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Review Article

Emerging treatment modalities for the management of diabetes mellitus: A review

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ABSTRACT

This narrative review focussed on Diabetes which has emerged as a significant public health problem after cardiovascular diseases and the sixth leading cause of mortality worldwide. India faces a massive burden of Diabetes, which parallels a similar rise in obesity and metabolic syndrome. (Diabetes mellitus currently had a global prevalence of 6.4%, aged 20-79 years in 2010). Diabetes prevalence among adults over 18 years has increased from 4.7% in 1980 to 8.5 % in 2014 (WHO) and is estimated to be 10.2% by 2030 (IDF). India has the second-largest number of diabetics (about a 61million, i.e., the prevalence of 8.8% and about 77 million, i.e., majority of 8.9%). The number is likely to increase to 101 million (prevalence of 9.9%) by 2030. These rising figures are primarily due to marked transitions leading to unhealthy diets and physical inactivity. That causes problems like retinopathy, cardiomyopathy, nephropathy, and neurodegenerative diseases. Diabetes is the most common progressive heterogeneous endocrine disorder with devastating multi-systemic complications characterized by altered glucose homeostasis and insulin resistance. Diabetes is principally divided into two types Diabetes Insipidus and Diabetes Mellitus (DM). Again, DM is of 2 types — Type 1(Juvenile/Insulin-dependent) and Type-2 (Insulin resistance). Type1-DM is prevalent in the young population, associated with a lack of insulin production due to auto-immune destruction of beta cells of the pancreas. In contrast, Type2-DM is due to the inability of cells/tissues to respond to insulin appropriately. Long-term chronic hyperglycemia leads to organ dysfunction leads to organ failure, especially kidney, eyes, heart, and blood vessels.

1. Introduction[1–4]

Type-2 Diabetes (T2DM) is caused by a decrease in insulin production or peripheral resistance to insulin action. Patients may be treated solely by diet, but they frequently require oral anti-diabetic medications or, when necessary, insulin. However, appropriate energy and carbohydrate consumption is needed. Obesity is one of the aspects linked to insulin resistance in type 2 diabetes. Exercise and increased activity should be prioritized. On the other hand, Diabetes Insipidus is due to insufficient production of ADH by the pituitary gland cause increased urine production and dehydration. Diabetes insipidus is either nephrogenic, gestational, dipsogenic. Despite these genetic, pregnancies, stress, is also accountable.

The goal of treatment is to attain the most effective possible management of plasma glucose levels and to prevent or delay consequences such as microvascular (retinopathy, albuminuria, neuropathy) and macrovascular (cardiovascular) problems. Other risk factors like cardiovascular disease, hypertension, hyperlipidemia, and obesity, should also be addressed. Prompt identification and proper management of associated conditions and

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complications are of utmost importance. Hyperlipidemia and hypertension control is much more important, along with control of blood glucose levels.

Recent studies have shown reduced microvascular complications with better glycemic control. However, evidence of reduction of risk of macrovascular complications with intensive glycemic control is not so robust. Several major trials over the past 3 years, ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation), ACCORD (Action to Control Cardiovascular Risk in Diabetes), and VADT (Veterans Affairs Diabetes Trial) have shown that an intensive glucose control with target HbA1c of less than 6.5% does not result in cardiovascular risk reduction. In fact, in the ACCORD trial, intensive glucose control with a target HbA1c of less than 6 % caused increased cardiovascular complications. On the other hand, long-term follow-up data from the DCCT (Diabetes Control and Complications Trial) conducted in patients with type 1 diabetes showed a 42% reduction in the risk of cardiovascular outcomes. This discrepancy is likely to be due to the differences in disease durations in these trials. Patients in the DCCT trial were randomized to intensive control very early after disease onset, and this may have contributed to the 'legacy effect.' In light of the above evidence, it is important to realize that glycemic control goals need to be individualized to maximize the benefit in terms of prevention of complications and minimize the risks associated with hypoglycemia.

The significance of intensive glycemic control for safety towards microvascular and cardiovascular disease (CVD) in Diabetes was established for type 1 diabetes in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study. Although the advantage of glycemic control on microvascular complications in type 2 diabetes was reported in the United Kingdom Prospective Diabetes Study (UKPDS), its role in reducing cardiovascular problems has not been likewise settled.

