Glitazones or thiazolidinediones (TZDs) are a class of oral insulin sensitizing agents. They act on the nuclear receptor of the target cells called as Peroxisome Proliferator Activated Receptor-γ (PPAR-γ).

They were introduced into clinical practice in 1997. The first agent troglitazone was extensively studied, later withdrawn for association with hepatotoxicity. Second generation TZDs are rosiglitazone and pioglitazone. Other members of the group are ciglitazone and englitazone. These compounds show qualitatively similar metabolic activity but vary in potency.

Site and Mechanism of Action (Fig. 1)

PPAR γ is a nuclear receptor found predominantly in adipose tissue, also present in skeletal muscle and liver. Natural ligands of PPAR γ include fatty acids (FA), prostaglandin metabolites and leukotrienes. TZDs are synthetic ligands of the intracellular PPAR-γ.

TZDs are lipophilic drugs which readily enter cells and bind to PPAR γ with high affinity. PPAR γ is complexed with the retinoid X receptor (RXR) and their activation results in activation of regulatory sequences of DNA that control the expression of specific genes. Besides pioglitazone also works through PPAR α at liver for regulation of lipid homeostasis.

![Fig. 1: Mechanism of action of thiazolidinediones](image-url)
TZDs can enhance expression of various genes including those encoding insulin dependant glucose transporter (GLUT-4), lipoprotein lipase, fatty acid transporter protein (FATP) and fatty acyl coenzyme-A synthase. TZDs amplify certain genomic effects of insulin on adipocytes and other cells as some of these genes are also regulated by insulin.

TZDs can enhance expression of various genes including those encoding insulin dependant glucose transporter (GLUT-4), lipoprotein lipase, fatty acid transporter protein (FATP) and fatty acyl coenzyme-A synthase. TZDs amplify certain genomic effects of insulin on adipocytes and other cells as some of these genes are also regulated by insulin.

TZDs amplify certain genomic effects of insulin on adipocytes and other cells as some of these genes are also regulated by insulin.

The biological effects of TZDs on adipocyte are to increase fatty acid uptake, thus lowering triglyceride (TG) and nonesterified FA levels and inducing adipocyte differentiation. They also increase peripheral glucose disposal and reduce hepatic glucose output.

It does not have a direct effect on pancreatic insulin secretion, rather it exerts an insulin sparing action restoring the pancreatic response to external stimuli. They are not effective in severely insulin deficient models, implying that their action requires the presence of insulin. They only improve insulin sensitivity in conditions of insulin resistance and have little action in models with normal insulin sensitivity. Their blood glucose lowering effect is accompanied by decrease in plasma insulin concentration and they do not normally tend to produce overt hypoglycemia.

Problems in Diabetes

Individuals with either type-2 diabetes or impaired glucose tolerance (IGT) associated with hypertension, central obesity, and dyslipidemia with or without other characteristics of metabolic syndrome pose a major therapeutic challenge. These patients are at very high risk of macrovascular disease, specially coronary artery disease. Amelioration of coexisting conditions like dyslipidemia is equally important as control of blood glucose in a type-2 diabetic. There is bounding evidence that insulin resistance and/or hyperinsulinemia is the common etiological factor for the components of metabolic syndrome.

Advantages of Glitazones

Rosiglitazone and pioglitazone lower glycosylated hemoglobin (HbA1c) by about 1 to 1.6% in patients with diabetes mellitus. Pioglitazone has an additional advantage as it increases HDL-cholesterol and reduces TG concentration. Further it induces redistribution of fat in the body. There occurs hyperplasia of smaller adipocytes in the subcutaneous tissue which reduce insulin resistance with concomitant reduction in visceral fat. Glitazones work at a genetic level breaking the vicious cycle of metabolic syndrome and promising the prevention of type-2 diabetes. Visceral fat poses higher insulin resistance in centrally obese individuals. Glitazones can be coprescribed with sulphonylureas, metformin and insulin for synergistic action. In patients with PCOD, there is decrease in insulin resistance and initiation of ovulation.

Adverse effects

TZDs reduce the hemoglobin of about 1 gm/dl which may be due to hemodilution and can cause weight gain of 1-4 kg after 6 months of treatment. Further, retention of fluid may be severe enough to exacerbate or precipitate heart failure.

| Table 1: Lipid and lipoprotein abnormality in type-2 diabetes mellitus |
|---------------------------------|---------------------------------|
| Usual level of glycemia (Euglycemia) | • Increased TGs |
| | • Decreased HDL-C |
| | • Preponderance of small, dense LDL particles |
| | • Increased LDL susceptibility to oxidation |
| Poor glycemic control | • Worsening of hypertriglyceridemia |
| | • Diabetic Nephropathy |
| Increased TG | • Decreased HDL-C |
| | • Increased lipoprotein (a) |
They undergo hepatic metabolism by cytochrome P-450 isoforms to active metabolites. Liver function tests (LFT) should be checked prior to initiating treatment and then 2 monthly for the first year and periodically there after. TZDs are contraindicated in patients with elevated baseline LFTs and should be discontinued if alanine transaminase levels are more than 2.5-3 times than the upper level of normal or there are clinical signs of hepatic impairment.

TZDs are contraindicated in patients with a history of cardiac failure, severe renal insufficiency or those on dialysis.

Dosage Recommendations
The usual dose of rosiglitazone is 2-4 mg/once or twice a day and pioglitazone is 15-45 mg/once a day with or without food, given alone or in combination with other oral drugs or insulin.

TZDs are not to be given to children and pregnant women.

References