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# "THE MECHANISM OF ACTION OF ORAL ANTIDIABETIC PILLS: AN EVALUATION OF RECENT LITERATURE"

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**ABSTRACT**

The presented study's recent literature review of oral antidiabetic pills their chemical nature, structure for Category 2 diabetes mellitus (DM) is a disorder this is putting a growing burden on health carrier delivery internationally. Therefore, it has to turn out to be more and more crucial that physicians who deal with such patients have an excellent understanding of antidiabetic capsules which might be currently to be had or will come onto the marketplace. This newsletter offers a top-level view of all of the significant drug lessons in addition to some statistics on pharmacokinetics, pharmacodynamics, aspect-impact profiles, and indications to be used.

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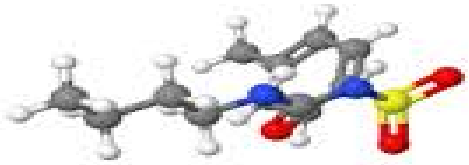
## INTRODUCTION

Category 2 diabetes mellitus (DM) is an ailment characterized by the resource of insulin resistance and a progressive decline in pancreatic beta-mobile characteristics associated with growing hyperglycemia. Faulty beta-mobile characteristic takes place early and may be detected in people with impaired fasting and/or submit-prandial glucose tiers (the so-referred to as 'pre-diabetics'). The UK ability Diabetes (UKPD) [1] looks at indicated that by the time category 2 DM is recognized, people have already misplaced as much as 50% of their beta-cell traits. The decline in characteristic proceeds at 6% constant with yr, that is 20 times more than that explained through normal getting older.

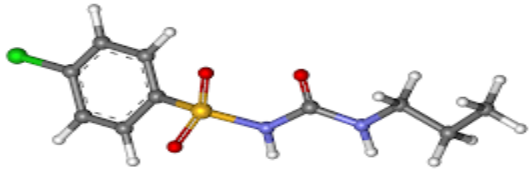
The objectives for glycaemic management as set by means of the American Diabetes Association (HbA1C<7%) [2] And the yank affiliation of medical Endocrinologists (HbA1C<6.5%) three sometimes appear daunting and impossible. It is consequently of the most significance to have a pinnacle-notch understanding of the mechanism of movement of those tablets so that you can optimize the affected person's remedy. The intention of this newsletter is to gift a pinnacle-degree view of all the to-be-had oral antidiabetic tablets according to their unique classes, mechanisms of movement, and pharmacological profiles, and to assist physicians to make the correct choice for their patients. [4]

**Insulin secretagogues: Sulfonylureas –**

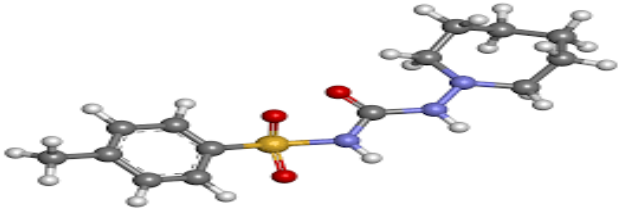
A) First generation Sulfonylureas – ('Tolbutamide, Chlorpropamide, Tolazamide, Acetohexamine.')



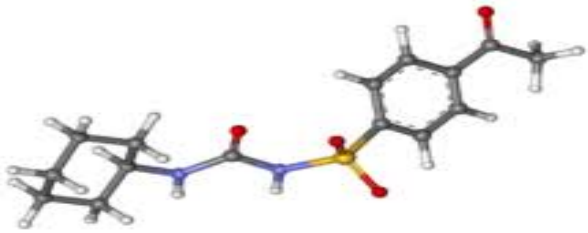
**'Tolbutamide'**
**N-[(Butylamino)carbonyl]-4-methylbenzene sulfonamide**



**'Chlorpropamide'**
**4-chloro-N-(propylcarbamoyl) benzene sulfonamide**



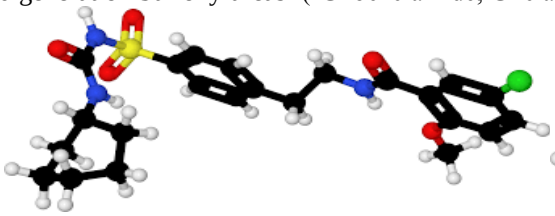
**'Tolazamide'**
**N-[(azepan-1-ylamino)carbonyl]-4-methylbenzene sulfonamide**



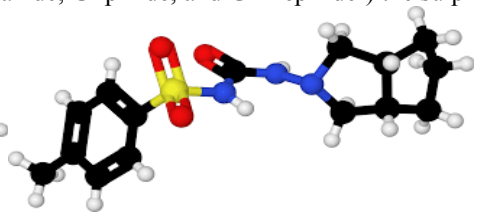
**'Acetohexamine'**
**1-[(4-acetylbenzene)sulfonyl]-3-cyclohexylurea 4-acetyl-N-(cyclohexyl carbamoyl)benzene sulfonamide**

**Fig 01: Structure and chemical name of Insulin secretagogues-First generation.**

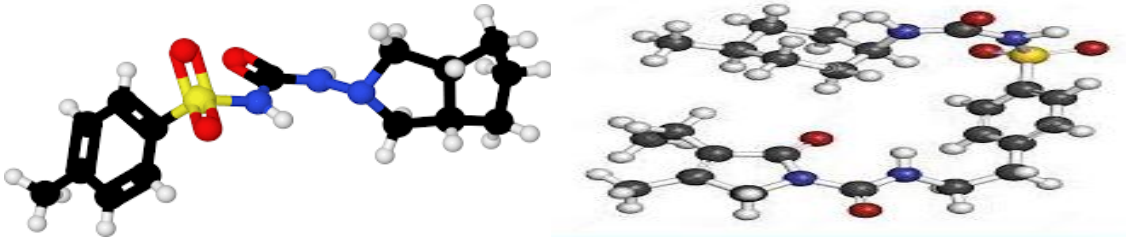
B) Second generation Sulfonylureas- ('Glibenclamide, Gliclazide, Glipizide, and Glimepiride') the sulphonylureas (SUs):



**'Glibenclamide'**
**5-chloro-N-[2-[4-(cyclohexyl carbamoyl sulfamoyl) phenyl] ethyl]-2-methoxy benzamide.**



**'Gliclazide'**
**N-(hexahydrocyclopenta[c]pyrrol-2(1H)-ylcarbamoyl)-4-methyl benzene sulfonamide**



**'Glipizide'**
**One-cyclohexyl-three-[[p-[two-(five-methylpyrazine-carboxamido) ethyl] phenyl] sulfonyl] urea.**

**'Glimepiride'**
**One-[[p-[two-(three-ethyl-four-methyl-two-oxo-three-pyrroline-one carboxamide) ethyl] phenyl] sulfonyl]-three-(trans-four-methylcyclohexyl) urea.**

