REVIEW ARTICLE

Drugs 2003; 63 (13): 1373-1405
0012-6667/03/0013-1373/$33.00/0

Thiazolidinediones in Type 2 Diabetes Mellitus

Current Clinical Evidence

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Abstract

Type 2 diabetes mellitus is characterised by insulin resistance as well as progressive pancreatic β cell dysfunction. The cornerstone of current oral blood-glucose lowering therapy consists of metformin, which primarily lowers hepatic glucose production, and the sulphonylureas that act by stimulating pancreatic β-cells to secrete insulin. Recently, a novel class of agents, the thiazolidinedi-

ones, has been introduced that favourably influence insulin sensitivity and possibly also pancreatic β-cell function. The thiazolidinediones are synthetic ligands that bind to the nuclear peroxisome proliferator-activated receptor-γ and exert their action by activating transcription of genes that, among others, regulate adipocyte differentiation and adipogenesis as well as glucose and lipid metabolism. To date, the precise mechanisms underlying the actions of thiazolidinediones are largely unknown. When given as monotherapy or in combination with sulphonylureas, metformin or insulin in patients with type 2 diabetes, the currently available thiazolidinediones (rosiglitazone and pioglitazone) ameliorate glycaemic control, by lowering fasting and postprandial blood glucose levels, and improve insulin sensitivity in placebo-controlled trials. They seem to have differential effects on dyslipidaemia in patients with type 2 diabetes; rosiglitazone increases total cholesterol as well as high-density lipoprotein (HDL) and low-density lipoprotein cholesterol levels and affects plasma triglyceride levels depending on the baseline values, whereas pioglitazone lowers triglycerides and increases HDL cholesterol levels. The adverse events of both agents that occur with greater frequency than in patients treated with placebo are fluid retention and oedema.

As demonstrated, mainly in preclinical studies to date, rosiglitazone and pioglitazone possess beneficial effects on other cardiovascular risk factors associated with the insulin resistance syndrome. Thus, these agents were shown to decrease blood pressure, enhance myocardial function and fibrinolysis, as well as possess anti-inflammatory and other beneficial vascular effects. Long-term efficacy and surveillance of this promising class of drugs in patients, however, still need to be demonstrated in outcome trials.

Worldwide, type 2 diabetes mellitus is a rapidly expanding health problem.[1] In 2025, the number of people with diabetes is expected to rise up to 300 million and more than 90% of these patients will have type 2 diabetes.[2] Type 2 diabetes mellitus is characterised by insulin resistance, that is, reduced insulin action at the level of the liver, adipose tissue and skeletal muscle as well as a progressive β-cell defect.[3-5] It has been proposed that the reduced action of insulin is fundamental to the cardiovascular risk factors that are part of the insulin resistance syndrome.[6] The exact determinants of both insulin resistance and β-cell failure still remain to be established; however, there seems to be an interplay between polygenetic susceptibility and environmental factors.[5,7,8] Obesity, in particular central or visceral fat accumulation, and lack of physical activity, are invariably linked to insulin resistance and type 2 diabetes mellitus.[9,10]

Current non-pharmacological strategies to improve insulin sensitivity include low energy and fat intake, weight reduction and increased physical activity.[11,12] Metformin, aside from lowering hepatic glucose production, was the only drug able to sensitise target tissues to insulin[13,14] before the introduction of troglitazone in 1997, the first drug of the thiazolidinediones or glitazones which was applied in clinical studies.[15-23] Thiazolidinediones activate nuclear peroxisome proliferator-activated receptor (PPAR)γ, which is expressed predominantly in adipose tissue and regulates the transcription of genes involved in adipocyte differentiation, and glucose and lipid metabolism.[24-28]

Thiazolidinediones lower blood glucose and insulin levels, and may preserve or even improve β-cell function.[25,26,29,30] Although the exact mechanism of action of thiazolidinediones still remains to be elucidated, the improvement in insulin sensitivity is, at least in part, attributed to a reduction in the

levels of circulating free fatty acids. Troglitazone has been withdrawn from the market in the US, UK and Europe because of hepatotoxicity.[31,32] Two new representatives of the thiazolidinediones class, rosiglitazone and pioglitazone, have been available in the US since 1999 and in Europe since 2000, for clinical use in patients with type 2 diabetes.[33,34] Despite the extensive use of rosiglitazone and pioglitazone, so far, the untoward effects on liver function documented in the literature are limited to three case reports for each agent.[35-40] However, recent meta-analyses of trials using rosiglitazone[41] and pioglitazone[42] found no evidence for a causal relationship between the use of these thiazolidinediones and hepatic dysfunction.

The major determinant of progression from insulin resistance to hyperglycaemia is β-cell dysfunction. The loss of early-phase insulin secretion, in the presence of insulin resistance, leads to impaired glucose tolerance.[43,44] These abnormalities contribute to postprandial and late hyperglycaemia, both of which lead to marked delay in inhibition of hepatic glucose production.[45-47] Post-challenge hyperglycaemia has been associated with cardiovascular mortality;[48-50] however, it may rather be a marker of the underlying metabolic derangements, clustered within the insulin resistance syndrome.[51] In as much as treatment of these abnormalities will reduce the cardiovascular risk of patients with type 2 diabetes, therapeutic strategies aimed at preserving pancreatic β-cell function may be an additional important treatment target.

Of the currently available oral antihyperglycaemic agents, only sulphonylureas and the recently introduced meglitinides act by stimulating insulin secretion.[52] Although the former agents, with or without the addition of metformin, are the cornerstone of current oral blood-glucose lowering therapy, they, as a result of enhancing late insulin secretion, are known to frequently induce hypoglycaemia.[53,54] The thiazolidinediones do not directly stimulate insulin secretion, however, recent studies suggest that they may influence pancreatic β-cell function.[29,55,56] Although the mechanisms underlying these effects are not entirely clarified, it seems they may be mediated indirectly by a decrease in insulin resistance, by reduction in free fatty acids or by a direct effect on β cells.[29,57]

This review summarises the currently available evidence of the clinical efficacy of thiazolidinediones, which may not only pertain to interference with insulin resistance but also to the associated cardiovascular risk. Clinical studies with rosiglitazone and pioglitazone only are described since troglitazone is no longer available in the US, UK and Europe. For clinical data on troglitazone the reader is referred to the original publications and reviews.[17-23,43] Compounds belonging to a new class of dual PPARα and PPARγ agonists, (intended to restore insulin sensitivity and improve dyslipidaemia) as well as the so-called selective PPARγ modulators, which, like the selective estrogen-receptor modulators, may possess different tissue-specific agonist and antagonist properties depending on the context of the target genes and cellular environment, are currently being investigated in phase II and III studies and these will be not discussed in this review.[26]

1. Thiazolidinediones: Basic Aspects and Mode of Action

Thiazolidinediones lower plasma glucose, insulin, triglyceride and fatty acid levels in various animal models of insulin resistance and type 2 diabetes, and in humans with these conditions.[25,26] Also, thiazolidinedione effects on inflammatory processes, vascular injury and carcinogenesis have been reported.[58-60] These agents seem to exert their effects, at least to a great extent, by activation of the PPARγ receptor. Their clinical potency correlates closely with their ability to bind to the PPARγ receptor. Rosiglitazone has a 100–200-fold and pioglitazone a 10–15-fold higher binding affinity for the PPARγ than troglitazone.[33] However, at present, it is not clear how this difference in binding affinity translates into quantitative and qualitative differences in clinical response.

The PPARs constitute a distinct subfamily of the superfamily of nuclear hormone receptors.[24,27,61] At present, three distinct PPARs have been identified,

that is, PPARα, PPARδ (also called PPARβ, NUC-1 or FAAR) and PPARγ, which differ with regard to tissue distribution, ligand binding and metabolic regulation.[61] PPARα is mainly expressed in brown adipose tissue and liver, then in kidney, heart and skeletal muscle. PPARδ has a wide distribution but is most abundant in the gut, kidney and heart.[61] PPARγ is mainly expressed in adipose tissue, to a lesser extent in the enteric system, the immune system and the retina. In contrast to mice, in whom only two PPARγ isoforms have been described so far, three PPARγ mRNA isoforms have been identified in humans, PPARγ-1, PPARγ-2 and PPARγ-3. The predominant PPARγ-1 is expressed in a great variety of tissues, whereas the less abundant PPARγ-2 is mainly expressed in adipose tissue.[27,61] The expression of PPARγ-3 is restricted to macrophages and the large intestine.[27]

PPARs can be activated by naturally occurring fatty acids or fatty acid derivatives. They heterodimerise with the retinoid X receptor and regulate the transcription of numerous target genes through binding to specific PPAR response elements in the promoter region of these genes. PPARs are ligand-dependent transcription factors, that is, activation of target gene transcription depends on the binding of a ligand to either PPAR or retinoid X receptor moiety of the heterodimer, while simultaneous binding of ligands to both PPAR and retinoid X receptor is more effective. The three isotypes share some ligands, such as unsaturated fatty acids and probably oxidised fatty acids. PPARα binds various compounds with high affinity, including long-chain unsaturated fatty acids such as linoleic acid, branched conjugated fatty acids such as phytanic acid and conjugated linolenic acid, and eicosanoids such as 8S-HETE and leukotriene B_4. The natural ligand for PPARγ is 15-deoxy-D-prostaglandin J_2.[61] Synthetic agents binding to PPARα include the fibric acid derivatives.

1.1 Metabolic Effects

Stimulation of PPARγ increases peripheral insulin sensitivity as well as adipogenesis and several mechanisms have been proposed to underlie these seemingly paradoxical effects. Adipose tissue is the major site of action for thiazolidinediones, but effects on skeletal muscle and the liver, both of which predominantly determine insulin sensitivity, have also been shown (see below in this section).

Firstly, activation of PPARγ induces differentiation of preadipocytes to small, insulin sensitive adipocytes.[62] Recently, increased expression of the glucose transporter GLUT4 in these adipocytes has been demonstrated.[63] Also, PPARγ-mediated adipogenesis seems to predominantly take place in preadipocytes in subcutaneous fat stores,[64] not in visceral fat, resulting in a metabolically more favourable redistribution of adipose tissue from visceral to subcutaneous stores. Visceral adipocytes have higher lipolytic activity, which, because of their anatomical location, increases the fatty acid flux via the portal vein and subsequently the substrate supply for hepatic gluconeogenesis.[9]

Secondly, activation of PPARγ in adipose tissue results in transcription of genes that are directly implicated in lipogenic pathways, including lipoprotein lipase, adipocyte fatty acid binding protein (A-FABP or aP2), acyl-CoA synthase and fatty acid transport protein.[24,25,29,61] Enhanced fatty acid uptake and storage decreases circulating levels of free fatty acids, which not only reduces peripheral insulin resistance but also the fatty acid flux to the liver.[4,8,29] Thus, thiazolidinediones induce a 'fatty acid steal' effect by redirecting lipids from non-adipose to adipose tissue.[26,65] Indeed, reversal of hepatic steatosis[66] and intracellular triglyceride accumulation in skeletal[67] and cardiac muscle[68] and also in pancreatic β cells[69] after thiazolidinedione treatment has been reported in rats. In view of these characteristics, thiazolidinediones may be an important therapeutic option to reduce lipotoxicity which occurs in obesity-related disorders, including type 2 diabetes, as a result of accumulation of fatty acids in non-adipose tissues.[70] Lipotoxicity is attributed to the damaging effect of products resulting from the non-oxidative metabolism of the excess fatty acids.

