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Recent Trends in Thiazolidinedione (TZDs) as Antidiabetic agents - A Review

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ABSTRACT:
Thiazolidinedione is also called glitazone.
Thiazolididione is an important class of insulin sensitizers used to treattype 2 diabetes mellitus (TZDM). These increase insulin sensitivity in peripheral tissues.
It is extensively metabolized in the liver and excreted in the feces, making it relatively safe for patients with impaired renal function. This report critically reviews TZDs, their history, chemistry, mechanism of action, recent advances, and future prospects.
2,4-thiazolidinediones are versatile scaffolds with unique features of hydrogen bond donor and hydrogen bond acceptor regions. This appears based on his 3rd position of 2,4-thiazolidinedione and his 5th position linker variation.

Graphical abstract :
The molecular target of these compounds is said to be the nuclear hormone receptor peroxisome proliferator-activated receptor Y (PPARY). Although PPARY is primarily expressed in adipose tissue, the key site for TZD-responsive glucose disposal is skeletal muscle.

Thiazolidinediones (TZDs) are the only current antibiotics whose efficacy is primarily based on increasing insulin sensitivity. However, despite their clear benefits in blood sugar control, this class of drugs has recently become more widely used due to concerns about side effects and adverse effects. TZDs were first described as an insulin sensitizers by the pharmaceutical company Takeda in 1980.

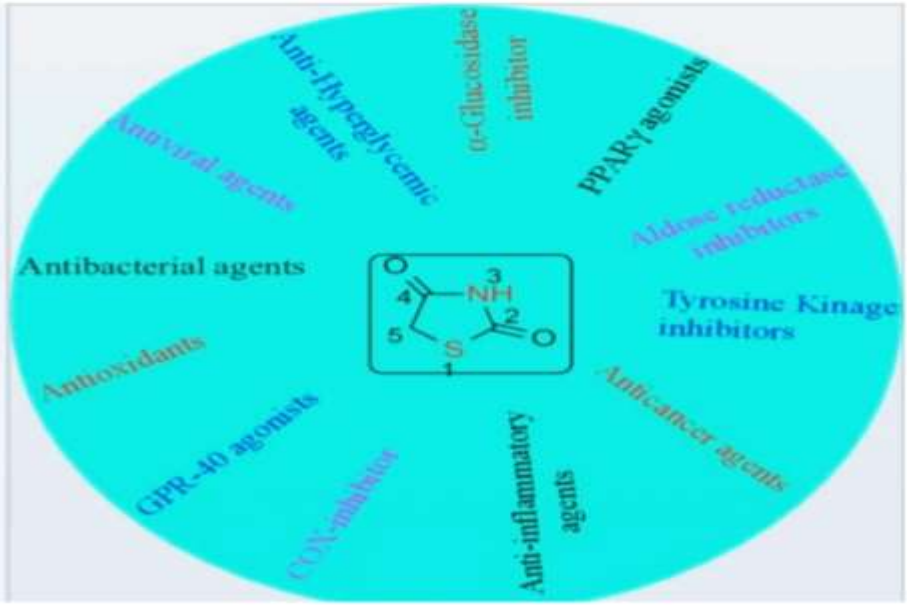

Fig .1Pharmacological Activity Of 2,4 Thiazolidinediones [TZDs].

TDZ is a potent insulin sensitizer that treats and prevents TZM. Tree TDS is FDA approved for diabetes, troglitazone (Rezulin), rosiglitazone (Avandia), and pioglitazone (Across).

Historical aspects of TZD:

In early 1975, the Japan-based Takeda Research Institute synthesized 71 clofibrate analogs and tested their hyperlipidemic activity in an effort

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to discover more potent fibrate hyperlipidemic drugs.Interestingly, some of these compounds showed hypoglycemic effects in diabetic mice. In 1982, through extensive structure-activity relationship studies, the first TZD, ciglitazone, was discovered to have promising lipid- and glucose-lowering effects in animal models.

Objective :

- ★ It acts on peroxisome proliferator-activated receptors (PPARY) to improve glucose and lipid metabolism.
- ★ GLUT-4 Improves insulin sensitivity in muscle and fat by increasing glucose transport. Examples: pioglitazone, rosiglitazone.
- ★ Positive effect on serum lipids. Lowers TG and increases HDL.
- ★ Troglitazone is associated with hepatitis.
- ★ We will discuss the possible side effects of thiazolidinediones.

