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Review Article

Peroxisome Proliferator-Activated Receptors in Diabetic Nephropathy

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Diabetic nephropathy is a leading cause of end-stage renal disease, which is increasing in incidence worldwide, despite intensive treatment approaches such as glycemic and blood pressure control in patients with diabetes mellitus. New therapeutic strategies are needed to prevent the onset of diabetic nephropathy. Peroxisome proliferator-activated receptors (PPARs) are ligand-activated nuclear transcription factors that play important roles in lipid and glucose homeostases. These agents might prevent the progression of diabetic nephropathy, since PPAR agonists improve dyslipidemia and insulin resistance. Furthermore, data from murine models suggest that PPAR agonists also have independent renoprotective effects by suppressing inflammation, oxidative stress, lipotoxicity, and activation of the renin-angiotensin system. This review summarizes data from clinical and experimental studies regarding the relationship between PPARs and diabetic nephropathy. The therapeutic potential of PPAR agonists in the treatment of diabetic nephropathy is also discussed.

1. INTRODUCTION

The incidence and prevalence of type 2 diabetes mellitus (DM) have been increasing worldwide since the 1980s, and this rise is estimated to continue in the future [1, 2]. Diabetic nephropathy is a common complication of DM and represents one of the major challenges for modern nephrology as the most common cause of end-stage renal disease, accounting for about 40% of new cases [3, 4]. The increasing prevalence of DM and its complications including diabetic nephropathy have therefore become a major health problem worldwide, and new therapeutic strategies to prevent diabetic nephropathy are urgently needed.

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear hormone receptor superfamily. They were originally cloned from rodent liver while screening for molecular mediators of peroxisome proliferation [5, 6]. Three isoforms have been cloned (PPARα, PPARβ/δ, and PPARγ) and characterized. Each has a unique expression pattern and ligand-binding specificity, as well as distinct metabolic functions [7]. PPARs regulate diverse cell functions, including fatty acid metabolism, adipocyte differentiation, inflammation, atherosclerosis, and cell cycle [8–11]. PPARα plays an important role in lipid metabolism in several tissues including liver and kidney [12]. PPARβ/δ is associated with cell survival and colon carcinogenesis [13] and was recently implicated as an important regulator of mitochondrial biogenesis and subsequent lipid metabolism in skeletal muscle [14]. PPARγ plays a pivotal role in adipogenesis, and its activation by thiazolidinediones (TZDs) improves insulin sensitivity via this role in adipocyte differentiation [15]. Accordingly, TZDs are widely used as oral antidiabetic agents in patients with type 2 diabetes [15, 16]. It is clear that substantial experimental and clinical research is still needed to clarify the role of PPARγ in the whole body physiology and the pathophysiology of various diseases such as diabetes, obesity, hypertension, atherosclerosis, and cancer.

In addition to the demonstrated physiological roles, several clinical and experimental studies have implicated PPARs in the pathogenesis of diabetic nephropathy. This review summarizes these clinical and experimental data with a particular focus on the therapeutic potential of PPAR modulators in diabetic nephropathy.

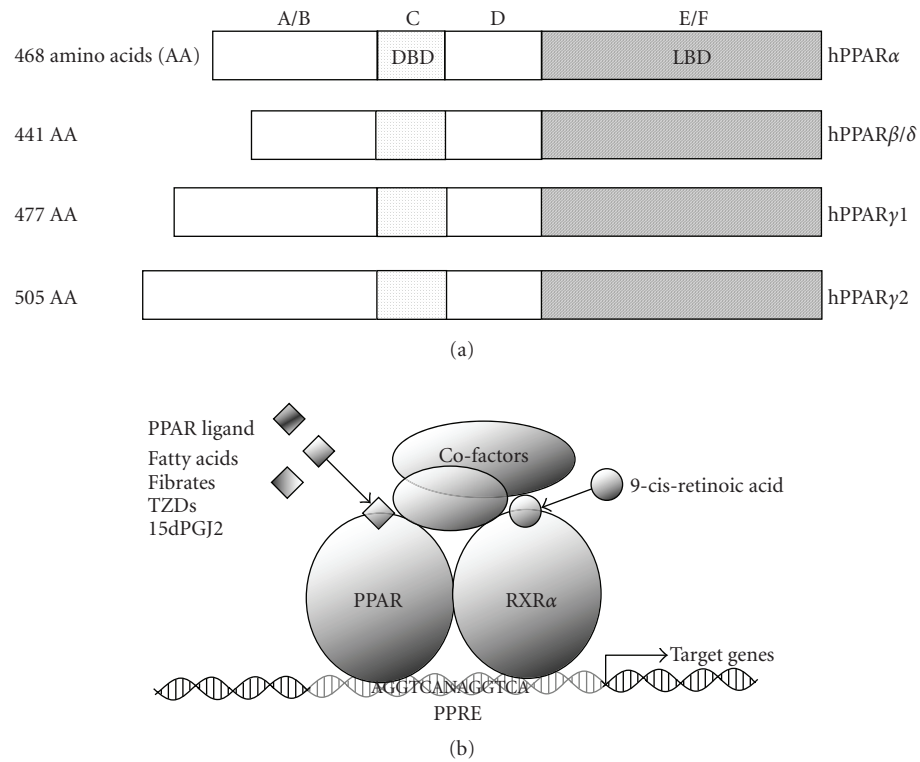

Figure 1: Structure and action of PPARs. (a) Domain structure of human PPARs. (b) Molecular mechanism of PPARs. After ligand binding, PPARs undergo conformational change with RXR and cofactors.

2. STRUCTURE OF PPARs

PPAR was initially identified in a mouse cDNA library in 1990 [6], and since then three PPARs have been cloned: PPARα, PPARβ/δ, and PPARγ (Figure 1(a)) [7]. PPARγ mRNA has three splicing forms derived from a single gene in human [17]. There are no splicing variants of PPARα or PPARβ/δ mRNA. Two PPARγ protein isoforms result from the translation of each of the three PPARγ mRNAs to produce PPARγ1 and γ2 [18], with both PPARγ1 and PPARγ3 mRNAs giving rise to the same protein, PPARγ1. PPARγ2 is the larger of the two isoforms, with 30 additional N-terminal amino acids. Due to different promoter usage, PPARγ1 and PPARγ2 have different expression patterns [19].

All PPARs possess four domains similar to those found in other nuclear hormone receptors [5, 20]: an NH2-terminal ligand-independent transactivation domain (activation function-1 (AF-1)), which regulates PPAR activity (A/B domain) [21, 22]; a DNA-binding domain of 70 amino acids (two zinc fingers) (DBD, C domain); a docking domain for cofactors (D domain); a COOH-terminal region containing the ligand-binding domain (LBD) and AF-2 domain (E/F domain). DBD and LBD are approximately 70% homologous among the three PPARs.

3. PPAR LIGANDS

PPARs are ligand-activated transcriptional factors belonging to the nuclear hormone receptor superfamily, whereby modulation of target gene transcription depends on the binding of ligands to the receptor. PPARs form heterodimers with the 9-cis retinoic acid receptor, retinoid X receptor (RXRα). Activation of the PPAR:RXRα heterodimers by PPAR ligands and/or RXR ligands triggers a conformational change in the receptors. This in turn allows the heterodimers to bind to PPAR responsible element containing the sequence AGGTCANAGGTCA in the promoter region of the target genes, and thus modulate gene transcription (Figure 1(b)).

Many ligands including natural and synthetic compounds have been identified for each PPAR isoform in both functional (cell-based transactivation efficiency) and in vitro interaction assays [8, 23]. The different amino acids sequences in the LBD of each PPAR provide the molecular basis for ligand specificity. Each PPAR can accommodate several structurally diverse ligands due to a large ligand-binding pocket [24]. PPARα binds unsaturated fatty acids with the highest affinity of the three isoforms [25–28]. Natural ligands for PPARγ also include several unsaturated fatty acids such as oleate, linoleate, eicosapentaenori and arachidonic acids, and 15dPGJ2 [8, 23, 29, 30]. TZD compounds such as troglitazone (was the first agent of this class on the market, but withdrawn due to liver toxicity), ciglitazone, pioglitazone, and rosiglitazone act as synthetic PPARγ ligands and promote adipocyte differentiation via activation of the receptor [23, 31–35]. Termisaltan, an angiotensin II type 1 receptor blocker (ARB), was recently shown to bind PPARγ and reduce blood glucose levels [36, 37].

