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Abstract

The thiazolidinediones (TZDs) rosiglitazone (ROS) and pioglitazone (PIO) are insulin-sensitising agents widely used to treat patients with type 2 diabetes mellitus (T2DM). Thiazolidinediones significantly improve glycaemic control in diabetics by reduced fasting glucose, insulin and glycated haemoglobin and they delay the progression of insulin resistance/impaired glucose tolerance into T2DM. It is well recognized that adequate glycaemic control and subsequent amelioration of hyperinsulinaemia and hyperglycaemia can delay the onset of vascular complications. TZDs, however, also have a number of anti-atherogenic effects independent of their influences on glucose and insulin metabolism. They improve lipid profiles, lower blood pressure, have anti-inflammatory properties, improve endothelial function and increase large artery compliance in patients with type 2 diabetes mellitus. When compared to rosiglitazone, pioglitazone has more favourable effects on the lipid profiles of patients with T2DM. The disease preventive actions of TZDs may be the result of their agonistic effects on peroxisome proliferator-activated receptors (PPARs), ligand-activated transcription factors that regulate the expression of numerous genes and affect metabolism and vascular parameters.

Thiazolidinediones, provide an effective treatment for populations with insulin resistance which is at high risk of developing cardiovascular disease. This paper discusses the differences between ROS and PIO and explores their anti-atherogenic effects with particular focus on post-menopausal women with type 2 diabetes mellitus.

Introduction

Diabetes Mellitus is a metabolic disorder characterised by increased blood glucose levels and premature development of micro and macrovascular disease. In Type 2 diabetes (T2DM) cardiovascular disease (CVD) is the most significant cause of decreased quality of life and increased mortality and morbidity. Approximately 80 per cent of all deaths in patients with T2DM are due to cardiovascular disease [1]. Patients with T2DM have a two to four-fold increased risk of both coronary heart disease and stroke compared with those without diabetes. T2DM is also associated with hyperinsulinaemia, insulin resistance and other metabolic abnormalities, including hypertension, obesity and dyslipidaemia. Insulin resistance is an important component of the metabolic syndrome, which includes a cluster of factors such as obesity, hypertension and dyslipidaemia and which contributes to the increased incidence of cardiovascular risk [2]. It is postulated that insulin resistance and hyperinsulinaemia are independent risk factors for coronary artery disease, with a level of increased risk similar to that of hyperlipidaemia [3].

Increasing body weight, age and menopause are the main catalysts for alterations in glucose and insulin metabolism, which, if left untreated, may lead to the development of insulin resistance or T2DM. Decreased oestrogen levels are associated with increased circulating glucose concentrations, reduced insulin responses to glucose and hyperinsulinaemia [4], possibly via alterations in insulin receptor concentrations. Reduced participation in physical activity, increased

adiposity and altered fat distribution, which occur at the time of menopause, may well be important factors that compound the effects of reduced oestrogen levels on altered glucose and insulin metabolism.

Diabetes and oestrogen deficiency at the time of menopause, are associated with increased stiffness of large arteries, which may contribute to the pathogenesis of CVD and subsequent morbidity and mortality in women. Post-menopausal women experience a sharp increase in the rate of cardiovascular disease [5], although whether this is independently related to menopause itself remains controversial.

Diabetes, aging and oestrogen reduction are associated with impaired endothelial function and altered arterial mechanical properties. Endothelial dysfunction plays an important role in the pathogenesis of vascular disease [6]. Similarly, arterial stiffening is associated with systolic hypertension [7], reduced coronary perfusion [8] and coronary artery disease [9]. Alterations in vascular structure and function are a feature of the micro– and macrovascular complications of diabetes. Assessment of the effects of drugs on the biological properties of vascular tissue has proved useful for identifying effective strategies for cardiovascular risk reduction.

This article will review some of the evidence regarding the biological and antiatherogenic effects of TZD. In view of the importance of the increased risk of

CVD after menopause particular reference will be made to post-menopausal women with type 2 diabetes mellitus.

