**ABSTRACT**

Type 2 diabetes mellitus is a metabolic disorder characterized by high blood glucose whose prevalence is increasing in the 21st century. Its management involves lifestyle modifications and drug therapy. The pathogenesis of type 2 diabetes mellitus is complex, and includes a significant reduction of the incretin effect. In patients with type 2 diabetes, glucagon like peptide-1 secretion may be impaired. Significant understanding of the role of incretin hormones in glucose homeostasis has led to the development of incretin-based therapies that offer advantages over previously used antidiabetics. Incretin-based therapies have significant glucose-lowering effects, promote weight loss (or are weight-neutral), inhibit glucagon secretion and protect beta cells. They are currently recommended to be used as an add on therapy to older antidiabetic drugs who show suboptimal glycemic control. Drug groups like glucagon-like peptide-1 mimetics which mimic the effect of incretin and dipeptidyl peptidase-4 inhibitors that prevent the degradation of glucagon-like peptide-1 specifically take care of the blunted response to incretin in type 2 diabetics.

**Key words: Diabetes mellitus, incretin, glucagon like peptide-1, dipeptidyl peptidase-4**

**INTRODUCTION**

Diabetes mellitus is a spectrum of common metabolic disorders caused by genetic and environmental factors which contribute to its pathogenesis. Its world wide prevalence has risen rapidly over the past two decades. Based on the current scenario, there would be more than 360 million individuals suffering from diabetes by the year 2030. (Powers, 2008). India has the largest number of people with diabetes and is known as the ‘diabetic capital’ of the world. It has been projected that by 2025, India will have more than 60 million people with diabetes. (Wild et al, 2004; Vaz et al, 2011). Diabetes mellitus is classified on the basis of pathogenesis which causes hyperglycemia and the two broad categories are type 1 and type 2 diabetes mellitus (Powers, 2008). Type 1 previously known as insulin dependent diabetes mellitus accounts for 5-10% of diabetes and occurs due to destruction of pancreatic islet β cells, predominantly due to an autoimmune process which can cause complete or near total insulin deficiency. Type 2 earlier called as non insulin dependent diabetes mellitus is a progressive metabolic blood glucose disorder due to multiple metabolic abnormalities including insufficient insulin secretion, impaired response of liver and peripheral tissues to insulin, loss of beta cell function, impaired regulation of glucagon secretion and disturbed incretin physiology (Andukuri et al, 2009). Incretins are involved in maintaining glucose homeostasis along with other hormones like insulin, glucagon and amylin. Incretins are released by enteroendocrine cells in the intestine in response to a meal. Incretin dysfunction, along with other defects, has been implicated in contributing to the pathogenesis of type 2 diabetes mellitus (Campbell et al, 2011).Despite a plethora of medications already available for tackling diabetes today, adequate control of diabetes and retardation of disease progression has not been possible yet. The current range of drugs used for diabetes include biguanides (metformin), sulphonylureas (glyburide, glimepiride, glipizide, gliclazide), thiazolidinediones (pioglitazone), meglinidines (nateglinide, repaglinide), alpha glucosidase inhibitors (miglitol, acarbose, voglibose) and insulin. Sulfonylureas and meglitinides are insulin secretagogues, causing the release of insulin by direct action on the K_ATP channel of the pancreatic beta
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cells. Blockage of this channel leads to depolarization and secretion of vesicles containing insulin. Their main side effects are hypoglycemia and weight gain. Biguanides and thiazolidinediones are known as insulin sensitizers i.e. they increase the sensitivity of target organs to insulin. Biguanides reduce hepatic gluconeogenesis by activating adenosine monophosphate-activated protein kinase (AMPK) and increase uptake of glucose by the peripheral tissues, including skeletal muscle. Metformin is the biguanide available for use in the market. The most frequent side effects with metformin are gastrointestinal (anorexia, nausea, vomiting, diarrhea). Thiazolidinediones, also known as ‘glitazones’, bind to peroxisome proliferator activated receptor-γ (PPARγ), a nuclear receptor involved in transcription of genes regulating the release of adipokines (resistin and adiponectin) from adipocytes. Stimulation of adiponectin secretion sensitizes peripheral tissues to the effects of insulin. There occurs increased glucose transporter (GLUT 1 and GLUT 4) expression which helps in uptake of glucose. Adverse effects noted are edema, increased fracture risk in women, anemia and weight gain. Alpha glucosidase inhibitors are not technically hypoglycemic agents because they do not have a direct effect on insulin secretion or sensitivity. Alpha glucosidase enzyme in the gut digests starch and sucrose. Alpha glucosidase inhibitors slow the digestion of starch in the small intestine, so that glucose from the starch of a meal enters the bloodstream more slowly, so less glucose is absorbed as the carbohydrates are not broken down into glucose molecules. These agents are effective as monotherapy only in the earliest stages of impaired glucose tolerance, but can be helpful in combination with other agents in type 2 diabetes mellitus. The main adverse effects seen with this class of drugs are flatulence and diarrhea. Insulin therapy with rapid and long acting insulin preparations form the mainstay of therapy for managing type 1 diabetics while it is used in type 2 diabetes patients when other oral antidiabetics fail to maintain adequate glycemic levels. Latest in the development of anti-diabetes treatment are incretin based therapies which restore incretin activity and may reduce the pathophysiologic consequences of diabetes. Two new classes of drugs based on the actions of the incretins are injectable long-acting stable analogues of glucagon like peptide-1 (GLP-1) known as incretin mimetics, and orally available incretin enhancers which inhibit dipeptidyl peptidase 4 (DPP4) enzyme, responsible for the rapid degradation of GLP-1 and glucose-dependent incretinotropic polypeptide (GIP) (Masharani, 2010).

