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Thiazolidinediones-PPAR-γ Agonists; for the treatment of Type II Diabetes Mellitus

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Abstract

Current treatment for diabetes mellitus cannot treat Insulin insensitivity, resistance, and destruction of the beta cells of the pancreas. Thiazolidinediones are the class of the drugs that binds to the PPAR-γ receptors and make proper utilization of secreted insulin by reducing insensitivity. It also reduces the lipid crowd in the liver. Increases the storage capacity in the adipose tissues for the triglycerides and the free fatty acid. The TZDs are reported with some side effects like CHF due to water retention, bone fracture, gain of the body weight, and bladder cancers are discussed in the review.

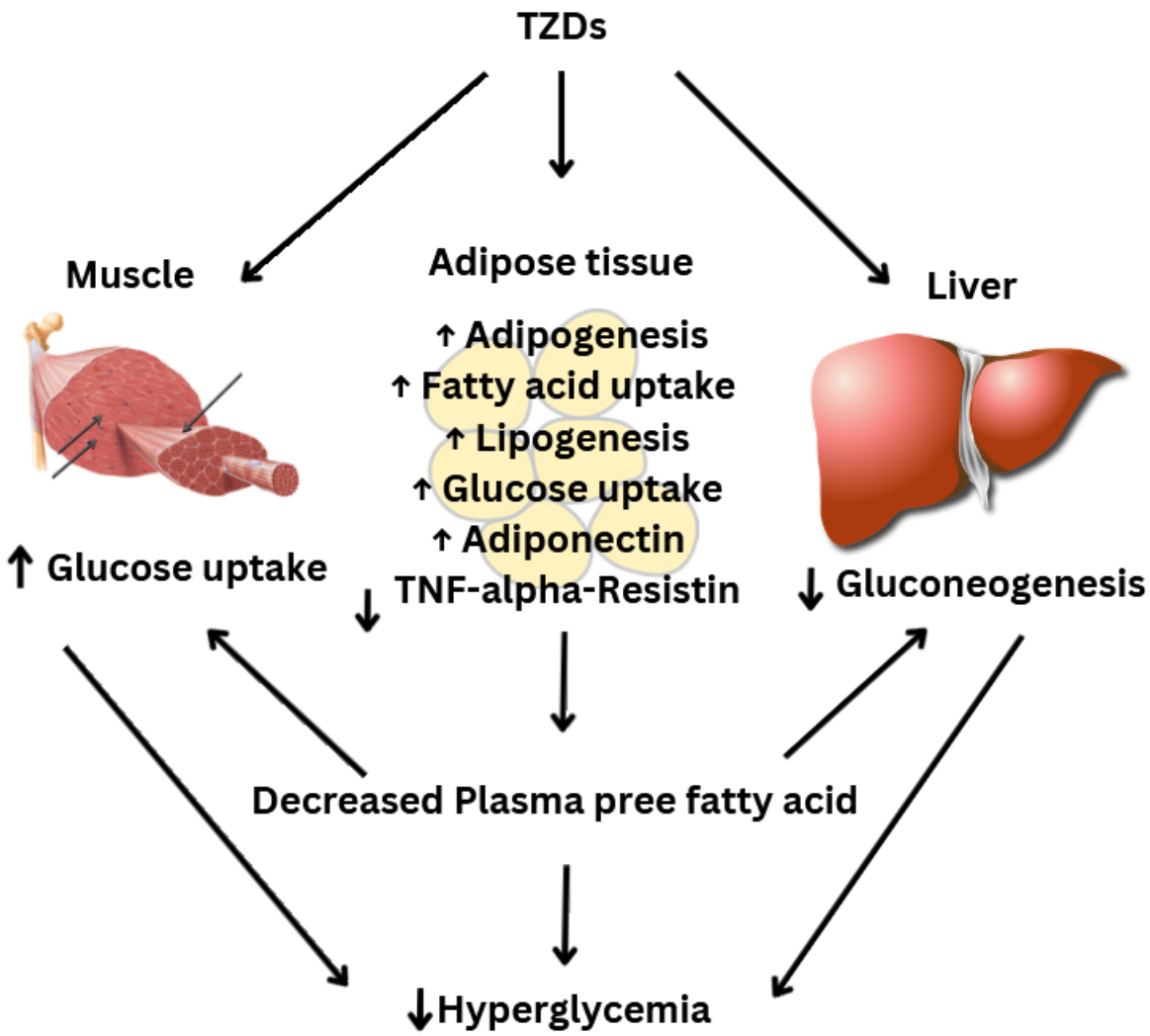


Fig. 01. Mechanism of action of TZDs [Graphical Abstract]

INTRODUCTION

Diabetes mellitus is a severe condition characterized by many complications associated with increased glucose level i.e., hyperglycemia. Patients with obesity, lipid disorder and arterial hypertension are more prone to the disease. Which leads to insulin resistance or insensitivity.[1]

Type 2 Diabetes mellitus is accompanied by reduced or no insulin secretion as well as loss of sensitivity of insulin to its receptors its advanced condition. Normally the glucose maintenance is carried out by Insulin stimulation, insulin stimulated glucose production suppression and hyperglycemic glucose production suppression and insulin mediated uptake of the glucose by other tissues.[2]

Many of the diabetic drugs helps to secrete insulin but, in some condition, the secreted insulin is not utilized properly especially in obese people and people with CVS diseases. Insulin insensitivity is seen. In that case Thiazolidinediones are the best choice of drug. Which improves proper utilization of glucose and insulin. Without further secretion of insulin. The risk of drug induced hypoglycemia is not seen here with this class of the drugs. Thiazolidinediones shortly TZDs are the ligands for PPAR-γ (peroxisome proliferators-activated receptor). [3], [4] TZDs are used in obese diabetic patients that improve insulin levels and glucose levels as well as proper lipid management by reducing the