Thiazolidinediones

Thiazolidinediones (often referred to colloquially as 'glitazones') are oral antidiabetic agents widely used to treat patients with T2DM that act primarily as insulin sensitizers, improving glucose control and decreasing insulin resistance. Rosiglitazone and pioglitazone are two compounds in this class of insulin sensitizing drugs presently approved for use in many countries as monotherapy or in combination with metformin, sulfonylureas or insulin. It is well established that they enhance peripheral glucose uptake and improve insulin sensitivity in patients with T2DM [10] and prevent progression to T2DM in patients with impaired glucose tolerance and insulin resistance [11].

Thiazolidinediones have a major effect on adipose tissue and skeletal muscle and are also active in liver [12]. They are more effective in increasing insulin sensitivity than the biguanide metformin [13], which acts primarily on the liver and to a lesser extent on the skeletal muscle by a still unknown mechanism [14].

Thiazolidinediones exhibit a number of potential anti-atherogenic actions in Type 2 diabetic patients, including: improvement in lipoprotein profiles via the reduction of oxidized LDL [15], circulating triglyceride levels [16,17], improvements in vascular reactivity via suppression of endothelin-1 levels and inhibition of extracellular

calcium uptake by vascular smooth muscle cells (VSMC), apparently through inhibition of L-type calcium channels [18]. TZD also inhibit vascular smooth muscle cell proliferation and migration [19]. They have also been shown to improve endothelial function, reduce inflammation and decrease plasma FFA and blood pressure [10, 20, 21].

Further details regarding the history of this class of medication, their chemical structure and their relationship to other antidiabetic agents can be found in recent reviews by Yki Jarvinen [22] and Natali and Ferrannini [23].

Modes of Action of Thiazolidinediones

Thiazolidinediones act on adipose tissue to decrease plasma free fatty acids (FFAs) and secretion of tumour necrosis factor-α (TNF- α) and resistin, often increased with obesity and diabetes, therefore improving insulin action in muscle, adipose tissue and liver. They are believed to increase insulin sensitivity by activating highly selective and potent nuclear receptors, the peroxisome proliferator-activated receptor-gamma (PPARγ), thereby directly regulating gene expression as a result of which peripheral glucose uptake is increased and hepatic glucose production is diminished [24]. The PPARs are a family of nuclear receptors comprised of three different subtypes, α, β and γ. PPARs receptors are found in target tissues for insulin action such as skeletal muscle, adipose tissue, and liver and it appears that they are important regulators for insulin action, lipid homeostasis and adipocyte differentiation. Once activated, the receptors alter

transcription of numerous target genes by interacting with specific DNA response elements located upstream of responsive genes (Fig 1).

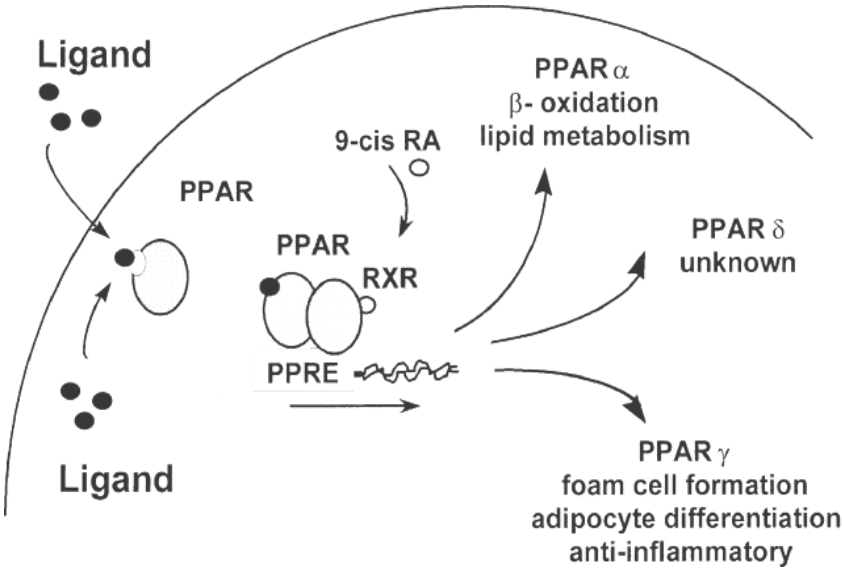

Fig 1. Activation of the PPAR receptors leading to the transcription of the responsive gene. *(From: David Bishop-Bailey, Br J Pharmacol 2000, 129:823-834)*