Incretin mimetics and enhancers

The incretin effect explains the augmentation in insulin secretion which is more pronounced in response to oral glucose stimulation as compared to equivalent intravenous glucose bolus (Elrick et al, 1964; McIntyre et al, 1965). Incretins are gastrointestinal hormones released after meals which can cause an increase in insulin secretion. The two best known hormones that fulfill this criterion are GIP and GLP-1. GIP also known as the glucose-dependent insulinotropic peptide is a member of the secretin family of hormones. It is a 42-amino acid peptide synthesized and released from enteroendocrine K cells located mostly in the duodenum and upper jejunum. Function of GIP is to induce insulin secretion, which is stimulated primarily by hyperosmolarity of glucose in the duodenum. GIP is also thought to have important effects on fatty acid metabolism by stimulation of lipoprotein lipase activity in adipocytes. It has been demonstrated that GIP in the ruminant animal may play a role in nutrient partitioning in milk production (Thorrens, 1995). GLP-1, is derived from proglucagon, a 180 amino acid precursor and exists in two bioactive forms, GLP-1 (7-36) amide and GLP-1 (7-37) with GLP-1 (7-36) comprising up to 80% of the GLP-1 in circulation (Chia and Egan, 2009). Production and secretion of GLP-1 occurs from enteroendocrine L cells of jejunum and ileum (Theodorakis et al, 2006). Together, the insulinotropic effect of GLP-1 and GIP accounts for up to 60% of the insulin secreted after eating food and plays a very important role in promoting glucose homeostasis and GLP-1 in addition may have the potential to improve pancreatic beta cell function. In addition, GLP-1 suppresses pancreatic glucagon secretion, enhances glucose disposal, slows gastric emptying, promotes satiety, preserves islet integrity and enhances resistance of beta cells to apoptosis. (Nauck et al, 2002; Meier et al, 2003; Drucker, 2006; Kaushal et al, 2006; Gallwitz, 2006; Nielsen et al, 2004). GLP-1 has a very short half life of 1-2 minutes
and is quickly metabolized by DPP-4 enzymes and neutral endopeptidase (NEP) (Hupe et al, 1995; Kieffer et al, 1995; Meier et al, 2004; Sharma and Sharma, 2011). Hence being a natural peptide itself is not a useful therapeutic agent. In diabetics, the normal incretin effect is lost and GLP-1 secretion is reduced. The response of beta cells to exogenously administered GLP-1 has been found to be three to five times lower in patients with Type2 diabetes mellitus as compared to healthy people (Kjems et al, 2003; Chia and Egan, 2009). Incretin mimetics or GLP-1 analogs boost GLP-1 to supra physiological levels by activating GLP-1 receptor which is a seven-member trans-membrane G protein-coupled receptor. GLP-1 receptors are expressed by beta cells, cells in the peripheral and central nervous system, the heart and vasculature, kidney, lung and gastrointestinal mucosa. When GLP-1 binds to its receptor, it activates cAMP-PKA pathway and several guanine nucleotide exchange factors which in turn alters the activity of several ion channels. In beta cells, it causes an increase in insulin biosynthesis and exocytosis in a glucose dependant manner. (Thorens et al, 1993; Ducker, 2006; Powers and D Alessio, 2011). When GLP-1 is infused in patients with type 2 diabetes mellitus, it stimulates insulin secretion and lowers glucose levels but unlike sulfonylureas, it has modest insulin stimulating effect at normoglycemic levels. Thus GLP-1 is associated with a low risk of hypoglycemia (Masharani, 2010). Prolongation of GLP-1 action by inhibition of its metabolic enzyme DPP-4 also is a promising therapeutic strategy in the incretin pathway and they are termed incretin enhancers or gliptins. Owing to tremendous potential therapeutic utility in treatment of type 2 diabetes mellitus, development of DPP-4 resistant GLP-1 analogs and DPP-4 inhibitors have been taken up.

