Recent Modalities in Management of Diabetes mellitus

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Abstract :

Diabetes mellitus is characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action or both. The currently available pharmacologic options include agents that not only target β-cell dysfunction or supplement insulin, but also act at various other relevant sites for achieving better glycemic control. The development of new classes of glucose-lowering medications to supplement older drugs (insulin, sulfonylureas, metformin) has broadened the value of available treatments. Future drug therapy of the disease will depend on the success of ongoing and planned intervention trials. This review focuses on the conventional and new investigational drugs that are being explored for use in future.

Keywords : Diabetes, oral agents, investigational agents, insulin, insulin delivery system

Introduction

The term "diabetes mellitus" describes a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. The effects of diabetes mellitus (DM) include long–term damage, dysfunction and failure of various organs (WHO 1999). [1] Complications related to diabetes can lead to serious morbidity and significantly reduced life expectancy. [2] 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. [3]

The vast majority of cases of diabetes fall into two broad etiopathogenic categories. In type 1 diabetes, the cause is an absolute deficiency of insulin secretion. This form of diabetes, which accounts for only 5–10% patients, results from an autoimmune destruction of the β-cells of the pancreas. In type 2 diabetes, which is much more prevalent and accounts for 90-95% of the patients, the cause is a combination of resistance to insulin action and an inadequately compensatory insulin secretary response. [4]

Diagnostic criteria

The diagnosis of diabetes mellitus is based on measuring blood glucose in the fasting state (≥ 126mg/dl) or ≥ 200mg/dl 2 hours after a 75 gram glucose load.The details of the diagnostic criteria are given in table 1. [5, 6]

Table 1: Diagnostic criteria for Diabetes mellitus [5]

Category	Fasting blood glucose	Blood glucose 2 hours after meal
Normal	99 mg/dl or below	139 mg/dl or below
Prediabetes	100 to 125 mg/dl	140 to199 mg/dl
Diabetes	126 mg/dl or above	200 mg/dl or above

Management of Diabetes mellitus

The goals of management are to provide the relief from symptoms, prevent microvascular complications (like retinopathy, neuropathy and nephropathy) and macrovascular complications (like cardiovascular, cerebro-vascular and peripheral vascular diseases), and various infections. [7]

Fortunately, the currently available pharmacologic options include agents that not only target □-cell dysfunction or supplement insulin, but also act at various other recognized sites for achieving better glycemic control.The pathophysiologic defects in DM commonly include insulin resistance and □-cell failure, but other factors like accelerated lipolysis in adipocytes, incretin deficiency/resistance in the gastrointestinal tract, hyperglucagonemia and increased glucose reabsorption in the kidneys are also recognized.[8,9] New and emerging drugs aim to correct some of these important defects. The development of new classes of glucose-lowering medications to supplement older

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drugs (insulin, sulfonylureas, metformin) has broadened the value of available treatments. The efficacy of individual drugs or combinations also depends upon duration of disease as well as baseline glycemia. [10]

Oral drugs

Commonly used oral agents primarily stimulate insulin secretion, sensitize tissues to the action of insulin or affect absorption of glucose. They comprise many drugs that are already in use (Fig 1) and several others under investigation. A brief description of these drugs is given below.

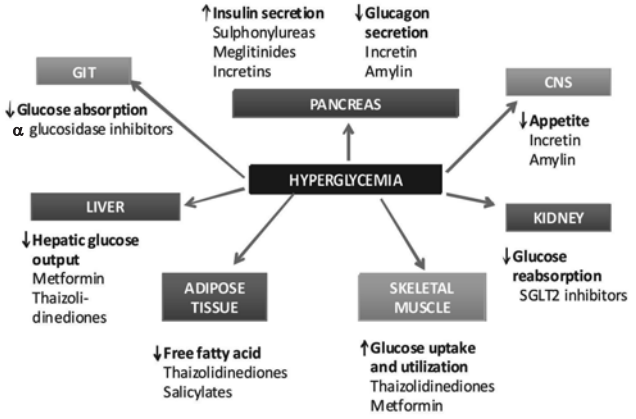

Fig 1 Mechanism of action of oral anti-diabetic drug [11]