4. DISTRIBUTION OF PPARs IN KIDNEY

Expression of the three PPAR isoforms has been examined in many species including Xenopus, rat, mouse, rabbit, and human. PPARα is mainly expressed in tissues exhibiting high catabolic rates of fatty acids such as adipose tissue, liver, heart, and skeletal muscle [38, 39]. PPARβ/δ is ubiquitously expressed, while PPARγ is highly expressed in white and brown adipose tissues that store large amounts of fatty acids, and in other selected tissues at low levels such as heart, liver, immune cells (monocytes and macrophages), placenta, and colon [40–42].

All three PPARs are expressed in the kidney [38, 41–43]. PPARγ mRNA has been demonstrated in the medullary collecting ducts and pelvic urothelium of kidney [44], as well as in isolated glomeruli and cultured mesangial cells [45, 46]. PPARα and γ1, but not γ2, protein was detected in kidney tissue by immunoblot analysis, while immunohistochemical analysis revealed PPARα and γ1 proteins in the nuclei of mesangial cells and epithelial cells in glomeruli, proximal and distal tubules, the loop of Henle, medullary collecting ducts, and the intima/media of renal vasculatures [47]. Large amounts of PPARα have also been detected in proximal tubular cells, and renal lipid metabolism is highly regulated by PPARα [48]. In contrast to PPARα, PPARγ protein is highly expressed in the nephron segment, predominantly in collecting ducts, implicating PPARγ in systemic water and sodium retention [49, 50].

5. EXPERIMENTAL (ANIMAL) STUDIES

PPARγ is the best characterized of the PPAR isoforms in diabetic animal models. The first evidence for a possible renoprotective effect of PPARγ agonists came 15 years ago, with the TZD compound troglitazone decreasing urinary albumin excretion and reducing blood pressure in obese Zucker rats [51]. Further studies since then also showed the beneficial effects of TZD compounds on renal injury in type 1 and type 2 diabetic animal models, as summarized in Table 1 [50, 52–60]. Several experimental studies also showed similar or superior protection against diabetic nephropathy for PPARγ agonists such as TZD, with results comparable to other renoprotective agents such as renin-angiotensin system blockers.

PPARα is highly expressed in renal proximal tubules and helps to maintain a sustained balance of energy production and expenditure in the kidney [61]. The role of PPARα in renal cortex lipid metabolism was demonstrated when the activation of PPARα by clofibrates induced expression of β-oxidation enzymes [62]. In *db*/*db* type 2 diabetic mice [63] and Zucker diabetic rats [64], treatment with PPARα activator, fenofibrate, improved urinary albumin excretion rates and glomerular mesangial expansion. These experimental studies suggest PPARα agonists as potentially useful therapeutic agents for diabetic nephropathy.

6. HUMAN CLINICAL TRIALS

Several clinical trials of PPARγ agonists have been conducted over the past decade that together confirm the renoprotective action of PPARγ (Table 2) [65–79]. PPARγ agonist, TZD, is an approved therapeutic agent for glycemic control in patients with type 2 DM, and thus is effective in preventing type 2 diabetic nephropathy. The beneficial effect of pioglitazone on urinary albumin excretion was also demonstrated in large, multicenter intervention studies, which compared the general efficacy and safety of TZD agents to other oral antidiabetic agents in patients with type 2 DM over 1 year. Either pioglitazone or the antidiabetic, metformin, was given to 639-randomized patients already receiving a sulfonylurea [72]. Although the two regimens had comparable effects on glycemic control, urinary albumin excretion was reduced by 15% in the group receiving pioglitazone and increased by 2% in the metformin group. In another study from the same group on drug-naive patients with type 2 DM, pioglitazone significantly reduced urinary albumin excretion, whereas metformin had no effect. A similar follow-up study showed that administration of pioglitazone in those patients who had previously received metformin therapy was associated with a decreased urinary albumin excretion of 10%, whereas another TZD compound, gliclazide, caused an increase of 6% [74]. Taken together, these data from both large and small clinical studies showed that PPARγ agonists have a beneficial effect on diabetic nephropathy compared to other antidiabetic agents.

It should be noted that PPARγ agonists could potentially cause heart failure due to the associated water retention. Recent clinical trials in patients with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) showed that rosiglitazone, which reduces the onset of diabetes, also reduced the development of renal disease; however, it increased the adverse risk of heart failure, compared to ramipril [79]. Therefore, PPARγ agonists should be used only with intensive monitoring of volume retention in patients with cardiac risk factors.

Clinical evidence also suggests the beneficial effect of PPARα ligands on diabetic nephropathy. Treatment of type 2 diabetes-associated dyslipidemia with gemfibrozil, an antidyslipidemic agent and PPARα activator, stabilized urinary albumin excretion rates [80, 81]. In addition, a large randomized controlled trial in 2005 determined that long-term fenofibrate therapy significantly reduced the rate of progression to albuminuria in patients with type 2 DM [82]. Although not extensive, these clinical data suggest the therapeutic efficacy of PPARγ agonists in preventing diabetic nephropathy.

6.1. *Effects of PPARγ ligands on diabetic nephropathy*

6.1.1. *Improving hyperglycemia*

The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) suggested that the adverse effects of hyperglycemia on metabolic pathways are the main causes of long-term complications such as kidney disease in diabetes [83, 84]. TZDs are a new class of oral antidiabetic agents used widely to improve insulin resistance, hyperinsulinemia, and hyperglycemia in patients with type 2 diabetes [85–87].

Table 1: Animal studies.

Authors	TZD	Animal model	Duration	Effect on UAE	Effect on BP	Other effects
Model of type 1 diabetes						
Fujii et al. [54]	Tro	STZ-induced diabetic rats	12 weeks	↓	NS	ND
Isshiki et al. [56]	Tro	STZ-induced diabetic rats	12 weeks	↓	ND	Hyperfiltration ↓
Nicholas et al. [58]	Tro	STZ-induced diabetic rats	12 weeks	↓	NS	ND
Yamashita et al. [60]	Tro, pio	STZ-induced diabetic SHR rats	12 weeks	↓	NS	Loss of glomerular basement membranes ↓
Model of type 2 diabetes						
Yoshioka et al. [51]	Tro	Obese Zucker rats	4 and 8 weeks	↓	↓	ND
Fujiwara et al. [55]	Tro	Wistar fatty rats	24 weeks	↓	↓	ND
Yoshimoto et al. [50]	Pio	Diabetic Wistar fatty rats	13 weeks	↓	↓	Glomerulosclerosis ↓ intrarenal arteriolosclerosis ↓
Tanimoto et al. [59]	Pio	Diabetic KK/Ta mice	4 and 8 weeks	↓	NS	Glomerular enlargement ↓
Buckingham et al. [53]	Rosi	Obese Zucker rats	4 and 9 months	↓	↓	Glomerulosclerosis ↓ tubulointerstitial fibrosis ↓
Baylis et al. [52]	Rosi	Obese Zucker rats	6 months	↓	NS	Glomerulosclerosis ↓ tubulointerstitial fibrosis ↓
Khan et al. [57]	Rosi	Obese Zucker rats	12 weeks	↓	↓	ND

TZD, thiazolidinedione; Tro, troglitazone; Pio, pioglitazone; Rosi, rosiglitazone; STZ, streptozotocin; SHR, spontaneously hypertensive rats; UAE, urinary albumin excretion; BP, blood pressure; NS, no significant effects; ND: not determined; ↓, significant reductions.

Since the improvement of hyperglycemia in such patients can prevent the development and progression of diabetic nephropathy, TZDs are potential protective agents for nephropathy in type 2 diabetes patients and animal models by virtue of their insulin-sensitizing action [66].

