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The Role of PPAR in Liver Cirrhosis: An Update Review

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Liver cirrhosis is the final stage of various chronic liver diseases characterized by fibrosis and nodule formation in the liver. The pathophysiology of liver cirrhosis involves a complex process, in which the role of peroxisome proliferator-activated receptors (PPAR) is very important. PPARα, which is mainly expressed in the liver, plays an important role in the regulation of hepatic lipid metabolism. In cirrhosis, PPARα expression is decreased, resulting in impaired fatty acid oxidation and increased lipogenesis. This contributes to the accumulation of fat in the liver, which is one of the characteristics of NAFLD that can progress to cirrhosis. PPARγ, although better known for its role in adipose tissue, also has important functions in the liver. In cirrhosis, PPARγ plays a role in inhibiting the activation and proliferation of HSCs, and modulating macrophage polarization. PPARγ activation can reduce liver inflammation and fibrosis, and increase insulin sensitivity. Recent studies have shown that PPARγ agonists can improve steatosis, reduce inflammation, and significantly improve the response to hepatitis viruses. PPARδ, which is widely expressed in various tissues including the liver, plays a role in lipid metabolism and liver inflammation. Moreover PPARs role in viral hepatitis induced liver chirrosis is still remain controversial. Although research on PPARδ in the context of liver cirrhosis is still limited, several studies have shown its potential anti-fibrotic effects. Thus, a deeper understanding of the role of PPARs in the pathophysiology of liver cirrhosis opens up new opportunities for the development of more effective therapies to treat this chronic liver disease.

Keywords: PPAR, Liver Cirhosis, Hepatitis

INTRODUCTION

Liver cirrhosis is the final stage of various chronic liver diseases, characterized by diffuse liver fibrosis and the replacement of normal liver architecture with regenerative nodules (Zhou et al., 2014; Liu & Chen, 2022). This irreversible damage severely affects liver function and represents a significant global health burden. The prevalence of cirrhosis has continued to rise in recent decades. In 2017, there were approximately 5.2 million cases of cirrhosis and chronic liver disease worldwide an increase compared to 1990 (Liu & Chen, 2022). Furthermore, cirrhosis was responsible for 1.48 million deaths globally in 2019, marking an 8.1% increase from 2017 (Liu & Chen, 2022).

The causes of cirrhosis are diverse and vary by region. All causes involve chronic liver injury that triggers inflammation and fibrotic scarring. One of the most well-known causes is alcoholic liver disease (ALD). Long-term alcohol consumption leads to direct hepatotoxicity, fat accumulation, and chronic inflammation. It is estimated that 15–20% of heavy drinkers eventually develop cirrhosis (Smith et al., 2019). Another major cause is chronic viral hepatitis, especially hepatitis B (HBV) and hepatitis C (HCV). These infections cause long-term inflammation and hepatocyte injury, eventually resulting in fibrosis. HBV is particularly prevalent in the Asia-Pacific region, making it a leading cause in that area (Liu & Chen, 2022).

In recent years, non-alcoholic steatohepatitis (NASH) has emerged as a significant contributor to cirrhosis. NASH is a severe form of fatty liver disease linked to obesity, type 2 diabetes, and metabolic syndrome. It causes liver damage similar to that seen in alcoholic liver disease, even without alcohol use (Zhou et al., 2014). Drug-induced liver injury also plays a role in cirrhosis development. Overdose or chronic use of paracetamol (acetaminophen) can lead to acute and chronic liver failure. Likewise, methotrexate, a medication used for autoimmune diseases, is associated with liver fibrosis when used long-term (Smith et al., 2019). Autoimmune hepatitis is another cause, resulting from the immune system mistakenly attacking liver tissue. It often affects young women and, if left untreated, progresses to cirrhosis. Long-term immunosuppressive therapy is usually required (Liu & Chen, 2022).

Additional causes include bile duct disorders, such as primary biliary cholangitis and secondary biliary cirrhosis, which cause bile retention and liver injury.

Inherited metabolic conditions like hemochromatosis (iron overload) and Wilson's disease (copper accumulation) can also cause cirrhosis if undiagnosed. Rarer causes include α1-antitrypsin deficiency, veno-occlusive disease, and cardiac cirrhosis due to chronic heart failure (Zhou et al., 2014; Smith et al., 2019). The predominant causes of cirrhosis vary by geography. In Western countries, the most common causes are alcohol abuse, HCV, and increasingly NAFLD due to rising obesity and sedentary lifestyles (Smith et al., 2019; Liu & Chen, 2022). In contrast, chronic HBV infection remains the top cause in Asia. Additionally, a number of cases remain cryptogenic, meaning no specific cause can be identified. Many of these are now thought to be "burnt-out" NASH in patients with underlying metabolic risk factors (Zhou et al., 2014).

The clinical course of cirrhosis progresses from an asymptomatic compensated stage to a symptomatic decompensated stage. Complications of decompensation include ascites, variceal bleeding, hepatic encephalopathy, renal dysfunction, and infections (Ginès et al., 2021; Liu & Chen, 2022). These significantly increase hospitalization rates, reduce quality of life, and are linked to higher mortality. Key mechanisms include portal hypertension, systemic inflammation, and liver failure (Ginès et al., 2021). Early diagnosis of cirrhosis is essential, though only one-third of individuals are aware of their condition (Smith et al., 2019). Patients are typically asymptomatic until decompensation occurs. When suspected, evaluation includes liver function tests, complete blood count, coagulation profile, viral hepatitis serology, iron studies (ferritin, transferrin saturation), and imaging such as abdominal ultrasound (Smith et al., 2019; Jameson et al., 2020).

Prognosis is commonly assessed using the Child-Turcotte-Pugh (CTP) score, which considers ascites, encephalopathy, bilirubin, albumin, and INR. CTP class A (5–6 points) predicts a 1-year survival rate of 100%, while class B (7–9) predicts 80%, and class C (10–15) predicts 45%. The MELD (Model for End-Stage Liver Disease) score, which includes creatinine, bilirubin, INR, and sodium, is another widely used tool for assessing disease severity and prioritizing patients for liver transplantation (Jameson et al., 2020). Management of cirrhosis focuses on slowing disease progression, treating complications, and assessing for liver transplantation. Esophageal varices are managed with endoscopy and beta-blockers, ascites with salt restriction and diuretics, and hepatic encephalopathy with lactulose or rifaximin (Ginès et al., 2021). Preventing infections such as spontaneous bacterial peritonitis is also a key aspect of care. Encouragingly, recent research has shown that liver fibrosis is a dynamic and potentially reversible process, especially in the early stages. This opens opportunities for new antifibrotic therapies and reinforces the importance of early diagnosis and intervention (Jung & Yim, 2017).