**GLP-1 analogs**
These are structurally altered chemical versions of GLP-1. They are receiving increased attention for treatment of type 2 diabetes mellitus due to their ability to stimulate insulin secretion only during hyperglycemic states (Arjona, 2008). Also there is decreased risk of rebound hypoglycemia with these agents as compared to other drugs used for diabetes. The GLP-1 analogs available are exenatide, liraglutide, taspoeglutide and lixisenatide. Exenatide was the first marketed GLP-1 analog which was approved by FDA in April 2005 as an adjunctive therapy for type 2 DM with metformin or sulfonylurea (Ittzjl, 2006). It should not be used in patients taking insulin. It is a synthetic version of a peptide exendin-4 originally found in the saliva of the Gila monster (*Heloderma suspectum*). Unlike native GLP-4, exenatide has a Glycine 8 in place of an Alanine8 of the N-terminus, which renders it resistant to the action of DPP 4 enzyme. It reaches a maximum plasma concentration in approximately 2 hours, and the mean half-life ranges from 3.3 to 4 hours (Kolterman 2005; Powers, 2008; Chia and Egan 2009). It is administered subcutaneously at a dose of 5µg twice daily, one hour before a meal and can be increased to a maximum of 10µg twice a day. It is equally absorbed from arm, abdomen, or thigh injection sites and duration of action is upto 10 hours (Powers, 2008; Nolte, 2009). The mean apparent volume of distribution after administration of a single subcutaneous dose is 28.3 L. Based on animal studies, the bioavailability of exenatide after subcutaneous injection has been estimated to be between 65% and 75%. The drug is predominantly eliminated by glomerular filtration followed by proteolytic degradation (Bray, 2006). Administration of exenatide once- or twice-daily by subcutaneous injections, in ten type 2 diabetes mellitus patients who were insulin naive showed improvement in HbA1c (P<0.009) after one month of treatment (Egan et al., 2003). In another study, exenatide alone or in combination with metformin, sulfonylurea or thiazolidinedione, was associated with modest reduction in HbA1c of about 1% (Amori, 2007). Exenatide long acting release (LAR) is in phase 3 development. Exenatide LAR is formulated with exenatide and poly (d,l lactic-co-glycolic acid) microspheres, a biodegradable medical polymer commonly used in extended drug release formulation. Once weekly subcutaneous injection is thought to be the desired dosing frequency (Drucker et al., 2008). When a weekly injection of 2 mg exenatide LAR was given, a therapeutic plasma level of 50 pg/mL was reached after the second injection. The steady state concentration of 232 pg/mL was reached by sixth week (Kim et al, 2007). It was seen in one of the studies that HbA1c of ≤7% was achieved in 77% of patients treated with exenatide LAR (once weekly).
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compared to 61% of those taking exenatide twice daily. Adverse events reported was nausea and pruritis at injection site. Other adverse effects of exenatide reported have been nausea, vomiting, diarrhea, dizziness, headache, dyspepsia, decrease in appetite, hypoglycemia (mainly when combined with a sulfonfylurea), increased sweating (Kaushal et al., 2006; Bray, 2006; Ezzo and Ambizas, 2006; (Levien et al., 2009). Exenatide delays gastric emptying, so it should be administered at least one hour before taking other drugs like digoxin, lovastatin, lisinopril, acetylaminothen, antiinfecives and oral contraceptives (Kaushal et al., 2006; Bray, 2006).

