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# Peroxisome Proliferator-Activated Receptor γ (PPAR γ): A Systemic Insulin Sensitizer Associated with Decreased Risk of Type 2 Diabetes

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**Abstract**

The peroxisome proliferator-activated receptors (PPARs) are three members of the nuclear receptor prearranged by separate genes as PPARα, PPARβ/δ, and PPARγ that differ in tissue distribution and specific function. PPARγ is a nuclear receptor highly expressed in the colon, and plays a key role in bacterial induced inflammation. It is a mediator of adipocyte differentiation that regulates transcription of several genes involved in fatty acid and energy metabolism. It is known as the glitazone reverse insulin resistance receptor or nuclear receptor subfamily 1, group C, member 3 (NR1C3). It is activated by anti-diabetic Thiazolidinedione (TZD) drugs and is used as insulin sensitizers and also a favorite option for the treatment of T2D patients. It is used as monotherapy or in combination with other oral hypoglycaemic agents, which are generally safe and well-tolerated. The aim of this mini review is to discuss the potential roles of PPARγ for the prevention and treatment of T2D.

**Keywords:** diabetes, PPARγ, nuclear receptor, regulation differentiation

## 1. Introduction

Peroxisome proliferation-activated receptors (PPARs) are a family of ligand-inducible transcription factors that belong to the nuclear hormone receptor superfamily and regulate the expression of specific target genes involved in energy and lipid metabolism, adipogenesis, vascular biology, cancer, proliferation, differentiation, and inflammation. These belong to the steroid, thyroid, and retinoic acid receptor superfamily (Smirnov, 2002). These mainly act as sensors for fatty acids and fatty acid-derived metabolites. Defects in these are linked to lipodystrophy, obesity, and insulin resistance as a result of impaired adipose tissue expansion and functionality (Wu et al., 2020). Adipose tissue is a nutrient-storing and fuel-burning organ, which is increased in obesity and likely plays a role in T2D progression (Iozzo, 2009).

PPARs influence insulin-sensitive genes that enhance production of mRNAs of insulin-dependent enzymes. These work in adipocytes and hepatocytes to increase insulin receptors (Watkins & Whitcomb, 1998). These regulate gene transcription by binding to specific direct repeat-1 response elements in enhancer sites of regulated genes (Smirnov, 2002). These improve the lipid profile and glucose homeostasis in animal models of dyslipidemia and diabetes, as well as in clinical trials. In humans, there are three isoforms of PPARs encoded by different genes: PPARα (NR1C1), PPARδ (NR1C2), and PPARγ (NR1C3) that have only partially overlapping activity profiles and are differently expressed in organs and tissues (Boitier et al., 2003).

The PPARγ is a nuclear receptor that regulates transcription of several genes in fatty acid and energy metabolism. It is highly expressed in adipocytes, skeletal muscle, liver, and kidney; and regulates the expression of genes that mediates adipocyte differentiation, lipid accumulation by adipocytes by modulating numerous genes regulating

adipogenesis, lipid uptake and lipid metabolism, energy metabolism, and insulin action (Berger, 2005). It has critical impact in many metabolic homeostasis disorders. It is used as insulin sensitizers for treatment of type 2 diabetes (T2D). It also has a wide spectrum of biological functions that regulates metabolism, reduces inflammation, influences the balance of immune cells, inhibits apoptosis, and reduces stresses, and improves endothelial functions (Ivanova et al., 2015).

PPARγ is presented in several tissues, such as in the skeletal muscle, liver adipose tissue, pancreatic β-cells, vascular endothelium, macrophages, heart, and kidney. It is one of the most extensively studied ligand-inducible transcription factors. It is identified in the early 1990s (Park et al., 1997). It lowers blood pressure, no hypoglycaemia, and progressive rise in HDL levels, reduces microalbuminuria and vascular intimal thickening (Khandwala, 2003). Obviously, this medication is expensive and the poor can use it hardly (Guan et al., 2005).

## 2. Literature Review

The literature review is an important and an introductory section of a research, where works of previous researchers are highlighted (Polit & Hungler, 2013). It enhances the activities of researchers through the understanding the core idea of the subject area that has been carried out before (Creswell, 2007). Ekaterina A. Ivanova and her coworkers have discussed the role of PPARγ in various conditions associated with cardiovascular risk, including diabetes mellitus, atherosclerosis, and hypertension. They have provided an overview of the potential use of PPARγ agonists in cardiovascular surgical intervention (Ivanova et al., 2015). Chi-Hung Liu and his coworkers' study suggests that the use of PPARγ in T2D and hypertensive ischemic stroke (IS) patients is associated with fewer recurrent IS events in an Asian population (Liu et al., 2020).

Istvan Szatmari and his coauthors have shown that PPARγ acts as a positive transcriptional regulator in human developing dendritic cells (DCs). They have observed that PPARγ controls genes that are involved in lipid metabolism and indirectly modifies the immune phenotype (Szatmari et al., 2007). Márcia V. de Carvalho and her coworkers describe activities of the PPARγ as a modulator of inflammation, focusing on lung injury and including definition and mechanisms of regulation, biological effects and molecular targets, and its role in lung diseases caused by inflammatory stimuli, bacteria and virus, and molecular-based therapy (de Carvalho et al., 2021).