Several medications and toxins can also induce liver damage leading to cirrhosis. For example, paracetamol (acetaminophen) in overdose can cause acute liver failure and chronic damage if repeatedly misused. Long-term use of drugs like methotrexate, often prescribed for autoimmune diseases, is also associated with liver fibrosis (Smith et al., 2019). In addition, autoimmune hepatitis is a condition where the body's immune system mistakenly attacks healthy liver cells, causing ongoing inflammation and fibrosis if left untreated. These cases are often seen in younger women and may require long-term immunosuppressive therapy (Liu & Chen, 2022).

Other important causes include diseases affecting the bile ducts. Primary biliary cholangitis (formerly called primary biliary cirrhosis) and secondary biliary cirrhosis result from obstruction or destruction of bile ducts, leading to toxic bile accumulation and liver damage. Inherited metabolic diseases like hemochromatosis, which causes excessive iron accumulation, and Wilson's disease, which causes copper buildup, are also well-documented causes of cirrhosis if not diagnosed early (Zhou et al., 2014). Moreover, cardiac-related liver congestion due to right-sided heart failure or constrictive pericarditis can lead to passive congestion in the liver, eventually progressing to fibrosis. α1-antitrypsin (AAT) deficiency, a genetic condition that leads to abnormal protein deposits in the liver, and veno-occlusive disease, which involves blockage of liver blood vessels, are rarer but significant contributors (Smith et al., 2019).

The predominant causes of cirrhosis vary across geographical regions. In Western countries, the most frequent causes are alcohol abuse, hepatitis C infection, and non-alcoholic fatty liver disease (NAFLD), which is increasingly prevalent due to rising rates of obesity and sedentary lifestyles (Smith et al., 2019; Liu & Chen, 2022). In contrast, in the Asia-Pacific region, chronic hepatitis B infection remains the primary cause of cirrhosis due to its high endemicity (Liu & Chen, 2022). Furthermore, a subset of cirrhosis cases remains idiopathic or cryptogenic, meaning no clear cause is identified despite investigation. Recent studies suggest that many cryptogenic cases may actually be "burnt-out" NASH, especially in patients with metabolic risk factors (Zhou et al., 2014).

The course of cirrhosis generally begins from the asymptomatic stage (compensated cirrhosis) to the symptomatic stage (decompensated cirrhosis) (Ginès et al., 2021). In the decompensation stage, various complications such as ascites, variceal bleeding, hepatic encephalopathy, kidney disorders, and infections can occur (Liu & Chen, 2022). These complications often result in hospitalization, decreased quality of life, and increased mortality (Ginès et al., 2021). Progressive portal hypertension, systemic inflammation, and liver failure are major driving factors in disease outcome (Ginès et al., 2021).

Early diagnosis of cirrhosis is crucial, but only one in three people with cirrhosis are aware of their condition (Smith et al., 2019). Most patients with cirrhosis remain asymptomatic until decompensation occurs. When clinical signs, symptoms, or abnormal liver function tests are found, further evaluation should be performed promptly. Initial testing includes hepatitis virus serology, ferritin, transferrin saturation, and abdominal ultrasonography, as well as complete blood count, liver function tests, and prothrombin time/INR (Smith et al., 2019; Jameson et al.,

2020). The prognosis of patients with liver cirrhosis can be assessed using the modified Child-Turcotte-Pugh (CP) scoring based on ascites, encephalopathy, and laboratory parameters (bilirubin, albumin, INR) where CP A (5–6 points) has a 1-year survival rate of 100%, CP B (7–9 points) 80%, CP C (10–15 points) 45%. The second scoring can use MELD (Model for End-Stage Liver Disease) used for therapy stratification and predicting 3-month survival in cirrhosis and some forms of acute liver disease based on creatinine, INR, total bilirubin, and sodium (Jameson et al., 2020).

Management of liver cirrhosis focuses on preventing disease progression, managing complications, and in some cases, liver transplantation (Ginès et al., 2021). The goal of treatment is to prevent cirrhosis, decompensation, and death. Varices are monitored endoscopically and often require prophylaxis with non-selective beta-blockers. Management of ascites includes diuresis, salt restriction, and antibiotic prophylaxis for spontaneous bacterial peritonitis when indicated. Hepatic encephalopathy is managed with lifestyle and nutritional modifications, and the use of lactulose and rifaximin when needed (Ginès et al., 2021). Recent studies have shown that liver fibrosis is a dynamic process and early-stage cirrhosis may be reversible, opening up new opportunities for more effective therapeutic interventions (Jung and Yim, 2017).

METHODS

This study was conducted in the form of a narrative literature review aimed at comprehensively evaluating the role of peroxisome proliferator-activated receptors (PPAR) in the pathogenesis and therapeutic potential of liver cirrhosis. The methodological approach in this study involves a systematic review of scientific literature conducted through various reputable scientific databases, including PubMed, ScienceDirect, Cochrane Library, SpringerLink, MDPI, ProQuest, Wiley Online Library, and Google Scholar. The literature search focused on articles discussing the involvement of PPAR—including PPAR-α, PPAR-γ, and PPAR-δ subtypes—in the context of liver cirrhosis or other relevant chronic liver diseases. The search strategy was developed using a combination of free terms and standard terms (Medical Subject Headings/MeSH) such as "liver cirrhosis," "chronic liver disease," "PPAR," "hepatic fibrosis," and "PPAR agonists," which were organised with the help of Boolean operators AND and OR to filter articles relevant to the topic.

The literature considered in this study includes articles published within the last ten years, from January 2014 to March 2024. The selection criteria were based on thematic relevance, direct relevance to the topic of liver cirrhosis and PPAR, and the availability of articles in full text in English or Indonesian. The included articles consist of peer-reviewed publications and encompass various types of scientific writings, such as original research, systematic reviews, meta-analyses, and high-quality narrative reviews. This review also includes experimental studies on animals and cell cultures, as well as clinical studies on humans, provided they discuss the molecular mechanisms of PPAR or its therapeutic effects on fibrosis and liver cirrhosis.

All articles found in the search were screened in several stages. The initial process began with selection based on titles and abstracts, which resulted in 156 articles considered relevant. These articles were then checked for duplication using reference management software. After the deduplication stage, 120 unique articles were obtained for further review. The next selection process was carried out on the full text based on predetermined criteria. Articles that did not align with the main theme, only briefly mentioned PPAR, did not focus on liver cirrhosis, or had not undergone peer review were excluded from the final analysis. Additionally, articles that were conference abstracts, editorials, opinions, or letters to the editor were also excluded from this analysis as they did not meet the established scientific standards. After undergoing a full selection process, 42 articles were considered in depth, and 22 of them were eliminated for failing to meet the criteria for substance or methodology. Thus, a total of 20 articles were selected for comprehensive analysis in this study.

