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

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Key Words

PPAR- γ agonists • Thiazolidinediones • Kidney disease • Diabetes mellitus

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.

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The term peroxisome proliferator-activated receptors (PPARs) arose approximately 18 years ago, when Isse-mann 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.

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Fig. 1. Structure of PPAR- γ . A/B = NH₂-terminal ligand-independent transactivation domain; C = DNA binding domain; D = hinge domain; E/F = ligand binding domain and ligand-dependent transactivation domain; PPRE = PPAR-responsive element.

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- γ 1 and PPAR- γ 2) have been identified in the mouse; two additional human isoforms PPAR- γ 3 and PPAR- γ 4 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

Fig. 2. Effects of TZDs on kidney.

absence of volume expansion. In the kidney, TZDs cause rat post-glomerular efferent arterioles to dilate probably by increasing renal nitric oxide bioavailability and thus can attenuate glomerular hyperfiltration [13, 14].

There is evidence of significant cross-talk between PPAR- γ signaling and the renin-angiotensin system (RAS). Some angiotensin-receptor blockers (ARB) can activate PPAR- γ . Conversely, TZDs reduce the production of ANG I and II (A-II) from human subcutaneous adipocytes [15], spontaneously hypertensive rat mesangial cells [16] and down-regulate the A-II type 1 receptor in vascular smooth muscle cells [17]. This has led to other studies showing that TZDs can confer equal or superior renal protection to RAS inhibitors, making the combination of both compounds an attractive therapeutic option [18, 19].

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 has 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- κ B, transforming growth factor (TGF)- β 1, 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 cyclosporine 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. Scherthaner 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 (metfor-

min, 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 and RAS blockers (ARB, ACEI or both), the subjects enrolled included IgA nephropathy (17/39), 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 cardiotoxicity [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 fur-

thermore 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 pre-diabetes 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

Authors, year ¹	TZD type	Animal model	Effect on urine and BP	Effect on renal morphology/function	Possible mechanism
Yoshioka et al. 1993 [1]	troglitazone	obese Zucker rats	urine protein excretion decrease; BP decrease	NA	improve insulin resistance
Buchanan et al. 1995 [2]	pioglitazone	fructose-fed and chow-fed rats	BP decrease	NA	inhibit agonist-mediated calcium uptake by VSMC
Fujii et al. 1997 [3]	troglitazone	streptozotocin-induced diabetic rats	urine albumin excretion decrease; BP unchanged	NA	NA
Yoshimoto et al. 1997 [4]	pioglitazone	diabetic Wistar fatty rats	proteinuria decrease; BP decrease	prevent glomerulosclerosis and renal arteriosclerosis	NA
Uchida et al. 1997 [5]	pioglitazone	sucrose-fed SHR rats	attenuate the development of hypertension	NA	improve insulin resistance and hyperinsulinaemia
Buckingham et al. 1998 [6]	rosiglitazone	obese Zucker rats	proteinuria decrease; BP decrease	prevent glomerulosclerosis and tubulointerstitial fibrosis	NA
Fujiwara et al. 2000 [7]	troglitazone	heminephrectomized Wistar fatty rats	proteinuria decrease; BP decrease	NA	improve insulin sensitivity
Isshiki et al. 2000 [8]	troglitazone	streptozotocin-induced diabetic rats	albuminuria decrease	NA	inhibit the DAG-PKC-ERK pathway
Nicholas et al. 2001 [9]	troglitazone	streptozotocin-induced diabetic rats	albuminuria decrease; BP unchanged	NA	inhibit mesangial growth or PAI-1 expression
Yoshida et al. 2001 [10]	troglitazone	5/6 nephrectomized SHR	albuminuria unchanged; BP decrease	decrease serum creatinine and glomerular sclerosis indices	NA
Ma et al. 2001 [11]	troglitazone	5/6 nephrectomized SD rats	albuminuria decrease; BP unchanged	prevent glomerulosclerosis	regulate glomerular cell proliferation and decreasing PAI-1, TGF- β expression
Yamashita et al. 2002 [12]	troglitazone, pioglitazone	streptozotocin-induced diabetic SHR	urine albumin excretion decrease; BP unchanged	prevent anionic sites loss of glomerular basement membranes; CCr unchanged	NA
Diep et al. 2002 [13]	troglitazone, pioglitazone	A-II-induced hypertensive SD rats	attenuate development of hypertension	NA	NA
Baylis et al. 2003 [14]	rosiglitazone	obese Zucker rats	proteinuria decrease; BP unchanged	prevent renal fibrosis, superior to ACEI; additive protection on GFR and tubulointerstitial damage when combined with ACEI	NA
Tanimoto et al. 2004 [15]	pioglitazone	diabetic KK/Ta mice	albuminuria decrease; BP unchanged	prevent glomerular enlargement in early diabetic disease	improve glomerular hyperfiltration
Dobrian et al. 2004 [16]	pioglitazone	obese, hypertensive SD rats	prevent hypertension	NA	reduce free radical production and increase nitric oxide availability
Khan et al. 2005 [17]	rosiglitazone	obese Zucker rats	albuminuria decrease; BP decrease	NA	NA
Yang et al. 2006 [18]	pioglitazone	puromycin amino-nucleoside nephropathy SD rats	proteinuria and BP unchanged	improve progression of glomerulosclerosis	reduce infiltration glomerular macrophages and PAI-1 expression
Benigni et al. 2006 [19]	pioglitazone vs. ARB	passive Heymann nephritis rats	reduced proteinuria as candesartan	ameliorate functional and structural renal damage	enhance nephrin gene transcription
Ohga et al. 2007 [20]	pioglitazone	STZ-inducible DM rats	albuminuria decrease	reduce glomerular hypertrophy	anti-inflammatory action
Ohtomo et al. 2007 [21]	pioglitazone	spontaneously hypertensive/NIH-corpulent rat (SHR/NDmcr-cp)	proteinuria decrease	improve renal function; reduce glomerular and tubulointerstitial fibrosis	reduce intrarenal TGF- β expression; normalize insulin levels

