Peroxisome Proliferator-Activated Receptor Gamma Agonists in Kidney Disease – Future Promise, Present Fears

Zhiguo Maoa–c    Albert C.M. Onga,b

aKidney Genetics Group, Academic Nephrology Unit, Henry Wellcome Laboratories for Medical Research, University of Sheffield Medical School, and bSheffield Kidney Institute, Northern General Hospital, Sheffield Teaching Hospitals Foundation Trust, Sheffield, UK; cDivision of Nephrology, Changzheng Hospital, Second Military Medical University, Shanghai, China

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Abstract
The peroxisome proliferator-activated receptor superfamily (PPARs) comprises a class of nuclear receptors with significant effects in regulating multiple cellular pathways. Much research and clinical interest has surrounded the PPAR-γ isoform because of its key role in the transcriptional regulation of metabolic pathways and the efficacy of thiazolidinediones, the most clinically used PPAR-γ agonist, in the management of type 2 diabetes mellitus. In this review, we discuss the pathogenic role of PPAR-γ in experimental models of kidney disease, clinical trials of thiazolidinediones in diabetic and non-diabetic kidney disease, recent safety concerns surrounding PPAR-γ agonists and reflect on their potential use in ‘orphan’ kidney diseases.

The term peroxisome proliferator-activated receptors (PPARs) arose approximately 18 years ago, when Isselmann and Green [1] observed that certain industrial compounds could bind to certain nuclear receptors and cause rodent hepatic peroxisomes to increase in volume and density. Although PPAR-γ agonists are not known to induce peroxisome proliferation in humans [2], these unusual nuclear hormone receptors have attracted great attention in recent years as their roles in the transcriptional regulation of key metabolic (including lipid metabolism, adipogenesis and insulin sensitivity), inflammatory, atherosclerotic pathways and in kidney protection have been clarified. As a consequence, thiazolidinediones (TZDs), the most clinically used PPAR-γ agonists, have become blockbuster drugs especially in the management of type 2 diabetes mellitus (T2DM). More recently, however, important long-term safety issues have arisen casting doubt over their future clinical use [3].

This review summarizes experimental and clinical evidence for PPAR-γ in relation to the kidney disease, recent safety concerns of PPAR-γ agonists in clinical use and provides some thoughts on their potential future uses in non-diabetic kidney diseases.
The Characteristics of PPAR-γ and Its Agonists

PPAR-γ is an isotype of the PPAR superfamily with four major functional domains (fig. 1): an NH2-terminal ligand-independent transactivation domain (A/B), a DNA-binding domain (C), a hinge domain (D) and a COOH-terminal domain including the ligand-binding domain and the ligand-dependent transactivation domain (E/F) [4–6]. To date, two major splice isoforms of PPAR-γ (PPAR-γ1 and PPAR-γ2) have been identified in the mouse; two additional human isoforms PPAR-γ3 and PPAR-γ4 have been found [7].

The highest levels of PPAR-γ can be found in adipose tissue with lower levels detected in kidney, urinary bladder, skeletal muscle, liver and heart. In addition, PPAR-γ is expressed in the vasculature and various immune cells. In the kidney, PPAR-γ is predominantly expressed in the distal medullary collecting ducts but also to a lesser extent in glomeruli, renal microvasculature and proximal tubules. In vitro expression of PPAR-γ has been reported in cultured glomerular mesangial cells, podocytes, proximal tubule and collecting duct cells. These findings are the basis of the diverse roles of PPAR-γ in regulating renal physiology and pathophysiology.

TZDs, also known as glitazones, were found to improve insulin sensitivity in diabetic animals more than 10 years before PPAR-γ was cloned [8]. The activation of PPAR-γ by TZD is through a ligand-dependent transactivation mechanism, modulating the transcriptional activity of key target genes. Troglitazone was the first TZD class drug approved for clinical use in 1997 followed by rosiglitazone and pioglitazone in 1999.

