REVIEW

Peroxisome proliferator-activated receptor gamma agonists in renal disease

Pedro Iglesias and Juan J Díez¹*Department of Endocrinology, Hospital General, Segovia, Spain and ¹Hospital Ramón y Cajal, Madrid, Spain**(Correspondence should be addressed to P Iglesias; Email: piglesias@hgse.sacyl.es)*

Abstract

Type 2 diabetes is a well recognised cause of chronic renal failure (CRF). Only few oral antidiabetic drugs can be used for treating type 2 diabetes in patients with CRF. Among them are repaglinide, a rapid-acting prandial insulin releaser, and peroxisome proliferator-activated receptor gamma (PPAR γ) agonists, such as rosiglitazone and pioglitazone. These compounds are metabolised in the liver, therefore accumulation of the drug and the risk of severe and prolonged hypoglycaemia are minimised. PPAR γ receptors are expressed in many tissues including the kidney. Recently, numerous healthful effects of PPAR γ agonists on several aspects related to renal function have been increasingly reported. These drugs have shown to possess many advantageous anti-inflammatory, haemodynamic, vascular and metabolic effects. In the present paper we have reviewed the more recent experimental studies that evaluated these potential beneficial effects of PPAR γ agonists on renal function and revised the results of their utilisation in patients with different degrees of renal impairment, in dialysis patients, and in patients with diabetes mellitus after kidney transplantation. Finally, tolerability and safety profile of PPAR γ agonists in patients with reduced glomerular filtration rate are also analysed.

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Introduction

Diabetes mellitus is the leading cause of end stage renal disease (ESRD) (1). It has been demonstrated that exhaustive glycaemic control is associated with a decrease in the development and progression of diabetic nephropathy both in type 1 and type 2 diabetic patients (2, 3). Numerous drugs with different mechanisms of action are being used with the aim of improving glycaemic control. The use of these agents in both monotherapy and in combined therapy contribute to the reduction of glycosylated haemoglobin (HbA1c) concentrations and, consequently, of glomerular hyperfiltration and urinary albumin excretion (UAE) (3, 4).

Multiple drugs with different pharmacological profiles are employed in the management of type 2 diabetes (Table 1). Insulin secretagogues (sulphonylureas (SU) and rapid-acting prandial insulin releasers, meglitinides), biguanides (metformin), α -glucosidase inhibitors and insulin have been used for many years with proven efficacy and safety (5, 6). The more recently introduced drugs include the peroxisome proliferator-activated receptor gamma (PPAR γ) agonists (thiazolidinediones or glitazones), the synthetic amylin analogues (pramlintide), the incretin mimetics

as glucagon-like peptide-1 (GLP-1) analogues (exenatide and liraglutide) and the inhibitors of the incretin-degrading enzyme dipeptidyl peptidase-IV (vildagliptine, LAF-237 and sitagliptine, MK-0431) (5–9).

Therapeutic alternatives in patients with type 2 diabetes and ESRD are limited because of reduced glomerular filtration rate (GFR) is accompanied by accumulation of some drugs and/or their metabolites (10). PPAR γ agonists are a new group of oral antidiabetic agents recently introduced in the therapy of type 2 diabetes (6, 11). These drugs are insulin sensitisers that reduce insulin resistance, increase glucose uptake in muscle and adipose tissue and, decrease hepatic glucose production (12). These antidiabetic oral agents are interesting in the clinical management of patients with type 2 diabetes and ESRD due to the fact that they are primarily metabolised at hepatic level, and therefore they do not accumulate in chronic renal failure (CRF). Moreover, these compounds might improve the uraemia-associated insulin resistance, and it has been shown that these agents give rise to some benefits on several aspects at the metabolic, inflammatory, vascular and haemodynamic levels. In this article we review the more recent aspects related to clinical efficacy and

Table 1 Pharmacological therapy in type 2 diabetes mellitus.

