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A Review on Oral Hypoglycemic Drugs

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Abstract

Globally, an estimated 422 million adults are living with diabetes mellitus, according to the latest 2016 data from the World Health Organization. Diabetes is a group of disorder characterized by high blood glucose level. Constant high level of blood glucose may lead to many life-threatening complications viz, cardiovascular disease, stroke, chronic kidney disease, foot ulcers, and damage to the eyes. The treatment strategy is mainly targeted to lower blood glucose level by one or other means. This can be achieved by either slowing down the rate by which glucose enters into the bloodstream (Biguanides: Metformin; α-Glucosidase inhibitor: Acarbose etc) or by stimulating body's ability to utilize the glucose present in the blood by the cells (Sulfonylureas: Chlorpropamide; Thiazolidinediones: Pioglitazone; GLP-1 analogue; DPP 4 inhibitors; Exenatide). This review focuses on conventional antidiabetics currently used and drawbacks associated with it and newer oral hypoglycemic agents with their advantages over the conventional ones.

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Introduction

Globally, an estimated 422 million adults are living with diabetes mellitus, according to the latest 2016 data from the World Health Organization (WHO) [1].

Diabetes mellitus (**DM**) is a metabolic disease characterized by raised blood glucose level above normal. Etiological factors include age, virus, obesity, hormonal changes, and genetic factors. The affected patient may suffer from symptoms such as frequent urination, increased thirst, and increased hunger[2]. Diabetes as such is not as life-threatening (rather hypoglycemia is) but the complications develop due to diabetes is something to be concerned. Constant hyperglycemia is detrimental to the body which ends up as vital organ damage. Complications can include diabetic ketoacidosis, polyneuritis or even death. Life long serious complications include cardiovascular disease, stroke, chronic kidney disease, foot ulcers, and damage to the eyes [3].

There are three main types of diabetes mellitus:[2]

- Type 1 DM or Insulin Dependent Diabetes Mellitus is a type of diabetes that is mostly encountered in juvenile which respond very well to exogenous Insulin. It results from the pancreas' failure to produce enough insulin due to loss of beta cells.
- Type 2 DM or "Non-Insulin-Dependent Diabetes Mellitus" (NIDDM) begins with

insulin resistance, a condition in which cells fail to respond to insulin properly. If this is untreated, over time it may result in lack of insulin as well The most common cause has been found to be a combination of excessive body weight, sedentary lifestyle and insufficient exercise.

- Gestational diabetes is seen in pregnancy. The pregnant women, without a previous history of diabetes, develop high blood sugar levels. Pregnant lady with Gestational diabetes often complains of restlessness, a sudden heaviness of the fetus and if untreated may become a victim of obstructed labor. These patients are very prone to suffer from type II diabetes mellitus within few years of delivery [4].

So generally speaking, Diabetes is a chronic disease that occurs when the pancreas is no longer able to make insulin, or when the body fails to make efficient use of the insulin it produces.

Insulin Structure and Function

Insulin is a protein hormone secreted by beta cells of the pancreas in response to the food we eat. The complex carbohydrate in the food is broken down into simple sugar (glucose) which is then taken up by the cell under the influence of Insulin.

Chemical structure

It is a protein hormone with 2 polypeptide chains, α, and β. α chain contains 21 amino acids while the β chain contains 30 amino acids. The 2 chains are joined to each other by disulfide bonds [5].

Every time there is secretion of insulin from the β-cell there is secretion of C-peptide. C-peptide has no significant biological activity as such. Estimation of C-peptide level in blood is a mainstay of differentiating between type I and type II diabetes as C-peptide is secreted in equimolar amounts to insulin. In type I diabetes, the level of C peptide is very less as the body is unable to produce Insulin require for glucose transport. C peptide measurement has one more clinical significance that is it reflects the normal amount of insulin secreted in diabetes (type I and type II) as exogenous insulin is devoid of C-peptide one can easily monitor the response (drop in blood glucose) produce by antidiabetic drugs. Measurement of Insulin as such could yield errors in the result as insulin readily undergoes the first-pass metabolism so actual systemic insulin available would be different from insulin secreted by the pancreas. If the C-peptide blood level is increased then there may be insulin-producing tumor [6].

C- peptide is present only in endogenous insulin. The principal factor that regulates insulin secretion is the change in the blood glucose level. Other factors are hormones and cholinergic stimuli.