Legend: PPAR= peroxisome proliferator-activated receptor, RA= retinoic acid**,** PPRE= peroxisome proliferators response element**,** RXR=retenoid X receptor

PPARγ regulation of gene expression occurs primarily in adipose tissue where, among other things, under anaerobic conditions it promotes lipogenesis [21]. The effects of PPARγ activation on glucose, lipid and insulin metabolism provide therapeutic potential for exogenous ligands of this receptor to reduce altered glucose and insulin metabolism and redress the metabolic abnormalities of T2DM

[15]. Further discussion regarding differential action of TZDs on PPAR can be found in Yki-Jarvinen's review paper [22[.

Anti-atherogenic Actions of Thiazolidinediones: Effects on Glycaemic Control and Cardiovascular Markers

The ability of thiazolidinediones to enhance peripheral glucose uptake and improve insulin sensitivity have been demonstrated in clinical studies of patients with T2DM. When used both as monotherapy and in combination therapy their effects appear to be similar in patients with T2DM and in individuals with impaired glucose tolerance and insulin resistance. Prospective and retrospective studies have shown that both ROS and PIO improve blood glucose and glycosylated haemoglobin levels (HbA1c) [24-26] and lead to similar degrees of weight gain [27, 28]. In addition to improving glycaemic control TZDs are associated with favourable effects on other cardiovascular risk parameters such as blood pressure, fibrinogen, cell wall inflammatory markers [20] and beta cell function [29].

Other properties of thiazolidinediones that may contribute to their blood pressure lowering actions include inhibitory effects on vascular smooth muscle cell (VSMC) migration and proliferation, mentioned above. In this manner, thiazolidinediones appear to inhibit a key step in the development of atherosclerotic plaque, which typically involves VSMC migration from media to intima [30, 31], proliferation of VSMCs and subsequent increased production of extracellular matrix proteins [32].

VSMC migration and proliferation are thought to represent essential processes in the development of vascular remodelling, atherosclerosis and diabetic organ complications (Fig 2). It is noted that the evidence for apparently beneficial effects of TZD on these processes derives from in vitro and animal studies and that their clinical implications for humans remain to be fully elucidated.

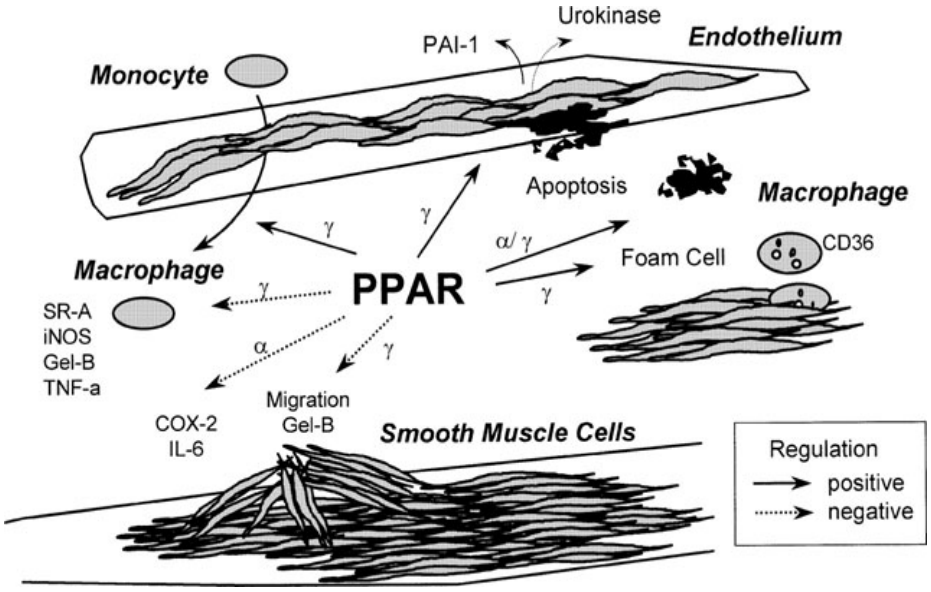

Fig2. PPAR regulate vascular and inflammatory cell functions. (From: *David Bishop-Bailey, Br J Pharmacol 2000, 129: 823-834)*