Liraglutide is an acylated human GLP-1 analogue while is nearly identical to it with lysine 34 to arginine substitution and an addition of a C-16 free-fatty acid derivative via a glutamoyl spacer at lysine 26. (Mudaliar, 2007; Chia and Egan, 2009). The free-fatty acid side chain promotes binding to albumin and other plasma proteins leading to delayed absorption rate from the injection site and extended plasma half life of 11-13 hours. Peak plasma concentration is attained within 10-14 hours after injection. The rate of renal clearance of liraglutide is also slowed. (Knudsen et al, 2003; Knudsen et al, 2000; Agerso et al, 2002; Powers and D’Alessio, 2011). It was approved for use by US FDA in January 2010 and in Europe in 2009 (Parks and Rosebraugh, 2010). Liraglutide is indicated for adjunctive therapy along with metformin, sulfonfylurea or their combination and like exenatide is administered by subcutaneous route. Liraglutide has been shown to lower blood glucose, cause weight loss, and improve beta cell functioning on adding it to metformin and thiazolidinedione in the treatment of type 2 diabetes mellitus. In a single comparative trial, liraglutide once a day reduced glycosylated hemoglobin levels to around 30% more than exenatide twice a day and was better tolerated too (Buse et al., 2009). In another 12 week clinical trial in 193 patients with type 2 DM, 0.75 mg liraglutide subcutaneously daily caused equivalent reductions of HbA1c compared with glimepiride and the treatment was associated with a weight reduction of 0.39 kg, whereas patients treated with glimepiride experienced a mean weight gain of 0.94 kg. (Madsbad et al., 2004; Mudaliar, 2007). FDA has expressed some serious concerns about safety of liraglutide. Data from preclinical studies in rodents suggested that liraglutide was associated with increase in the risk of thyroid C-cell focal hyperplasia and C-cell tumors. But though this is a troublesome news, its relevance to humans is unknown. Also, a data from a long-term study did not show any notable difference in mean calcitonin levels between liraglutide and control groups over 2 years of follow-up. So the FDA concluded that statistically significant increases in cancer occurred only at drug levels many times those used in humans but careful monitoring in humans and additional animal studies should be carried out. There were some cases of pancreatitis reported in phase 2 and 3 studies with liraglutide but such small data is difficult for forming any conclusion so the patients need to be aware that persistent nausea and vomiting with liraglutide need careful evaluation and it should be discontinued if signs of pancreatitis appear (Parks and Rosebraugh, 2010). More and more post approval clinical trials will give us a better picture about their safety profile.

Another GLP-1 analog taspglutide has 93% homology with native polypeptide where amino acids 8 and 35 of the native GLP-1 peptide are substituted with aminoisobutyric acid to prevent DPP-4 and protease-mediated cleavage at the N- and C-terminus, respectively. It is to be injected subcutaneously once weekly and is also effective given bi-weekly (Retterstol, 2009). Phase II trials have shown that weekly administration of a slow-release formulation was associated with enhanced glycemic control, reduction in body weight and improved beta cell function. Mild gastrointestinal adverse effects were reported and apart from that it is generally well tolerated (Arjona, 2008). Lixisenatide is a modified exendin-4 based molecule with a short half-life of 2–4 hours, and it is classed as a short-acting GLP-1 receptor agonist but despite that it is intended for once-daily dosing as it has a strong binding affinity to the GLP-1 receptor. Various clinical studies with lixisenatide have shown beneficial effects on HbA1c when combined with commonly used antidiabetes agents. Limited data with the intended once-daily 20 µg subcutaneous dosing necessitate further evaluation of lixisenatide as add-on to various antihyperglycemic treatments. There was no increased risk of hypoglycemia while beneficial weight reduction was seen. Adverse effects were similar to other GLP-1 receptor agonists, the most frequent
being gastrointestinal. Due to the pronounced effect of lixisenatide on postprandial plasma glucose it seems rational to combine it with long-acting basal insulin analogs, so as to achieve additive effects on glycemic control. (Barnett, 2011).