Data extraction was performed using a thematic narrative approach, namely by identifying the main findings from each article relevant to a specific PPAR subtype. The analysis focused on biological and molecular aspects, including PPAR expression in liver cells, its role in lipid and glucose metabolism, its effects on inflammation and oxidative stress, and its influence on the modulation of hepatic stellate cells, which are key components in the fibrogenesis process. Additionally, articles discussing the efficacy of PPAR agonists, both preclinical and clinical, were analysed to describe the therapeutic potential of PPAR for liver cirrhosis and its associated complications.

RESULTS AND DISCUSSION

PPAR

PPARs are nuclear receptors that play an important role in regulating metabolism and energy homeostasis. The three-dimensional structure of PPARs consists of a DNA-binding domain at the N-terminus and a ligand-binding domain (LBD) at the C-terminus (Grygiel-Górniak, 2014). PPARs have five main functional domains in their canonical structure, namely activation function-1 (AF-1), DNA-binding domain (DBD), hinge region, ligand-binding domain (LBD), and activation function 2 (AF-2) (Lin et al., 2022).

The DNA-binding domain (DBD) of PPARs consists of two highly conserved zinc finger motifs. These motifs play a role in recognizing and binding specific DNA sequences called peroxisome proliferator response elements (PPREs) to target genes (Grygiel-Górniak, 2014; Lin et al., 2022). After interacting with agonists, PPARs translocate to the nucleus and form heterodimers with another nuclear receptor, the retinoid X receptor (RXR). The PPAR-RXR heterodimer complex then binds to PPRE to activate target gene transcription (Grygiel-Górniak, 2014).

The ligand-binding domain (LBD) of PPARs is approximately 1300-1400 Å3 in size, relatively large compared to other nuclear receptors (Honda et al., 2022).

This allows PPARs to bind a variety of ligands with lower affinity. The LBD consists of 13 α-helices and one β-sheet region, with the ligand-binding pocket located in the center of the domain. Ligand binding to the LBD causes a conformational change that facilitates release of corepressors and recruitment of coactivators (Honda et al., 2022).

There are three subtypes of PPAR, namely PPARα, PPARγ, and PPARβ/δ, which have different but overlapping tissue distributions and biological functions (Hong et al., 2019; Wagner & Wagner, 2020). PPARα is mainly expressed in the liver, brown adipose tissue, heart, kidney and muscle, and plays an important role in the regulation of lipid metabolism (Hong et al., 2019). PPARγ is abundant in adipose tissue and immune cells, and plays a role in adipocyte differentiation and insulin sensitivity. While PPARβ/δ is widely expressed in various tissues and is involved in lipid and glucose metabolism (Hong et al., 2019; Wagner & Wagner, 2020).

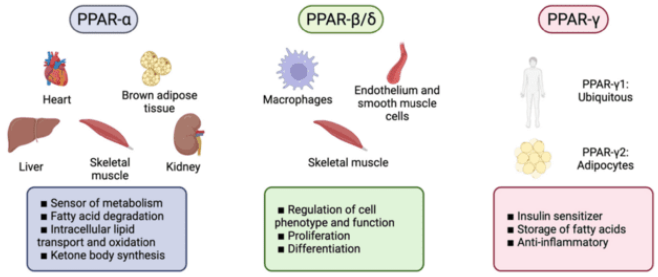

Figure 1. PPAR expression in various tissues and its main roles (Guixé-Muntet et al., 2022)

PPARs are a subfamily of nuclear receptors that play a role in metabolism and inflammation. There are three isotypes of PPARs: PPARα, PPARβ/δ, and PPARγ which are expressed in various cell types and tissues, and have different functions. Figure 1 describe the PPARs expression in various tissues and its main roles. PPARs function as fatty acid sensors that control various metabolic processes. Activation of PPARs can regulate the expression of genes involved in lipid and glucose homeostasis, cell differentiation, proliferation, inflammation, and energy metabolism (Lu et al., 2017; Hassan et al., 2021). Due to their important role in metabolism, PPARs are potential therapeutic targets for various metabolic diseases such as diabetes, obesity, and metabolic syndrome (Lu et al., 2017; Wagner & Wagner, 2020). In addition, PPARs are also involved in the pathogenesis of cancer and inflammatory diseases, making them a target for research for the development of new therapies (Gou et al., 2017; Christofides et al., 2021).

PPAR in The Pathogenesis of Liver Chirrosis

Liver sinusoidal endothelial cell (LSEC) dysfunction is one of the key components in the pathophysiology of liver cirrhosis and portal hypertension. Under normal conditions, LSECs play a crucial role in regulating intrahepatic blood flow and maintaining hepatic vascular homeostasis. However, in liver cirrhosis, significant structural and functional changes occur in LSECs (Iwakiri at al., 2014).

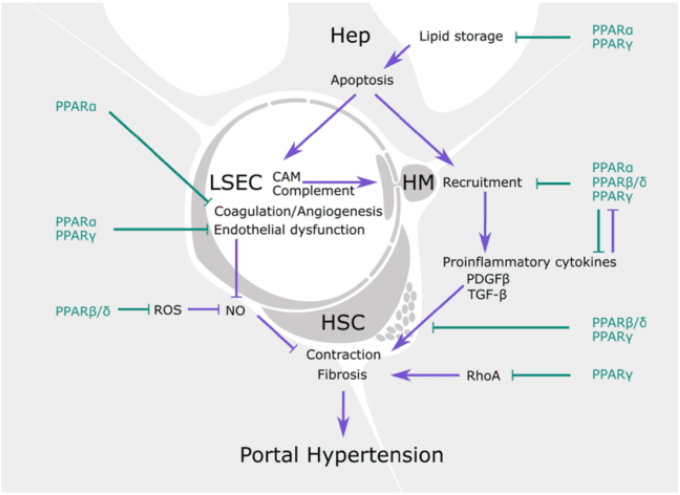

Figure 2. The potential effects and underlying mechanisms of PPAR agonists on hepatic vascular dysfunction (Guixé-Muntet et al., 2022).

Figure 2 described that the hepatic microvasculature plays a crucial role in both healthy liver and chronic liver disease. Under normal conditions, LSECs closely communicate with hepatic stellate cells (HSCs) to regulate intrahepatic blood flow. In a healthy state, LSECs synthesize nitric oxide (NO) and other vasodilators, which are detected by HSCs, thereby triggering vasodilation. However, during chronic liver disease, LSECs lose their specialized phenotype, and their ability to produce NO decreases, leading to reduced HSC sensitivity to vasodilators. This condition results in microvascular dysfunction. In liver chirrosis, activated HSCs respond by contracting and proliferating, further affecting intrahepatic blood flow. These vascular abnormalities are known as the dynamic component of increased intrahepatic vascular resistance in liver disease and represent a major factor in the development of portal hypertension (Guixé-Muntet et al., 2022; Qiu et al., 2023).

