

## Review Article

# Update on Ppar $\gamma$ and Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is the most common initial presentation of obesity and insulin resistance. Uninterrupted progression of hepatic lipid accumulation often leads to fatty liver disease and eventually cirrhosis. Insulin resistance is one of the characteristics of type 2 diabetes. Several types of treatment have been employed against type 2 diabetes some of which ameliorate NAFLD. The frequent line of treatment to improve insulin sensitivity is the use of thiazolidinediones (TZD) which activate the nuclear receptor, peroxisome proliferator activated receptor gamma (*Ppar $\gamma$* ). Although TZDs are proven to be very effective in promoting insulin sensitivity, its actions on *Ppar $\gamma$*  have been complicated, specifically on NAFLD. According to studies in different models, *Ppar $\gamma$*  manifests both beneficial and undesirable effects on NAFLD. This paper will focus on the current knowledge of *Ppar $\gamma$*  and its effect on NAFLD.

## 1. Introduction

Hepatic steatosis without excessive alcohol intake, called nonalcoholic fatty liver disease (NAFLD), is commonly associated with obesity and insulin resistance [1, 2]. NAFLD affects the general population and its incidence is linked with the epidemics of obesity and type 2 diabetes [3]. The metabolic pathways leading to hepatic steatosis include enhanced nonesterified fatty acid release from the adipose tissue, increased *de novo* lipogenesis, decreased  $\beta$ -oxidation and reduced VLDL export [4, 5]. Steatosis in the liver is characterized by a large intracytoplasmic fat droplet or well-defined droplets displacing the nucleus to the cell periphery [6]. The accumulation of hepatic lipids could be due to elevated peripheral fatty acids, *de novo* lipogenesis and defective apolipoprotein biosynthesis [7, 8]. The progression of hepatic steatosis often leads to liver inflammation or steatohepatitis and, if unchecked, will worsen liver fibrosis and cirrhosis [9]. Several mouse models are used to elucidate the mechanisms of fatty liver disease [10, 11]. The bulk of studies on NAFLD have been through the administration of high fat diets or methionine-choline-deficient diets and the use of genetically leptin-deficient (*ob/ob*) or leptin-receptor-deficient (*db/db*) mouse models [12]. These models exhibit insulin resistance which is one sequelae of NAFLD [13].

Increased insulin secretion has been directly implicated in the development of fatty liver disease [14]. The therapy used for insulin resistance frequently include the administration of TZDs which are agonists for the nuclear receptor peroxisome proliferator activated receptor gamma (*Ppar $\gamma$* ) [15]. However, studies have demonstrated that TZDs have also exhibited deleterious side effects that warrant their withdrawal from the market [16]. Of interest, selective *Ppar $\gamma$*  modulators (SPPARMs) that do not have the undesirable effects of TZDs have been recently identified [17, 18]. Since NAFLD often leads to insulin resistance, this paper focuses on the relationship between *Ppar $\gamma$*  and NAFLD.

## 2. Ppar-gamma (*Ppar $\gamma$* )

*Ppar $\gamma$*  is a member of the nuclear receptor superfamily of ligand-activated transcription factors [19] highly expressed in adipocytes [20, 21] and plays a role in improving glucose homeostasis and adipocyte differentiation [22]. It increases insulin sensitivity by upregulating the glucose transporter 4 (*Glut4*) [23]. *Ppar $\gamma$*  also enhances the transcription factors adipocyte determination and differentiation-dependent factor 1 (*Add1*) and sterol regulatory element binding protein 1 (*Srebp1*) which results in the expression of lipogenic genes such as fatty acid synthase (*Fas*) [24]. *Ppar $\gamma$*  is expressed as

2 major isoforms,  $\gamma 1$  and  $\gamma 2$ , generated from the same gene by alternate promoter usage and RNA splicing [25]. Both isoforms could stimulate adipogenesis when introduced to fibroblasts [26]. Adipocytes treated with the *Ppar $\gamma$*  ligand, TZD, stimulate expression of uncoupling protein 2 (*Ucp2*) and therefore increase energy expenditure [27]. Another mechanism of action by TZDs in the adipose tissue is to upregulate the expression of AMP-activated protein kinase (*Ampk*) which increases fatty acid oxidation while decreasing lipogenesis via downregulation of *Srebp-1c* and carbohydrate response element binding protein (*Chrebp*) [28]. The upregulation of hepatic *Ppar $\gamma$*  is frequently observed in mice fed a high fat diet [29]. In addition, liver specific deletion of *Ppar $\gamma$*  in mice established its role as a prosteatotic factor in the development of NAFLD [30]. Of importance is that *Ppar $\gamma$*  activation by TZDs promotes efflux of free fatty acids from the liver and muscle while increasing fat mass which consequently improves insulin sensitivity [31]. Therefore, whether the upregulation of *Ppar $\gamma$*  causes steatosis or vice versa remains unclear.

