Role of PPARγ in renoprotection in Type 2 diabetes: molecular mechanisms and therapeutic potential

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ABSTRACT

DN (diabetic nephropathy) is a chronic disease characterized by proteinuria, glomerular hypertrophy, decreased glomerular filtration and renal fibrosis with loss of renal function. DN is the leading cause of ESRD (end-stage renal disease), accounting for millions of deaths worldwide. TZDs (thiazolidinediones) are synthetic ligands of PPARγ (peroxisome-proliferator-activated receptor γ), which is involved in many important physiological processes, including adipose differentiation, lipid and glucose metabolism, energy homoeostasis, cell proliferation, inflammation, reproduction and renoprotection. A large body of research over the past decade has revealed that, in addition to their insulin-sensitizing effects, TZDs play an important role in delaying and preventing the progression of chronic kidney disease in Type 2 diabetes. Although PPARγ activation by TZDs is in general considered beneficial for the amelioration of diabetic renal complications in Type 2 diabetes, the underlying mechanism(s) remains only partially characterized. In this review, we summarize and discuss recent findings regarding the renoprotective effects of PPARγ in Type 2 diabetes and the potential underlying mechanisms.

INTRODUCTION

In 2000, an estimated 171 million patients worldwide had diabetes (mainly Type 2), and the number could reach 366 million by the year 2030 [1]. Diabetes is becoming one of the major diseases endangering our health [1]. With the greatly increasing prevalence of Type 2 diabetes, diabetic renal complications, or DN (diabetic nephropathy), have become a very serious public health concern [2]. DN is one of the major diabetic complications and the leading cause of ESRD (end-stage renal disease), accounting for approx. 40–50% of all new cases [2,3]. DN is characterized by sequential pathophysiological events, including glomerular hypertrophy, decreased glomerular filtration rate, extracellular matrix accumulation and renal fibrosis with loss of renal function. Over the past decades, the therapeutic results from numerous studies on the prevention and delay in DN have been unsatisfactory [2]. Among the many experimental drugs that have been shown to effectively attenuate the development of...

Key words: chronic kidney disease, diabetic nephropathy, peroxisome-proliferator-activated receptor (PPAR), renoprotection, Type 2 diabetes.

Abbreviations: ABCA1, ATP-binding-cassette transporter A1; AGE, advanced glycation end-product; AngII, angiotensin II; BP, blood pressure; CKD, chronic kidney disease; 15dPGJ2, 15-deoxy-D12,14-prostaglandin J2; DN, diabetic nephropathy; ESRD, end-stage renal disease; FXR, farnesoid X receptor; ICAM, intercellular adhesion molecule; IL, interleukin; LXR, liver X receptor; NEFA, non-esterified fatty acid; NF-κB, nuclear factor κB; OLETF rat, Otsuka Long-Evans Tokushima Fatty rat; PPAR, peroxisome-proliferator-activated receptor; RXRα, retinoid X receptor α; SNP, single nucleotide polymorphism; SREBP, sterol-regulatory-element-binding protein; TGF-β, transforming growth factor-β; TIMP, tissue inhibitor of metalloproteinase; TNF-α, tumour necrosis factor-α; TZD, thiazolidinedione.

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DN in animal models of Type 2 diabetes, the insulin sensitizers TZDs (thiazolidinediones) might hold great promise for treating both insulin resistance and diabetic renal complications. TZDs are a group of compounds including rosiglitazone and pioglitazone, both of which are currently widely used in clinical therapy for Type 2 diabetes. TZDs are synthetic ligands of a nuclear receptor transcription factor called PPARγ (peroxisome-proliferator-activated receptor γ), a member of the PPAR subfamily that includes PPARα, PPARβ/δ and PPARγ [4,5]. PPARγ is expressed predominantly in adipose tissue and to some extent in many other tissues in Xenopus, rodents and humans. It is a key regulator of adipocyte differentiation, triacylglycerol (triglyceride) storage and energy homoeostasis [4,5]. After being bound by endogenous ligands, including 15dPGJ2 (15-deoxy-Δ12,14-prostaglandin J2) and long-chain NEFAs [non-esterified fatty acids (‘free’ fatty acids)], or synthetic agonists, such as TZDs, PPARγ heterodimerizes with another nuclear receptor called RXRα (retinoid X receptor α). The PPARγ/RXRα heterodimer then binds to a specific DNA sequence, the PPRE (PPAR-responsive element), located in promoter regions of the target genes of PPARγ, to initiate or silence gene transcription, therefore modulating glucose homoeostasis in peripheral tissues via various actions [6]. Increasing evidence has suggested that activation of PPARγ in adipose tissues contributes much to its insulin-sensitizing effects via suppressing the release of insulin-desensitizing factors, such as NEFAs, TNF-α (tumour necrosis factor-α), leptin, IL-6 (interleukin)-6 and resistin, and stimulating the secretion of insulin-sensitizing factors adiponectin and visfatin [7,8].

