# 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 Four TZDs are known till date: Troglitazone, Rosiglitazone, Ciglitazone & Pioglitazone (Troglitazone was later withdrawn as it caused severe idiosyncratic liver injury).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 al[4,5] showed that hyperproinsulinemia is associated with an increased risk for the components of the metabolic syndrome. Nagi et al[6] found similar association between proinsulin and dyslipidemia. The Framingham Offspring Study[7] 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 carries a significant and independent predictive value for cardiovascular disease (CVD).[8,9] TZDs improve peripheral especially skeletal muscle insulin sensitivity in both animals & humans.[10-15] The enhancement of adipocyte differentiation by TZDs and the redistribution of fat from abdomen to subcutaneous space may also improve insulin sensitivity.[16,17] As a result the need for exogenous or endogenous insulin is reduced and circulating insulin levels are decreased.[18-21] 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 increases[31] 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

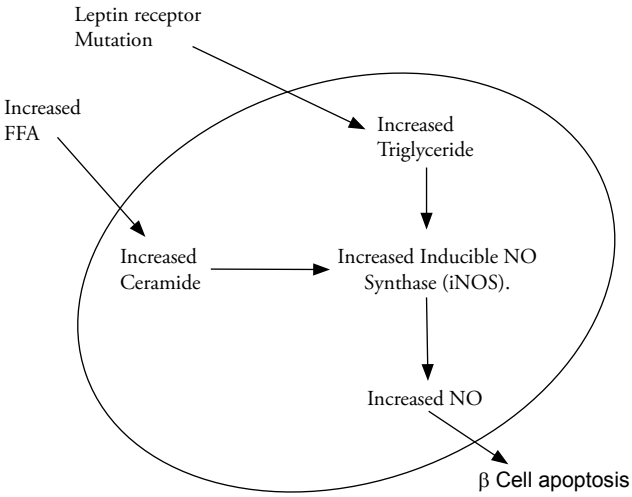


**Fig. 1 :** Theory of β-cell lipotoxicity. Leptin receptor mutation causes increased expression of inducible Nitric Oxide Synthase (iNOS) which is also activated by increased Free Fatty Acid (FFA). Increased nitric oxide synthesis induces cell death. (Source: Modified from Ref. 30)

concentration[44] that result in an increased resistance of LDL cholesterol to oxidation.[44-47]

## 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.[48,49] Nitric oxide has additional physiological role in the form of restraining smooth muscle cell proliferation and maintenance of a mature contractile phenotype. In insulin resistance and diabetes, endothelial secretion of nitric oxide and vasodilation are distrupted.[50,51] There is impaired flow-mediated vasodilation, decreased expression of tissue plasminogen activator, increased thrombotic potential, transition of macrophages to foam cells, enhanced expression of adhesion molecules and proliferation of vascular smooth muscle cells (VSMC). TZDs improve flow-mediated vasodilation and decrease macrophage and VSMC activation.[52] VSMC activation is decreased by decreasing the effect of proinflammatory transcription factor agent egr-I[53] and lowering its action on the cell cycle.[54] TZDs also increase vascular and cardiac expression of cyclic adenosine monophosphate (CAMP) response element binding protein (CREB) and CREB-dependent genes such as PDGFR-α. CREB plays an important role in controlling VSMC proliferation and migration, whereas PGDFR-α receptor blockade by TZDs is believed to be one of mechanism of anti-atherosclerotic effect of TZDs.[55-58] Decreased expression of pro-inflammatory transcription factor C/EBP - δ by TZDs is another mechanism of improved vascular function by TZDs.

## Effect on Smooth Muscle Cell Proliferation and Atherosclerosis

Vascular smooth muscle cells (VSMCs) of adults are normally quiescent and their growth is arrested in Go/G1 phase of cell cycle. Their proliferation occurs in response to arterial injury by factors like high plasma glucose and free fatty acids, dyslipidemia and hypertension. Compensatory hyperinsulinemia associated with insulin resistance strongly predicts neointimal tissue proliferation after implantation of coronary stents in patients with impaired glucose tolerance.[59] TZD inhibit VSMC proliferation by interfering with the function of multiple cell-cycle regulators. They inhibit transition of cell cycle from $G_1$ to S phase through reduction of mitogen –induced p-$27^{Kip1}$ which leads to a decreased cyclin-dependent kinase (CDK) activity and reduced levels of retinoblastoma tumor suppressor protein (Rb) phosphorylation,[60] this is the principal molecular mechanism underlying the ability of TZDs to inhibit VSMC proliferation in vitro and intimal hyperplasia in vivo. Mitogen-activated protein kinase (MAPK)-dependent mitogenic signals to nucleus of VSMCs are blocked by TZDs[61] 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.[62,63] In diabetes and insulin-resistance states the heart uses an excess of FFAs and has reduced glucose and lactate metabolism.[64-66] 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[67] and activates malonyl–CoA dehydrogenase[68] 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.[69,70] TZDs also influence the expression and function of glucose transporters[69-71] in heart with studies showing an improved glucose metabolism in myocardium with continuous rosiglitazone treatment.[69] In some studies TZD activation of GLUT translocation was quite rapid suggesting that this effect is mediated by non-PPAR-γ mechanism,[72] probably through AMP-Kinase activation. This molecule is activated by stress and mediates GLUT 4 translocation during ischemia in the myocardium[70,73] and skeletal muscle.

## Polycystic Ovary Syndrome

Polycystic ovary syndrome is a disease of young females in which insulin resistance and hyperinsulinemia are important pathogenetic mechanisms.[74] Drugs that lower insulin resistance therefore improve many abnormalities associated with this syndrome including ovulatory and β cell dysfunction.[74-76]

## Weight Gain and Fluid Sequestration

Weight gain in the range of 1-3Kg[77] occurs with rosiglitazone or pioglitazone monotherapy taken for 26-52 weeks that may plateau after some time,[78] eventhough the occurrence of clinically evident edema is relatively uncommon occurring in 4.8% of patients being treated by rosiglitazone or pioglitazone therapy.[79,77] A number of factors contribute to weight gain including improved

glycemic control, differentiation of adipocytes, increased appetite, decreased loss of calories in urine and fluid retention.[80,81] Edema results from a direct sodium retaining action of TZDs on kidney[82] 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.[74,83] 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.[84]

## 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.

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