The Beneficial Properties of PPAR-γ Agonists in the Kidney

An enormous body of research has identified beneficial functions of TZDs on the kidney in laboratory and clinical settings, although the exact mechanisms of the renoprotective effects is unclear. The majority of studies have addressed aspects of the metabolic syndrome, i.e. obesity, insulin resistance and dyslipidaemia. As there is evidence correlating metabolic syndrome and the development of chronic kidney disease (CKD), the beneficial effects of TZDs in improving glucose tolerance could indirectly improve CKD progression. More recently, however, investigators have begun to uncover direct effects of TZDs on the kidney such as anti-proteinuric, vascular protective, anti-inflammatory and anti-fibrotic effects which are all independent of the capacity to improve glucose tolerance (fig. 2). TZDs thus have the potential to become attractive therapeutic agents for other kidney diseases apart from diabetic nephropathy (DN).

Reduction in Proteinuria

To date, most animal models (diabetic and non-DN) and many clinical trials have convincingly demonstrated the anti-proteinuric effect of TZDs [9, 10]. Since proteinuria (or albuminuria) is a modifiable risk factor for the progression to end-stage renal disease and a marker of endothelial dysfunction, the anti-proteinuric effect of TZDs could be a significant advantage in reducing renal and cardiovascular risk in CKD patients.

Vascular Effects

Laboratory and clinical data have demonstrated a small but significant effect of TZDs in lowering systemic blood pressure [11] – this could be due to enhanced insulin sensitivity or to a direct action on resistance vessels. Since PPAR-γ is expressed in both endothelial and vascular smooth muscle cells, the direct regulation on blood pressure could be through modulating vasoactive factor release by endothelium (endothelin-1, prostacyclin and nitric oxide) or by reducing vascular smooth muscle cells tone (e.g. down-regulating the ANG II type 1 receptor) [12]. A reduction in sympathetic overactivity may also play a role in TZD-mediated BP lowering. As a common side-effect of TZDs is fluid retention, the antihypertensive effect of TZDs could be even more significant in the
TZDs effects on Kidney

Indirect effects
- Metabolic syndrome modulation
- Anti-proteinuria
- Vascular effects
- Anti-inflammatory effects
- Anti-fibrotic effects
- Other effects

Direct effects

Anti-Inflammatory Effects

TZDs have prominent local and systemic anti-inflammatory effects. They can suppress cytokine synthesis by a number of cell types such as macrophages, renal mesangial cells and renal tubular cells. The range of cytokines studied includes interleukin (IL)-1, IL-6, macrophage chemoattractant protein-1, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 and tumor necrosis factor-α. In patients with overt DN, TZDs have been shown to reduce markers of systemic inflammation such as plasma IL-6 and C-reactive protein [20, 21].

Pioglitazone attenuates disease progression in a rat model of T2DM by down-regulating NF-κB, transforming growth factor (TGF)-β1, plasminogen activator inhibitor type-1 (PAI-1) and VEGF [22]. Other studies showed that rosiglitazone attenuates pro-inflammatory responses (increased IL-6, A-II and TGF-β production) and stimulates anti-inflammatory responses (through IL-4 synthesis and restoring nitric oxide availability) in the remnant kidney [23] and ureteric obstruction models [24]. TZDs could also directly attenuate the renal injury caused by free radicals and oxidant stress, which themselves lead to inflammation [25, 26].

Anti-Fibrotic Effects

Sclerosis and fibrosis are common end points for many chronic and severe renal diseases: TGF-β is believed to play a crucial role in this process. TZDs could reduce kidney fibrosis and sclerosis by attenuating the hyperinsulinaemia and hyperglycaemia which are important stimulators for the production of TGF-β from renal mesangial cells and proximal tubule epithelial cells [27–29]. In addition, TZDs have been shown to decrease glomerular TGF-β directly independent of serum insulin or glucose [18, 30–34], or indirectly by inhibiting A-II synthesis. TZDs could increase matrix degradation by modulating matrix metalloproteinases and PAI-1 secretion [35, 36]. A direct inhibitory effect of pioglitazone on human renal fibroblast proliferation has been demonstrated [37].