Mechanism of insulin release

Glucose present in blood stream is taken up by the β-cells of the pancreas. This glucose then undergoes glycolysis liberating ATP. This ATP blocks the ATP sensitive K^+ channel in the β-cells

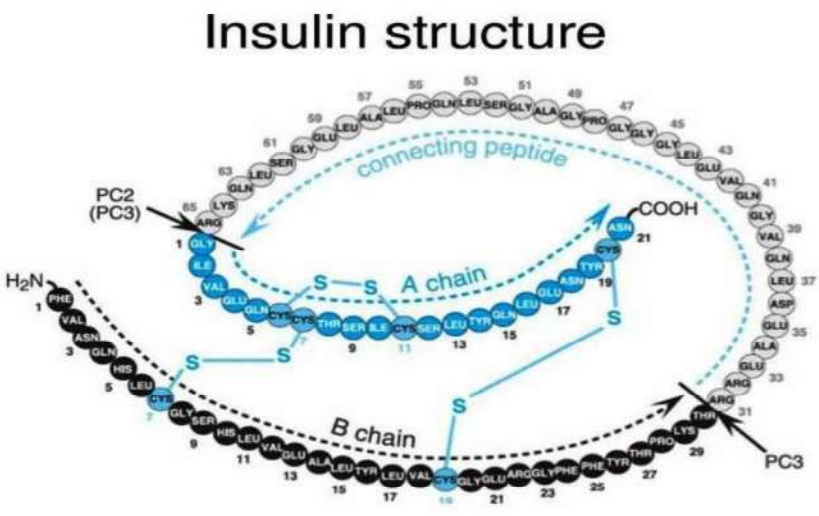

Fig. 1:

of the pancreas. So the cell becomes depolarized. Now Ca^{++} enters through the Ca^{++} channels. Ca^{++} binds with the insulin-containing granules; insulin is secreted from the β-cells by exocytosis.

When secreted it is called pre-pro-insulin (110 amino acids) which forms proinsulin (86 amino acids) and signal peptide (24 amino acids). From the pro-insulin peptide-C (35 amino acids) is removed and insulin (51 amino acids) is formed which contains α chain (21amino acids) and β chain (30 amino acids).

The drug used for the treatment of diabetes mellitus includes both oral and parenteral agents. This review is restricted to oral hypoglycemic agents. Since type I diabetes mainly involves deficiency of Insulin due to loss of beta cells so oral hypoglycemic drugs are not the prime therapy rather exogenous insulin should be the indicated. Also, since Insulin is a protein which is degraded readily by the gastric juices of the stomach so only parenteral forms are beneficial for type I diabetes mellitus [7].

Type II diabetes mellitus initially reflects as the resistance of body tissue to insulin and this soon also leads to reducing insulin secretion as well. Oral hypoglycemic drugs may be classified as:

Sulfonylureas – Sulfonylureas, as stated above, are the drugs that stimulate insulin secretion by the beta cells of the pancreas. These are most widely used drugs for the treatment of type 2 diabetes mellitus. The net effect is increased responsiveness of ß-cells (insulin secreting cells located in the pancreas) to both glucose and non-glucose secretagogues, resulting in more insulin being released at all blood glucose concentrations. Sulfonylureas have been reported to enhance the sensitivity of tissue towards glucose (decreases insulin resistance) [8].

Pharmacokinetics – Sulfonylureas differ mainly in their potency & their duration of action. Glipizide, glyburide (glibenclamide), and glimepiride are so-called second-generation sulfonylureas. These are more potent than first-generation agents hence lower doses are used to achieve similar effects.

Once daily oral dose is used for drugs with longer half-lives (chlorpropamide, glyburide, and glimepiride). However more potent and longer acting thus also means they are the potential candidates for causing hypoglycemia [9].

Side effects – Sulfonylureas are usually well tolerated. Hypoglycemia is the most common side effect with long-acting sulfonylureas. Patients discharged from hospital and who are asked to maintain on long-acting sulphonylureas are at greater risk of hypoglycemia. Patients should be cautioned about those settings in which hypoglycemia are most likely to occur (after exercise or missed meal). Other infrequent side effects that can occur with all sulfonylureas include nausea, skin reactions, and abnormal liver function tests. Weight gain can also occur unless the diabetic diet and exercise program is followed. Chlorpropamide has two unique effects: it can cause an unpleasant flushing reaction after alcohol ingestion and it can cause hyponatremia (low blood sodium), primarily by increasing the action of antidiuretic hormone [10].

