Review Article

Thiazolidinediones: Antidiabetic Drugs with Cardiovascular Effects

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Patients with type 2 diabetes have cardiovascular morbidity and mortality at least four times higher compared to patients without diabetes.[1,2] Moreover, it is well established nowadays that the cardiovascular risk of diabetic patients without a history of a prior myocardial infarction is similar to the risk of non-diabetic patients who have already had one.[3] Hence, the reduction of cardiovascular risk in type 2 diabetic patients using antidiabetic medication is of great importance.

In the last few years thiazolidinediones (glitazones), a new class of antidiabetic drugs, have been developed. These drugs are potent and highly selective agonists for peroxisome proliferator-activated receptors (PPAR γ), directly improving insulin sensitivity at the sites of insulin action in type 2 diabetes patients.[4,5] Furthermore, thiazolidinediones seem to have pleiotropic vascular protective effects, as they appear to improve diabetic dyslipidaemia, hypertension and abnormalities of the coagulation-fibrinolysis system, thus reducing the overall cardiovascular risk in patients with the metabolic syndrome.[6] There is substantial evidence to suggest that glitazones not only ameliorate insulin resistance at the level of adipocytes, skeletal muscles and liver, but also may play a beneficial role in other underlying pathophysiological mechanisms of vascular impairment, such as atherosclerosis and inflammation.[7,8] Troglitazone, which became available in practice in 1997, was the first agent of this class, but it was subsequently withdrawn from the market in 2000 because of hepatotoxicity. The two currently available members of the thiazolidinedione family, rosiglitazone and pioglitazone, have entered clinical practice since 1999.[9] In this review we will try to present the current evidence concerning the cardioprotective role of these new antidiabetic regimens.

Mechanism of action of thiazolidinediones

The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptors superfamily and there are three subtypes currently identified, PPAR γ, PPAR α and PPAR δ, which play a significant role in lipid metabolism.[10] Various fatty acids and natural eicosanoids serve as endogenous ligands for PPARs, whereas fibrates and thiazolidinediones are potent synthetic ligands affecting lipid and glucose metabolism.[11] After ligand binding, PPARs undergo specific conformational changes that allow recruitment of one coactivator protein or more. Once activated, the PPARs form heterodimers with another nuclear receptor, the 9-*cis*-retinoic acid receptor (RXR). These heterodimers PPAR/RXR bind to specific DNA sequences

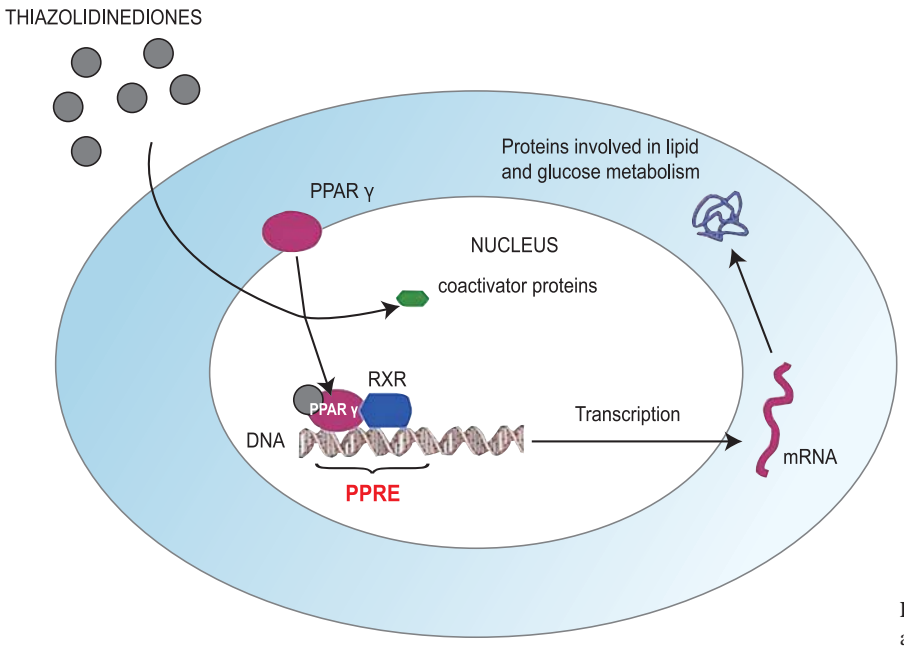

Figure 1. Molecular mechanisms of action of thiazolidinediones.