### 3. The Effect of *Ppar $\gamma$* Variants in the Development of NAFLD

Variants in the *Ppar $\gamma$*  gene found in human genotyping studies have been reported to affect hepatic steatosis. A Japanese cohort was first reported to have a polymorphism in the peroxisome proliferator activator receptor gamma coactivator 1 alpha (*Ppar $\gamma$ 1c1a*) gene [32]. The polymorphism in the T allele of rs2290602 was found in patients with nonalcoholic steatosis which was further confirmed by quantitative real time PCR [32]. In addition, single nucleotide polymorphisms (SNPs) in the C161T genotype in the *Ppar $\gamma$*  gene found in a Chinese population was associated NAFLD possibly through the adiponectin pathway [33]. Moreover, the Pro12Ala variant in the *Ppar $\gamma$*  gene was found to be associated with pathogenesis of NAFLD in Indian, Chinese, and North American cohorts but not in German and Italian cohorts [34–38]. Taken together, polymorphisms in the *Ppar $\gamma$*  gene could be useful to identify individuals that are at high risk for NAFLD but should not be considered as the main factor for the disease.

### 4. The Role of *Ppar $\gamma$* in the Development of Hepatic Steatosis

The mode of action of *Ppar $\gamma$*  in liver was suggested to promote insulin sensitivity but with concomitant development of fatty liver. High-fat diet fed mice develop hepatic steatosis and have increased *Ppar $\gamma$*  expression [39]. This could be due to the suppression cAMP response element binding protein (*Creb*) levels, the upstream regulator of *Ppar $\gamma$* , in high fat diet fed mice [39]. In hepatic overexpression studies, Yu et al. showed that *Ppar $\gamma$ 1* leads to adipogenic hepatic steatosis [40]. This group employed the *Ppara* deleted (*Ppara*-KO) mouse model and then injected the mice with adenovirus overexpressing *Ppar $\gamma$ 1* [40]. They showed that hepatic overexpression of *Ppar $\gamma$ 1* induced adipocyte specific

gene expression patterns in the livers of *Ppara*-KO mice [40]. Therefore, they propose that excess *Ppar $\gamma$*  activity can lead to the development of adipogenic hepatic steatosis [40]. In addition, hepatic adenoviral overexpression of *Ppar $\gamma$ 2* in lean mice increased liver triglyceride content and induced hypertension [41]. This occurrence was reported to involve the target of *Ppar $\gamma$* , fat specific protein 27 (*Fsp27*) [42] and its actions on the afferent vagal signals in the liver [41]. In a liver specific *Ppar $\gamma$*  deletion study, Gavrilova et al. reported that the A/ZIP/F-1 mouse model, which develops severe lipoatrophic diabetes, exhibited attenuation of hepatic steatosis but compromised triglyceride clearance [43]. The same group also showed that the liver *Ppar $\gamma$*  is essential for the effects of a *Ppar $\gamma$*  agonist, rosiglitazone, to improve glucose metabolism [43]. Moran-Salvador et al. reported that hepatocyte specific deletion of *Ppar $\gamma$*  in mice protected high fat diet fed mice from accumulation of lipids and, therefore, further implicated its role in the development of hepatic steatosis [30]. They also showed that the *Ppar $\gamma$*  in Kupffer cells might not be involved in the development of hepatic steatosis [30]. In addition, a mouse model of dyslipidemia showed that hepatic *Ppar $\gamma$ 2* upregulation induced hepatic *de novo* lipogenesis [44]. Zhang et al. fed a western-type diet to mice that express the human apolipoprotein B and lack the brown adipose tissue (*apoB/BATless*) [44]. These mice are obese, insulin resistant and have hepatic steatosis [44]. They showed that hepatic *Ppar $\gamma$ 2* expression is increased due to elevated rates of lipogenesis via the upregulation of *de novo* lipogenic genes *Fas* and acetyl-CoA carboxylase (*Acc*) [44]. Taken together, these studies strongly implicate *Ppar $\gamma$*  in the development of hepatic steatosis.

### 5. The Role of *Ppar $\gamma$* in the Reduction of Hepatic Steatosis

Diet induced hepatic fibrosis mouse models that were either treated with rosiglitazone or administered with adenovirus overexpressing *Ppar $\gamma$*  were shown to ameliorate hepatic steatosis [45, 46]. Mice fed a methionine-choline-deficient (MCD) diet developed severe hepatic steatosis, inflammation, and fibrosis with downregulation of *Ppar $\gamma$*  levels [45]. Meanwhile, mice that were fed the same diet supplemented with rosiglitazone were protected from the adverse effects of the MCD diet [45]. The protection from nutritional fibrosing steatohepatitis by *Ppar $\gamma$*  could be due to the inhibition of hepatic stellate cell activation which is one of the main causes for fibrosis [45]. Similarly, the hepatic adenoviral overexpression of *Ppar $\gamma$*  in MCD diet-fed mice elicited protection from fibrotic steatohepatitis [46]. This could be explained by the genetic upregulation of adiponectin (*adipoQ*) and hemoxygenase 1 (*Hmox1*) and the downregulation of inflammatory markers such as tumor necrosis factor alpha (*Tnfa*) and interleukin 6 (*Il-6*) [46]. In a model of hepatic steatosis involving alcohol, mice that were fed ethanol showed amelioration of hepatic steatosis following administration of rosiglitazone due to stimulation of fatty acid oxidation in the liver [47]. In addition, the Long Evans rats, which exhibit moderate obesity and