abnormalities in the lipid metabolism. [5] TZDs bind to PPAR-γ with the high affinity. The distribution of PPAR-γ receptor varies in number in different locations. PPAR-γ are present in large numbers in the adipose tissues. Which cause expansion of the cells present there increase storage and enhance uptake of the lipid and triglyceride from the liver. In liver the action of TZDs results in reduction of Free fatty acid intake and lipid crowd is reduced and hence insulin insensitivity is overcome. [6]

There are other class of drugs available for the treatment of diabetes type 2 like Sulfonylureas which increase the insulin secretion and might cause hypoglycemia and Meglitinides are also have similar action like that of

sulfonylureas, but action is seen for short duration of the time. Biguanides reduce hepatic glucose production and increase peripheral insulin sensitivity. But causes lactic acidosis. Alpha-glucosidase inhibitors inhibit the absorption of glucose from the GIT.[7], [8]

THIAZOLIDINEDIONES (TZD's)

Thiazolidinediones, also known as Glitazones are important group of drugs for the treatment of type 2 Diabetes Mellitus which is administered orally.[9] Type 2 Diabetes Mellitus is related with three underlying pathophysiological abnormalities like increased glucose production, reduced insulin secretion and insulin resistance in different tissues of skeletal muscle, liver and adipose tissues.[10] Thiazolidinediones are the selective agonists for the nuclear transcription factor PPARγ (Peroxisome-proliferator-activated-receptor) and TZDs are the choice of drug for the insulin resistance in patients suffering from type 2 diabetes mellitus.[11] TZDs have its significant role in lipid, protein and glucose metabolism. The primary function of TZDs is to maintain normal blood glucose levels in the patients Diabetes patients and it also slows the rate of beta cells destruction in the patients. [12][13][14] Rosiglitazone and Pioglitazones are the two thiazolidinediones are approved drugs by USFDA to manage type 2 diabetes mellitus. Thiazolidinedionesdespite having wide spectrum of action,[15]its clinical use is limited due tomany other complications like congestive heart failure, body weight gain, bone fractures and bladder cancer, fluid retention, anaemia etc.[16], [17][18]