(PPAR response elements: PPRE) (Figure 1).[12] Furthermore, PPARs can interact with other transcription factors in a DNA binding-independent manner and exhibit anti-inflammatory properties by repressing gene expression for some cytokines (interleukins IL-2, IL-6, IL-8, tumour necrosis factor TNF-α, and metalloproteases). There is probably a repression of nuclear factor-κB and activator protein-1 (AP-1) transcription pathways.[13] PPAR α are expressed predominantly in the heart, liver, kidneys and skeletal muscle and are the main target for fibrates (fenofibrate, ciprofibrate, and gemfibrozil), which have hypolipidaemic and anti-inflammatory effects.[14] PPAR δ are expressed primarily in the adipose tissue and are involved in lipid metabolism, body weight reduction and modulation of skeletal muscle to training or fasting.[15] PPAR γ are expressed more abundantly in adipose tissue but are also found in vascular endothelium, monocytes, macrophages, pancreatic beta cells and atherosclerotic lesions *in vivo*.[13,16] Their expression is low in tissues that express predominantly PPAR α, such as the liver, the heart, and skeletal muscles. Thus, it is clear that adipose tissue, in addition to other sites, is the main target for glitazones, which increase insulin sensitivity, reducing plasma concentrations of free fatty acids (Figure 2).[17]

Epidemiological studies have shown that insulin resistance is an independent risk factor for cardiovascular disease and is associated with other risk factors for metabolic syndrome.[18] These have been defined by the World Health Organisation (WHO) and National Cholesterol Education Program (NCEP) Adult Treatment Panel III and include fasting hyperglycaemia, abdominal obesity, hypertension, hypertriglyceridaemia, low levels of high density lipoprotein cholesterol (HDL-C), and microalbuminuria.[19] Thiazolidinediones lower fasting and postprandial insulin and glucose plasma concentrations, increase glucose uptake in peripheral tissues and reduce free fatty acid levels.[20] In skeletal muscles, insulin resistance is greater compared to other tissues; thiazolidinediones activate two proteins, phosphatidylinositol3-kinase and Akt, [21] which are inactivated in patients with type 2 diabetes. Another important effect of thiazolidinediones is the proliferation of small adipocytes in comparison to larger ones,[22] a process that promotes glucose uptake from adipose tissue. In this way, the use of glitazones leads to weight gain, as they increase subcutaneous adipose tissue mass (a more insulin-sensitive type of fat tissue) and cause redistribution of fat between visceral (decrease) and subcutaneous (increase) body compartments. In addition, by reducing plasma concentrations of free fatty acids, thiazolidinediones decrease their toxic effects upon the pancreatic beta cells.[23] Furthermore, various inflammatory mediators, such as adiponectin, TNF-α and resistin, are regulated by PPAR γ agonists in a manner which results in improved adipose tissue function. Adiponectin's plasma concentration is low