The potential effects and underlying mechanisms of PPAR agonists on hepatic function have been investigated through both preclinical and clinical studies. Preclinical research, largely based on animal models and in vitro systems, has demonstrated that PPAR agonists—particularly those targeting PPAR-α, PPAR-γ, and PPAR-δ—can exert anti-inflammatory, antifibrotic, and lipid-lowering effects. These benefits are primarily mediated through the regulation of genes involved in fatty acid oxidation, insulin sensitivity, and inhibition of hepatic stellate cell activation, which are key processes in liver fibrosis (Gross et al., 2017; Lefebvre et al., 2018). In clinical settings, several PPAR agonists have shown potential in improving liver histology in patients with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). For instance, pioglitazone, a PPAR-γ agonist, has been associated with histological improvements in NASH patients (Cusi et al., 2016), while elafibranor, a dual PPAR-α/δ agonist, showed early

promise, though later trials failed to meet primary endpoints (Ratziu et al., 2021).

However, the translation of preclinical results into clinical success has faced significant challenges. These include interspecies differences in liver metabolism, inconsistencies in patient response, variability in disease progression, and concerns about the long-term safety and tolerability of some PPAR agonists (Friedman et al., 2018). Consequently, more robust, targeted, and longitudinal clinical trials are needed to establish the definitive role of PPAR agonists in the treatment of advanced liver disease, including cirrhosis.

All three PPAR subtypes play a role in NO synthesis by endothelial cells and help prevent vascular dysfunction, which is typically associated with a pro-oxidant phenotype in endothelial cells. PPARβ/δ agonists enhance the expression of antioxidant enzymes such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), catalase, and thioredoxin, which reduce reactive oxygen species (ROS). PPARα activation exhibits similar effects, particularly in the hepatic microvasculature of cirrhotic rats. In contrast, vascular smooth muscle cell-specific deletion of PPARγ results in exaggerated responses to angiotensin II, worsening vascular dysfunction. PPARα and PPARγ also play a role in preventing smooth muscle cell proliferation and vascular remodeling by blocking the PDGF and TGF-β pathways in the regulation of vascular tone (Guixé-Muntet et al., 2022). Impaired NO production by LSECs is also a key factor in endothelial dysfunction in cirrhosis. Under normal conditions, NO acts as an important vasodilator that helps regulate hepatic vascular tone. However, in cirrhosis, there is a significant reduction in NO production and bioavailability at the sinusoidal level. This is caused by several factors, including decreased activity and expression of endothelial nitric oxide synthase (eNOS), increased levels of eNOS inhibitors such as caveolin-1, and elevated oxidative stress that inactivates NO (Iwakiri et al., 2014; Iwakiri e al., 2021).

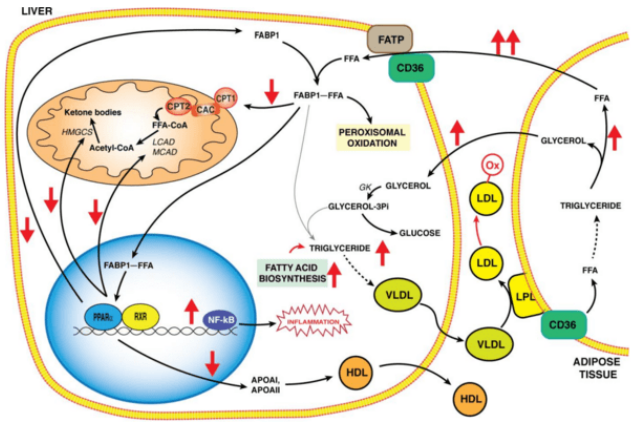

Figure 3. The role of PPARα in hepatic lipid metabolism pathways (Todisco et al., 2022).

Alterations in lipid and glucose metabolism are key aspects in the pathophysiology of liver cirrhosis. In cirrhotic conditions, significant disturbances in glucose and lipid homeostasis occur, contributing to disease progression. Fat accumulation in the liver (steatosis) is a common hallmark frequently observed in liver cirrhosis. This steatosis results from an imbalance between lipid input and output in the liver. Several mechanisms contribute to hepatic fat accumulation, including increased lipolysis in adipose tissue, enhanced de novo fatty acid synthesis in the liver, and impaired secretion of very low-density lipoprotein (VLDL) from the liver (Liu et al., 2010; Bhat & Mani, 2023).

Figure 2.2 illustrates the role of PPARα in hepatic lipid metabolism and the pathogenesis of NASH. In hepatocytes, PPARα regulates the expression of genes involved in lipid metabolism pathways, such as FABP1 (fatty acid-binding protein-1), which controls the transport, trafficking, and storage of free fatty acids (FFAs), as well as LCAD (long-chain acyl-CoA dehydrogenase) and MCAD (medium-chain acyl-CoA dehydrogenase), which are involved in mitochondrial β-oxidation. The accumulation of FFAs in the liver partly due to triglyceride mobilization from adipose tissue combined with reduced PPARα activation, disrupts hepatic lipid homeostasis and promotes lipotoxicity in NASH (indicated by red arrows) (Todisco et al., 2022).

Another underlying pathogenesis of liver cirrhosis is the activation of Kupffer cells and inflammation. Kupffer cells, the macrophages of the liver, play a crucial role in hepatic immune and inflammatory responses. Upon liver injury, Kupffer cells become activated and release various inflammatory mediators, including pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. These cytokines not only trigger a local inflammatory response but also stimulate the activation HSCs, which are key players in the fibrogenesis process. In addition to cytokines, activated Kupffer cells also produce chemokines such as IL-8, MCP-1, and MIP-1α. These chemokines play an important role in recruiting additional inflammatory cells to the liver, including neutrophils and monocyte-derived macrophages, further amplifying the inflammatory response. The production of ROS by activated Kupffer cells also contributes to hepatocyte damage and the perpetuation of inflammation. ROS can induce oxidative stress in liver cells, which in turn can trigger cell death and further stimulate inflammatory responses (Zhou et al., 2014; Kolios et al., 2006; Zhang dan Bansal, 2020).

