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Combined Thiazolidinedione-Insulin Therapy

Should We Be Concerned About Safety?

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Abstract

Thiazolidinediones, also called glitazones, are insulin sensitisers that act as agonists of the peroxisome proliferator-activated receptors-gamma (PPARγ). After the withdrawal of troglitazone due to hepatotoxicity, only pioglitazone and rosiglitazone can be used for treating patients with type 2 diabetes mellitus, either as monotherapy or in combination with metformin or with sulphonylureas (or glinides). The combination of glitazones with insulin is also appealing, as it allows improvement of glycaemic control while decreasing the daily insulin requirement. Insulin dosage has to be adjusted regularly to avoid hypoglycaemic episodes. However, some concerns have been raised about such combined glitazone-insulin therapy because it may favour weight gain due to both enhanced adipogenesis and fluid retention. Such adverse effects are commonly observed in all diabetic individuals receiving glitazones, whatever the mode of use, but they appear to be exacerbated in insulin-treated patients. Body fat gain is a major drawback of treatment with adipogenic compounds such as glitazones. However, some evidence suggests that the fat is redistributed in a favourable direction, that is, from visceral to subcutaneous depots, although no long-term follow-up is yet available. An estimated 2–5% of patients receiving glitazone monotherapy and 5–15% receiving concomitant insulin therapy experience peripheral oedema. Some anecdotal cases of pulmonary oedema have also been reported, especially in insulin-treated patients, although the actual incidence of this complication is unknown. All glitazones increase the intravascular volume by approximately 6–7% in a dose-dependent manner. Rather than a direct effect on cardiac or renal function, fluid retention and tissue oedema seem to be part of a vascular 'leak' syndrome. Such a phenomenon may have greater consequences in patients with type 2 diabetes treated with insulin because such patients are usually older, have had the disease long-term and have worse cardiac or renal function. Additionally, glitazones may potentiate the renal effects of insulin on sodium and water retention. Regardless of the mechanism, it is conceivable that additional fluid retention caused by glitazones may alter the already precarious volume status in patients with underlying cardiac or renal dysfunction, thus leading to oedema and congestive heart failure. Thus, it is prudent to either avoid glitazones or use them cautiously in individuals with impaired cardiac function. Further studies are clearly needed to define the mechanisms of fluid retention associated with

glitazone use and to determine the safety of cautious use of these new insulin sensitisers in insulin-treated patients with type 2 diabetes.

Type 2 diabetes mellitus is characterised by a dual defect in insulin secretion and insulin action.[1-3] Furthermore, it is a progressive disease during which a continuous decline in β-cell function is observed.[4] First-line therapy for type 2 diabetes includes medical nutritional therapy and meal planning, exercise and appropriate weight reduction.[5] Should these lifestyle measures fail to provide adequate glycaemic control, oral pharmacological therapy is generally initiated.[6-9] For a large proportion of patients, however, oral therapy eventually fails as well, most often because of a progressive decline in endogenous insulin production. Patients with type 2 diabetes who have inadequate responses to oral agents often progress to insulin therapy.[10,11] In fact, approximately half of all patients with type 2 diabetes take injected insulin to help improve glycaemic control,[12] and one might predict that this proportion will further increase if target glycosylated haemoglobin (HbA_{1c}) levels <7.0%[5] or <6.5%[13] are to be achieved.

Combined therapy with insulin and an oral agent is common in the management of type 2 diabetes.[14-18] The combination of bedtime insulin to control fasting glycaemia and a pre-meal sulphonylurea to stimulate residual insulin secretion and control postprandial hyperglycaemia has been advocated and widely used.[19] Alternatively, the combination of insulin with metformin has been recommended in obese individuals to reduce their insulin needs and limit insulin-induced weight gain.[20] With the introduction of the thiazolidinediones, also called glitazones, a new class of oral agents with a novel mechanism of action has become available to reduce insulin resistance and improve glycaemic control.[21-23] Glitazones act as agonists of a group of nuclear receptors known as the peroxisome proliferator-activated receptors-gamma (PPARγ) to enhance the actions of insulin, with resulting improvements in insulin-dependent glucose disposal and reductions in hepatic glucose output.[24,25] Troglitazone was the first glitazone to be commercialised,[26,27] but had to be withdrawn because of liver toxicity.[28,29] Currently, two other glitazone compounds are widely used in clinical practice, i.e. pioglitazone[30-32] and rosiglitazone.[33-35] These compounds have proven efficacy as monotherapy and more particularly in combination therapy with either metformin or sulphonylureas.[36,37] From a theoretical point of view, the combination of an insulin sensitiser such as a glitazone with exogenous insulin is appealing, as it may allow reduction of insulin requirement and improvement of metabolic control.[38] In addition, glitazones may exert some beneficial effects beyond improvement of glycaemic control, especially by improving cardiovascular prognosis.[39-42] However, some safety concerns have been raised, especially the risk of fluid retention and congestive heart failure (CHF).[43,44]

The aim of this concise review is to analyse the safety issues of the glitazone-insulin combination in the management of type 2 diabetes. A brief summary of the known and potential efficacy of this combination is followed by a more extensive discussion of the available safety data, especially the risk of severe hypoglycaemia, weight gain, fluid retention, CHF and liver toxicity.