Summary:

Thaizolidinedione is now generic and cheaper than treatments promoted by pharmaceutical companies. A better understanding of the side effects along with clear benefits for components of insulin resistance syndrome should facilitate the use of her TZDs in the treatment of patients with type 2 diabetes. Metformin is considered the first-line drug for most TZD patients due to its hypoglycemic effects, hypoglycemia, weight loss effects, good tolerability, and low cost.

Key words: PPAR-Y agonists, thiazolidinediones, type 2 diabetes, insulin resistance, CV outcomes, heart failure, fractures.

GIP receptor inflammation Hypertrophic adipocytes Thiazolidinedione PPARγ, Introduction

I. INTRODUCTION:

What is Diabetic ?

Also known as diabetes mellitus, diabetes mellitus. Diabetes is a "chronic disease" characterized by elevated blood sugar levels, known as hyperglycemia. Patients with two types of diabetes. One of these is type I, so-called insulin-dependent diabetes, and the other is type 2, so-called non-insulin-dependent diabetes. Type 2 diabetes is characterized by insulin resistance and hyperglycemia. Thiazolidinedione drugs (TZDs) are currently the only antibiotics whose efficacy is primarily based on increasing insulin sensitivity. However, there are concerns about side effects and side effects with this class of drugs. TZDs were first described as an insulin sensitizers by the pharmaceutical company Takeda Pharmaceutical in the early 1980s. PPARY is expressed at high levels in adipose tissue, where it functions as a master regulator of adipocyte differentiation, but at much lower levels in other tissues.

Diabetes mellitus,also known as diabetes.

Diabetes mellitus is a ' chronic condition ' that is characterized by increased blood glucose (sugar) level i.e called as (hyperglycemia).

TZD are potent insulin sensitizers which treat and prevent TZDM :

Three TZDs are approved by the FDA as troglitazone (Rezulin), rosiglitazone (Avandia), and pioglitazone (Cross) for diabetes. Troglitazone was introduced in 1997 but was withdrawn from the market in 2000 due to an increased risk of liver failure in fulminant hepatitis. Some studies suggest that the cause is hepatotoxic reactive metabolite of troglitazone. Rosiglitazone and pioglitazone were both approved by the FDA in 1999. Pioglitazone reduced progression to TZDM by 74% over 2.4 years. The main purpose of TZDs is to control hyperglycemia in T2DM patients by lowering fasting blood glucose levels to normal levels (HbA1c-type hemoglobin. . Rosiglitazone and pioglitazone both work similarly in improving blood sugar levels. Unfortunately, TZDs have not been emphasized in recent guidelines due to their questionable effects on heart failure and DM during pregnanc

- 22 million women between the ages of 20 and 39 have diabetes - 2010 data. -She is expected to increase by 20% in the next 10 years.
- 54 million women with IGT or prediabetes may develop GDM if they become pregnant.
- The prevalence of her GDM in India varies from 3.8 to 21% in different regions of the country, depending on the geographical location and the diagnostic method used.

-GDM is found to be more common in urban areas than in rural areas. Diagnostic microbial-derived biomarkers can provide insight into treatment response and serve as a means of learning about the side effects of antibiotics and other drugs. The hormonal balance of insulin and glycagon supports glucose homeostasis by controlling blood concentrations and triggering an increase in insulin-mediated signals to lower elevated glucose levels by increasing glucose uptake in skeletal muscle To do. Promotes utilization and storage in fat cells and kidneys, as well as the liver.

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When blood sugar levels drop, glycagon stimulates the production and release of glucose in the liver and increases lipolysis from adipose tissue. Traditional drugs used to treat diabetes include insulin and oral antidiabetic agents such as sulfonylureas, biguanides, thiazolidinediones, TZDs, and alpha-glycoside inhibitors. These activate nuclear peroxisome proliferator-activated receptor gamma (PPAR-gamma). This increases the transcription of various insulin-sensitivity genes, improves insulin action,