**Fig 02: Structure and chemical name of Insulin secretagogues- Second generation.**

Sulfonylureas first and second technology ('Tolbutamide, Chlorpropamide, Tolazamide, Acetohexamine.') (Glibenclamide, Gliclazide, Glipizide, and Glimepiride) the sulphonylureas (SUs) have been, initially, advanced in the Twenties and have grown to be crucial in the control of category 2 DM. The sulfonylureas lower blood glucose thru a boom inside the secretion of insulin from the pancreatic beta cells. They'll additionally produce other greater-pancreatic hypoglycemic moves that are vital in the course of prolonged remedy. Their number one mechanism of action is to shut ATP-sensitive ok-channels in the beta-mobile plasma membrane, and so initiate a sequence of activities that outcomes in insulin release. The mechanism of motion entails a direct secretory impact on the pancreatic islet beta-cells. Adenosine triphosphate (ATP) - touchy potassium channels (okay+) of the beta-cells play an essential function inside the launch of insulin and encompass two components: a pore and a regulatory subunit (SUR-1). The sulphonylureas act to enhance the sensitivity of the beta-cell to glucose and, even as positive to the transmembrane sulphonylureas receptor (SUR-1), mediate the very last of the potassium-sensitive ATP channels at the cell membrane. Cellular efflux of potassium is reduced and membrane depolarization takes place. Calcium influx is mediated via the hollow of voltage-based Ca2+-channels that sell the discharge of pre-long-established insulin granules which lie simply adjacent to the plasma membrane (Fig. 3).[5]

Sulphonylureas decorate the so-known first section of insulin secretion whereby the insulin-containing granules close to the plasma membrane are released in addition to the so-known as 2nd phase of insulin launch a couple of minutes later whilst more excellent insulin granules are translocated from the cytoplasm to the beta-cell membrane and launched by ATP-established exocytosis.[6] Hypoglycemia can occur because those capsules potentiate the release of insulin even if glucose concentrations are beneath the everyday threshold for glucose-stimulated insulin launch (<5 mmol/l).[7, 8[

Sulphonylureas are well absorbed after oral administration and reach peak plasma concentrations within 2 - four hours.[9] food ingestion appears to have little or no effect on their efficacy, however, it's far despite the fact that it suggested that they be taken a minimum of 15 - 20 mins earlier than a meal.

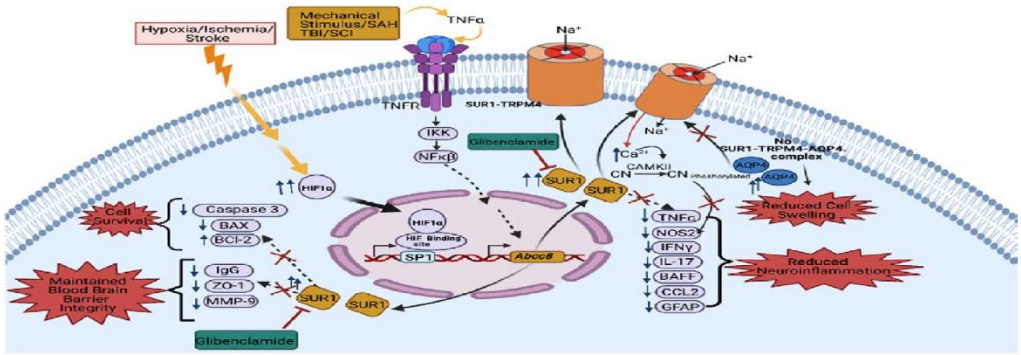


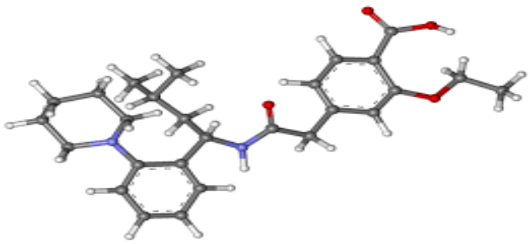

**Fig 03: Sulfonylurea receptor.**

Glibenclamide is considered an intermediate-acting drug (12 - 24 hours) with lively metabolites of which about 50% are eliminated by way of the liver.[9,10,11] Gliclazide (Diamicron) additionally has a duration of motion of 12 - 24 hours, however, as much as 65% of active metabolites are excreted especially by the kidneys.[12] Glimepiride has a length of action of approximately 24 hours and is removed with the aid of the liver.[13] it is very crucial to take into account that given that all sulphonylureas are pretty sure to plasma proteins, they could doubtlessly have interaction with other protein-certain capsules, e.g. Warfarin. Displacement from plasma proteins due to drug interactions has been implicated as a cause of severe SU-triggered hypoglycemia.

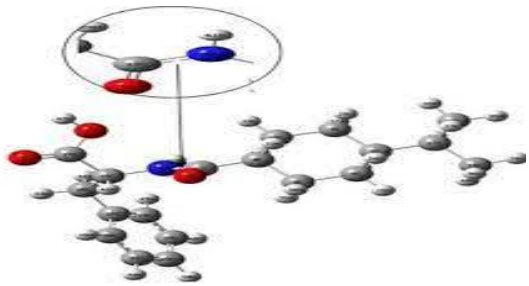
Sulphonylureas stay a well-known desire for first-line remedy in a category 2 diabetic patient who has failed on non-pharmacological measures Hyperglycemia is worsened and the HbA1C levels are adversely affected. The meglitinides were advanced to address this problem. Taken orally unexpectedly before a meal, they could stimulate speedy, quick-lived insulin launch. The mechanism of movement of prandial insulin releasers shows that they bind to the SUR-1 receptor in lots the identical way because of the sulphonylureas. The fast half of-life of those pills potentiates and is non-obese (no matter the reality that Metformin is now recommended as a number one-line remedy for all class 2 diabetics).[14] they may be utilized in combination with wonderful instructions of antidiabetic pills besides for one-of-a-type a secretagogue (which includes meglitinides). They also can be utilized in a mixture with longer-appearing insulin as part of the sunlight hours- sulphonylureas-night time time-time-insulin recurring.[15] starting with a low oral dose; dosages may be up-titrated at intervals of 4 weeks to reap last glycaemic manipulation.