Oral agents	
1) Insulin secretagogues	
Sulphonylureas	
First-generation: tolbutamide, acetohexamide, and chlorpropamide	
Second-generation: glyburide, glipizide, gliclazide, and glimepiride	
Meglitinides	
Repaglinide	
Nateglinide	
2) Biguanides	
Metformin	
3) α -Glucosidase inhibitors	
Acarbose	
Miglitol	
4) PPAR γ agonists (glitazones or thiazolidinediones)	
Pioglitazone	
Rosiglitazone	
5) Dipeptidyl peptidase-IV inhibitors	
Vildagliptine (LAF-237)	
Sitagliptine (MK-0431)	
Parenteral agents	
1) Insulin	
2) Insulin analogues	
Short-acting	
Lyspro	
Aspart	
Glulisine	
Long-acting	
Glargine	
Detemir	
3) Amylin analogues	
Pramlintide	
4) Incretin mimetics: glucagon-like peptide-1 (GLP-1)	
Exenatide	
Liraglutide	

safety profile of this new group of oral antidiabetic agents in patients with several renal conditions such as diabetic nephropathy, CRF on conservative management or dialysis therapy, and finally, post-transplant diabetes mellitus.

PPAR receptors and PPAR agonists

PPAR receptors are members of the steroid hormone nuclear receptor family. They belong to nuclear hormone superfamily of ligand-dependent transcription factors expressed in many tissues of the body including the kidney (13). In 1990, it was identified as the first PPAR receptor, now designated PPAR α (14). Two years later two additional isoforms of PPAR were identified, PPAR β/δ and PPAR γ (15). Among PPAR ligands are hypolipidaemic drugs as fibrates (PPAR α agonists) and insulin sensitisers agents as thiazolidinediones or glitazones (PPAR γ agonists). Whereas the former activate genes related to lipid metabolism, the latter produce several biological effects on adipogenesis, carbohydrate and lipid metabolism, inflammation processes, and cellular proliferation (13). Although both

glitazones are basically PPAR γ agonists, pioglitazone has a slight PPAR α agonistic property. Newer dual-acting PPAR α and PPAR γ agonists (glitazars) such as muraglitazar, ragaglitazar and tesaglitazar are currently being evaluated (16–18).

The interaction between PPAR agonists and their receptors at nuclear level allow the formation of a complex with another nuclear receptor known as retinoid X receptor (RXR), which is bound with its own ligand, retinoic acid (19). This heterodimeric complex results in a conformational change of these receptors, allowing the PPAR:RXR to recognise specific DNA response elements (PPAR response elements, PPRE) in the promoter region of target genes modulating gene transcription. This complex can turn on or turn off the expression of different genes involved in different metabolic pathways. Anti-inflammatory actions of PPAR receptors might be explained by other mechanisms interfering with other transcription-factor pathways in a DNA-independent way (20).

The antidiabetic effect of PPAR γ agonists is based essentially in the reduction of insulin resistance at adipose tissue level after decreasing circulating free fatty acids through an increase of their cellular uptake and triglyceride synthesis, and in the promotion of the differentiation of pre-adipocytes. Glitazones increase glucose utilisation in muscle after activating gene expression of glucose transporter-4 (GLUT-4). These drugs also decrease both hepatic gluconeogenesis and the secretion and activity of the adipocyte-derived cytokine tumour necrosis factor- α (TNF- α), a cytokine implicated in the development of impaired insulin action in muscle (6, 12). Other biologically promising effects of these drugs are related to other components of the metabolic syndrome such as hypertension, inflammation, and vascular dysfunction. Helpful actions on endothelial function have been reported. These effects include an increment of nitric oxide (NO) expression, vascular remodelling after reducing the progression of intima-media thickness associated with atherosclerosis and, finally, on microvascular effects (5, 12).

Both rosiglitazone and pioglitazone have similar glucose-lowering effects, decreasing HbA1c levels by around 0.5–1.5% (21–24). These drugs also exhibit some beneficial effects on lipid profile. While pioglitazone increases HDL-cholesterol and reduces triglycerides, rosiglitazone only elevates HDL-cholesterol levels. Moreover, rosiglitazone increases total cholesterol and LDL-cholesterol. Either drug reduces the proportion of the smaller and more dense LDL particles, with more atherogenic properties, increasing that of bigger and lower dense particles (12). A favourable effect of pioglitazone on secondary prevention of macrovascular events in patients with type 2 diabetes has been recently reported (25). However, in relation to newer dual PPAR α/γ agonists, it has been recently reported that muraglitazar, compared with placebo or pioglitazone, was associated with an excess incidence of the

composite end point of death, major adverse cardiovascular events and congestive heart failure in patients with type 2 diabetes (18).