The overall management of Diabetes consists of the following components:

1. Achieving/maintaining optimum body weight by diet modification and exercise. These modalities of treatment are constant throughout the management cycle, with appropriate corrections from time to time
2. Maintaining euglycemia and avoid acute complications related to marked hyperglycemia
3. Delaying chronic microvascular and macrovascular complications
4. Treatment of associated conditions such as hypertension, dyslipidemia, etc.
5. Positive lifestyle changes such as smoking cessation, restricting alcohol intake.

2. Role of Oral Hypoglycaemic Drugs[5–7]

To maintain individualised glycemic goals in T2DM an interprofessional approach required including both lifestyle adjustment and pharmacological therapies. Emphasis on combination of lifestyle modification and oral pharmacological therapies for maintaining glycemic levels must be given by healthcare professionals particularly in T2DM. Oral Hypoglycemic medications are most prescribed pharmacological therapy around the world.

1. Sulfonylureas (Glibenclamide, Glipizide, Gliclazide, Glyburide, Glimepiride)
2. Biguanides (Metformin)
3. Non-Sulfonylurea secretagogues -Meglitinides (Repaglinide and Nateglinide)
4. Thiazolidinediones (Rosiglitazone, Pioglitazone)
5. A-Glucosidase inhibitors (Acarbose, Miglitol, Voglibose)
6. DPP-4 inhibitors (Sitagliptin, Saxagliptin, Vildagliptin, Linagliptin, Alogliptin)
7. SGLT2 inhibitors (Dapagliflozin and Canagliflozin)
8. Cycloset (Bromocriptine)

Sulphonylureas are the insulin secretagogues and trigger insulin release by inhibiting adenosine triphosphate (ATP) dependent potassium channels in beta cells of the pancreas. They are very potent in lowering HbA1c. Their use is limited by weight gain, a high risk of hypoglycemia, and secondary failure. These derivatives are avoided during pregnancy (except Glyburide), and attention is required in the elderly and those with renal or hepatic inadequacy. Insulin therapy is vital during an inter-current illness such as myocardial infarction, coma, infection, and trauma, during surgery and also during pregnancy.[8]

Biguanide is a parent entity used to synthesize drugs like Metformin, phenformin; buformin lowers blood glucose levels by inhibiting hepatic gluconeogenesis and by increasing peripheral utilization of glucose. Due to some side effects Phenformin and buformin withdrawn from market during 1970s. Metformin has insulin-lowering effects by improving insulin sensitivity and first line drug of choice in non-insulin-dependent DM (T2DM). It does not upregulate endogenous insulin release. Metformin triggers adenosine monophosphate-activated protein kinase in the liver, causing hepatic uptake of glucose and downregulates gluconeogenesis through the mitochondrial enzymes. Its two remarkable clinical features include no risk of hypoglycemia and no weight gain. Also, there is evidence that Metformin reduces the risk of developing carcinoma due to diabetes. The most common side effects of Metformin are gastrointestinal; these can be controlled with lowering of dose. With metformin, there is a risk of lactic acidosis and is contraindicated in patients with chronic kidney disease, heart failure, significant liver disease and circulatory failure.[8,9] Non-sulphonylurea category

class of oral anti-hyperglycemic includes repaglinide and nateglinide. These are short-acting insulin secretagogues. These drugs have modest efficacy and need to be taken within 30 minutes of each meal. They cause slight weight gain and mild hypoglycemia. These drugs cause no gastrointestinal side effects and are contraindicated in liver failure. Alpha-glucosidase inhibitors inhibit the cleavage of oligosaccharides to monosaccharides, thereby impairing carbohydrate absorption in the proximal small intestine. These drugs show moderate lowering of postprandial glucose. They often cause gastrointestinal side effects like abdominal distension and diarrhea.[8,9]

3. Some Issues[10,11]

Thiazolidinediones, these drugs act as agonists of peroxisome proliferator-activated receptor-gamma receptors (PPAR). They are insulin sensitizers and increase glucose uptake in muscles. Major adverse effects include increased weight and fluid retention, which must be avoided during congestive heart failure. Rosiglitazone has been withdrawn from India because of cardiovascular adverse effects. Recently some studies have reported an increased risk of bladder cancers due to pioglitazone. These drugs also increase the risk of bone fractures.