Using sulphonylureas is contraindicated in category 1 DM, being pregnant (magnificence C indication for use), and renal and liver sickness. The plasma concentrations are up to three times, which contributes drastically to the stepped-forward risk of hypoglycemic sports. It isn't always advisable to apply those capsules as quickly as the glomerular filtration rate (GFR) falls beneath 40 ml/min. [8, 11] it's far essential to word that the receptor-particular binding trends of all of the one-of-a-type sulphonylureas range. The state of affairs has been expressed that those drugs may additionally moreover worsen angina symptoms in diabetic sufferers with gift coronary artery sickness (CAD). [16, 17] Sulphonylureas furthermore bind SUR-2 A and B receptors in the cardiac muscle, commencing contraction at immoderate concentrations. Another trouble is the fact that the SUR-2-associated adequate+-channel inside the heart mediates protecting ischemic preconditioning of cardiac muscle, and if this channel closes due to sulphonylureas stimulation, the mortality of diabetic patients on sulphonylureas with myocardial infarctions also can broaden. Use of the sulphonylureas sorts that bind the SUR-2 A and B receptors (Glibenclamide, Glipizide, and Glimepiride) need to be prevented in high-risk sufferers suspected of having widespread CAD. [18, 19] when sulphonylureas are used as monotherapy with a strict food regimen, a further discount in fasting glucose of 2- 4 mmol/l and a reduction in HbA1C levels of 1 - 2% may be expected. [20] Efficacy of aggregate remedy depends on which drug is used. With the addition of Metformin or any thiazolidinedione, a most additional reduction of 1% can be performed (and 0.5% within the case of α-glucosidase inhibitors).[21] facet effects that have been described include hypoglycemia, weight benefit (1 - 4 kg over 6 months), skin reactions, acute porphyria, and, not often, hyponatremia.[15, 16] There were reviews within the literature of glimepiride-brought on acute cholestatic hepatitis.[22] In patients with the overt liver artificial disorder, glimepiride ought to additionally be avoided due to the expanded chance of hypoglycemia (glimepiride metabolized inside the liver).

**Fast-acting prandial insulin releasers (‘Repaglinide, Nateglinide’):**



**‘Repaglinide’**
**(S)-2-Ethoxy-4-(1-[2-{piperidin-1-yl}phenyl]-3-Methylbutylcarbamoylmethyl) benzoic acid)**



**‘Nateglinide’**
**(2R)-2-({[Trans-4-(1-methylethyl)cyclohexyl] carbonyl} amino)-3-phenylpropanoic acid**

**Fig04: Structure and chemical name of Fast-acting prandial insulin releasers.**

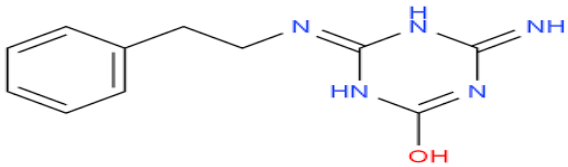
In the natural history of Category 2 diabetes, a blunted reaction of the primary section of glucose-inspired insulin launch has been determined. An initial surge of insulin is important to suppress hepatic gluconeogenesis inside the postprandial length. If this mechanism fails, the postprandial effect of the first phase of insulin secretion, but the effect on the second phase is not sustained. [23] Repaglinide pharmacokinetic profile shows that it is rapidly absorbed after oral intake and can reach peak concentrations within 1 hour (t½ =0.6 hours). The duration of action is 4 - 5 hours; the drug is metabolized by the liver and excreted in both feces and urine. [24] Nateglinide has t½ = 1.5 hours and a duration of action of 5 - 6 hours. In contrast to repaglinide, this drug has active metabolites. Excretion is in bile and urine. [25]

Repaglinide can be used in patients who do not achieve glycaemic control on diet and lifestyle measures alone or who live irregular lifestyles where meals are missed or taken irregularly. These drugs should be taken immediately before meals. [26, 27] the lower risk of hypoglycemia, compared with sulphonylureas, makes these drugs an attractive choice in elderly patients; they may cause minimal weight gain.

Monotherapy causes a reduction in HbA1C of 1 - 2% and, when combined with Metformin, the reduction can be pushed up by 1.5%.28 these drugs can also be combined with other oral hypoglycemic agents (excluding SUs) with added benefit. [24]

**Insulin Sensitizers:**

**Biguanides ('Metformin Phenformin'):**




**'Metformin'**
**(1, 1-Dimethylbiguanide hydrochloride)'**

**'Phenformin'**
**2-(N-phenethylcarbamimidoyl)guanidine**

**Fig 05: Structure and chemical name of Biguanides ('Metformin, Phenformin'):**

Metformin has been available since the 1950s. Its historic roots and origin can be traced back to the guanidine-rich Galega officinalis (goat's rue or French lilac) which has traditionally been used in Europe to treat diabetes. Metformin has a variety of clinical actions that extend beyond just the glucose-lowering effects such as weight reduction, improving lipid profiles, and vascular effects, which includes improving endothelial function, as well as decreasing PAI-1 levels. [4]
The molecular mechanisms of action have not as yet been clearly established. However, it is thought that insulin sensitivity is improved and mediated via modification of post-receptor signaling in the insulin pathway. A protein, adenosine 5'-monophosphate protein kinase, has been identified as a possible target of Metformin. [29, 30]

Patients started on Biguanides had a lower myocardial infarction risk (of 39%) than a patient on conventional therapy.1 the mechanism of the cardioprotective effects is still unclear. Side effects can include lactic acidosis. Metformin increases lactate production in the splanchnic bed and portal venous system due to a reduction in the activity of pyrovate dehydrogenase enzyme, thereby shifting the metabolism towards the anaerobic spectrum. However, the incidence of Metformin-induced lactic acidosis is extremely rare, with only 0.03 cases per 1000 patient-years

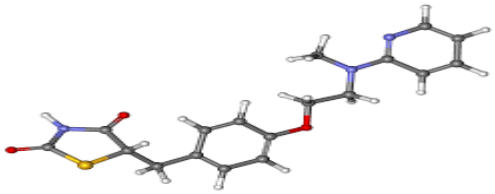
The mainstay of action of this magnificence of drug may be attributed to its hepatic effects. Hepatic sensitivity to insulin is multiplied, thereby lowering gluconeogenesis in addition to glycogenolysis, which contributes to the submit-prandial plasma glucose-reducing effects. Skeletal muscle and adiposities undergo up-law of the insulin-touchy GLUT-4 and GLUT-1 transporters to the cell membranes, thereby growing glucose uptake. [31] Glucose metabolism in the splanchnic mattress also increases. Similarly, metabolic outcomes include suppression of fatty acid oxidation in addition to triglyceride reduction. [31, 32]

