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Review Article

Peroxisome proliferator-activated receptors in metabolic and renal health: a comprehensive review

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ABSTRACT

Peroxisome proliferator-activated receptors (PPARs), including α, β/δ and γ isoforms, play crucial roles in regulating metabolic and renal health. This study explores their involvement in lipid metabolism, inflammation, chronic kidney disease (CKD) and diabetic nephropathy, emphasizing the therapeutic potential of both synthetic and natural PPAR agonists. A comprehensive literature review was conducted using PubMed, Scopus and Google Scholar, with search terms such as "Peroxisome proliferator-activated receptors," "PPAR agonists," "lipid metabolism," "chronic kidney disease," and "diabetic nephropathy." Boolean operators and MeSH terms were applied and studies from 2000 to 2024 were included. Eligibility criteria focused on experimental, clinical and review articles detailing PPAR mechanisms, physiological roles and therapeutic applications. Findings indicate that PPARs are critical in lipid and glucose metabolism, oxidative stress reduction and fibrosis mitigation. Synthetic ligands such as thiazolidinediones and fibrates demonstrate therapeutic efficacy in CKD and metabolic syndrome, though challenges such as side effects and variability persist. While PPAR-targeted treatments offer promise in metabolic and renal disorders, their clinical application requires further refinement through selective modulators, combination therapies and biomarker-guided strategies.

Keywords: Chronic kidney disease, Diabetic nephropathy, Glucose metabolism, Lipid metabolism, PPAR agonists, Peroxisome proliferator-activated receptors

INTRODUCTION

Peroxisome proliferator-activated receptors (PPARs) are nuclear transcription factors that heterodimerise with retinoid X receptor to bind peroxisome proliferator response elements and control genes linked to differentiation, metabolism and cancer.[1] Three isoforms PPARα, PPARγ and PPARβ/δ fine-tune lipid and glucose

homeostasis.[2] PPARα is highly expressed in liver, heart and proximal tubules; it up-regulates fatty acid β-oxidation and ketogenesis, preventing steatosis and hyper-triglyceridaemia.[3] Fibrates, selective PPARα agonists, safely improve dyslipidaemia even in moderate CKD when hepatically cleared agents such as pemafibrate are used.[4] PPARγ predominates in adipose tissue and renal collecting ducts, promoting adipogenesis, insulin sensitivity and anti-inflammatory adipokine secretion.[5] Thiazolidinediones activate PPARγ to reduce albuminuria and glomerulosclerosis independent of glycaemic control^6, although fluid retention limits use in advanced CKD.[6] PPARβ/δ, widely expressed in muscle and kidney, enhances mitochondrial fatty acid oxidation, suppresses oxidative stress and prevents lipid accumulation.[7] Pre-clinical agonists improve glucose tolerance and renal inflammation, but safety data are incomplete.

Metabolic syndrome obesity, insulin resistance, dyslipidaemia and hypertension drives CKD through hyperglycaemic, haemodynamic and lipotoxic injury.[13] Chronic hyperglycaemia, elevated free fatty acids and renin-angiotensin activation induce podocyte loss, glomerulosclerosis and tubulo-interstitial fibrosis.[14] PPARα and PPARβ/δ agonists counter lipotoxicity by increasing fatty acid oxidation and limiting inflammatory cytokines, while PPARγ activation mitigates fibrosis via TGF-β/Smad inhibition.[15] Targeting PPAR pathways with lifestyle and pharmacological interventions offers a multi-level strategy to prevent and slow CKD progression in patients with metabolic disorders.[16]

MECHANISMS OF PPAR ACTIVATION IN KIDNEY HEALTH

PPARα is most abundant in mitochondrial-dense proximal tubules, thick ascending limbs, podocytes and mesangial cells, where it governs fatty-acid β-oxidation (FAO) and maintains ATP balance.

Acute kidney injury

Ischaemia–reperfusion (I/R) or cisplatin lowers PPARα and PGC-1α, impairing FAO and precipitating necrosis. Knockout models exhibit worse I/R outcomes; pharmacological activation (fibrates, pemafibrate) restores CPT-1, acyl-CoA oxidase expression, decreases TNF-α, IL-6 and limits tubular death and inflammation. CypD inhibition sustains PPARα activity and mitochondrial integrity during AKI, preserving metabolic homeostasis.[2]

Chronic kidney disease and diabetic nephropathy

Reduced PPARα in DN biopsies amplifies insulin resistance and lipid accumulation; fenofibrate up-regulates PPARα, reduces TGF-β, IL-1β, IL-6, TNF-α and slows fibrosis progression.[2] SPPARMα modulators (pemafibrate) improve lipid profiles and renal outcomes without myotoxicity in CKD patients on statins.