6.1.2. Lowering blood pressure with or without improved insulin resistance

Hypertension is commonly linked to obesity and insulin resistance [88]. TZDs have a possible antihypertensive effect through improvement of insulin resistance because insulin sensitivity is related to blood pressure levels both in diabetic animals and patients [50, 89–92]. On the other hand, PPARγ ligands could directly affect vascular function because of their expression in endothelial cells and vascular smooth muscle cells (VSMCs) [93–95]. Indeed, pioglitazone lowered the blood pressure in 5/6 nephrectomized hypertensive rats, and the effect was not associated with insulin resistance [96, 97]. The demonstrated antihypertensive effects of TZDs could involve the release of vasodilators such as nitric oxide and prostaglandins [98], the decrease in fatty acid levels, and/or modification of vasoactive peptide synthesis including endothelin-1 [47]. Recently, PPARγ downregulated the expression of angiotensin II type 1 receptor and in turn decreased vascular smooth muscle tone, thereby reducing vascular contractility [99]. Although the underlying functional mechanisms remain unclear, PPARγ expression probably contributes to blood pressure regulation through multiple mechanisms.

6.2. Renoprotective effects of PPARγ ligands due to mechanisms other than changes in blood glucose levels

TZD treatment ameliorated renal abnormalities in streptozotocin- (STZ-) induced diabetic rats, a type 1 diabetic model, without changing blood glucose levels [54, 56]. These findings suggest that the protective effects of PPARγ ligands on diabetes-induced renal dysfunction are independent of its insulin-sensitizing property. Multiple biochemical mechanisms have been proposed to explain the adverse effects of hyperglycemia in diabetes, and the effects of PPARγ ligands on each of these mechanisms is discussed below.

6.2.1. Amelioration of DGK-DAG-PKC pathway activation

The diacylglycerol- (DAG-) protein kinase C- (PKC-) extracellular signal-regulated kinase (ERK) pathway is enhanced in mesangial cells cultured under high-glucose conditions and in glomeruli isolated from streptozotocin- (STZ-) induced diabetic rats [100–103]. In these animals, troglitazone ameliorated the diabetes-associated increases in glomerular filtration rate, urinary albumin excretion, and mRNA expressions of extracellular matrix (ECM) proteins (fibronectin and type IV collagen) and transforming growth factor-β (TGF-β) without changing the blood glucose levels [56]. These findings provided the first evidence that PPARγ ligands can protect glomerular function independent of their insulin-sensitizing action. In mesangial cells cultured under high-glucose conditions and in isolated glomeruli from diabetic rats, it was confirmed that TZDs inhibited

Table 2: Human clinical studies.

Authors	subjects (Type 2 DM)	n	regimens	Duration	Effect on UAE (%)	Effect on BP (mmHg)
Sironi et al. [65]	hyp	40	200 mg toroglitazone versus plb	8 weeks	+11%	−4/−3
Imano et al. [66]	mA, hyp	30	400 mg toroglitazone versus 500 mg metformin	12 weeks	−39%[a]	−3/0
Nakamura et al. [67]	mA or MA	32	400 mg toroglitazone versus 5 mg glibenclamide	12 months	−67%[a] in mA 0% in MA	−6[c]
Nakamura et al. [68]	mA	45	30 mg Pio versus 5 mg glibenclamide versus 0.6 mg Vog	3 months	−66%[a]	−6/−4
Nakamura et al. [69]	mA	28	30 mg Pio versus plb	6 months	−59%[a]	−4[c]
Aljabri et al. [70]	mA, hyp	62	30–45 mg Pio versus isophane insulin	16 weeks	−44%	−8/−5
Yanagawa et al. [71]	mA, hyp	40	Pio versus Met or glibenclamide	12 weeks	−45%[a]	NA
Hanefeld et al. [72]	mA, hyp	639	15–45 mg Pio versus 850–2550 mg metformin	12 months	−15%[a]	NA
Schernthaner et al. [73]	hyp	1199	15–45 mg Pio versus 850–2550 mg metformin	12 months	−19%[a]	NA
Matthews et al. [74]	hyp	630	15–45 mg Pio versus 80–320 mg glibenclamide	12 months	−10%[a]	NA
Agarwal et al. [75]	MA, hyp	44	Pio versus Glip	4 months	−7%	+3.7/+2.2
Lebovitz et al. [76]	mA, hyp	493	4 or 8 mg Rosi versus plb	26 weeks	4 mg group: −14% 8 mg group: −22%[a]	NA
Sarafidis et al. [77]	hyp, mA	20	4 mg Rosi	6 months	−35%[a]	−5.4[a]/−4.1[a]
Pistrosch et al. [78]	mA, hyp	19	non-mA patients: Rosi versus Nat, mA patients: Rosi versus plb	12 weeks	non-mA patients: +18%[b], mA patients: −66%[a,b],	NA

[a]Significant changes from baseline levels or other groups;
[b]change versus the group compared;
[c]mean change for systolic BP versus baseline in patients treated with the TZD.
DM, diabetes mellitus; hyp, hypertension; mA, microalbuminuria; MA, macroalbuminuria; Glip, glipizide; Nat, nateglinide; plb, placebo; Pio, pioglitazone; Vog, voglibose; UAE, urine albumin excretion; NA, changes in blood pressure levels not applicable.

the accumulation of DAG and its subsequent activation of the PKC-ERK pathway. Furthermore, another TZD, pioglitazone, also prevented DAG-PKC-ERK pathway upregulation in mesangial cells exposed to high glucose [56]. Finally, TZDs and potent PPARγ ligand, 15dPGJ2, increased the protein expression of DGK to block DAG-PKC signaling in endothelial cells [103].

6.2.2. Attenuation of oxidative stress

Increased oxidative stress is observed in renal glomeruli and a variety of vascular and nonvascular tissues exposed to hyperglycemia [104–106]. Troglitazone has potent antioxidant effects, evident by it suppressing phosphoenolpyruvate gene expression in vitro and scavenging reactive oxygen species in vivo [107]. It also normalizes the decrease in plasma lipid hydroperoxide concentration and increase of superoxide dismutase activity in Otsuka Long-Evans Tokushima Fatty rats, a type 2 diabetic animal model, and improves the decreased skin blood flow in STZ-induced diabetic rats [98, 108, 109]. Pioglitazone also reduces oxidative stress in the kidney of alloxan-induced diabetic rabbits [110, 111] and reduces renal lipid peroxides, urinary isoprostane excretion, and expression of p47 *phox* and gp91 *phox* in high-fat diet-induced obese rats [112].

6.2.3. Suppression of inflammation

Hyperglycemia and the diabetic state can induce cytokine production in some tissues. In diabetic nephropathy, macrophages infiltrates appear in glomeruli and the interstitial spaces between tubules [113, 114]. Both PPARα and γ have potent anti-inflammatory effects in macrophages [115, 116]. The endogenous and potent PPARγ ligand, 15dPGJ2, is a natural metabolite derived from prostaglandin (PG)D2, the most abundant prostaglandin in normal tissues with the highest binding affinity to PPARγ of the J-series prostaglandins [117]. Several studies demonstrated that the anti-inflammatory effect of 15dPGJ2 or TZDs seems to be regulated through transcriptional inhibition by both PPARγ-dependent [115, 116, 118] and PPARγ-independent mechanisms [119–121]. Nuclear factor-κB (NF-κB), a well-known inflammatory transcription factor, is repressed by 15dPGJ2 in a PPARγ-independent manner [122]. It was also reported that 15dPGJ2 inhibits interleukin-1β- (IL-1β-) induced cyclooxygenase-2 expression and PGE2 production independently of PPARγ activation in mesangial cells, by suppressing ERK and c-Jun NH2-terminal kinase (JNK) pathways and AP-1 activation [123]. Another TZD agent, ciglitazone, inhibited platelet-derived growth factor-induced mesangial cell proliferation without changing ERK activation, through

inhibiting the activation of serum response element directly [124].