Metformin is fast absorbed and completely removed inside the urine via tubular secretion. Consequently its miles prudent to keep away from this drug in sufferers with impaired renal characteristics. Metformin needs to be discontinued prior to contrast studies, e.g. angiographic evaluations because it has been implicated in the development of comparison-precipitated nephropathy. The iodinated contrast media compete with Metformin for tubular secretion, and caution is important if the management of competing substances is needed. In view that Metformin isn't bound to plasma proteins and isn't always metabolized; it no longer intervenes with co-administered pills. In patients with the everyday renal feature, the plasma t½ is 2 - 5 hours, with 90% of the dosage eliminated within 12 hours. Biguanides are generally taken into consideration as the medication of choice in obese Category 2 diabetics. Metformin can be used in aggregate with another magnificence of oral antidiabetic drug or with insulin. Metformin is likewise used within the treatment of polycystic ovarian syndrome (PCOS) to enhance insulin sensitivity and decrease circulating androgen degrees. It also improves ovulation and menstrual cyclicity. America's meals and Drug management nevertheless considers this an unlicensed indication of this drug within the absence of diabetes. The American association of medical Endocrinologists recommends that Metformin be considered because the initial intervention in maximum women with PCOS, particularly folks who are obese and obese. [33] Using Metformin for gestational diabetes appears to be safe, as indicated by the lately published MiG observation. [34]

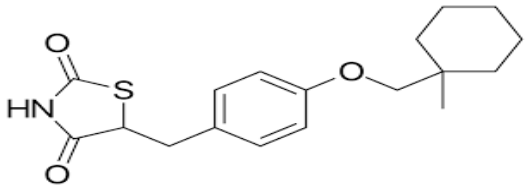
Contraindications include the presence of underlying impairment of renal function, conditions predisposing to hypoxia or reduced perfusion because of the increased risk of lactic acidosis, liver disease, and alcoholabuse and, a history of a previous episode of lactic acidosis. Contraindications include the presence of underlying impairment of renal function, conditions predisposing to hypoxia or reduced perfusion because of the improved danger of lactic acidosis, liver disorder, alcohol abuse, and a history of a previous episode of lactic acidosis reported in the literature. Abdominal discomfort and diarrhea are the most frequent side effects. Vitamin $B_{12}$ deficiencyowing to decreased GIT absorption cans occur. [35]

**Thiazolidinedione ('Pioglitazone, Rosiglitazone, Ciglitazone, Troglitazone'):**

**'Pioglitazone'**
**(RS)-5-(4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl)thiazolidine-2,4-dione**



**'Rosiglitazone'**
**(RS)-5-[4-(2-[methyl(pyridin-2-yl)amino]ethoxy)benzyl]thiazolidine-2,4-dione**




**'Ciglitazone'**
**'5-[4-(1-methylcyclohexylmethoxy) benzyl]-thiazolidine-2,4-dione'**

**'Troglitazone'**
**(RS)-5-(4-[(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)methoxy]benzyl)thiazolidine-2,4-dione**

**Fig 06: Structure and chemical name of Thiazolidinedione.**

With the introduction of this new class of drugs in 1997, the world has watched the peroxisome proliferator -activated receptor (PPAR) - η agonists with anticipation. The net effect of these drugs results from the stimulation of a nuclear PPAR-η that regulates the transcription of genes culminating in an increase in insulin sensitivity. Troglitazone, the forerunner drug, was withdrawn in 2000 following reports of fatal hepatotoxicity, and the future of Rosiglitazone currently hangs in the balance, owing to a possible increased risk of myocardial infarction and cardiovascular-related deaths. [36]

Thiazolidinedione (TZDs) mediate their function through binding to the PPAR- η receptor that is expressed predominantly in adipocytes (Fig. 2). It is expressed to a lesser extent in muscle and liver tissue. The Binding of the PPAR receptor in turn mediates binding to the retinoic-X receptor (RXR-receptor). This heterodimer then binds to a nuclear response element which then switches on gene transcription. Many of the genes that are activated play a central role in carbohydrate and lipid metabolism. TZDs, like Metformin, require the presence of insulin to mediate a blood glucose-lowering effect. Interestingly, thiazolidinedione also suppresses the expression of TNF-α by adipocytes. The pharmacokinetics of these drugs indicates that both Rosiglitazone and Pioglitazone are rapidly absorbed after a meal, reaching peak concentrations within 1 - 2 hours. Both drugs undergo hepatic metabolism, with Rosiglitazone excreted mainly in urine and Pioglitazone in bile. Although Rosiglitazone and Pioglitazone are metabolized by CYP 2C8 and CYP 3A4 respectively, no major drug interactions have been reported. This class of drug can be used as monotherapy in obese as well as non-obese patients who have failed other conservative measures. TZDs can be used in combination with Metformin and sulphonylureas their use is not recommended in this condition, since these drugs display gene activity that may be harmful in early pregnancy.

Another complication related to the use of this class of drug is that of TZD-induced low-formation osteoporosis. Already in 2006, evidence of increased fracture risk with Rosiglitazone emerged as the data of the ADOPT trial were published.[42] these trial data reported an increased fracture risk in women but not in men. Significant bone loss with an increased fracture risk only became the use in aggregate with insulin is illegitimate in Europe because of the increased risk of weight gain inside the form of adipogenesis and fluid retention. The usage of TZDs has been contraindicated in acute liver ailment thanks to the increased hazard of hepatotoxicity. Seeing that they lower hepatic glucose output, the priority exists that they may probably aggravate hypoglycemia.

The outcomes of glitazones on cardiovascular morbidity and mortality remain topical trouble. It seems, from the literature, that pioglitazone especially has a greater favorable effect on important cardiovascular consequences. The Proactive take look confirmed a sizable discount of sixteen% inside the major secondary endpoints of all-reason mortality.[37] is a far concept that the beneficial results of Glitazones expand beyond their Influence on glycaemic control through so-called pleiotropic effects.

Ciglitazone (INN) is a thiazolidinedione. Developed by Takeda Pharmaceuticals in the early 1980s, it is considered the prototypical compound for the thiazolidinedione class.

Ciglitazone become never been used as a remedy, but it sparked interest in the results of thiazolidinedione. Several analogs have later developed, a number of which—inclusive of Troglitazone—made it to the market.

Ciglitazone drastically decreases VEGF manufacturing by way of the use of human granulosa cells in vitro take a look at and can doubtlessly be applied in ovarian hyperstimulation syndrome. Ciglitazone is a first-rate and selective PPARγ ligand. It binds to the PPARγ ligand-binding area with an EC50 of three. Zero μM. Ciglitazone is active in vivo as an anti-hyperglycemic agent in the ob/ob murine version. [6] Inhibits HUVEC differentiation and angiogenesis and also stimulates adipogenesis and reduces osteoblastogenesis in human mesenchymal stem cells.