PPARβ/δ–tubular repair and immune balance

Renal expression and acute kidney injury response

Lower PPARβ/δ after I/R injury correlates with worse tubular damage; agonists activate Akt signalling, enhance repair and suppress TNF-α/IL-6.[2]

Chronic kidney disease and Autoimmunity

Deficiency in type-1 diabetes causes excessive FAO and triglyceride accumulation, while overexpression protects against hypertonic stress and lipid-induced injury. TAK1–NF-κB pathway inhibition by PPARβ/δ agonists reduces macrophage infiltration, glomerulosclerosis and hypertension in lupus nephritis.[2]

PPARγ-Anti-fibrotic & metabolic gatekeeper

Structure and splice variants

Chromosome 3p25.2 encodes four isoforms (γ1–γ4); γ2 is adipose-specific, γ1 ubiquitous. Both heterodimerise with RXR to bind PPREs and recruit co-activators PGC-1α, SRC-2 or co-repressors NCOR1/2.[3]

Renal protection mechanisms

Anti-proliferation and Anti-apoptosis

Pioglitazone down-regulates p27, Bcl-2 and MAPK, inhibiting mesangial proliferation and proteinuria. Rosiglitazone prevents mesangial hypertrophy, up-regulates Bcl-xl and blocks caspase-3 in PAN nephrosis3.

Anti-inflammation

15d-PGJ$_2$, TZDs suppress NF-κB, AP-1 and JAK/STAT1, lowering TNF-α, IL-6, MCP-1 release.[3]

Anti-fibrosis

Blocks TGF-β/SMAD signalling, up-regulates HGF, down-regulates CTGF and PAI-1, reducing extracellular matrix deposition.[3]

Epigenetic and metabolic control

miR-27a targets PPARγ, promoting β-catenin/Snail1 and podocyte injury; lncRNA TUG1 modulates miR-377 to influence ECM accumulation in DN.[3]

Integrated renal outcomes

PPARα/γ dual agonists (tesaglitazar) simultaneously correct lipid dysregulation and suppress fibrosis in diabetic kidneys. Nrf2 and eNOS up-regulation by PPARγ lowers oxidative stress, preserving mitochondrial and podocyte function. Next-generation SPPARMs aim to maximise

renal protection while minimising systemic side-effects 17.

PPAR-γ AGONISTS IN DIABETES-ASSOCIATED KIDNEY DISEASE

The incidence of diabetes mellitus (DM) is rising globally. Expected to grow over 50% by 2045 compared to 2017, DM is predicted to be the 7th leading cause of mortality worldwide by 2030.[18] Diabetic Kidney Disease (DKD) cases are projected to rise nearly 50% (from 537 to 783 million people) over the next 24 years. There is an urgent need to improve DKD diagnosis and management, with therapies targeting disease mechanisms to slow kidney failure progression and reduce related high cardiovascular (CV) risk.[19]

Pathophysiology of diabetic nephropathy

Diabetic Nephropathy's pathogenesis develops via multifactorial pathways, initiated by elevated renal glucose, enhanced by metabolic factors (excess fatty acids, carbonyl, oxidative stress) and hemodynamic factors (shear stress from systemic hypertension, impaired autoregulation, hyperperfusion, hypoperfusion, renin-angiotensin-aldosterone system (RAAS) activation). Each damages via multiple mediators or pathway interactions. Renal fibrosis is the final common pathway leading to Diabetic Nephropathy.[19]

High glucose stimulates miR-27a expression, negatively targeting PPARγ and activating β-catenin signaling. This is shown by upregulated β-catenin target genes (snail1, α-smooth muscle actin (α-SMA)) and downregulated podocyte-specific markers (podocin, synaptopodin). These changes cause podocyte injury: increased podocyte mesenchymal transition, disrupted podocyte architectural integrity and increased podocyte apoptosis.[3] miR-27a thus contributes to unfavorable renal function and increased podocyte injury in diabetic rats.[19]

Mechanisms of kidney protection: PPAR-γ improves insulin sensitivity, reduces inflammation and combats renal fibrosis in diabetes.