Mitochondrial dysfunction also occurs in liver cirrhosis, which is characterized by a reduction in oxidative phosphorylation (OXPHOS) capacity and ATP production. Recent studies have shown that in patients with decompensated cirrhosis, there is a metabolic shift from OXPHOS to aerobic glycolysis. This results in decreased energy production efficiency and reduced flexibility in substrate utilization by cells. Mitochondrial DNA (mtDNA) damage caused by oxidative stress also plays a significant role. Damaged mtDNA can be released into the circulation and act as damage-associated molecular patterns (DAMPs), triggering immune system activation and exacerbating systemic inflammation in advanced cirrhosis. Mitochondrial oxidative stress also contributes to hepatocyte death through apoptosis (Engelmann et al., 2021; Iwakiri et al., 2014).

PPARα

PPARα plays an important role in the pathogenesis of liver cirrhosis through several mechanisms. First, PPARα plays a crucial role in the regulation of hepatic lipid metabolism. PPARα activation increases the expression of genes involved in fatty acid transport and oxidation, thereby helping to reduce lipid accumulation in the liver (Gong et al., 2023). This is important because hepatic steatosis is an early stage in the development of NAFLD which can progress to cirrhosis (Lin et al., 2022).

Second, PPARα has significant anti-inflammatory effects on the liver. Studies have shown that activation of PPARα can suppress the pro-inflammatory NF-κB signaling pathway and inhibit the expression of inflammatory cytokines such as TNF-α, IL-6, and COX-2. In addition, PPARα also increases the expression of anti-inflammatory factors such as adiponectin and heme oxygenase-1 (HO-1). These anti-inflammatory effects play an important role in reducing liver damage and fibrosis development (Gong et al., 2023).

Third, PPARα has antioxidant effects that help protect liver cells from oxidative stress. PPARα activation increases the expression of antioxidant enzymes such as catalase and superoxide dismutase, and reduces the production of ROS. This is important because oxidative stress is one of the main factors contributing to liver cell damage and the development of cirrhosis (Lin et al., 2022; Gong et al., 2023).

Fourth, PPARα plays a role in inhibiting the activation of HSCs. HSCs are the main cells responsible for the production of extracellular matrix and scar tissue formation in cirrhosis. Studies have shown that PPARα activation can inhibit the proliferation and activation of HSCs, thereby reducing collagen production and fibrogenesis (Nan et al., 2013; M. Zardi et al., 2013).

Dysregulation of lipoprotein metabolism leads to decreased HDL and formation of LDL and oxidized LDL, which contribute to foam cell formation and ultimately lead to atherosclerosis. Finally, PPARα is also involved in the regulation of bile acid metabolism, which may influence the development of cirrhosis. PPARα activation alters bile acid composition by increasing the production of cholic acid and taurocholic acid. These changes may affect bile acid signaling and lipid metabolism, which in turn may influence the development of chronic liver diseases such as cirrhosis (Xie et al., 2019).

PPARγ

PPARγ plays an important role in the pathogenesis of liver cirrhosis through several major mechanisms. First, PPARγ plays a role in inhibiting the activation and proliferation of HSCs. Under normal conditions, HSCs are in a quiescent state and express high amounts of PPARγ. However, during the process of liver fibrosis, PPARγ expression decreases along with the activation of HSCs into myofibroblasts that produce excess extracellular matrix (Li et al., 2021; Yum et al., 2023). Activation of PPARγ agonists or overexpression of PPARγ has been shown to inhibit HSCs activation and reduce liver fibrosis in animal models (Ni et al., 2021; Yum et al., 2023).

Moreover, PPARγ plays a role in modulating macrophage polarization. PPARγ activation can shift macrophage polarization from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype (Chen et al., 2021). This is important because M2 macrophages play a role in the resolution of inflammation and tissue repair. Recent studies have shown that human umbilical cord mesenchymal stem cell therapy can increase PPARγ expression in liver macrophages, thereby promoting macrophage polarization from M1 to M2 type (Yao et al., 2023).

Furthermore, PPARγ has significant anti-inflammatory and anti-fibrotic effects. PPARγ activation can inhibit pro-inflammatory signaling pathways such as NF-κB and reduce the production of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 (Yuan et al., 2004). In addition, PPARγ also inhibits the TGF-β1/Smad signaling pathway which plays an important role in liver fibrogenesis. PPARγ agonists such as rosiglitazone have been shown to reduce liver inflammation and fibrosis in animal models of cirrhosis (Ni et al., 2021).

Thus, PPARγ is a promising therapeutic target for liver cirrhosis. The development of PPARγ agonists, both synthetic and natural, is ongoing to harness the protective effects of PPARγ against inflammation, oxidation, fibrosis, and fatty liver. However, further research is needed to optimize the balance between the beneficial and side effects of PPARγ activation in the treatment of chronic liver disease (Wu et al., 2020).

PPARδ

The role of PPARδ in the pathogenesis of liver cirrhosis has been the focus of research in recent years. PPARδ plays an important role in lipid metabolism and liver inflammation, and has shown promising potential anti-fibrotic effects. PPARδ is involved in the regulation of lipid metabolism in the liver. Activation of PPARδ has been shown to reduce intrahepatic lipid accumulation and stimulate β-oxidation of fatty acids in the liver and hepatic cells (Wang et al., 2020). This is important in the context of liver cirrhosis, as excessive lipid accumulation in the liver (steatosis) may contribute to the development of chronic liver disease (Iwaisako et al., 2012).

In addition, PPARδ has significant anti-inflammatory effects in the liver. Studies have shown that PPARδ can inhibit NF-κB activity by directly binding to the p65 subunit, thereby reducing the inflammatory response. This anti-inflammatory effect may help prevent further liver damage and the development of fibrosis (Wang et al., 2020).

PPARδ also shows potential in prevention and reduction of liver fibrosis. A study using the PPARδ agonist KD3010 demonstrated significant hepatoprotective and anti-fibrotic effects in an animal model of liver fibrosis. This agonist was able to reduce the deposition of extracellular matrix proteins and decrease the expression of profibrogenesis connective tissue growth factor (Iwaisako et al., 2012).

Interestingly, PPARδ also plays a role in modulating autophagy in liver cells. Recent studies have shown that PPARδ can increase hepatic autophagy flow,

which plays an important role in lipid clearance and protection against liver steatosis. This mechanism involves the AMPK/mTOR signaling pathway and may contribute to the anti-steatosis and anti-fibrotic effects of PPARδ (Tong et al., 2019).

However, the role of PPARδ in liver cirrhosis still requires further research. Several studies have shown conflicting results, especially regarding the effects of various PPARδ agonists. In addition, the potential long-term side effects of PPARδ activation, including the risk of carcinogenesis, still need to be carefully evaluated (Wang et al., 2020).