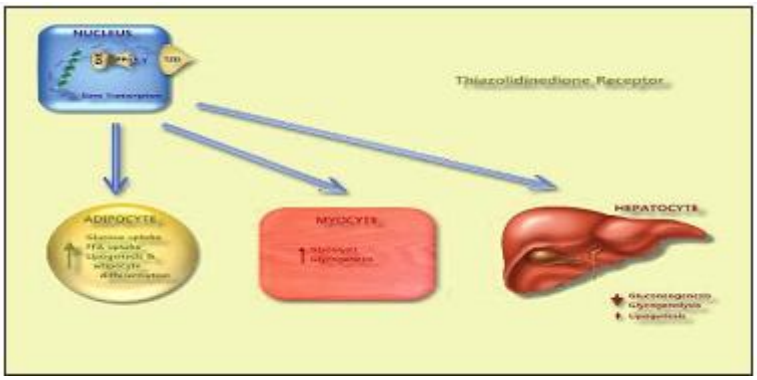
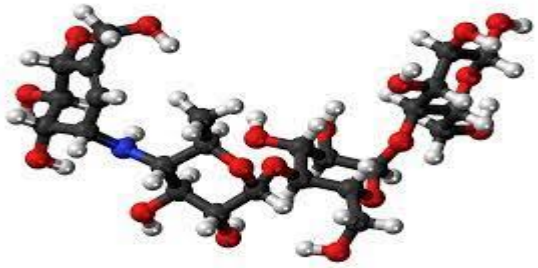



**Fig 07: The PRAR-η receptor.**

Those consist of an increase in coronary float reserve, a lower intimate media thickness, and development of endothelial features as well as a decrease in inflammatory and seasoned-coagulant biomarkers.[38, 39] the use of TZDs in patients with new York coronary heart affiliation (NYHA) magnificence III or IV coronary heart failure isn't always encouraged in view of the aspect consequences of fluid retention and weight benefit. The Pathophysiology of TZD-related fluid retention includes several ability mechanisms which include expanded vascular permeability, decreased urinary sodium excretion, elevated sympathetic tone, and changed interstitial ion transport. It has also been postulated that TZDs can also surely unmask previously undiagnosed cardiac dysfunction due to their results on salt and water retention. [40] The initial dose should be very low in sufferers who've danger factors for heart failure. The concurrent use of those capsules in combination with insulin is not encouraged as weight benefits can be aggravated. [41] Protection of the glitazones in pregnant and lactation has not yet been installed. In some research, TZDs have demonstrated a useful effect on ovulation in patients with PCOS. Following this trial, the producers of Pioglitazone reviewed their scientific trial databases and, in 2007, pronounced an increase of fracture risk in females who dealt with Pioglitazone, but not in guys. It become additionally said that the fractures came about mainly inside the distal upper limb or distal lower limb.[42, 43] The TZD impact on bone appears to be an inhibition of osteoblast differentiation, with a resultant bad effect on cortical bone formation without an exchange in bone resorption. A boom in marrow adiposity accompanies bone loss because of the Rosiglitazone remedy. It appears that activation of PPAR- η will increase the allocation of stem cells Inside the route of adipocytes on the rate of osteoblast [44] there aren't any studies on treatments that could save you bone loss precipitated through TZDs. [45] treatments that boom bone formation is currently restricted to parathyroid hormone (PTH) and strontium alienate, and will potentially be used to target TZD-brought-on osteoporosis. These tablets have been proven to correctly decrease the HbA1C by way of ±zero.5 - 1.5%. Aspect results that can be commonly skilled encompass weight advantage (around 1-4 kg over 6 - one year), oedema with worsening cardiac failure, liver toxicity, and anemia (most probably because of haemodilution). [46]

**Glucosidase inhibitors (Acarbose):**

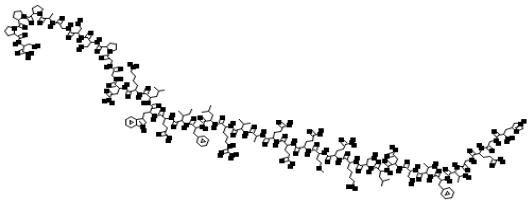


**'Acarbose'**
**Dideoxy-four-[four,5,6-trihydroxy-three-(hydroxymethyl)cyclohex-2-en-1-yl C7 cyclitol moiety [called valienol (or valienamine)]**

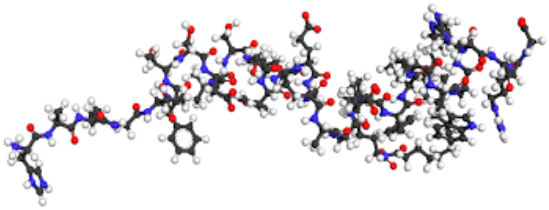
**Fig 08: Structure and chemical name of Glucosidase inhibitors.**

Acarbose turned into the primary glucosidase inhibitor and was introduced to the market in the early 1990s. This magnificence of the drug has the advantage of decreasing postprandial hyperglycemia without associated weight gain. Its usage is at gift hampered with the aid of unfortunate gastrointestinal side consequences in spite of an awesome safety document. The α-glucosidase inhibitors inhibit the activity of the glucosidase enzymes which might be present inside the brush border of enterocytes within the intestinal villi. Disaccharide and oligosaccharide cleavage is prevented with a net decrease in intestinal carbohydrate absorption. Typical, α -glucosidase inhibitors reduce postprandial insulin concentrations via the attenuated rise in postprandial glucose levels much less than 2% of the drug is absorbed. It's far broken down by means of intestinal amylases and positive intestinal microorganisms. Some degradation products are taken up and subsequently eliminated within the urine. The drug needs to be desirous about the primary chewing of meals delays gastric emptying reduces food consumption and allows weight reduction. This drug is ideal for the initiation of pharmacotherapy in category 2 diabetic sufferers. The stop-NIDDM trial showed that acarbose may be applied in the prevention of category 2 diabetes by using delaying development from an impaired fasting glucose kingdom to overt category 2 diabetes. [47, 48] Combination cures with another antidiabetic agent are possible. Using those tablets is contraindicated in pregnancy and breastfeeding. Efficacy measures show that postprandial glucose levels may be lowered by means of 1 - 4 mmol/l. A median decrease in HbA1C of 0.5 - 1.0% can be predicted. Side outcomes consist of flatulence, stomach discomfort, and diarrhea, but tolerance to the aspect effects fast develops. Hypoglycemia can occur most effectively if used together with sulphonylureas or insulin.