Biguanides

Despite some inter-individual variability in response biguanide (metformin) remains the most widely used first-line agent in type 2 diabetes mellitus (T2DM). It is an old and widely accepted agent, stands out not only for its effect in diabetes but also for its effects beyond glycemic control such as improvement in endothelial dysfunction, hemostasis and oxidative stress, insulin resistance, lipid profile, and fat redistribution. Recently, it has also gained attention as a potential treatment for neurodegenerative diseases such as Alzheimer's disease. Its efficacy, safety profile and beneficial cardiovascular as well as metabolic effects make this drug the first glucose lowering agent of choice when treating patients with type 2 diabetes mellitus (TDM2). It reduces hepatic gluconeogenesis, slows down gastrointestinal absorption of glucose, promotes insulin binding to its receptors and increases up-take of glucose by skeletal muscles. It can be used alone or in combination with sulfonylureas, thiazolidinediones or insulin. It is contraindicated in patients with impaired renal function. Common side effects are usually gastrointestinal and include anorexia, nausea, vomiting, abdominal discomfort and diarrhea. Lactic acidosis, though uncommon, is reported in cases with associated risk factors such as renal, hepatic, or cardio-respiratory insufficiency, alcoholism and advanced age. [12]

Sulfonylureas

Sulfonylureas have the advantage of multiple formulations, low cost, minimal side effects, efficacy in controlling hyperglycemia and reducing microvascular complications. The proposed mechanism of action includes:(a) augmentation of insulin release from pancreatic β cells and (b) potentiation of insulin action on its target cells.[13] First-generation agents have largely been replaced by newer second-generation sulfonylureas, such as glyburide, glipizide, and glimepiride, which have improved safety profile. Since sulfonylureas act by stimulating insulin release from β-cells, patients without sufficient number of β-cells, such as those with type 1 diabetes, do not respond to these medications.Hypoglycemia and weight gain are the commonest side effects of these agents but they differ in their risk of hypoglycemic episodes. [14]

Glinides

Glinides (e.g. repaglinide, nateglinide and mitiglinide) help to mimic early-phase insulin release. Similar to sulfonylureas, they stimulate insulin secretion by binding to a different site within the sulfonylurea receptor. Compared to sulfonylureas they are rapid and short acting but are relatively less potent and so have less chance of producing hypoglycemia. [10] They are chemically different from sulfonylureas and so are not contraindicated in patients with history of allergy to sulfa drugs. [14] However, cost and need for frequent dosing adversely affect patient compliance.

Thiazolidinediones

These agents (i.e. pioglitazone and rosiglitazone) sensitize peripheral tissues to insulin by binding to a nuclearreceptor called peroxisome proliferators-activated receptor-gamma (PPARγ) and decrease hepatic glucose output. Rosiglitazone and pioglitazone are used as monotherapy, or in combination with sulfonylureas, metformin, and insulin.[13]Pioglitazone

improves lipid profile but both have several other potential side effects, which make them less appealing as initial or second step therapy. Common side effect is weight gain while hepatotoxicity and heart failure may occur. [14]

α-glucosidase inhibitors

These agents (i.e. acarbose, voglibose, miglitol) are metabolic modifiers that can reduce the risk of cardiovascular diseases in patients with diabetes. They reduce the rate of absorption of polysaccharides in the small intestine and lower postprandial glucose levels without causing hypoglycemia. [15]Due to increased delivery of carbohydrates to the colon, they are commonly associated with flatulence and other gastrointestinal symptoms, causing discontinuation in 25% to 45% of patients. [16]

Amylin agonists

Pramlintide is a synthetic analogue of the β-cell hormone amylin and is used only as an adjunct with insulin. Administered subcutaneously before meals, it is known to slow gastric emptying, inhibit glucagon production, enhance satiety, and reduce food intake resulting in decreased postprandial glucose excursions. [16]

