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Thiazolidinediones and their Fluid-Related Adverse Effects

Facts, Fiction and Putative Management Strategies

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Abstract

Thiazolidinediones (TZDs) or glitazones are agents that are widely used for the treatment of type 2 diabetes mellitus. These drugs have a multitude of therapeutic effects including reduction in insulin resistance and hyperglycaemia, anti-inflammatory effects and amelioration of hypertension, microalbuminuria and hepatic steatosis.

The TZD molecular target, peroxisome proliferator-activated receptor γ (PPARγ), a nuclear transcription factor, is expressed diffusely in humans, including many tissues comprising the cardiovascular and renal systems. This suggests a potential for TZDs to elicit perturbing effects on these systems, which are independent of their effects on glucose and lipid metabolism.

One of the most common adverse effects of TZDs is fluid retention, which can result in, or exacerbate, oedema and congestive heart failure (CHF). The frequency of peripheral oedema is approximately 5% when TZDs are used in mono- or combination oral therapy, and about 15% when used with insulin.

Patients with type 2 diabetes are at high risk of myriad morbid complications, including CHF. The development of CHF, particularly in the elderly, is a harbinger of premature mortality. TZD-induced oedema is largely peripheral, may have its origins in changes in haemodynamics, with some contribution from molecules, which regulate cell and tissue permeability (e.g. vascular endothelial growth factor and protein kinase Cβ), and remains the preponderant manifestation of TZD-induced fluid retention even in those with existing heart failure. Preclinical and pilot clinical data attest to the fact that at least part of the fluid retention derives from a direct effect of TZDs on sodium reabsorption via the renal

medullary collecting duct, a mechanism that is sensitive to diuretic agents that have this nephron segment as their site of action, in whole or in part (spironolactone, amiloride and hydrochlorothiazide). Our review suggests various potential clinical strategies by which TZD-induced fluid retention might be effectively monitored and addressed.

1. Thiazolidinediones (TZDs): the Good, the Bad and the Ugly

The thiazolidinedione class of drugs, otherwise known as glitazones or TZDs, are believed to exert their pleiotropic actions in humans via a diffusely expressed nuclear transcription factor, peroxisome proliferator-activated receptor γ (PPARγ),[1] and were approved for the oral treatment of type 2 diabetes mellitus during the late 1990s. Troglitazone was the first agent of this type to be approved but was withdrawn following a rising number of reports in the US and Japan of idiosyncratic hepatotoxicity, occasionally resulting in liver failure.[2] However, this toxic adverse effect of troglitazone proved to be drug-specific and the hepatic safety of rosiglitazone and pioglitazone, follow-up drugs in the same chemical and therapeutic class, has been reassuringly good according to abundant data from clinical trials and subsequent postmarketing surveillance. In fact, paradoxically, both rosiglitazone and pioglitazone may yet find a place in the treatment of non-alcoholic fatty liver disease by virtue of their ability to ameliorate hepatic steatosis, inflammation and fibrosis.[3,4]

Indeed, TZDs also have many potential virtues as antidiabetic agents, not least in their ability to reduce elevated plasma levels of non-esterified fatty acids and insulin resistance,[5,6] pivotal metabolic perturbations on the road to type 2 diabetes in the majority of affected individuals.[7] Moreover, these key actions of TZDs, most likely related to the abundant expression of PPARγ in human adipose tissue,[8] probably explain recent observations that rosiglitazone substantially blocks, or at least postpones, the transition from pre-diabetes to type 2 diabetes[9] and, compared with glibenclamide or metformin, delays the progression of the disease once established.[10]

As well as bestowing potential benefits to the steatotic liver and, by implication from above, to the pancreas, TZDs may also have protective PPARγ-related effects in the diabetic kidney[11,12] and blood vessel wall,[13-15] the latter including stabilising of atherosclerotic plaques[16] and leading to reduced macrovascular events.[17-19]

Even so, as with all drugs, there is a flip-side to this benevolent picture which, once more, is seemingly rooted in the diffuse sites of expression of PPARγ. The most recent insidious adverse effect of TZDs to surface, the incidence and importance of which has yet to be clarified, is the potential to promote bone loss and fractures in older women with diabetes.[10,20] However, there is a spectrum of other significant, better known, but still unwanted effects that extends from straightforward increased adiposity, through expanded plasma volume, to variable degrees of oedema and even to congestive heart failure (CHF).