6.2.4. Modification of atherosclerotic changes

Renal atherosclerotic changes such as renovascular stenosis and atheroemboli are common findings in elderly diabetic patients and are known to accelerate renal dysfunction [125, 126]. PPARγ activation also may modify the progression of atherosclerosis through multiple mechanisms including foam cell differentiation, inflammatory reactions, and cell proliferation [127]. The infiltrating monocytes take up oxidized low-density lipoprotein (OxLDL) via scavenger receptors, resulting in the accumulation of intracellular lipids and generation of foam cells [127]. The OxLDL scavenger receptor, CD36, is under direct control of PPARγ [29, 30]. OxLDLs include natural PPARγ agonists such as 9-hydroxyoctadecadienoic acid (HODE) and 13-HODE. Furthermore, OxLDL induces the expression of PPARγ [115], which has an anti-inflammatory effect in monocytes by reducing proinflammatory cytokine production [115] via inhibition of proinflammatory transcription factors such as NFκB, AP-1, and STATs [116]. PPARγ has other effects on atherosclerosis including induction of apoptosis in monocytes [128], inhibition of VSMC proliferation [94, 129], and suppression of matrix metalloproteinase-9 expression [130].

6.3. Effects of PPARγ ligands in tubular tissue

Patients with diabetic nephropathy frequently show a nephrotic state, whereby large quantities of albumin enter the renal tubular system and carry with it a heavy load of fatty acids. Albumin-bound fatty acids can activate PPARγ and induce apoptosis of proximal tubular cells. PPARγ agonists might inhibit tubular cell proliferation, whereas activation of albumin-bound fatty acids is accompanied by increased proliferation [131]. In particular, pioglitazone increases the tubular cell albumin uptake and reverses the expression of inflammatory and profibrotic markers, monocyte chemoattractant protein-1 (MCP-1) and TGF-β [132].

7. INVOLVEMENT OF PPARα AND PPARβ/δ IN DIABETIC NEPHROPATHY

PPARα agonists have renoprotective effects as mentioned above. One possible mechanism underlying PPARα action on mesangial matrix production may be related to hyperglycemia or TGFβ signaling [133]. Clofibrate directly inhibited oxidative stress-induced TGFβ expression in mesangial cells [133], while fenofibrate downregulated TGFβ and TGFβ receptors type II expression and decreased type IV collagen accumulation in diabetic glomeruli, and inhibited the production of PAI-1 in diabetic animals [63, 64].

PPARβ/δ is expressed equally in the renal cortex and medulla, although the role of PPARβ/δ in the kidney remains poorly understood [41]. Overexpression of this isoform protected cultured medullary interstitial cells from hypertonicity-induced cell death, suggesting that PPARβ/δ is an important survival factor under hypertonic conditions in renal medulla [134]. However, there are no reports regarding the effect of PPARβ/δ on diabetic nephropathy. Further evidence from both clinical and experimental studies is necessary to clarify the therapeutic potential of PPARβ/δ and PPARα agonists in diabetic nephropathy.

Several recent studies suggested lipotoxicity from renal lipid accumulation as a possible pathogenic mechanism underlying certain forms of renal injury including diabetic nephropathy [135–137]. PPARα regulates lipid metabolism in the kidney [48], and PPARα knockout mice develop severe interstitial lesions induced by fatty acid overload [138]. PPARα agonists may, therefore, decrease lipotoxicity and, consequently, inhibit the progression of diabetic nephropathy. PPARβ/δ also regulates lipid metabolism and particularly lipid oxidation in several tissues, although its exact roles in the kidney remain unclear. Thus, both PPARβ/δ and PPARα agonists could be implemented in new therapeutic strategies designed to prevent diabetic nephropathy by reducing renal lipotoxicity. Further studies are required to prove this possibility.

8. CONCLUSION AND PERSPECTIVES

The increased incidence of diabetic nephropathy has become a major health problem worldwide. As discussed in this review, PPARs comprise a subfamily of nuclear receptors and transcription factors that play critical roles in modulating insulin resistance, hypertension, dyslipidemia, obesity, hypertension, and inflammation. Given the close relationship between PPAR activity and these metabolic alterations, PPAR agonists are promising therapeutic agents for diseases including type 2 diabetes, obesity, hypertension, hyperlipidemia, and atherosclerosis. Fibrate PPARα agonists and TZD PPARγ agonists are already used successfully as clinically effective hypolipidemic drugs and insulin sensitizers. PPARβ/δ agonists may provide additional insulin and lipid modulators via their effects on skeletal muscle. In addition, there is an increasing evidence suggesting that all three PPARs contribute to the metabolic control of renal function and are involved in the pathogenesis of diabetic nephropathy. PPARγ agonists are available as optional therapeutic agents for nephropathy in type 2 diabetes. In the near future, both PPARα and PPARβ/δ agonists might be added to that strategy with further evidence that these agents have a proven renoprotective effect in diabetic animals and patients.

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REFERENCES

[1] A. H. Mokdad, E. S. Ford, B. A. Bowman, et al., "Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001," *The Journal of the American Medical Association*, vol. 289, no. 1, pp. 76–79, 2003.

[2] A. F. Amos, D. J. McCarty, and P. Zimmet, "The rising global burden of diabetes and its complications: estimates and projections to the year 2010," *Diabetic Medicine*, vol. 14, supplement 5, pp. S7–S85, 1997.

[3] A. N. Lasaridis and P. A. Sarafidis, "Diabetic nephropathy and antihypertensive treatment: what are the lessons from clinical trials?" *American Journal of Hypertension*, vol. 16, no. 8, pp. 689–697, 2003.

[4] M. E. Molitch, R. A. DeFronzo, M. J. Franz, et al., "Nephropathy in diabetes," *Diabetes Care*, vol. 27, supplement 1, pp. S79–S83, 2004.

[5] J. C. Corton, S. P. Anderson, and A. Stauber, "Central role of peroxisome proliferator-activated receptors in the actions of peroxisome proliferators," *Annual Review of Pharmacology and Toxicology*, vol. 40, pp. 491–518, 2000.

[6] I. Issemann and S. Green, "Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators," *Nature*, vol. 347, no. 6294, pp. 645–650, 1990.

[7] C. Dreyer, G. Krey, H. Keller, F. Givel, G. Helftenbein, and W. Wahli, "Control of the peroxisomal β-oxidation pathway by a novel family of nuclear hormone receptors," *Cell*, vol. 68, no. 5, pp. 879–887, 1992.

[8] B. Desvergne and W. Wahli, "Peroxisome proliferator-activated receptors: nuclear control of metabolism," *Endocrine Reviews*, vol. 20, no. 5, pp. 649–688, 1999.

[9] L. Fajas, M. B. Debril, and J. Auwerx, "Peroxisome proliferator-activated receptor-γ: from adipogenesis to carcinogenesis," *Journal of Molecular Endocrinology*, vol. 27, no. 1, pp. 1–9, 2001.

[10] Y. Guan and M. D. Breyer, "Peroxisome proliferator-activated receptors (PPARs): novel therapeutic targets in renal disease," *Kidney International*, vol. 60, no. 1, pp. 14–30, 2001.

[11] T. M. Willson, M. H. Lambert, and S. A. Kliewer, "Peroxisome proliferator-activated receptor γ and metabolic disease," *Annual Review of Biochemistry*, vol. 70, pp. 341–367, 2001.

[12] B. Staels, J. Dallongeville, J. Auwerx, K. Schoonjans, E. Leitersdorf, and J.-C. Fruchart, "Mechanism of action of fibrates on lipid and lipoprotein metabolism," *Circulation*, vol. 98, no. 19, pp. 2088–2093, 1998.

[13] G. D. Wu, "A nuclear receptor to prevent colon cancer," *The New England Journal of Medicine*, vol. 342, no. 9, pp. 651–653, 2000.

[14] C.-H. Lee, P. Olson, A. Hevener, et al., "PPARδ regulates glucose metabolism and insulin sensitivity," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 9, pp. 3444–3449, 2006.

[15] J. Auwerx, "PPARγ, the ultimate thrifty gene," *Diabetologia*, vol. 42, no. 9, pp. 1033–1049, 1999.

[16] A. B. Jones, "Peroxisome proliferator-activated receptor (PPAR) modulators: diabetes and beyond," *Medicinal Research Reviews*, vol. 21, no. 6, pp. 540–552, 2001.

[17] L. Fajas, J.-C. Fruchart, and J. Auwerx, "PPARγ3 mRNA: a distinct PPARγ mRNA subtype transcribed from an independent promoter," *FEBS Letters*, vol. 438, no. 1-2, pp. 55–60, 1998.