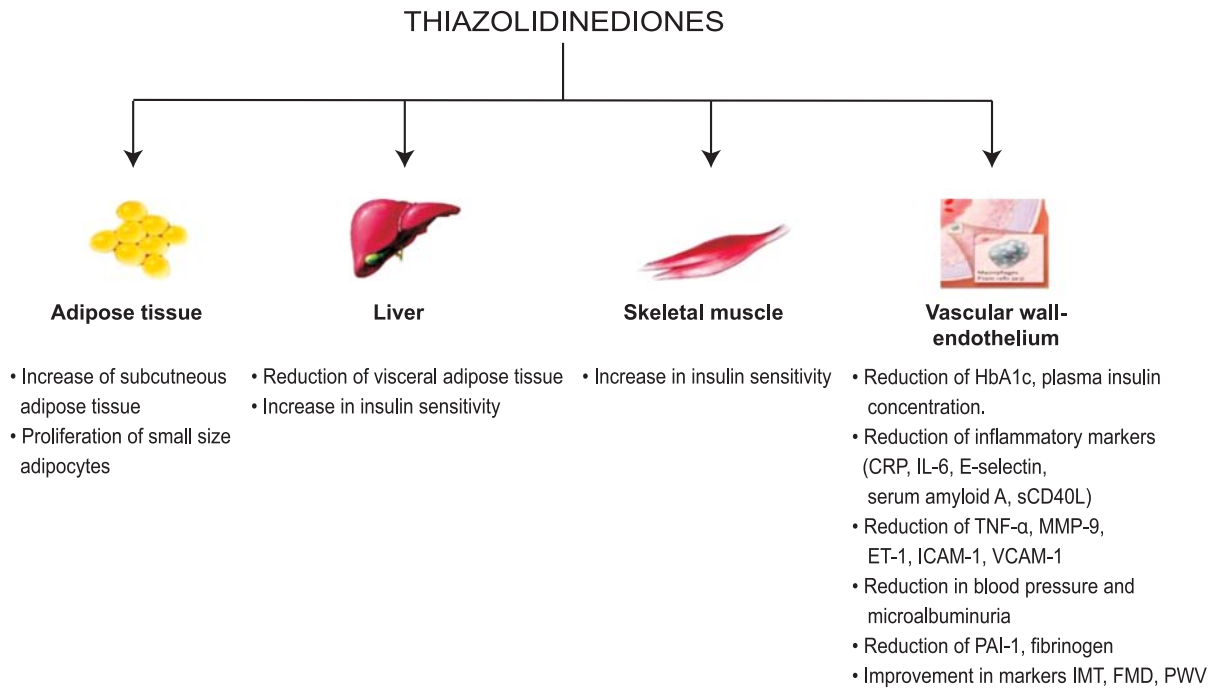

Figure 2. Effects of thiazolidinediones at the level of adipose tissue, liver, skeletal muscles and vascular wall. (See text for abbreviations.)

in patients with type 2 diabetes, especially in obese patients, and thiazolidinediones have been shown to increase it *in vivo*. In animals this process can ameliorate insulin resistance, but this does not occur in humans.[24] Several clinical studies indicate that rosiglitazone has a greater PPAR γ binding affinity than does pioglitazone, which translates to a clinical dose that is about 1/6 that of pioglitazone.[25]

Cardiovascular effects of thiazolidinediones

Rosiglitazone and pioglitazone are oral antidiabetic agents that have been available for use since 1997, either as monotherapy or in combination with sulfonylureas or metformin. In the USA thiazolidinediones can be used officially in combination with insulin. Their hypoglycaemic effects are well documented. The reduction of fasting blood glucose ranges from 60 to 80 mg/dl and of glycosylated haemoglobin (HbA_{1c}) from 0.5% to 1.5%. Rosiglitazone and pioglitazone have similar clinical efficacy.

Effects on lipid metabolism

Thiazolidinediones seem to have a major impact on the process of atheromatosis and are of great importance, particularly during its early stages, since they reduce triglyceride plasma levels, which are major risk factors for cardiovascular disease. On the other hand, thiazolidinediones increase both low density lipoprotein cholesterol (LDL-C) and total cholesterol levels. Rosiglitazone has been observed to have a more consistent increasing effect than pioglitazone.[27] Nevertheless, the increase is predominantly in the larger, buoyant particles of LDL-C, which may be less atherogenic than the small, dense LDL-C particles.[28,29] These changes in the size of atherogenic LDL-C particles may make cholesterol less susceptible to oxidation, a step that is mandatory for the development of atherosclerotic plaque.[30] Generally, PPAR γ agonists inhibit oxidised LDL-receptor expression on endothelial cells by reducing intracellular superoxide radical generation. Furthermore, similarly to statins, PPAR agonists inhibit lectin-like oxidised LDL receptor-1 (LOX-1), a major receptor for oxidised low-density lipoprotein on endothelial cells, by reducing intracellular superoxide radical generation.[31] Lewin et al,[32] as part of the Simvastatin/Thiazolidinedione study group, organised a 24-week, multi-centre, randomised, double-blind, placebo-controlled, parallel group trial, which compared the effects of 40 mg of simvastatin or placebo in type 2 dia-

betes patients who were taking a stable dose of pioglitazone or rosiglitazone, and had HbA_{1c} ≤9.0% and LDL-C >100 mg/dL. In the simvastatin patient group LDL-C was reduced significantly, by approximately 34%, whereas in the placebo group no change was observed, indicating a possible synergistic beneficial effect of thiazolidinediones with statins in plasma lipids.