1. Efficacy of the Thiazolidinedione-Insulin Combination

Most studies with glitazones were performed in diet-treated patients with type 2 diabetes or in combination with either metformin or sulphonylureas, and only few clinical trials have been reported in patients with type 2 diabetes receiving insulin.[30-35] None of the available trials with glitazones studied the effects of these new compounds on diabetic complications. However, owing to the recognised deleterious role of insulin resistance in the pathogenesis of atherosclerosis and cardiovascular complications,[45,46] ongoing randomised clinical trials are currently investigating the possible protective

effect of pioglitazone and rosiglitazone in diabetic patients with a high cardiovascular risk.[39]

This review considers only the effects of glitazones on glycaemic control, assessed by HbA_{1c} levels, as a primary endpoint. The effects of glitazones on lipid parameters are not discussed further, as they do not appear to be different in insulin-treated patients as compared with those with type 2 diabetes on diet regulation alone or on oral agents.[37,47]

1.1 Troglitazone

The effect of troglitazone or placebo was studied in 350 patients with poorly controlled type 2 diabetes despite therapy with at least 30U of insulin daily.[48] The patients were randomly assigned to receive troglitazone 200mg (n = 116) or 600mg (n = 116), or placebo (n = 118) daily for 26 weeks (table I). Insulin doses were not increased and were reduced only to prevent hypoglycaemia. The adjusted mean HbA_{1c} levels decreased by 0.8% and 1.4% in the troglitazone 200mg and 600mg groups respectively, despite decreases in the insulin doses of 11% and 29% ($p < 0.001$ for all comparisons with the placebo group).

Similar favourable results have been reported in a Canadian 24-week randomised, placebo-controlled trial of insulin therapy plus troglitazone 200–400 mg/day (reported only as an abstract).[49] In two subgroups of patients with either moderate or major increases in HBA_{1c} levels, troglitazone significantly improved overall glycaemic control (HbA_{1c} levels −0.90% and −1.35%, respectively; $p < 0001$) and reduced the mean total daily insulin dose (−17.7% and −12.5% respectively; $p < 0.001$) in spite of the fact that patients were instructed to maintain their insulin dose, except to avoid hypoglycaemia.

In another 26-week study, insulin-treated patients for whom prior therapy with oral antidiabetic agents had failed were randomly assigned to receive troglitazone 200mg or 400mg once daily or placebo with a goal of determining how much of an insulin-sparing effect could be demonstrated.[50] Troglitazone treatment decreased daily dose requirements for injected insulin by 22% and 27% in the

Table I. Adverse effects reported in three pivotal randomised, placebo-controlled trials with either troglitazone (TRO), pioglitazone (PIO) or rosiglitazone (RSG) in combination with insulin therapy in patients with type 2 diabetes mellitus

Study	Insulin plus	No. of pts	Duration of follow-up (wk)	HbA_{1c} change (%)	Insulin dose change (% of baseline)	Hypoglycaemic episodes (% of pts)	Bodyweight change (kg)	Haematocrit change (% of baseline)	Oedema (% of pts)	CHF (no. of pts)	ALT levels >3 × ULN (no. of pts)
Schwartz et al.[48]	Placebo	118	26	−0.1	+1	8	+1.5	NC	NA	0	3
	TRO 200mg	116	26	−0.8	−11	14	+1.9	NC	NA	0	2
	TRO 600mg	116	26	−1.4	−29	23	+3.6	−5	NA	1	3
Rosenstock et al.[51]	Placebo	187	16	−0.3	−0.8	5	−0.04	0	7.0	0	0
	PIO 15mg	191	16	−1.0	−6.9	8	+2.3	−1.4	12.6	2	0
	PIO 30mg	188	16	−1.3	−11.2	15	+3.7	−3.5	17.6	2	1[a]
Raskin et al.[52]	Placebo	104	26	+0.1	−0.6	6	+0.9	−0.9	4.7	1	0
	RSG 4mg	106	26	−0.6	−5.6	12	+4.0	−1.9	13.1	2	0
	RSG 8mg	103	26	−1.2	−12.0	14	+5.3	−3.0	16.2	2	0

a Patient was a chronic active carrier of hepatitis B.

ALT = alanine aminotransferase; **CHF** = congestive heart failure; **HbA_{1c}** = glycated haemoglobin; **NA** = not available; **NC** = no change; **pts** = patients; **ULN** = upper limit of normal.

200mg and 400mg treatment groups, respectively, reaching the target endpoint of at least a 50% reduction in injected insulin and a 15% reduction in fasting blood glucose level (or a blood glucose concentration of <140 mg/dL). Finally, in a direct comparative study, the insulin-sparing action of troglitazone 600mg once daily in intensively treated type 2 diabetes patients exceeded that of metformin 850mg twice daily.[38]

1.2 Pioglitazone

The glycaemic effects of treatment with pioglitazone in combination with insulin were evaluated in patients with type 2 diabetes.[51] Patients (n = 566) receiving stable insulin regimens for >30 days who had HbA_{1c} levels >8.0% and plasma C-peptide levels >0.7 μg/L were randomised to receive once-daily pioglitazone 15mg or 30mg or placebo, in a 16-week multicentre, double-blind, placebo-controlled trial (table I). Per study protocol, the insulin dose was to remain unchanged, but could be decreased in response to hypoglycaemia. At the end of treatment, patients receiving pioglitazone 15mg or 30mg showed statistically significant decreases in HbA_{1c} levels compared with baseline (−1.0% and −1.3%, respectively; $p < 0.0001$).

Similar results were obtained in a prospective, multicentre, double-blind, but not placebo-controlled, study comparing pioglitazone 30mg versus 45mg in addition to insulin in patients with type 2 diabetes.[53] A total of 690 patients, whose diabetes was poorly controlled with a stable insulin dose of >30 U/day, were randomised to receive pioglitazone 30mg or 45mg once daily. The mean insulin dose decreased steadily throughout the study period in both treatment groups. At week 24, the least squares mean change was −6.5 U/day (−9.4%) for the pioglitazone 30mg group and −10.6 U/day (−15.4%) for the pioglitazone 45mg group (significantly greater compared with 30mg; $p < 0.05$). Meanwhile, HbA_{1c} levels decreased by 1.17% and 1.46% with pioglitazone 30mg and 45mg, respectively. The improvement in blood glucose control was significantly greater with pioglitazone 45mg than with pioglitazone 30mg ($p < 0.05$).