PPAR-γ regulates renal physiological processes, maintaining normal function. It is expressed in podocytes, glomerular endothelial cells, mesangial cells, proximal convoluted tubules and inner medullary collecting ducts. PPAR-γ (especially PPAR-γ2) is vital for renal lipid metabolism (including free fatty acids (FFAs)) and insulin sensitivity. It controls glomerular filtration and fibrotic/inflammatory factor proliferation in glomeruli. PPAR-γ also regulates adipokine expression, renoprotective by improving insulin sensitivity and inhibiting inflammation. Juxtaglomerular apparatus cells express PPAR-γ, regulating renin expression/transcription, a key RAAS element. As a negative angiotensin II receptor 1 transcription regulator, PPAR-γ activation reduces proteinuria and inflammation in diabetes and hypertension.[20]

Emerging research highlights peroxisome proliferator-activated receptor-γ (PPAR-γ)'s role in cell cycle regulation; its agonists protect against high glucose, proteinuria and tissue fibrosis. In UUO mice, oral curcumin (50 mg/kg and 100 mg/kg for 14 days) enhanced PPAR-γ expression and reduced phosphorylated Smad 2/3 levels. Similar effects occurred in TGF-β1-stimulated proximal tubular epithelial HK-2 cells and 5/6 nephrectomized rats. Given PPAR-γ's established connection with angiotensin-converting enzyme (ACE), further curcumin research on ACE expression in renal diseases is warranted.[21]

Role Ppar- γ agonist in therapeutics

Peroxisome proliferator-activated receptors (PPARs) regulate metabolic lipid/lipoprotein levels (e.g., triglycerides (TGs)), blood glucose and abdominal adiposity. PPARs classify into α, β/δ and γ subtypes. PPAR-α agonists (fibrates, omega-3 fatty acids) effectively lower TGs via catabolism, with fibrates increasing high-density lipoprotein cholesterol (HDL-C). PPAR-γ agonists, primarily glitazones, are powerful glucose-lowering agents, despite lower TG activity. Newer PPAR-α/δ agonists (e.g., elafibranor) combine TG-lowering, HDL-C-raising, insulin-sensitizing and antihyperglycemic effects, promising for non-alcoholic fatty liver disease (NAFLD) management (linked to MetS). The PPAR system offers significant potential for treating atherogenic dyslipidaemias.[22]

PPARγ is highly expressed in adipose tissue; its activation stimulates preadipocyte differentiation. PPARγ agonists improve insulin sensitivity and glucose homeostasis by promoting free fatty acid uptake/storage in adipose tissue and modifying adipocyte-derived signaling molecules (adipocytokines). They decrease pro-diabetic adipocytokines (tumor necrosis factor-α (TNF-α), interleukin (IL)-6, leptin, resistin) and increase anti-diabetic adiponectin. However, PPARγ agonists' anti-diabetic effects are often with approximately 2 kg weight gain, edema, fluid retention and lower blood pressure. In renal tissue, PPARγ is predominantly expressed in collecting ducts, less so in glomeruli, mesangial cells, proximal tubules and the renal microvasculature.[23]

Synthetic PPAR-γ agonists show therapeutic potential improving diabetic nephropathy via multiple mechanisms, activating PPARgamma in kidneys and other tissues. They are renoprotective in polycystic kidney disease, chemotherapy-associated nephropathy, IgA nephropathy and renal ischemia-reperfusion injury.[24]

Thiazolidinediones (TZDs), initially insulin-sensitizing drugs, found in 1995 to bind and activate PPARγ. As PPARγ agonists, TZDs improve insulin sensitivity in liver, muscles and adipocytes, enhancing insulin signaling by

stimulating inhibiting the MAPK pathway and insulin receptor substrate 1 (IRS-1). In adipose tissue, TZDs increase adiponectin secretion while inhibiting lipolysis and inflammatory cytokine release (e.g., transforming growth factor β (TGF-β)). Spiegelman et al, proposed TZDs prevent insulin resistance via Cdk5-mediated PPARγ Ser273 phosphorylation inhibition.[8] MEK/ERK inhibition also blocked PPARγ phosphorylation; Cdk5 suppressing the MEK/ERK cascade indicates Cdk5 controls PPARγ function.[25]