Rosiglitazone and pioglitazone have been approved for use in type 2 diabetes both in monotherapy and combined therapy. In the United States (US) these drugs are available for therapy in obese and non-obese patients with type 2 diabetes in which non-pharmacological measures have not been successful. In Europe they can be used in monotherapy only when metformin is not tolerated or is contraindicated, as it occurs in CRF. In combined therapy, in US, glitazones can be associated with other oral antidiabetic agents and insulin, while in Europe it is allowed only in association with SU or metformin (6).

Metabolism of PPAR γ agonists

Pharmacokinetic profiles of PPAR γ agonists makes these drugs potentially suitable for their use in patients with type 2 diabetes and CRF. Furthermore, the two available glitazones have an adequate oral bioavailability and are extensively metabolised by the liver. Rosiglitazone is mainly metabolised by cytochrome P450 (CYP) 2C8 into inactive metabolites. Less than 1% of the parent drug appears in the urine in unchanged form (6, 26). Both total and unbound plasma concentrations of rosiglitazone after a single 8-mg oral dose were not affected by the presence of mild, moderate, and severe renal insufficiency, thus indicating that the starting dose of rosiglitazone need not be adjusted in patients with renal impairment (27). Moreover, similar values of area under the concentration–time curve, maximum observed plasma concentrations, and half-life were observed in a group of 10 haemodialysis (HD) patients (non-dialysis day) in comparison with a group of healthy individuals after a single 8 mg oral dose of rosiglitazone. These parameters were not markedly influenced by HD (28).

Metabolites of pioglitazone are more active and are excreted predominantly in the bile. Both pioglitazone as its metabolites M-III and M-IV do not accumulate in CRF. Pharmacokinetic profile of pioglitazone was similar in healthy subjects and in patients with moderate and severe renal failure (29).

Possible nephroprotective actions of PPAR γ agonists

PPAR receptors are expressed in several tissues including the kidney (13, 30–32). PPAR α is predominantly expressed in proximal tubules and medullary thick ascending limbs, PPAR β/δ is equally expressed in renal cortex and medulla, while PPAR γ is selectively expressed in medullary collecting ducts, glomeruli and pelvic urothelium (13). Through PPAR activation, PPAR γ agonists exert some beneficial effects on the kidney, although the exact mechanism is not well understood. It is also

unknown whether this protecting effect is due to a direct action on PPAR γ at the glomerular, tubular and/or vascular level (33). Main protecting mechanisms at kidney level are summarised in Table 2.

Some of the nephroprotective actions of glitazones take place at haemodynamic level. PPAR γ agonists reduced blood pressure in obese, diabetic, and hypertensive rats (34–38). Some authors have found a vasodilator effect of troglitazone, a PPAR γ agonist, on the postglomerular efferent arteriole in rats (39). This drug has been shown to reduce blood pressure in type 2 diabetic patients (40). Moreover, rosiglitazone and pioglitazone reduced blood pressure in both hypertensive and non-hypertensive type 2 diabetic patients (41–45). Experiments in rats have demonstrated an increment in the NO production induced by PPAR γ ligands after stimulating the expression of dimethylarginine dimethylaminohydrolase-II expression, an enzyme that degrades asymmetric dimethylarginine, one of the endogenous NO synthase (NOS) inhibitor (46). Multiple mechanisms on PPAR γ -induced haemodynamic effects have been suggested (13, 47). Among them are: (1) reduction in insulin resistance, which has been found to be associated with lower blood pressure in humans (42, 43, 48), (2) direct vasodilator effects of PPAR γ agonists, whose receptors have been found in both endothelium and vascular smooth muscle (49, 50), (3) modulation of release of vasodilator substances such as prostaglandins and NO (46, 51),

Table 2 Actions of glitazones potentially protecting kidney function.