Other Effects

Acute Kidney Injury

TZDs reduce ICAM-1 expression and PMN infiltration following ischaemia-reperfusion injury [38–40]. Pioglitazone additionally can reduce cyclosporin nephrotoxicity in allografts [41, 42]. With the high incidence of
post-transplantation diabetes mellitus, the use of TZDs in post-transplant management may confer additional benefit over other oral diabetic agents.

**Polycystic Kidney Disease**

Of interest, maternal administration of pioglitazone improved survival of Pkd1null embryos, ameliorated the cardiac defects and reduced renal cystic enlargement. Since patients with autosomal dominant polycystic kidney disease account for 10% of all end-stage renal disease (ESRD) cases, further confirmatory and clinical studies are needed to test the potential use of TZDs in PKD disease progression [43].

**PPAR-γ Gene Polymorphisms**

In recent years, numerous studies have investigated the possible role of genetic polymorphisms of PPAR-γ as susceptibility factors. The C1431T polymorphism was reported to be associated with higher plasma leptin levels and obesity [44, 45]. The Pro12Ala polymorphism has been linked to a higher incidence of DN in T2DM [46], accelerated GFR loss in T1DM nephropathy, higher ESRD and all-cause mortality in T1DM nephropathy [47]. Although the significance of PPAR-γ polymorphisms in different ethnic populations could vary [48], these observations have contributed to heightened interest in the pathological role of PPAR-γ in kidney disease, especially in DN.

**Clinical Application of TZDs**

**Diabetic Nephropathy**

In the past decade, a large number of clinical trials have demonstrated that TZDs reduce urinary albumin excretion, lower blood pressure and suppress systemic inflammation in normotensive or hypertensive patients with DN. Schernthaner et al. [49] reported a 12-month parallel-group double-blind trial comparing pioglitazone and metformin in T2DM patients. This trial recruited 1,199 patients from 167 centers in 12 countries in Europe. The urinary albumin/creatinine ratio was reduced by 19% in the pioglitazone group but remained unchanged in the metformin group. The incidence of overall and cardiovascular adverse events was similar between both groups. Similarly, a number of other investigators compared TZDs (troglitazone, pioglitazone and rosiglitazone) with placebo or traditional diabetic medication (metformin, glibenclamide, insulin etc.) in T2DM patients in different clinical trials and found a consistent efficacy of TZDs on lowering urinary protein excretion and blood pressure [50–56]. More recently, the effects of pioglitazone and glipizide on oxidative stress and inflammation in patients with advanced DN were compared in a randomized, open-label, blinded end-point, 16-week trial [21]. Of interest, pioglitazone reduced the WBC count, C-reactive protein, IL-6 and MMP-9 indicating an anti-inflammatory effect in patients with overt DN. Miyazaki et al. [20] compared the effect of rosiglitazone with placebo in T2DM patients and found that urinary albumin-to-creatinine ratio was significantly decreased by rosiglitazone after 3 months’ treatment. Jin and Pan [57] investigated the effects of a pioglitazone and losartan combination versus losartan monotherapy on CKD progression in 60 T2DM patients over a 12-month study period. They found that combination therapy significantly slowed GFR decline compared to the losartan-only group.

**Other Kidney Diseases**

To date, only one clinical trial examining the therapeutic effects of TZDs in non-T2DM patients has been published. In this open-label randomized crossover study comparing rosiglitazone with RAS blockers (ARB, ACEI or both), the subjects enrolled included IgA nephropathy [56], focal and segmental glomerulosclerosis (6/39), obesity-related focal and segmental glomerulosclerosis (6/39), reflux nephropathy and other kidney diseases. With rosiglitazone treatment, there was a decrease in urinary protein and systolic blood pressure [58]. However, it should be noted that 78% of the participants were overweight/obese and ~8% subjects also had diabetes. The beneficial effect observed could relate to the metabolic improvement seen with TZDs rather than to a direct effect on the kidney.