Evidence suggests TZDs reduce early diabetic nephropathy progression; PPAR-gamma agonists significantly attenuate typical glomerular and tubular changes. This effect is independent of insulin, glucose or blood pressure changes. TZDs increase PPAR-γ expression in podocytes and other glomerular/tubular cells (mRNA and protein levels). TZDs are also podocyte-protective in rodent nephropathy models (e.g., aldosterone, adriamycin, puromycin aminonucleoside) and glomerular capillary hypertension. PPAR-γ activation in podocytes appears a key protective response to injury, its upregulation observed in various kidney diseases.[26]

TZDs also exhibit anti-cancer effects, dependent or independent of PPAR-γ activation, at transcriptional and protein levels. Mechanisms involve cell cycle, apoptosis, hormonal reactions and stromal regulation. These include partial intracellular Ca2+ depletion, proteasomal degradation of proteins inducing cell cycle arrest/apoptosis, transcriptional repression of sex hormone receptors and decreased macrophage activation.[18,19]

PPAR-A AND LIPID METABOLISM IN CHRONIC KIDNEY DISEASE PREVENTION

Patients with chronic kidney disease (CKD) frequently present with atherogenic dyslipidemia, including elevated triglyceride-rich lipoproteins and reduced high-density lipoprotein cholesterol (HDL-C).[27,28] This lipid profile marked by high LDL-C, elevated triglycerides, low HDL-C and small dense LDL particles contributes to renal injury through mechanisms involving oxidative stress, lipotoxicity and inflammation.[28] These effects stem from dysregulation in nuclear receptors, including PPARα, PPARγ, PPARδ, SREBP-2 and Farnesoid X Receptor (FXR).[29] Disrupted lipid metabolism causes energy depletion, cell apoptosis and fibrosis, worsening CKD.[30] Excess lipids within renal tubular cells surpass their metabolic capacity, promoting breakdown of triglycerides and accumulation of free fatty acids (FFAs), resulting in oxidative and ER stress and ultimately tubular apoptosis.[31] CKD shares overlapping molecular pathways with non-alcoholic fatty liver disease (NAFLD), including SREBP-2 activation and dysregulation of microRNA-21 (miR-21), suggesting shared lipid-mediated pathology.[32,33] ATF6α, a key transcription factor in the Unfolded Protein Response (UPR), suppresses mitochondrial fatty acid oxidation (FAO) by downregulating PPARα, aggravating lipid accumulation, lipotoxicity and tubular interstitial fibrosis (TIF).[34]

PPAR-α agonists in renal protection

PPARα is a ligand-activated nuclear receptor regulating genes for FAO, making it a valuable therapeutic target in CKD[78]. Among available agents, pemafibrate, a selective PPARα modulator (SPPARMα), offers significant promise. It improves lipid profiles regardless of renal impairment and is hepatically cleared, minimizing nephrotoxicy.[35] Unlike conventional fibrates, pemafibrate does not elevate serum ALT, creatinine or γ-glutamyl transferase (γ-GT).[36] Tanaka et al demonstrated that low-dose pemafibrate reduced proteinuria in IgA nephropathy without impairing kidney function. In addition, it mitigated ATF6α-induced lipotoxicity and renal fibrosis in ischemia-reperfusion injury models. Fenofibrate, another PPARα agonist, has shown renoprotective effects in murine diabetic nephropathy by enhancing FAO, reducing lipotoxicity, glomerular injury and albuminur. However, due to renal excretion and the potential for rhabdomyolysis (particularly in combination with statins), its use in advanced CKD is restricted.[32]

Aleglitazar, a dual PPAR-α/γ agonist, initially showed improved lipid control compared to pioglitazone but was linked to transient declines in estimated glomerular filtration rate (eGFR), increased serum creatinine, edema and cardiovascular complications. These concerns ultimately halted its clinical development.[37]