Legend: *COX2=*cyclo-oxygenase expression, *TNF-α=*tumour necrotic factor- α, *CD36=*OxLDL scavenger receptor **,** *Gel-B=*gelatinase-B**,** PAI-1= plasminogen activator inhibitor-1**,** IL-6= interlukin-6

Effects on Lipid Metabolism

Dyslipidaemia associated with diabetes is often associated with an increase in triglyceride levels, a decrease in HDL-C levels and mild elevation of LDL-C levels, while insulin resistance with or without hyperglycaemia is associated with qualitative changes in LDL cholesterol levels, which in turn are associated with a greater risk of cardiovascular disease and atherosclerosis [14]. There is also extensive evidence of deterioration in lipid profiles after menopause [5]. Both comparative and non-comparative studies of TZDs suggest that PIO and ROS have significantly different effects on plasma lipids independent of glycaemic control and other antihyperglycaemic therapy [26, 28].. Even in the absence of obvious hyperglycaemia, insulin resistance is associated with dyslipidaemia. Although plasma levels of LDL-C in patients with Type 2 diabetes might not differ greatly from those in non-diabetic patients, LDL-C particle sizes and concentrations differ. T2DM patients have smaller, dense particles rich in LDL-cholesterol which make the cholesterol more susceptible to oxidation and in turn may stimulate the inflammatory changes which promote atherosclerosis [15]. It is hypothesized that changes in the composition of LDL-C particles are associated with greater risk for atherosclerosis and cardiovascular complications and that the increased triglyceride levels in T2DM patients are partially responsible for the atherogenic changes in LDL-C profile [15].

Both ROS and PIO appear to substantially increase HDL cholesterol [22]. Overall, however, pioglitazone has been shown to have a more favourable effect on lipid

profiles in patients with T2DM, by also significantly reducing serum triglycerides, total cholesterol and LDL-C [16-17, 22, 26-27], Furthermore, pioglitazone improves LDL-C particle concentration and size, converting small, dense LDL-C particles into larger, less atherogenic lipoprotein particles [15]. These differences between the effects of ROS and PIO on lipids appear to be due to the different modes of action on PPAR receptors PIO seems to act like a partial PPAR(α) agonist in vivo, while ROS seems to act like a pure PPAR(γ) agonist [33]. Increases in LDL-C have been noted with rosiglitazone [22], but not with PIO. The cause of this difference is unknown. Despite the fact that the two TZDs belong to the same broad pharmaceutical class, as the differences in the responses of lipid profiles show, they act through slightly different mechanisms, with different affinities for specific subtypes of the peroxisome proliferator-activated receptors (PPARs). It is thought that rosiglitazone interacts exclusively with PPARγ receptor, providing its insulin-sensitizing effects, while pioglitazone may activate both PPARα and PPARγ. The PPARα activation by pioglitazone may explain its different effect on TG levels [26].

The hypertriglyceridaemia, hyperglycaemia and hyperinsulinaemia seen in patients with T2DM have been associated with increased levels of plasminogen activator inhibitor factor-1 (PAI-1), known to increase the predisposition towards coronary artery thrombosis. Reductions in PAI-1 have been noted in patients taking TZDs [34].

Although the evidence is suggestive, whether the differences in lipid profiles between the two TZDs lead to different cardiovascular outcomes remains uncertain. It is expected that clinical trials currently underway will provide further information about this important clinical issue.