**New drug modalities:**
**Incretins ('Exendin-4, Liraglutide, Vildagliptin, Sitagliptin, Alogliptin, Teneligliptin, Saxagliptin'):**



**'Exendin-4'**



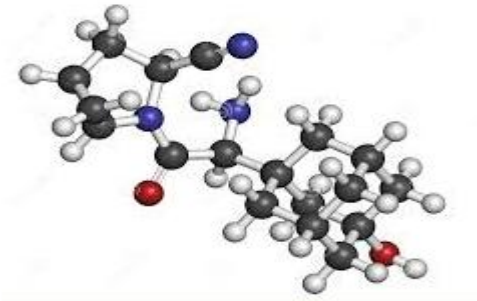
**'Liraglutide'**

**'Vildagliptin'**

**'Sitagliptin'**

**'Alogliptin'**
**2-({6-[(3R)-3-Aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl}methyl)benzonitrile**

**'Teneligliptin'**
**[(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)-1-piperazinyl]-2-pyrrolidinyl]-3-thiazolidinyl-methanone, hydrobromide hydrate**



**'Saxagliptin'**
**(1S,3S,5S)-2-[(2S)-2-amino-2-[(5S,7R)-3-hydroxy-1-adamantyl]acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile**

**Fig 09: Structure and chemical name of New drug modalities- Incretins.**

The small intestine secretes glucagon-like peptide-1 (GLP-1) as well as glucose-dependent insulin tropic polypeptide (GIP, previously called a gastric inhibitory peptide) in response to food intake. These hormones stimulate insulin secretion, insulin gene expression, and pancreatic beta-cell growth. Furthermore, they mediate the incretin effect which augments insulin secretion following oral administration of glucose. The GLP-1 molecule is subject to rapid degradation by the DPP-IV (dipeptidyl peptidase) enzyme.
Patients with Category 2 diabetes have greatly impaired or absent incretin-mediated insulin secretion due to a decrease in the level of GLP-1 which leads to a decrease in the glucose-dependent secretion of insulin by the pancreatic beta-cells.[49, 50] Several therapeutic strategies are currently undergoing clinical trials, namely:

- Enzyme-resistant GLP-1 analogues (exendin-4)
- Albumin-bound GLP-1 derivatives (liraglutide)
- DPP-IV enzyme inhibitors (Vildagliptin, Sitagliptin).

**'Exendin-4 (Exenatide)':**

This molecule was originally isolated from the venom of the Gila monster (Heloderma lizard species), and has a synthetic version (Exenatide). The synthetic 39-amino acid peptide sequence overlaps with that of GLP-1, but has a longer half-life than native GLP-

1. This 'incretin mimic' improves glycaemic control mainly by stimulating glucose-dependent insulin secretion and suppressing postprandial glucagon secretion.
2. It is given as a twice-daily subcutaneous injection and can decrease HbA1C levels by a further 1% if given in combination with other drugs. Once-daily injections did not achieve satisfactory control in clinical trials. [51]

**'Liraglutide':**

This drug is currently in phase III of clinical development. The results look extremely promising. In June 2007, a 26-week study was conducted in which liraglutide was compared with insulin-glargine. This formed part of the more significant liraglutide effect, and action in diabetes (LEAD) program. At the end of the 26 weeks, the liraglutide group showed that >50% of patients reached the $HbA_{1C}$ goal of <7% as well as an average weight loss of 3.5 kg. This drug, given as a once-daily subcutaneous injection, has a plasma half-life of 12 hours. [52]

**'Vildagliptin':**

This drug is taken in oral form at a once-daily dosage. Inhibition of dipeptidyl peptidase-IV (DDP-IV) stimulates insulin secretion in a glucose-dependent fashion, minimizing possible hypoglycemic side effects. Inhibition of DDP-IV is dose-dependent. Recent data suggest restorative effects on pancreatic islet cells, thereby fuelling the hope that the DDP-IV inhibitors could potentially slow or reverse the course of beta-cell failure. [53-55]

**'Sitagliptin':**

This drug is also a DDP-IV inhibitor and can be used as monotherapy in Category 2 diabetes or in combination with Metformin, the SUs, or the TZDs if the existing regimen no longer provides adequate glycaemic control. It has not yet been studied in combination with insulin. Sitagliptin is taken orally and has been shown to reduce HbA1C levels by 0.6 - 1%.

**'Alogliptin':**

After eating a sensible diet and exercising frequently, people who nevertheless have high blood sugar are prescribed the medication "Alogliptin." It works by increasing the amount of insulin that your body produces. The hormone that regulates blood sugar levels is insulin. It is advisable to obtain an Alogliptin with a prescription.

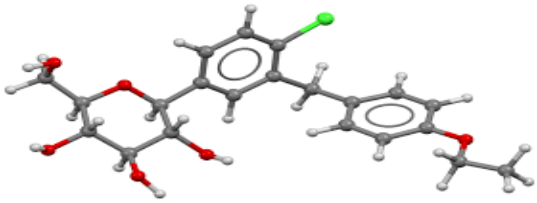
**'Teneligliptin':**

Teneligliptin is a recently created oral dipeptidyl peptidase 4 inhibitor that is used to treat category 2 diabetes mellitus (T2DM) in adults together with a healthy diet and exercise.

**'Saxagliptin':**

Saxagliptin: Saxagliptin is used to treat high blood sugar (glucose) levels in people with category 2 diabetes when they follow the correct diet and exercise regimen. Saxagliptin controls blood sugar levels by altering the

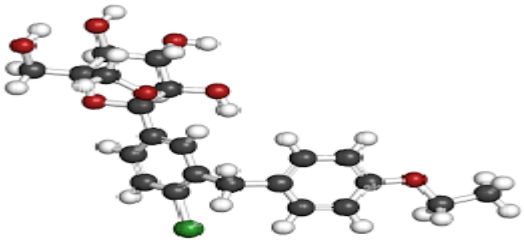
**SGLT-2 inhibitors – 'Dapagliflozin, Canagliflozin, Empagliflozin, and Ertugliflozin'**.



**'Dapagliflozin'**
**C-glycosyl contains beta-D-glucose and has a four-chloro-three-(four-ethoxy benzyl)phenyl group in place of the anomeric hydroxy group**

**'Canagliflozin'**
**Thiophene family member and organofluorine chemical, the C-glycosyl compound.**

**'Empagliflozin'**
**Beta-glucosyl residue with a four-chloro-three-[(3S)-tetrahydrofuran-three-yloxy] benzyl phenyl group at the anomeric center makes up the C-glycosyl molecule.**



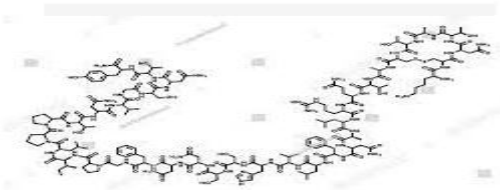
**'Ertugliflozin'**
**(1S,2S,3S,4R,5S) -5-(4-chloro (3-(4-ethoxybenzyl) phenyl) -1-(hydroxymethyl) -6, 8-dioxabicyclo**

**Fig 10: Structure and chemical name of SGLT-2 inhibitors.**

In individuals with category 2 diabetes, the use of SGLT2 inhibitors, a class of prescription medications, along with dietary restrictions and exercise programmes, may be allowed by the FDA. The SGLT2 inhibitor class of medications consists of Dapagliflozin, Canagliflozin, Empagliflozin, and Ertugliflozin.