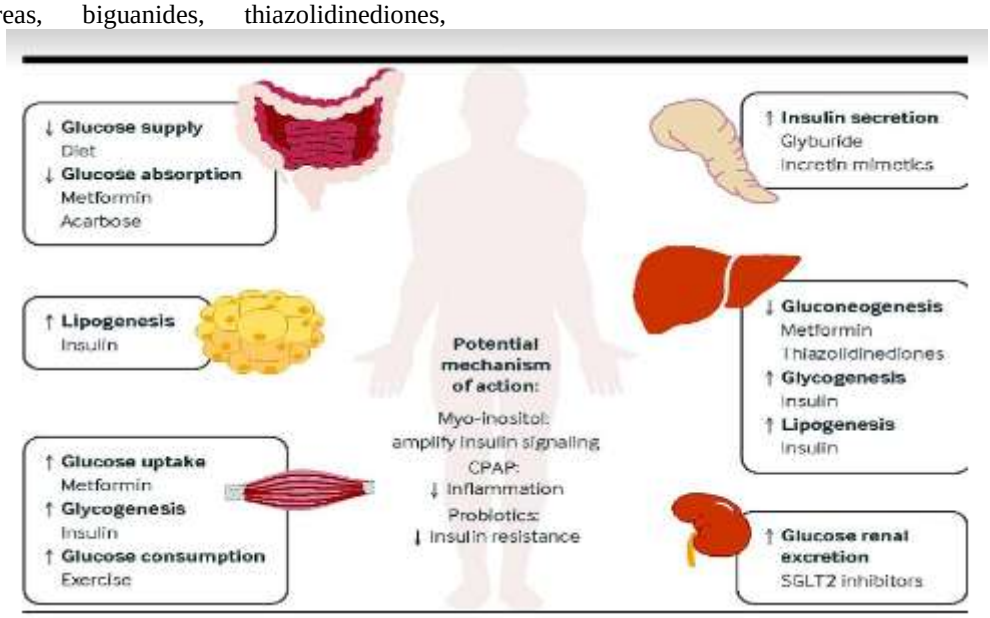

Fig .2 Novel therapies for the diabetes mellitus in pregnancy.

and lowers blood glucose concentrations. The TZDs currently in clinical use for the treatment of type 2 diabetes are rosiglitazone and pioglitazone. Troglitazone was withdrawn from the market due to hepatotoxicity. Other TZDs (such as ciglitazone) have undergone preclinical studies but have not been introduced into clinical use.

Mudalial and Henry consider TZDs to be antihyperglycemic agents (not hypoglycemic agents) because they do not cause severe hypoglycemia. An interesting fact is that even before PPARs became popular, thiazolidinedione (TZD) derivatives were reported to have the potential to treat diabetes.

Takeda Chemical Industries Ltd, Japan was the first to report Ciglitazone

SAR of Thaizolidinedione [TZDs]:

(5-[4-(1-methyl-cyclohexylmethoxy)benzyl]thiazolidine-2,4-dione) as an effective antidiabetic agent in the year 1983.

The hypoglycemic and hypolipidemic activities of the reported TZDs were tested. It was only after 1995 that their affinity for PPARγ was also tested.

Therefore, we have summarized thiazolidinediones as hypoglycemic agents along with their PPARγ activity wherever they are encountered/reported.

The classification of these drugs mainly focused on the side chain substitution pattern at the 5-position of his TZD.2,4-thiazolidinediones [TZDs] are a type of active

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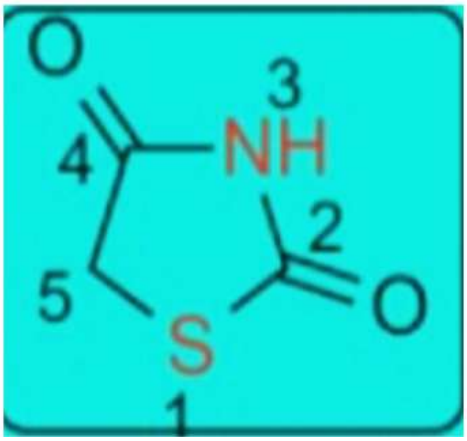

Fig .4 Therapeutic journey of 2,4 Thiazolidinediones as a versatile scaffold.

pharmacophore with a wide range of antidiabetic effects. They consist of a five-membered ring containing sulfur and nitrogen as heteroatoms, and "sulfur is a magical element." 1st and 3rd place in the ring, Two carbonyl groups each in the 2nd and 4th positions. Different substitutions occur at positions 3 and 5. Among this position, the ``number 5" is the most likely to be substituted. It brings about major changes in the characteristics of diabetes.

Advantages of thiazolidinediones:

- No hypoglycemia
- Target insulin resistance
- Use in renal insufficiency
- Preserve B - cell function
- Relatively inexpensive
- Once a day administration
- Reduce NASH [Non Alcoholic Steato Hepatitis]
- No dose adjustment for renal disease
- Durability of effect
- Only muscle and adipocyte insulin sensitizer

Disadvantage of thiazolidinediones:

- Bladder cancer
- Weight gain
- Edema
- Delayed / slow onset of action
- Hepatotoxicity
- Congestive Heart failure [CHF]
- Lack of long term safety data
- Osteoporosis
- Bone fractures
- Can not use in patients with HF
- Low to moderate cost

Physical properties of thiazolidinediones :

Solubility:

Thiazolidinedione exists as a white crystalline solid with a melting point 125 - 127 ° C stable when kept below 30° C.In terms of solubility , TZD is only sparing soluble in a variety of common organic solvents including water,MeoH ,EtoH, DMSO and Et2 O.