[18] E. D. Rosen and B. M. Spiegelman, "PPARγ: a nuclear regulator of metabolism, differentiation, and cell growth," *Journal of Biological Chemistry*, vol. 276, no. 41, pp. 37731–37734, 2001.

[19] L. Fajas, D. Auboeuf, E. Raspé, et al., "The organization, promoter analysis, and expression of the human PPARγ gene," *Journal of Biological Chemistry*, vol. 272, no. 30, pp. 18779–18789, 1997.

[20] P. Escher and W. Wahli, "Peroxisome proliferator-activated receptors: insight into multiple cellular functions," *Mutation Research*, vol. 448, no. 2, pp. 121–138, 2000.

[21] C. E. Juge-Aubry, E. Hammar, C. Siegrist-Kaiser, et al., "Regulation of the transcriptional activity of the peroxisome proliferator-activated receptor α by phosphorylation of a ligand-independent *trans*-activating domain," *Journal of Biological Chemistry*, vol. 274, no. 15, pp. 10505–10510, 1999.

[22] D. Shao, S. M. Rangwala, S. T. Bailey, S. L. Krakow, M. J. Reginato, and M. A. Lazar, "Interdomain communication regulating ligand binding by PPAR-γ," *Nature*, vol. 396, no. 6709, pp. 377–380, 1998.

[23] S. A. Kliewer, H. E. Xu, M. H. Lambert, and T. M. Willson, "Peroxisome proliferator-activated receptors: from genes to physiology," *Recent Progress in Hormone Research*, vol. 56, pp. 239–263, 2001.

[24] D. Moras and H. Gronemeyer, "The nuclear receptor ligand-binding domain: structure and function," *Current Opinion in Cell Biology*, vol. 10, no. 3, pp. 384–391, 1998.

[25] P. Ellinghaus, C. Wolfrum, G. Assmann, F. Spener, and U. Seedorf, "Phytanic acid activates the peroxisome proliferator-activated receptor α (PPARα) in sterol carrier protein 2-/sterol carrier protein x-deficient mice," *Journal of Biological Chemistry*, vol. 274, no. 5, pp. 2766–2772, 1999.

[26] S. A. Kliewer, S. S. Sundseth, S. A. Jones, et al., "Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors α and γ," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, no. 9, pp. 4318–4323, 1997.

[27] Q. Lin, S. E. Ruuska, N. S. Shaw, D. Dong, and N. Noy, "Ligand selectivity of the peroxisome proliferator-activated receptor α," *Biochemistry*, vol. 38, no. 1, pp. 185–190, 1999.

[28] S. Y. Moya-Camarena, J. P. Vanden Heuvel, S. G. Blanchard, L. A. Leesnitzer, and M. A. Belury, "Conjugated linoleic acid is a potent naturally occurring ligand and activator of PPARα," *Journal of Lipid Research*, vol. 40, no. 8, pp. 1426–1433, 1999.

[29] L. Nagy, P. Tontonoz, J. G. A. Alvarez, H. Chen, and R. M. Evans, "Oxidized LDL regulates macrophage gene expression through ligand activation of PPARγ," *Cell*, vol. 93, no. 2, pp. 229–240, 1998.

[30] P. Tontonoz, L. Nagy, J. G. A. Alvarez, V. A. Thomazy, and R. M. Evans, "PPARγ promotes monocyte/macrophage differentiation and uptake of oxidized LDL," *Cell*, vol. 93, no. 2, pp. 241–252, 1998.

[31] K. G. Lambe and J. D. Tugwood, "A human peroxisome-proliferator-activated receptor-γ is activated by inducers of adipogenesis, including thiazalidinedione drugs," *European Journal of Biochemistry*, vol. 239, no. 1, pp. 1–7, 1996.

[32] B. B. Lowell, "PPARγ: an essential regulator of adipogenesis and modulator of fat cell function," *Cell*, vol. 99, no. 3, pp. 239–242, 1999.

[33] E. D. Rosen, P. Sarraf, A. E. Troy, et al., "PPARγ is required for the differentiation of adipose tissue in vivo and in vitro," *Molecular Cell*, vol. 4, no. 4, pp. 611–617, 1999.

[34] B. M. Spiegelman, E. Hu, J. B. Kim, and R. Brun, "PPARγ and the control of adipogenesis," *Biochimie*, vol. 79, no. 2-3, pp. 111–112, 1997.

[35] Z. Wu, E. D. Rosen, R. Brun, et al., "Cross-regulation of C/EBPα and PPARγ controls the transcriptional pathway of adipogenesis and insulin sensitivity," *Molecular Cell*, vol. 3, no. 2, pp. 151–158, 1999.

[36] S. C. Benson, H. A. Pershadsingh, C. I. Ho, et al., "Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARγ-modulating activity," *Hypertension*, vol. 43, no. 5, pp. 993–1002, 2004.

[37] M. Schupp, J. Janke, R. Clasen, T. Unger, and U. Kintscher, "Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-γ activity," *Circulation*, vol. 109, no. 17, pp. 2054–2057, 2004.

[38] O. Braissant, F. Foufelle, C. Scotto, M. Dauça, and W. Wahli, "Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue distribution of PPAR-α, -β, and -γ in the adult rat," *Endocrinology*, vol. 137, no. 1, pp. 354–366, 1996.

[39] J.-L. Su, C. J. Simmons, B. Wisely, B. Ellis, and D. A. Winegar, "Monitoring of PPAR alpha protein expression in human tissue by the use of PPAR alpha-specific MAbs," *Hybridoma*, vol. 17, no. 1, pp. 47–53, 1998.

[40] D. Auboeuf, J. Rieusset, L. Fajas, et al., "Tissue distribution and quantification of the expression of mRNAs of peroxisome proliferator-activated receptors and liver X receptor-α in humans: no alteration in adipose tissue of obese and NIDDM patients," *Diabetes*, vol. 46, no. 8, pp. 1319–1327, 1997.

[41] Y. Guan, Y. Zhang, L. Davis, and M. D. Breyer, "Expression of peroxisome proliferator-activated receptors in urinary tract of rabbits and humans," *American Journal of Physiology*, vol. 273, no. 6, pp. F1013–F1022, 1997.

[42] R. Mukherjee, L. Jow, G. E. Croston, and J. R. Paterniti Jr., "Identification, characterization, and tissue distribution of human peroxisome proliferator-activated receptor (PPAR) isoforms PPARγ2 versus PPARγ1 and activation with retinoid X receptor agonists and antagonists," *Journal of Biological Chemistry*, vol. 272, no. 12, pp. 8071–8076, 1997.

[43] S. A. Kliewer, B. M. Forman, B. Blumberg, et al., "Differential expression and activation of a family of murine peroxisome proliferator-activated receptors," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 91, no. 15, pp. 7355–7359, 1994.

[44] T. Yang, D. E. Michele, J. Park, et al., "Expression of peroxisomal proliferator-activated receptors and retinoid X receptors in the kidney," *American Journal of Physiology*, vol. 277, no. 6, pp. F966–F973, 1999.

[45] T. Asano, M. Wakisaka, M. Yoshinari, et al., "Peroxisome proliferator-activated receptor γ1 (PPARγ1) expresses in rat mesangial cells and PPARγ agonists modulate its differentiation," *Biochimica et Biophysica Acta*, vol. 1497, no. 1, pp. 148–154, 2000.

[46] Y. Iwashima, M. Eto, S. Horiuchi, and H. Sano, "Advanced glycation end product-induced peroxisome proliferator-activated receptor γ gene expression in the cultured mesangial cells," *Biochemical and Biophysical Research Communications*, vol. 264, no. 2, pp. 441–448, 1999.

[47] K. Sato, A. Sugawara, M. Kudo, A. Uruno, S. Ito, and K. Takeuchi, "Expression of peroxisome proliferator-activated receptor isoform proteins in the rat kidney," *Hypertension Research*, vol. 27, no. 6, pp. 417–425, 2004.

[48] Y. Kamijo, K. Hora, N. Tanaka, et al., "Identification of functions of peroxisome proliferator-activated receptor α in proximal tubules," *Journal of the American Society of Nephrology*, vol. 13, no. 7, pp. 1691–1702, 2002.