In addition to their effects on the amelioration of insulin resistance and improving Type 2 diabetes, TZDs are increasingly being shown to reduce proteinuria and delay the progression of DN, dependent or independent of glycaemic control [2,9,10]. Although PPARγ is generally accepted as a renoprotective factor in Type 2 diabetes [2,3,11–14], how PPARγ exerts its favourable effects remains unclear. To date, many investigators and clinicians have reported the numerous renoprotective actions of PPARγ, including improved insulin resistance, decreased blood glucose, reduced levels of circulating NEFAs and insulin-desensitizing cytokines, increased plasma adiponectin level, lowered BP (blood pressure) and direct renal actions [2,3,11–18].

In this review, we discuss some of the latest experimental and clinical studies evaluating the renoprotective effects of PPARγ on DN and the potential underlying mechanisms, and discuss the implications for clinical therapy with TZDs.

**PPARγ EXPRESSION IN THE KIDNEY**

PPARγ has been shown to be functionally expressed in various species, including Xenopus, rodents and humans. In general, PPARγ is predominantly enriched in adipose tissues [19], where it controls adipogenesis and lipid storage. PPARγ is also expressed at low levels in many non-adipose tissues, including the kidney and vasculature [20,21], which suggests that it might play an important role in renal function and BP regulation. To date, the intrarenal localization of PPARγ has been investigated intensively. Within the kidney of humans and rodents, PPARγ is mainly localized in the medullary collecting duct [22,23]. Its expression has also been detected in many other nephron segments, including the glomeruli and proximal tubules [23]. In addition, constitutive expression of PPARγ has been revealed in cultured glomerular mesangial cells [24,25], podocytes [26], proximal epithelial cells and epithelial cells of collecting ducts [26,27]. Because multiple renal cell types have endogenous PPARγ expression and activity, the kidney could be one direct target tissue of PPARγ agonists, and PPARγ activation in the kidney may be critical for maintaining normal renal function.

**PPARγ AND RENOPROTECTION: EVIDENCE FROM ANIMAL AND CLINICAL STUDIES**

Over the past decade, growing evidence has suggested that PPARγ activation is associated with the attenuation of DN. Treatment of various rodent models of Type 2 diabetes [db/db mice, obese Zucker rats and OLETF (Otsuka Long-Evans Tokushima Fatty) rats] with TZDs not only improved insulin resistance and glycaemic control, but also ameliorated DN by inhibiting glomerular hypertrophy, reducing mesangial matrix expansion, and improving proteinuria and renal function [10,28,29]. Several studies have demonstrated that PPARγ activation by troglitazone and rosiglitazone prevented glucose-induced TGF-β (transforming growth factor-β) expression in the kidney, a central event in the pathogenesis of diabetic glomerulosclerosis [30]. In vitro studies have shown that PPARγ activation in cultured renal mesangial cells modulated cell proliferation and differentiation [25], and inhibited high-glucose- or TGF-β-stimulated synthesis of type I collagen [31]. Treatment of cultured primary mesangial cells isolated from diabetic rat kidney with rosiglitazone significantly decreased proliferation and apoptosis and blunted responsiveness to AngII (angiotensin II) stimulation [32]. In cultured glomerular endothelial cells, activation of PPARγ by pioglitazone effectively inhibited high-glucose-induced activation of NF-κB (nuclear factor κB), which plays an important role in renal inflammatory processes [33]. Therefore activation of PPARγ may block glomerulosclerosis by directly targeting glomerular cells.