An open-label, parallel-group study confirmed the efficacy and safety of combining insulin aspart/insulin protamine aspart, also known as biphasic insulin aspart (BIAsp), with pioglitazone (BIAsp/pioglitazone) versus BIAsp monotherapy or a combination of pioglitazone and glibenclamide (glyburide) in patients with type 2 diabetes inadequately controlled with oral agents.[54] In total, 246 patients completed the 18-week trial. The 8-point blood glucose profiles, average blood glucose and breakfast prandial increment decreased over time in the two insulin groups. HbA_{1c} levels at end-of-trial were significantly lower in the BIAsp/pioglitazone than in the BIAsp monotherapy group ($p < 0.05$). Minor hypoglycaemic episodes were rare and tended to be lower in the combined BIAsp/pioglitazone group than in the BIAsp monotherapy group.

1.3 Rosiglitazone

To determine the efficacy and safety of rosiglitazone when added to insulin in the treatment of patients with type 2 diabetes inadequately controlled by insulin monotherapy, 319 patients with mean HbA_{1c} levels ≥7.5% while receiving twice-daily insulin therapy (total daily dose ≥30U) were randomised to 26 weeks of additional treatment with rosiglitazone 4mg and 8mg daily or placebo[52] (table I). Insulin dose could be reduced only for safety reasons. The primary endpoint was reduction of HbA_{1c} levels from baseline. Rosiglitazone 4mg and 8mg daily significantly improved glycaemic control, which was unchanged with placebo. By intent-to-treat analysis, treatment with rosiglitazone 8mg plus insulin resulted in a mean reduction in HbA_{1c} levels from baseline of 1.2% ($p < 0.0001$), despite a 12% mean reduction in insulin dosage. More than 50% of patients treated daily with rosiglitazone 8mg plus insulin had a reduction in HbA_{1c} levels of >1.0%.

Finally, in a pilot open-label study in eight massively obese patients with type 2 diabetes (median body mass index of 42 kg/m^2), who were on large doses of insulin and/or had poor glycaemic control, the addition of rosiglitazone 8mg was associated with a fall in median HbA_{1c} level from 8.1% to

6.7% ($p < 0.01$) and a reduction in median insulin dose from 204 to 159 U/day ($p < 0.01$), after 24 weeks of follow-up.[55] In this study, there was an average weight gain of 3kg ($p < 0.01$).

2. Safety of Thiazolidinedione-Insulin Combination Therapy

2.1 Risk of Hypoglycaemia

Drug-induced hypoglycaemia is a major limiting factor in the quest for normoglycaemia in the diabetic patient.[56] Although the occurrence of such complication is much less frequent in patients with type 2 diabetes than in those with type 1 diabetes, it may occur in all patients receiving insulin therapy and potentially may be exacerbated in individuals receiving an insulin sensitiser in addition to exogenous insulin administration.

In the troglitazone-insulin combination study by Schwartz et al.,[48] symptoms of hypoglycaemia occurred in 41% of patients in the placebo group, 45% of those given troglitazone 200mg and 62% of those given troglitazone 600mg. Concurrent capillary-blood glucose level readings of ≤50 mg/dL (≤2.8 mmol/L) were observed in 8%, 14% and 23% of the patients of the respective groups (table I). The hypoglycaemic events tended to occur early in the course of troglitazone treatment and decreased in frequency after the insulin dose was reduced. With the exception of one patient who lost consciousness and was treated with intravenous glucose, all episodes of symptomatic hypoglycaemia were successfully treated with food or glucose tablets. No patient was withdrawn from the study because of hypoglycaemic symptoms.

In a randomised, controlled trial comparing pioglitazone 15mg and 30mg and placebo, in combination with insulin,[51] 29 patients (15%) receiving pioglitazone 30mg, 15 patients (8%) receiving pioglitazone 15mg and 9 patients (5%) receiving placebo reported hypoglycaemia (table I). All hypoglycaemic episodes were considered mild or moderate, and most were self-treated with caloric intake. Study medication was interrupted for two patients in the pioglitazone 30mg group because of hypoglycaemic events. One patient receiving pioglitazone 15mg withdrew from the study because of hypoglycaemia that was possibly related to study medication in combination with insulin. The dosage of insulin was lowered for six patients receiving pioglitazone 30mg, for three patients receiving pioglitazone 15mg and for one patient receiving placebo. Only mild hypoglycaemic episodes were also reported in two other clinical trials evaluating the combination of pioglitazone with insulin.[53,54]

In the rosiglitazone-insulin combination study by Raskin et al.,[52] the most common adverse event was symptoms consistent with hypoglycaemia, reported in 57 of 107 patients (53%) in the insulin plus rosiglitazone 4mg group and 70 of 105 (67%) in the insulin plus rosiglitazone 8mg group compared with 41 of 107 (38%) in the insulin plus placebo group. In all but four of these patients, the investigator classified the hypoglycaemia as mild or moderate. Documented hypoglycaemia (≤2.8 mmol/L) was observed in 12%, 14% and 6% of patients, after addition of rosiglitazone 4mg, rosiglitazone 8mg or placebo, respectively (table I). In general, patients were managed by insulin dose reductions. Three patients withdrew as a result of signs of hypoglycaemia; one was receiving placebo, and two were receiving rosiglitazone 8mg.