Clinical evidence

In a phase III trial by Yokote et al involving 295 hypertriglyceridemic patients, pemafibrate significantly reduced triglyceride levels over 52 weeks, with consistent efficacy across all eGFR strata including dialysis patients. Of these, 170 completed treatment. Adverse drug reactions occurred in 31.7% of patients, while the overall adverse event rate was 82.0%, indicating good tolerability even in patients with renal impairment.[28] Ruilope et al conducted a randomized, double-blind, phase IIb study comparing aleglitazar and pioglitazone in 118 CKD patients with type 2 diabetes. Aleglitazar led to a greater eGFR decline (−15%) than pioglitazone (−5.4%) by the end of treatment; however, eGFR values reverted to baseline levels after discontinuation. Adverse events occurred at comparable rates (67% vs. 68%), suggesting both drugs were similarly tolerated despite transient renal effects.[37]

Komatsu et al conducted a real-world retrospective study involving 126 hypertriglyceridemic patients, including 54 with CKD. Pemafibrate effectively lowered triglycerides in both CKD and non-CKD subgroups without significant changes in renal, hepatic or muscle enzyme levels. These findings affirmed its safety and efficacy in routine clinical practice. Lipid dysregulation drives renal inflammation and fibrosis, making it a pivotal contributor to CKD progression. While older fibrates such as fenofibrate have

proven efficacy, their renal excretion poses a toxicity risk in CKD. Among newer therapies, pemafibrate stands out for its potent lipid-lowering effects and favorable renal safety profile. Dual PPAR-α/γ agonists like aleglitazar, despite initial promise, have been limited by adverse outcomes. Future studies are warranted to confirm the long-term benefits and safety of PPAR agonists in CKD populations.[36]

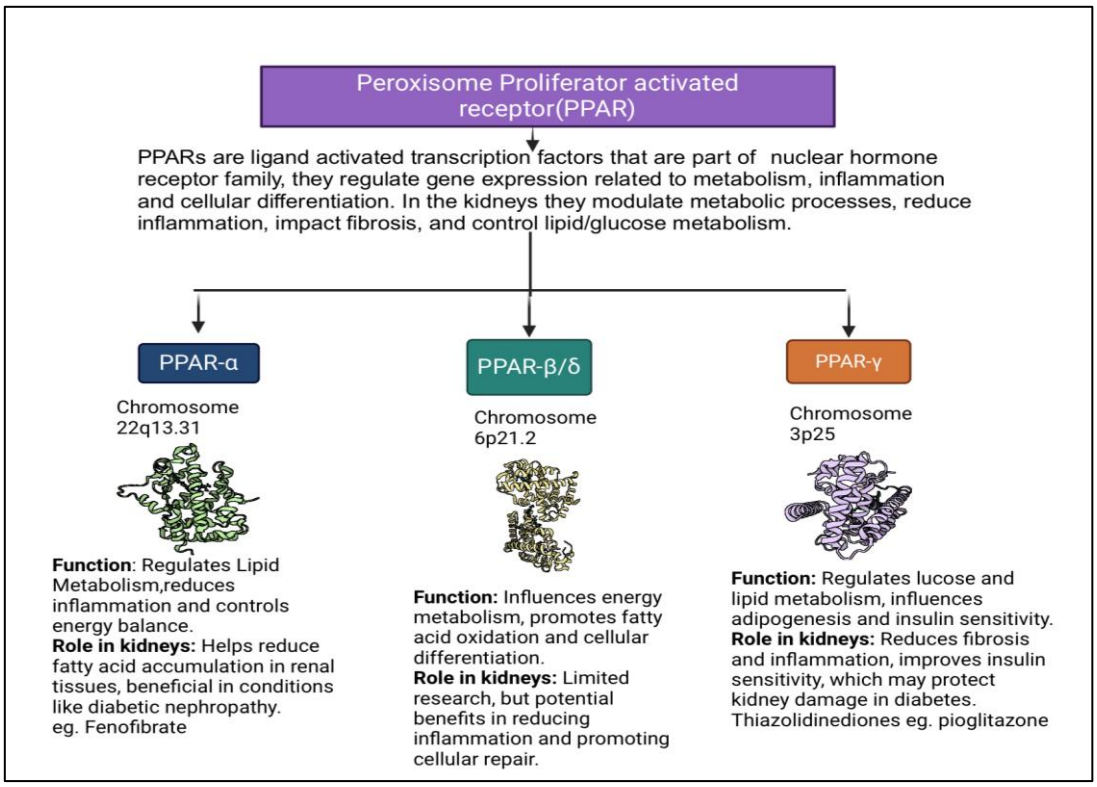

Figure 1: Introduction into types of PPARs and their functions.