STRUCTURE OF THIAZOLIDINEDIONES

Thiazolidinediones were introduced by the end of 20th century in late 1990s. It has molecular formula $C_3H_3NO_2S$ and 123-125 ^0C melting point.
Thiazolidinediones are heterocyclic in nature which are derivatives of thiazolidine ring for type 2 diabetes mellitus treatment.[19], [20]It consists of a five membered thiazole ring and non-aromatic analogue thiazolidine. It has carbonyl groups at 2 and 4 positions. Substitutions occur at 3 and 5 positions, any change at position 2 leads to greatest change in structure.[21]

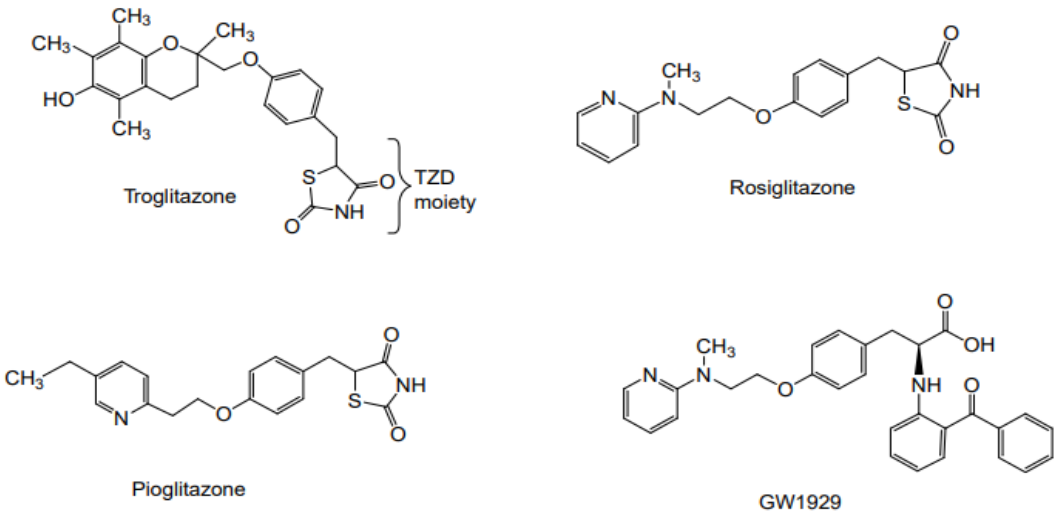


Fig.01. Structures of TZD's [1]

Troglitazone a TZD drug which was taken back due to its ability to cause hepatotoxicity and many other drugs like ciglitazone are not introduced into market, but they underwent preclinical studies. These are contraindicated in patients with heart disease and hepatic disorder. [18]

Peroxisome proliferator activated receptors.
The Peroxisome proliferator activated receptors (includes PPAR-α, PPAR-β/δ, PPAR-γ) play major role in metabolism process [22].The primary PPAR right now known as PPAR-α was found in 1990 and the other two isoforms are PPAR- β/δ and PPAR- γ.[22], [23]

Table 01: Peroxisome proliferator activated receptors location

Receptors	location	Roles
PPAR-alpha	liver, kidney, heart, and muscles. [24]	Glucose metabolism, neuroinflammation, oxidative stress, amyloidogenic pathway, neurotransmission process [25]
PPAR- beta/delta	Gastrointestinal tract, stomach, small and large intestine [24]	Promotes FA metabolism, supresses macrophage derived inflammation regulates body weight, lipid metabolism. [26], [27]
PPAR-gamma	Adipose tissues [24]	Gene expression of obesity, diabetes and cancer Lipogenesis and lipid synthesis. [26], [28]

PATHOGENESIS

Insulin resistance is also reason for type 2 diabetes mellitus and metabolic syndrome. Insulin resistance is characterized with reduced sensitivity of insulin to its receptor.[29] Insulin receptor contains two extracellular alpha-subunits and two transmembrane beta-subunits.[30]Insulin first binds to alpha subunit and that brings conformational change in beta subunit.[31]which results in activation of tyrosine kinase activity in beta-subunit.[31]Phosphorylation of tyrosine residues occurs which leads to phosphorylation in substrates of insulin receptor and they interact with Phosphatidyl-inositol 3-kinase which connects to glucose transporter-4[GLUT-4] which includes impact on glucose uptake.[31], [32].