Effects on Endothelial Function

Vascular endothelial cells play an important role in maintaining cardiovascular homeostasis in healthy individuals. In addition to providing a physical lining to the blood vessels, endothelial cells secrete various factors that influence vessel tone, platelet function, coagulation and fibrinolysis [35]. These include vasoconstrictive substances, such as thromboxane A_2, endothelin-1, and vasodilating substances, such as prostaglandins (PGI_2) and nitric oxide (NO). NO is a key factor in controlling vascular tone in large coronary and systemic arteries. Individuals with increased cardiovascular risk often have abnormalities of endothelial function, well before the onset of clinically symptomatic cardiovascular disease [19]. PGI_2 and NO also inhibit platelet aggregation and reduced levels of these substances are often found in patients at high risk of atherosclerotic disease.

In addition, insulin resistance is associated with increased cell adhesion and VSMC proliferation, which may contribute to increased cardiovascular risk. There is evidence to support the hypothesis that glucose has the ability to scavenge NO, thus contributing to endothelial dysfunction [36] and hyperglycaemia is recognised as an independent risk factor for the development of CVD [37]. Accumulation and

oxidation of plasma LDL-C in endothelial spaces in T2DM patients leads to the activation of endothelial cells and the synthesis of chemotactic molecules in the sub-endothelial space [19]. Long-term hyperglycaemia results in the accumulation of advanced glycation end products on collagen fibres, affecting arterial mechanical properties and reducing arterial elasticity [38].

Impaired endothelial function also plays an important role in the development of hypertension [39]. A number of mechanisms for endothelial dysfunction have been demonstrated in various vascular beds of animal models and in humans with diabetes. These include reduced substrate availability [40], impaired signal transduction pathways [41], attenuated release, and increased destruction of endothelial derived relaxation factors (EDRF) [42], increased release of endothelial derived constricting factors [43], and a reduced sensitivity of vascular smooth muscle cells to EDRF [44]. It is well established that the hormonal changes associated with menopause also lead to development of endothelial dysfunction [6-9].

Thiazolidinediones have been shown to improve endothelial function [10, 22, 45-46]. Enhanced glycaemic control itself is likely to be an important contributing factor, but TZD treatment leads to stabilisation of endothelial cells [47], and in addition, results in direct anti-inflammatory actions on endothelial cells, probably mediated via PPARγ receptors [48]. Experiments in bovine endothelial cells in culture have shown inhibition of vasoconstriction due to endothelin-1, as a result of

diminished endothelin 1 mRNA expression and secretion [49],

Thiazolidinediones have been shown to influence endothelium-dependent and endothelium-independent vascular tone in potentially beneficial ways. They inhibit extracellular calcium uptake by VSMC by blocking L-type calcium channels [18]. These actions may also contribute to the demonstrated effect of TZDs of reducing blood pressure and retarding the development of hypertension in T2D [50]. Inhibitory effects on vascular smooth muscle cell proliferation and migration, previously mentioned, may also add to this antihypertensive effect [51].

Troglitazone, an older TZD, now withdrawn from sale because of hepatic toxicity, has also been shown to up-regulate cytokine-stimulated nitric oxide synthesis in VSMCs [52], an action which may inhibit the effects of numerous growth factors on VSMCs. Data concerning similar actions of ROS and PIO in clinical settings are lacking; if, however, these two drugs work in similar ways it this would have important implications for the possible prevention of the development and progression of atherosclerosis.

In summary, TZDs appear to act in a manner that is potentially favourable with respect to cardiovascular risk through a number of separate pathways. Of crucial importance, however, is whether these actions translate into clinical endpoints, including a reduction in cardiovascular events or mortality from cardiovascular causes. These agents are not problem-free and the long term implications of

adverse effects associated with them - such as weight gain, peripheral and pulmonary oedema [53] and congestive heart failure [54] - remain to be clarified. (These issues are further discussed in the section 'Adverse Effects of Thiazolidinediones' below).

Studies with sufficient power to test long term clinical outcomes, such as impact on mortality, cardiovascular events and other clinical indices of progression of complications of diabetes, are clearly needed. Such studies will contribute to resolving the uncertainty about the role of these medications with respect to reducing cardiovascular risk in everyday clinical practice. .