Molecular Formula : C3H3N02S .
Molecular weight: 117- 122 g/ mol
Melting point: 125 - 127 ° C
Boiling point : 178 - 179 ° C
IUPAC Name: 1 ,3 thiazolidinedione.
Synonym : 2,4 Thiazolidinediones.

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Mechanism of action of thiazolidinediones [TZDs] :

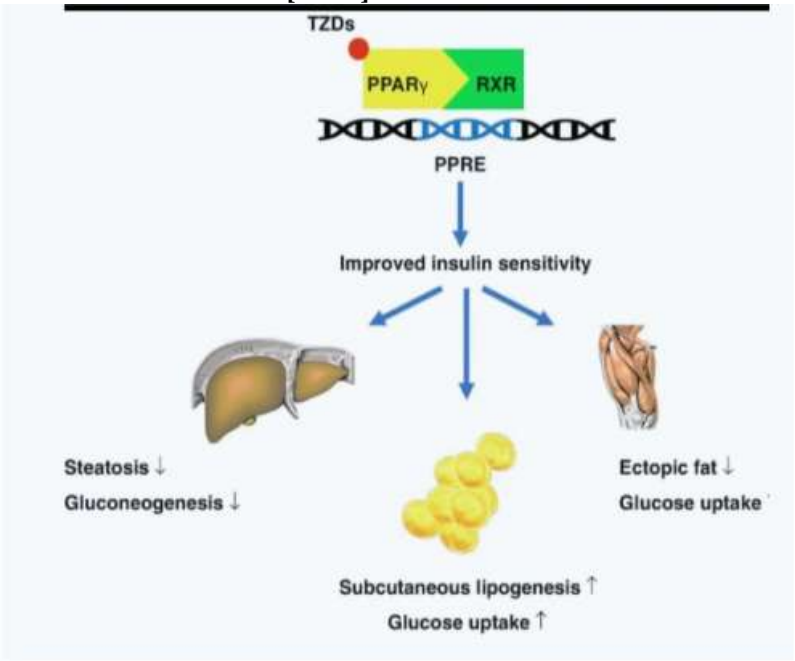

Fig.5 MOA Of Thiazolidinedione [TZDs]

- selective agonists for (PPAR-Y) peroxisome proliferator activated receptor (y).
- The receptors are complexed with retinoid x receptors and bind to DNA.this increase the transcription of insulin responsive genes involved in the control of glucose production transport and utilization.
- need insulin to be effective.

Actions of glitazones (TZDs):

Improves insulin sensitivity in muscle and adipose tissue by increasing glucose expression and decreasing hepatic gluconeogenesis.

It reduces insulin resistance in peripheral tissues, reduces hepatic glucose transporterproduction by increasing adnectin ablation, and reduces lipolysis and plasma fatty acid levels.

Increased adipocyte number and adipogenesis lead to increased PPAR-Y activity and adipocyte remodeling through induction of FGf21 expression.

Pioglitazone is a selective agonist of PPAR-Y, which is expressed in adipocytes and increases transcription of several insulin-responsive genes.

They prevent insulin resistance by increasing expression and translocation. The main effect is to improve peripheral insulin sensitivity.

Administration:

Thiazolidinediones (TZDs) are taken orally once daily with or without food.

Diabetic intranasal route:

- The intranasal route of administration is used for insulin administration in diabetic patients because of its advantages over parenteral routes of administration. Easy access to the nasal cavity allows patients to self-medicate for long-term treatment.
- Insulin administered intranasally can better control postprandial hypoglycemia. LFT values (liver function tests) and HbAIC values (hymoglobin AlC) should be monitored before starting treatment and periodically during treatment.
- The maximal hypoglycemic effects of TZDs are observed only after 6 weeks to 6 months, as changes in gene expression delay the onset of action. To treat type 2 diabetes, TZDs must be used in conjunction with lifestyle modifications and can also be used with biguanides, sulfonylureas, and insulin injections.

Dosage to treat TZDM:

Pioglitazone:

Initially 15 to 30 mg orally. (per os – means the drug is taken orally or orally). Once a day with a

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meal. With careful monitoring, the dose may be increased from 15 mg to 45 mg once daily. The maximum dose is 45mg.