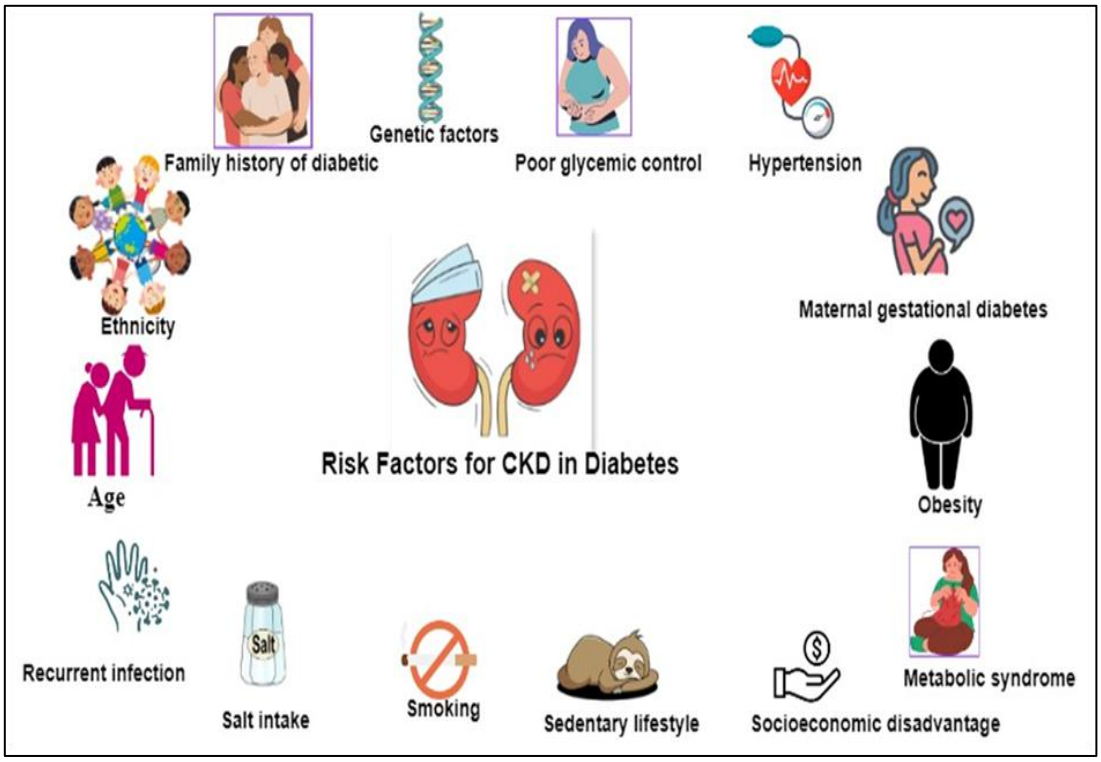

Figure 2: Illustrates chronic kidney disease risk factors.