The FDA has approved the use of Dapagliflozin, Canagliflozin, Empagliflozin, and Ertugliflozin for treating category 2 diabetes mellitus (DM) in individual patients in order to enhance blood sugar control in conjunction with diet and exercise. The four retailers all work to lower the renal threshold for glucose (RTG), increase urine glucose excretion, and inhibit sodium-glucose transport protein 2 (SGLT2) proteins expressed inside the renal proximal convoluted tubules. This curiosity will emphasize the mechanism of motion, the profile of adverse events, and other crucial

**Amylin analog ('Pramlintide'):**



**'Pramlintide'**
**L-lysyl-L-cysteinyl-L-asparagyl-L-threonyl-L-alanyl-L-threonyl-L-glutaminyl-L-arginyl-L-leucyl-L-alanyl-L-phenylalanyl-L-leucyl-L-valyl-L-histidyl-L-s -disulfide**

**Fig 11: Structure and chemical name of Amylin analog.**

The pancreatic beta-cells release human Amylin, a 37-amino acid glucoregulatory peptide, along with insulin. A synthetic derivative of Pramlintide works by delaying stomach emptying and boosting satiety. It lowers postprandial glucose levels and lowers the reintroduction of glucose into the bloodstream. Subcutaneous injections of Pramlintide are given right before meals. The peptide is cleared by the kidneys and has a half-life of 50 minutes. It is well tolerated and has no risk of causing hypoglycemia. [56, 57]

**RESULT AND DISCUSSION:**

The presented study's recent literature review of oral antidiabetic pills their chemical nature, structure for Category 2 diabetes mellitus (DM) is a disorder this is putting a growing burden on health carrier delivery internationally. Therefore, it has to turn out to be more and more crucial that physicians who deal with such patients have an excellent understanding of antidiabetic capsules which might be currently to be had or will come onto the marketplace.

**CONCLUSION:**

The recent challenge of treating oral antidiabetic pills for category 2 DM grows by the day as the number of patients' increases. Therefore, a good understanding of the available treatment modalities is of great value. As the pathogenesis of diabetes becomes clearer, exciting new targets for drug therapy will be identified, which provide physicians with more 'fire power' and treatment options in the fight against this disease.

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**Disclosure of conflict of interest:**

The authors hereby declare that there is no conflict of interest.

**REFERENCES:**

1. UK Prospective Diabetes Study Group: Intensive blood glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with Category 2 diabetes (UKPDS 33). Lancet 1998; 52: 837-853.
2. American Diabetes Association; European Association for the Study of Diabetes; International Federation of Clinical Chemistry and Laboratory; International Diabetes Federation Medicine. Consensus statement on the worldwide standardization of the HbA1c measurement. Diabetologia 2007; 50(10): 2042-2043.
3. American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for the management of diabetes mellitus. Endo Pract 2007; 13(suppl 1): 1-68.
4. Krentz A, Bailey C. Oral antidiabetic drugs – current role in Category 2 diabetes mellitus. *Drugs* 2005; 65(3): 385-411. Aguilar-Bryan L, Nichols CG, Wechsler SW, *et al*. cloning the β-cell high-affinity sulphonylureas receptor: a regulator of insulin secretion. Science 1995; 268: 423-426.
5. Pratley R, Weyer C. The role of impaired insulin secretion in the pathogenesis of type II diabetes mellitus. Diabetologia 2001; 44: 929-945.
6. Rydberg T, Jönsson A, Roder M, Melander A. Hypoglycemic activity of Glyburide (Glibenclamide) metabolites in humans. Diabetes Care 1994; 17: 1026-1030.
7. Shorr RI , Ray WA, Daugherty JR, *et al*. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. Arch Intern Med 1997; 157: 1681-1686.
8. Bressler R, Johnson DG. Pharmacological regulation of blood glucose levels in non- insulin dependent diabetes mellitus. Arch Intern Med 1997; 157: 836-848.

9. Jönsson A, Rydberg Y, Ekberg G, *et al*. Slow elimination of Glyburide in NIDDM subjects. Diabetes Care 1994; 17: 142-145.
10. Jönsson A, Rydberg T, Sterner G, Melander A. Pharmacokinetics of glibenclamide and its metabolites in diabetic patients with impaired renal function. Eur J Clin Pharmacol 1998; 53(6): 429-435.
11. Tessier D, Dawson K, Tétrault JP, Bravo G, Meneilly GS. Glibenclamide vs. gliclazide in Category 2 diabetes of the elderly. Diabet Med 1994; 11(10): 974-980.
12. Langtry HD, Balfour JA. Glimepiride. A review of its use in the management of type diabetes mellitus. Drugs 1998; 55(4): 563-584.
13. Nathan DM, Buse JB, Davidson MB, *et al*. Management of hyperglycaemia in Category 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: Update regarding the thiazolidinedione. Diabetologia 2008; 51(1): 8-11.
14. DeFronzo RA. Pharmacologic therapy for Category 2 diabetes mellitus. Ann Intern Med 2000; 133(1): 73-74.
15. Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes DR Jr. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. J Am Coll Cardiol 1999; 33(1): 119-124.
16. Simpson SH, Majumdar SR, Tsuyuki RT, Eurich DT, Johnson JA. Dose-response relation between sulfonylurea drugs and mortality in Category 2 diabetes mellitus: a population-based cohort study. CMAJ 2006; 174(2): 169-174.
17. Bell DS. Do sulfonylurea drugs increase the risk of cardiac events? CMAJ 2006; 174(2): 185-186.

Wilson SH, Kennedy FP, Garrat KN. Optimization of the management of patients with coronary artery disease and Category 2 diabetes mellitus. Drugs Aging 2001; 18: 325-333.

18. Inzucchi SE. Oral antihyperglycemic therapy for Category 2 diabetes: scientific review. JAMA 2002; 287(3): 360-372.
19. Monami M, Lamanna C, Marchionni N, Mannucci E. Comparison of different drugs as add-on treatments to Metformin in Category 2 diabetes: a meta-analysis. Diabetes Res Clin Pract 2008; 79(2): 196-203.