Rosiglitazone:

Initially 4 mg orally. once a day. If response is insufficient after 8 to 12 weeks, the dose may be increased to 8 mg PO. Once daily or 4 mg twice daily.

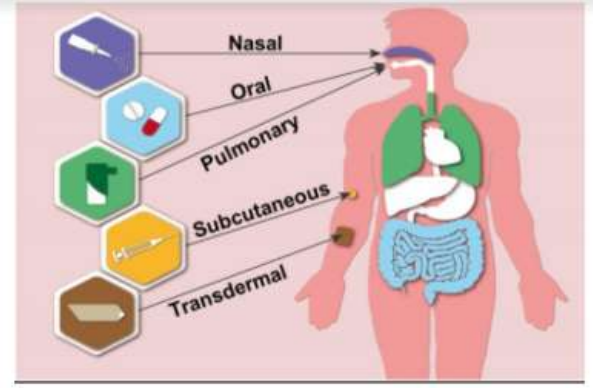

Fig .6 Various routes of administration of TZDs drug.

Adverse Effects :

Thiazolidinediones have some undesirable side effects, especially with long-term use. Consideration of the risk-benefit ratio requires discussion with patients and trial of alternative first-line drugs before using TZDs.

Hepatotoxicity:

The original His PPAR gamma activator, troglitazone, was withdrawn from the market primarily due to hepatotoxicity. However, the other drugs, rosiglitazone and pioglitazone, have little association with acute liver injury. Monitoring alanine aminotransferase levels initially and periodically for clinical signs of liver injury is recommended. Edema and heart failure:

TZDs have been shown to cause dose-dependent fluid retention in up to 20% of patients. Methods of fluid retention include his PPAR gamma receptors in the distal nephron and insulin-activated epithelial sodium channels in the collecting tubule. Activation of PPAR-gamma stimulates sodium reabsorption and acts at the same site as aldosterone.

Patients with pre-existing edema or receiving concurrent insulin therapy are at an increased risk of edema and should be started on the lowest available dose. In most patients, fluid retention responds to diuretics, such as thiazides or spironolactone, if the edema is mild, or to loop diuretics, if the edema is severe. Additionally, lower doses of 15 mg and 30 mg per day reduce the risk of edema and weight gain. There are reports that increased intravascular volume causes heart failure. Therefore, TZDs should be used with caution in patients with a history of diastolic dysfunction or CHF. The risk of heart failure and death is higher with rosiglitazone than with pioglitazone.

Bladder Cancer :

In some studies, pioglitazone has been associated with an increased risk of bladder cancer. This effect varies depending on duration and dose. The latest analysis also shows no increased risk. In contrast, rosiglitazone was not associated with an increased risk of bladder cancer in any of the analyses. This suggests that the risk is drug-specific and not a class effect. Weight gain:

Fat cells have the highest concentration of PPAR gamma receptors in the body. The mechanism behind weight gain is due to a combination of different factors. TZDs upregulate her PPARgamma receptors in the central nervous system, resulting in increased food intake. TZD drugs increase adipose tissue mass through the maturation of preadipocytes to mature adipocytes and increase fat storage by increasing the movement of free fatty acids into the cells. Additionally, fluid retention can lead to weight gain . Fat gain occurs primarily in the subcutaneous tissue and does not affect the visceral area. As with edema and CHF, concomitant use of insulin increases weight gain, but the use of metformin and the low dose of his TZD reduces the risk.

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Diabetic mascular edema:

Combination of TZD and insulin therapy was associated with increased incidence of diabetic mascular edema at 1-year and 10-year follow-up. However, further studies are underway to evaluate confounding factors and determine the frequency of this adverse event. Fraction:

Some studies have shown that patients taking TZDs have an increased risk of fractures and decreased bone mineral density compared to patients taking other oral medications such as insulin or sulfonylureas. Shown. The proposed mechanism for this is activation of PPAR-gamma and downregulation of insulin-like growth factors, which redirects osteoblast differentiation into adipocytes and causes bone loss. . These fractures appear to be more likely to occur in the distal end (forearm, wrist, ankle, foot, tibia) than in the axial skeleton (hip, pelvis, femur). The risk of fractures is further increased by other risk factors, such as postmenopausal women and patients who are also taking glucocorticoids or proton pump inhibitors (PPIs).

Increased ovulation and Teratogenic Effect:

In patients with polycystic ovary syndrome, the use of TZDs and other insulin sensitizers increases ovulation rates. This effect may induce ovulation in some premenopausal anovulatory women and improve natural pregnancy rates. However, TZDs have also been shown to have teratogenic potential by delaying fetal maturation. Premenopausal women should use contraception when they do not want to become pregnant and switch to another insulin sensitizer, such as metformin, after pregnancy.