Glucagon-like peptide-1 (GLP-1) agonists act via GLP-1 receptors and cause postprandial insulin release. They are administered by subcutaneous route. They have good efficacy in lowering HbA1c. These drugs show a low risk of hypoglycemia and lead to significant weight loss. The major side effect is nausea. Also, there are concerns regarding pancreatitis and medullary carcinoma of the thyroid in experimental animals.

Dipeptidyl peptidase 4 inhibitors block DPP4 enzymes and activate integrin to stimulate insulin release. They have a low risk of hypoglycemia, but few cases of pancreatitis have been reported with these drugs. These drugs show moderate lowering of postprandial glucose and glycosylated hemoglobin reduction by an average of 0.7%. They also reduce cardiac mortality and morbidity due to diabetes. Linagliptin is most nephron safe, followed by sitagliptin and vildagliptin.

SGLT2 Inhibitors are the latest class of non-secretagogues oral hypoglycemia drugs with an original insulin-independent mode of action. It also has a low risk of hypoglycemia along with a weight-lowering effect. SGLT2 inhibitors are drugs that reduce glucose independently of insulin with their mechanism of action. According to recent findings regarding efficacy and benefits, this drug is rapidly establishing its role in the treatment of diabetes. Specifically, in patients with type 2 diabetes who are unwilling or unprepared to start insulin, SGLT2 inhibitors may be another choice for patients requiring additional blood sugar lowering and for patients with an acceptable risk factor profile. Although there appear to be some positive benefits for cardiovascular endpoints, further studies are needed on the long-term outcomes of people taking SGLT2 inhibitors.

4. Insulin Therapy[9,10]

Insulin is the endogenous anabolic peptide hormone secreted by beta cells of Islets of Langerhans in the pancreas. It consists of two polypeptide chains of 30 and 21 amino acids, each connected by disulfide bonds. It is physiologically secreted in response to hyperglycemia and converts excess glucose into glycogen and fat, which are mobilized again and converted to glucose in times of shortage.

Insulin is the most physiological amongst available treatments to restore euglycemia. Insulin is the mainstay of treatment of T1DM. In T2DM, the following are the significant indications of insulin therapy[9–11]

1. Pronounced symptomatic hyperglycemia with rapid weight loss.
2. Acute stress, infection, surgery
3. Pregnancy
4. Steroid use
5. Significant renal or hepatic disease
6. Primary or secondary failure of oral agents.
7. Intolerance to oral agents.

4.1. Classification of insulin preparation according to the duration of action (Subcutaneous injection)[10–13]

1. Ultra-short acting- Insulin Lispro, Aspart, glulisine
2. Short-acting- rapid onset of action, e.g., soluble or neutral insulin, Plain Human Insulin
3. Intermediate-acting- Those with an intermediate action, e.g., NPH insulin, premixed formulations of Lispro and Aspart, isophane insulin, and zinc-insulin suspension.
4. Long-acting- relatively slow onset and long duration of action, e.g., crystalline insulin zinc suspension, insulin Glargine, Insulin Detemir.
5. 70/30 (insulin degludec and insulin aspart injection)

Subcutaneous injection of soluble insulin shows rapid onset of action (after 30-60 min), upto 8hrs and a peak action between 2-4 hrs. Soluble intravenous insulin is used for emergency treatment and fine control of critical illness and preoperative period. When injected intravenously, the half-life of soluble insulin is very short, only about 5 minutes.

When injected subcutaneously, intermediate-acting insulin has an effect of approximately 1 to 2 hours, the maximum effect is 4 to 12 hours, and the duration of action is 16 to 24 hours. These can be used twice a day with short-acting insulin or once a day, especially in elderly patients. These can be mixed with the soluble insulin in the syringe, essentially preserving the characteristics of each

ingredient. Long-acting insulin preparations are used to provide basal insulin levels throughout the day also known as peak less insulins.