The Insulin resistance cause hyperinsulinemia, which brings about reduced beta cell function and increased beta cell toxicity and leads to inflammation of the islets of Langerhans. These inflamed conditions lead to programmed cell death i.e., apoptosis of beta cells which in turn results in reduced insulin secretion.[33]–[35]

MECHANISM OF ACTION

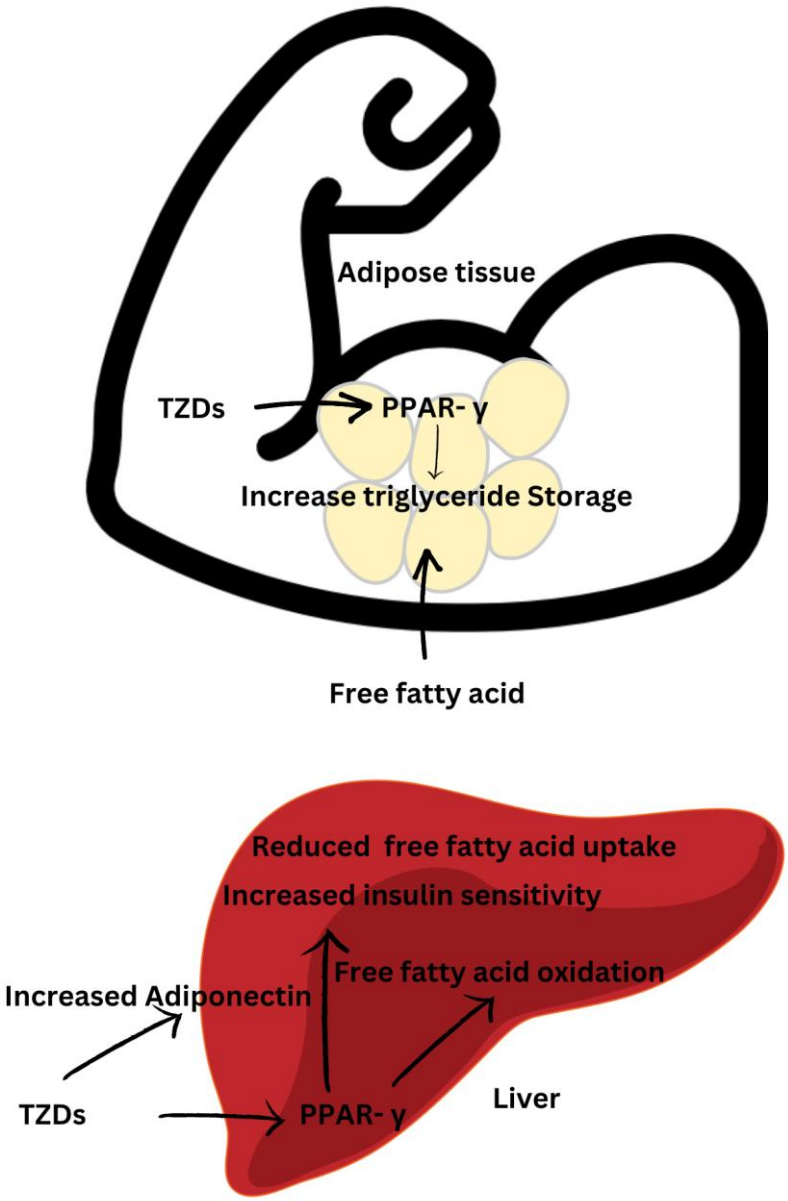
Thiazolidinediones are ligands that bind to PPAR gamma receptor which later forms heterodimers with the Retinoid-X-Receptors. These heterodimers bind to the responsive element of PPAR and brings about transcription. These formed elements have their role in homeostatic metabolism.[36]Thiazolidinediones are insulin sensitizers, they enhance insulin sensitivity in liver and adipose tissue.[37]PPAR- γ receptors are present more in adipose tissues and they actuate triglyceride synthesis and differentiation. [38]Thiazolidinediones act as agonist for Peroxisome Proliferator Activated Receptor gamma.[39]