Haemodynamic effects
Blood pressure reduction
Vasodilator effect on postglomerular efferent arteriola
Increase NO production
Metabolic effects
Reduction of insulin resistance
Reduction of UAE
Anti-inflammatory and antiproliferative effects
Inhibition of cytokine production by macrophages
Reduction of oxidative stress
Diminution of TGF-beta1-induced fibronectin expression in mesangial cells
Reduction of polymorphonuclear infiltration
Diminution of expression of ICAM-1 and VCAM-1 in tubular epithelial cells and interstitium
Inhibition of cell growth and reduction of matrix production in human kidney fibroblasts
Inhibition of mesangial proliferation induced by VEGF and PDGF
Reduction in the secretion of type IV collagen and fibronectin
Decrease in proline incorporation
Reduction of the activity of TIMP-1, TIMP-2, and MMP-9
Mechanic effects
Attenuation of mesangial contractile dysfunction

Abbreviations: NO, nitric oxide; UAE, urinary albumin excretion; TGF-beta1, transforming growth factor-beta1; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; TIMP-1, tissue inhibitor of metalloproteinase-1; TIMP-2, tissue inhibitor of metalloproteinase-2; MMP-9, metalloproteinase-9.

and (4) regulatory effects on salt and water absorption at medullary collecting ducts (52, 53).

Another important renoprotective mechanism of PPAR γ agonists is related to the inflammatory process. PPAR γ stimulation seems to inhibit inflammatory cytokine production by macrophages (54, 55). Pioglitazone has been shown to diminish the oxidative stress at kidney level in diabetic rats and rabbits (56–59). Furthermore, it reduced TGF- β 1-induced fibronectin expression in mouse glomerular mesangial cells by inhibiting activator protein-1 (AP-1) (56, 58, 60). In a murine sepsis model, a reduction in renal injury and dysfunction has also been reported in association with the anti-inflammatory effects of glitazones (61).

Pioglitazone inhibited cell growth and reduced matrix production in human kidney fibroblasts through mechanisms that included a reduction in the secretion of type IV collagen and fibronectin, a decrease in proline incorporation and a reduction of the activity of tissue inhibitor of metalloproteinase-1 (TIMP-1), TIMP-2, and metalloproteinase-9 (MMP-9) (62, 63). Other reported beneficial effects of PPAR γ agonists include (i) antinephritic effects, by suppressing the recruitment of inflammatory cells; (ii) antiproliferative effects, by inhibiting mesangial proliferation induced by vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF); and (iii) mechanic effects, by attenuating mesangial contractile dysfunction (64–69).

Finally, glitazones reduced UAE in obese and diabetic rats (36, 70, 71–73) and in type 2 diabetic patients (74). Although this glitazone-induced reduction in UAE is a consequence more than a cause, of the renoprotective effect of the drugs, it might contribute to the long-term beneficial effects reported in patients with renal disease.

Diabetic nephropathy

PPAR γ agonists seem to have favourable effects on the development and/or progression of diabetic nephropathy. Exact mechanisms are not completely understood, although they might be related to haemodynamic changes or to the insulin-sensitising effect (Table 3).

Yoshimoto *et al.* (1997) demonstrated that therapy with pioglitazone not only improved lipid and glucose metabolism, but also lowered blood pressure, decreased proteinuria, and prevented glomerular injury, renal arteriosclerosis and aortic medial wall thickening in genetically obese diabetic rats (35). Pioglitazone also improved the urinary albumin/creatinine ratio (ACR) and the glomerular and Bowman's capsule volume ratios, and reduced endothelial constitutive nitric oxide synthetase (eNOS) in the endothelium of glomerular vessels in early stage of type 2 diabetic nephropathy in mice (75). An increase in renal tubular cell albumin uptake induced by pioglitazone has also been reported (76). The urinary albumin excretion rate (AER) was

Table 3 Actions of glitazones potentially protecting against the progression of diabetic nephropathy.