Similarly, treatment of human kidney fibroblasts with pioglitazone resulted in (i) decreased type IV collagen secretion, fibronectin secretion and proline incorporation;
(ii) decreased MMP-9 (matrix metalloproteinase-9) activity; and (iii) decreased secretion of TIMP (tissue inhibitor of metalloproteinase)-1 and TIMP-2 [34], which suggests that PPARγ activation may have a specific role in ameliorating the course of progressive tubulointerstitial fibrosis. Importantl, several clinical studies have shown rosiglitazone and pioglitazone to significantly improve proteinuria and serum type IV collagen levels, improve glomerular hyperfiltration and restore renal endothelial dysfunction in patients with Type 2 diabetes with renal complications [35–40]. Human genetic studies have shown an association between SNPs (single nucleotide polymorphisms) in the gene encoding PPARγ (PPARG) and susceptibility to DN [41]. The Pro12Ala polymorphism in the PPARγ gene was revealed to be a putative determinant of DN, and the presence of the A12 allele was significantly associated with a decreased risk of DN [42]. Moreover, when compared with the 161TT or 161C/T genotypes, the 161CC genotype was associated with an increased risk of ESRD [41]. Taken together, these results show that PPARγ is an important factor in maintaining normal renal function. Endogenous PPARγ activity is associated with the pathogenesis of DN, and activation of PPARγ by TZDs may be effective in delaying and even preventing CKD (chronic kidney disease) in patients with Type 2 diabetes.

**MECHANISMS INVOLVED IN THE RENOPROTECTIVE EFFECT OF PPARγ**

In the following section, we summarize the underlying mechanism(s) by which PPARγ may exert renal protective actions in Type 2 diabetes.

**Improved insulin resistance and glycaemic control**

Over the past decade, enormous research effort has identified PPARγ as a crucial regulator of insulin resistance. PPARγ agonists, including rosiglitazone and pioglitazone, have been widely used for treatment of insulin resistance and Type 2 diabetes [7]. Extensive human genetic studies have shed further light on a critical role of PPARγ in the regulation of insulin sensitivity [43]. Loss-of-function mutations in the ligand-binding domain of human PPARγ resulted in severe insulin resistance, diabetes, hypertension and dyslipidaemia [44,45]. Hyperglycaemia is associated with increased proteinuria and renal dysfunction in patients with DN. Chronic hyperglycaemia leads to renal dysfunction by a mechanism of ‘renal glucotoxicity’, referred to as non-enzymatic protein glycation, activation of PKC (protein kinase C) and accumulation of AGEs (advanced glycation end-products) [46–49]. In support of this mechanism, an AGE inhibitor has been shown to reduce proteinuria in diabetic rats [50]. Because of the well-established role of PPARγ in reducing blood glucose in patients with Type 2 diabetes, it is reasonable to speculate that amelioration of hyperglycaemia may play an important role in mediating the renoprotection of PPARγ agonists [6,7,15].

A decade ago, the insulin receptor was reported to be expressed in kidney cell lines of rats and humans [51,52], and the kidney was recognized as an insulin target tissue [53,54]. The function of insulin in renal epithelial cells is physiologically important in regulating nutrient reabsorption and BP control. Hyperinsulinaemia in patients with Type 2 diabetes may have a direct impact on renal regulation of salt, water and other nutrients via renal insulin signalling pathways, which results in renal dysfunction and global dysmetabolism [55–58]. Hyperinsulinaemia-induced TGF-β expression in the kidney of a rat model of Type 2 diabetes was reported to be associated with increased proteinuria and renal dysfunction, which were reversed by pioglitazone treatment independent of glycaemic control [57]. A later study by Tiwari et al. [58] demonstrated the reduced expression of the insulin receptor in the kidney of insulin-resistant rats, which was restored in part by rosiglitazone treatment; thus attenuation of a renal insulin signalling defect may contribute to PPARγ-mediated renoprotection. Moreover, salicylate, an effective agent in reversing insulin resistance in Type 2 diabetic rats and mice [59], can repress TNF-α-induced phosphorylation (Ser106) of IRS-1 (insulin receptor substrate-1) and insulin resistance in HEK-293 cells (human embryonic kidney cells) [52], supporting further the possibility that the improvement in renal insulin signalling by TZDs may be beneficial in DN. Collectively, all of these results indicate that PPARγ can exert its renoprotective effects in Type 2 diabetes by preventing renal glucotoxicity and improving a renal insulin signalling defect via reducing blood glucose, lowering circulating insulin levels and restoring normal insulin signalling in the kidney.