TZDs enhance the transcription of genes that are present in adipose tissue and bind and activate peroxisome proliferator activated receptor- γ and they undergo conformational change and bind to nuclear elements as a heterodimer with retinoid X receptor (RXR) that undergo specific DNA sequence transcription [peroxisome proliferator response elements[8] the coactivators influence the set of transcribed genes by interacting with nuclear receptors which are involved in lipid and glucose metabolism. [40]–[50]

Adipogenesis is formation of adipocytes in the body that is increased by this PPAR gamma[36]. These TZDs bind to receptor and increase the insulin sensitivity throughout the body by increasing the lipid storing capacity in adipocytes by enhancing its storage and reduce lipotoxicity by transferring intracellular lipids/triglycerides from liver and muscle to adipocytes.[51]

Adiponectin's and adipokinin's are produced by TZDs which are having main role in enhancing insulin sensitivity in the body.[52], [53] TNF alpha and interleukin production is reduced and hence the inflammation of beta cells due to hyperinsulinemia is reduced. [54]

Fig 02: TZD's MOA in liver and adipose tissues. [55]



TZDs are suspected to cause CHF due to water retention, and bone fracture, Weight gain and bladder cancer.

Risk associated with CHF.

Diabetes is a chronic, worsening disease associated with many complications, one such complication is cardiovascular disease (CVD)which is the Major cause of death in the patients[56].The enema or the CHF associated with the use of thiazolidinedione derivatives suggest that an increase in the plasma volume is the main cause for the heart disease to occur, few studies have been reported that TZDs have effect on cardiac function and structure. A study show that upon long term administration of the troglitazone at high doses which is a derivative of TZDs has an effect of increase in left ventricular mass which leads to volume expansion[57].But the clinical trial studies of troglitazone however did not show any significant effect of left ventricular mass[58].

Other studies which includes the use of rosiglitazone and glyburide an echocardiogram was patient before and after to check the changes in left ventricular mass index, end diastolic volume, ejection fraction. Neither a drug has produced decrease in left ventricular ejection or increase in the left ventricular mass index, but both the drugs have shown the increase in left ventricular end diastolic volume this leading to fluid retention results in increased plasma volume which has effect on cardiac structure and function effects as recorded on echocardiography[59].The effect of rosiglitazone causes ischemia due to the increase of volume in left

ventricular has been studied through the experimental animal models[60].An another which included the drug pioglitazone in this it has been observed that there is an improved left ventricular remodelling and partially normalised systolic function of the heart in a mouse [61].Some of these cardioprotective activity of TZDs may be due to antioxidant, anti-inflammatory or glucometabolic properties of the drugs.
In a study it has shown that the patients hospitalized for heart failure and diabetes mellitus the use of antihyperglycemic agents was not recommended which may cause serious side effects like renal dysfunction, so thiazolidinedione are not recommended for a patient with advanced heart failure. The recognition of the potential hazards of fluid retention due to thiazolidinedione in patients with heart failure has increased over a period, the treatment of thiazolidinedione in case of heart failure should only be given when the benefits of the treatment are outweighed the potential risks, despite of all these thiazolidinedione exert a positive effect on cardiovascular risk factors with newly diagnosed diabetes patient.[62]

Risk associated with bone fracture.