[49] D. M. Gorson, "Significant weight gain with rezulin therapy," *Archives of Internal Medicine*, vol. 159, no. 1, p. 99, 1999.

[50] T. Yoshimoto, M. Naruse, M. Nishikawa, et al., "Antihypertensive and vasculo- and renoprotective effects of pioglitazone in genetically obese diabetic rats," *American Journal of Physiology*, vol. 272, no. 6, pp. E989–E996, 1997.

[51] S. Yoshioka, H. Nishino, T. Shiraki, et al., "Antihypertensive effects of CS-045 treatment in obese Zucker rats," *Metabolism*, vol. 42, no. 1, pp. 75–80, 1993.

[52] C. Baylis, E.-A. Atzpodien, G. Freshour, and K. Engels, "Peroxisome proliferator-activated receptor γ agonist provides superior renal protection versus angiotensin-converting enzyme inhibition in a rat model of type 2 diabetes with obesity," *Journal of Pharmacology and Experimental Therapeutics*, vol. 307, no. 3, pp. 854–860, 2003.

[53] R. E. Buckingham, K. A. Al-Barazanji, C. D. Toseland, et al., "Peroxisome proliferator-activated receptor-γ agonist, rosiglitazone, protects against nephropathy and pancreatic islet abnormalities in Zucker fatty rats," *Diabetes*, vol. 47, no. 8, pp. 1326–1334, 1998.

[54] M. Fujii, R. Takemura, M. Yamaguchi, et al., "Troglitazone (CS-045) ameliorates albuminuria in streptozotocin-induced diabetic rats," *Metabolism*, vol. 46, no. 9, pp. 981–983, 1997.

[55] K. Fujiwara, K. Hayashi, Y. Ozawa, H. Tokuyama, A. Nakamura, and T. Saruta, "Renal protective effect of troglitazone in Wistar fatty rats," *Metabolism*, vol. 49, no. 10, pp. 1361–1364, 2000.

[56] K. Isshiki, M. Haneda, D. Koya, S. Maeda, T. Sugimoto, and R. Kikkawa, "Thiazolidinedione compounds ameliorate glomerular dysfunction independent of their insulin-sensitizing action in diabetic rats," *Diabetes*, vol. 49, no. 6, pp. 1022–1032, 2000.

[57] O. Khan, S. Riazi, X. Hu, J. Song, J. B. Wade, and C. A. Ecelbarger, "Regulation of the renal thiazide-sensitive Na-Cl cotransporter, blood pressure, and natriuresis in obese Zucker rats treated with rosiglitazone," *American Journal of Physiology*, vol. 289, no. 2, pp. F442–F450, 2005.

[58] S. B. Nicholas, Y. Kawano, S. Wakino, A. R. Collins, and W. A. Hsueh, "Expression and function of peroxisome proliferator-activated receptor-γ in mesangial cells," *Hypertension*, vol. 37, no. 2, pp. 722–727, 2001.

[59] M. Tanimoto, Q. Fan, T. Gohda, T. Shike, Y. Makita, and Y. Tomino, "Effect of pioglitazone on the early stage of type 2 diabetic nephropathy in KK/Ta mice," *Metabolism*, vol. 53, no. 11, pp. 1473–1479, 2004.

[60] H. Yamashita, Y. Nagai, T. Takamura, E. Nohara, and K. Kobayashi, "Thiazolidinedione derivatives ameliorate albuminuria in streptozotocin-induced diabetic spontaneous hypertensive rat," *Metabolism*, vol. 51, no. 4, pp. 403–408, 2002.

[61] D. Portilla, "Energy metabolism and cytotoxicity," *Seminars in Nephrology*, vol. 23, no. 5, pp. 432–438, 2003.

[62] F. Ouali, F. Djouadi, C. Merlet-Bénichou, and J. Bastin, "Dietary lipids regulate β-oxidation enzyme gene expression in the developing rat kidney," *American Journal of Physiology*, vol. 275, no. 5, pp. F777–F784, 1998.

[63] C. W. Park, Y. Zhang, X. Zhang, et al., "PPARα agonist fenofibrate improves diabetic nephropathy in *db/db* mic," *Kidney International*, vol. 69, no. 9, pp. 1511–1517, 2006.

[64] X. Zhao and L.-Y. Li, "PPAR-alpha agonist fenofibrate induces renal CYP enzymes and reduces blood pressure and glomerular hypertrophy in Zucker diabetic fatty rats," *American Journal of Nephrology*, vol. 28, no. 4, pp. 598–606, 2008.

[65] A. M. Sironi, S. Vichi, A. Gastaldelli, et al., "Effects of troglitazone on insulin action and cardiovascular risk factors in patients with non-insulin-dependent diabetes," *Clinical Pharmacology and Therapeutics*, vol. 62, no. 2, pp. 194–202, 1997.

[66] E. Imano, T. Kanda, Y. Nakatani, et al., "Effect of troglitazone on microalbuminuria in patients with incipient diabetic nephropathy," *Diabetes Care*, vol. 21, no. 12, pp. 2135–2139, 1998.

[67] T. Nakamura, C. Ushiyama, S. Suzuki, et al., "Effect of troglitazone on urinary albumin excretion and serum type IV collagen concentrations in type 2 diabetic patients with microalbuminuria or macroalbuminuria," *Diabetic Medicine*, vol. 18, no. 4, pp. 308–313, 2001.

[68] T. Nakamura, C. Ushiyama, N. Shimada, K. Hayashi, I. Ebihara, and H. Koide, "Comparative effects of pioglitazone, glibenclamide, and voglibose on urinary endothelin-1 and albumin excretion in diabetes patients," *Journal of Diabetes and its Complications*, vol. 14, no. 5, pp. 250–254, 2000.

[69] T. Nakamura, C. Ushiyama, S. Osada, M. Hara, N. Shimada, and H. Koide, "Pioglitazone reduces urinary podocyte excretion in type 2 diabetes patients with microalbuminuria," *Metabolism*, vol. 50, no. 10, pp. 1193–1196, 2001.

[70] K. Aljabri, S. E. Kozak, and D. M. Thompson, "Addition of pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: a prospective, randomized trial," *American Journal of Medicine*, vol. 116, no. 4, pp. 230–235, 2004.

[71] T. Yanagawa, A. Araki, K. Sasamoto, S. Shirabe, and T. Yamanouchi, "Effect of antidiabetic medications on microalbuminuria in patients with type 2 diabetes," *Metabolism*, vol. 53, no. 3, pp. 353–357, 2004.

[72] M. Hanefeld, P. Brunetti, G. H. Schernthaner, D. R. Matthews, and B. H. Charbonnel, "One-year glycemic control with a suifonyurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes," *Diabetes Care*, vol. 27, no. 1, pp. 141–147, 2004.

[73] G. Schernthaner, D. R. Matthews, B. Charbonnel, M. Hanefeld, and P. Brunetti, "Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial," *The Journal of Clinical Endocrinology & Metabolism*, vol. 89, no. 12, pp. 6068–6076, 2004.

[74] D. R. Matthews, B. H. Charbonnel, M. Hanefeld, P. Brunetti, and G. Schernthaner, "Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study," *Diabetes/Metabolism Research and Reviews*, vol. 21, no. 2, pp. 167–174, 2005.

[75] R. Agarwal, C. Saha, M. Battiwala, et al., "A pilot randomized controlled trial of renal protection with pioglitazone in diabetic nephropathy," *Kidney International*, vol. 68, no. 1, pp. 285–292, 2005.

[76] H. E. Lebovitz, J. F. Dole, R. Patwardhan, E. B. Rappaport, and M. I. Freed, "Rosiglitazone monotherapy is effective in patients with type 2 diabetes," *The Journal of Clinical Endocrinology & Metabolism*, vol. 86, no. 1, pp. 280–288, 2001.

[77] P. A. Sarafidis, A. N. Lasaridis, P. M. Nilsson, et al., "The effect of rosiglitazone on urine albumin excretion in patients with type 2 diabetes mellitus and hypertension," *American Journal of Hypertension*, vol. 18, no. 2, pp. 227–234, 2005.