Wenxiang Hu and his collaborators have generated mouse lines in which endogenous PPARγ1 and PPARγ2 were epitope-tagged to interrogate isoform-specific genomic binding, and mice deficient in either PPARγ1 or PPARγ2 to assess isoform-specific gene regulation (Hu et al., 2022). Hui Wu and her coworkers have investigated the effect of regulating PPARγ on adipocyte differentiation. They have also considered the structural characteristics, expression patterns, and molecular mechanisms of PPARγ function in adipocyte differentiation (Wu et al., 2020). Devajit Mohajan and Haradhan Kumar Mohajan have studied obesity and its related complications, such as diabetes mellitus, eating disorders, and various anthropometric indices. They have also studied on insulin and various oral medications for the treatment of T2D (Mohajan & Mohajan, 2023a-y).

## 3. Research Methodology

Research is a hard-working search, scholarly inquiry, and investigation that aim for the discovery of new facts and findings (Adams et al., 2007). To an academician there is no alternative but research and it is considered as an essential and influential work for his/her carrier development (Pandey & Pandey, 2015). Methodology is a guideline to complete a good research successfully that follows scientific methods efficiently (Kothari, 2008). Therefore, research methodology is the collection of a set of principles for organizing, planning, designing and conducting a good research (Legesse, 2014).

In the main research area we have highlighted on the historical background of PPARγ. Then we have discussed the isoforms of PPARγ. We have also discussed the functions of PPARγ, and finally, we have discussed the side-effects of PPARγ. To prepare this article we have used the secondary data sources that are related to PPARγ. We have taken help from the published journal articles, and books and handbooks of famous authors to complete the paper. We have also collected valuable information from websites and internets to enrich the study.

## 4. Objective of the Study

Diabetes mellitus (DM) is not a pathogenic entity but a group of aetiologically different metabolic defects. The effects of DM are long-term damage, dysfunction and failure of various organs (WHO, 2002). PPARγ is a known essential mediator for the maintenance of whole body insulin sensitivity, and can be used for the treatment of T2D patients (Kaundal & Sharma, 2010). Chief objective of this study is to discuss aspects of PPARγ. Some other minor objectives of the study are as follows:

- to introduce the historical background and isoforms of PPARγ,
- to focus on the functions of PPARγ, and
- to show the side-effects of PPARγ.

## 5. Historical Background of PPARs

PPARs were originally identified in *Xenopus* frogs as receptors that induce the proliferation of peroxisomes in cells in 1992. The name "PPAR" was derived from the initial identification of PPAR$\alpha$ in rodents for their ability to stimulate the proliferation of peroxisomes. But PPARs have no function in peroxisome proliferation in humans (Issemann & Green, 1990). PPARα is mainly expressed in the liver (hepatocytes), enterocytes, kidney, heart (cardiomyocytes), brown adipose tissue, and muscle; and is closely linked to the lipid metabolism. PPARα was discovered in 1990 during the search for a molecular target of a group of *peroxisome proliferators* agents (Kersten et al., 2000). PPARδ was identified in humans in 1992. It is expressed in most cell types mostly in the brain, adipose tissue and skin, and plays roles in fatty acid oxidation and energy balance (Dreyer et al., 1992). PPARγ is a nuclear receptor discovered in mammals in 1993 as an orphan receptor (Zhu et al., 1993). It is a 477 amino acid protein that is broadly expressed with relative high levels in the brain, adipose tissues (both white and brown), muscle, liver, colon, heart, kidney, pancreas, spleen, various epithelial cell types, and skeletal muscle and plays roles in fatty acid oxidation and energy balance (Tontonoz et al., 1994). It is also expressed in numerous cells of the immune system, such as monocytes/macrophages, dendritic cells, and T lymphocytes. It is a vital regulator of adipogenesis, insulin sensitivity, and lipid metabolism (Hu et al., 2022).

## 6. Isoforms of PPARγ

PPARγ is abundantly expressed in the adipose tissue and to a lesser extent in macrophages and other cell types, and regulates adipogenesis, lipid storage, and glucose homeostasis (Ivanova et al., 2015). All isoforms of PPARγ play an important role in adipocyte differentiation and glucose metabolism; but their expressions are different. PPARγ has two major isoforms generated by alternative promoter usage: PPARγ1 and PPARγ2. The isoform-specific regulation and function of γ1 and γ2 remain unclear yet. However, it is estimated that these regulate differentially, for example, the glucose and fatty acid metabolism (Strand et al., 2012).

Both isoforms are identical except for an additional 30 amino acids at the N-terminus of PPARγ2 in comparison to PPAR$\gamma$1. These are mostly expressed in adipocytes, with PPARγ1 also expressed at low levels in other tissues, such as macrophages, liver, brain, and muscle. These are essential for the development of adipose tissue and the control of insulin sensitivity (Vidal-Puig et al., 1996). The PPARγ1 isoform is expressed in nearly all cells. However, it is widely expressed in the colon, retina and hematopoietic cells and has also been detected at low levels in other organs, such as in the spleen and heart. PPARγ2 isoform is expressed mainly in adipose tissue. It is 30 amino acids in its NH2-terminus. It is also expressed in urothelial cells that are highly specialized transitional epithelial cells that line the organs of the urinary system, such as the bladder, and in regulatory T cells and other T cell populations (Moseti et al., 2016).