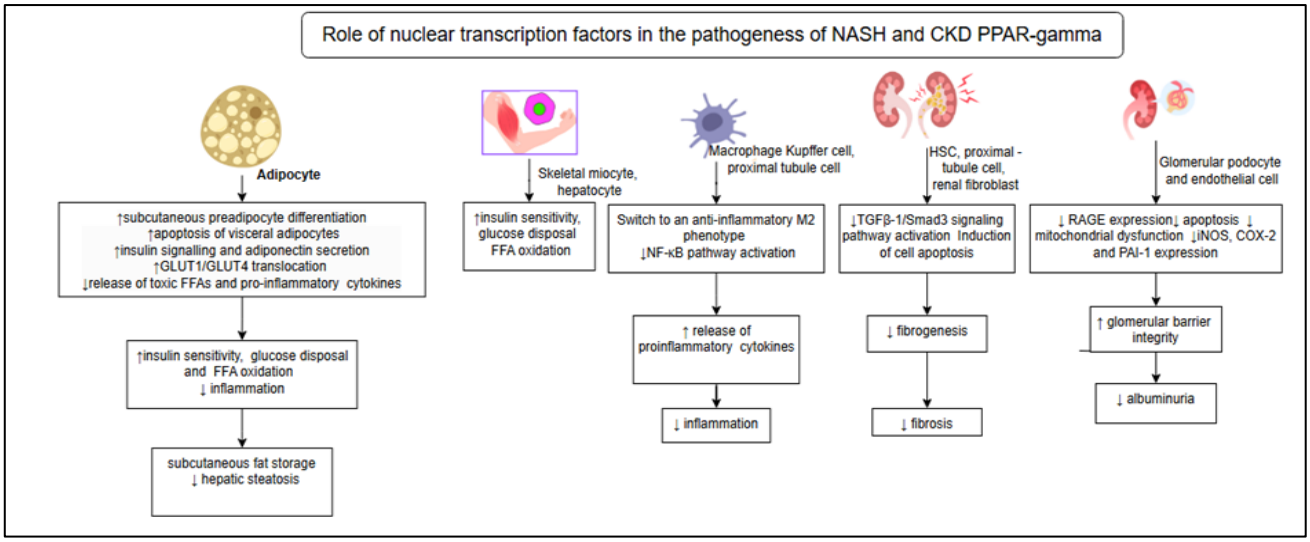

Figure 3: Nuclear transcription factors in pathogenesis of Nash and CKD PPAR gamma.

PPAR-DELTA AND METABOLIC HEALTH

PPAR-delta overview

PPAR-Delta plays a vital role in maintaining metabolic homeostasis. Its activation promotes fatty acid oxidation and improves insulin sensitivity, making it a valuable target in metabolic syndrome a condition encompassing obesity, dyslipidemia, hypertension and insulin resistance. In animal studies involving obese rhesus monkeys, PPAR-δ agonists improved glucose tolerance and reduced body fat, emphasizing its anti-obesity potential.[38]

Furthermore, PPAR-δ modulates inflammation through its effects on macrophages and adipocytes, reducing the expression of pro-inflammatory cytokines such as TNF-α and IL-6. These effects attenuate the chronic low-grade inflammation linked to insulin resistance, cardiovascular disease and obesity. Seldadelpar (MBX-8025), a selective PPAR-δ agonist, has shown promise in patients with primary biliary cholangitis (PBC) who were intolerant to ursodeoxycholic acid (UDCA), improving liver biochemistry and pruritus. Similarly, elafibranor, a dual PPAR-α/δ agonist, has demonstrated potential in treating non-alcoholic steatohepatitis (NASH).[39,40] PPAR-δ agonists including GW501516, MBX-8025, GW0742, Telmisartan, Tetradecylthioacetic Acid (TTA) and fenofibrate demonstrate beneficial effects on lipid metabolism, glucose regulation, inflammation and fatty acid oxidation, making them attractive for managing obesity-linked disorders.

PPAR-delta activation and kidney protection

PPAR-δ activation confers renal protection via multiple mechanisms.

Reducing inflammation

PPAR-δ decreases expression of TNF-α and IL-6, mitigates oxidative stress and reduces macrophage infiltration in renal tissue, thereby protecting against obesity-related renal injury.[40]

Enhancing fatty acid oxidation

By facilitating lipid utilization, PPAR-δ prevents ectopic lipid accumulation in renal tubular cells. Animal studies support its role in reducing renal lipotoxicity and improving kidney function in diet-induced obesity.[41]

Preserving glomerular structure

PPAR-δ agonists have been shown to maintain podocyte architecture and prevent glomerulosclerosis in CKD models.[42]

Future directions: therapeutic uses and challenges

Clinical trials

Although preclinical studies are promising, human trials are needed to validate the efficacy and safety of PPAR-δ agonists. GW1516 (cardarine) improved endurance in mice by 60–75% but is restricted due to insufficient human safety data.[43]

Combination therapies

Preclinical data suggest synergistic effects when combining PPAR-δ agonists like L165,041 with metformin or SGLT2 inhibitors in managing type 2 diabetes mellitus.[44]

Biomarker identification

GW501516 has reduced fibrosis markers in bronchial fibroblasts from asthma patients, indicating PPAR-δ's utility in respiratory conditions and its potential biomarkers.[45]

Mechanistic studies

In lupus-prone mice, PPARβ/δ agonists decreased renal inflammation, hypertension and anti-dsDNA antibodies, providing mechanistic insights into its immunomodulatory effects.[46]

Population diversity

Studies in diseases like Duchenne muscular dystrophy and primary mitochondrial myopathy (e.g., ASP0367) are needed to understand demographic variability in response.[47]

Safety concerns

Trials on GW501516 were halted due to carcinogenicity in animal studies. A case of rhabdomyolysis and liver dysfunction from its misuse (combined with MK2866) highlights the need for caution.[48] PPAR-δ's roles in lipid regulation, anti-inflammation and renal protection make it a promising therapeutic target across metabolic and kidney disorders.[49]

Table 1: Comparative analysis of PPAR agonists: efficacy, safety, and clinical applications.