Cell and Vascular Biology

Expression of PPARγ, initially thought to be restricted to adipose tissue and effects on lipid and carbohydrate metabolism, is now known to be highly expressed in all major cell types participating in vascular injury, including endothelial cells, macrophages, inflammation and vascular smooth muscle cells (VSMS). As already mentioned, TZDs inhibit inflammation and vascular smooth cell proliferation by decreasing inflammatory cytokine expression, inhibiting endothelial expression of adhesion molecules, normalising cell growth, inhibiting migration of VSMCs, decreasing hypertension and improving endothelial dysfunction [55]. Other anti-inflammatory actions may result from the effects of TZD in decreasing various pro-inflammatory chemokines, such as C-reactive protein, MMP9, PAI-1 and sCD40 in obese and T2DM patients [56], TNF-α, IL-6, and IL-8 in synoviocyte in rheumatoid arthritis patients [56]. Reduction in circulating mononuclear cells,

nuclear NF-kB content and increase in the same cells the expression of IkB, an NK-kB inhibitor have also been shown . Pioglitazone reduces mRNA levels of MCP-1 and intercellular adhesion molecule-1 as well as the number of infiltrating macrophages in ischaemic cardiac tissue in a rat [57] experimental model. These effects suggest that the anti-inflammatory effects of TZDs are likely, at least to some extent, to be independent of their insulin sensitising effects [57].

Angiotensin (Ang) II plays a major role in hypertension, vascular remodelling and insulin resistance. Ang II–induced hypertensive rats exhibit abnormal vascular structure. Rosiglitazone treatment in Ang II–infused rats differentially modulates PI3K and MAPK signalling in a conduit vessel, aorta, and in mesenteric vessels [58]. Rosiglitazone reverses negative changes in the aorta of an Ang II infused rat, including Ang II induced elevated blood pressure and intracellular signalling in aorta and mesenteric vessels [59].

Renal Effects

Thiazolidinediones have been shown to have protective effects on the kidney. The antiproteinuric effects of the TZDs have been demonstrated in genetically obese diabetic rodents [60] and patients with type 2 diabetes and diabetic nephropathy [61-62].. In animal models ROS treatment improved renal function and histopathology, decreasing pro-inflammatory and pro-fibrotic molecules such as AngII, OPN and TGF-beta1 and apoptotic cell death [60,63], while in diabetic

patients with hypertension and patients with diabetic nephropathy, TZDs have been shown to have hemodynamic and antihypertensive effects suggesting that the favourable renal effect of PPARγ ligants is probably due to the improved glucose metabolism and insulin resistance [64] and might be independent of their capacity to improve glucose tolerance [65]. In addition, results showing the efficacy of PPAR-gamma agonists to ameliorate the progression of glomerulosclerosis [60, 65] suggest that TZDs may provide a novel intervention strategy to prevent vascular and glomerular sclerosis.

Rosiglitazone in Postmenopausal Diabetic Women

We have recently demonstrated the effectiveness of rosiglitazone in improving vascular function in postmenopausal women with T2DM. We examined the effects of rosiglitazone 4mg/day for 12 weeks on glycaemic control, blood pressure and compliance of large proximal arteries, as measured by distensibility index (DI). Distensibility index is an accessible and reproducible measure of arterial elasticity which provides an estimate of the underlying mechanical properties of large arteries independent of vessel size [66]. This property may be a modifiable target for treatments aiming to reduce cardiovascular disease risk factors associated with diabetes and menopause. We found that rosiglitazone improved glycaemic control, reduced blood pressure and increased compliance of large proximal arteries. The changes induced in the last two variables appeared to be independent of the improvements in blood glucose levels [45]. We concluded that that these actions of rosiglitazone offer important therapeutic potential for the improvement of endothelium dependent and independent function, blood pressure and arterial

compliance and maybe reduction of the risk of cardiovascular disease in postmenopausal women with type 2 diabetes.