Overall, PPARδ appears as a promising therapeutic target for liver cirrhosis, with its ability to modulate lipid metabolism, reduce inflammation, and inhibit fibrosis. However, further research is needed to fully understand its mechanism of action and optimize its therapeutic potential in the treatment of chronic liver disease (Wang et al., 2020).

Table1.

Summary Comparison of PPAR Types

Parameter	PPARα	PPARγ	PPARβ/δ
Expression in Liver Cells	Dominant in hepatocytes and Kupffer cells	Dominant in hepatic stellate cells (HSCs) and macrophages	Expressed in hepatocytes and sinusoidal endothelial cells (LSECs)
Anti-Fibrotic Mechanism	- Inhibits HSCs activation via TGF-β reduction- Increases fatty acid β-oxidation	- Suppresses HSCs proliferation- Increases apoptosis of activated HSCs	- Modulation of macrophage polarization (M1→M2)- Increases lipid oxidation
Effects on Inflammation	Decreases production of IL-6, TNF-α, and pro-inflammatory chemokines	Inhibits NF-κB activation and ROS production	**Reduce**VCAM-1 expression and leukocyte adhesion
Role in Steatosis	Prevents lipid accumulation by increasing fatty acid oxidation	Reducing lipogenesis through SREBP-1c inhibition	Increases energy expenditure and fatty acid oxidation
PPAR Agonists (Drug)	- Fenofibrate (ALD) - Pemafibrate (NAFLD), Bezafibrate, Gemfibrozil	- Pioglitazone (NASH)- Rosiglitazone (insulin resistance)	**GW501516**(preclinical trial), Seladelpar
Effects on Portal Hypertension	Correcting LSECs dysfunction and NO production	Reducing portal pressure via ET-1 inhibition	Stabilizes intrahepatic vascular tone
Related Paths	- CPT1A-ACOX1-FGF21	- Adiponectin-GLUT4-TIMP-1	- PDK4-ANGPTL4- UCP2
Therapy Challenges	Hepatoprotective effect is limited to advanced cirrhosis.	Risk of fluid retention and weight gain	Limited clinical data in humans

PPAR agonists

PPARα agonists have shown promising potencies in the therapy of liver cirrhosis, especially in reducing liver steatosis and fibrosis. Recent studies have revealed that PPARα activation can prevent the development of liver fibrosis through multiple mechanisms (Nan et al., 2014). One of the main mechanisms is by increasing fatty acid oxidation in the liver and suppressing lipogenesis, which can reduce fat accumulation in the liver. This is important because liver steatosis is an early stage that can progress to cirrhosis if untreated (Durairajan et al., 2024).

In addition to their effects on lipid metabolism, PPARα agonists also have anti-inflammatory and anti-oxidant properties that play an important role in preventing further liver damage (Nan et al., 2014). Studies in mouse models have shown that PPARα agonists can reduce ethanol-induced liver injury by decreasing oxidative stress and inflammation (Durairajan et al., 2024). This anti-inflammatory effect is not only limited to hepatocytes, but also affects immune cells such as Kupffer cells and macrophages, which play an important role in the development of liver fibrosis (Lefere et al., 2020).

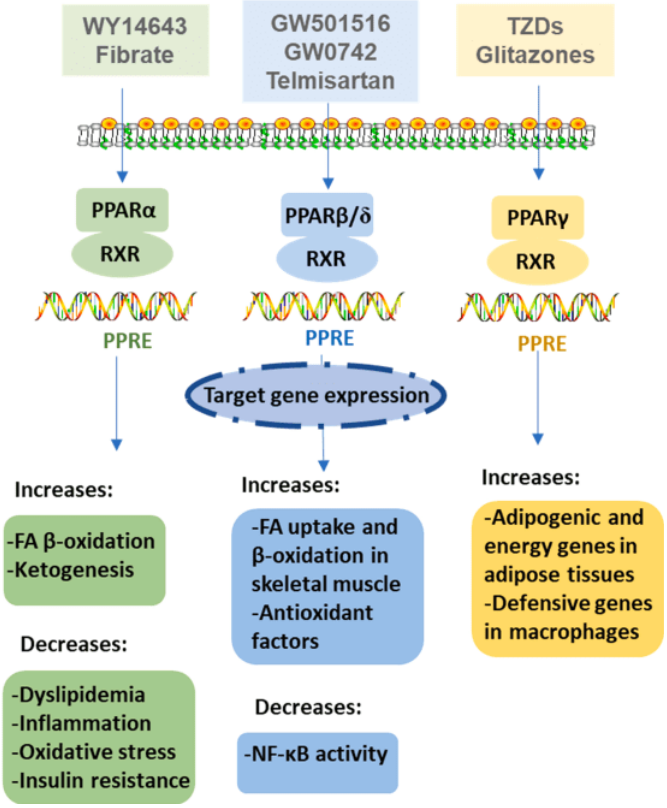

Figure 4. Schematic diagram of the physiological roles of different PPAR agonists types (Qiu et al., 2023).

Figure 4 illustrates the physiological roles of different types of PPAR agonists. After binding to their respective ligands, PPARs translocate to the nucleus, where they heterodimerize with the retinoid X receptor (RXR) and bind to specific DNA sequences known as PPAR response elements (PPREs), leading to transcriptional regulation of target genes. PPARs are naturally activated by fatty acids and eicosanoids, and pharmacologically activated by synthetic small molecules such as fibrates (PPARα agonists), GW501516 and telmisartan (PPARβ/δ agonists), and glitazones (PPARγ agonists). PPARα plays a crucial role in lipid metabolism, particularly in the hypolipidemic effects of fibrates, which are clinically used for the treatment of hypertriglyceridemia and hypoalphalipoproteinemia. Mechanistically, fibrates reduce the hepatic expression of apolipoprotein C-III (Apo CIII) and enhance the expression of lipoprotein lipase (LPL), thus promoting triglyceride (TG) catabolism (Qiu et al., 2023). Clinical evidence supports the efficacy of PPARα agonists in improving lipid profiles in patients with primary hypertriglyceridemia and mixed hyperlipidemia. Similarly, PPARγ agonists have been widely used in the management of type 2 diabetes mellitus (T2D) due to their insulin-sensitizing effects. In contrast, several preclinical studies have demonstrated that PPARα agonists also exert antifibrotic effects by inhibiting hepatic stellate cell (HSC) activation, which plays a central role in the pathogenesis of liver fibrosis (Lange et al., 2022). These findings suggest that PPAR activation may attenuate collagen and extracellular matrix deposition, potentially slowing or reversing liver fibrosis (Gong et al., 2023). However, despite promising preclinical results, translational challenges remain. These include differences in PPAR isoform expression, metabolic pathways, and drug metabolism between animal models and humans, as well as concerns about long-term safety and efficacy in human populations. Therefore, while PPAR agonists hold significant therapeutic potential in metabolic and fibrotic liver diseases, further well-designed clinical trials are needed to confirm their effectiveness and safety profiles in patients with chronic liver disease.