**Dipeptidyl peptidase- 4 (DPP-4) inhibitors**

DPP-4 gene family include four enzymes, DPP-4, DPP-8, DPP-9, fibroblast activation protein (FAP) and catalytically inactive proteins DPP-6 and DPP-10 (Gupta and Kalra, 2011). Dipeptidyl peptidase 4 is a complex cell surface, 766 amino acid serine protease that is widely distributed throughout the body, expressed as an ectozyome on endothelial cells, on the surface of T-lymphocytes and in a circulating form. (Drucker 2007; Powers and D’Alessio, 2011). It was originally known as the lymphocyte cell surface marker CD26, or as the adenosine deaminase (ADA)-binding protein. Both GLP-1 and GIP are endogenous physiological substrates for DPP-4 and it was seen that chemical inactivation of DPP-4 results in increased levels of intact bioactive GIP and GLP-1. (Drucker, 2007). So these agents increase insulin secretion, reduce glucagon levels and improve both fasting and postprandial hyperglycemia. Other physiological substrates of DPP-4 include neuropeptide-Y which has a role in appetite, energy homeostasis, and blood pressure control, substance P which has a role in pain and inflammation. Sitagliptin, saxagliptin, linagliptin, alogliptin and vildagliptin are the DPP-4 inhibitors available (sitagliptin, saxagliptin and linagliptin in USA, vildagliptin in Europe, alogliptin in Japan), with several others like gemigliptan and dutaglipin are in various phases of clinical trials for use in type 2 diabetes mellitus. Sitagliptin, saxagliptin and vildagliptin are also approved for use in India. (Palalau, 2009; Gupta and Kalra 2011; Powers and D’Alessio, 2011).These drugs are orally available and quite effective in reducing HbA1c. Sitagliptin, is a selective competitive DPP-4 inhibitor that results in two times increase in postmeal active plasma GLP-1 (Palalau et al, 2009). It can be given once daily in a dose of 50 to 100 mg. The use of higher doses or twice-daily administration of sitagliptin did not provide additional benefits (Aschner et al, 2006; Raz et al, 2006; Hanefeld et al, 2007). It has minimum metabolism by hepatic microsomal enzymes. Sitagliptin is generally well tolerated and has been approved for use as monotherapy and in combination with metformin or a thiazolidinedione (Mudliar, 2007).

Saxagliptin, binds the enzyme DPP-4 covalently and reversibly and can be given once daily. It gets metabolized in the body by CYP3A4/5 to an active metabolite. (Powers and D’Alessio, 2011). When administered as initial therapy in type 2 diabetics, it showed 1.69% reduction in HbA1c while there was 1.99% reduction with metformin alone and 2.49-2.53% with a combination of saxagliptin and metformin. Adverse reactions reported with it have been nasopharyngitis, headache, diarrhea, urinary tract infection (Levien and Baker, 2009). It was also seen that improvements in glycemic parameters from saxagliptin (2.5–10 mg daily) in combination with metformin were sustained for at least 102 weeks and is weight neutral (Defranzo et al, 2009; Palalau et al, 2009). In another monotherapy study, 521 patients with T2DM were randomized to placebo, sitagliptin 100 mg once daily or sitagliptin 200 mg once daily for 18 weeks. A greater reduction of 0.60% in glycosylated hemoglobin was seen with sitagliptin 100 mg and 0.48% with sitagliptin 200 mg, respectively as compared with placebo. Fasting glucose levels were also reduced with sitagliptin. In addition, sitagliptin 100 mg was associated with improvement in homeostasis model of assessment of beta-cell function (HOMA-B), suggestive of beneficial effects on beta-cell function (Gallwitz, 2007). Vildagliptin is another selective DPP-4 inhibitor yet to be approved for use in USA but was approved in Europe in 2008. It is used as an adjunct in cases of type 2 diabetes whose blood sugar is not sufficiently controlled by metformin, sulfonylurea or a thiazolidinedione. In a randomized, double-blind, placebo-controlled, parallel-group study in 60 healthy Chinese volunteers, single and multiple dose pharmacokinetics and pharmacodynamics, safety and tolerability of vildagliptin were assessed after administration of 25, 50, 100, or 200 mg qid. OR 50 mg twice daily. Vildagliptin was rapidly absorbed (tmax 1.5-2.0 hours) in the dose range of 25 to 200 mg and was rapidly eliminated with a terminal elimination half-life of approximately 2 hours. No accumulation of vildagliptin was observed following the administration of multiple doses (Hu et al, 2009). A study with vildagliptin 50 mg/day was
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compared with placebo for 12 weeks (with a further 40 week extension) in 107 patients with type 2 diabetes on metformin therapy. At 1 year, vildagliptin caused reduction in the prandial glucose by 43 mg/dl, fasting glucose by 20 mg/dl and HbA1c by 1.1 per cent. (Mudaliar, 2007). Rare case of hepatic dysfunctions have been reported with it and the liver function tests normalize after vildagliptin is discontinued. So it is recommended that liver functions should be analysed before starting therapy with vildagliptin and regularly evaluated after the treatment begins. At a dose of 100 mg as monotherapy, vildagliptin was seen to cause dizziness, headache, constipation, peripheral edema, arthralgia and upper respiratory tract infections. (Palau et al 2009).