Thirdly, PPARγ activators affect the release of adipocyte-derived signals regulating insulin sensitivity, including tumour necrosis factor (TNF)α,[71]

adiponectin[72] or free fatty acids, as such. Although one may expect that the secretion of numerous adipocytokines would be proportional to the thiazolidinedione-induced increase in body fat stores, PPARγ activators both stimulate and inhibit the production of adipocyte secretory products. Alternatively, thiazolidinediones may operate through adipose-tissue independent mechanisms. Although the numerous complex regulatory pathways involved are currently not fully understood, several mechanisms have been put forward explaining this phenomenon.

Increased adipocyte TNFα production induces systemic insulin resistance by interference with the insulin signalling cascade,[73,74] and elevated levels of circulating TNFα have been demonstrated in insulin-resistant patients and obese patients with type 2 diabetes.[75,76] Thiazolidinediones reduce adipose tissue TNFα expression and block the inhibitory effects of TNFα on insulin signalling[77] as well as the TNFα-induced lipolysis.[78] Also, PPARγ-mediated inhibition of resistin, a recently discovered adipocyte-derived substance, may also contribute to the insulin-sensitising actions of PPARγ agonists.[79] In mice, resistin induces insulin resistance, but in humans its significance still remains to be determined.[80,81] Similarly, PPARγ activation increased expression and plasma levels of the adipose tissue specific plasma protein adiponectin.[72] Circulating plasma levels of this adipocytokine were decreased in obese humans, despite increased adiposity, and in insulin resistant patients with type 2 diabetes.[82,83]

Leptin, the product of the *ob* gene, is secreted by adipocytes but its membrane receptor, encoded by the *db* gene, has been found in adipocytes, muscle cells and pancreatic β cells.[84] In adipocytes, leptin not only stimulates lipolysis but also glucose utilisation, while in pancreatic β cells, leptin decreases the expression and secretion of insulin. By inhibiting the expression of leptin, thiazolidinediones can counteract these effects, and the resulting reduction of circulating free fatty acid levels and enhanced insulin secretion may contribute to the observed improvement of insulin resistance.[85,86] It seems that thiazolidinediones do not merely increase the number of adipocytes, but they interfere with adipocyte metabolic regulatory pathways and autocrine and paracrine feedback loops, resulting not only in changes in adipose tissue distribution but also in alterations in the adipocyte phenotype.

It was proposed that adipose tissue is required for glucose homeostasis in response to insulin, since lipoatrophic individuals[87] and transgenic mice engineered to lack adipose tissue (e.g. the A-ZIP/F-1 mice),[88] are extremely insulin resistant. The inability to adequately store the ingested energy results in metabolic disturbances resembling those observed in diabetes including hyperglycaemia, hyperinsulinaemia and hyperlipidaemia. In these models, it is unlikely that the observed insulin resistance is due to TNFα or leptin production and signalling since adipose tissue is absent. In contrast to these arguments, however, in another fatless transgenic mouse (the aP2/DTA mouse), treatment with thiazolidinediones was found to normalise high glucose levels, as well as insulin and lipid levels, indicating that the action of these agents also involves mechanisms that are adipocyte independent.[89] More recently, it was shown in the A-ZIP/F-1 mouse model that adipose tissue is required for the glucose-lowering and insulin-sensitising, but not for the hypolipidaemic effect of thiazolidinediones.[90]

In view of the complex interaction between adipocytes, leptin and PPARγ activation, the findings in humans, showing that both thiazolidinedione[91] and leptin replacement therapy[92] reverse insulin resistance and other metabolic abnormalities associated with lipodystrophy, seem controversial and can not be readily explained.

As stated earlier (in section 1), despite the predominant abundance of PPARγ in adipose tissues, thiazolidinedione-induced effects also seem to involve non-adipose target organs. In humans, the largest proportion of insulin-stimulated glucose disposal occurs in skeletal muscle,[3-6,8] while PPARγ receptors are present in skeletal muscle at about 10% the level of their adipose tissue expression.[93] Thiazolidinediones, in addition to decreasing intramyocellular lipid deposition,[64,66] may act directly on the small amount of PPARγ in muscle, by

inducing GLUT4,[94] as well as PPARγ expression in muscle cells.[95] Although adverse effects on liver function have ultimately lead to withdrawal of troglitazone, the thiazolidinediones may also possess potentially beneficial hepatic effects. In Zucker fatty rats, treatment with thiazolidinedione markedly and durably reduced hepatic steatosis and liver volume.[57]

Although preliminary studies in humans showed improvement in liver test results and histological findings in patients with non-alcoholic steatohepatitis treated with troglitazone,[96] and decrease of hepatic triglyceride content, as estimated by ^{1}H-nuclear magnetic resonance (^{1}H-MR) spectroscopy in type 2 diabetic patients treated with rosiglitazone for 3 months,[97] the long-term efficacy of these agents to reverse diabetic steatohepatitis in humans still remains to be demonstrated. Thiazolidinedione treatment of Zucker diabetic fatty rats prevented structural pancreatic islet cell changes[98] and lowered fat content of pancreatic islets, thus restoring β-cell function.[70]

Mutations in the PPARγ gene have been identified that are associated with adipocyte differentiation and fat storage (reviewed in Auwerx[27]). Recently, two mutations in the ligand-binding domain of PPARγ, Pro467Leu and Val290Met, were found in non-obese patients with severe insulin resistance and type 2 diabetes.[99] The Pro12Ala polymorphism of the PPAR-γ2 gene, which is most abundantly present in adipose tissue, was associated with lower body mass index (BMI) and improved insulin sensitivity in lean humans,[100] whereas other studies found no association with BMI in different populations,[101] or reported a positive association between the Ala allele and higher BMI.[102] These findings point to the importance of gene environment interactions in the determination of the phenotype.

1.2 Cardiovascular and Anti-Atherogenic Effects

In addition to the metabolic effects, PPARγ activators have profound effects on the myocardium and major cells of the vasculature, including endothelial cells, monocytes/macrophages and vascular smooth muscle cells.[103-105] PPARγ activation may protect the vasculature from injury and prevent the formation of atherosclerotic lesions.

Improvement of myocardial function has been observed after thiazolidinedione therapy, resulting from ligand-induced decrease in myocardial collagen content[106] but also from vasodilatory effects on myocardial microcirculation.[107] Only recently, a reduction in pressure-overload-induced left ventricular (LV) hypertrophy was demonstrated in mice after treatment with thiazolidinediones.[108]

Thiazolidinedione treatment lowers blood pressure in rats and humans,[109,110] and this effect seems to be associated with improvement of insulin sensitivity. However, direct vascular effects have also been demonstrated, which appear to be mediated, in part, by the stimulation of the production of endothelium-derived vasodilatory substances[111] and, in part, by the inhibition of calcium uptake by vascular smooth muscle cells.[112]

Activation of PPARγ inhibits proliferation and migration of vascular smooth muscle cells, by blocking the re-entry of quiescent vascular smooth muscle cells into the cell cycle and by interfering with mitogen-activated protein kinase pathways, respectively.[104] PPARγ reduces cytokine (TNFα, interleukin-1β, interleukin-6) production by inhibiting the activity of pro-inflammatory transcription factors such as AP-1, STAT and nuclear factor-kappa B (NF-κB).[24] Also, PPARγ activation decreases expression of matrix metalloproteinases (MMP), including MMP-9, which are implicated in plaque destabilisation.[113] Recently, thiazolidinedione treatment resulted in reduction in infarct size and improvement in myocardial function in rats subjected to ischaemia/reperfusion, by inhibiting the inflammatory response.[114] In addition, a regulatory role for PPARγ was found in the reverse-cholesterol transport pathway through the activation of the ABCA-1 transporter-mediated cholesterol efflux in macrophages.[115] However, another study showed PPARγ-mediated stimulation of the uptake of oxidised low-density lipoprotein (LDL) particles, a critical step in foam cell formation.[24]

Thus, the role of PPARγ in atherogenesis and vascular protection still poses numerous questions and the beneficial effects of thiazolidinediones, which have been mainly demonstrated in animal and *in vitro* models, need to be established in humans.[116,117]

2. Thiazolidinediones: Clinical Studies

Thiazolidinediones have been studied most extensively in patients with type 2 diabetes.[17,25,26,42,52] The studies reviewed here are all prospective randomised placebo-controlled trials using rosiglitazone and pioglitazone. These drugs are given as monotherapy (licensed in Japan and US), in combination with sulphonylureas (licensed in Europe, US and Japan) and metformin (licensed in Europe and US). Only in the US, pioglitazone and, very recently, rosiglitazone, have been licensed for combination therapy with insulin.

The clinical effects of thiazolidinediones, both as monotherapy and combination therapy, in patients with type 2 diabetes can be summarised as follows: they lower fasting and postprandial blood glucose as well as circulating insulin levels. In addition, they lower glycosylated haemoglobin (HbA_{1c}) values by 1–2%, which is comparable to the effectiveness of metformin and sulphonylureas. Some studies showed a decrease in hepatic glucose production but this was not a consistent finding. A reduction in plasma triglycerides, an increase in high-density lipoprotein (HDL) cholesterol as well as LDL cholesterol levels were observed.[26,33,34] Although the blood-glucose lowering effects of rosiglitazone and pioglitazone are comparable, they differently affect lipid and lipoprotein levels. At present, there are no prospective randomised trials directly comparing the two thiazolidinediones. Data on the clinical efficacy and safety of rosiglitazone versus pioglitazone in patients previously treated with troglitazone were primarily published in abstract form[118,119] and only recently as full papers (see section 2.4).[120,121] Relevant clinical effects may occur as early as 2–4 weeks after the start of thiazolidinedione therapy; however, in some individuals, the full effectiveness of these agents may not be manifest until 8–12 weeks of therapy and beyond.[17,122-125]

Hepatic toxicity was the most serious concern with troglitazone; however, the most frequently observed adverse events with rosiglitazone and pioglitazone are weight gain, fluid retention and elevation of LDL cholesterol.[26] Although marked reductions in insulin doses have been reported when thiazolidinediones are combined with insulin, an increased incidence of cardiac failure due to excessive fluid retention was observed in clinical trials evaluating either drug in combination with insulin.[126] When used as monotherapy, thiazolidinediones rarely cause hypoglycaemia.[127]

In addition to patients with type 2 diabetes, thiazolidinediones have been used in obese individuals, patients with impaired glucose tolerance and women with polycystic ovary syndrome (PCOS).[128,129] In these patients, thiazolidinediones invariably improved insulin sensitivity. Moreover, in women with PCOS, ovulation and fertility was restored following thiazolidinedione therapy.[129]

It should be noted that thiazolidinediones are effective only in the presence of adequate insulin levels. Available data suggest, approximately 25% of patients may not respond adequately to thiazolidinedione therapy as a result of – among other reasons – insulin deficiency due to progressive β-cell failure.[15,52,130-132] Also, obese patients seem to respond better than lean patients.[132] Another clinically important issue may be the gender difference in responses to thiazolidinediones;[133,134] the plasma glucose lowering effect of thiazolidinediones was greater in women than in men, and was associated with a more marked increase in BMI and subcutaneous fat area in women.[134] Although the effects of PPARγ agonists on sex hormones were implicated in these findings, the underlying mechanism still needs further investigation.

Similar to observations from animal studies, one may expect that thiazolidinedione treatment of patients with type 2 diabetes may confer benefits beyond decreases of glucose and lipid levels. Indeed, the anti-atherogenic, vascular, haemodynamic and cardiovascular effects, in part associated with im-

proved insulin sensitivity in patients, are of considerable research interest.[135] In this article, we outline these effects in humans. However, it should be stated again that, at present, the absolute long-term benefits of these non-hypoglycaemic actions of thiazolidinediones are uncertain.