Increased adiposity with TZDs is relatively easily explained via the expression of PPARγ in pre-adipocytes, which are stimulated by these drugs to differentiate and store surplus triglyceride.[21] Although undoubtedly cosmetically and orthopaedically undesirable, this increased but orderly fat storage at least implies less undesirable ectopic fat deposition (e.g. in the liver), and almost certainly comprises a key component of the insulin-sensitising and anti-hyperglycaemic actions of these drugs. Furthermore, since the increased fat mass is, seemingly, non-visceral in its location,[22] and characterised by a theoretically beneficial change in its myriad adipocytokine gene expression,[23] we can probably consider it to be of less pathophysiological importance than the fluid-related adverse effects of TZDs, which also contribute to overall weight gain. This being the case, the primary focus of this review is

TZD-related fluid retention, its mechanisms, consequences and possible management but, in passing, also some other interesting observations, which provide yet another twist to the unfolding TZD story and that may even dispel a few fictions and fears.

We begin with a brief review of the epidemiology and pathophysiology of heart failure in type 2 diabetes, since it is something of a Cinderella 'opathy', gaining scant attention in major diabetes congresses yet occurring with high prevalence, particularly amongst the elderly,[24] and presents a major, resource-intensive, challenge to physicians.

2. Heart Failure in Obesity and Type 2 Diabetes Mellitus

Heart failure is a significant risk associated with obesity even in the absence of type 2 diabetes,[25] and may originate early in life since childhood adiposity is predictive of left ventricular mass in young adulthood;[26] obese adolescents may also exhibit evidence of mild left ventricular dysfunction.[27]

The common trigger linking body phenotype with these changes in cardiac architecture and performance may well be insulin resistance.[28] Later in the course of deteriorating cardiac performance, insulin resistance is a significant predictor of CHF,[29] its severity[30] and CHF-related mortality.[31]

Of greater significance here is the fact that CHF is a prevalent complication of type 2 diabetes. For example, in the Framingham Heart Study, the risk of CHF was reported to be elevated 2.4-fold in men and 5-fold in women with diabetes.[32] In a Kaiser Permanente study, each 1% increase in glycosylated haemoglobin (HbA_{1c}) level was associated with an 8% increase in the risk of heart failure.[33]

In summary, heart failure is a common complication of diabetes and may even originate early in life as a pathophysiological spin-off from childhood or adolescent obesity. CHF, once established in diabetes, is a harbinger of a truncated life-span, at least in the elderly. With that picture as a back-drop, let us now focus on TZDs and their propensity to retain fluid, since fluid retention has the potential to precipitate or exacerbate oedema and, under some circumstances, CHF.

3. TZDs and Fluid Retention: Clinical Data and New Molecular Mechanisms

At the outset, and particularly in view of the discussion in the previous section, it is important to remind the reader that clinical trials evaluating the efficacy and safety of rosiglitazone and pioglitazone (i.e. those on which drug approval was based) excluded patients with New York Heart Association (NYHA) class III or IV cardiac functional status. Thus, patients with moderate-to-severe impairment of physical activity related to symptoms of angina or CHF during daily activities or at rest were excluded from these studies.