Thus, even if insulin sensitisers such as glitazones may favour insulin-induced hypoglycaemia, such adverse effects appear to be mild in most cases in insulin-treated patients with type 2 diabetes. Hypoglycaemia usually occurs in the first few days or weeks of combined therapy and could be quite easily avoided by an appropriate reduction in daily insulin dosages.

2.2 Risk of Weight Gain

Most individuals with type 2 diabetes are overweight or obese[57] and are characterised by visceral adiposity.[58] In those patients, weight excess may aggravate the stress on the β-cell, hyperglycaemia and other cardiovascular risk factors associated with insulin resistance, such as arterial hypertension and dyslipidaemia.[58] Thus, the adequate management

of the obese type 2 diabetic patient implies addressing both weight excess and hyperglycaemia.[59]

The PPARγ nuclear hormone receptor is primarily expressed in adipose tissue, where it is a major player in the regulation of adipocyte differentiation.[24] Glitazones, as PPARγ receptor agonists, are able to recruit and convert preadipocytes into adipocytes and, thus, are considered as adipogenic compounds.[60] Accordingly, moderate but significant weight gain has been consistently reported in most clinical trials with those compounds,[61] and such weight increase may be important in some patients. Thus, the question arises whether increased fat deposits are commensurate with long-term efficacy.[62]

In the initial combined troglitazone-insulin study by Schwartz et al.,[48] the small increases in bodyweight at 26 weeks in the troglitazone groups (1.9kg with troglitazone 200mg daily and 3.6kg with troglitazone 600mg daily) were statistically significant ($p < 0.001$) compared with those in the placebo group (1.5kg) [table I].

In the randomised, controlled trial comparing pioglitazone 15mg and 30mg and placebo, in combination with insulin,[51] patients in the placebo treatment group in general experienced no alterations in bodyweight (−0.04kg mean change from baseline). However, at the end of the double-blind treatment, mean change from baseline bodyweight was +2.3kg for patients who received pioglitazone 15mg and +3.7kg for those who received pioglitazone 30mg (table I). At all measured timepoints, mean bodyweight was slightly greater for the pioglitazone 30mg group than for the pioglitazone 15mg group. Linear regression analysis demonstrated that weight gain was strongly associated with decreases in HbA_{1c} levels ($r = 0.8844$; $p = 0.002$).

In the rosiglitazone-insulin combination study by Raskin et al.,[52] bodyweight increased significantly in all treatment groups, but the increase was greater in the two groups receiving rosiglitazone and insulin (mean values of 4.0kg with rosiglitazone 4mg and 5.3kg with rosiglitazone 8mg) compared with the group receiving placebo and insulin (0.9kg) [table I]. There was no significant change in mean waist-to-hip ratio in either rosiglitazone and insulin treatment group compared with either baseline values or the placebo and insulin group.

Weight gain associated with glitazones in insulin-treated patients with type 2 diabetes appears to be similar or even slightly higher compared with the weight gain reported in monotherapy or when glitazones are given in combination with metformin or sulphonylureas. Rosiglitazone caused a dose-dependent increase in bodyweight ranging from 0.7kg to 3.5kg, whereas placebo recipients had a mean weight loss of 1.0kg.[34] Likewise, clinically effective doses of pioglitazone dose-dependently increased bodyweight.[32] The weight gain during glitazone therapy was highest during the first few weeks of treatment and tended to stabilise thereafter. However, such weight gain was also observed on a long-term basis and it may be speculated whether this weight gain will increase with continuous treatment.[62]

The cause of weight gain in humans remains unclear.[61,62] Weight increase can be ascribed to either increasing feeding efficiency or increased hunger. Increased adipogenic efficiency because of PPARγ stimulation and possibly a slight decrease in urinary glucose excretion in some individuals are likely to contribute to increased feeding efficiency. Indeed, the size of the weight gain is generally correlated to the decrease in HbA_{1c} level, suggesting that better metabolic control, and thus reduced glucosuria, may contribute to the weight gain observed with glitazones, as is the case with sulphonylureas or insulin.[61,62] Treatment with troglitazone has been reported to increase hunger in humans, an effect perhaps due to the lowering of leptin levels.[63]

The excess weight gain associated with glitazone use in humans has consistently been ascribed to an increase in the amount of subcutaneous fat, whereas the amount of visceral fat is unchanged or decreased.[61,62] Such an effect was initially described with troglitazone,[64-69] and thereafter confirmed with pioglitazone[70] and rosiglitazone.[71,72] A recent study confirmed a site-specific responsiveness of adipose tissue to pioglitazone; however, it showed that pioglitazone improves insulin sensitivity without decreasing intra-abdominal fat and that this ef-

fect was accompanied by a selective increase in lower subcutaneous body fat.[73] Differential effects of rosiglitazone and metformin on adipose tissue distribution and glucose uptake have been reported in patients with type 2 diabetes.[74] The cause of this apparent fat-redistributing effect of glitazone treatment remains unknown.[62] Recent results suggest that PPARγ are more highly expressed in subcutaneous than omental preadipocytes[75] and the differentiating capacity of subcutaneous adipocyte precursor cells is higher than that of visceral fat precursor cells.[76] This so-called fat redistribution may partly explain the insulin-sensitising effect of PPARγ agonists such as glitazones, considering the well-established association between visceral adiposity and insulin resistance.[58,62]