2.1 Rosiglitazone

Rosiglitazone has been evaluated in clinical trials in patients with type 2 diabetes mellitus who have been previously treated by diet, other oral antihyperglycaemic agents or insulin. Table I lists the effects of rosiglitazone given as monotherapy or as combination treatment on variables of glycaemic control, plasma insulin and bodyweight. To date, eight randomised-controlled trials have been published as full papers with a blinded treatment duration of 8–26 weeks.[125,133,136-141] In five studies, rosiglitazone was given as monotherapy,[133,136-139] and in three studies the agent was combined with a sulphonylurea,[140] metformin[141] and insulin,[125] respectively. Rosiglitazone was administered once,[136,141] or twice daily,[125,133,137,138,140] or both once and twice daily.[139] In these studies, a total of 2758 patients were treated with rosiglitazone (at doses ranging between 0.1–12 mg/day) or placebo. The mean age of the study populations varied from 55.6 to 63.5 years, mean duration of disease was 4.0–12.7 years and mean BMI ranged between 28.1–32.7 kg/m^2. Mean baseline fasting plasma glucose (FPG) levels varied between 9.8–12.8 mmol/L and mean HbA_{1c} ranged from 8.6–9.2%.

2.1.1 Effects on Glycaemic Control

A decrease in HbA_{1c} was observed in patients treated with rosiglitazone monotherapy versus placebo at a daily dose of 4mg or higher (0.4–1.5%),[133,137,139] whereas significant lowering of FPG levels was found already at a dose of 2mg per day (table I).[133] In addition, glycaemic control at baseline determined the magnitude of the response; greater reductions in mean HbA_{1c} were observed in patients treated with rosiglitazone who had more severe disease (HbA_{1c} ≥9.0%) before treatment than patients with milder disease (HbA_{1c} <9.0%).[142] Analysis by previous therapy revealed that drug-naive patients, who are regarded as having less severe disease, responded to rosiglitazone at doses of both 4 and 8 mg/day, whereas patients previously treated with blood-glucose lowering therapy (either as monotherapy or combination therapy), showed the most marked response to rosiglitazone 4mg twice daily.[139]

When combined with sulphonylureas, rosiglitazone 2 or 4 mg/day decreased mean HbA_{1c} by 0.6 and 1.0%, respectively, and mean FPG levels by 1.3 and 2.4 mmol/L, respectively, compared with placebo.[140] Higher doses, (4 and 8 mg/day of rosiglitazone) were added to metformin or insulin.[125,141] At these respective doses, mean HbA_{1c} dropped significantly by 1.0 and 1.2% (metformin) and 0.7 and 1.3% (insulin), whereas mean FPG were reduced by 2.2 and 2.9 mmol/L (metformin) and 2.2 and 2.6 mmol/L (insulin). Dose-dependent decreases of fasting plasma insulin (FPI) levels were reported in all but one monotherapy trial,[139] and these were significant at dose of 2 mg/day or higher. However, mean FPI levels dropped most markedly when rosiglitazone was added to metformin (see section 2.1.3).[141]

Rosiglitazone dose-dependently increases bodyweight (see table I; see also section 2.5). Despite the weight gain, the waist-to-hip ratio remained unchanged[125,141] or was reduced.[138] The highest mean increase in bodyweight from baseline was seen in patients receiving rosiglitazone (8 mg/day) in combination with insulin for 26 weeks.[125]

2.1.2 Effects on Lipid and Lipoprotein Profile

Table II lists the effects of rosiglitazone alone or as combination therapy on plasma lipid parameters. Compared with placebo, rosiglitazone monotherapy dose-dependently increased plasma triglyceride levels (0.02–0.47 mmol/L; only significant at the highest dosage of 12 mg/day), HDL cholesterol (0–0.1 mmol/L; not significant), total cholesterol (0.02–0.88 mmol/L; significant at dosages ranging from 4–12 mg/day) and LDL cholesterol levels (0.04–0.68 mmol/L; significant at a dosage of ≥4 mg/day; see table II). Similar effects on lipid parameters were found when rosiglitazone was used in combination therapy. The total : HDL cholesterol

Table I. The effect of rosiglitazone on glycaemia, insulinaemia and bodyweight in patients with type 2 diabetes mellitus

Reference	Treatment	n	Duration of treatment (week)	Mean ΔHbA$_{1c}$ (%)		Mean ΔFPG (mmol/L)		Mean ΔFPI (pmol/L)		Mean ΔBW (kg)	
				vs placebo	vs baseline	vs placebo	vs baseline	vs placebo	vs baseline	vs placebo	vs baseline
Patel et al.[133]	Placebo	75	12	NA	+0.3	NA	+0.3	NA	+0.7	NA	−0.5
	Rosiglitazone 0.05mg bid	74	12	+0.3	+0.6	+0.1	+0.4	−8.6	−8.8	−0.4	−1.0
	Rosiglitazone 0.25mg bid	72	12	+0.3	+0.6	+0.1	+0.4	0	0	0	−0.5
	Rosiglitazone 1.0mg bid	79	12	−0.1	+0.1	−1.6[a]	−1.3[b]	−0.7	0	+0.7	+0.2
	Rosiglitazone 2.0mg bid	80	12	−0.4[a]	−0.1	−2.3[a]	−2.0[b]	−19.4[a]	−19.4[b]	+0.9[a]	+0.4[b]
Nolan et al.[136]	Placebo	93	8	NA	NR	NA	+0.4	NA	−19.0	NA	−0.3
	Rosiglitazone 4mg od	95	8	NR	NR	−1.3[a]	−0.9[b]	−2.0	−21.0[b]	+0.5	+0.2
	Rosiglitazone 8mg od	90	8	NR	NR	−2.4[a]	−2.0[b]	−1.0	−20.0[b]	+1.0[a]	+0.7[b]
	Rosiglitazone 12mg od	91	8	NR	NR	−2.1[a]	−1.7[b]	−4.0	−23.0[b]	+0.9[a]	+0.6[b]
Raskin et al.[137]	Placebo	69	8	NA	+1.0[b]	NA	+1.1[b]	NA	−10.5	NA	NR
	Rosiglitazone 2mg bid	73	8	NR	+0.4[b]	−3.1[a]	−2.0[b]	−7.2	−17.7[b]	NR	NR
	Rosiglitazone 4mg bid	66	8	NR	NS	−3.5[a]	−2.4[b]	−2.5	−13.0[b]	NR	+0.7
	Rosiglitazone 6mg bid	76	8	NR	NS	−3.6[a]	−2.5[b]	−16.7[a]	−27.2[b]	NR	+1.5
Lebovitz et al.[138]	Placebo	158	26	NA	+0.9	NA	+1.1	NA	−4.1	NA	−1.0
	Rosiglitazone 2mg bid	166	26	−1.2[a]	−0.3[b]	−3.2[a]	−2.1[b]	−2.4	−6.6[b]	+2.6[a]	+1.6[b]
	Rosiglitazone 4mg bid	169	26	−1.5[a]	−0.6[b]	−4.2[a]	−3.0[b]	−6.6	−10.5[b]	+4.5[a]	+3.5[b]
Philips et al.[139]	Placebo	173	26	NA	+0.9	NA	NR	NA	NR	NA	−0.9
	Rosiglitazone 4mg od	181	26	−0.8[a]	+0.1	NR[a]	NR	NR, NS	NR	+2.1[a]	+1.2[b]
	Rosiglitazone 2mg bid	186	26	−0.9[a]	0	NR[a]	NR	NR, NS	NR	+2.4[a]	+1.5[b]

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Table I. Contd

Reference	Treatment	n	Duration of treatment (week)	Mean ΔHbA_{1c} (%)		Mean ΔFPG (mmol/L)		Mean ΔFPI (pmol/L)		Mean ΔBW (kg)	
				vs placebo	vs baseline	vs placebo	vs baseline	vs placebo	vs baseline	vs placebo	vs baseline
	Rosiglitazone 8mg od	181	26	−1.1[a]	−0.2	NR[a]	NR	NR, NS	NR	+3.5[a]	+2.6[b]
	Rosiglitazone 4mg bid	187	26	−1.5[a]	−0.6	NR[a]	NR	NR, NS	NR	+4.2[a]	+3.3[b]
Wolffenbuttel et al.[140]	Sulphonylureas + placebo	192	26	NA	+0.1	NA	+0.3	NA	0	NA	NR
	Sulphonylureas + rosiglitazone 1mg bid	199	26	−0.6[a]	−0.5[b]	−1.3	−0.9[b]	−4.2	−4.2[b]	NR	+0.8[b]
	Sulphonylureas + rosiglitazone 2mg bid	183	26	−1.0[a]	−0.9[b]	−2.4	−2.1[b]	−6.4	−6.4[b]	NR	+1.8[b]
Fonseca et al.[141]	Metformin + placebo	113	26	NA	+0.5[b]	NA	+0.3	NA	−11.1[b]	NA	−1.2
	Metformin + rosiglitazone 4mg od	116	26	−1.0[a]	−0.6[b]	−2.2[a]	−1.8[b]	−2.1	−13.0[b]	+1.9	+0.7[b]
	Metformin + rosiglitazone 8mg od	110	26	−1.2[a]	−0.8[b]	−2.9[a]	−2.7[b]	−20.0	−31.1	+3.1	+1.9[b]
Raskin et al.[125]	Insulin + placebo	104	26	NA	+0.1	NA	+0.6	NA	NA	NA	+0.9[b]
	Insulin + rosiglitazone 2mg bid	106	26	−0.7[a]	−0.6[b]	−2.2[a]	−2.3[b]	NA	NA	+3.1	+4.0[b]
	Insulin + rosiglitazone 4mg bid	103	26	−1.3[a]	−1.2[b]	−2.6[a]	−2.5[b]	NA	NA	+4.4	+5.3[b]

a Significantly different from placebo.

b Significantly different from baseline.

BW = bodyweight; **bid** = twice daily; **FPG** = fasting plasma glucose; **FPI** = fasting plasma insulin; **HbA_{1c}** = glycated haemoglobin; **n** = number of patients; **NA** = not applicable; **NR** = not reported; **NS** = non significant; **od** = once daily.