Table 1 (continued)

Authors, year ¹	TZD type	Animal model	Effect on urine and BP	Effect on renal morphology/function	Possible mechanism
Doi et al. 2007 [22]	Rosiglitazone	renal ischemia-reperfusion injury rat	NA	decrease in apoptosis	induce HGF expression
Omasu et al. 2007 [23]	pioglitazone	spontaneously hypercholesterolemic rats	proteinuria decrease	preserve renal function; reduce renal fibrosis as candesartan	inhibit PAI-1
Namikoshi et al. 2007 [24]	pioglitazone	obese Zucker rats fed high protein diet	proteinuria and BP decrease	improve glomerular and interstitial fibrosis	reduce nitrate stress
Westerweel et al. 2008 [25]	rosiglitazone	anti-Thy1-glomerulonephritis rats	proteinuria decrease	preserve renal function	reduce renal cortical TGF- β , PAI-1, and fibronectin-1 expression
Ko et al. 2008 [26]	pioglitazone	Otsuka Long-Evans Tokushima Fatty rats	albuminuria decrease; BP unchanged	ameliorate glomerulosclerosis	attenuate renal inflammatory process
Namikoshi et al. 2008 [27]	pioglitazone combined with ARB	obese Zucker rats fed high protein diet	augment antihypertensive and anti-proteinuric effect of ARB	further improvement in renal interstitial fibrosis over ARB alone	NA
Sen et al. 2008 [28]	ciglitazone	alloxan-inducible DM C57BL/6J mice	NA	normalize hyperfiltration induced by DM	decrease glomerular homocysteine content
Kawai et al. 2009 [29]	trogliatone	UUO C57BL/6J mice	NA	reduce renal interstitial fibrosis and inflammation	reduce TGF- β expression

NA = Not available; BP = blood pressure; VSMC = vascular smooth muscle cells.

¹ The complete reference list for this table is available as online supplementary material (www.karger.com/doi/10.1159/000224789).

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 m²) 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 car-

diovascular 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

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

BP = Blood pressure; NA = not available; MA = microalbuminuria; Tro = trosglitazone; 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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Editorial Comment

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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...