**Cell-cycle-dependent actions**

Glomerular cell hypertrophy is one of the earliest pathophysiological changes in the development of DN. Cell hypertrophy is defined as cell enlargement due to increased protein and RNA content without DNA replication, which results from cell entry into the G1-phase of the cell cycle, but failure to pass through the S-phase [61]. Cellular hypertrophy can also be defined as G1-phase cell-cycle arrest because of its essential underlying mechanism [61,62]. With the development of CKD in patients with diabetes, the cell cycle is dysregulated, and G1-phase cell-cycle arrest is thought to be responsible for high-glucose-induced mesangial hypertrophy, increased protein synthesis and consequential accumulation of extracellular matrix proteins [63,64]. In diabetic mice, deficiency in the cyclin kinase inhibitor p21 or p27, which induces G1-phase cell-cycle arrest by inhibiting CDK (cyclin-dependent kinase), delays and
prevents the progression of DN [65,66]. Diabetic p27−/− mice had no renal hypertrophy, glomerular hypertrophy or proteinuria, and mesangial expansion was low when compared with p27+/+ diabetic mice [66]. Consistently, high glucose can induce p27 expression in renal tubular epithelial cells [67], and the increased expression of p21 and p27 in the kidney is associated with glomerular hypertrophy and an increased risk of DN [68,69]. Okada et al. [10] have demonstrated that PPARγ agonist TZDs ameliorated DN by reversing high-glucose-induced G1-phase cell-cycle arrest in OLETF rats. In that study, 8-week-old male OLETF rats were treated with pioglitazone (1 mg·kg−1·day−1) or insulin for 42 weeks. At 50 weeks of age, rats treated with pioglitazone or insulin had similar HbA1c (glycated haemoglobin) levels, significantly lower than that of control rats, and therefore similar glycaemic control during the experiments. When compared with control rats, rats treated with pioglitazone had significantly reduced glomerular hypertrophy, mesangial matrix expansion and proteinuria. In contrast, insulin treatment failed to prevent the progression of DN, although it effectively lowered blood glucose. The authors [10] revealed further that the improvement in renal function might be achieved by the down-regulation of p27 in glomerular cells. In support of this, a recent study [57] indicated that TZDs provide better renoprotection than insulin in diabetic rats, independent of glycaemic control. In summary, PPARγ can exert its renoprotective effects by a cell-cycle-dependent mechanism(s), depending [63,64,70] or not [10,57] on glycaemic control.

**Actions via increasing adiponectin expression**

Adiponectin is a relatively recently identified adipose cytokine and believed to be one of the most abundant circulating proteins, with concentrations greater than 5 μg/ml [7,71,72]. Over the past decade, a large number of studies have demonstrated that adiponectin plays an important role in the pathogenesis of insulin resistance and Type 2 diabetes [73–75]. More recently, adiponectin was reported to have a possible involvement in the development of DN. In a large-scale epidemiological study of patients with Type 1 diabetes from Denmark, Finland and France, Vionnet et al. [13] found that SNPs in the adiponectin gene were associated with a risk of DN [13]. Fujita et al. [76] further observed elevated circulating adiponectin levels in patients with overt DN, and the elevated adiponectin level was presumed to be a protective response to renal tubular injury and to slow the progression of DN. In a 7-year follow-up study of patients with non-diabetic CKD, Kollerits et al. [16] identified adiponectin as a novel predictor of CKD in men but not women. Moreover, rats with Type 1 diabetes induced by streptozotocin had decreased circulating adiponectin levels and renal expression of adiponectin receptors, and the impaired adiponectin signalling in the kidney was proposed to be associated with excessive renal triacylglycerol accumulation, which might result in renal lipotoxicity [77]. PPARγ activation has been shown to elevate circulating adiponectin levels in patients with Type 2 diabetes [7] and up-regulate the expression of adiponectin receptors in the liver and adipose tissue of rodents with Type 2 diabetes [78,79], which implies that the adiponectin signalling pathway might be involved in renoprotection by PPARγ in DN. We have recently demonstrated that a 3-month treatment with the PPARα/γ dual agonist tesaglitazar significantly attenuated albuminuria and renal glomerular fibrosis in db/db mice, with a markedly increased expression of adiponectin in epididymal adipose tissue and elevated circulating adiponectin levels [80]. In addition, a recent clinical study has shown that a 3-month treatment of rosiglitazone significantly decreased proteinuria without changing BP in patients with Type 2 diabetes [9]. The reduction in proteinuria was correlated with decreased plasma NEFA and TNF-α levels, increased adiponectin concentrations, and improved insulin sensitivity. Further multivariate regression analysis revealed that only the decrease in TNF-α and increase in adiponectin concentrations independently associated with reduced urine albumin excretion [9]. Taken together, these results suggest that the beneficial effects of PPARγ on DN are achieved, at least in part, through activation or restoration of adiponectin signalling in both renal and non-renal tissues [2,9,77–80]. Further studies involving specific activation of renal PPARγ and/or renal adiponectin signalling will shed new light on the therapeutic potential of adiponectin signalling pathway(s) in the prevention of DN.