Table II. The effect of rosiglitazone on lipid parameters in patients with type 2 diabetes mellitus

Reference	Treatment	n	Duration of treatment (week)	Mean ΔTG (mmol/L)		Mean ΔHDL-C (mmol/L)		Mean ΔTC (mmol/L)		Mean ΔLDL-C (mmol/L)	
				vs placebo	vs baseline	vs placebo	vs baseline	vs placebo	vs baseline	vs placebo	vs baseline
Patel et al.[133]	Placebo	75	12	NA	+0.18	NA	+0.05	NA	+0.15	NA	+0.04
	Rosiglitazone 0.05mg bid	74	12	+0.12	+0.30	−0.05	0	+0.02	+0.17	−0.02	+0.02
	Rosiglitazone 0.25mg bid	72	12	+0.09	+0.27	−0.02	+0.03	+0.12	+0.27	+0.04	+0.08
	Rosiglitazone 1.0mg bid	79	12	−0.10	+0.08	0	+0.05	+0.08	+0.23	+0.05	+0.09
	Rosiglitazone 2.0mg bid	80	12	+0.02	+0.20	+0.10[a]	+0.15[b]	+0.55[a]	+0.70[b]	+0.40[a]	+0.44[b]
Nolan et al.[136]	Placebo	93	8	NA	−0.14	NA	+0.09[b]	NA	−0.02	NA	+0.12
	Rosiglitazone 4mg od	95	8	+0.13	+0.27	+0.02	+0.11[b]	+0.62[a]	+0.60[b]	+0.37[a]	+0.49[b]
	Rosiglitazone 8mg od	90	8	+0.11	+0.25	+0.03	+0.12[b]	+0.80[a]	+0.78[b]	+0.68[a]	+0.80[b]
	Rosiglitazone 12mg od	91	8	+0.33[a]	+0.47[b]	+0.07	+0.16[b]	+0.88[a]	+0.86[b]	+0.61[a]	+0.73[b]
Raskin et al.[137]	Placebo	69	8	NA	0	NA	+0.05[b]	NA	+0.10	NA	0
	Rosiglitazone 2mg bid	73	8	+0.10	+0.10	+0.02	+0.07[b]	+0.70[a]	+0.80[b]	+0.50[a]	+0.50[b]
	Rosiglitazone 4mg bid	66	8	+0.20	+0.20	+0.03	+0.08	+0.70[a]	+0.80[b]	+0.40[a]	+0.40[b]
	Rosiglitazone 6mg bid	76	8	+0.30	+0.30	+0.08	+0.13[b]	+0.70[a]	+0.80[b]	+0.60[a]	+0.60[b]
Lebovitz et al.[138]	Placebo	158	26	NA	NS	NA	+0.06[b]	NA	+0.15	NA	+0.15[b]
	Rosiglitazone 2mg bid	166	26	NS	NS	+0.05	+0.11[b]	+0.51	+0.66[b]	+0.28	+0.43[b]
	Rosiglitazone 4mg bid	169	26	NS	NS	+0.05	+0.11[b]	+0.58	+0.73[b]	+0.46	+0.61[b]
Philips et al.[139]	Placebo	173	26	NA	−0.04	NA	+0.13	NA	−0.02	NA	−0.07
	Rosiglitazone 4mg od	181	26	+0.19	+0.30	+0.01	+0.10	+0.47	+0.62	+0.39	+0.37
	Rosiglitazone 2mg bid	186	26	+0.19	+0.23	+0.07	+0.10	+0.60	+0.61	+0.52	+0.36

Continued next page

Table II. Contd

Reference	Treatment	n	Duration of treatment (week)	Mean ΔTG (mmol/L)		Mean ΔHDL-C (mmol/L)		Mean ΔTC (mmol/L)		Mean ΔLDL-C (mmol/L)	
				vs placebo	vs baseline	vs placebo	vs baseline	vs placebo	vs baseline	vs placebo	vs baseline
	Rosiglitazone 8mg od	181	26	+0.45	+0.29	0	+0.11	+0.80	+0.85	+0.67	+0.54
	Rosiglitazone 4mg bid	187	26	+0.25	0	+0.02	+0.15	+0.64	+0.75	+0.41	+0.39
Wolffenbuttel et al.[140]	Sulphonylureas + placebo	192	26	NA	+0.10	NA	0	NA	+0.10	NA	0
	Sulphonylureas + rosiglitazone 1mg bid	199	26	+0.30[a]	+0.40[b]	+0.10	+0.10[b]	+0.20[a]	+0.30[b]	+0.10	+0.10
	Sulphonylureas + rosiglitazone 2mg bid	183	26	+0.10	+0.20[b]	+0.10[a]	+0.10[b]	+0.30[a]	+0.40[b]	+0.20[a]	+0.20[b]
Fonseca et al.[141]	Metformin + placebo	113	26	NA	+0.15/−0.12[c]	NA	+0.05[b]	NA	+0.18[b]	NA	+0.13/+0.07[d]
	Metformin + rosiglitazone 4mg od	116	26	−0.06	+0.16/+0.15[c]	+0.08[a]	+0.13[b]	+0.53[a]	+0.72[b]	+0.36[a]	+0.54/+0.31[d]
	Metformin + rosiglitazone 8mg od	110	26	−0.10	+0.07/ NR[c]	+0.10[a]	+0.16[b]	+0.60[a]	+0.82[b]	+0.40[a]	+0.54/+0.34[d]
Raskin et al.[125]	Insulin + placebo	104	26	NA	+0.53[b]	NA	+0.06[b]	NA	+0.19[b]	NA	+0.01
	Insulin + rosiglitazone 2mg bid	106	26	−0.28	+0.25	+0.11	+0.17	+0.32	+0.51[b]	+0.27	+0.28[b]
	Insulin + rosiglitazone 4mg bid	103	26	−0.48	+0.05	+0.10	+0.16[b]	+0.56	+0.75[b]	+0.37	+0.38[b]

a Significantly different from placebo.

b Significantly different from baseline.

c The first value represents changes in patients with baseline TG <2.26 mmol/L, the second those in patients with baseline TG ≥2.26 mmol/L.

d The first value represents changes in patients with baseline LDL-C <3.37 mmol/L, the second those in patients with baseline LDL-C 3.37 mmol/L.

bid = twice daily; **HDL-C** = high density lipoprotein cholesterol; **LDL-C** = low density lipoprotein cholesterol; **n** = number of patients; **NA** = not applicable; **NS** = not significant; **od** = once daily; **TC** = total cholesterol; **TG** = triglycerides.

ratio, did not change significantly in most studies.[125,133,137,140,141] Eighteen-month follow-up data in patients using rosiglitazone 8 mg/day indicated that LDL cholesterol levels stabilised after approximately 3 months, while HDL cholesterol levels continued to increase, leading to an overall decrease of total : HDL and LDL : HDL cholesterol ratios.[143]

The effect of rosiglitazone on plasma triglycerides depends on baseline triglyceride levels. Among patients whose baseline triglyceride levels were >2.26 mmol/L, rosiglitazone (at 8 mg/day) lowered triglyceride levels, whereas in those with low baseline values (<2.26 mmol/L), the agent increased triglyceride levels.[141] Rosiglitazone, both as monotherapy (≥4 mg/day) and in combination (≥4 mg/day), reduced circulating levels of free fatty acids.[125,133,136-141]

Using density gradient ultracentrifugation, it was demonstrated that the rosiglitazone-induced rises in LDL cholesterol is paralleled by an increase in relative flotation rate, indicating a shift in LDL density from small dense to the less atherogenic large buoyant particles.[144] The increases in LDL cholesterol are not accompanied by a similar rise in apolipoprotein B.[122] Together with the increase in HDL cholesterol levels after rosiglitazone therapy, a larger increment in HDL_2 cholesterol than in HDL_3 cholesterol was observed.[144] It was suggested that, in spite of the seemingly adverse effects on plasma total cholesterol and LDL cholesterol levels, rosiglitazone treatment may have an overall anti-atherogenic effect on the lipid profile.

2.1.3 Effects on Insulin Resistance and β-Cell Function

A limited number of studies have specifically addressed the effect of thiazolidinediones on the two key mechanisms underlying type 2 diabetes, insulin resistance and β-cell dysfunction.[56,97,125,139,145] The majority of studies assessed changes in FPI only, as an indicator of improved insulin sensitivity. Table I lists the mean decrease of FPI after 8–26 weeks of rosiglitazone treatment. In five studies using rosiglitazone monotherapy, significant dose-related reductions in FPI were observed in patients taking ≥4 mg/day, but these were only significant when compared with baseline values, as FPI also fell in patients receiving placebo. Thus, the mean rosiglitazone-induced reduction in FPI ranged from 6.6–27.2 pmol/L, whereas mean changes in FPI in the placebo-group varied from +0.7 to −19 pmol/L. Interestingly, at 8 mg/day, rosiglitazone combined with metformin resulted in a mean FPI-reduction of 31.1 pmol/L.

In the study combining rosiglitazone with insulin, clinically relevant reductions of insulin dose requirements were reported, indicating a beneficial effect of the agent on insulin sensitivity.[125] Homeostasis model assessment (HOMA) analyses in patients treated with rosiglitazone alone or in combination with metformin, revealed improvements in insulin sensitivity and β-cell function compared with placebo.[56,125,139] Using an oral glucose tolerance test (OGTT) and a two-step euglycaemic insulin clamp in patients with type 2 diabetes before and after rosiglitazone (8 mg/day) for 12 weeks, an increase in hepatic and peripheral (muscle) tissue insulin sensitivity and a reduction of free fatty acid turnover were found.[145] However, no changes in mean C-peptide and insulin levels or insulinogenic index (ΔAUC insulin/ΔAUC glucose; where AUC∞ area under concentration time curve) during OGTT, an estimate of β-cell function, were observed.[145] It was suggested that both an improvement in insulin sensitivity and a reduction in glucose toxicity, in the presence of unchanged plasma insulin or C-peptide levels, may still indicate an enhancement of β-cell function.

Recently, rosiglitazone was shown to improve insulin sensitivity and increase plasma adiponectin levels in patients with type 2 diabetes.[146] Lower plasma levels of adiponectin have been documented in humans with the metabolic syndrome,[147] therefore, elevation of the level of this possibly protective adipocytokine by PPARγ agonists may be beneficial in these high-risk patients.[72,148]

2.2 Pioglitazone

In a recent review the clinical effectiveness of pioglitazone, both as monotherapy and in combination with other blood-glucose lowering drugs, has

been summarised.[42] In this review, 17 reports fulfilled the search criteria and they related to 11 trials, only six of which were available as full reports and four of these six were published in a Japanese journal.[149-154] However, four more studies have now appeared as full papers in English.[155-158] All trials have a prospective, randomised, controlled set-up, but the Japanese studies involve different, in particular less obese populations, and some data, such as several baseline values, are missing. The studies published as abstracts cannot readily be compared with regard to methodology, the quality of which can only be assessed in full reports. Therefore, in table III and table IV, which list the effects of pioglitazone on glycaemic and lipid parameters, respectively, the data from full papers only are included.

Pioglitazone has been evaluated in the treatment of type 2 diabetes mellitus as monotherapy,[149,150,153,155] or in combination with a sulphonylurea,[151,152,156,157] metformin[154] or insulin.[158] In all studies, pioglitazone was given once daily. It should be noted that, similar to the published trials of rosiglitazone, the duration of these studies ranges from 12–26 weeks, with an open label extension of up to 2 years.

The populations included in the US studies resemble those participating in the trials with rosiglitazone. The mean age ranged between 53.8–57.5 years and more male (45–60%) than female (40–55%) patients and multiple ethnicities were included. Mean baseline HbA_{1c} levels in all studies were at least 8.0%, although most patients had HbA_{1c} values well above 9.0% (9.8–10.6%). Mean baseline BMI of participants in non-Japanese studies was above 28.7 kg/m^2, typically ranging between 30.7–34.3 kg/m^2.

2.2.1 Effects on Glycaemic Control

In the majority of studies, a decline in FPG, on average, started within 2 weeks and achieved statistical significance 4 weeks after the start of pioglitazone treatment, reaching a maximum decrement after 6–12 weeks of therapy. Pioglitazone monotherapy in non-obese Japanese patients with type 2 diabetes at dosages of 15, 30 or 45 mg/day given for 12 weeks reduced HbA_{1c} levels non-significantly from baseline in a dose-dependent fashion by 0.48–0.96%.[152] In obese US patients, pioglitazone, only at a dose of 45 mg/day given for 26 weeks, resulted in a relevant mean HbA_{1c} reduction of 0.9%. Those treated with lower doses, showed HbA_{1c} decreases of a maximum of 0.3% (table III).[153] In the same study, a subset of patients who were naive to blood-glucose lowering therapy and were treated with pioglitazone 45 mg/day, experienced a 2.6% decrease in HbA_{1c} levels, compared with placebo. In patients who had previously received blood-glucose lowering therapy, the same dosage of pioglitazone resulted in a more modest 1.4% decrease in HbA_{1c} levels relative to placebo.