A phase I study of rosiglitazone (3 mg/m²/day for 16 weeks) in young patients with primary focal segmental glomerulosclerosis (FSGS) suggested it was safe and well-tolerated, although oral clearance was increased by up to 300% [59]. It seems likely that phase II/III trials will be conducted in FSGS patients.

It should be noted that all the trials performed so far (with one exception) have studied DN patients and relied on surrogate markers of disease progression rather than harder clinical end points such as ESRD or GFR decline. The latter are needed to establish the benefit-risk ratio of using TZDs in both DN and non-DN patients especially in the light of more recent safety concerns regarding long-
term TZD use (see below). Nevertheless, there is an impressive body of pre-clinical (table 1) and clinical (table 2) data which support further exploration of TZD use in other kidney diseases.

**Concerns on the Safety of TZDs**

One advantage of TZDs is that they do not require dose reduction in patients with impaired renal function and can thus be readily used in advanced kidney disease and kidney transplantation patients [26, 60]. TZDs are generally well tolerated, but their administration has been associated with several prominent side-effects and a number of safety issues. Troglitazone, the first TZD approved for clinical use, was withdrawn in 1999 due to hepatotoxicity. More recently, a meta-analysis of clinical trials on TZDs has raised concerns over potential cardio-toxicity [61].

**Hepatotoxicity**

Hepatotoxicity is one of the most studied complications in the use of TZDs because of several cases of severe liver failure reported with troglitazone, but is rare with rosiglitazone and pioglitazone. Conversely, recent studies suggest that these TZDs may protect against certain forms of liver injury such as chemical-induced liver toxicity and non-alcoholic steatohepatitis [62, 63]. Indeed, some have suggested chronic TZD treatment could help to treat non-alcoholic steatohepatitis [64]. Studies on liver cell-specific PPAR-γ-null mice could help to clarify the liver-specific roles of PPAR-γ.

**Other Organs**

In vitro reports that TZDs are nephrotoxic [65, 66] and carcinogenic [67] have not been confirmed.

**Fluid Retention**

Fluid retention has long been recognized as a common side effect of TZDs. It could be due to up-regulation of the epithelial sodium channel [68, 69], increased sympathetic nervous system activity or altered endothelial permeability [70, 71]. Fluid retention accounts for at least 75% of body weight gain in patients receiving TZDs [72, 73], and furthermore contributes to the increased incidence of congestive heart failure (see below). Whether diuretics can effectively reverse the fluid overload is still controversial [74].

**Cardiovascular System**

**Increased Heart Failure**

The PROactive study was the first to raise alarm over the potential cardiac side effects of TZDs. This investigated the effects of pioglitazone versus non-TZD antidiabetic therapy on a combined vascular end point in T2DM patients with known vascular disease. They found that patients treated with pioglitazone had a higher incidence of congestive heart failure (CHF) [75].

**Cardiovascular Mortality and TZDs**

In 2007, Nissen and Wolski [61] published an influential meta-analysis of all randomized controlled TZD trials in T2DM patients. Compared with the control group, rosiglitazone was associated with a significant increase in the risk of myocardial infarction (odds ratio 1.43) and a borderline significant increase in the risk of death from cardiovascular causes (odds ratio 1.64). As a consequence, the US Food and Drug Administration added a 'black box' warning on the label of TZDs of the increased risks of congestive heart failure.