[78] F. Pistrosch, K. Herbrig, B. Kindel, J. Passauer, S. Fischer, and P. Gross, "Rosiglitazone improves glomerular hyperfiltration, renal endothelial dysfunction, and microalbuminuria of incipient diabetic nephropathy in patients," *Diabetes*, vol. 54, no. 7, pp. 2206–2211, 2005.

[79] G. R. Dagenais, H. C. Gerstein, R. Holman, et al., "Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial," *Diabetes Care*, vol. 31, no. 5, pp. 1007–1014, 2008.

[80] L. F. Fried, T. J. Orchard, and B. L. Kasiske, "Effect of lipid reduction on the progression of renal disease: a meta-analysis," *Kidney International*, vol. 59, no. 1, pp. 260–269, 2001.

[81] Y. M. Smolders, A. E. van Eeden, C. D. A. Stehouwer, R. N. M. Weijers, E. H. Slaats, and J. Silberbusch, "Can reduction in hypertriglyceridaemia slow progression of microalbuminuria in patients with non-insulin-dependent diabetes mellitus?" *European Journal of Clinical Investigation*, vol. 27, no. 12, pp. 997–1002, 1997.

[82] A. Keech, R. J. Simes, P. Barter, et al., "Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial," *The Lancet*, vol. 366, no. 9500, pp. 1849–1861, 2005.

[83] H. Shamoon, H. Duffy, N. Fleischer, et al., "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus," *The New England Journal of Medicine*, vol. 329, no. 14, pp. 977–986, 1993.

[84] UK Prospective Diabetes Study (UKPDS) Group, "Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)," *The Lancet*, vol. 352, no. 9131, pp. 837–853, 1998.

[85] V. A. Fonseca, T. R. Valiquett, S. M. Huang, et al., "Troglitazone monotherapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled study," *The Journal of Clinical Endocrinology & Metabolism*, vol. 83, no. 9, pp. 3169–3176, 1998.

[86] S. Kumar, A. J. M. Boulton, H. Beck-Nielsen, et al., "Troglitazone, an insulin action enhancer, improves metabolic control in NIDDM patients," *Diabetologia*, vol. 39, no. 6, pp. 701–709, 1996.

[87] R. L. Prigeon, S. E. Kahn, and D. Porte Jr., "Effect of troglitazone on B cell function, insulin sensitivity, and glycemic control in subjects with type 2 diabetes mellitus," *The Journal of Clinical Endocrinology & Metabolism*, vol. 83, no. 3, pp. 819–823, 1998.

[88] P. Ferrari and P. Weidmann, "Editorial review: insulin, insulin sensitivity and hypertension," *Journal of Hypertension*, vol. 8, no. 6, pp. 491–500, 1990.

[89] J. W. Grinsell, C. K. Lardinois, A. Swislocki, et al., "Pioglitazone attenuates basal and postprandial insulin concentrations and blood pressure in the spontaneously hypertensive rat," *American Journal of Hypertension*, vol. 13, no. 4, pp. 370–375, 2000.

[90] B. H. Sung, J. L. Izzo Jr., P. Dandona, and M. F. Wilson, "Vasodilatory effects of troglitazone improve blood pressure at rest and during mental stress in type 2 diabetes mellitus," *Hypertension*, vol. 34, no. 1, pp. 83–88, 1999.

[91] A. Uchida, T. Nakata, T. Hatta, et al., "Reduction of insulin resistance attenuates the development of hypertension in sucrose-fed SHR," *Life Sciences*, vol. 61, no. 4, pp. 455–464, 1997.

[92] A. B. Walker, P. D. Chattington, R. E. Buckingham, and G. Williams, "The thiazolidinedione rosiglitazone (BRL-49653) lowers blood pressure and protects against impairment of endothelial function in Zucker fatty rats," *Diabetes*, vol. 48, no. 7, pp. 1448–1453, 1999.

[93] K. Iijima, M. Yoshizumi, J. Ako, et al., "Expression of peroxisome proliferator-activated receptor γ (PPARγ) in rat aortic smooth muscle cells," *Biochemical and Biophysical Research Communications*, vol. 247, no. 2, pp. 353–356, 1998.

[94] R. E. Law, S. Goetze, X.-P. Xi, et al., "Expression and function of PPARγ in rat and human vascular smooth muscle cells," *Circulation*, vol. 101, no. 11, pp. 1311–1318, 2000.

[95] N. Marx, U. Schönbeck, M. A. Lazar, P. Libby, and J. Plutzky, "Peroxisome proliferator-activated receptor gamma activators inhibit gene expression and migration in human vascular smooth muscle cells," *Circulation Research*, vol. 83, no. 11, pp. 1097–1103, 1998.

[96] F. Zhang, J. R. Sowers, J. L. Ram, P. R. Standley, and J. D. Peuler, "Effects of pioglitazone on calcium channels in vascular smooth muscle," *Hypertension*, vol. 24, no. 2, pp. 170–175, 1994.

[97] H. Y. Zhang, S. R. Reddy, and T. A. Kotchen, "Antihypertensive effect of pioglitazone is not invariably associated with increased insulin sensitivity," *Hypertension*, vol. 24, no. 1, pp. 106–110, 1994.

[98] T. Fujiwara, T. Ohsawa, S. Takahashi, et al., "Troglitazone, a new antidiabetic agent possessing radical scavenging ability, improved decreased skin blood flow in diabetic rats," *Life Sciences*, vol. 63, no. 22, pp. 2039–2047, 1998.

[99] A. Sugawara, K. Takeuchi, A. Uruno, et al., "Transcriptional suppression of type 1 angiotensin II receptor gene expression by peroxisome proliferator-activated receptor-γ in vascular smooth muscle cells," *Endocrinology*, vol. 142, no. 7, pp. 3125–3134, 2001.

[100] M. Haneda, S.-I. Araki, M. Togawa, T. Sugimoto, M. Isono, and R. Kikkawa, "Mitogen-activated protein kinase cascade is activated in glomeruli of diabetic rats and glomerular mesangial cells cultured under high glucose conditions," *Diabetes*, vol. 46, no. 5, pp. 847–853, 1997.

[101] R. Kikkawa, M. Haneda, T. Uzu, D. Koya, T. Sugimoto, and Y. Shigeta, "Translocation of protein kinase C α and ζ in rat glomerular mesangial cells cultured under high glucose conditions," *Diabetologia*, vol. 37, no. 8, pp. 838–841, 1994.

[102] D. Koya, M. R. Jirousek, Y.-W. Lin, H. Ishii, K. Kuboki, and G. L. King, "Characterization of protein kinase C β isoform activation on the gene expression of transforming growth factor-β, extracellular matrix components, and prostanoids in the glomeruli of diabetic rats," *Journal of Clinical Investigation*, vol. 100, no. 1, pp. 115–126, 1997.

[103] D. Koya, I.-K. Lee, H. Ishii, H. Kanoh, and G. L. King, "Prevention of glomerular dysfunction in diabetic rats by treatment with d-α-tocopherol," *Journal of the American Society of Nephrology*, vol. 8, no. 3, pp. 426–435, 1997.

[104] J. W. Baynes and S. R. Thorpe, "Role of oxidative stress in diabetic complications: a new perspective on an old paradigm," *Diabetes*, vol. 48, no. 1, pp. 1–9, 1999.

[105] P. Dandona, K. Thusu, S. Cook, et al., "Oxidative damage to DNA in diabetes mellitus," *The Lancet*, vol. 347, no. 8999, pp. 444–445, 1996.

[106] J. Leinonen, T. Lehtimäki, S. Toyokuni, et al., "New biomarker evidence of oxidative DNA damage in patients with non-insulin-dependent diabetes mellitus," *FEBS Letters*, vol. 417, no. 1, pp. 150–152, 1997.

[107] G. F. Davies, R. L. Khandelwal, L. Wu, B. H. Juurlink, and W. J. Roesler, "Inhibition of phosphoenolpyruvate carboxykinase (PEPCK) gene expression by troglitazone: a peroxisome proliferator-activated receptor-γ (PPARγ)-independent, antioxidant-related mechanism," *Biochemical Pharmacology*, vol. 62, no. 8, pp. 1071–1079, 2001.

[108] T. Fukui, T. Noma, K. Mizushige, Y. Aki, S. Kimura, and Y. Abe, "Dietary troglitazone decreases oxidative stress in early stage type II diabetic rats," *Life Sciences*, vol. 66, no. 21, pp. 2043–2049, 2000.