Incretinmimetics

Insulin has been shown to be released more effectively through an oral glucose load than intravenous and this is known as the incretin effect. This incretin effect is mediated by number of peptides released from intestine. Insulin stimulating benefits of peptides such as GLP-1(Glucagon like Peptide-1) are rapidly diminished due to its faster metabolism by dipeptidylpeptidase IV (DPP-IV). It is possible to enhance incretin effect either by increasing the effect of GLP-1 or by slowing its breakdown. [13] Incretin-based therapies are characterized by an overall favorable safety profile and effect on body weight, a low risk of hypoglycemia, and clinically meaningful improvement in glycosylated hemoglobin (HbA1c).

Incretinmimetics are of two types as described below:

(A) Glucagon-like polypeptide 1 analogues

Exenatide is the first synthetic agent belonging to the class of GLP-1agonists.They (exenatide, albiglutide, taspoglutide, liraglutide) augment insulin release in response to ingested glucose and suppress high glucagon values resulting in decreased hepatic glucose output. It also reduces the rate of gastric emptying promoting satiety and results in reduced caloric intake and weight reduction. [13]

(B) Dipeptidyl Peptidase IV (DPP-IV) inhibitors

Dipeptidyl Peptidase-IV (DPP-IV) inhibitors (sitagliptin, vildagliptin, saxagliptin), also known as incretin enhancers, act by inhibiting the enzymatic degradation of glucagon-like peptide 1 (GLP-1). Use of DPP-IV inhibitors increases levels of endogenously produced GLP-1 which enhances insulin secretion and decrease glucagon release resulting in decreased postprandial glucose excursions.[17] They also suppress the appetite by delaying gastric emptying.[18] They are unlikely to cause hypoglycemia when used alone; however, combination therapy with metform in and/or sulfonylureas which is commonly employed in the treatment of type 2 diabetes mellitus may require monitoring for hypoglycemia.[18] A major limiting factor with DPP-IV inhibitors is cost and side effects like nasopharyngitis, GIT distress and diarrhea.[18]

GLP-1 analogues and DPP-4 inhibitors appear to have beneficial effects on cardiac risk factors by reducing blood pressure, body weight, triglycerides and low-density lipoprotein cholesterol and increasing high-density lipoprotein cholesterol. [19]

Sodium Glucose Co-transporter-2 (SGLT-2) inhibitors

Sodium Glucose co-transporter 2 (SGLT2) present in the proximal renal tubules, has a dominant role in the renal glucose absorption. [20]Its inhibitors may be useful add-on agents with low risk of hypoglycemia and good potential for weight loss. The main advantage of these drugs is that they act independently of the severity of β cell dysfunction or insulin resistance. Pharmacologic agents such as dapagliflozin, sergliflozin, remogliflozin and empagliflozin targeting SGLT2 prevent renal glucose reabsorption and lower serum glucose by increasing urinary excretion of glucose. The resultant glycosuria leads to reduction of plasma glucose, glucotoxicity, and body weight. Expectantly, however, effects may be less pronounced in patients with renal impairment. [21] Risk factors associated with these agents are bladder and breast cancer, hepatotoxicity,

risk of dehydration and electrolyte imbalance, as well as infection in urogenital tract.[22] The risk/benefit ratio of this class of drug will decide their place for clinical use in the future.

Investigational agents for type 2 diabetes mellitus

Despite the abundance of FDA-approved therapeutic options for type 2 diabetes, the majority of patients with diabetes are not achieving appropriate glycemic control. The development of new options with new mechanisms of action may potentially improve outcome and reduce the clinical and cost burden of this condition.

Some of the recent research agents which are under development are described below.