Since this report, not all subsequent studies have confirmed this gloomy prognosis. TZDs do not adversely affect myocytes or myocardial function [76]. Conversely, emerging data suggest that TZDs may even be cardioprotective following acute ischaemic injury [77–79]. It is notable that in the PROactive study, T2DM patients receiving pioglitazone did not have a significant difference in CHF-related mortality compared to placebo [75]. The meta-analysis by Lago et al. [80] showed that TZDs increased the risk for CHF in patients with T2DM and prediabetes but did not increase the risk of cardiovascular death, results similar to the PROactive study. An interim analysis from the ongoing RECORD study, a long-term multicentre randomized open-label study to evaluate cardiovascular outcomes in patients with T2DM treated with rosiglitazone published following Nissen and Wolski’s [61] meta-analysis, did not demonstrate an excess risk of death in rosiglitazone compared to comparator drug groups. However, these authors did find that rosiglitazone was associated with an increased risk of CHF [81]. Finally, a recent meta-analysis re-analysed the same data set as Nissen and Wolski [61] using different modeling and weighting methods, but concluded that neither in-
Table 1. TZDs in experimental models in kidney disease

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>TZD type</th>
<th>Animal model</th>
<th>Effect on urine and BP</th>
<th>Effect on renal morphology/function</th>
<th>Possible mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujiwara et al. 2000 [7]</td>
<td>troglitazone</td>
<td>heminephrectomized Wistar fatty rats</td>
<td>proteinuria decrease; BP decrease</td>
<td>NA</td>
<td>improve insulin sensitivity</td>
</tr>
<tr>
<td>Nicholas et al. 2001 [9]</td>
<td>troglitazone</td>
<td>streptozotocin-induced diabetic rats</td>
<td>albuminuria decrease; BP unchanged</td>
<td>NA</td>
<td>inhibit mesangial growth or PAI-1 expression</td>
</tr>
<tr>
<td>Yoshiida et al. 2001 [10]</td>
<td>troglitazone</td>
<td>5/6 nephrectomized SHR</td>
<td>albuminuria unchanged; BP decrease</td>
<td>decrease serum creatinine and glomerular sclerosis indices</td>
<td>NA</td>
</tr>
<tr>
<td>Ma et al. 2001 [11]</td>
<td>troglitazone</td>
<td>5/6 nephrectomized SD rats</td>
<td>albuminuria decrease; BP unchanged</td>
<td>prevent glomerulosclerosis</td>
<td>regulate glomerular cell proliferation and decreasing PAI-1, TGF-β expression</td>
</tr>
<tr>
<td>Yamashita et al. 2002 [12]</td>
<td>troglitazone, pioglitazone</td>
<td>streptozotocin-induced diabetic SHR</td>
<td>urine albumin excretion decrease; BP unchanged</td>
<td>prevent anionic sites loss of glomerular basement membranes; CCr unchanged</td>
<td>NA</td>
</tr>
<tr>
<td>Baylis et al. 2003 [14]</td>
<td>rosiglitazone</td>
<td>obese Zucker rats</td>
<td>proteinuria decrease; BP unchanged</td>
<td>prevent renal fibrosis, superior to ACEI; additive protection on GFR and tubulointerstitial damage when combined with ACEI</td>
<td>NA</td>
</tr>
<tr>
<td>Dobrian et al. 2004 [16]</td>
<td>pioglitazone</td>
<td>obese, hypertensive SD rats</td>
<td>prevent hypertension</td>
<td>NA</td>
<td>reduce free radical production and increase nitric oxide availability</td>
</tr>
<tr>
<td>Yang et al. 2006 [18]</td>
<td>pioglitazone</td>
<td>puromycin amino-nucleoside nephropathy SD rats</td>
<td>proteinuria and BP unchanged</td>
<td>improve progression of glomerulosclerosis</td>
<td>reduce infiltration glomerular macrophages and PAI-1 expression</td>
</tr>
<tr>
<td>Benigni et al. 2006 [19]</td>
<td>pioglitazone vs. ARB</td>
<td>passive Heymann nephritis rats</td>
<td>reduced proteinuria as candesartan</td>
<td>ameliorate functional and structural renal damage</td>
<td>enhance nephrin gene transcription</td>
</tr>
<tr>
<td>Obtomo et al. 2007 [21]</td>
<td>pioglitazone</td>
<td>spontaneously hypertensive/NIH-corruptent rat (SHR/NDmcr-cp)</td>
<td>proteinuria decrease</td>
<td>improve renal function; reduce glomerular and tubulointerstitial fibrosis</td>
<td>reduce intrarenal TGF-β expression; normalize insulin levels</td>
</tr>
</tbody>
</table>
creased nor decreased risk could be established for myocardial infarction and cardiovascular death in T2DM patients taking rosiglitazone [82].