Rosiglitazone comes with a warning about a potential increased risk of myocardial infarction and angina pectoris.

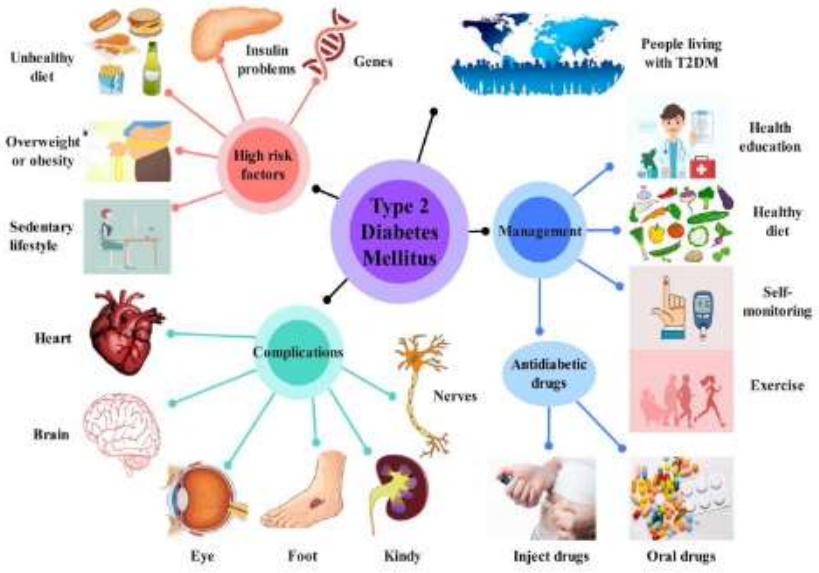

Fig.7 Effect of type 2 Diabetes mellitus in the body.

Contraindications :

Drug prescribing :

Pioglitazones : Not recommended for renal replacement therapy, no dose adjustment required. 4 ml/min increase in creatinine clearance, contraindicated if there is impaired liver function, contraindicated if there is a history of heart failure, contraindicated if there is a history of bladder cancer, or if microscopic or gross hematoma is investigated , increased risk of fractures, including hip fractures2.

Rosiglitazone: License approval was granted by the EMA (European Medicines Agency) in 2010 due to cardiovascular safety concerns.

Troglitazone: Authorization withdrawn by EMA 2000. Causes of hepatotoxicity. When treating T2DM, the main intervention should be lifestyle changes such as diet, exercise, and weight loss. Metformin or sulfonylureas should be used as first-line monotherapy because of their favorable side effect profile. However, TZDs can be used as monotherapy or as combination therapy when first-line drugs are contraindicated. TZDs may be

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required in high-risk patients with hypoglycemia. However, contraindications should be clarified before starting treatment.

There are several contraindications to the use of thiazolidinediones, including:

Heart Failure (New York Heart Association Class III, IV): The American Heart Association and American Diabetes Association recommend that patients with symptomatic New York Heart Association Class III, IV heart failure use TZDs at the lowest possible dose or not at all. It states that it should not be. This is due to the risk of fluid retention and diastolic heart dysfunction.

Moderate to Severe Hepatic Impairment: Troglitazone has been withdrawn from the market due to hepatotoxicity. Although rosiglitazone or pioglitazone have not shown the same hepatotoxic effects, it is still recommended that patients undergo basic and regular monitoring of liver function. Patients with AST or ALT
≥3 times the upper reference value should discontinue TZD treatment.

Bladder cancer: Pioglitazone should not be used in patients with active bladder cancer. In patients with a history of bladder cancer, the risk of recurrence should be weighed against the benefits of glycemic control before initiating treatment with pioglitazone. A similar risk for bladder cancer has not been identified with rosiglitazone.

Pregnancy: Because PPAR-gamma is required for terminal trophoblast differentiation and placental vascularization, the FDA has designated TZDs as a potentially teratogenic pregnancy class C. Pregnant women should be switched to another insulin sensitizer, such as metformin. High risk of fracture: Patients at high risk of fracture due to high risk of fracture, e.g. B. Patients with a history of osteoporosis, postmenopausal women, or patients taking other drugs that increase the risk of fractures (such as glucocorticoids or PPIs) should not begin TZD therapy. Cytochromes CYP 2C8 and CYP 3A4 are required for the metabolism of TZDs. Therefore, cytochrome inducers and inhibitors should be used with caution as they may affect drug plasma levels of TZDs.