11β-hydroxysteroid dehydrogenase type 1 inhibitor

11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) catalyses the intracellular conversion of inert cortisone to active cortisol. Cortisol plays an important role in visceral adiposity, insulin action and resistance, proinsulin processing leading to hyperglycemia. Thus, inhibition of 11β-HSD1increases insulin sensitivity and glucose metabolism and decreases total cholesterol level. Selective 11β-HSD1 inhibitor, INCB13739, may prove to be important in regulating glycemia and cardio-metabolic risk. [23]

Glucagon antagonist

Glucagon maintains glucose homeostasis during the fasting state by promoting hepatic gluconeogenesis and glycogenolysis. Antagonizing these effects is expected to result in reduced hepatic glucose overproduction, leading to overall glycemic control. Glucagon antagonist, skyrin markedly reduces glucagon-stimulated cyclic adenosine monophosphate (cAMP) production and glycogenolysis in human hepatocytes.[24]

Glucokinase activators

Glucokinase(GK), found in the beta cells of the pancreas and also in hepatocytes, is responsible for phosphorylation of glucose (changing glucose to glucose-6-phosphate). Phosphorylation by these drugs promotes insulin release from pancreatic β-cells and glucose uptake by liver cells. [25] Piragliatin, a drug thought to act by this mechanism, is undergoing clinical trials to establish efficacy and safety in diabetic patients.

Ranolazine

Ranolazine is a piperazine derivative having anti-anginal action. In addition to its anti-anginal effect, it has been shown to lower glycosylated hemoglobin (HbA1c) in patients with coronary artery disease and diabetes. Its mechanism of action for lowering glucose concentration is unknown, but may include augmentation of glucose induced insulin release and a beta cell protective effect. [26]

Fructose-1, 6 - bisphosphatase (FBPase) Inhibitors

Fructose 1,6-bisphosphatase converts fructose 1,6-bisphosphate to fructose 6-phosphate, leading to gluconeogenesis. Inhibitors of fructose 1,6-bisphosphatasee.g., MB06322 (CS-917) is important in the treatment of DM. They produce glucose lowering effect without signs of hypoglycemia or significant elevations in plasma lactate or triglyceride levels. [27]Clinical evaluation of CS-917 shows a favorable safety profile and significant reduction in fasting glucose levels in patients with T2DM. Future trials of MB07803, a second generation FBPase inhibitor with improved pharmacokinetics is thought to provide a safe and long-term glycemic control.

Protein Tyrosine Phosphatase 1B (PTP1B) inhibitors

Protein tyrosine phosphatase 1B (PTP1B) enzyme acts as a negative regulator of insulin signaling (i.e., it deactivates the insulin receptor). Deactivation of the insulin receptor may result in decreased insulin release and/or increase in insulin resistance. Inhibition of this enzyme may improve insulin action and it may bean option for the treatment of diabetes.Hence, PTP1B inhibitors like safranal, sunitinib are anticipated to improve insulin resistance in type 2 diabetic subjects. [28]

Salicylate derivatives

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) plays a central role in the development of diabetes mellitus and various complications associated with the disease. In DM, NF-κB is activated by a number of pro-inflammatory cytokines, to regulate both survival and death of β-cells. In type 1 diabetes

mellitus, interleukin-1 β-induced NF-κB activation causes the apoptosis of β-cells in the pancreas. However, in type 2 diabetes, activated NF-κB induces both apoptosis and insulin resistance. Sustained activation of NF-κB induces the systemic inflammation, a contributory factor for the development of various complications like cardiomyopathy, retinopathy, nephropathy and neuropathy. Hence, an NF-κB-based therapeutic approach may be adopted for the treatment of disease.[29] A non-acetylated salicylate (salsalate) inhibits NF-kB which results in decreased production of cytokines and free fatty acid levels leading to increased insulin sensitivity. [30]

G protein–coupled receptor (GPR)–40 agonist

G-protein-coupled receptor (GPR)-40 is highly expressed in pancreatic β cells and mediates free fatty acid-induced insulin secretion. GPR-40 agonist (TAK-875) enhances glucose-dependent insulin secretion and improves both postprandial and fasting hyperglycemia with a low risk of hypoglycemia and no evidence of β cell toxicity. [31]

Bromocriptine

Bromocriptine is a dopamine agonist that is used in the treatment of pituitary tumors, Parkinson's disease (PD), hyperprolactinaemia and neuroleptic malignant syndrome. It is currently unknown how this drug improves glycemic control, but it is believed to augment low hypothalamic dopamine levels and inhibit excessive sympathetic tone in CNS resulting in suppression of hepatic glucose production. Bromocriptine has not been shown to augment insulin secretion or enhance insulin sensitivity in peripheral tissues. [32]

Carnitinepalmitoyltransferase (CPT)–1 inhibitors, acetylco A carboxylase (ACC)–1 and –2 inhibitors, immunomodulator drugs, bile acid sequesters (covlesalam) are some of the other groups which are under investigation. More can be known about them in future.