Whatever the exact mechanistic cause of the PPARγ-induced weight gain, and despite the apparent beneficial redistribution of fat mass, it may be counterintuitive to treat insulin resistance with a compound that induces weight gain, knowing that the degree of obesity is highly associated with insulin resistance.[59,62] Thus, it is speculated that the negative effects of weight gain may compromise the positive effects of treatment. However, even if higher baseline body mass index is likely to predict a higher weight gain during treatment with glitazones,[77] it also predicts a greater improvement in HbA_{1c} level, a finding that suggests an absence of counterproductive effect at least on a short-term basis. However, as long-term effects of glitazones have not been extensively investigated, monitoring of weight and glucoregulatory ability is recommended when glitazones are used on a long-term basis in patients with type 2 diabetes.[62]

2.3 Risk of Oedema and Congestive Heart Failure

CHF has been estimated to occur in as many as 12% of patients who have type 2 diabetes.[78-80] The Framingham Heart Study determined that the risk of CHF in patients with type 2 diabetes was increased by 2.4-fold in men and 5-fold in women.[81] Age, duration of diabetes, poor glycaemic control, ischaemic heart disease, elevated serum creatinine levels, and also insulin use, are independent risk factors for CHF in individuals with diabetes. However, the true prevalence of CHF in diabetes is difficult to determine because of the lack of reliable data and large differences in the definitions and methods used to diagnose its presence.[82] A careful history will detect symptoms of dyspnoea on effort, orthopnoea, nocturnal cough or wheezing, easy fatigability, oedema and nocturia. However, most of these symptoms are difficult to interpret in individuals with type 2 diabetes, as most of them are obese, have arterial hypertension (treated with diuretics, β-adrenoceptor antagonists or calcium channel antagonists) and have glucosuria-associated polyuria. Many patients with symptoms do not have CHF, while many with left ventricular dysfunction do not report symptoms. Therefore, diagnosis of CHF in the diabetic patient may require further testing, especially the measurement of brain (B-type) natriuretic peptide (BNP) plasma level[83,84] and two-dimensional and pulsed Doppler echography.[79,80] In clinical practice, it is important to make a clear distinction between dyspnoea or peripheral oedema and true heart failure, especially in obese, hypertensive patients with diabetes. As recently pointed out,[79] only a minority of the oedema cases reported in glitazone-treated diabetic patients are associated with CHF.

CHF is an insulin-resistant state, as is arterial hypertension.[85-87] Glucose and insulin abnormalities relate to functional cardiac capacity in patients with CHF.[88,89] Interestingly, a higher incidence of new-onset diabetes has been reported in patients with CHF.[90,91] Thus, glitazones are likely to have an expanded therapeutic role, particularly in the growing number of cardiac patients with established CHF, impaired insulin sensitivity and deteriorated glucose tolerance.[92-94] Furthermore, because of their favourable effect on insulin resistance and various associated risk factors, glitazones may exert positive cardiovascular effects.[39,95,96] However, glitazones are not recommended for patients with New York Heart Association (NYHA) class III or IV status because these agents expand intravascular volume and may exacerbate CHF.[97,98] Fluid reten-

tion is a class effect of all glitazones, and it occurs in a dose-dependent manner. The fluid retention related to glitazone use may present as dilution anaemia,[99,100] weight gain (mild to moderate in most cases, but which may be important in some instances[101]), peripheral oedema of lower limbs (unilateral ankle oedema has been exceptionally reported[102]) or even, in rare cases, central/pulmonary oedema.[103-106] In individuals with borderline cardiac function, this volume expansion may be sufficient to result in symptomatic CHF.[44,97]

Fatalities and hospitalisations for cardiovascular events reported from four large randomised, double-blind, active comparator-controlled European trials, in more than 3700 patients with type 2 diabetes, have been combined to compare cardiovascular profiles of treatment with pioglitazone (as monotherapy or combination therapy) with treatment with either gliclazide or metformin (as monotherapy or combination therapy) for 1 year.[107] Reports of all CHF (hospitalised and non-hospitalised) occurred in 12 of 1857 pioglitazone-treated patients and 10 of 1856 patients randomised to metformin or gliclazide. There was no evidence of CHF directly associated with pioglitazone treatment. The overall safety of rosiglitazone was confirmed in daily practice in a non-interventional quality-controlled observational study (AOCS: Audited Observational Cohort Study) performed in Germany on 22 808 type 2 diabetic patients newly initiated on rosiglitazone in combination with either metformin or a sulphonylurea.[108] After a mean observational period of 6 months per patient, rosiglitazone appeared to be safe and well tolerated. Adverse experiences were reported in 3.1% of the patients and serious adverse events in 1.1%, with only rare cases of documented CHF. However, the situation might be somewhat different in insulin-treated diabetic patients,[109] because of the well-known effects of insulin on renal sodium metabolism.[110-112]

In the troglitazone-insulin combination clinical trial performed by Schwartz et al.,[48] the mean red blood cell count, haematocrit and haemoglobin values decreased by 5% in the group given troglitazone 600mg in combination with insulin, but the values remained within the normal range. These decreases occurred soon after treatment was begun, while the values did not change significantly in the other groups given troglitazone 200mg or placebo. One patient in the group given troglitazone 600mg was withdrawn from the study because of CHF (table I).

In the randomised, controlled trial comparing pioglitazone 15mg and 30mg and placebo, in combination with insulin,[51] oedema was reported in 7.0% of patients in the placebo plus insulin arm versus 12.6% in the pioglitazone 15mg plus insulin arm and 17.6% in the pioglitazone 30mg plus insulin arm (table I). All episodes of peripheral oedema were considered mild or moderate. CHF was reported for two patients receiving pioglitazone 15mg and two receiving pioglitazone 30mg. None of these adverse events was considered by the study investigator to be related to study medication, as all four patients had a history of cardiovascular disease. Nevertheless, these results are included in the US FDA-approved prescribing information for pioglitazone,[113] which reports that four patients receiving pioglitazone (1.1% of the pioglitazone- + insulin-treated patients in the trial) developed CHF compared with none in the group receiving insulin alone.