Pioglitazone treatment, at the most frequently studied dose of 30 mg/day, resulted in HbA_{1c} reductions ranging between 0.3–1.08% from baseline. These were always significant when compared with placebo since HbA_{1c} in the placebo-treated patients rose invariably (up to 0.76%), depending on the duration of the study (table III). In addition, in all four monotherapy studies, pioglitazone dose-dependently lowered FPG by 1.0–3.1 mmol/L, with significant reductions already occurring at a dosage of 7.5 mg/day.[153] Some patients from the 26-week study by Aronoff et al.[153] underwent a 3h OGTT before and after completion of the therapy period. Compared with baseline and placebo, a significant ($p < 0.05$) dose-related reduction of glucose AUC was found, starting at a dose of 15 mg/day pioglitazone.[159]

When pioglitazone was added to sulphonylurea therapy, HbA_{1c} was reduced by 0.65–1.7% from baseline, the largest decline only being reached at a dosage of 45 mg/day.[156] In all studies using pioglitazone 30 mg/day added to a sulphonylurea, a significant mean decrease in HbA_{1c} of 1.2% was observed.[151,152,157] Similarly, pioglitazone 30 mg/day given to sulphonylurea-treated patients, resulted in significant FPG reductions from baseline ranging from 2.1–2.9 mmol/L. Although not formally compared, the effects with pioglitazone combined with a sulphonylurea seem greater than with pioglitazone alone. Possibly, sulphonylurea-induced insulin se-

Table III. The effect of pioglitazone on glycaemia, insulinaemia and bodyweight in patients with type 2 diabetes mellitus

Reference	Treatment (mg/day)	n	Duration of treatment (week)	Mean ΔHbA_{1c} (%)		Mean ΔFPG (mmol/L)		Mean ΔFPI (pmol/L)		Mean ΔBW (kg)	
				vs placebo	vs baseline	vs placebo	vs baseline	vs placebo	vs baseline	vs placebo	vs baseline
Kaneko et al.[149]	Placebo	66	12	NA	+0.4	NA	+0.2	NA	NR	NA	−0.1
	Pioglitazone 15	71	12	−0.9[a]	−0.5	−1.5[a]	−1.3	NR	NR	−0.3	−0.4
	Pioglitazone 30	67	12	−1.4[a]	−1.0	−1.9[a]	−1.7	NR[a]	NR	+0.6[a]	+0.6
	Pioglitazone 45	69	12	−1.4[a]	−1.0	−2.5[a]	−2.3	NR[a]	NR	+0.8[a]	+0.7
Kaneko et al.[150]	Placebo	75	12	NA	−0.02	NA	+0.3	NA	NR	NA	+0.3
	Pioglitazone 30	77	12	−1.1[a]	−1.1	−1.8	−1.6	NR, NS	NR	+0.5[a]	+0.8
Aronoff et al.[153]	Placebo	79	26	NA	+0.7[b]	NA	+0.5	NA	−9.8, +0.6[c]	NA	−1.3
	Pioglitazone 7.5	81	26	−0.5[a]	+0.2	−1.5[a]	−1.0[b]	NR	NR	+0.7	−0.6
	Pioglitazone 15	81	26	−1.0[a]	−0.3[b]	−2.2[a]	−1.6[b]	NR	NR	+2.6	+1.3
	Pioglitazone 30	87	26	−1.0[a]	−0.3[b]	−2.3[a]	−1.8[b]	NR	−30.6, −16.4[bc]	+2.6	+1.3
	Pioglitazone 45	80	26	−1.6[a]	−0.9[b]	−3.6[a]	−3.1[b]	NR	−36.7, −10.7[bc]	+4.1	+2.8
Rosenblatt et al.[155]	Placebo	96	23	NA	+0.8[b]	NA	+0.4	NA	+11.1	NA	−1.9[b]
	Pioglitazone 30	101	23	−1.4[a]	−0.6[b]	−3.2[a]	−2.8[b]	−23.0[a]	−12.0[b]	−3.2[a]	+1.4[b]
Kaneko et al.[151]	Sulphonylureas + placebo	66	12	NA	+0.5	NA	+0.04	NA	NR	NA	−0.1
	Sulphonylureas + pioglitazone 15	72	12	−1.1[a]	−0.7	−1.4	−1.4	NR	NR	+0.7	+0.6[b]
	Sulphonylureas + pioglitazone 30	68	12	−1.6[a]	−1.2	−2.7[a]	−2.6	NR[a]	NR	+1.3	+1.3[b]
	Sulphonylureas + pioglitazone 45	70	12	−1.6[a]	−1.1	−2.6[a]	−2.6	NR[a]	NR	+1.1[a]	+1.0[b]
Kaneko et al.[152]	Sulphonylureas + placebo	73	12	NA	−0.1	NA	+0.2	NA	NR	NA	−0.1

Continued next page

Table III. Contd

Reference	Treatment (mg/day)	n	Duration of treatment (week)	Mean ΔHbA_{1c} (%)		Mean ΔFPG (mmol/L)		Mean ΔFPI (pmol/L)		Mean ΔBW (kg)	
				vs placebo	vs baseline	vs placebo	vs baseline	vs placebo	vs baseline	vs placebo	vs baseline
	Sulphonylureas + pioglitazone 30	76	12	−1.2[a]	−1.2	−2.3[a]	−2.1[b]	NR[a]	NR	+1.5[a]	+1.4[b]
Miyazaki et al.[156]	Sulphonylureas + placebo	11	16	NA	0	NA	+1.4	NA	−20.7	NA	+0.3
	Sulphonylureas + pioglitazone 45	12	16	−1.7	−1.7[b]	−4.2	−2.8[b]	+6.9	−13.8	+3.3[a]	+3.6[b]
Kipnes et al.[157]	Sulphonylureas + placebo	184	16	NA	+0.1	NA	+0.3	NA	+1.4	NA	−0.8
	Sulphonylureas + pioglitazone 15	189	16	−0.9[a]	−0.8[b]	−2.2[a]	−1.9[b]	−15.1	−13.6	+2.7[a]	+1.9
	Sulphonylureas + pioglitazone 30	187	16	−1.3[a]	−1.2[b]	−3.2[a]	−2.9[b]	−21.5[a]	−20.8[b]	+3.7[a]	+2.9
Einhorn et al.[154]	Metformin + placebo	160	16	NA	+0.2	NA	−0.2	NA	+6.9	NA	−1.4
	Metformin + pioglitazone 30	168	16	−0.8[a]	−0.6[b]	−2.1[a]	−2.3[b]	−2.5[a]	−36.2[b]	+2.3	+1.0
Rosenstock et al.[158]	Insulin + placebo	187	16	NA	−0.3[b]	NA	−0.03	NA	NA	NA	NR
	Insulin + pioglitazone 15	191	16	−0.7[a]	−1.0[b]	−1.9[a]	−1.9[b]	NA	NA	NR	NR
	Insulin + pioglitazone 30	188	16	−1.0[a]	−1.3[b]	−2.7[a]	−2.7[b]	NA	NA	NR	NR

a Significantly different from placebo.

b Significantly different from baseline.

c Only range reported.

BW = bodyweight; **FPG** = fasting plasma glucose; **FPI** = fasting plasma insulin; **HbA_{1c}** = glycated haemoglobin; **n** = number of patients; **NA** = not applicable; **NR** = not reported or reported as percentage change; **NS** = non significant.

Table IV. The effect of pioglitazone on lipid parameters in patients with type 2 diabetes mellitus

Reference	Treatment (mg/day)	n	Duration of treatment (week)	Mean ΔTG (%)		Mean ΔHDL-C (%)		Mean ΔTC (%)		Mean ΔLDL-C (%)	
				vs placebo	vs baseline	vs placebo	vs baseline	vs placebo	vs baseline	vs placebo	vs baseline
Aronoff et al.[153]	Placebo	79	26	NA	+4.8[a]	NA	+8.1[a]	NA	+4.4	NA	+4.8
	Pioglitazone 7.5	81	26	+4.1	+8.9	−0.2	+7.9[a]	−2.1	+2.3	+0.7	+1.0
	Pioglitazone 15	81	26	−13.8	−9.0[a]	+6.0	+14.1[a]	+0.2	+4.6[a]	+2.6	+7.2[a]
	Pioglitazone 30	87	26	−14.4	−9.6[a]	+4.1	+12.1[a]	−1.1	+3.3	+2.6	+5.2
	Pioglitazone 45	80	26	−14.1	−9.3[a]	+11.0[b]	+19.1[a]	+2.0	+6.4[a]	+4.1	+6.0[a]
Rosenblatt et al.[155]	Placebo	96	23	NA	+1.8	NA	+3.2	NA	0	NA	+5.0
	Pioglitazone 30	101	23	−16.6[b]	−14.8[a]	+12.6[b]	+15.8[a]	+3.5	+3.5	−0.5	+4.5
Kaneko et al.[151][c]	Sulphonylureas + placebo	66	12	NA	+0.1	NA	0	NA	NR[d]	NA	NR
	Sulphonylureas + pioglitazone 15	72	12	−0.2	−0.1	+0.1[b]	+0.1[a]	NR[d]	NR[d]	NR	NR
	Sulphonylureas + pioglitazone 30	68	12	−0.3	−0.3[a]	+0.1[b]	+0.1[a]	NR[d]	NR[d]	NR	NR
	Sulphonylureas + pioglitazone 45	70	12	−0.4[b]	−0.3[a]	+0.2[b]	+0.2[a]	NR[d]	NR[d]	NR	NR
Kaneko et al.[152][c]	Sulphonylureas + placebo	73	12	NA	0	NA	+0.1[a]	NA	+0.1	NA	NR
	Sulphonylureas + pioglitazone 30	76	12	−0.4[b]	−0.4[a]	+0.1[b]	+0.2[a]	0	+0.2	NR	NR
Miyazaki et al.[156]	Sulphonylureas + placebo	11	16	NA	+0.8	NA	−2.7	NA	−0.6	NA	0
	Sulphonylureas + pioglitazone 45	12	16	−24.8[b]	−24[a]	+5.4	+2.7	−3.5	−4.1	−1.9	−1.9
Kipnes et al.[157]	Sulphonylureas + placebo	184	16	NA	+10.2[a]	NA	−1.0	NA	+4.1	NA	+7.0
	Sulphonylureas + pioglitazone 15	189	16	−16.6[b]	−6.4	+5.9[b]	+5.0[a]	−2.6	+1.4	−2.2	+4.8
	Sulphonylureas + pioglitazone 30	187	16	−26.0[b]	−15.9[a]	+12.9[b]	+12.0[a]	−1.7	+2.3	−0.4	+6.6
Einhorn et al.[154]	Metformin + placebo	160	16	NA	+8.5	NA	+1.5	NA	+1.1	NA	+11.9
	Metformin + pioglitazone 30	168	16	−18.2[b]	−9.7	+8.7	+10.2[a]	+3.0	+4.1[a]	−4.2	+7.7[a]

Continued next page

Table IV. Contd

Reference	Treatment (mg/day)	n	Duration of treatment (week)	Mean ΔTG (%)		Mean ΔHDL-C (%)		Mean ΔTC (%)		Mean ΔLDL-C (%)	
				vs placebo	vs baseline	vs placebo	vs baseline	vs placebo	vs baseline	vs placebo	vs baseline
Rosenstock et al.[158][e]	Insulin + placebo	187	16	NA	+13.3[a]	NA	−0.2	NA	−0.7	NA	−1.4
	Insulin + pioglitazone 15	191	16	−8.0	−5.4	+7.3[b]	+7.1[a]	+2.1	+1.4	+6.5[b]	+5.1[a]
	Insulin + pioglitazone 30	188	16	−23.7[b]	−10.4	+9.3[b]	+9.1[a]	+1.1	+0.4	+4.2	+2.8

a Significantly different from baseline.

b Significantly different from placebo.

c Changes in lipids/lipoproteines are reported in mmol/L only.

d It was reported that there were no changes in cholesterol levels.

e Data reported as least-square mean difference in percentage.

