Thiazolidinediones:
Beyond Glycemic Control
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INTRODUCTION
Thiazolidinediones (TZDs) are a new class of oral drugs used for lowering blood glucose. Four TZDs are known till date: Troglitazone, Rosiglitazone, Ciglitazone & Pioglitazone (Troglitazone was later withdrawn as it caused severe idiosyncratic liver injury). The glucose lowering effects of TZDs are mediated primarily by decreasing insulin resistance in muscle and adipose tissue and inhibiting hepatic gluconeogenesis.¹ These novel drugs act primarily through activation of peroxisome proliferator-activated receptor-γ (PPAR-γ) a nuclear receptor that has a regulatory role in differentiation of cells particularly adipocytes,²,³ besides also having a number of contradictory actions within inflammatory and vascular cells, causing both anti-inflammatory action as well as inducing foam cell formation and programmed cell death. TZDs therefore by virtue of acting through these receptors elicit numerous effects in addition to lowering the blood glucose.

EFFECT ON HYPERINSULINEMIA, INSULIN RESISTANCE AND METABOLIC SYNDROME
Insulin resistance and hyperinsulinemia are central to the pathogenesis of the metabolic syndrome, besides being associated with a significantly increased risk of cardiovascular disease, regardless of the degree of glucose tolerance. Haffner et al⁴,⁵ showed that hyperproinsulinemia is associated with an increased risk for the components of the metabolic syndrome. Nagi et al⁶ found similar association between proinsulin and dyslipidemia. The Framingham Offspring Study⁷ demonstrated a significant and consistent relation between increasing degrees of fasting hyperinsulinemia and a procoagulant state as depicted by levels of plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator, Von Willebrand factor, fibrinogen, plasma viscosity and factor VII antigen. Fasting and post-oral glucose loading hyperinsulinemia is associated with an increased risk for the components of the metabolic syndrome.

Some studies indicate that TZDs independently improve insulin secretory response to oral glucose load.¹³

β-Cell Rejuvenation and TZDs
Patients with type 2 diabetes have gradual pancreatic β cell destruction that begins more than a decade before diabetes is diagnosed.²²,²³ Damage to β cells occurs initially due to elevated serum free fatty acids that results in an increase in ceramide concentration. This in turn causes increased expression of nitric oxide synthase and consequently enhanced β cell apoptosis. Free fatty acids also suppress the expression of genes responsible for formation or replacement of β cells from stem cells in the pancreatic duct.²⁶ TZDs by lowering tissue triglyceride level therefore cause decreased β cell death and an increase in β cell mass and endogenous insulin production.²⁷,²⁸ Studies in mice susceptible to diabetes (db/db) have proved the rejuvenatory capability of TZD rosiglitazone on pancreatic β -cells.²⁴

In type 2 diabetes as pancreatic β cells fail, more of the insulin precursor proinsulin is produced and the proinsulin to insulin ratio increases³¹ but use of rosiglitazone for treatment results in a significant decrease in proinsulin to insulin ratio thereby indicating that rosiglitazone use improves β cell function.³² Moreover the C-peptide concentration also increases implying an enhanced endogenous insulin production. Because of these effects it has been postulated that use of TZDs may prevent the development of diabetes in susceptible population as was shown in the Troglitazone in The Prevention Of Diabetes (TRIPOD) study, which showed a >50% reduction in the development of diabetes in women with a history of gestational diabetes as compared to the placebo group.³³

Effect on Lipid metabolism and Oxidation
Type 2 diabetics exhibit a characteristic pattern of dyslipidemia that includes an elevated plasma triglyceride level, low plasma high density lipoprotein (HDL) cholesterol level and a qualitative change in low density lipoprotein (LDL) cholesterol with increase in small dense atherogenic LDL cholesterol.³⁴-³⁹ All TZDs substantially increase HDL cholesterol level with troglitazone and pioglitazone also decreasing the triglyceride levels.⁴⁰-⁴³ LDL and total cholesterol levels increase with TZDs use, however the rise in LDL cholesterol is predominantly in the larger buoyant particles and the small dense atherogenic particles decrease in
mechanism of anti-atherosclerotic effect of TZDs. Decreased PGDFR-α role in controlling VSMC proliferation and migration, whereas FFA are disrupted. There is impaired flow-mediated vasodilation, diabetes, endothelial secretion of nitric oxide and vasodilation of a mature contractile phenotype. In insulin resistance and restraining smooth muscle cell proliferation and maintenance of vascular smooth muscle cells (VSMC). TZDs improve flow-mediated vasodilation and decrease macrophage and VSMC activation. TZD activation is decreased by decreasing the expression of tissue plasminogen activator, increased expression of inducible Nitric Oxide Synthase (iNOS) which is also activated by increased Free Fatty Acid (FFA). Increased nitric oxide synthesis induces cell death. (Source: Modified from Ref. 30)