In the rosiglitazone-insulin combination trial by Raskin et al.,[52] a total of 36 patients (placebo plus insulin [n = 5], rosiglitazone 4mg plus insulin [n = 14] and rosiglitazone 8mg plus insulin groups [n = 17]) had at least one episode of oedema during the double-blind treatment period. Thus, more type 2 diabetic patients in the rosiglitazone plus insulin groups reported oedema (13.1% with rosiglitazone 4mg plus insulin and 16.2% with rosiglitazone 8mg plus insulin) than in the placebo plus insulin group (4.7%) [table I]. Investigators classified these events as mild to moderate, and none was considered serious; therefore, no patients were withdrawn. CHF was reported in two patients in each rosiglitazone group and in one patient in the placebo group. Of these, one patient in each rosiglitazone group had a prior documented history of CHF. Again, this information is included in the US FDA-approved prescribing information for rosiglitazone.[114]

Several well-documented case reports have described the occurrence of pulmonary oedema in patients receiving glitazones.[103-106] To evaluate the effect of glitazones on the development of cardiac failure and pulmonary oedema during treatment of type 2 diabetes, Kermani and Garg[106] reviewed the medical reports of six men (aged 66–78 years) who developed signs and symptoms of CHF and pulmonary oedema after 1–16 months of therapy with pioglitazone (one patient, with a daily dosage of 45mg) or rosiglitazone (daily dosage of 4mg in one patient and 8mg in four patients). Three patients were on insulin therapy at a rather high dosage (82, 140 and 740 U/day). Four patients had chronic renal insufficiency and only one had ischaemic cardiomyopathy. Five patients received both a drug inhibiting the renin-angiotensin system and a diuretic at baseline. Symptoms resolved promptly in all six patients after intravenous administration of furosemide and discontinuation of the glitazone.[106]

Various reports mentioned that pulmonary oedema may occur as early as 3 days, and as long as 13 months, after exposure to a glitazone.[115,116] Although symptomatic pulmonary oedema is rather exceptional, its actual incidence in patients receiving glitazones is largely unknown. The difficulty in dealing with drug toxicity issues is access to data showing significant adverse effects. The fact that US FDA statistics are generally based on submission of MedWatch forms that are submitted voluntarily may contribute to largely underestimating real drug toxicity rates. Nevertheless, it has been recognised that all glitazones may exacerbate heart failure.[117] Older age, longer duration of diabetes, and concomitant use of insulin appear to be risk factors for the development of pulmonary oedema. Concomitantly, the recognition of the potential hazards of fluid retention due to glitazones in patients with CHF has increased over time.[118,119]

The original package insert for troglitazone included a statement that use in patients with advanced CHF symptoms should be considered only if the perceived benefits of treatment outweighed the potential risks. The package inserts for pioglitazone and rosiglitazone were changed in the year 2000 to include a specific caution to avoid use in patients with NYHA class III and IV heart failure unless the benefit was judged to outweigh the risk. In response to postmarketing events, the US FDA strengthened this precaution to a warning in April 2002. According to the manufacturers' information, troglitazone, pioglitazone and rosiglitazone may cause fluid retention in 2–5% of patients receiving monotherapy and 5–15% receiving concomitant insulin therapy. The largest percentage of patients reporting oedema was 15.3% with the pioglitazone-insulin combination, compared with 7.0% in patients treated with insulin plus placebo.[120] However, in direct contrast with this explicit warning, the use of glitazones is common and has increased rapidly in Medicare beneficiaries with diabetes and heart failure in the US.[119]

A retrospective population-based cohort analysis of information from health insurance claims investigated the relationship between exposure to glitazone antidiabetic agents and the risk of CHF among patients with type 2 diabetes.[121] Adjusted incidence of CHF at 40 months was 9.2% for patients receiving a glitazone and 5.3% for controls, with a hazard ratio of 1.7 ($p < 0.001$) after controlling for other confounding variables. Interestingly, in this study, the incidence CHF was not higher in the group treated with insulin than in the group not receiving insulin, and in fact the multivariate hazard ratio for glitazone use was not significantly above 1 in patients with insulin use in the 3 months before the index date ($n = 2965$).[121]

A retrospective chart review was performed to determine the incidence of fluid retention in a cohort of 111 consecutive diabetic patients with chronic systolic heart failure who were treated with a glitazone;[122] 19 patients taking a glitazone (17%) developed fluid retention, which reversed after drug withdrawal and presented predominantly as peripheral and not central oedema. Comparing patients in the upper and lower tertiles of weight gain (used as a marker for fluid retention), more patients taking insulin developed glitazone-related fluid retention ($p < 0.01$). However, no direct association between the risk of fluid retention and the baseline degree of

severity of CHF was observed. It is noteworthy that a large proportion of patients taking glitazone continued to take the glitazone in the long term, without significant fluid retention, supporting the notion that these drugs can be used safely and effectively in individuals with stable CHF under careful monitoring.[122] However, as discussed by Malone et al.,[123] the safety of glitazones may have been overstated in type 2 diabetic patients with stable CHF.