The risk of bone mineral density (BMD) and bone fractures has been the price for the treatment of diabetes mellitus type 2[63]. A number of publications suggest that there is a negative impact on the bones on the the usage of thiazolidinedione derivatives however the manufacturer of these TZDs have issued a letter to the health care providers regarding the effect of bone fractures in women population.in December 2006 when the studies were conducted in women of T2DM it has been reported that there is a higher risk for women taking the rosiglitazone than compared to the women taking the Metformin or Glyburide. Pioglitazone the other TZDs also reported the negative skeletal effects in women but not in men[64]. In a study conducted where Japanese T2DM patient with 161 men of age greater than 50 and 137 post-menopausal women and non DM- control (76 and 622, respectively) were examined by lateral spine radiography showed the increased risk factor of vertebral fractures with odds ratio of (OR=1.86,p=0.0.19) in women and (OR=4.73,p<0.001) in males were higher in T2DM patient compared to the controls.[65]
As the thiazolidinedione derivatives molecular Target PPAR- γ is, a family of nuclear receptor which has ability to regulate the gene transcription. PPAR- γ expression is particularly abundant in adipocytes where they differentiate and functionthis PPAR- γ is also expressed in skeletal tissue.so upon conducting the pre-clinical studies it has two pathways by which the bone fractures may occur.
(i) it inhibits bone formation by diverting mesenchymal stem cells from the osteogenic to the adipocytic lineage.
(ii) may increase bone reabsorption by stimulating the development of osteoclasts.[66]
There is also an indirect adverse effect upon stimulation of PPAR- γ in skeletal tissue which may modulate the circulating levels of hormones and cytokines known to influence the bone metabolism [67]. However, the association between the use of thiazolidinedione and bone fractures is not understood clearly, the study conducted between the use of sulphonyl urea and thiazolidinedione reported that the patients treated with thiazolidinedione was associated with 28% increased risk of bone fractures, between the two-thiazolidinedione derivatives pioglitazone and the rosiglitazone it has showed that the patients taking pioglitazone are strongly associated with fractures than rosiglitazone [68].

Risk associated with bladder cancer.

The use of thiazolidinedione increases the risk of bladder cancer in patients with T2DM[69].Several studies have reported that the PPAR- γ /TZD's decrease the IGF-1(insulin like growth factor -1) levels which reduces the growth of the cancer cells of pancreas, colon, liver and prostate, the other side of the studies have reported that they have potential effect on stimulating the bladder cancer[70].The increased dose and duration have increased the occurrence rates of the bladder cancer, with 30% risk of developing bladder cancer for patients on therapy for a period of 12-24 months, further 50% risk of developing bladder cancer of patients with therapy for 2 or more years [16], and 78% risk of developing bladder cancer in case of patients who are in therapy for 1.5-4 years[71].
There has been increased evidence which show that the TZDs show effect on bladder cancer and other complications. The TZDs, pioglitazone and rosiglitazone are synthetic ligands acting on PPAR- γ [72]. upon binding to PPAR- γ they active the process of adipogenesis, which is a process of converting the preadipocyte stem cell into fully matured adipocyte [73]. potentially PPAR- γ signalling in bladder cancer cells may provide the tumour environment that allow the process of de-novo synthesis for development of tumour cell, however the role of PPAR- γ in bladder cell is unknown [74]. The report studies carried out between the pioglitazone and rosiglitazone, the pioglitazone showed an increased risk, most studies didn't show the higher risk for rosiglitazone [75].

Combinational therapy

TZDs generally lead to increase weight gain. Studies have shown that Rosiglitazone of dose 4 mg leads to a mean weight gain of 1.9 kg over 52 weeks. Rosiglitazone of dose 8 mg leads to a 2.9 kg weight gain over the same period. When used in combination with a sulfonylurea, rosiglitazone leads a weight gain of 1.8 kg greater than sulfonylurea monotherapy. Even the combination therapy with metformin results in similar weight gain [76]

Insulin when given in monotherapy it led to weight gain of 1kg over a period of 6 months when they are given in combination with rosiglitazone of 4 mg leads 4.1 kg weight gain, rosiglitazone of 8 mg leads 5.4 kg weight gain also the TZDs when used in combination with oral agents, and in combination with insulin lead to increase the weight of the body [77].