Patients with type 2 diabetes or insulin resistance are characterised by a reduction in HDL-C plasma concentration, which is an independent risk factor for coronary disease. Thiazolidinediones increase HDL-C levels by approximately 10%, without significant differences between them, whereas their reducing effect on triglycerides is different.[24] Pioglitazone has been shown to increase HDL-C and to reduce triglycerides more than rosiglitazone, which may be due to its greater PPAR α binding affinity. PPARs can also bind fibrates, which are drugs that exhibit a great triglyceride-lowering effect.[33] In the study of Khan et al,[27] of 127 patients who had previously been treated with troglitazone, conversion to pioglitazone was associated with a greater effect upon total cholesterol, LDL-C and triglycerides compared to rosiglitazone. Rosiglitazone raises HDL-C levels, but its effect on triglyceride concentrations remains a controversial issue, since in some clinical trials no significant variation in triglycerides was demonstrated, while in others there was a lowering effect on both triglycerides and HDL-C. For troglitazone, the third member of the thiazolidinedione family, clinical trials have suggested an increase in HDL-C of 5-8% and a reduction in triglyceride levels of 15-20 %.[34]

Lp(a) is another independent risk factor[35] for cardiovascular disease in type 2 diabetic patients, although several studies did not report increased Lp(a) levels in these patients.[36] The effect of thiazolidinediones on Lp(a) is unclear, as there is evidence that pioglitazone does not affect Lp(a) levels,[37] in contrast to troglitazone, which seems to increase Lp(a) in diabetic patients.[38] In a study involving diabetic patients, the addition of rosiglitazone resulted in an increase of about 15% in Lp(a) after 12 weeks of treatment.[39] In contrast to these findings, in a recently published study with a longer follow up period, Lp(a) levels slightly decreased (~9%) with rosiglitazone.[40] It is possible that the inconsistency of glitazone's effect on the lipid profile of patients and the discrepancies between the results of different studies could be attributed to the small number of subjects included in those studies and to their different population characteristics.

Effects on blood pressure

Generally, thiazolidinediones reduce blood pressure in animal models as well as in diabetic and non-diabetic subjects. Additionally, they reduce microalbuminuria, which is a manifestation of early nephropathy in diabetic patients.[41,42] It is notable that patients with type 2 diabetes mellitus have a 1.5 to 2-fold risk for hypertension compared with the general population.[43] Thiazolidinediones prevent hypertension in angiotensin II infused rats and abrogate the structural, functional, and molecular changes induced by angiotensin II in blood vessels, leading to inhibition of cell growth and inflammation.[44] Pioglitazone, particularly administrated in a high dosage, reduced blood pressure in normotensive rats, inhibiting L-type calcium channels.[44] Both rosiglitazone and pioglitazone have been found to decrease blood pressure substantially, due to their ability to ameliorate endothelium function and to inhibit endothelin-1 expression. Other potential mechanisms include a decrease in calcium influx and enhancement of NO synthase phosphorylation, which increases NO production.[46,47] In diabetic patients rosiglitazone reduces blood pressure and improves insulin resistance (assessed by Homeostasis Model Assessment [HOMA], plasma insulin concentration, HbA_{1c}), which potentially indicates a common cause leading to these two effects.[48]

Microalbuminuria is an important predictor of cardiovascular disease in patients with type 2 diabetes.[49] In two recently published multi-centre, double blind randomised studies with large numbers of patients (2444 and 1269), pioglitazone, as monotherapy or combined with sulfonylurea, reduced the ratio of urinary albumin to creatinine compared with metformin.[50] Troglitazone has similar effects on this ratio, as was indicated by the study of Imano et al.[42] Additionally, rosiglitazone seems to improve glomerular hyperfiltration in the early stages of diabetic nephropathy and intrarenal disposal of NO, thus inhibiting the worsening of renal failure.[51]

Effects on endothelial function and inflammatory process

The above effects of thiazolidinediones on the lipid profile and blood pressure of diabetic patients has been shown to partially inhibit the atheromatosis process. Thiazolidinediones have a significant role in endothelial dysfunction, as PPAR γ regulate monocyte chemotaxis at sites of endothelium injury and the inflammatory response of macrophages and vascular smooth muscle cells (VSMCs).[52] Thus, thiazolidine-

diones reduce the production of adhesion molecules (vascular cell adhesion molecule-1 [VCAM-1] and intracellular adhesion molecule [ICAM-1]), which contribute to the adhesion of lymphocytes and monocytes on atherosclerotic lesions.[53] Additionally, thiazolidinediones have been shown to enhance synthase NO expression, which is diminished with inflammation, while they also reduce the production of endothelin-1 (ET-1), which is a potent endothelial-derived vasoconstrictor compound.[54,55] Atherosclerosis involves the migration of VSMCs from the media into the intima and their proliferation there in response to endothelial injury. Thiazolidinediones inhibit this process by reducing leukocyte and macrophage adhesion to the lesion, as well as VSMC growth and the expression of matrix metalloproteinases (MMPs) expression from it.[56,57] MMP-9 is the most important metalloproteinase, and its expression is high in the fibrous cap of an atherosclerotic lesion, implying a potential association with plaque rupture.[58] It is noteworthy that in patients with acute coronary syndromes, or after initiation of cardiopulmonary bypass (a high stress condition), circulating MMP-9 is increased more than 6-fold.[59] Thiazolidinediones inhibit neointima formation, and there is evidence from a study in rats that they can inhibit the growth and migration of VSMCs towards endothelium that has been injured by a balloon catheter, regardless of their antidiabetic and hypolipidaemic effects.[56]