Recent Trend Of Thiazolidinediones ; (Novel Approach Of TZDs) :

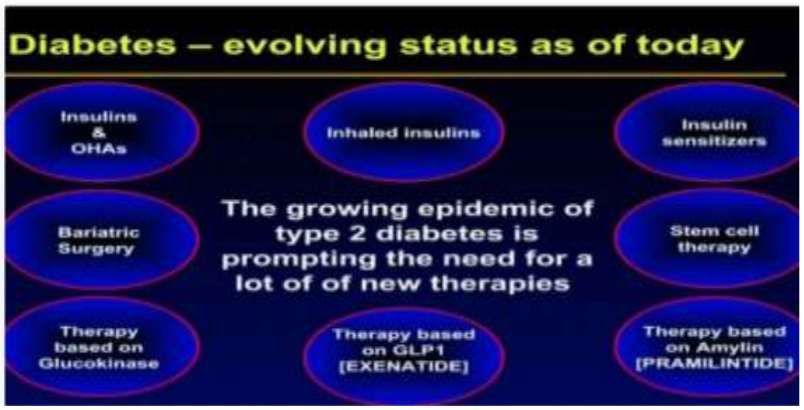

Fig .8 The verious activity of insulin

The Global antidiabetic thiazolidinediones market is anticipated to rise at a considerable rate during the forecast period, between 2023 and 2030.

In 2022, the market is growing at a. Steady rate and with the rising adoption of strategies by kye players , the market is expected to rise our the projected horizon."Antidiabetic thiazolidinediones in market"

Research report 2023 includes detailed market segmentation based on regions, applications (hospitals, clinics, other and types (rosiglitazone pioglitazones).

The largest manufacturers of **antidiabetic thiazolidinediones market** worldwide.

Takeda pharmaceuticals

- Eli Lilly
- Pfizer
- Novo Nordisk
- Bristol - Myers squibb
- They types of antidiabetic thiazolidinediones in the market , based on product types the market is categorized into below type that held the largest antidiabetic.thiazolidinediones market shere in 2023.

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- Rosiglitazone
- Pioglitazones

Stress management strategies represent an innovative approach to effectively

Prevents the occurrence of T2DM. Continued exposure to stressors increases your risk of developing type 2 diabetes. Long-term stress is associated with dysregulated blood glucose metabolism and neuroendocrine abnormalities due to chronic low-grade inflammation. Most of the risk factors for diabetes are influenced by the release of intravascular glucose and lipid components, the release of inflammatory cytokines, and psychiatric disorders that affect hypertension. Therefore, it is certain that the main factor in the increased risk of T2DM is the allostatic load on the body after long-term exposure to psychological stress. Increased stress levels are associated with decreased treatment compliance and glycemic balance in patients with type 2 diabetes.

The Clinical Efficacy of Thiazolidinediones :

Introduced approximately 20 years ago for the treatment of diabetes, pioglitazone acts at the level of the cell nucleus by modulating the activation or repression of many genes. The effect of controlling blood sugar levels lasts longer than sulfonylureas. Pioglitazone improves serum lipids, especially triglycerides and HDL-C. It has anti-inflammatory and antithrombotic properties and has been shown to have important cardiovascular effects in patients with myocardial infarction and stroke, and even in non-diabetic patients. Pioglitazone is specifically indicated for DM patients with heart attack or stroke and is recommended by scientific societies. A prospective, randomized, double-blind study investigated the effect of pioglitazone treatment on the progression from unstable atrial fibrillation (AF) to stable AF in T2DM and elucidated the mechanism of the beneficial effect. 1

Patients who received metformin or pioglitazone did not have significantly fewer new lesions or enlargement of existing lesions on brain magnetic resonance imaging (MRI). Additionally, fasting blood glucose, insulin resistance, HbA1c, serum lipids, and systolic blood pressure were significantly reduced after 12 months in both the metformin and pioglitazone groups. The emergence of TZDs for diabetes prevention in post-GDM, PCOS, metabolic syndrome, and lipodystrophy represents a new therapeutic perspective, and considering the positive effects observed so far in clinical studies, it is likely that metformin and other May replace the use of hypoglycemic agents. There are many pathological conditions that can be treated with pleiotropic hypoglycemic drugs such as glitazones. Pharmacological combinations of glitazones with GLP1-RA/SGLT2is and/or nutraceuticals have potential for the treatment of fatty liver and neurodegenerative diseases.