In healthy volunteers who received rosiglitazone (8mg once daily) for 8 weeks, there was a small but statistically significant increase in mean plasma volume of approximately 1.8 mL/kg compared with placebo. In patients with type 2 diabetes, falls in haemoglobin ranged from 0.8 to 1.1 g/dL, and in haematocrit from 2.3% to 3.6%, depending on whether the drug was used as monotherapy or in combination with other oral agents or with insulin.[34] Similar decreases in haemoglobin and haematocrit have been observed with pioglitazone.[35] These changes are usually observed during the first 8 weeks of therapy with the values tending to reach a plateau thereafter.

Whilst there are clear gains in plasma volume, total body water (TBW) and extracellular fluid (ECF) volume with TZDs,[36-38] favouring a significant role for haemodilution in the falls in haemoglobin and haematocrit, we cannot exclude the possibility of some additional effect on erythropoiesis, since one report at least has demonstrated that PPARγ ligands, including pioglitazone, modulate the differentiation process of erythroid progenitor cells *in vitro*.[39]

The mechanisms mediating fluid retention by TZDs remain conjectural at this time, but reports of falls in blood pressure with these drugs are commonplace.[40,41] Both a fall in systemic vascular resistance[37] and increased sodium reabsorption via the proximal tubule, presumably linked via reflex activation of the renin-angiotensin system (RAS),[42] have been reported. Nonetheless, recent data from

experiments in mutant mice suggest that TZDs may also stimulate salt and water reabsorption in the renal medullary collecting duct by virtue of a PPARγ-dependent up-regulation of the aldosterone-sensitive epithelial sodium channel (ENaCα).[43,44] In these studies, selective deletion of PPARγ in the collecting duct cells blocked the fluid retention and weight gain caused by TZDs, as indeed did amiloride, a selective inhibitor of ENaC,[45] in normal (PPARγ-bearing) mice. The molecular mechanism by which TZDs increase ENaCα activity appears to be a combination of increased expression of the channel protein and its trafficking to the cell membrane by increased cellular levels of a regulator protein, serum and glucocorticoid-regulated kinase-1 (SGK1).[46]

That oedema, one manifestation of fluid retention, is generally worse when TZDs are combined with insulin than when combined with other oral antidiabetic agents is probably no coincidence, since insulin itself is independently culpable.[47] Not only is insulin a predominantly vasodilator hormone and its vascular effects, perhaps, exacerbated by TZDs,[48] but it too increases ENaCα trafficking to the medullary collecting duct cell membrane via SGK1.[49] However, in the only pertinent paper published so far, pioglitazone did not enhance insulin-stimulated Na^+ flux through ENaC.[50]

Although the strong overall implication of these reports is that TZDs may well elicit Na^+ retention via a direct action in the distal segment of the human nephron, it is difficult to estimate its precise contribution to fluid retention and bodyweight gain. In isolation, a significant direct salt- and water-retaining effect of TZDs in the kidney, whether accompanied or not by hyperinsulinaemia, might be anticipated, like hyperaldosteronaemia, to raise blood pressure rather than to reduce it, as is generally reported. Indeed, a fall in blood pressure, by recruiting normally operating homeostatic mechanisms, is entirely compatible with some salt and water retention to prevent blood pressure falling even further. Thus, this is an interesting conundrum that has not yet been fully unravelled clinically. However, one other factor that needs to be worked into this model, and which we have already mentioned briefly, is that TZDs can cause or exacerbate oedema in some patients with type 2 diabetes.

4. TZDs and Oedema: Clinical Data and Putative Mechanisms

Mild-to-moderate oedema is a common adverse effect of TZD therapy, although precise drug-related rates vary considerably between studies, not least because background rates seen with other antihyperglycaemic treatments and their combinations also vary appreciably. In ADOPT (A Diabetes Outcomes Progression Trial), a 4-year randomised monotherapy comparator study, an oedema rate of 14.1% with rosiglitazone was reported compared with 7.2% for metformin and 8.5% for glibenclamide.[10] When pioglitazone was added to other antihyperglycaemic agents in the randomised major cardiovascular outcome study PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events Study), in which one-third of high-risk patients were receiving insulin, the non-CHF-related oedema rate was 21.6% compared with 13.0% in the matched group randomised to placebo.[17]