Clinical use – Sulfonylureas usually lower blood glucose concentrations by about 20 percent. They are most likely to be effective in patients whose weight is normal or slightly increased.

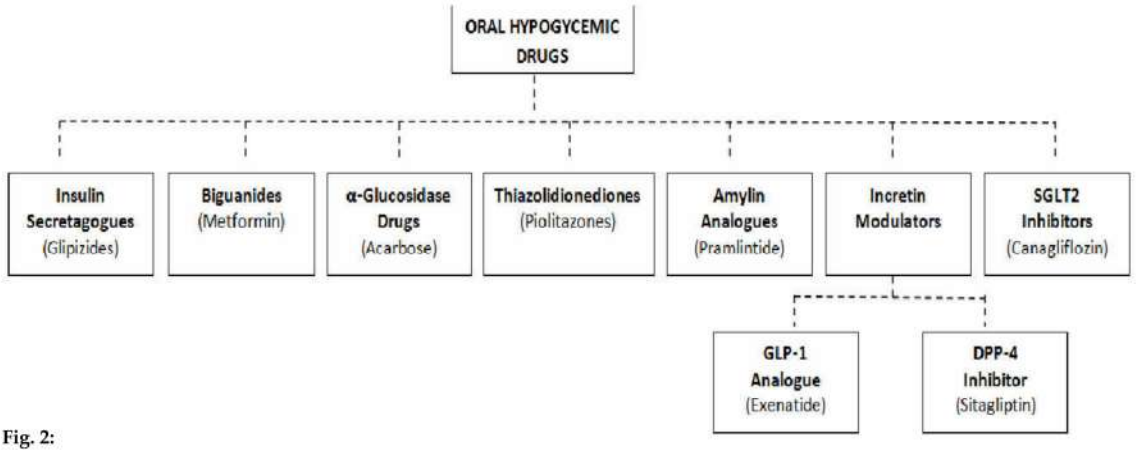

Fig. 2:

Source: A.J. Trevor, B.G.Katzung, M.Kruidering-Hall: Katzung & Trevor's Pharmacology: Examination & Board Review, 11th Ed.

As drugs like glyburide and chlorpropamide are potent and longer acting sulfonylureas these are therefore best avoided in elderly patients due to the risk of developing potent hypoglycemia. Since all sulphonylureas produce similar efficacy so the selection of the drug could be made based on the availability of the drug and cost-effectivenes [1].

Meglitinides (Repaglinide and Nateglinide)

Repaglinide – Repaglinide is a short-acting glucose-lowering drug recently approved by the Food and Drug Administration for therapy of type 2 diabetes alone or in combination with metformin. It is structurally different but functionally similar to sulphonylureas (insulin secretagogue). The clinical efficacy of repaglinide and sulfonylureas are quite similar. 0.5 mg dose is generally recommended for initial therapy of diabetes mellitus in patients. One should not take more than 4 mg tablet at once in which case severe toxicity may occur.

Nateglinide – Nateglinide is a very short-acting glucose lowering drug whose mode of action is similar to the sulfonylureas a. A potential advantage of this drug is that it seems to have its effect on the first phase of insulin release rather than the late phase of insulin release. The first phase of insulin release is brisk, of short duration and occurs within minutes of ingesting food. It is this first phase of insulin release that is abnormal in early diabetes and can often be found in patients with impaired glucose tolerance prior to the onset of diabetes. The usual dose is 120 mg before meals [11].

Biguanides (Metformin and Phenformin)

Metformin is the only drug which is routinely prescribed for controlling type II diabetes mellitus since decades. It enhances the tissue utilization of glucose. Presence of Insulin is a prerequisite for its action and unlike sulphonylurea, it stimulates the action of insulin rather than secreting insulin. Its major effect is to increase insulin action. These group of drugs are unique in the fact they are weight neutral and even may lead to weight loss which is in contrast to sulfonylureas that causes weight gain. The possible mechanism of biguanides is activation of Adenosine MonoPhosphate activated Protein Kinase (AMPK) [12]. The AMPK is responsibly decreasing the glucose production by inhibiting gluconeogenesis and glycogenolysis and at the same time, it also acts as a catalyst in increasing the utilization of glucose via stimulation of glycolysis and tissue uptake of glucose. A minor mechanism is these drugs also hamper the intestinal absorption of free glucose into the bloodstream [13].