In the context of alcoholic liver disease (ALD), which is one of the leading causes of cirrhosis, PPARα agonists have shown promising results. Animal model studies have shown that treatment with PPARα agonists such as fenofibrate can protect against hepatic steatosis by increasing hepatic β-oxidation of fatty acids and reducing hepatic insulin resistance. This suggests the potential of PPARα agonists as a therapy for ALD, which often progresses to cirrhosis if not properly managed (Durairajan et al., 2024).

Although these results are very promising, it should be noted that most of the evidence comes from preclinical studies. Further clinical trials are needed to confirm the efficacy and safety of PPARα agonists in patients with liver cirrhosis. However, considering the central role of PPARα in hepatic lipid metabolism and its anti-inflammatory effects, PPARα agonists remain an attractive therapeutic target for the development of new drugs in the treatment of liver cirrhosis (Durairajan et al., 2024; Qiu et al., 2023).

PPARγ agonists

PPARγ agonists have shown promising potential in the treatment of liver cirrhosis, especially in addressing insulin resistance and liver inflammation. Based on recent studies, PPARγ activation has beneficial effects on lipid and glucose metabolism, as well as having strong anti-inflammatory properties (Lange et al., 2022; Durairajan et al., 2024).

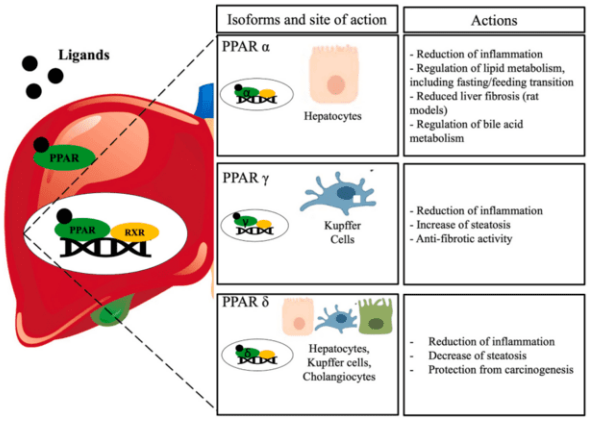

Figure 5. Mechanism and location of action of different types of PPARs (Colapietro et al., 2023).

Figure 5 shows that PPAR has different sites of action and mechanisms in the pathogenesis of cirrhosis ranging from hepatocytes, Kupffer cells and cholangiocytes with various effects ranging from inflammation reduction, regulation of lipid metabolism, fibrosis and steatosis to protection from carcinogenesis

(Colapietro et al., 2023). One of the main mechanisms of PPARγ agonists is their ability to increase insulin sensitivity. This is especially important in the context of NAFLD, which is often associated with insulin resistance. PPARγ activation has been shown to increase adipogenesis and fatty acid uptake in adipose tissue, which in turn can reduce fat accumulation in the liver (Lange et al., 2022). In addition, PPARγ agonists also increase the production of adiponectin, an adipokine that has anti-atherogenic effects and increases fatty acid oxidation (Lange et al., 2022; Colapietro et al., 2023).

The anti-inflammatory effects of PPARγ agonists are also very significant in the treatment of liver cirrhosis. Studies have shown that PPARγ activation can reduce the production of pro-inflammatory cytokines such as TNF-α and IL-6, and inhibit the activity of NF-κB, a transcription factor that plays a key role in inflammation. Furthermore, PPARγ agonists have been shown to modulate macrophage polarization toward an anti-inflammatory phenotype, which may help reduce chronic inflammation in the liver (Stienstra et al., 2007).

In the context of NAFLD and NASH, several clinical trials are ongoing to investigate the beneficial effects of PPARγ agonists (Zaiou, 2023). Thiazolidinediones, a class of PPARγ agonists, have shown promising results in reducing steatosis and inflammation in patients with NASH. However, it should be noted that the use of PPARγ agonists can also have side effects, such as weight gain, which need to be considered in their use (Stienstra et al., 2007).

Recent advances in research also suggest the potential use of natural PPARγ agonists as a safer alternative. These natural compounds have been shown to partially activate PPARγ, which may increase adiponectin levels and insulin sensitivity, thereby improving NAFLD with fewer side effects. Although the results from preclinical studies are very promising, further research is needed to determine optimal dosage and efficacy in humans (Singh et al., 2024).

Pan PPAR Agonist

Pan-PPAR agonists have emerged as a promising therapeutic strategy for the treatment of liver cirrhosis, owing to their ability to simultaneously target multiple metabolic and fibrotic pathways. Among them, lanifibranor is a notable example, acting as a pan-PPAR agonist that activates all three PPAR subtypes (PPAR-α, PPAR-γ, and PPAR-δ). In preclinical studies, particularly in a mouse model of advanced chronic liver disease (ACLD), lanifibranor demonstrated significant hemodynamic and antifibrotic effects. Boyer-Diaz et al. (2021) reported that lanifibranor reduced portal pressure by 15% without altering portal blood flow, suggesting an improvement in intrahepatic vascular resistance. Moreover, lanifibranor treatment resulted in a 32% reduction in hepatic fibrosis, indicating a robust antifibrotic effect at the tissue level.

In early-phase clinical studies, lanifibranor has also shown encouraging results in patients with non-alcoholic steatohepatitis (NASH), a condition that can progress to cirrhosis. A phase IIb trial (NATIVE study) demonstrated that lanifibranor significantly improved liver histology, steatosis, and inflammation, and showed a trend toward fibrosis regression, particularly at higher doses (Francque et al., 2021).

However, the translation of these findings to the context of liver cirrhosis—especially in decompensated or advanced stages—remains a challenge. Differences between animal models and human disease, particularly in terms of disease progression, immune response, and drug metabolism, may limit the generalizability of preclinical results. Moreover, long-term safety, optimal dosing, and efficacy in cirrhotic patients require further validation in large-scale phase III clinical trials.

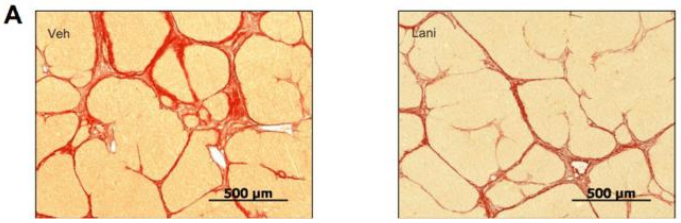

Figure 6. Histopathological image of liver tissue of rats given lanofibranor (right) and methylcellulose (left) (Boyer-Diaz et al., 2021).