Reduction of blood pressure
Decrease of UAE
Improvement of urinary ACR and glomerular and Bowman's capsule volume ratio
Reduction of eNOS in the endothelium of glomerular vessel
Increase in renal tubular cell albumin uptake
Reduction of glomerular size and glomerular hyperfiltration
Diminution of production of extracellular matrix in glomeruli
Improved of endothelial dysfunction
Protective role on podocytes decreasing urinary podocyte excretion
Improvement of insulin sensitivity

Abbreviations: UAE, urinary albumin excretion; ACR, albumin/creatinine ratio; eNOS, endothelial constitutive nitric oxide synthetase.

significantly decreased after 12 weeks of treatment with thiazolidinediones, and there was a suppression of the loss of anionic sites of glomerular basement membranes (GBM) in streptozotocin-induced diabetic spontaneous hypertensive rats (73). Other authors have demonstrated that glitazones not only reduce, but also prevent, glomerular hyperfiltration, AER, and excessive production of extracellular matrix in glomeruli in streptozotocin-induced diabetic rats (72).

Preliminary results in human studies have been promising. Therapy with pioglitazone, 30 mg/day, was accompanied by a significant reduction in UAE in 15 normotensive type 2 diabetic patients with microalbuminuria by about 40% and 69% at 6 and 12 months of therapy, respectively. At 12 months, UAE was also significantly lower in pioglitazone-treated patients in comparison with those treated with glibenclamide and voglibose (77). More recently, Agarwal *et al.* (78) reported the result of a randomised, open-label, study comparing glipizide with pioglitazone over 16 weeks in 44 type 2 diabetic patients with overt diabetic nephropathy. Glipizide produced a mean increase in proteinuria of 6.1%, whereas pioglitazone therapy was followed by a proteinuria reduction of 7.2%. This difference, however, was not statistically significant (78).

Similar findings have been reported with rosiglitazone. Treatment with rosiglitazone, 4 mg b.i.d. for 52 weeks, was accompanied by a significant reduction (~25%) of microalbuminuria in a group of type 2 diabetic patients. This effect was not observed in those patients treated with glyburide. A greater proportion of patients treated with rosiglitazone achieved normoalbuminuria (ACR < 30 μ g/mg) than did patients treated with glyburide (43% vs 6%). Conversely, fewer patients in the rosiglitazone group developed microalbuminuria than in the glyburide group (11% vs 7%). Reduction in ACR did not strongly correlate with changes in fasting plasma glucose and HbA1c, but showed strong correlation with changes in mean 24-h systolic and diastolic blood pressure (79).

The first human study evaluating the effects of rosiglitazone on haemodynamic changes and endothelial

function at renal level has been recently reported (80). Therapy with rosiglitazone improved glomerular hyperfiltration, renal endothelial dysfunction, and microalbuminuria of incipient diabetic nephropathy in type 2 diabetic patients. Rosiglitazone therapy was followed by a reduction of 60% in albuminuria. In these patients a positive correlation between the reductions of UAE and GFR was also found (80). Another study showed that the addition of rosiglitazone to glyburide produced a significant reduction of UAE (~38%) in patients with type 2 diabetes and hypertension (44). This effect was negatively correlated with changes in insulin sensitivity and positively with changes in systolic and diastolic blood pressure (44). More recently it has been reported that combined therapy with rosiglitazone and metformin was followed by a reduction of microalbuminuria significantly higher than that found with the combination of glyburide and metformin (22.8% vs 7.1%, $p < 0.001$) in a group of subjects with microalbuminuria and type 2 diabetes. Moreover, rosiglitazone and metformin therapy was accompanied by a significant reduction in both systolic and diastolic 24-h ambulatory blood pressure (81).

Different mechanisms should be considered for the favourable effects of PPAR γ agonists on diabetic nephropathy: (i) reduction of glomerular size and, therefore, glomerular hyperfiltration, in early phases of the diabetic nephropathy development, in association with an increment in the albumin uptake in renal tubular cells, probably through inhibition of DAG-PKC-ERK pathway (71, 72); (ii) improvement of endothelial dysfunction related to an increase in NO bioavailability which reduces intraglomerular capillary pressure and filtration fraction (80); (iii) protective role on podocytes in the initial phases of diabetic nephropathy (82); and (iv) improvement of insulin sensitivity (74) and blood pressure reduction (74, 79, 81).