HDL-C = high density lipoprotein-cholesterol; **LDL-C** = low density lipoprotein -cholesterol; **n** = number of patients; **NA** = not applicable; **NR** = not reported; **TC** = total cholesterol; **TG** = triglycerides.

cretion may potentiate the effect of pioglitazone. However, a difference in patient populations receiving monotherapy versus combination therapy cannot be entirely ruled out.

The only study published as a full paper that combined pioglitazone 30 mg/day with metformin, showed significant mean decreases in HbA_{1c} of 0.6% and in FPG of 2.1 mmol/L at 16 weeks.[154] Combination therapy of pioglitazone 15 or 30 mg/day with insulin decreased HbA_{1c} by 1.0 and 1.3%, respectively, and FPG by 1.9 and 2.7 mmol/L, respectively.[158] Interestingly, a fall in HbA_{1c} of 0.3% was also observed in patients treated with placebo.

Taken together, pioglitazone, whether given as monotherapy or in combination with sulphonylureas, metformin or insulin, at a dose-range of 15–45 mg/day, on average, lowers HbA_{1c} by 0.3–1.7% and FPG by 1.0–3.1 mmol/L from baseline after 12–26 weeks of treatment.

2.2.2 Effects on Lipid and Lipoprotein Profile

Table IV lists the changes in lipid and lipoprotein profile in patients with type 2 diabetes taking pioglitazone monotherapy,[153] or in combination with sulphonylureas,[151,152,156,157] metformin[154] or insulin.[158] In contrast to the studies using rosiglitazone, which report the treatment-induced changes in absolute values (table II), the majority of papers describing pioglitazone-induced effects on lipid parameters use mean percentage changes from baseline or relative to placebo (table IV).

Pioglitazone monotherapy resulted in a non dose-related mean percentage decrease from baseline in triglycerides, compared with an increase for placebo in one study of patients with type 2 diabetes.[153] The mean percentage increase in HDL cholesterol from baseline was higher with pioglitazone than with placebo, however, this was only significant with pioglitazone 45 mg/day (8.1% for placebo vs 19.1% for pioglitazone 45 mg/day, $p < 0.05$). At week 26, a rise from baseline in LDL cholesterol was observed with pioglitazone 15, 30 and 45 mg/day (7.2%, 5.2% and 6.0%, respectively), but these were was comparable to placebo (4.8%). Similar findings were reported by Rosenblatt et al.[155] That is, compared with placebo, pioglitazone 30 mg/day decreased

triglyceride levels (16.6%, $p < 0.02$), and increased HDL cholesterol (12.6%, $p < 0.01$). In addition, a non-significant rise in LDL cholesterol was observed in the active treatment group. In this study, the pioglitazone-induced improvements in lipid profiles were independent of the use of lipid-lowering medication (see section 2.4). Pioglitazone, both as monotherapy and in combination, has been shown to decrease plasma free fatty acids in other studies of patients with type 2 diabetes.[149,156]

The findings from four studies that evaluated the use of pioglitazone in combination with sulphonylureas are difficult to compare because two studies (both Japanese) reported the treatment-induced changes in absolute values only. Nevertheless, in the study by Kipnes et al.,[157] 16 weeks of pioglitazone 30 mg/day combined with a sulphonylurea significantly lowered triglyceride levels (which had increased in placebo-treated patients) and increased HDL cholesterol, without significantly affecting total cholesterol and LDL cholesterol. The treatment-related changes were well within the range of those observed after pioglitazone monotherapy. When pioglitazone 30 mg/day was combined with metformin, similar effects on triglycerides and HDL cholesterol were observed to those seen in pioglitazone monotherapy trials (table IV).

Overall, pioglitazone reduces the atherogenic lipid and lipoprotein profile in patients with type 2 diabetes. This was shown indirectly by the pioglitazone-induced reduction of the so-called Atherogenic Index of Plasma (AIP = log [triglyceride/HDL cholesterol]), which correlated inversely with LDL particle size.[160] Also, a more direct assessment of the anti-atherogenic effect of pioglitazone on LDL size and composition was reported, by Winkler et al.,[161] who found a significant reduction of apolipoprotein B in the most dense LDL subfraction, as determined by equilibrium density gradient ultracentrifugation. In addition, the estimated average diameter of LDL particles increased significantly from 19.5 to 19.8nm.[161]

2.2.3 Effects on Insulin Resistance and β-Cell Function

Similar to the trials evaluating the effects of rosiglitazone, the majority of studies that have assessed the use of pioglitazone, measured FPI levels to estimate changes in insulin sensitivity (table III).[153-157] Pioglitazone at dosages of 30 and 45 mg/day, administered as monotherapy and also in combination with sulphonylureas or metformin, significantly lowered FPI levels.[153-155,157] In obese patients with type 2 diabetes, 23 weeks of pioglitazone 30 mg/day monotherapy, in addition to reducing FPI and C-peptide levels, resulted in a significant decrease in insulin resistance (12.4% from baseline) and improvement of β-cell function (47.7% from baseline), as estimated by HOMA model analyses.[155]

In sulphonylurea-treated patients, the addition of pioglitazone 45 mg/day for 16 weeks decreased fasting and mean plasma free fatty acids during OGTT.[156] Pioglitazone decreased endogenous glucose production and increased total and non-oxidative glucose disposal, as measured by a two-step euglycaemic insulin clamp. In diet-treated patients with type 2 diabetes, 26 weeks of pioglitazone 30 and 45 mg/day monotherapy, but not 7.5 and 15 mg/day, significantly reduced FPG and mean glucose levels post-OGTT, as well as the insulinogenic index during the OGTT, the latter indicating an improvement of β-cell function.[162] In addition, pioglitazone 30 and 45 mg/day, improved whole-body and hepatic insulin sensitivity, as estimated from OGTT data.

Similar to the findings reported in patients treated with rosiglitazone,[146] pioglitazone 15 mg/day for 12 weeks increased circulating adiponectin levels in relation to an improvement of insulin resistance in patients with type 2 diabetes, as assessed by HOMA.[163]

2.3 Effects on Cardiovascular Risk Factors and Diabetic Microvascular Complications

In addition to the above described improvement of atherogenic lipid profile (see sections 1.2, 2.1.2, and 2.2.2), thiazolidinediones, as demonstrated in

numerous experimental studies, have the potential to favourably modulate cardiovascular risk factors, partly indirectly, by improving insulin sensitivity, but also directly, by affecting the vascular wall and cells involved in atherogenic processes.[58-60,103-105,111-115] In patients with type 2 diabetes, troglitazone resulted in beneficial effects on body fat distribution,[164] blood pressure,[110] endothelial function,[165] arterial wall,[166] myocardial function,[167,168] pro-thrombotic states[169] and pro-inflammatory states.[170] In addition, it was suggested that thiazolidinedione therapy might ameliorate diabetic microvascular complications.[171-173] To date, there are but a few reports describing the beneficial effects of rosiglitazone and pioglitazone on cardiovascular (risk) variables and diabetic complications in humans. A very recently published substudy to the trial by Lebovitz et al.,[138] showed that 26 weeks of rosiglitazone therapy significantly reduced plasma levels of C-reactive protein (CRP) and MMP-9.[174] In addition, in a study in patients with type 2 diabetes and angiographically proven coronary artery disease, rosiglitazone 4mg twice daily for 12 weeks reduced serum levels of the proinflammatory marker CD40.[175] The major findings in patients with type 2 diabetes are summarised below in section 2.3; however, it should be noted that the majority of these data are preliminary in nature and have been published in abstract form only.

2.3.1 Body Fat Distribution

Despite the weight gain reported in all studies in patients receiving thiazolidinedione treatment, which may equal as much as 0.5 kg/month for monotherapy and higher rates when combined with a sulphonylurea or insulin, mean waist-to-hip ratio remained invariably unchanged. An even favourable effect on body fat distribution was demonstrated when patients with type 2 diabetes were treated with pioglitazone 45 mg/day for 16 weeks.[176] Using MR imaging, pioglitazone decreased visceral fat area and increased subcutaneous fat mass. Concomitant improvements of insulin-induced suppression of hepatic glucose production and glucose metabolic clearance rate during an insulin clamp were observed. In the same patients, using ^{1}H-MR spectroscopy, a significant decrease in liver fat content was demonstrated after pioglitazone therapy.[177] Similarly, 3 months of rosiglitazone treatment in obese patients with type 2 diabetes resulted in significant reductions in hepatic triglyceride content, as measured by ^{1}H-MR spectroscopy, but unexpectedly also produced an increase in extramyocellular lipid content.[97] In an observational study, a significant decrease in the liver enzyme ALT levels was observed in patients treated with pioglitazone 45 mg/day for more than 6 months,[178] and this was associated with a thiazolidinedione-induced reduction of intrahepatic fat and an improvement of steatohepatitis. Rosiglitazone therapy showed a comparably favourable effect on body fat distribution, despite a significant weight gain in patients with type 2 diabetes.[179,180] In a study using [^{18}F]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET), rosiglitazone differentially affected insulin-stimulated glucose uptake in the various fat depositions; in contrast to its effect on visceral adipose tissue, the agent enhanced insulin-stimulated glucose uptake in the femoral subcutaneous area and this in part explained the improved whole-body insulin senstivity.[180]

Thus, thiazolidinediones have favourable effects on body fat distribution, intra-hepatic fat content and adipose tissue metabolism, all resulting in increased insulin sensitivity. However, it has been shown that a 4-month diet and exercise programme resulted in greater metabolic improvements and also favourably modified body fat distribution compared with pioglitazone therapy in obese patients with type 2 diabetes.[181] This small study demonstrates that drug therapy should not replace lifestyle modification in high-risk populations.

2.3.2 Blood Pressure

The trials evaluating rosiglitazone and pioglitazone (described above in sections 2.1 and 2.2) focus on metabolic effects and safety parameters and only one of these trials, in patients receiving rosiglitazone 8 mg/day in combination with insulin, reported a significant decrease in diastolic blood pressure (2.6mm Hg, $p < 0.005$).[125] In a review by the UK National Institute of Clinical Excellence

(NICE),[143] which summarises the clinical efficacy of rosiglitazone, only a small but statistically significant decrease (1.8mm Hg [range 0.3–3.3mm Hg]) in diastolic blood pressure was found at 26 weeks in patients receiving rosiglitazone combined with metformin, compared with those receiving metformin only. Also in the NICE report, when describing an early analysis of the study by Wolffenbuttel et al.,[140] a small but significant difference in systolic blood pressure was found in patients receiving rosiglitazone 4 mg/day in combination with sulphonylureas; however, this was not reported in the final publication of the study. A meta-analysis of 6-month blood pressure levels of the studies included in the NICE analysis showed no significant difference between the groups.[143]

In an open-label, 52-week cardiac safety study comparing rosiglitazone 4mg twice daily with glibenclamide, Bakris et al.[182] found significant reductions from baseline in the rosiglitazone group at week 52 in systolic (3.5mm Hg, $p < 0.05$), diastolic (2.7mm Hg, $p < 0.01$) and mean arterial pressure (2.8mm Hg, $p < 0.02$). In addition, rosiglitazone-treated patients experienced a decrease in both systolic and diastolic blood pressure during the day (3.0 ± 5.9mm Hg [SD]) and night (3.0 ± 8.1mm Hg) hours at week 28, which persisted at week 52. In contrast, in glibenclamide-treated patients, blood pressure increased from baseline at weeks 28 and 52.[182] In a more recent, small study in patients with impaired glucose tolerance, 12-weeks' treatment with rosiglitazone 4mg twice daily versus placebo lowered both systolic (9.8mm Hg, $p < 0.01$) and diastolic (8.0mm Hg, $p < 0.05$) 24h ambulatory blood pressure.[183] However, patients receiving rosiglitazone had higher mean baseline systolic/diastolic blood pressure values than those given placebo (132/76mm Hg vs 121/69mm Hg). A recent review summarising the clinical efficacy of pioglitazone in patients with type 2 diabetes,[42] to a large extent based on the studies described here in detail, did not report blood-pressure-lowering effects of the drug.