The clinical trials conducted for regulatory submission purposes, in which either rosiglitazone or pioglitazone was added to background insulin to improve glycaemic control, were more limited in scope, both in terms of the numbers of patients studied and the durations of combined treatment. Nonetheless, rather similar data to those noted in the previous paragraph have been reported. Thus, in one combined insulin plus rosiglitazone study, oedema rates of 13.1% (4mg) and 16.2% (8mg) exceeded the 4.7% seen for placebo/insulin.[51] In an analogous study with pioglitazone, oedema rates were 12.6% (15mg) and 17.6% (30mg) compared with 7.0% in the placebo/insulin group.[52]

The localisation of TZD-related oedema and its severity are also important issues, not least because of their potential association with CHF, but particularly since some physicians are so sensitised to the warnings that TZDs can precipitate CHF that they equate one with the other. In fact, the relationship between oedema, particularly peripheral oedema,

and CHF is not straightforward. After all, extravasated fluid in peripheral tissues, by definition, poses no direct threat to the heart. So where is the oedema caused by TZDs to be found?

Rather surprisingly, this phenomenon has not been the focus of many detailed reports. However, in one study of 166 US veterans started on TZDs, 30 (18.1%) developed oedema and, of these, 16 had their glitazone discontinued because of the severity of this adverse effect.[53] In part mitigation, the authors reported that >90% of their patients had poor glycaemic control at baseline and many had other medical problems. In many clinics, TZDs are introduced as a last option before insulin; in this study 17 of 30 of those who developed oedema were already receiving insulin. As for the oedema itself, this was most often peripheral in nature and generally localised in the lower limbs.

In a further study, this time in patients with type 2 diabetes and established chronic but stable systolic heart failure, 19 of 115 (17%) TZD users developed signs and symptoms of fluid retention.[54] When compared with a group of 80 age- and gender-matched non-TZD users, who also satisfied the criteria for fluid retention, the patterns of oedema were strikingly different between groups. Oedema in TZD users was peripheral in 95%, pulmonary in 11% and manifested as jugular venous distension in 32%. For non-TZD users, the comparable figures were 63%, 80% and 73%, respectively. This differential distribution of fluid, with less central fluid accumulation in TZD users, suggests a less 'precarious' picture for pump function in this group than in the non-TZD users.

The mechanisms underpinning TZD-induced oedema are largely conjectural at this point, though the finger of suspicion points in the direction of at least two noteworthy factors. Firstly, as already mentioned, TZDs reduce systemic vascular resistance,[37] suggesting that the distal parts of the vascular tree, including the capillary network, may be exposed to higher perfusion pressures than they are accustomed to under normal conditions of autoregulation. Under such circumstances, the downward drag of gravity would polarise the extravasation of fluid towards the lower limbs, as seems to occur in practice.[53]

Whether a haemodynamic action of TZDs alone could explain their propensity to cause peripheral oedema is a moot point. More likely is the possibility that increased expression of a potent vascular permeability factor, vascular endothelial growth factor (VEGF) in vascular smooth muscle cells is a contributory factor.[55] Indeed, a recent report found a link between troglitazone-induced oedema in patients with type 2 diabetes and a raised plasma level of VEGF.[56]

But there also remains scope for other molecular contributors to this phenomenon. In a further recent animal study, rosiglitazone increased vascular permeability in adipose tissue of mice, an effect that was inhibited by protein kinase Cβ (PKCβ) knockout or by ruboxistaurin, a PKCβ isoform inhibitor.[57] In the same report, rosiglitazone increased both VEGF and PKCβ gene expression in the retina of lean, fatty and diabetic Zucker rats, and caused increased retinal vascular leakage. Pertinently, TZDs have been reported to cause macular oedema in some patients with type 2 diabetes,[58,59] an effect that is also difficult to reconcile solely by invoking a role for 'gravitational' haemodynamics. Whether patients susceptible to the development of macular oedema on TZD treatment represent a minority at the end of the pathophysiological spectrum, is presently unknown. However, what seems clear is that the susceptible patients tend to gain enormous amounts of weight during treatment, much of which is presumably fluid, and that the majority are also being treated with a sulfonylurea and/or insulin.[59]