**Anti-inflammatory and antioxidative actions**

Inflammatory markers are well known to be associated with the development of renal disease in diabetes [12,81]. Anti-inflammatory drugs have been reported to prevent renal injury in diabetic rats by reducing macrophage infiltration and the expression of TGF-β, type IV collagen and ICAM-1 (intercellular adhesion molecule-1) in renal cells [11]. Macrophage infiltration and increased expression of leucocyte adhesion molecules are directly associated with the progression of DN [82]. ICAM-1 is one of the major adhesion molecules that promote leucocyte attachment to the endothelium, and increasing evidence has revealed an important role of ICAM-1 in macrophage infiltration and the pathogenesis of DN [29,83–85]. Recently, TZDs were reported to ameliorate renal injury in diabetic rats through inhibition of ICAM-1 expression, NF-κB activation and macrophage infiltration in the kidney [33]. In mice, pre-treatment with rosiglitazone attenuated cisplatin-induced renal damage through suppression of TNF-α overproduction and NF-κB activation [86]. In cultured proximal tubular epithelial
cells, rosiglitazone dose-dependently attenuated AGE-induced IL-8 and ICAM-1 expression [87]. In patients with diabetes, troglitazone and pioglitazone suppressed the release of inflammatory cytokines, including TNF-α, IL-1β and IL-6 from isolated monocytes [88], and reduced circulating levels of leptin, NEFAs, TNF-α and PAI-1 (plasminogen-activator inhibitor-1) [7]. Reduction of these inflammatory cytokines and factors is expected to be beneficial for ameliorating renal injury in patients with diabetes. Therefore PPARγ may exert its renoprotective effects by suppressing the release of inflammatory cytokines from peripheral tissues [7,88] and inhibiting and even preventing local inflammation in the kidney [33,86,87]. This suggestion was supported further by a recent observation that inhibition of renal expression of TGF-β by TZDs attenuated proteinuria and glomerular hypertrophy in diabetic rats, independent of glycaemic control [57].

In addition, renal diseases, including DN, are associated with renal oxidative stress [89–91]. PPARγ activation is beneficial for renal damage induced by oxidants, aging and ischaemia/reperfusion [92–94]. Although more studies are needed to elucidate the underlying mechanism(s), the current findings support an idea that anti-inflammatory and antioxidative actions of PPARγ may be useful in preventing and treating DN.

Prevention of lipid accumulation in the kidney
Hyperlipidaemia and excessive renal lipid accumulation are important events in the progression of CKD, and lipid-lowering agents such as atorvastatin have been shown to ameliorate proteinuria and DN in diabetic animals [95,96]. In various animal models, increased accumulation of lipids and cholesterol in the kidney was associated with glomerulosclerosis, renal inflammation and DN [14,97,98]. Increased accumulation of lipids and cholesterol in the kidney was largely due to increased expression of SREBP (sterol-regulatory-element-binding protein)-1, SREBP-2, acetyl-CoA carboxylase and fatty acid synthase, and decreased expression of LXRα (liver X receptor α), LXRβ and FXR (farnesoid X receptor) [14,97,98]. LXR is one of the target genes of PPARγ [99], and our previous studies have indicated that LXR activation in glomerular mesangial cells and proximal straight tubule cells increases cholesterol efflux and fatty acid desaturation respectively [100,101]. In addition, FXR ligands were reported to up-regulate PPARγ expression in the liver [102]. Moreover, activation of PPARγ by 15dPGJ2 suppressed IL-1β-induced intracellular lipid accumulation, and activation of LXR by TO 901317 decreased cellular free cholesterol content via increasing ABCA1 (ATP-binding-cassette transporter A1)-mediated cholesterol efflux in mesangial cells [17,100]. In addition to attenuating lipid and cholesterol accumulation via an LXR/ABCA1-dependent pathway, PPARγ may also have a beneficial effect on renal lipid toxicity through suppression of cytokine-induced renal lipid uptake and reduction of systemic hyperlipidaemia [7].

