see if they could help with diabetes. Two drugs have gained FDA (Food and Drug Administration) approval for treating type 2 diabetes:

Bromocriptine (Parlodel). This drug has many uses including treating menstrual problems, infertility, and Parkinson's disease. The FDA approved it in type 2 diabetes under the brand name, Cycloset. Cycloset helps people have better long-term blood sugar control. Doctors check this with a lab test called an A1c.

Colesevelam (Welchol). Doctors usually use this drug to treat high cholesterol. It turns out that people with type 2 diabetes who took this drug in combination with their usual diabetic therapy had better A1c results than those who didn't take it. Now, doctors can prescribe it along with other diabetes treatments [9].

CONCLUSION

There are wide ranges of development that provide examples for changing the way of treatment of diabetes. The ideas have direct influence on the modernization of route of medication. Also the newer techniques will be aimed to minimize the risk factors associated with the previous ways of treatment.

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