Drug	Target receptor	Key efficacy	Renal effects	Adverse effects	References
Saroglitazar	Dual α/γ	Improves cholesterol, LDL, HDL; reduces TG in diabetics; lowers ALP at Week 16.	No specific data.	Diarrhea, cough, abdominal pain, bronchitis; elevated liver enzymes (4 mg dose).	58, 59
Fenofibrate	PPAR-α	Long-term reduction in macroalbuminuria; improves dyslipidemia.	Increases risk of adverse kidney events.	Creatinine doubling affected.	60
Pioglitazone	PPAR-γ	Enhances insulin sensitivity; improves metabolic syndrome parameters.	No specific data.	Weight gain, increased fat mass; reduces TGF-β1-driven renal fibrosis in mice.	61, 62
Rosiglitazone	PPAR-γ	Improves insulin sensitivity.	No specific data.	NA	63
Chiglitazar	Pan-agonist	NA	NA	Well-tolerated; no age-based dose adjustment needed.	64
Seladelpar	PPAR-δ	Promising in managing metabolic markers in PBC.	No specific data.	Gastrointestinal side effects (abdominal pain, distension, nausea).	39

FUTURE DIRECTIONS AND THERAPEUTIC POTENTIAL OF PPARS IN KIDNEY DISEASE

PPARs (α, β/δ, γ) orchestrate crucial physiological processes, including metabolism, inflammation and renal function. However, systemic activation may also induce adverse effects due to receptor expression across various tissues.[50]

PPAR subtypes and related risks

PPAR-α

Used for dyslipidemia; risks include myopathy, thrombosis and gallstones.[51]

PPAR-γ

Offers renoprotective benefits; concerns involve hepatotoxicity, fluid retention and cardiovascular events.[20]

PPAR-β/δ

Promising in renal/metabolic health, but animal data suggest potential tumorigenicity.[50]

Advances in modulator development

Selective PPARγ modulators

Designed as partial agonists to improve metabolic profiles while minimizing side effects.[29]

K-877 (Pemafibrate)

A selective PPAR-α modulator (SPPARM) with efficacy in reducing macrovascular/microvascular complications in diabetes/metabolic syndrome.[52]

Dual agonists

Compounds like Aleglitazar (PPAR-α/γ) and GFT505 (PPAR-α/δ) are in advanced clinical testing.[29]

Innovative therapeutic strategies

Combination therapies

Lobeglitazone+Empagliflozin

Synergistically manage hyperglycemia and early diabetic nephropathy without dose modification.[53]

Bezafibrate+Statins

Enhance lipid regulation, reduce cardiovascular risk and mitigate statin-induced diabetogenicity.[54]

ARBs with PPAR activity

Telmisartan derivatives combine AT1 receptor blockade and PPARγ activity to benefit patients with hypertension and insulin resistance.[55]

Nutraceutical approaches

Natural PPARγ agonists (e.g., polyunsaturated fatty acids, flavonoids, amorfrutins) show promise in managing renal disease without side effects like weight gain or edema.[56] Understanding gene variants, isoforms and post-translational modifications of PPARs, especially PPARG, may enable personalized therapies.[57]

CONCLUSION

This review highlights the essential regulatory roles of PPARs in metabolism and renal health. The three isoforms (α, β/δ, γ) function through distinct yet complementary pathways involving inflammation modulation, lipid metabolism and fibrosis prevention especially relevant in CKD and diabetes-related complications. Despite the therapeutic promise of fibrates and TZDs, concerns about adverse effects, variability in response and long-term safety have limited their widespread clinical adoption. Future success in PPAR-targeted therapies will rely on advances in selective modulation, combination regimens and biomarker-driven strategies. Greater mechanistic insights and drug design innovations are imperative to realize the full potential of PPARs in renal and metabolic medicine.

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