Parenteral drugs

Insulin

Insulin has a major role in the control of hyperglycemia for type 1diabetic patients while it may be required at a later stage or in selective individuals suffering from type 2 diabetes. [33] Insulin therapy began with beef/pork insulin, followed by an era of recombinant human insulin, and now we are in third phase in which newer analogues are being used and non-invasive delivery methods are under intense investigation. [33]

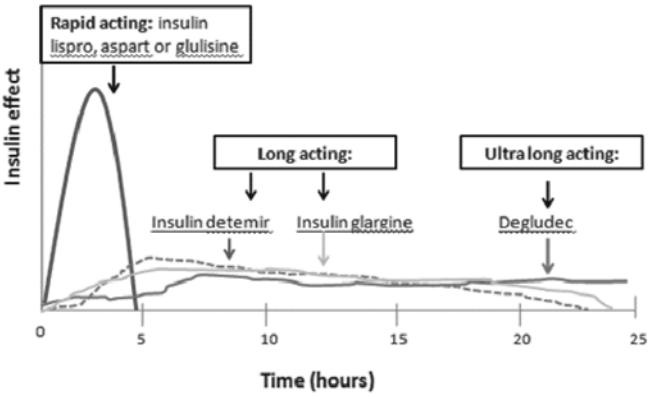

Fig: 2 Subtypes and approximate duration of action of different insulin formulations [37]

Insulin analogues were developed in an attempt to overcome the problems associated with human insulin. They include short (rapid)-acting (aspart, lispro, glulisine), long-acting (glargine, detemir), ultralong acting (degludec) and premixed insulin formulations (75% neutral protamine lispro + 25% lispro; 50% neutral protamine lispro + 50% lispro and 70% protamine aspart+ 30% aspart).[34] These formulations allow a closer replication of a normal insulin profile (Fig 2)

Insulin analogues are classified according to their duration of action and their pharmacokinetic characteristics are shown in table 2.

Ultra long acting insulin analogues

Degludec is new insulin with long duration of action which differs from other long-acting preparations in having a longer half life, less likely to cause hypoglycemia and less glycemic variability. [35, 36]

Long acting analogues

These analogues are absorbed more gradually when injected subcutaneously and thus their duration of action is prolonged. They are often given at bedtime to normalize fasting blood glucose. [37]

Short (rapid) acting analogues

These analogues are absorbed more rapidly from subcutaneous sites than regular insulin. Consequently, there is a more rapid increase in plasma concentration and rapid response. It should be injected ≤ 15 minutes before a meal. [37]

Premixed analogues

These formulations have been developed to minimize the errors that can occur when patients self-mix insulin preparations. Fixed combinations may simplify the insulin regimen and reduce the number of daily injections. [34]

Table 2 : Pharmacokinetic characteristics of insulin preparations [18]

Preparation	Analogues	Onset of action	Peak action	Duration of action
Short acting	Aspart	< 15 minutes	30-90 minutes	3-4 hours
	Glulisine	< 15 minutes	30-90 minutes	3-4 hours
	Lispro	< 15 minutes	30-90 minutes	3-4 hours
Long acting	Detemir	1-4 hours	Peakless	20-24 hours
	Glargine	1-4 hours	Peakless	20-24 hours
Ultra long acting	Degludec	30-90 minutes	Peakless	> 24 hours
Premixed	75% Protamine Lispro +25% Lispro	<15 minutes	90 minutes	Up to 10-16 hours
	50% Protamine Lispro +50% Lispro	<15 minutes	90 minutes	Up to 10-16 hours
	70% Protamine Aspart + 30% Aspart	<15 minutes	90 minutes	Up to 10-16 hours