Furthermore, in patients with diabetes or metabolic syndrome, levels of plasminogen activator inhibitor type-1 (PAI-1), a molecule which normally inhibits fibrinolysis, and fibrinogen are elevated, contributing to the pathogenesis of acute coronary syndromes.[60] Immunohistochemical analysis of coronary lesions from patients with type 2 diabetes and coronary artery disease has demonstrated increased coronary artery tissue levels of PAI-1.[61] Thiazolidinediones reduce PAI-1 and fibrinogen levels, and specifically troglitazone has been demonstrated in vitro to decrease its hepatic synthesis due to attenuation of hyperinsulinaemia.[62] Thiazolidinediones also lead to diminished expression of inflammatory markers such as TNF-α, IL-6, C-reactive protein (CRP), E-selectin and serum amyloid A.[63] In a double blind, randomised study in patients with diabetes type 2, Haffner et al[64] showed that rosiglitazone treatment for 26 weeks caused a significant reduction in plasma CRP, MMP-9 and leukocyte concentrations. The most remarkable findings were the reduction of serum amyloid A after only 2 weeks of rosiglitazone treatment and the significant decrease in TNF-α levels after 6 weeks' treatment.[65] Thiazolidinediones exhibit maximal glucose lowering effects only after 8 to 12 weeks.[66] However, decreased sCD40L levels as well as serum levels of MMP-9 have been observed as early as 2 weeks after the initiation of treatment.[67] This fact indicates that thiazolidinediones might directly affect the levels of these biomarkers, independently of their metabolic action.

In clinical practice, impaired endothelial function, a surrogate marker of coronary risk, can be assessed non-invasively by ultrasound B-mode assessment of brachial artery flow-mediated vasodilation (FMD) or by measurement of pulse wave velocity (PWV). There are several studies suggesting the improvement of brachial artery FMD after treatment with thiazolidinediones, irrespective of their hypoglycaemic effects.[68] However, Sidhu et al[69] suggested that rosiglitazone treatment in non-diabetic patients with coronary disease did not improve FMD, despite the reduction in inflammatory and endothelial dysfunction markers. On the other hand, rosiglitazone administered in non-diabetic patients with metabolic syndrome ameliorated endothelium-dependent FMD and endothelium-independent, nitroglycerine-induced vasodilation of the brachial artery, despite an increase in the levels of LDL and apolipoprotein-B.[70] Satoh et al[71] showed that pioglitazone treatment for three months in diabetic patients significantly reduced levels of both CRP and PWV, in both non-responders to its antidiabetic effect (HbA_{1C} reduction $<1\%$) and responders (HbA_{1C} reduction $>1\%$).

Clinical evidence from the effect of thiazolidinediones on atheromatosis

Intima media thickness (IMT) measured by M-mode ultrasound is considered an early marker of atherosclerosis and has been related directly to insulin resistance.[72] Sidhu et al[73] suggested that rosiglitazone reduced the progression of carotid IMT in non-diabetic patients with angiographically documented coronary artery disease (CAD) compared to placebo. However, IMT's improvement was not statistically significant, and this may be due to the fact that the rosiglitazone-treated group had more patients on medication likely to improve IMT, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or β-blockers. Koshiyama et al[74] observed that treatment with 30 mg pioglitazone for three months in type 2 diabetes patients caused significant regression of IMT at 6 months compared to placebo, with no further reduction thereafter.

A highly significant restenosis rate in patients with type 2 diabetes after coronary artery stenting (approximately 32-66 % higher than non-diabetic patients) is a common clinical problem.[75] It has been reported that thiazolidinediones reduce the rate of restenosis in diabetic patients who have undergone coronary stenting and can have an additive beneficial effect to that of drug-eluting stents. A recently-published randomised, placebo-controlled trial in non-diabetic patients with coronary artery disease showed that pioglitazone treatment significantly reduced neointima volume, assessed by intravascular ultrasound after coronary stent implantation (34% in the pioglitazone group versus 32.3% in controls).[76] Similarly, a recent trial by Takagi et al.[77] involving 76 diabetic patients, suggested that tziazolidinedione treatment significantly reduced neointimal tissue proliferation in restenotic lesions after coronary stent implantation. Choi et al[78] demonstrated that rosiglitazone significantly reduced in-stent restenosis in type 2 diabetic patients (17.6% in the rosiglitazone group versus 38.2% in controls) independently of glycaemic control. However, Osman et al,[79] in a trial involving a small population of diabetic patients, suggested that rosiglitazone did not improve the restenosis rate after 6 months' treatment.