Long-term studies performed in a higher number of patients are needed to confirm these results and to consider these drugs as a part of the initial management of diabetic nephropathy.

Chronic renal insufficiency

PPAR γ agonists are one of few therapeutic options for treatment of patients with type 2 diabetes and CRF with oral agents. Only few studies performed in this population have been reported up to date. Thiazolidinediones seem to be interesting because they might contribute to reduce the uraemia-associated insulin resistance. Moreover, agonists would maintain their efficacy on glycaemic control regardless of the presence or absence of CRF. Agrawal *et al.* (83) studied the effects of the addition of rosiglitazone to a SU (glyburide, glipizide and glipizide) treatment regimen for 6 months, in patients with type 2 diabetes mellitus with mild to moderate renal impairment inadequately controlled

by SU monotherapy. Results showed similar efficacy in patients with normal renal function, and in patients with mild to moderate renal impairment (83).

Dialysis patients

Therapy with PPAR γ agonists has been recently evaluated in uraemic patients undergoing dialysis in combination with both oral antidiabetic agents and insulin (Table 4).

In a randomised, placebo-controlled study, pioglitazone significantly reduced HbA1c levels approximately by 0.6% in comparison with placebo in a group of 20 HD patients with type 2 diabetes. In addition, pioglitazone significantly reduced triglyceride and increased HDL-cholesterol levels (84). A retrospective study evaluated the clinical efficacy and safety profile of two glitazones in HD patients with type 2 diabetes (85). Forty patients were treated either with rosiglitazone or pioglitazone for 3 months associated to their habitual treatment (oral agents or insulin). The addition of a glitazone produced a reduction in HbA1c levels of about 0.6%, without differences between both drugs. Moreover, a significant reduction in both systolic (~6.0 mmHg) and diastolic (~3.2 mmHg) blood pressures was also reported.

Insulin resistance, a risk factor for cardiovascular disease, is present in both diabetic and non diabetic uraemic patients on continuous ambulatory peritoneal dialysis (CAPD) (86–88). PPAR γ agonists have shown to be effective in the reduction of insulin resistance in these patients. Rosiglitazone therapy, 4 mg/day for 12 weeks in 15 non diabetic CAPD patients, was accompanied by a reduction in both insulin resistance, estimated by the homeostasis model assessment method (HOMA-IR), and the area under the curve of glucose and insulin after an oral glucose tolerance test (OGTT) with an improvement in insulin sensitivity index (ISI) (89). In an open-label randomised study performed in 52 insulin-treated patients with type 2 diabetes on CAPD therapy and stable glycaemic control, the addition of rosiglitazone (4 mg/day) improved insulin sensitivity and decreased inflammatory response (90).

Table 4 Favourable effects reported of PPAR γ agonists in CRF patients.

Similar efficacy on glycaemic control in combination with SU that patients with normal renal function
Reduction of HbA1c ~0.6% with combined therapy in type 2 diabetic patients on HD
Reduction of systolic and diastolic blood pressures in type 2 diabetic patients on HD
Diminution of insulin resistance in non diabetic uraemic patients on CAPD
Reduction of exogenous insulin needs in diabetic patients on CAPD
Diminution of serum levels of CRP in diabetic patients on CAPD

Renal transplantation

Post-transplant diabetes mellitus (PTDM) is associated with reduced graft and patient survival in renal transplant recipients (91, 92). Insulin resistance contributes to the development of PTDM, therefore the effects of insulin sensitisers might be potentially beneficial in patients with post-transplant glucose intolerance or diabetes (93). A protective effect on cyclosporine-induced pancreatic and renal injury has been reported in rats treated with rosiglitazone (94). Beneficial effects of rosiglitazone have also been reported in humans (95, 96). Rosiglitazone therapy was followed by an increase in insulin sensitivity, a reduction in fasting and 2 hours plasma glucose and an improvement of endothelial function in renal transplant recipients with glucose intolerance (95). More recently, It has been reported that rosiglitazone adequately controlled mean fasting blood glucose in 16 of 22 patients with PTDM (96).