Alogliptin is a potent, quinazoline based non covalent inhibitor of DPP-4, used alone or in combination with insulin, metformin, sulphonylurea or a thiazolidinedione. Across all its doses, it has a mean half life of 12.4-21.4 hours. In a study in type 2 diabetes patients who were not adequately controlled with insulin alone or insulin plus metformin, alogliptin when added to insulin showed greater reduction in HbA1c levels. It is well tolerated with few adverse effects like pruritis, nasopharyngitis and headache (Andukuri et al, 2009 ; Levien and Baker, 2009). Alogliptin showed improvements in fasting blood glucose levels and HbA1c, which were sustained for at least 26 weeks. Alogliptin is weight neutral, and is associated with very low incidence of hypoglycemia (Defronzo et al, 2008; Nauck et al, 2009; Pratley et al, 2009).

Linagliptin, a xanthine based DPP-4 inhibitor is currently being assessed as once daily tablet for monotherapy or in combination with pioglitazone, metformin / metformin plus a sulfonylurea. It has demonstrated around 80% inhibition of DPP-4 activity at a dose of 5 mg per day in phase II clinical trials. The effects were sustained, and were associated with minimum risk of hypoglycemia (Tiwari, 2009; Deacon and Holst, 2010). In a short-term study in healthy adult male Japanese volunteers, multiple oral doses of linagliptin inhibited plasma DPP-4 activity and elevated active GLP-1 concentrations in a dose-dependent fashion, with no episodes of hypoglycemia. After oral administration of a single 5-mg dose to healthy subjects, peak plasma concentrations of linagliptin occurred at approximately 1.5 hours post dose (tmax). The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of linagliptin 5 mg, is approximately 12 hours. The absolute bioavailability of linagliptin is approximately 30%. Following oral administration, the majority (about 90%) of linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway (Sarashina et al, 2010).

Dutogliptin, another small molecule inhibitor of DPP-4 underwent a single-center, randomized, open-label, crossover study in type 2 diabetic patients was carried out where all patients received three treatment regimens, each of 5 days duration: 400 mg OD of dutogliptin; 1000 mg metformin twice daily and concomitant administration of 400 mg dutogliptin once daily and 1000 mg metformin twice daily. The time to maximum plasma concentrations (tmax) was essentially the same for dutogliptin with or without metformin (Li J et al, 2010). All three treatment regimens were well tolerated.

CONCLUSION

There continues to be regular development in the field of anti-diabetics which has generated a lot of interest. The newfound class of medications is a welcome addition to the existing armamentarium against type 2 diabetes as their potential strengths and weaknesses are becoming better defined. GLP-1 agonists and DPP-4 inhibitors have a promising future due to their potential in retarding the disease process in type 2 diabetes mellitus and less chance of hypoglycemic episodes. However, they will need continuous evaluation both in long-term efficacy and safety controlled trials and in clinical practice to
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Further assess their effectiveness in glycemic control, safety profile and whether they will alter the micro and macrovascular complications of uncontrolled diabetes. This will determine their position among the many available and well-established therapies for type 2 diabetes. Therefore it becomes important for medical professionals to understand, initiate, and adjust treatment with the above medications to provide appropriate care and safety for the well-being of their patients.

REFERENCES


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