Methods of insulin administration

A. Insulin Syringes and Needles

Single unit disposable syringes with microfine needles are available for injection of insulin. [13]

B. Pen devices

Pen devices combine the insulin container and the syringe into a single unit. They eliminate the inconvenience of carrying insulin and syringes separately. There are two main types of pens, reusable and prefilled. In reusable, the patient must load an insulin cartridge prior to use. Disposable pens are generally more convenient than reusable pens because there is no need to load any cartridges but they are usually costlier. These pens are accurate, easy to store and use, cause minimal pain due to the finest and shortest disposable needles but proper patient education is essential. [36]

C. Continuous Subcutaneous Insulin Infusion pump (CSII)

Pump therapy is capable of producing a physiological profile of insulin replacement. It provides constant basal infusion with an option of different infusion rates as well as bolus injection programmed according to size and nature of the meal. Insulin deficiency and ketoacidosis may develop rapidly on accidental failure of device as only short acting insulin is used. There is also possibility of subcutaneous abscess and cellulites. [37]

Future prospects

Several devices and new approaches are under development as given below:

Intranasal

Intranasal insulin has a low bioavailability and the dose needed for glycemic control is 20 times higher than that of subcutaneous administration. Permeability enhancers (e.g. lecithin) are incorporated in most nasal formulations to augment the low bioavailability. High rates of treatment failure and occurrence of nasal irritation makes this route less feasible. [38]

Insulin inhalers

Insulin inhaler (Exubera, Afrezza) is a new way of delivering pre-mealtime insulin. They work like an

asthma inhaler and can deliver dry power or the solution into the blood stream via lungs. Peak effect may be achieved within 15-20 minutes and the duration of action is 2-3 hours. This method can only be used to deliver fast-acting insulin while long-acting insulin must still be injected. Large doses are needed because only around 10% of the dose actually reaches the bloodstream. [39]Inhaler may not be effective in smokers and in patient's having chronic lung disease. Effectiveness is also not much studied in patients who are having common cold, sore throat etc. Most common side effect observed is cough.

Buccal

Insulin is administered by buccal route through an aerosol spray into the oral cavity. It is absorbed through the inside of the cheeks and in the back of the mouth instead of the lungs. However, it may be noted that the continuous (but variable) saliva flow and the multilayered structure of the oral epithelium work as a barrier for penetration of drugs and this may hamper the buccal absorption of insulin. The side effect noted is mild, self-limited dizziness. [33]

Transdermal patches

Insulin patches are also currently under development, but it is difficult for the drug to be absorbed through the skin. [39]

Islet cell transplantation

This is a recently developed surgical procedure called the Edmonton protocol whereby islet cells from a donated human pancreas are injected into the liver of a recipient with type 1 diabetes. The transplanted cells begin to secrete insulin, while the recipient needs to take immunosuppressive medications for life to prevent the rejection of the transplanted tissue. Clinical trials are under way to establish the safety and long term effectiveness of this procedure as a means of supplying insulin. [39]

Oral and rectal delivery, jet injectors and immuno therapy are other methods of insulin delivery that continue to be investigated. These options represent long-term possibilities for insulin delivery but difficulties in obtaining adequate amounts of insulin in the blood stream are yet to be overcome.

Summary

In coming years, much of the morbidity and mortality related to disease may be reduced with multiple new therapeutic options. New therapies may perhaps produce beneficial effects on cardiovascular risk factors (e.g. hypertension, dyslipidemia) and other factors influencing long term glycemic control (e.g. insulin resistance and insulin secretary capacity). The increasing availability of numerous classes of medications, ongoing research of investigational drugs and new delivery systems for insulin may ultimately optimize the treatment outcome. Efforts should be made to simplify the treatment regimens. However, the mainstay of prevention of diabetes lies in healthy lifestyle, dietary modification and adequate physical activity.

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