Clinical use – Metformin is most often used in patients with type 2 diabetes who are obese because it promotes moderate weight reduction or at least weight stabilization. It has been proved that fasting blood glucose concentrations is lowered as much as 20 percent by Metformin. Metformin given in combination with a sulfonylurea lowers blood glucose concentrations more than either drug alone. Metformin is superior as compared with sulfonylurea pertaining to its lipid-lowering ability and less potential to cause hypoglycemia. Reduction in LDL cholesterol and elevation in the level of HDL cholesterol has been found in patients taking metformin. Two major disadvantages of biguanides group of drugs are the risk for lactic acidosis [14] and prominent gastrointestinal side effects [14].

Pharmacokinetics – Metformin should be taken with meals and should be started at a low dose to avoid intestinal side effects. The dose can be gradually increase depending on the response achieved.

Side effects – Common side effects includes lactic acidosis and gastrointestinal distress. Metallic taste, nausea, abdomen discomfort, and sometimes diarrhea may occur with these drugs. However, the side effects are mild and most of the patients get relieved after reducing the dose. A rare problem is a lactic acidosis, which may be fatal in some cases (maximum is seen with phenformin). This lead to discontinuation of use of phenformin by many developed countries. Serious lactic acid accumulation usually occurs only in the presence of predisposing conditions including: Renal insufficiency, current liver disease or alcohol abuse, heart failure, past history of lactic acidosis, severe infection with decreased tissue perfusion, hypoxic states, serious acute illness, hemodynamic instability [15].

Drug interactions – A potential drug interaction exists between metformin and drugs causing potential enzyme inhibition such as cimetidine and valproate resulting in an increase in metformin blood levels. This interaction could increase the risk of hypoglycemia in patients taking metformin plus a sulfonylurea or insulin, and could increase the risk of lactic acidosis in those with impaired renal function. As cimetidine is available over-the-counter so one should be advised not to take any medication without consulting physician. Other H2-blockers are less likely to cause this problem.

The manufacturer also recommends discontinuing metformin for 48 hours after any radiologic procedure involving the administration of iodinated contrast material into the blood. The rationale for this recommendation is to avoid the potential for high plasma metformin concentrations if the patient develops contrast-induced acute renal failure [16].

Thiazolidinediones (Glitazones)

The thiazolidinediones such as Rosiglitazone and Pioglitazone has been extensively used to reverse insulin resistance in type II diabetes mellitus. They are otherwise also called as insulin sensitizers as they enhance the sensitivity of the tissue to the insulin. They act as a catalyst of PPAR nuclear receptors. Peroxisome proliferator-activated receptors (PPARs) are a family of nuclear receptors for lipid and glucose metabolism. They exist in three different forms viz PPARα, PPARβ and PPARγ. Activation of these receptors is thought to regulate the transcription of essential proteins required for lipid and glucose metabolism. PPAR-γ is mostly expressed in adipose tissue [17]. The possible mechanism by which they are acting as agonists of a nuclear receptor; peroxisome proliferator-activated receptor gamma (PPARγ). It regulates the transcription of genes involved in glucose and lipid metabolism. Glitazones act by activating PPARγ subunit but also found in skeletal muscle, Liver, intestine, endothelial cells, cardiac muscle, kidney and in scavenging cells. Important genes that are up-regulated by PPAR-γ are adiponectin, a fatty acid transport protein, Insulin receptor substrate (IRS), and Glucose Transporter-4 (GLUT – 4; (extensively found in muscle and adipose tissue). They mainly increase the sensitivity of muscle and fat and to a lesser extent liver to increase glucose utilization and diminish glucose production. It has been found to cause redistribution of fat from the visceral compartment to the subcutaneous compartment. Visceral fat is one of the major cause of insulin resistance is a well known fact. Troglitazone was once used extensively for type II diabetes mellitus but withdrawn from the market due to severe hepatotoxicity caused by it. Rosiglitazone also could not take the market for long as many studies suggested that Rosiglitazone use has been associated with increased risk of heart attack and stroke for which its use was also banned by some countries like the UK in late 2010 [18].

Reports claim that although metformin is being currently used as first-line therapy for type II diabetes, thiazolidinediones are far superior as they do not affect any metabolic processes of the body (no hypoglycemia) rather they increase the sensitivity of the tissue towards insulin which is normally secreted by the body [19].

Side effects: The most common side effects of the drug under this group are water retention which initially begins with peripheral edema which then progress to pulmonary edema and ultimately congestive heart failure. The worst part of this is it is resistant to diuretic and can only be relieved by drug discontinuation. Other possible side effects includes weight gain, eyesight problems, reduced sense of touch, chest pain and infections and allergic skin reactions [20].