insulin resistance, were given rosiglitazone and subsequently ameliorated hepatic steatosis which could be modulated by Sirtuin 6 (*Sirt6*) and its target genes *Ppar $\gamma$ 1a*, forkhead box protein O1 (*Foxo1*), liver kinase B1 (*Lkb1*) and 5' adenosine monophosphate-activated protein kinase (*Ampk*) [48]. *In vitro* experiments, confirmed the function of *Sirt6* by using the free fatty acid stimulated mouse hepatocyte cell line, AML 12, which also showed the protection from hepatic steatosis following rosiglitazone treatment [48]. Similarly, Sprague-Dawley rats that were given high sucrose and high fat diet showed amelioration of hepatic steatosis following treatment with rosiglitazone [49]. The decrease in liver triglycerides in these rats could be due to the effect the *Ppar $\gamma$*  agonist in increasing serum adiponectin and the upregulation of fatty acid oxidation genes, carnitine palmitoyl transferase 1 (*Cpt1*) and acyl coenzyme A oxidase (*Aco*) [49]. Furthermore, dietary methionine restriction (MR) in F344 rats upregulated hepatic *Ppar $\gamma$*  expression, improved insulin sensitivity, and increased fatty acid oxidation [50–52]. Overall, these sets of data suggest that *Ppar $\gamma$*  ameliorated hepatic steatosis due to increased fatty acid oxidation.

## 6. The Development of Selective *Ppar $\gamma$* Modulators (SPPARMS)

Although *Ppar $\gamma$*  agonists have direct actions to improve insulin sensitivity, this line of treatment also has undesirable side effects. For example, rosiglitazone was reported to reduce bone mass in mice [53]. In addition, mice that are obese and diabetic develop hepatic steatosis following treatment with TZDs [54]. More recently, a meta-analysis of type 2 diabetes patients showed that pioglitazone is associated with increased risk for urinary bladder cancer [55]. The development of SPPARMS could potentially reduce these negative effects. Modifications in the *Ppar $\gamma$*  ligands showed direct effects on insulin sensitivity but not on adipogenesis [56, 57]. The ligand FMOC-L-Leucine, a chemically distinct ligand for *Ppar $\gamma$* , was reported to improve insulin sensitivity but did not affect hepatic lipid metabolism in *db/db* mice [58]. Telmisartan, an angiotensin receptor blocker that acts as a *Ppar $\gamma$*  ligand, enhanced insulin sensitivity and decreased body fat in high fat diet fed mice [59]. A synthetic *Ppar $\gamma$*  ligand, nTZDpa, ameliorated fasting hyperglycemia and hyperinsulinemia and caused decrease in weight gain and adipose tissue size in high fat diet fed mice [60]. In addition, results using a gene expression-based screening identified N-acetylfarnesylcysteine (AFC) as a full and partial agonist of *Ppar $\gamma$*  [61]. The compound upregulated *Ppar $\gamma$*  agonist target genes adipose differentiation-related protein (*Adrp*), angiopoietin-related protein 4 (*Angptl4*) and *adipoq*, but was only a partial agonist of adipocyte fatty acid binding protein 2 (*ap2*) [61]. The AFC also improved glucose homeostasis and reduced adipose tissue inflammation and expansion in diet-induced obese mice [61]. Furthermore, a synthetic *Ppar $\gamma$*  antagonist, SR-202, decreased expression of *Ppar $\gamma$*  target genes and promoted insulin sensitivity in diet-induced obese mice as well as in *ob/ob* mice [62]. Moreover, a partial *Ppar $\gamma$*  agonist, INT131, was designed to

mitigate insulin sensitivity while minimizing the side effects of thiazolidinediones [63]. It was reported that INT131 reduced fasting plasma glucose in humans and also increased insulin sensitivity in *db/db* and diet induced obesity in mice [64, 65]. Taken together, recent data on the use of SPPARMS maintain the effects of *Ppar $\gamma$*  as an insulin sensitizing agent but with decreased risks for undesirable effects.

## 7. Conclusion

With all these data surrounding the effect of *Ppar $\gamma$*  on the development of NAFLD and improvements in insulin sensitivity in several models, it is still not conclusive as to whether the nuclear receptor is beneficial or detrimental. Therefore, further investigations are necessary to elucidate the effect of specific conformational and structural differences between the nuclear receptor and its ligands. The advent of the development of SPPARMS points to the direction of specifically eliciting the desirable effects of *Ppar $\gamma$*  activation.

## Conflict of Interests

The author reports no conflict of interests.

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