[109] I. Inoue, S. Katayama, K. Takahashi, et al., "Troglitazone has a scavenging effect on reactive oxygen species," *Biochemical and Biophysical Research Communications*, vol. 235, no. 1, pp. 113–116, 1997.

[110] A. Gumieniczek, "Effect of the new thiazolidinedione-pioglitazone on the development of oxidative stress in liver and kidney of diabetic rabbits," *Life Sciences*, vol. 74, no. 5, pp. 553–562, 2003.

[111] A. Gumieniczek, "Effects of pioglitazone on hyperglycemia-induced alterations in antioxidative system in tissues of alloxan-treated diabetic animals," *Experimental and Toxicologic Pathology*, vol. 56, no. 4-5, pp. 321–326, 2005.

[112] A. D. Dobrian, S. D. Schriver, A. A. Khraibi, and R. L. Prewitt, "Pioglitazone prevents hypertension and reduces oxidative stress in diet-induced obesity," *Hypertension*, vol. 43, no. 1, pp. 48–56, 2004.

[113] T. Furuta, T. Saito, T. Ootaka, et al., "The role of macrophages in diabetic glomerulosclerosis," *American Journal of Kidney Diseases*, vol. 21, no. 5, pp. 480–485, 1993.

[114] K.-I. Shikata and H. Makino, "Role of macrophages in the pathogenesis of diabetic nephropathy," *Contributions to Nephrology*, vol. 134, pp. 46–54, 2001.

[115] C. Jiang, A. T. Ting, and B. Seed, "PPAR-γ agonists inhibit production of monocyte inflammatory cytokines," *Nature*, vol. 391, no. 6662, pp. 82–86, 1998.

[116] M. Ricote, A. C. Li, T. M. Willson, C. J. Kelly, and C. K. Glass, "The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation," *Nature*, vol. 391, no. 6662, pp. 79–82, 1998.

[117] P. R. Colville-Nash and D. W. Gilroy, "COX-2 and the cyclopentenone prostaglandins—a new chapter in the book of inflammation?" *Prostaglandins and Other Lipid Mediators*, vol. 62, no. 1, pp. 33–43, 2000.

[118] H. Inoue, T. Tanabe, and K. Umesono, "Feedback control of cyclooxygenase-2 expression through PPARγ," *Journal of Biological Chemistry*, vol. 275, no. 36, pp. 28028–28032, 2000.

[119] A. Chawla, Y. Barak, L. Nagy, D. Liao, P. Tontonoz, and R. M. Evans, "PPAR-γ dependent and independent effects on macrophage-gene expression in lipid metabolism and inflammation," *Nature Medicine*, vol. 7, no. 1, pp. 48–52, 2001.

[120] T. V. Petrova, K. T. Akama, and L. J. Van Eldik, "Cyclopentenone prostaglandins suppress activation of microglia: down-regulation of inducible nitric-oxide synthase by 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 8, pp. 4668–4673, 1999.

[121] S. Vaidya, E. P. Somers, S. D. Wright, P. A. Detmers, and V. S. Bansal, "15-deoxy-$\Delta^{12,1412,14}$-prostaglandin J_2 inhibits the β_2 integrin-dependent oxidative burst: involvement of a mechanism distinct from peroxisome proliferator-activated receptor γ ligation," *The Journal of Immunology*, vol. 163, no. 11, pp. 6187–6192, 1999.

[122] A. Rossi, P. Kapahi, G. Natoli, et al., "Anti-inflammatory cyclopentenone prostaglandins are direct inhibitors of IκB kinase," *Nature*, vol. 403, no. 6765, pp. 103–108, 2000.

[123] H. Sawano, M. Haneda, T. Sugimoto, K. Inoki, D. Koya, and R. Kikkawa, "15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 inhibits IL-1β-induced cyclooxygenase-2 expression in mesangial cells," *Kidney International*, vol. 61, no. 6, pp. 1957–1967, 2002.

[124] S. S. Ghosh, T. W. Gehr, S. Ghosh, et al., "PPARγ ligand attenuates PDGF-induced mesangial cell proliferation: role of MAP kinase," *Kidney International*, vol. 64, no. 1, pp. 52–62, 2003.

[125] E. D. Crook, "The role of hypertension, obesity, and diabetes in causing renal vascular disease," *American Journal of the Medical Sciences*, vol. 317, no. 3, pp. 183–188, 1999.

[126] B. C. van Jaarsveld, P. Krijnen, H. Pieterman, et al., "The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis," *The New England Journal of Medicine*, vol. 342, no. 14, pp. 1007–1014, 2000.

[127] T. Sawamura, N. Kume, T. Aoyama, et al., "An endothelial receptor for oxidized low-density lipoprotein," *Nature*, vol. 386, no. 6620, pp. 73–77, 1997.

[128] G. Chinetti, S. Griglio, M. Antonucci, et al., "Activation of proliferator-activated receptors α and γ induces apoptosis of human monocyte-derived macrophages," *Journal of Biological Chemistry*, vol. 273, no. 40, pp. 25573–25580, 1998.

[129] R. E. Law, W. P. Meehan, X.-P. Xi, et al., "Troglitazone inhibits vascular smooth muscle cell growth and intimal hyperplasia," *Journal of Clinical Investigation*, vol. 98, no. 8, pp. 1897–1905, 1996.

[130] K. Murakami, K. Tobe, T. Ide, et al., "A novel insulin sensitizer acts as a coligand for peroxisome proliferator-activated receptor-α (PPAR-α) and PPAR-γ: effect of PPAR-α activation on abnormal lipid metabolism in liver of Zucker fatty rats," *Diabetes*, vol. 47, no. 12, pp. 1841–1847, 1998.

[131] M. Arici, R. Chana, A. Lewington, J. Brown, and N. J. Brunskill, "Stimulation of proximal tubular cell apoptosis by albumin-bound fatty acids mediated by peroxisome proliferator activated receptor-γ," *Journal of the American Society of Nephrology*, vol. 14, no. 1, pp. 17–27, 2003.

[132] S. Zafiriou, S. R. Stanners, T. S. Polhill, P. Poronnik, and C. A. Pollock, "Pioglitazone increases renal tubular cell albumin uptake but limits proinflammatory and fibrotic responses," *Kidney International*, vol. 65, no. 5, pp. 1647–1653, 2004.

[133] W. A. Wilmer, C. L. Dixon, C. Hebert, L. Lu, and B. H. Rovin, "PPAR-α ligands inhibit H_2O_2-mediated activation of transforming growth factor-β1 in human mesangial cells," *Antioxidants & Redox Signaling*, vol. 4, no. 6, pp. 877–884, 2002.

[134] C.-M. Hao, R. Redha, J. Morrow, and M. D. Breyer, "Peroxisome proliferator-activated receptor δ activation promotes cell survival following hypertonic stress," *Journal of Biological Chemistry*, vol. 277, no. 24, pp. 21341–21345, 2002.

[135] T. Jiang, Z. Wang, G. Proctor, et al., "Diet-induced obesity in C57BL/6J mice causes increased renal lipid accumulation and glomerulosclerosis via a sterol regulatory element-binding protein-1c-dependent pathway," *Journal of Biological Chemistry*, vol. 280, no. 37, pp. 32317–32325, 2005.

[136] S. Kume, T. Uzu, S.-I. Araki, et al., "Role of altered renal lipid metabolism in the development of renal injury induced by a high-fat diet," *Journal of the American Society of Nephrology*, vol. 18, no. 10, pp. 2715–2723, 2007.

[137] G. Proctor, T. Jiang, M. Iwahashi, Z. Wang, J. Li, and M. Levi, "Regulation of renal fatty acid and cholesterol metabolism, inflammation, and fibrosis in Akita and OVE26 mice with type 1 diabetes," *Diabetes*, vol. 55, no. 9, pp. 2502–2509, 2006.

[138] Y. Kamijo, K. Hora, K. Kono, et al., "PPARα protects proximal tubular cells from acute fatty acid toxicity," *Journal of the American Society of Nephrology*, vol. 18, no. 12, pp. 3089–3100, 2007.