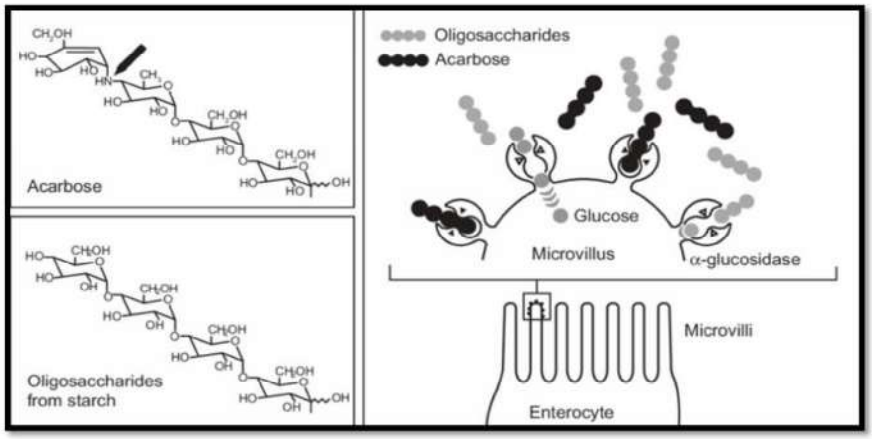

Fig. 3:

Alpha-Glucosidase Inhibitors (Acarbose and Miglitol)

Acarbose and Miglitol are the drugs available under this group. Glucose monomers are linked together by a glycosidic linkage to form polysaccharides. The enzyme α-glucosidase is responsible for breaking the linkage and produces glucose monomer the latter is then absorbed into the circulation causing glucose elevation. Inhibition of α-glucosidase prevents the release of glucose into the circulation. Drugs like Acarbose and Miglitol acts by blocking the enzyme [21].

These drugs inhibit the enzyme responsible for the conversion of dietary cellulose, starch, and glycogen into simple sugars which can be absorbed. This slows down the rate of formation and rate of absorption of glucose after meals. This overall decreases the rise in postprandial blood glucose levels. Apart, acarbose inhibits pancreatic alpha-amylase which hydrolyzes complex starches to oligosaccharides in the small intestines [23]. The unabsorbed carbohydrate reaches the large intestine where they will be acted upon by gut microflora leading the flatulence and diarrhea as the mild but common side effects. These symptoms are usually mild and do not necessitate the cessation of therapy [24].

Newer Oral Hypoglycemics

Amylin Analogues: Amylin or Islet amyloid polypeptide is a 37 amino acid peptide co-secreted with insulin from the beta cells of pancreas. This hormone helps insulin in controlling post prandial glucose rise. It acts by various mechanism such as it decreases glucagon secretion (by neuroendocrine mechanism); delays gastric emptying (Nucleus accumbens and dorsal vagal complex of CNS are rich in amylin receptor, stimulaiton of these receptors lead to vagal stimulation in GIT resulting in slowing gastric emptying and reduced movement) and also lowers appetite (by stimulation of central amylin receptors, which are different from GLP-1 receptors). Amylin works very similarly to Glucagon Like Peptide – 1 with exception of insulin secreting potential. Amylin analogues mimics these functions and has been proven to reduce the dose of insulin required in diabetic patients. It is commonly prescribed as an adjuct therapy with Insulin and is taken by subcutenous route just prior to meal. Pramlintide acetate is the only available drug in this class.

Pharmacokinetics: Peak plasma concentration reaches in 20 minutes and action lasts for almost 1.5 hours [25]. It is metabolized and excreted by kidney but can be safely given in renal impairment patients.

Side effects: Frequently observed side effects includes nausea, vomiting, headache and severe hypoglycemia. Since amylin is generally co-administered with insulin the risk of hypoglycemia is marked. So, general recommendation is reduction in the dose of insulin. It occurs mostly within three hours of amylin injection. The patient should be adviced to take proper rest and should be adviced not to involve in machinery work or driving work where constant attention is needed.