Adverse Effects of Thiazolidinediones

As mentioned, the original member of the TZD class troglitazone was withdrawn from use as a result of its association in rare cases with serious liver injury. Furthermore, troglitazone failed to increase insulin sensitivity in nondiabetic Hispanic women with previous gestational diabetes treated in the Troglitazone in Prevention of Diabetes (TRIPOD) study [67]. Although some case reports of liver injury inconclusively attributed to ROS and PIO have been reported in the literature over the years [68] it is now widely agreed that serious adverse hepatic events with ROS and PIO are extremely rare, if they occur at all [69]. Nevertheless, in view of the previous experience it is accepted that all TZDs should be avoided in patients with liver disease and that regular monitoring should be undertaken of liver function tests during the first year of use.

The most common adverse effects associated with thiazolidinedione therapy are oedema and weight gain. Both ROS and PIO have been associated with fluid retention and peripheral oedema [20, 53, 54], while severe pulmonary oedema has been reported to occur more frequently with rosiglitazone use [70,-72], especially in elderly patients with congestive heart failure [53, 71] and when combined with insulin therapy [73, 74]. To date, the mechanisms underlying these effects have

not been fully clarified, although it appears likely that several pathways of action are involved [75]. Although spontaneous resolution of oedema has been reported with discontinuation of the thiazolidinediones, their use should be avoided in patients with congestive heart failure (CHF) or chronic renal insufficiency. TZDs have also been associated with increased weight gain in some patients [10, 20, 28] independently of fluid retention, reflecting increased body fat, although intra-abdominal fat mass may actually decrease with redistribution to subcutaneous tissues [76]. In addition, these agents have been reported to cause anaemia in some patients [10], possibly due to haemodilution related to fluid retention.

It is noted that recent results from the PROactive study [54] have shown that pioglitazone significantly reduces the composite of all-cause mortality, non-fatal myocardial infarction and stroke in patients with T2DM who are at high risk of macrovascular events. It showed that PIO is beneficial in patients with T2DM and pre-existing macrovascular disease who do not develop heart failure. Nonetheless, concern about the possible role of TZDs in worsening congestive heart failure has been expressed. Several case reports of acute congestive heart failure have been documented [54, 71, 74]. Accordingly, ROS and PIO should not be used in patients with acute heart failure [53, 74] and should be discontinued if heart failure develops.

New agents may present a more favourable spectrum of action. However, the new α/γ TZD, muroglitazar, despite producing greater improvements in glycemic control

and lipid profiles [77], has been associated with increased mortality, due either to cardiovascular or to cerebrovascular events [78], as a result of which the approval of this agent by the U.S. Food and Drug Administration has been deferred until the results from large clinical trials on the prognosis of heart failure become available. At this time, therefore, the use of ROS and PIO in patients with heart disease should be undertaken with caution and patients should be advised that there is evidence that such medications may lead to the development or exacerbation of CHF.

Conclusions

TZDs are important insulin-sensitizing agents for improving glucose control and reducing insulin resistance. In addition, they improve many other cardiovascular risk factors that frequently occur in patients with T2DM, such as endothelium dependent and independent dysfunction, hypertension, and arterial stiffness. The cardiovascular effects on TZDs are summarized in Table 1.

Despite their effectiveness, ROS and PIO are still widely employed as second line agents in the treatment of Type 2 diabetes, after metformin and sulphonylureas, medications that have been associated over many years with reduction in cardiovascular risk. Results from further large clinical studies are needed to confirm the use of TZDs in prevention of T2DM and cardiovascular disease and to clarify their long-term impact in diabetic patients.

	Lipids	**Glycemic control**	**Endothelial function**	**Inflammatory markers**	**Oedema**	**Renal function**	**Weight Gain**	**Arterial Stiffness**
ROS	LHL↓ HDL ↑ TG ↓	Improved	↑	↓	↑	Improved	↑↓	↓
PIO	LDL↓↓ HDL ↑ TG ↓	Improved	↑	↓	↑	Improved	↑↓	↓
MUR	LDL↓ HDL ↑ TG ↓	Improved	N/A	N/A	↑	N/A	↑↓	N/A

Table 1. Cardiovascular effects of TZDs

Legend: ↑= Increased, ↓=Decreased,↔ =No change,↑↓ =Increased/Decreased, N/A= Not applicable

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