Early studies with troglitazone in animal models suggested direct cardiac toxicity.[124] However, although cardiac hypertrophy was noted, there was no change in cardiac function. In addition, controversial results were reported, as inhibition of cardiac hypertrophy in cardiac monocytes was shown with PPARγ agonists.[125] Furthermore, recent studies showed cardioprotection with rosiglitazone[126] and pioglitazone[127] in animal models of the ischaemic heart. Because of the preclinical findings related to the cardiovascular system, a thorough cardiovascular assessment was done in human studies. In general, the percentages of cardiovascular adverse events were similar in the pioglitazone-treated groups and in the placebo groups. There were some cardiovascular events of specific interest, i.e. cardiomegaly (chest x-ray diagnosis), left ventricular hypertrophy (ECG diagnosis) and cardiac failure (echographic evaluation). There was no evidence of cardiac differences between pioglitazone and placebo.[120]

At present, there is little or no evidence to suggest a direct negative effect of glitazones on cardiac performance.[128,129] In most patients, fluid retention appears to be independent of baseline cardiac function.[122] In contrast, there is growing evidence to suggest that glitazones may have many positive effects on cardiac function (including improved myocardium metabolism, positive inotropic effect, coronary vasodilation, improved endothelial function, diminished vascular resistance),[44] on cardiovascular risk factors (including various proinflammatory markers)[130] and even on atherosclerosis (including carotid arterial wall thickness).[131]

A growing body of evidence suggests that glitazones counter angiotensin activation, thus having a beneficial effect on ventricular remodelling in diabetic patients with heart failure.[44] Evidence from animal models also suggests that glitazones significantly reduce the production of tumour necrosis factor-α, a key factor in the development and progression of CHF.[44] Finally, acute administration of troglitazone 400mg has been shown to improve cardiac function without activation of the sympathetic nervous system in patients with CHF.[132] All these observations suggest that glitazones may exert positive cardiovascular effects in both pre-diabetic and diabetic individuals.[96,133]

Because fluid retention following use of a glitazone is not accompanied by decreased left ventricular systolic performance,[128,129] the clinical relevance of this phenomenon is not clear. Many cases of glitazone-induced CHF may represent peripheral oedema unrelated to worsening cardiac function, similar to the oedema seen in patients taking calcium channel antagonists of the dihydropyridine family. The reasons for such a vascular 'leak' syndrome remain unknown, although it may be related to an enhancement in endothelially-mediated vasodilation.[118] An acute effect of rosiglitazone on endothelial permeability has been reported in an established *in vitro* system of pulmonary artery endothelial cell monolayers.[134] Thus, rosiglitazone may exert a direct reversible effect on pulmonary endothelial permeability, independent of other *in vivo* variables, such as glucose, insulin and blood pressure. Since such an effect was observed after exposure to high therapeutic concentrations of rosiglitazone, it was concluded that it could be clinically relevant especially at higher doses and at times of peak plasma drug concentration.[134]

Increased permeability and oedema must be separated from the primary effect of glitazone on the PPARγ because this receptor effect takes weeks if not months to express, whereas fluid retention can occur and be reversed in a few days. glitazones increase plasma concentrations of vascular permeability factors, such as vascular endothelial growth factor,[135-137] implying a role of these factors in glitazone-induced oedema. One study suggested that glitazones may induce changes in renal haemodynamics.[105] In most studies, a larger pro-

portion of patients who developed glitazone-related fluid retention were taking concomitant insulin therapy. It is possible that glitazones potentiate the well-known effects of insulin on sodium and water retention, thus favouring oedema formation.[110-112] In 40 ambulatory diabetic patients receiving haemodialysis, the addition of either rosiglitazone or pioglitazone was well tolerated and resulted in a significant reduction of arterial blood pressure. However, during the 3 months of follow-up, three patients were hospitalised for new or worsening CHF.[138] It is conceivable that additional fluid retention caused by glitazones, regardless of the mechanism, may alter the already precarious volume status in patients with underlying cardiac or renal dysfunction. From a practical point of view, recent glitazone treatment initiation should still be considered in the differential diagnosis of a diabetic patient with cardiac dysfunction who presents with signs and symptoms of volume overload.

Thus, glitazones could increase the risk of heart failure via direct effects on the heart, the kidneys, and/or the vasculature, or indirectly by facilitating the action of insulin to promote renal sodium retention. Therefore, it may be prudent to use glitazones with particular care among patients with diabetes who are predisposed to the development of heart failure, such as the elderly or those receiving insulin.[121] Detailed recommendations about the use of thiazolidinediones in diabetic patients without or with symptomatic heart disease have been recently published in a consensus statement from the American Heart Association and the American Diabetes Association.[98] This statement also includes extensive recommendations for monitoring patients on glitazone therapy, especially those who develop early or advanced signs of CHF. A recent Japanese study[83] showed that pre-treatment increased BNP levels may be a good marker of pioglitazone-induced CHF in patients with type 2 diabetes although this observation requires further confirmation.[84] The management of glitazone-related fluid retention consists of discontinuation of the drug and an increase in diuretic medications. This strategy has been reported to be highly effective in reversing glitazone-related fluid retention.[122] However, as oedema and volume expansion are possibly attributable to increased permeability of the microcirculature, symptoms respond more quickly to drug withdrawal than to intervention with diuretic therapy.[79] Dose reductions of the glitazone, instead of complete withdrawal, have also been reported,[118] but the effectiveness of this strategy needs prospective validation. Further studies to establish the safety and effectiveness of glitazone-insulin combined therapy are needed to ensure optimal care of patients with diabetes and heart failure.[119,123]