Tolerance and safety profile of PPAR γ agonists in CRF

The main concerning adverse effects of PPAR γ agonists in the treatment of type 2 diabetic patients with CRF are weight gain, oedema, and congestive heart failure (CHF) (5, 6, 97). The mechanism involved is water retention which is due to activation of PPAR γ pathway at the collecting duct, increasing sodium and water transport (47, 52, 53). Weight gain is also influenced by an increase in subcutaneous fat stores at the expense of newly formed insulin-sensitive adipocytes (98). Oedema appears in approximately 3–5% of patients treated with PPAR γ agonists. Both oedema and weight gain are more prevalent when using PPAR γ agonists in combination with insulin. CHF rarely develops in patients treated with PPAR γ agonists in monotherapy, although the frequency of this complication increases when combined with insulin. CHF symptoms usually improve after the administration of diuretics and discontinuation of glitazone therapy (99). The potential for developing worsening CHF has propitiated that glitazones therapy has been considered a contraindication in patients with class 3 and 4 New York Heart Association (NYHA) heart failure (97). In patients with pre-existing nephropathy the combined therapy with glitazones and fibrates should be monitored by frequent measurements of serum creatine kinase and creatinine because of the risk of acute myopathy (100).

Because of these adverse effects some authors do not recommend treatment with PPAR γ agonists in CRF patients (99). However, recent studies have shown that tolerance and safety profile of PPAR γ agonists are appropriate in these patients. Pioglitazone was safe and well tolerated in a group of patients with several degrees of renal insufficiency and comparable to

that observed in subjects with normal renal function (29). Therapy with rosiglitazone, 8 mg/day, was not accompanied by severe adverse events in a group of 57 patients with mild, moderate and severe renal insufficiency (27). In patients with advanced diabetic nephropathy, pioglitazone therapy produced a similar number of serious adverse events in comparison with those observed in patients treated with glipizide (78). Finally, combined therapy with rosiglitazone and SU was well tolerated in a group of 301 type 2 diabetic patients with mild to moderate CRF inadequately controlled with monotherapy (83).

PPAR γ agonists therapy in dialysis (HD and CAPD) patients has shown adequate safety and tolerance profiles. In the study of Manley (85), there were 3 hospitalisations for new or worsening CHF (2 patients on rosiglitazone and one on pioglitazone) in a group of 40 HD patients with type 2 diabetes treated with glitazones. Interdialytic weight gain significantly increased ~ 0.3 kg in rosiglitazone treated patients (85). Rosiglitazone therapy has been well tolerated in both diabetic and non diabetic uraemic patients on CAPD. Oedema in lower extremities and weight gain in approximately 2% of the patients have been reported (89, 90).

Altogether, these results suggest that PPAR γ agonists might be an adequate alternative in the antihyperglycaemic therapy of diabetic patients with CRF, regardless of the treatment used for renal failure. According to the American Heart Association and the American Diabetes Association recommendations, in patients without clinical data of CHF but with one or more risk factors for its development, as it is the case in CRF patients, therapy with glitazones should be initiated at low doses, i.e. rosiglitazone 4 mg/day and pioglitazone 15 mg/day. The increases in dose should be gradual, with tight monitoring for signs of excessive weight gain, peripheral oedema, and/or CHF (97).

Conclusions

Although therapeutic possibilities with oral agents in type 2 diabetes mellitus are increasing, the presence of CRF is an important limitation for using the majority of the currently available oral antidiabetic drugs. In recent years several promising drugs have been introduced in the therapeutical armamentarium of these patients. PPAR γ agonists are drugs essentially metabolised in the liver that have proven to exert beneficial effects in the kidney and in different conditions such as diabetic nephropathy and uraemia-associated insulin resistance. The few studies performed so far with PPAR γ agonists in diabetic patients with CRF have shown favourable effects on several aspects of renal function without severe adverse effects. Moreover, the anti-inflammatory, haemodynamic, vascular and metabolic effects of these drugs and their potential benefits in other pathological conditions are also to be taken

into account. Further studies are needed to clarify and clearly establish the therapeutic role of these agents in patients with renal diseases.

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