The beneficial effects of lanifibranor were not limited to improvements in portal hemodynamics and fibrosis. The study also reported decreased ascites, improved phenotype of liver sinusoidal endothelial cells (LSECs) and HSCs, and reduced liver inflammation. More interestingly, these effects were also seen in liver cells isolated from patients with cirrhosis, indicating strong translational potential (Boyer-Diaz et al., 2021; Gastaldelli, 2022)

Figure 6 is a histopathological picture of mice given lanofibranor compared to the control group using sirius red staining showing significantly reduced fibrosis with a picture of thinner, less striking fibrous septa, and often perforated (Boyer-Diaz et al., 2021). In a phase 2b clinical trial in patients with NASH, lanifibranor showed promising results. At a dose of 1200 mg per day for 24 weeks, lanifibranor achieved a composite endpoint of NASH resolution and fibrosis improvement in 35% of patients, compared to 9% in the placebo group. In addition, lanifibranor also improved metabolic parameters such as HbA1c, triglycerides, insulin, and HDL cholesterol (Gastaldelli, 2022).

The mechanism of action of lanifibranor involves modulation of multiple pathways involved in the pathogenesis of cirrhosis. PPARα activation increases fatty acid oxidation and reduces lipogenesis, while PPARγ activation inhibits hepatic stellate cell activation and promotes regression of liver fibrosis (Lange et al., 2022). PPARδ, on the other hand, plays a role in increasing energy expenditure and fatty acid oxidation, which may help reduce hepatic steatosis (Gastaldelli, 2022).

The Role of PPAR in Hepatic Cirrhosis Due to Hepatitis Virus Infection

Although PPAR agonists have shown potential anti-inflammatory and antifibrotic effects in various liver

diseases, their use in liver cirrhosis due to chronic hepatitis B virus (HBV) infection remains controversial. This is due to emerging evidence of complex interactions between PPARs and HBV replication pathways. Several preclinical studies have revealed that PPARα activation may directly enhance HBV replication. Specifically, PPARα can bind to HBV enhancer regions and increase viral transcription in a receptor-dependent manner (Du et al., 2017). Moreover, HBV proteins, such as HBx, have been shown to upregulate PPARγ expression and activity, which in turn promotes lipid accumulation in hepatocytes by stimulating the expression of adipogenic and lipogenic genes (Dubuquoy et al., 2019). This reciprocal regulation between HBV and PPARs may contribute to disease progression, including steatosis and fibrosis.

In in vivo mouse models, PPAR agonists such as bezafibrate, fenofibrate, and rosiglitazone were associated with a significant increase in HBV replication (Du et al., 2017). These findings suggest that, while PPAR agonists may be beneficial in treating metabolic liver conditions, their use in HBV-infected patients could inadvertently exacerbate viral replication. Therefore, PPAR agonist therapy in HBV patients should be approached with caution, and serum HBV DNA levels should be closely monitored in clinical settings.

Given these concerns, there is growing interest in the development of PPAR antagonists as a potential strategy to suppress HBV replication and prevent virus-associated metabolic disturbances. However, translating these preclinical findings into clinical application remains challenging. Differences in human and murine immune responses, PPAR expression patterns, and long-term safety considerations must be addressed in future research before adopting such approaches in clinical practice.

In cases of chronic hepatitis C virus (HCV)-induced liver cirrhosis, PPAR agonists—particularly those that target insulin resistance (IR) have shown therapeutic potential, especially in patients with coexisting metabolic syndrome. Preclinical studies have suggested that PPARγ activation may improve hepatic insulin sensitivity and reduce steatosis and inflammation, mechanisms that could theoretically enhance antiviral treatment response. However, clinical evidence remains inconclusive. Pioglitazone (PIO), a thiazolidinedione and PPARγ agonist, has been evaluated in clinical studies for its ability to improve insulin resistance and potentiate the efficacy of standard antiviral therapies, such as pegylated interferon (PEG-IFN) and ribavirin. In some trials, pioglitazone improved early virological responses (EVR) and led to reductions in IR and hepatic steatosis, particularly in patients infected with HCV genotypes 1 and 4 (Eslam et al., 2019). However, other studies have failed to demonstrate significant improvements in sustained virological response (SVR) rates, leading to inconsistent clinical conclusions. This variability in outcomes may be attributed to several factors, including differences in HCV genotype, treatment regimens, pioglitazone dosage, and host genetic polymorphisms affecting insulin signaling and lipid metabolism. Moreover, as HCV treatment has rapidly evolved with the advent of direct-acting antivirals (DAAs), the relevance of pioglitazone as an adjunct therapy must be reevaluated in this new therapeutic context. However, the challenges persist, particularly due to the heterogeneity of clinical trial designs, the complex metabolic interplay between HCV infection and insulin resistance, and uncertainties about the long-term safety of PPARγ agonists in cirrhotic patients. As such, larger, well-controlled clinical trials are still needed to determine the definitive role of insulin-sensitizing agents like pioglitazone in improving HCV-related liver outcomes.

CONCLUSIONS

Liver cirrhosis is the final stage of various chronic liver diseases and involves complex metabolic and fibrotic processes, in which peroxisome proliferator-activated receptors (PPARs) play a central role. PPARα, predominantly expressed in the liver, regulates fatty acid oxidation, and its decreased expression in cirrhosis leads to hepatic fat accumulation a key feature of NAFLD-related progression to cirrhosis. PPARγ has been shown to inhibit hepatic stellate cell (HSC) activation, reduce liver inflammation, modulate macrophage polarization, and improve insulin sensitivity. PPARδ, though less studied, also appears to have anti-inflammatory and antifibrotic effects. Collectively, PPARs help maintain HSCs in a quiescent state, and reduced expression of these receptors promotes fibrosis progression. Therefore, therapeutic strategies that enhance PPAR activity particularly via selective agonists hold promise for the treatment of liver cirrhosis.

However, despite encouraging results from preclinical studies, there are important limitations and translational challenges. Clinical evidence remains limited and sometimes conflicting, particularly in cirrhosis due to viral hepatitis. For instance, PPARα agonists may promote HBV replication, raising safety concerns in infected patients. Moreover, variability in treatment outcomes may arise due to differences in disease etiology, patient genetics, and drug response. Long-term safety and tolerability of PPAR-targeted therapies in cirrhotic patients have yet to be fully established. Thus, future research should focus on well-powered clinical trials, the development of selective or dual PPAR modulators, and identification of biomarkers to guide patient selection. These steps are essential to translate the therapeutic potential of PPAR agonists into effective, targeted treatments for liver cirrhosis (Eslam et al., 2019).

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