2.4 Risk of Liver Toxicity

Troglitazone, the first compound approved by the US FDA, proved to be hepatotoxic and was withdrawn from the market after reports of several dozen deaths and cases of severe hepatic failure requiring liver transplantation.[28] An observational retrospective inception cohort of patients treated with troglitazone was assembled using claims data from a large multistate healthcare organisation in the US.[139] The study confirmed that troglitazone use was associated with a marked increase in risk of acute idiopathic liver injury and acute liver failure leading to hospitalisation. Fortunately, such severe liver complication have not been observed with the two other glitazones, pioglitazone and rosiglitazone, thus indicating that hepatotoxicity with glitazones is not a class effect.[29,140,141] In controlled clinical trials, the incidence of significant (>3 × the upper limit of normal [ULN]) increases in liver enzyme levels (ALT in particular) was similar with pioglitazone or rosiglitazone to that with placebo, whereas troglitazone was associated with a 3-fold greater incidence.[29] Some rare cases of liver injury have been reported with pioglitazone and rosiglitazone, but the causal relationship remains doubtful because of the presence of many confounding factors (e.g. coadministration of other hepatotoxic drugs, alcohol consumption).[29] One of the confounding factors is the high prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in obese patients with insulin resistance and type 2 diabetes.[142] Therefore, it is not easy to decide a causal relation-

ship in case of liver alterations in patients with diabetes treated with oral antidiabetic agents.[143] Instead of aggravating this phenomenon, both pioglitazone[144,145] and rosiglitazone[146,147] appear to reduce liver fat content and secondary elevated ALT levels in obese patients with type 2 diabetes. This favourable effect may be related to the fat redistribution and concomitant reduction in insulin resistance observed with glitazones, as these compounds have been reported to consistently reduce the visceral fat depot while increasing the subcutaneous fat depot.[64-72] Apparently, insulin treatment does not seem to significantly alter the relationship between glitazone treatment and liver alterations in patients with type 2 diabetes.

In the troglitazone-insulin combination study by Schwartz et al.,[48] three patients in the group given troglitazone 600mg had serum ALT levels that were >3 × ULN during the 26-week treatment period (table I). Treatment was discontinued in one patient because of jaundice and hyperbilirubinaemia. In addition, the elevated levels of ALT returned to normal in two patients in the group treated with troglitazone 200mg after therapy was interrupted. In the three patients with elevated ALT levels in the placebo group, serum ALT levels subsequently returned to baseline values without interruption of treatment. Thus, while several troglitazone-treated patients had abnormalities in liver function, therapy was permanently discontinued for this reason in only one patient.

During the course of the multicentre study comparing pioglitazone with placebo in addition to insulin,[51] no patient in the placebo or pioglitazone 15mg treatment groups had an ALT level >3 × ULN. One patient in the pioglitazone 30mg treatment group had elevated ALT values >3 × ULN, but it was subsequently determined that this patient was a chronic active carrier of hepatitis B. There was no evidence of drug-induced hepatotoxicity or drug-induced elevations of ALT levels. In the study by Raskin et al.[52] comparing the addition of rosiglitazone 4mg and 8mg or placebo to insulin, no patients showed an increase of ALT values >2.5 times ULN, confirming the liver safety of this glitazone. Thus, in contrast to troglitazone, neither pioglitazone nor rosiglitazone has potential hepatotoxicity in patients with type 2 diabetes, including those treated with insulin.

3. Conclusions

A substantial body of evidence indicates that combination therapy with insulin and oral antidiabetic agents can safely establish adequate glycaemic control in most patients with type 2 diabetes, while reducing the required daily dosage of insulin. Several large prospective, randomised clinical trials have documented the benefits of glitazones in combination with insulin. In fact, the combination of glitazone with injected insulin may serve as a bridge from oral therapy to insulin-only therapy, a tool for incrementally enhancing glycaemic control beyond the level achieved by insulin alone, or a means of reducing insulin dosage in patients already receiving insulin. Hypoglycaemic episodes may be prevented by an appropriate reduction in insulin dosage. In contrast to troglitazone, the new glitazones pioglitazone and rosiglitazone do not exhibit liver toxicity, but rather may reduce non-alcoholic fatty liver and related high serum liver enzyme levels associated with insulin resistance, obesity and type 2 diabetes.

The other adverse effects of the three glitazones in combination with insulin therapy in patients with type 2 diabetes are similar to those reported in patients not receiving insulin, although they may be more prevalent and more severe. This appears to be the case for weight gain and fluid retention. Weight gain associated with glitazone therapy, especially in combination with insulin, may result from both an adipogenic effect and a fluid retention effect. Adipogenesis seems to be predominantly located in the subcutaneous fat depot, whereas some reduction in visceral fat content has been reported. The fluid retention effect appears to be due to a vascular 'leak' effect rather than to cardiac dysfunction. Although the glitazone-associated weight gain is usually moderate (a few kilograms after several months of treatment), it may be important in some patients, being aggravated by peripheral oedema. In rare predis-

posed patients, glitazone-associated fluid retention may lead to CHF and pulmonary oedema, so glitazones should not be used in patients with NYHA classes III and IV, and should be used with caution in older patients who have had long-term diabetes before being treated with insulin. Because many patients with diabetes have asymptomatic cardiac dysfunction, it is reassuring that fluid retention, when it does occur with glitazones, appears to be easily manageable by dose withdrawal or dose reduction and the addition of a diuretic agent.

Because of the multiple metabolic and cardiovascular effects of glitazones, the benefit-risk ratio of this new pharmacological class remains undefined in the diabetic population as a whole. Ongoing large prospective, controlled studies will probably answer many of the unresolved questions using hard clinical data rather than surrogate markers of cardiac or vessel health. At present, it is prudent to either avoid glitazones or use them cautiously in individuals with impaired cardiac function or in diabetic patients receiving insulin therapy.

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