The type, dose, time and duration of insulin preparation vary from one person to another and this must be taken into account during treatment. For patients with acute onset diabetes, a soluble solvent should be used at the beginning of treatment, 3 times a day, and intermediate-acting insulin should be used before going to bed. For patients with milder illnesses, a mixture of short-acting and intermediate-acting premixed insulins (for example, 30% soluble insulin and 70% isophane insulin) is usually used at the beginning of treatment, administered twice a day. Soluble insulin levels may increase in patients with postprandial hyperglycemia. [13]

Currently, the recommended approach to start insulin therapy in T2DM is to add a single dose of long acting or intermediate insulin and titrate the dose to control fasting blood glucose. This is followed by addition of rapid or short acting insulin 1 – 3 times a day before meals to achieve postprandial glucose control. A combination of regular insulin with intermediate acting insulin twice daily continues to be use d with good effects. Patients with T1DM will require multiple doses of subcutaneous insulin. Self-monitoring of blood glucose is significant to titrate the dose and detect hypoglycemia. [14]

An appropriate insulin treatment plan must be developed for each patient. Insulin requirements can be affected by lifestyle changes (diet and exercise), such as corticosteroids, infections, stress, accidental or surgical trauma, adolescence and pregnancy (second and third trimesters) can increase insulin requirements; kidney or liver dysfunction and certain endocrine diseases. diseases (such as Addison's disease, hypopituitarism) or celiac disease can reduce demand. During pregnancy, insulin requirements can vary. [15]

Hypoglycemia is a prominent obstacle in all patients receiving insulin or (antidiabetic) medications. The effects of hypoglycemia include confusion, seizures, coma, and stroke. Recently, it has been shown to be a significant factor in myocardial ischemia. In patients receiving insulin therapy, lack of low blood sugar warnings is common, which can be a serious hazard, especially for drivers and people in hazardous occupations. Very tight control will lower the blood glucose concentration needed to trigger hypoglycemic symptoms; an increase in the frequency of hypoglycemic episodes reduces the warning symptoms that patients experience. Beta-blockers can also reduce hypoglycemia awareness (and delay recovery). Diabetic patients who participate in tasks / sports that involve physical exertion (i.e., swimming, driving, etc.) should pay special attention to hypoglycemia. [16,17]

Hypoglycemia is a potential complication in all patients treated with insulin or (anti-diabetic) agents. The consequences of hypoglycemia include confusion, seizures, coma and cerebral infarction. Recently, it has been shown to be an important factor for myocardial ischemia. Loss of warning of hypoglycemia is common among insulin treated patients and can be a serious hazard especially for drivers and those in dangerous occupations. Very tight control lowers the blood glucose concentration needed to trigger hypoglycemic symptoms; increase in the frequency of hypoglycemic episodes reduces the warning symptoms experienced by patients. Beta-blockers can also blunt hypoglycemia awareness (and delay recovery). Diabetics involved in tasks/sports involving physical exertion (viz. swimming driving etc.) should be particularly careful toward hypoglycemia. [18,19]

Diabetic ketoacidosis is a life-threatening disease caused by a relative or absolute lack of insulin; this usually occurs when the insulin dose adjustment fails to compensate for the increase in insulin demand, such as during severe infections or major complications. Diabetic ketoacidosis mainly occurs in DM1 patients. It also occurs in DM patients who temporarily require insulin. Diabetic ketoacidosis is characterized by hyperglycemia, hyperketonemia, acidemia along with electrolyte disturbances causing dehydration. Providing soluble insulin (and intravenous fluids) for its treatment is essential. Patients with poorly controlled diabetes are more likely to develop infections. These must be treated promptly and effectively to avoid diabetic ketoacidosis. [17,18]

Surgery: When diabetic patients undergo surgery, they may need an intravenous infusion of insulin for more than 12 hours, and special attention should be paid to their insulin needs. Soluble insulin should be infused with glucose and potassium chloride intravenously (provided the patient is not hyperkalemic) and adjusted to provide a blood glucose concentration of 7 to 12 mmol / L. Therefore, the duration of action of intravenous insulin is only a few minutes; Unless the patient is clearly hypoglycemic, the infusion should not be interrupted. For patients with non-insulin-dependent diabetes mellitus, insulin therapy is almost always required during surgery (oral hypoglycemic agents have been omitted). [19,20] Insulin is presently available in the form of a pre-filled vials and syringe. Because the gastrointestinal enzyme is inactivating the insulin, should be administered by injection. In general, insulin is given by subcutaneous injection to the upper abdomen, thighs, arms, etc. It is essential to use only calibrated syringes for specific insulin concentrations administered.

5. Conclusion

The review article explores the emerging tretament modalities for Diabetes mellitus and focuses on the mechanism and adverse effects of these newer antidiabetic drugs for clinical therapeutic use.

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None.

7. Conflict of Interest

None.

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