BP-lowering actions
A critical role of intensive BP control in amelioration and prevention of DN has been well documented in a series of large clinical trials, including the UKPDS 38 (UK Prospective Diabetes Study), ABCD (Appropriate Blood Pressure Control in Diabetics) study, IRMA-2 (Irbesartan in Reduction of Microalbuminuria-2) study and IDNT (Irbesartan in Diabetic Nephropathy Trial) [18,103–105], with intensive control of BP significantly decreasing urinary albumin and delaying the progression of DN in patients with hypertension and Type 2 diabetes. To date, the role of PPARγ in BP regulation remains controversial. Gene-targeting studies have shown that mice with global PPARγ gene deletion were hypotensive [106], which is consistent with a finding that a PPARγ agonist stimulates renin gene expression [107]. However, a large number of studies also revealed that PPARγ activation by TZDs reduced BP or protected against the development of hypertension in animal models of insulin resistance or hypertension and patients with metabolic syndrome [108–111]. Despite controversial results, increasing evidence suggests that PPARγ exerts its renoprotective effect by lowering BP, which might be due in part to the suppression of AngII production or AngII receptor expression in the kidney and VSMCs (vascular smooth muscle cells) and increased endothelial NO biosynthesis [112–115].

Other potential actions
Recently, amylin, also known as IAPP (islet amyloid polypeptide), was reported to be deposited in the kidneys of patients with DN, and the deposition of amylin in the kidney was associated with renal disease severity [116]. This observation was consistent with a previous study showing the association of increased amylin-binding density in the kidney with elevated BP and renal activation of TGF-β in diabetic animals [117]. High blood glucose activates amylin gene expression in pancreatic β-cells and stimulates its secretion with insulin, which results in elevated circulating amylin under Type 2 diabetic conditions [118–122]. Deposition of amylin in the kidney might represent an additional mechanism in the pathogenesis of DN in Type 2 diabetes [116,117]. In support of this, fibrillogenic amylin was shown to induce apoptosis in human mesangial cells in vitro [123], and soluble amylin was shown to stimulate renin secretion in perfused rat kidney [124]. Moreover, metformin was reported to reduce the circulating amylin level in patients with Type 2 diabetes with improved insulin resistance [125]. In addition, rosiglitazone protected against amylin-induced cell apoptosis in human islets [126]. In a mouse model specifically overexpressing human amylin in islets, Hull et al. [127] demonstrated that rosiglitazone...
Figure 1  Possible mechanisms by which PPARγ may exert its renoprotective effects in DN
COX-2, cyclooxygenase-2; FFA, NEFA ('free' fatty acids); GFR, glomerular filtration rate; iNOS, inducible NO synthase; TGs, triacylglycerols.

LIMITATIONS OF TZD TREATMENT

Although it is widely acknowledged that TZDs are beneficial for amelioration of insulin resistance, Type 2 diabetes and DN, just like any other single intervention, TZD treatment to activate PPARγ has limitations. For example, a common side effect of PPARγ activation by TZDs is weight gain and fluid retention, and patients receiving TZD treatment are at high risk of developing oedema. The potential mechanism may involve collecting-duct PPARγ activation, as mice with specific knockout of PPARγ in collecting ducts were resistant to TZD-induced water and sodium retention [129]. Moreover, rosiglitazone stimulated sodium transport in primary collecting duct cells expressing PPARγ, but not in cells lacking this receptor [129]. These findings reveal a PPARγ-mediated pathway controlling sodium/water transportation in the kidney, which might, at least in part, account for fluid retention, oedema and haemodilution in patients with Type 2 diabetes treated with TZDs [20,129,130]. Furthermore, it has recently been reported that the long-term use of rosiglitazone might be associated with congestive heart failure and even an increased number of fatal cardiovascular events [131].
although there is no solid evidence showing pioglitazone has similar side effects. Therefore caution must be taken in clinical practice, especially with TZDs given to patients with hypertension and impaired heart function.

**SUMMARY AND PERSPECTIVES**

PPARγ activation slows the progression of DN via multiple mechanisms (Figure 1), with both systemic and direct renal actions involved in the renoprotective effect of PPARγ. A combined intervention of TZDs, ACE (angiotensin-converting enzyme) inhibitors, physical exercise, weight reduction, lifestyle modification and control of the metabolic syndrome may represent a better therapeutic strategy for prevention and treatment of Type 2 diabetes and DN than current intervention strategies.

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