Interestingly, a recent report showed beneficial effects of pioglitazone 45 mg/day on diastolic blood pressure in 60 non-diabetic individuals with hypertension. With pioglitazone, mean systolic blood pressure fell by 6.7mm Hg (vs 3.1mm Hg with placebo; nonsignificant difference from baseline or placebo) but a significant decline in mean diastolic blood pressure of 7.9 (vs 1.8mm Hg with placebo; $p = 0.016$) was observed.[184]

In animal studies it was demonstrated that thiazolidinediones may lower blood pressure by ameliorating insulin resistance and also by direct effects on the vascular wall.[112] However, the ability of thiazolidinediones to produce long-term, clinically relevant blood pressure reductions in humans needs further evaluation in large, long-term prospective studies.

2.3.3 Endothelial Functions

In physiological states, the vascular endothelium possesses many properties that collectively serve to conserve its anti-atherogenic (i.e. anti-inflammatory and anticoagulant) activities and to guarantee its integrity and protection. Endothelial injury is a key factor in atherogenesis and abnormalities in various endothelial functions are associated with cardiovascular morbidity and mortality in insulin-resistant patients and patients with type 2 diabetes. Therefore, it seems feasible that, although not established in long-term prospective studies, drug-induced improvement of endothelial function(s) may be beneficial for patients at high risk for cardiovascular disease. Animal experiments have suggested that rosiglitazone[185] and pioglitazone[112,186] may improve some of the endothelial functions.

In patients with type 2 diabetes, the effect of 16 weeks of therapy with rosiglitazone or pioglitazone on ultrasound measured post-ischaemic flow-mediated vasodilatation (FMD) in the brachial artery was compared with sulphonylurea compounds.[187] Despite improvements in glycaemic control and insulin sensitivity, no changes in FMD were observed in the thiazolidinedione groups. It was suggested that a longer treatment period may be necessary to induce changes in FMD, however, the number of patients was too small (n = 10–12 per group) to detect significant differences when using FMD to estimate endothelial function *in vivo*. In contrast, in another

small group of patients with type 2 diabetes (n = 9), pioglitazone treatment for approximately 4 months increased FMD (from 5.0% to 7.8%, $p < 0.03$).[188] In another study in 11 obese diabetic patients, rosiglitazone 4 mg/day for 6 weeks resulted in an increase in FMD (from 3.4 to 8.6%, $p < 0.05$). Simultaneously, there was a significant fall in NF-κB-binding activity to mononuclear cells (MNC), reactive oxygen species generation by MNC and CRP levels.[189] Endothelium-dependent vasodilatation (estimated by measurements of forearm blood flow response to graded intra-arterial infusions of acetylcholine [and sodium nitroprusside to assess endothelium-independent vasodilatation] by plethysmography) was improved after rosiglitazone, but not after metformin or placebo treatment.[190] In a small group of insulin-resistant Mexican-Americans, treatment with rosiglitazone for 3 months improved coronary artery endothelial dysfunction, measured as the response of myocardial blood flow to cold-pressor test by PET.[191]

The long-term beneficial effects of the available thiazolidinediones on (markers of) endothelial functions and the prognostic implications still remain to be demonstrated.

2.3.4 Carotid Intimal Medial Thickness

Carotid artery intimal medial wall thickness (IMT) is associated with an increased risk of cardiovascular disease and reduction of IMT may reduce the risk of cardiovascular events. To date, there are no data reporting the effect of rosiglitazone on carotid IMT. Three-month treatment with pioglitazone 30 mg/day in patients with type 2 diabetes resulted in a significant decrease in carotid IMT, as assessed by B-mode ultrasound, and a further reduction was observed after 6 months of therapy.[116] These effects may be due to anti-atherogenic properties but also to the insulin-sensitising actions of pioglitazone. The implications of these findings need to be determined in large, long-term studies.

2.3.5 Myocardial Function and Metabolism

Data from animal studies suggested that thiazolidinedione treatment may cause LV hypertrophy and adversely affect cardiac function;[192,193] therefore, long-term echocardiographic assessment was performed in patients taking rosiglitazone[194] and pioglitazone.[195,196] Treatment with rosiglitazone 4mg twice daily for 52 weeks had small, clinically irrelevant effects on LV mass index, ejection fraction and LV end-diastolic volume, which were similar to the effects of glibenclamide.[194] Pioglitazone 15, 30 and 45 mg/day for up to 26 weeks had no adverse effect on cardiac structure and function.[195] This was also the case in another study evaluating patients after 48 weeks of pioglitazone treatment.[196]

Myocardial functional improvement due to treatment with rosiglitazone or pioglitazone has not yet been documented. However, thiazolidinediones may favourably affect LV function, since rosiglitazone 8 mg/day for 6 months was found to enhance resting and stress-induced myocardial flow, as measured by PET,[197] as well as increase insulin-stimulated myocardial glucose uptake in patients with type 2 diabetes.[198] Several studies are underway evaluating thiazolidinedione-induced myocardial metabolic and functional changes. At all times, caution should be exercised since rapid and excessive fluid retention may cause congestive heart failure (see section 2.5.3).

2.3.6 Diabetic Microvascular Complications

Microalbuminuria and albuminuria are early manifestations of diabetic nephropathy and important predictors of cardiovascular disease. The pathophysiological mechanisms linking microalbuminuria to cardiovascular disease may be endothelial dysfunctions. Evidence from one of the early monotherapy studies comparing glibenclamide and rosiglitazone suggested that only the latter reduced microalbuminuria in patients with type 2 diabetes.[143] In the earlier mentioned study by Bakris et al.[182] (see section 2.3.2) treatment with rosiglitazone (4mg twice daily) was associated with a decrease in urinary albumin excretion.[199] In a long-term, open-label trial of pioglitazone (mean dose 36.8 mg/day) in patients with type 2 diabetes, a significant decline in urinary albumin excretion levels was found at weeks 48 and 108, suggesting that pioglitazone may slow the progression of microalbuminuria.[200] A previous study showed that pioglitazone decreased

urinary albumin excretion as well as urinary endothelin-1 levels in patients with type 2 diabetes.[117]

At present, no studies have reported the effect of the available thiazolidinediones on the course or incidence of diabetic retinopathy. However, provided that the mechanisms underlying diabetes-related retinal microvascular changes resemble those operating in the pathophysiology of microalbuminuria, then, although it remains to be demonstrated, beneficial effects from thiazolidinedione therapy may be expected. However, future studies should clarify whether the previously reported increases in circulating vascular endothelial growth factor (VEGF) levels in patients with type 2 diabetes following troglitazone[201] and pioglitazone[202] treatment, are unrelated phenomena attributable to, for example, platelet activation, or whether these elevations are associated with the development and progression of retinopathy and nephropathy.

2.4 Comparing the Thiazolidinediones

To date, no long-term studies have been published comparing the two thiazolidinediones in a prospective, randomised, controlled and blinded design. However, two recent papers have compared the metabolic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone.[120,121]

In the first study, after 1-week washout from troglitazone, 67 patients were given pioglitazone and 77 received rosiglitazone.[120] After a mean 3.2-month observation, HbA_{1c} decreased by 0.08% in both groups. Mean total cholesterol, triglyceride and LDL cholesterol levels dropped in the pioglitazone group by 4.7%, 11.3% and 7.3%, respectively, but increased by 8.4%, 38.4% and 8.1%, respectively, in the rosiglitazone group. Mean HDL cholesterol levels were increased by 2.6% with pioglitazone and decreased by 6.3% with rosiglitazone therapy. Unexpectedly, patients receiving HMG-CoA reductase inhibitors, when switched to rosiglitazone, had a mean rise in triglyceride levels of 51.9%, compared with 25.7% in those who had not received HMG-CoA reductase inhibitors. In contrast, in patients who were switched from HMG-CoA reductase inhibitors to pioglitazone, mean triglyceride levels fell by 14.2%, compared with 6.2% in those who had not received HMG-CoA reductase inhibitors. The interaction between rosiglitazone and HMG-CoA reductase inhibitors in these studies cannot be explained.

At a 12.6-month follow up of these patients from the first study, pioglitazone was associated with a reduction in total cholesterol levels, a progressive increase in HDL cholesterol levels by 22.1% and a further decline in triglyceride levels by 26.4%, whereas rosiglitazone was associated with an increase in HDL cholesterol by 13.3%, as well as a rise in triglyceride levels by 15.3% and in total cholesterol.[203]

The differential effects on the lipid profiles of thiazolidinedione preparations, which are independent of glycaemic effects, have also been reported in other studies.[118,119]

In the second study, after a 2-week washout from troglitazone, 127 patients were randomly assigned to receive either pioglitazone or rosiglitazone.[121] At baseline, there were no differences in gender, age, weight, HbA_{1c} or fasting lipid profile between groups. However, it should be noted, that mean baseline HbA_{1c} levels were lower in these patients (8.0% in patients receiving pioglitazone and 7.9% in those receiving rosiglitazone) than in patients included in the earlier described studies with thiazolidinediones. After 4 months of randomised treatment, no change in HbA_{1c} was found. Both groups experienced similar weight gain from baseline of about 2kg. In patients treated with pioglitazone, mean total cholesterol levels dropped significantly by 0.13 ± 0.1 mmol/L ($p < 0.03$) and this was more pronounced in patients receiving concomittant HMG-CoA reductase inhibitors (0.76 ± 0.21 mmol/L; $p < 0.01$). In contrast, an increase in mean total cholesterol levels was noted in patients treated with rosiglitazone (0.43 ± 0.16 mmol/L; $p < 0.03$), which was attenuated by concomittant HMG-CoA reductase inhibitors (0.1 ± 0.15 mmol/L).

Interestingly, these findings in patients given rosiglitazone using HMG-CoA reductase inhibitors[121] do not support those reported in the study by

Gegick and Altheimer.[120] Although no conclusions can be drawn regarding the possible mechanism underlying these clinical observations, it was suggested that the lipid-lowering effects of HMG-CoA reductase therapy may have been blunted by troglitazone as this drug induces the cytochrome P450 (CYP) isoform CYP3A4 and, therefore, may lower serum levels of CYP3A substrates such as atorvastatin and simvastatin. Since discontinuation of troglitazone abolishes hepatic enzyme induction, in patients treated with HMG-CoA reductase inhibitors, this may enhance the favourable effects of pioglitazone on the lipid profile and blunt the increase in lipids observed with conversion to rosiglitazone.[120]

Taken together, compared with rosiglitazone, pioglitazone results in greater increases in HDL cholesterol, smaller increases in LDL cholesterol and greater decreases in triglyceride levels. This consistent difference between the two available thiazolidinediones has, among others, been attributed to the *in vitro* observation that pioglitazone at therapeutic concentrations activates both PPARγ and α receptors, while rosiglitazone predominantly activates PPARγ.[204]

2.5 Safety and Tolerability

To date, the use of rosiglitazone and pioglitazone has not been associated with liver failure.[41,42,205] For both agents, the most frequently reported adverse events are weight gain (see section 2.5.2), fluid retention and oedema (see section 2.5.3), and anaemia.[205] Other adverse events, which occur more frequently in patients treated with these agents than with placebo, include upper respiratory tract infections, sinusitis and headache.[122,123] Myalgia occurs more often with pioglitazone (5.4% of patients) compared with placebo (2.7% patients), and, occasionally, a transient rise in creatine phosphokinase may occur.[205] The clinical significance of these findings is as yet unclear.