Most of these studies have been conducted on patients with normal or near-normal kidney function. However, a recent post hoc analysis of the PROactive study data found that pioglitazone treatment decreased the tendency for CKD patients (eGFR $< 60$ ml/min/1.73 m$^2$) to reach a composite end point of all-cause death, myocardial infarction, and stroke independent of the severity of renal impairment [83]. Although promising, these data require direct confirmation in an RCT of a CKD patient population.

### TZDs and Serum Lipids

The reported effects of rosiglitazone and pioglitazone on lipid profiles have been inconsistent. In 2004, a meta-analysis of 23 RCTs in T2DM patients concluded that both TZDs raised HDL-cholesterol but had different effects on triglyceride and LDL-cholesterol levels [84]. However, more recent studies have found that both drugs raise LDL-cholesterol and LDL particle size in T2DM patients [85]. It is unclear what effects TZDs have on serum lipids in non-T2DM patients. Given these opposite effects, it seems unlikely that there is a class effect on cardiovascular mortality mediated through alterations in circulating lipids.

### Clinical Guidelines for TZD Use

The patient’s volume status may be the most important factor to consider prior to starting TZDs. A recent consensus statement from the American Heart Association and American Diabetes Association recommended that TZDs should not be used in patients with NYHA class III or IV for obvious reasons. In patients without established heart disease but with risk factors for congestive heart failure, TZDs should be started at low doses and gradually increased with close monitoring for signs of fluid retention and heart failure [86].

**Summary**

Since their initial identification, the PPAR-γ nuclear hormone receptor and its major agonist TZDs have rapidly emerged as key regulators of metabolic and other disease pathways. The recognition that TZDs regulate the
**Table 2. Clinical trials of TZDs in kidney patients**