## 7. Functions of PPARγ

PPARγ is the master regulator of adipogenesis and fat cell function, and the target of anti-diabetic thiazolidinedione drugs (Rangwala & Lazar, 2004). It is associated with cardiovascular risk, including diabetes mellitus, atherosclerosis, and hypertension (Ivanova et al., 2015). For the treatment of diabetes, PPARγ agonists normalize the glucose profile by indirectly increasing insulin-stimulated glucose uptake by peripheral tissues and decreasing hepatic gluconeogenesis (Spiegelman, 1998). PPARγ also modifies the immunophenotype of monocytederived dendritic cells (DCs) (Szatmari et al., 2007). It is involved with the development of cardiac hypertrophy that is frequently associated with diabetes, demonstrating contradictory effects. It is used for the treatment of atherosclerosis to improve the endothelial function, slow down the progression of atherosclerotic plaques, and reduce chronic inflammation and thrombosis resulting in lowering the risk of cardiovascular events (Staels, 2005).

Several clinical studies have found blood pressure-lowering effects in PPARγ without affecting the renin-angiotensin-aldosterone system components by interfering with angiotensin II-mediated pathways (Tsai et al., 2009). PPARγ increases whole-body insulin sensitivity by activating nuclear receptors, and promoting esterification; and storage of circulating free fatty acids in subcutaneous adipose tissue. It enhances the effect of insulin in skeletal muscle, adipose, and hepatic tissues without increasing pancreatic secretion of insulin. TZDs lower glycated hemoglobin (HbA1c) values within 1.5–2.0% (Henry, 1997). It has protective effects in renal dysfunction, including diabetic nephropathy, and non-diabetic conditions (Yang et al., 2009).

PPARγ controls cell proliferation in various tissues and organs, such as in colon, breast, prostate, and bladder. It plays an important role in inflammation and metabolism. It is important for the maturation and function of various immune system-related cell types, such as monocytes, dendritic cells, and lymphocytes. The PPAR-γ lessens renal ischemia reperfusion injury (IRI) by attenuating neutrophil infiltration (Kapil et al., 2013).

PPAR-γ activation improves insulin sensitivity and glucose, adiponectin, and fatty acid uptake (Berger, 2005). It has an insulinsensitizing effect by increasing glucose uptake and reduces hunger, postprandial blood glucose and the concentration of free fatty acid (Akyurek et al., 2013). It is an important regulator of cardiac metabolism. It

controls myocardial metabolism by transcriptionally regulating genes encoding enzymes involved in fatty acid and glucose utilization (Huang et al., 2012).

It is used for the treatment of various conditions that are linked to dyslipidemia, atherosclerosis, and diabetes, which are frequently associated with cardiovascular disorders. Its glucose-lowering activity is not very complicated by hypoglycaemia or gastrointestinal adverse effects, as in the case of Sulphonylureas and Metformin. It reduces cardiovascular risk in patients with T2D by affecting the risk factors as altered blood lipid profile or elevated blood pressure (Ivanova et al., 2015).

**8. Side-Effects of PPARγ**

The main side-effects of PPARγ are fluid retention and weight gain of 2 to 4 kg. Fluid retention shows lower extremity edema, hemodilution-anemia, and in susceptible individuals may cause congestive heart failure (CHF). A low sodium diet can reduce the frequency and severity of the fluid retention. Weight increase is found in both Rosiglitazone and Pioglitazone due to the fluid retention and mobilization of fat from the intra-abdominal or visceral sites to the subcutaneous tissue (Khandwala, 2003).

PPARγ may increase sodium retention and alter endothelial permeability leading to peripheral edema and heart failure and cause imbalance in osteoblast and osteoclast formation resulting in bone fractures (Krishnaswami et al., 2010). Some other side effects are LDL elevation, worsens osteoporosis, and occasional fluid overload. These may create ulcers of the colon, intestinal obstruction, and kidney disease (Lichtor et al., 2008). The medication should not be initiated if the patient exhibits clinical evidence of active acute or chronic liver disease of increased serum transaminase levels (Mohajan & Mohajan, 2023y).

**9. Conclusions**

From this study we have observed that the expression of PPAR-γ is widespread and its dysregulation is linked to the development of several metabolic diseases, such as overweight and obesity, type 2 diabetes, atherosclerosis, inflammatory, neuroinflammatory, autoimmune, Alzheimer, and gastrointestinal diseases. PPARγ performs various biological functions, for example, it regulates fatty acids and glucose metabolism, reduces inflammation, influences the balance of immune cells, inhibits apoptosis, and improves endothelial functions. At present it has been widely prescribed for the treatment of glucose and lipid disorders among type 2 diabetes (T2D) patients.

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