Incretin Modulator: Incretins, Glucose Dependent Insulinotropic Polypeptide (GIP) and Glucagon Like Peptide – 1(GLP-1) are intestinal peptide hormones secreted by upper and lower GIT. Upper GIT (K cell) secreted GIP while GLP-1 is secreted by lower GIT (L cell). They act as amplifier of insulin secretion i.e; they enhance volume of insulin secretion. Oral glucose stimulates 4 times higher insulin release than intravenous glucose. This is because oral glucose releases incretins that amplifies the glucose-induced insulin release. In patients with diabetes the role of GIP is substantially reduced and is unresponsive to any external therapy. However the insulinotropic and glucagonostatic effects of GLP-1 is retained to the level that any exogenous stimulation significantly reduces plasma glucose and improves glycaemic control. The action of GLP-1 in turn is degraded by dipeptidyl peptidase 4 (DPP-4). Hence, GLP-1 analogues and drugs that prevents GLP-1 (by inhibiting DPP-4) are discussed under incretin modulator [26].

Exenatide and Dulaglutide are longer acting while Liraglutide and Lixisenatide are shorter acting GLP-1 agonists**.** These are administered *subcutaneously* and act by mimicking the role of GLP-1. These includes suppression of glucagon secretion, preserves Islet cell integrity and decreases apoptosis and delays gastric emptying resulting in reduced appetite. Exenatide has 53% sequence resemblance to natural GLP-1 and is commonly used either as a monotherapy or in combination with metformin/sulphonylureas. Since it is short acting with half life of 140 minutes twice daily dosing is recommended. However, Liraglutide has got an additional C16 fatty acide side chain attached which makes it long acting an (half life of more

than 24 hours) [27]. Once daily dosing is suffient to maintain blood glucose in type II diabetes. It is well tolerated except mild and short lived nausea as soon as therapy begins. Use of GLP-1 agonist has a benefit over other oral hypoglycemic medicine in that is do not cause significant hypoglycemia as their action is glucose mediated. These group of drugs has also been found to reduce body weight and cardiovascular complicacies (desirable in diabetes) [28].

DPP-4 inhibitors or Gliptins are group of drugs that inhibit DPP-4 and thereby enhances the level GLP-1 level are used to treat diabetes mellitus type 2 [26]. Common side effects includes gastrointestinal problems including nausea, diarrhoea and stomach pain flu-like symptoms such as headache, runny nose, sore throat skin reactions, painful skin followed by a red or purple rash [27]. Risk of pancreatic cancer is increased when a patient is maintained solely on DPP-4 inhibitors. Sitagliptin, Vildagliptin, Saxagliptin and Linagliptin are the drugs under this group [29].

Sodium Glucose Co-Transport 2 (Sglt-2) Inhibitors

Drugs under this group includes Dapagliflozin and canagliflozin. Sodium Glucose Co-transport exist in the body under two forms namely, SGLT-1 and SGLT-2. SGLT-1 is encoded by the gene SLC5A1 and is predominantly expressed in intestinal lumen which accounts for 2% of the glucose reabsorbtion while SGLT-2 is expressed in Proximal Convulated Tubules of the nephron (SLC5A2) is responsible for 98% glucose reabsorbtion.Since most of the body glucose is replenished via kidney so emphasis has been given to block this reabsorption by SGLT-2 inhibitiors. Glucose upon reaching the afferent arterioles of glomerulus gets freely filtered and 98% on the filtered glucose is reabsorbed from the proximal tubule via sodium glucose co-transport 2 channel [30].

This group of drug blocks SGLT-2 channel and causes excretion of glucose via urine (glycosuria). These are administered by oral route and tends to cause weight loss. Since it acts in the kidney so the efficacy of these agents is reduced in renal impairment and it increased incidence of urinary tract infections and genital infections. Higher rates of breast and bladder cancers have been reported in patients taking dapagliflozin [31]. Nevertheless, whatsoever may be the drug, it must be taken under the guidance of a physician.

Conclusion

Diabetes is a household ailment of modern society which if untreated may lead to serious life-threatening complicacies. Apart from heredity, obesity is a major contributing factor. Type I diabetes generally responds well to insulin supplied exogenously while Type II diabetes need insulin sensitizers and Insulin precursor in combination. Although many drugs have been developed so far but the common drawback is hypoglycemia and weight gain induced by such drugs. Newer drugs such as amylin analogue and incretin modulators alone or in combination of older drugs are preferred along with life style changes. The following combinations are commonly used drugs: Thiazolidinedione + biguanide, DPP-4 inhibitors + biguanide, SGLT2 inhibitor + biguanide, DPP-4 inhibitor + SGLT2 inhibitor, GLP-1 agonist + degludec insulin and GLP-1 agonist + glargine insulin.

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