<table>
<thead>
<tr>
<th>Type of patients</th>
<th>Authors, year</th>
<th>Study design</th>
<th>Patients</th>
<th>Regimens</th>
<th>Duration</th>
<th>Effects on urine protein vs. control/baseline</th>
<th>Effects on BP, mm Hg</th>
<th>Effects on renal function or other important factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2DM</td>
<td>Sironi et al. 1997 [30]</td>
<td>randomized controlled</td>
<td>40</td>
<td>200 mg Tro vs. placebo</td>
<td>8 weeks</td>
<td>unchanged</td>
<td>unchanged</td>
<td>NA</td>
</tr>
<tr>
<td>T2DM with MA</td>
<td>Imano et al. 1998 [31]</td>
<td>randomized controlled</td>
<td>30</td>
<td>400 mg Tro vs. Met</td>
<td>12 weeks</td>
<td>−38.5%</td>
<td>unchanged</td>
<td>NA</td>
</tr>
<tr>
<td>T2DM with MA</td>
<td>Nakamura et al. 2000 [32]</td>
<td>randomized controlled</td>
<td>45</td>
<td>30 mg Pio vs. 5 mg Gli vs. 0.6 mg Vog</td>
<td>3 months</td>
<td>−66%</td>
<td>unchanged</td>
<td>NA</td>
</tr>
<tr>
<td>T2DM</td>
<td>Lebovitz et al. 2001 [33]</td>
<td>randomized controlled</td>
<td>493</td>
<td>4 or 8 mg Ros vs. placebo</td>
<td>26 weeks</td>
<td>−22% with 8 mg</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>T2DM with MA or macroalbuminuria</td>
<td>Nakamura et al. 2001 [34]</td>
<td>randomized controlled</td>
<td>32</td>
<td>400 mg Tro vs. placebo</td>
<td>12 months</td>
<td>−67% with MA</td>
<td>unchanged</td>
<td>NA</td>
</tr>
<tr>
<td>T2DM with MA, normotensive</td>
<td>Nakamura et al. 2001 [35]</td>
<td>controlled</td>
<td>28</td>
<td>30 mg Pio vs. 5 mg Gli</td>
<td>6 months</td>
<td>−58.9%</td>
<td>unchanged</td>
<td>NA</td>
</tr>
<tr>
<td>T2DM</td>
<td>Bakris et al. 2003 [36]</td>
<td>open-label, randomized</td>
<td>129</td>
<td>8 mg Ros vs. Gli</td>
<td>1 year</td>
<td>−30%</td>
<td>−0.1/−2.3</td>
<td>NA</td>
</tr>
<tr>
<td>T2DM</td>
<td>Aljabri et al. 2004 [37]</td>
<td>open-label, randomized controlled</td>
<td>62</td>
<td>30–45 mg Pio vs. insulin</td>
<td>16 weeks</td>
<td>similar to control</td>
<td>similar to control</td>
<td>NA</td>
</tr>
<tr>
<td>T2DM with MA</td>
<td>Yanagawa et al. 2004 [38]</td>
<td>controlled</td>
<td>40</td>
<td>Pio vs. Gli</td>
<td>12 weeks</td>
<td>similar to control</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>T2DM</td>
<td>Hanefeld et al. 2004 [39]</td>
<td>multicentre, randomized double-blind</td>
<td>639</td>
<td>15–45 mg Pio vs. 850–2,550 mg Met</td>
<td>1 year</td>
<td>−15%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>T2DM</td>
<td>Schernthaner et al. 2004 [40]</td>
<td>multicenter, randomized double-blind</td>
<td>1,199</td>
<td>15–45 mg Pio vs. 850–2,550 mg Met</td>
<td>1 year</td>
<td>−19%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>T2DM</td>
<td>Matthews et al. 2005 [41]</td>
<td>randomized double-blind</td>
<td>630</td>
<td>15–45 mg Pio vs. 80–320 mg Gli</td>
<td>1 year</td>
<td>−10%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Overt DN</td>
<td>Agarwal et al. 2005 [42]</td>
<td>open-label, blinded randomized end point trial</td>
<td>44</td>
<td>Pio vs. Gli</td>
<td>4 months</td>
<td>unchanged</td>
<td>unchanged</td>
<td>NA</td>
</tr>
<tr>
<td>T2DM with/without MA</td>
<td>Pistrosch et al. 2005 [43]</td>
<td>double-blind crossover trial</td>
<td>19</td>
<td>with MA; Ros vs. placebo; without MA: Ros vs. nat</td>
<td>12 weeks</td>
<td>−65.3%</td>
<td>unchanged</td>
<td>NA</td>
</tr>
<tr>
<td>T2DM hypertensive</td>
<td>Sarafidis et al. 2005 [44]</td>
<td>observational trial</td>
<td>20</td>
<td>4 mg Ros</td>
<td>26 weeks</td>
<td>−35%</td>
<td>−5.4/−4.1</td>
<td>NA</td>
</tr>
<tr>
<td>DM with ESRD</td>
<td>Mohideen et al. 2005 [45]</td>
<td>open label, randomized, controlled</td>
<td>12</td>
<td>Tro+Base diabetes medicine vs. base diabetes medicine</td>
<td>6 months</td>
<td>NA</td>
<td>NA</td>
<td>safe and effective hyperglycemia control</td>
</tr>
<tr>
<td>T2DM</td>
<td>Bakris et al. 2006 [46]</td>
<td>double-blind, parallel-group</td>
<td>389</td>
<td>Ros vs. Gli</td>
<td>32 weeks</td>
<td>−22.7%</td>
<td>−3.4/−2.5</td>
<td>NA</td>
</tr>
<tr>
<td>T2DM</td>
<td>Miyazaki et al. 2007 [47]</td>
<td>double-blind, randomized controlled</td>
<td>29</td>
<td>Ros vs. placebo</td>
<td>3 months</td>
<td>−53.7%</td>
<td>unchanged</td>
<td>GFR unchanged</td>
</tr>
<tr>
<td>DN (CKD 3 or 4 stage)</td>
<td>Jin and Pan 2007 [48]</td>
<td>randomized controlled</td>
<td>60</td>
<td>Pio 30 mg + losartan (100 mg) vs. losartan (100 mg)</td>
<td>1 year</td>
<td>decrease proteinuria</td>
<td>NA</td>
<td>slower decrease in GFR</td>
</tr>
<tr>
<td>Non-diabetic renal disease</td>
<td>Kincaid-Smith et al., 2008 [49]</td>
<td>open-label randomized controlled crossover study</td>
<td>40</td>
<td>Ros 4 mg vs. usual treatment (ACEI/ARB)</td>
<td>4 months</td>
<td>−22.9%</td>
<td>−7.8/NS</td>
<td>NA</td>
</tr>
</tbody>
</table>