Chounta A, Zouridakis S, Ellinas C, *et al*. Cholestatic liver injury after glimepiride therapy. J Hepatol 2005; 42(6): 944-946.

20. Fuhlendorff J, Rorsman P, Kofod H, *et al*. Stimulation of insulin release by repaglinide and glibenclamide involves both common and distinct processes. Diabetes 1998; 47(3): 345-351.

Culy CR, Jarvis B. Repaglinide: a review of its therapeutic use in Category 2 diabetes mellitus. Drugs 2001; 61(11): 1625-1660.

21. Dunn C, Faulds D. Nateglinide. Drugs 2000; 60: 607-615.
22. Gribble FM, Manley SE, Levy JC. Randomized dose ranging study of the reduction of fasting and postprandial glucose in Category 2 diabetes by nateglinide (A-4166). Diabetes Care 2001; 24(7): 1221-1225.
23. Moses RG, Gomis R, Frandsen KB, Schlienger JL, Dedov I. Flexible meal-related dosing with repaglinide facilitates glycemic control in therapy-naive Category 2 diabetes. Diabetes Care 2001; 24(1): 11-15.
24. Moses R, Slobodniuk R, Boyages S, *et al*. Effect of repaglinide addition to Metformin monotherapy on glycemic control in patients with Category 2 diabetes. Diabetes Care 1999; 22(1): 119-124.
25. Hawley SA, Gadalla AE, Olsen GS, Hardie DG. The antidiabetic drug Metformin activates the AMP-activated protein kinase cascade via an adenine nucleotide- independent mechanism. Diabetes 2002; 51(8): 2420-2425.
26. Shaw RJ, Lamia KA, Vasquez D, *et al*. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of Metformin. Science 2005; 310(5754): 1642-1646.
27. Klip A, Leiter LA. Cellular mechanism of action of Metformin. Diabetes Care 1990; 13(6): 696-704.

Bailey CJ. Metformin. N Engl J Med 1996; 334(9): 574-579.

28. Nestler JE. Metformin for the treatment of polycystic ovarian syndrome. N Engl J Med 2008; 358(1): 47-54.
29. Roiwan JA, Hague WM, Gao W, Battin MR, Moore P. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med 2008; 358: 2003-2015.
30. Varughese GI, Tahrani AA, Scarpello JH. The long and short of Metformin-related vitamin B12 deficiency. Arch Intern Med 2007; 167(7): 729-730.
31. Diamond GA, Bax L, Kaul S. Uncertain effects of Rosiglitazone on the risk for myocardial infarction and cardiovascular death. Ann Intern Med 2007; 147(8): 578-581.
32. Dormandy JA, Charbonnel B, Eckland DJ, *et al*. Secondary prevention of macrovascular events in patients with Category 2 diabetes in the Proactive Study (Prospective pioglitazone Clinical Trial In macrovascular Events): a randomized control trial. *Lancet* 2005; 366: 1279-1289.
33. Stafylas PC, Sarafidis PA, Lasaridis AN. The controversial effects of thiazolidinedione on cardiovascular morbidity and mortality. *Int J Cardiol* 2008; 4 Aug. (Epub ahead of print).
34. Nesto RW, Bell D, Bonow, *et al*. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Circulation 2003; 108: 2941-2948.
35. Erdmann E, Wilcox RG. Weighing up the cardiovascular benefits of thiazolidinedione therapy: the impact of increased risk of heart failure. Eur Heart J 2008; 29(1): 12-20.
36. Patel C, Wyne KC, McGuire DK. Thiazolidinedione, peripheral oedema and congestive cardiac failure: What is the

evidence? Diab Vasc Dis Res 2005; 2(2): 61-66.
37. Kahn SE, Zinman B, Lachin JM. Rosiglitazone-associated fractures in type 2diabetes: an analysis from ADOPT. *Diabetes Care* 2008, 31(5): 845-851.
38. Takeda Pharmaceutical Co. Observation of an increased incidence of fractures in female patients who receive long-term treatment with ACTOS (pioglitazone HCL) tablets for Category 2 diabetes mellitus (Letter to Health Care Providers). http://www.fda. gov/medwatch/safety/2007/Actosmar0807.pdf. (Accesse 19 March 2007).
39. Sottile V, Seuwen K, Kneissel M. Enhanced marrow adipogenesis and bone resorption in estrogen-deprived rats treated with the PPAR-gamma agonist BRL40653 (Rosiglitazone). Calcified Tissue International 2004; 75(4): 329-337.
40. Reid DM, Hughes RA, Laan RFJM, *et al*. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized control trial. *J Bone Miner Res* 2000:15(6): 1006-1013.
41. Semple RK, Krishna K. PPAR-η and human metabolic disease. J Clin Invest 2006; 116: 581-586.
42. Chiasson JL. Prevention of Category 2 diabetes: fact or fiction? Expert Opin Pharmacother 2007; 8(18): 3147-3158.
43. Chiasson JL. Acarbose for the prevention of diabetes, hypertension, and cardiovascular disease in subjects with impaired glucose tolerance: the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) Trial. Endocr Pract 2006; 12 (suppl 1): 25-30.
44. Inzucchi SE, McGuire DK. New drugs for the treatment of diabetes: part II: Incretin- based therapy and beyond. Circulation 2008; 117(4): 574-584.
45. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in Category 2 diabetes. Lancet 2006; 368(9548): 1696-1705.
46. Todd JF, Bloom SR. Incretins and other peptides in the treatment of diabetes. Diabet Med 2007; 24: 223-232.
47. Vilsbøll T, Brock B, Perrild H, *et al*. Liraglutide, a once-daily human GLP-1 analogue, improves pancreatic B-cell function and arginine-stimulated insulin secretion during hyperglycaemia in patients with Category 2 diabetes mellitus. *Diabet Med* 2008; 25(2): 152-156.
48. Idris I, Donnely R. DDP-IV inhibitors: a major new class of oral anti-diabetic drug. Diabetes Obes Metab 2007; 9: 153-156
49. Rosenstock J, Fitchet M. Vildagliptin: clinical trials programme in monotherapy and combination therapy for Category 2 diabetes. Int J Clin Pract 2008; suppl 159: 15-23.
50. Ahrén B, Foley JE. The islet enhancer Vildagliptin: mechanisms of improved glucose metabolism. Int J Clin Pract 2008; suppl 159: 8-14.
51. Kruger DF, Gloster MA. Pramlintide for the treatment of insulin-requiring diabetes mellitus. Drugs 2004; 63(13): 1419-1432.
52. VanDeKoppel S, Choe HM, Sweet BV. Managed care perspective on three new agents for Category 2 diabetes. J Manag Care Pharm 2008; 14(4): 363-380.