Nevertheless, all the above trials included a limited number of patients and had relatively soft endpoints. Larger multi-centre studies with harder endpoints (i.e. cardiovascular morbidity and mortality) are under way. PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) is the only large multi-centre study published so far. It took place in 19 European centres and enrolled 5238 patients with type 2 diabetes.[80] The primary endpoint was composite and included reduction in risk of death from any cause, non-fatal myocardial infarction and acute coronary syndromes, stroke, leg amputation, coronary or leg revascularisation. The findings showed that pioglitazone did not significantly reduce the risk of the primary endpoint. The main secondary endpoint, all-cause mortality, myocardial infarction or stroke, was reduced significantly in the pioglitazone group. Another trial called RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) is under way, in the phase of patient recruitment, and will investigate the effects of rosiglitazone on cardiovascular risk reduction in a large population.[81] Another study, PERISCOPE (Pioglitazone Effects on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation), is investigating the effect of pioglitazone in reduction of in-stent restenosis in diabetic patients who have undergone coronary angioplasty.

Adverse effects of thiazolidinediones

The weight gain associated with the use of thiazolidinediones is one of their main side effects and is probably due to several interacting factors. One of these is the increase in subcutaneous adipose tissue and the concomitant decrease in visceral fat, which alters the distribution of adipose tissue.[82,83] Fluid retention and the induced increase in plasma volume are another potential cause of increased body weight. In healthy volunteers who received rosiglitazone (8 mg once daily) for 8 weeks, there was a small but statistically significant increase in plasma volume of about 1.8 ml/kg.[7] This increase in body water may result from the synergistic interaction between thiazolidinediones and insulin, which causes arterial vasodilation leading to sodium reabsorption and reduction of glucosuria in the kidney, and from other factors, such as increased sympathetic nervous system activity.[84] The incidence of weight gain is greater when thiazolidinediones are used in combination with insulin and lower when it is coadministered with metformin, sulfonylurea, or used as monotherapy.[85]

Despite the increase that has been noticed in left ventricular mass due to volume expansion in animals given long-term troglitazone,[86] no similar effects of thiazolidinediones in clinical trials in humans have been reported so far.[87,88] Regarding the effect of thiazolidinediones in myocardial ischaemia, animal studies have been performed with both rosiglitazone and pioglitazone. These experimental studies have shown that the administration of thiazolidinediones prior to the induction of ischaemia is associated with more rapid recovery of left ventricular function compared with control animals.[89,90] These effects of thiazolidinediones seem to be independent of glucose lowering and may be related to their antioxidant and anti-inflammatory properties.

It should be noted that cases of congestive heart failure manifested as acute pulmonary oedema or peripheral oedema have been reported in humans after the administration of thiazolidinediones.[91,92] In a trial involving 111 diabetic patients with congestive heart failure who were receiving thiazolidinediones, 19 of them (17%) manifested peripheral oedema, which was eliminated when the drugs were withdrawn.[93] Nevertheless, the incidence of congestive heart failure has been low in clinical trials. However, in clinical practice

there have been reported cases of congestive heart failure, specifically when thiazolidinediones were coadministered with insulin.[83] Thus, it should be kept in mind that thiazolidinediones should not be used in diabetic patients with symptoms and signs of New York Heart Association class III or IV congestive heart failure.

Conclusion

In summary, it is evident that thiazolidinediones have pleiotropic effects, as they reduce hyperglycaemia in type 2 diabetic patients and on the other hand improve endothelial function, reduce hyperlipidaemia and inhibit the atheromatosis process. However, despite their clear insulin sensitising effect, there are still many unanswered questions about the role of thiazolidinediones in the reduction of stent restenosis and about their potential beneficial effects in non-diabetic patients with metabolic syndrome. Clearly, more trials are needed to determine whether these agents are able to fulfil this potential. Moreover, the safety of thiazolidinediones and their side effects, especially in diabetic patients suffering from congestive heart failure, should be more thoroughly investigated.

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