BP = Blood pressure; NA = not available; MA = microalbuminuria; Tro = trosgliltazone; Pio = pioglitazone; Ros = rosiglitazone; Met = metformin; Gli = glibenclamide; Vog = voglibose; NS = not significant.  
1 The complete reference list for this table is available as online supplementary material (www.karger.com/doi/10.1159/000224789).
transcription of multiple genes has raised the possible utility of this class of compounds in other diseases beyond diabetes. The major off-target effect of TZDs is fluid retention and this may underlie the recent reports of increased heart failure. This could be managed by patient selection and careful monitoring. However, concerns over the increase in all-cause and cardiovascular mortality with TZDs (especially rosiglitazone) are likely to reduce prescribing of TZDs in patients with risk factors for IHD – these include CKD and DN patients. The recent development of partial agonists to PPAR-γ could be one solution to reducing the off-target effects of full agonists [87]. Further preclinical and clinical studies are needed to establish the true risk-benefit ratio for using TZDs in non-diabetic nephropathies, especially ‘orphan diseases’ without any effective treatment.

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The comprehensive review by Mao and Ong in this issue of *Nephron Clinical Practice* reminds the reader that PPAR-γ agonists have attracted great attention in recent years due to their roles in the regulation of key metabolic, inflammatory, atherosclerotic pathways and in kidney protection. As a consequence, thiazolidinediones (TZDs), the most widely clinically used PPAR-γ agonists, have become, over the last decade, blockbuster drugs in the management of type 2 diabetes mellitus (T2DM). These agents promised a lot, delivered a little and are now struggling to maintain a role in the management of diabetes in view of a high risk/benefit ratio. As highlighted in the review, they promised improved metabolic control, reduction and slowing of the progression of diabetic microvascular complications including diabetic nephropathy. They did indeed prove effective in reducing proteinuria in diabetic and even some non-diabetic chronic kidney diseases (CKD), along with a reduction in systemic blood pressure. But the TZDs are associated with significant fluid retention and have been shown to exacerbate congestive heart failure. Controversy remains as to whether they are associated with increased all-cause and/or cardiovascular mortality. In elderly patients with T2DM, CKD is often associated with diffuse atherosclerotic vascular disease. These agents should be used with extreme caution, if at all, in these individuals. Furthermore, recent data suggest that rosiglitazone is also associated with increased mortality in diabetic patients on haemodialysis [Ramirez et al.: J Am Soc Nephrol 2009 Apr 8, Epub ahead of print]. Patients with CKD, in general, are at the highest risk of cardiovascular morbidity and mortality, the use of potentially cardiotoxic agents should be contraindicated. Mao and Ong draw attention to the development of partial agonists of PPAR-γ that may have a more acceptable profile. They conclude that such agents may still have a role to play in ‘orphan kidney diseases’ without any effective treatment. Only time will tell whether TZDs have a future...