Pioglitazone, similar to troglitazone, is in part metabolised by CYP3A4 and this may interfere with the metabolism of numerous drugs, such as antibacterials, calcium-channel antagonists, benzodiazepines, HMG-CoA reductase inhibitors and oral contraceptives.[205] Conversely, inhibitors of CYP3A4 such as ketoconazole, may potentially inhibit the metabolism of pioglitazone.[26,205] Rosiglitazone is predominantly metabolised by the CYP2C8 pathway, which involves the metabolism of a limited number of agents. So far, no significant drug interactions have been noted in clinical studies with rosiglitazone[205] or pioglitazone.[206] Finally, it should be pointed out that, since thiazolidinediones have the potential to induce numerous effects in a large variety of tissues, only long-term use in humans may reveal unforeseen effects which may prove harmful.

2.5.1 Hepatotoxicity

Three case reports have been published describing non-fatal hepatic dysfunction in association with the use of rosiglitazone and pioglitazone.[35-40] Evaluations of 5006 patients receiving rosiglitazone alone or as combination therapy[41] and 2096 patients taking pioglitazone[206] during clinical trials showed no evidence of hepatotoxic effects of the thiazolidinediones. The percentage of all patients with ALT values >3 times the upper limit of normal of the reference range was 0.32% with rosiglitazone, 0.38% with pioglitazone, 0.17% for placebo, and 0.40% for sulphonylureas, metformin or insulin therapy.[41,206] ALT elevations in patients receiving thiazolidinediones were indistinguishable from placebo in controlled trials. At present, pending the results of additional large, long-term controlled clinical trials and post-marketing safety data, it is recommended that liver enzymes are monitored before the initiation of rosiglitazone and pioglitazone therapy, every 2 months during the first year of therapy and periodically thereafter.[122] Thiazolidinediones should not be given to patients with ALT >2.5 times the upper limit of normal at baseline.[123] However, because steatohepatitis, which constitutes a hallmark of insulin resistance, is often associated with elevated liver enzymes, one may argue that patients with this condition, in particular, may benefit from thiazolidinedione treatment.[177,178]

2.5.2 Weight Gain

Treatment with all thiazolidinediones is associated with weight gain.[26,205] The causes for this

weight gain could be fluid retention, increased fat mass or improvement in hyperglycaemia. As stated earlier, thiazolidinediones promote body fat redistribution with accumulation occurring in the subcutaneous, rather than the visceral fat depots.

Treatment with rosiglitazone 8 mg/day for 26 weeks resulted in an average weight gain of 3.1kg when given as monotherapy, 1.8kg when combined with a sulphonylurea, 2.1kg when co-administered with metformin and up to 5.4kg in combination with insulin.[122] Similar dose-related weight changes were observed in all clinical studies with pioglitazone.[123] Although weight gain was associated with an improvement in glycaemic control,[133,138,153,154,158] a recent study showed that weight continued to increase at about 0.5kg per month despite HbA_{1c} changes stabilising after 5 months of pioglitazone therapy.[207]

The most important characteristics of patients who gained most weight, compared with those not gaining weight, were shorter duration of diabetes and greater adiposity.[207] Combined data from studies with pioglitazone monotherapy and combination therapy showed that weight continued to increase for as long as data were recorded, i.e. up to 60 weeks in European and Japanese studies, and up to 84 weeks in US studies.[42] Therefore, studies of a longer duration are required to determine whether thiazolidinedione-induced weight gain reaches a plateau.

2.5.3 Fluid Retention

Thiazolidinedione therapy is associated with fluid retention and plasma volume expansion causing peripheral oedema.[122,123,205] Paradoxically, the use of these agents is associated with a reduction, albeit modest, in blood pressure (see section 2.3.2). Several mechanisms may underlie these effects, including thiazolidinedione-induced enhancement of insulin-mediated vasodilatation, a direct vasoactive effect,[208] inhibition of vasoconstrictors such as endothelin-1[103,111] and increased VEGF production.[201]

Moderate oedema was observed in 4–5% of patients taking rosiglitazone alone or in combination with metformin, 2.2% in those receiving metformin and 1.3% in the placebo group.[205] Similarly, oedema was reported in 4.8% of patients taking pioglitazone monotherapy compared with 1.2% receiving placebo; no patient was discontinued because of oedema. The overall incidence of oedema in controlled studies was 6.6% among pioglitazone-treated patients and 2.3% among those receiving placebo.[206]

Only recently, has the prescription information of both agents been modified, ushering a warning regarding the risk of congestive heart failure in patients receiving rosiglitazone or pioglitazone in combination with insulin.[126] Although some, but not all patients who developed heart failure had a history of cardiac disease, it was not possible to determine specific risk factors that could identify all patients at risk of heart failure on combination therapy. In the US, rosiglitazone and pioglitazone are not recommended in patients with New York Heart Association (NYHA) Class III and IV cardiac status.

Small reductions in haemoglobin and haematocrit have been reported from all clinical studies with rosiglitazone and pioglitazone.[205] Haematological changes have been associated with fluid retention and haemodilution, and seem to occur during the initial phase of treatment. Thiazolidinedione-associated anaemia was not clinically relevant and did not lead to withdrawal from the studies. No effect of rosiglitazone on red blood cell turnover was found.[209]

2.6 Some Unresolved Issues

The long-term efficacy of thiazolidinediones with regard to glycaemic control in patients with type 2 diabetes has been questioned in two recent reports,[210,211] suggesting secondary treatment failure, as known for other oral blood-glucose lowering agents.[52] In patients switched from troglitazone to rosiglitazone or pioglitazone, HbA_{1c} rose significantly by 1.18% and 0.66%, respectively, after 18 months despite the use of standard antihyperglycaemic drugs during the study.[211] In part, this observation may be explained by progressive β-cell failure and the decreasing availability of insulin. Also, these findings may be linked to the unsettled

issue of the relatively high non-responder rate (primary treatment failure), reportedly between 25–30%, observed in clinical trials with both rosiglitazone and pioglitazone.[15,52]

Another concern was raised about possible carcinogenic effects of thiazolidinediones when experimental studies showed that these agents induced liver tumours in mice and rats,[61] and colon tumours in a murine model of familial adenomatous polyposis coli.[212,213] High expression of PPARγ was found in various tumour cells indicating that the activation of PPARγ may be important in controlling tumour proliferation.[61] Thiazolidinediones induced expression of VEGF, an angiogenic mitogen which may be involved in tumour progression. However, no increase in carcinogenesis was found in 2-year safety studies with high-dose rosiglitazone[122] and pioglitazone[123] in mice and rats. In fact, recent data indicate that thiazolidinediones may rather inhibit tumour growth and induce apoptosis in a variety of tumours, rendering these agents as potential anticancer drugs.[24,26,61,130] Many investigations are underway to clarify these controversies.

An unexposed issue may be the reported inhibitory effect of troglitazone, but not rosiglitazone, on the glyoxalase system in rat hepatocytes, resulting in increases in advanced glycation end product formation and oxidative stress.[214] The glyoxalase system consists of the enzymes glyoxalase I and II, which are involved in the metabolism of methylglyoxal, a precursor for advanced glycation end products.[215] The effect of pioglitazone on these processes is currently unknown and no data exist with regard to the effect of either available thiazolidinediones on the glyoxalase system in human tissues.

Finally, a preliminary analysis in older adults with type 2 diabetes revealed an association between thiazolidinedione use and lower hip bone mineral density.[216] In mice, activation of PPARγ by thiazolidinediones was shown to increase bone marrow adiposity, decrease osteoblast number and lower bone mass.[217] Similar to the other effects of thiazolidinediones, large prospective studies should demonstrate the clinical implications of these findings.

3. Future Perspectives

Although the working mechanism of thiazolidinediones as a concept is appealing, and their beneficial effects in animals and short-term clinical studies are promising, many uncertainties remain regarding the long-term efficacy and safety of these agents in high-risk populations. Also, the potential of these compounds to affect processes such as angiogenesis, carcinogenesis, cell growth, and bone metabolism should be explored in humans. Therefore, large, prospective, randomised, controlled trials assessing end-points such as overall cardiovascular mortality as well as non-fatal cardiovascular events are needed to establish the place of thiazolidinediones in the management of type 2 diabetes and to settle the uncertainties. At present, several large trials for both of the clinically available agents are ongoing, addressing these issues.

Long-term effects of rosiglitazone on cardiovascular outcome will be evaluated in A Diabetes Outcome Progression Trial (ADOPT)[218] and the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD) trial. In the latter, the long-term effects (scheduled median follow up of 6 years) of rosiglitazone, in combination with a sulphonylurea or metformin, on cardiovascular endpoints and glycaemia will be studied in approximately 4000 patients. The effect of long-term pioglitazone therapy versus placebo on mortality and non-fatal cardiovascular events will be studied in the PROspective Pioglitazone Clinical Trial In MacroVascular Events (PROACTIVE) trial (scheduled median follow up of 2.5–4 years), enrolling about 5000 patients.

It may be expected that these studies will possess sufficient power to reliably establish the effect of the thiazolidinedione compounds on relevant endpoints, and settle questions as to whether the treatment-induced improvement in metabolic control will be maintained over the prolonged follow-up periods and whether the beneficial actions outweigh the potentially deleterious effects on bodyweight, lipids, angiogenesis and glycation. Similar to earlier discussions regarding hepatotoxicity, these studies may differentiate between the possible unique (adverse)

effects of each representative of the thiazolidinedione class. Finally, long-term studies may reveal characteristics or markers that will help to identify patients who will benefit most from thiazolidinedione therapy.

4. Conclusions

Type 2 diabetes develops in the presence of insulin resistance and β-cell dysfunction. Insulin resistance is associated with various risk factors for cardiovascular disease, including central obesity, hypertension, dyslipidaemia, hypercoagulability and low-grade inflammation. Thiazolidinediones constitute an attractive treatment option because they reverse insulin resistance and have the potential to improve many of the associated abnormalities in patients with type 2 diabetes. Several clinical trials in patients with type 2 diabetes have demonstrated the beneficial effects of rosiglitazone and pioglitazone alone or in combination with sulphonylureas, metformin or insulin on glycaemic control and insulin sensitivity. However, many aspects of the working mechanism of thiazolidinediones, in particular the mechanisms operating down-stream of the PPARγ, remain obscure and need further exploration.

After binding to PPARγ, thiazolidinediones can act as partial agonists and antagonists with respect to a given endogenous gene, and whether or not transcription occurs will depend on the actual context of gene co-activators and co-repressors and their direct cellular environment. Thus, different thiazolidinedione compounds may induce overlapping, but substantially different sets of genes and gene products, resulting in a phenotype (clinical response) that may or not be beneficial for the organism. This complex phenomenon may, in part, explain the sometimes conflicting findings reported for thiazolidinedione-mediated actions in both animal and patient studies.

At present, it seems the two currently available thiazolidinediones, pioglitazone and rosiglitazone, can be safely used, but patients using these compounds should be monitored carefully, in particular with regard to fluid retention and congestive heart failure. The long-term efficacy and safety of thiazolidinediones needs to be substantiated in large outcome studies. Furthermore, considerable effort is required to further elucidate the role of PPARγ in metabolic and insulin-signalling pathways, and the precise mechanisms of thiazolidinedione action to enable the development of new agents for insulin resistance therapy.

Acknowledgements

No sources of funding were used to assist in the preparation of this manuscript. The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

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