Future Direction of thiazolidinediones :

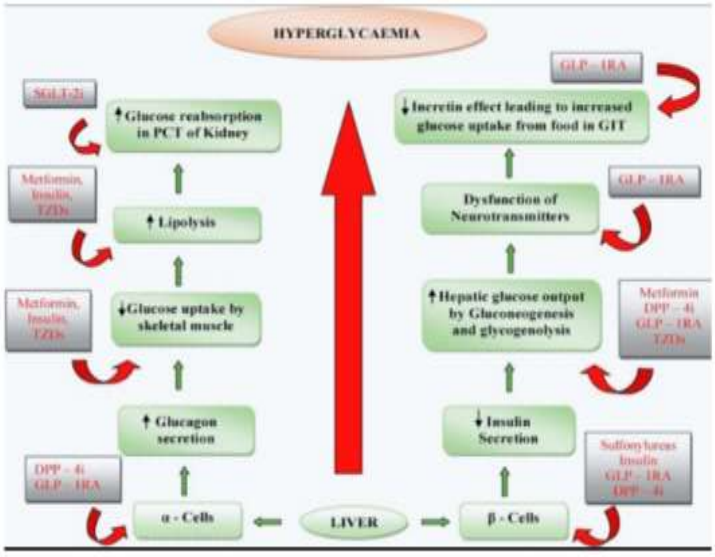

Fig .9 Type || diabetes mellitus

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TZDs are an important class of drugs that act by increasing the transactivation activity of PPARs, as a result of which, they reduce hepatic glucose production, increase peripheral utilization of glucose and lipid metabolism. These actions, therefore, reduce the preload and after load on β-cells and lipid homeostasis. As a result, the effect of endogenous insulin improves so as to maintain the level of blood glucose. Unfortunately, the clinically used TZDs, Troglitazone, Pioglitazone and TZDs represent a breakthrough in the treatment of type 2 DM,new are likely to result from basic research in a variety of direction.

The discovery of a physiological ligand for PPARY might provide clut to the site and substarates of the normal hormonal or metabolic pathways,regulating insulin action.tissue - specific knockouts of PPARY will not only test the hypothesis that PPARY is the molecular target of TZDs but will support or eliminate various call types as candidate sites of TZD action, the discovery of new TZD dependent PPARY target genes will also contribute to a conceptual bridge between TZD activation of PPAR-Y and insulin action .

Finally, a deeper understanding of the mechanistic relationship between TZD binding to PPARY and enhancement of insulin action in vivo could inform the development of additional therapeutics targeting this TZD receptor, e.g. It may be possible to connect. Phosphorylation of PPAR-Y negatively regulates its function, suggesting that therapies aimed at increasing the dephosphorylated state may synergize with TXD in enhancing insulin action. .

II. CONCLUSIONS:

TZDs have various biological activities such as antidiabetic, anticancer, anti-inflammatory, antibacterial, antiviral, antiproliferative, antifungal, and antispasmodic properties. Previously, his TZDs were only known for their antidiabetic effects.

But now, one day after the research was expanded, its use is being expanded for many diseases, including antibiotics and cancer. In the near future, for biochemists, a deeper understanding of the synthetic approach (SAR, Aim) will help him design and synthesize TZD derivatives. Consider and design strategies for effective search.

PPAR gamma agonists affect the liver, adipose tissue, and muscle and have many effects, including: B. Reduced insulin resistance in the liver and peripheral tissues, reduced gluconeogenesis in the liver, reduced blood sugar levels and HbA1c (and other metabolic benefits). . There is evidence that modification of mitochondrial target functions by thiazolidinediones may contribute to hypolipidemic and/or antidiabetic effects. The persistence of beneficial effects on blood sugar is likely to be long-lasting, so the benefits and risks should be carefully weighed. Rosiglitazone is currently off the market in many countries due to its negative impact on cardiovascular risk profiles, and pioglitazone has no significant contraindications to its use, except for the potential risk of heart failure in susceptible individuals. Apparently not.

The use of his once widely prescribed and effective T2D treatment has been greatly reduced due to safety concerns and side effects such as heart failure and increased risk of fractures. These drugs are generic, inexpensive, and the most effective drugs for treating insulin resistance. This review article focuses on the effects of his TZDs on diabetic patients. In this review, we have discussed the current status of TZDM and several machine learning approaches in repositioning drug candidates. Additionally, we summarized some reliable evidence regarding antidiabetic drugs in the treatment of diabetic patients, cancer, neurodegenerative diseases, and cardiovascular diseases. Repositioning antidiabetic drugs with superior efficacy and safety in the treatment of cancer and diabetes patients.

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