Troglitazone was shown to lower triglyceride levels by 15-20% and increase HDL by 5-8%. Pioglitazone lowers triglycerides by 9% and increases HDL by 12-19% [78]. Lewin et al. demonstrated that statins are an effective and generally well tolerated treatment for hyperlipidaemia when used in combination with TZD therapy in patients with type 2 DM [79]. Another study compared the use of pioglitazone in combination with insulin-to-insulin monotherapy in patients with poorly controlled diabetes. The combination therapy was associated with significant improvements in HbA1c levels, as well as improvements in lipid profiles [80].

Combined treatment with thiazolidinedione and hydralazine causes re-expression of PPAR-γ, inhibits proliferation, and induces apoptosis in MDA-MB-231 cells. Especially they act on the breast cancer cells of the cell line MDA-MB-231[81]. From the experiment it has shown that a reduction of proliferation by thiazolidinediones at 1 h (from the start of tetrazolium reaction) [of 11% and 25%, with rosiglitazone, 10 or 20 ($P = 0{\cdot}0001$) μM, respectively; of 7% and 17%, with pioglitazone, 10 or 20 ($P = 0{\cdot}0125$) μM, respectively], and at 2 h [of 14% and 24%, with rosiglitazone, 10 ($P = 0{\cdot}0043$) or 20 ($P < 0{\cdot}0001$) μM, respectively; of 9% and 21%, with pioglitazone, 10 ($P = 0{\cdot}0397$) or 20 ($P = 0{\cdot}0001$) μM, respectively] was shown[80].

In patients who are unable to maintain the hba1c levels less than 7% on monotherapy a combination therapy is used where thiazolidinedione is combined with biguanide improves the insulin sensitivity and lowers the blood glucose through complementary pathways, and providing an additive effect of these compounds [82].The use of thiazolidinedione with sulphonyl urea decreases the hba1c by 1%.agressive use of the combination therapy provides the long term effect of glycaemic control n it's complications [83].in case a patient don't respond to combination therapy of 2 agents then a combination of thiazolidinedione biguanide and a sulphonyl urea can be used to improve the glycaemic control and reduce its complications [84].

Table 02: Different class of drugs for treatment of type II Diabetes Mellitus

Class of drug	MOA	Pharmacological effect
Sulfonylureas	ATP sensitive K^+ Channel blocked, depolarization causing calcium influx resulting in release of insulin.[85]	Stimulate insulin production[86] May lead to hypoglycaemic condition on overdosage[85]
Meglitinides (Repaglinide and Nateglinide)	Non -sulfonylureas acting like sulfonylureas. [87]	Stimulate insulin production[86]
Biguanides (Metformin)	Inhibit complex I and inhibit Oxygen consumption, thereby causing energy stress, increase in AMP/ATP ratio, and activation of AMP Kinase (AMPK)[88]	Reduce glucose formation and excretion of glucose from liver is reduced.[86]
Acarbose	Alpha glucosidase inhibitor, and hence slows down breakdown of carbohydrates.[89]	Reduce absorption of glucose from the GIT.[86]
TZDs	PPAR-gamma receptors agonists.[90]	Reduce insulin resistance in obese type 2 DM patients[86]

Major problem wit other class of drug is dose dependent hypoglycaemia, and another is insulin resistance. Though insulin in secreted using drugs it is of no use in insulin resistance. Combination therapy with TZDs can overcome this problem and show beneficial effect in treatment of type 2 Diabetes mellitus.[91]

CONCLUSION

The Type 2 Diabetes mellitus has become the lifestyle disease now a days. It involves reduced insulin secretion, Insulin insensitivity etc. There are several types of medications available for the treatment of the T2DM. among them TZDs are used to treat insulin resistance and insulin insensitivities in people with

diabetes mellitus with metabolic abnormalities. Though there exist certain side effects continues work is going on for optimising the safety of the drug. TZDs are the class of drug for the treatment of T2DM where many more research are yet to be done. Since this is the class of drugs which do not cause drug induced hypoglycaemia, which is very beneficial for the mankind.

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