Effect on Vascular Function and Reactivity

The ability of blood vessels to dilate in response to stimuli including ischemia is called vascular reactivity or flow-mediated dilatation. Under normal conditions insulin dilates arterioles supplying skeletal muscle through activation of nitric oxide synthesis. Nitric oxide has additional physiological role in the form of NO-dependent mitogenic signals to nucleus of VSMCs are blocked by TZDs that prevents quiescent VSMCs from re-entering the cell cycle. In addition to these effects Rb phosphorylation blocks E2F-dependent transcription of minichromosome maintenance 6 (MCM6) and MCM7 genes, which prevents the transition of cell cycle from G1 to S phase.

**Effect on Cardiac Metabolism**

Free fatty acid (FFA) uptake and oxidation by heart are directly related to the supply of plasma FFA, cardiac workload and oxygen availability. In diabetes and insulin-resistance states the heart uses an excess of FFAs and has reduced glucose and lactate metabolism. Fatty acid uptake in excess of oxidation leads to accumulation of triglycerides and fatty acid intermediates that induces nitric oxide synthase and consequently cellular apoptosis occurs. TZD by lowering FFA plasma level decrease the myocardial injury caused by FFA. They act by activating AMP-activated kinase that inhibits acetyl-CoA carboxylase and activates malonyl-CoA dehydrogenase that leads to an increase in activity of carnitine palmityl transferase-1 (CPT1) and enhanced FFA oxidation. Recent studies indicate that TZD administration may improve the recovery of myocardial function in the post-ischemic period. TZDs also influence the expression and function of glucose transporters in heart with studies showing an improved glucose metabolism in myocardium with continuous rosiglitazone treatment. In some studies TZD activation of GLUT translocation was quite rapid suggesting that this effect is mediated by non-PPAR-γ mechanism probably through AMP-Kinase activation. This molecule is activated by stress and mediates GLUT 4 translocation during ischemia in the myocardium and skeletal muscle.

**Polycystic Ovary Syndrome**

Polycystic ovary syndrome is a disease of young females in which insulin resistance and hyperinsulinaemia are important pathogenic mechanisms. Drugs that lower insulin resistance therefore improve many abnormalities associated with this syndrome including ovulatory and β cell dysfunction.

**Weight Gain and Fluid Sequestration**

Weight gain in the range of 1-3Kg occurs with rosiglitazone or pioglitazone monotherapy taken for 26-52 weeks that may plateau after some time, eventhough the occurrence of clinically evident edema is relatively uncommon occurring in 4.8% of patients being treated by rosiglitazone or pioglitazone therapy. A number of factors contribute to weight gain including improved

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**Fig. 1:** Theory of β-cell lipotoxicity. Leptin receptor mutation causes increased expression of inducible Nitric Oxide Synthase (iNOS) which is also activated by increased Free Fatty Acid (FFA). Increased nitric oxide synthesis induces cell death. (Source: Modified from Ref. 30)
glycemic control, differentiation of adipocytes, increased appetite, decreased loss of calories in urine and fluid retention. Edema results from a direct sodium retaining action of TZDs on kidney, and does not appear to reflect occult heart failure. Both weight gain and edema are dose-dependent and may be controlled with appropriate dietary and drug therapy including diuretics.

Effect on Fibrinolytic Process and Coagulation Cascade

Plasminogen activator inhibitor type-1 (PAI-1) is the main molecule that regulates endogenous fibrinolysis and increased PAI-1 is now considered as one of the novel cardiovascular risk factor for coronary artery disease. Patients with diabetes and PCOD treated with troglitazone had significantly decreased plasma levels of PAI-1. In vitro studies of troglitazone have demonstrated not only a direct effect on the vessel wall leading to a decreased synthesis of PAI-1 but also an indirect effect on hepatic synthesis secondary to attenuation of hyperinsulinemia.

CONCLUSION

Thiazolidinedione eventhough initially adapted for lowering blood glucose have shown a wide spectrum of actions, with some of the effects mediated by PPAR-γ receptors and some by unknown mechanisms that result in a multitude of effects including decreased insulin resistance, decreased lipid oxidation and FFA level increase in HDL cholesterol, decrease in vascular resistance, improved endothelial function and β cell proliferation. However further long term clinical trials are required to determine the full potential clinical application of this class of drugs.

REFERENCES