5. TZDs and Congestive Heart Failure: Epidemiology, Mechanisms and Outcomes

Often, large-scale retrospective reviews of health insurance claims, one of the main sources of epidemiological data, are not particularly helpful in establishing the true prevalence of drug adverse effects or their outcomes. In the case of CHF, the diagnosis itself may be imprecise and may, sometimes, be based solely on the appearance of peripheral oedema

in the out-patient setting rather than following detailed in-hospital cardiological work-up. This is an important issue since, as we described earlier, CHF is a common complication of diabetes and it gives rise to a high-background signal in the population, and particularly in the elderly.

Often, individual medical records are unavailable, which means that details of glycaemic control, diabetic complications and even disease duration are frequently beyond reach. Therefore, a huge heterogeneity of patients can be accommodated under a single category in the claims database.

In one often-cited study, using the PharMetrics Integrated Outcomes Database, incident CHF was recorded for cohorts of TZD-exposed and non-exposed patients with type 2 diabetes.[60] Whilst the adjusted incidence of CHF for TZD-users at 40 months was higher (8.2%) than in the non-users (5.3%), it seems quite likely, as suggested by the authors, that TZDs were being added to existing therapies in a less well controlled and otherwise sicker population than the non-TZD users.

Although a similar scenario was seen in another study, this time in data from the Kaiser Permanente Northern California Diabetes Register,[61] here the effects of initiation of TZD treatment were compared with the initiation of other antidiabetic drugs, including insulin. Also, diagnosis of heart failure was made during hospitalisation, suggesting more certainty of the medical condition. In this study, pioglitazone treatment was no more a culprit in causing CHF than the referent (generally first-line) sulfonylurea treatment, whereas the introduction of insulin was clearly detrimental. Metformin, relative to sulfonylurea, significantly protected against incident CHF.

In a further study, this time of the PharMetrics Patient-Centric database and again with a hospitalisation dimension, the initiation of pioglitazone treatment resulted in less incident CHF than the initiation of insulin.[62]

The only prospective, randomised, controlled trial of a TZD in patients with type 2 diabetes at high risk of fatal and non-fatal myocardial infarction and stroke is the PROactive study.[17] Although the primary and secondary endpoints of the study were centred on changes in the incidence of cardiovascular events, intervention procedures and mortality, drug-related adverse events and particularly CHF were obviously of great interest. In retrospect, it is surprising that these events were not properly adjudicated. Even so, 6% of pioglitazone-treated patients required hospital treatment for CHF, which is significantly more than the 4% in the control group. However, what is not clear is how many of these patients in both groups were receiving insulin and/or a sulfonylurea.

Only isolated reports have detailed the host characteristics that predispose patients with type 2 diabetes to CHF when treated with TZDs. In each of the two papers, the likely predisposing factors in six affected patients were described.[63,64] These factors can best be summarised as: the co-existence of variable degrees of hypertension, left ventricular hypertrophy, diastolic dysfunction, microvascular disease, chronic renal insufficiency, simultaneous treatment with a sulfonylurea or insulin, and recent precipitous weight gain of 5.4–17kg. Most, although not all, patients were elderly.

From these observations and the known effects of TZDs, we can attempt to elaborate the sequence of pathophysiological events that lead to precipitation or exacerbation of CHF by these drugs. Fluid retention is, most likely, the pivotal precipitating factor. A chronic expansion of blood volume, even if non-progressive, imposes an additional burden on the heart. For example, in one study in patients with type 2 diabetes without significant pre-existing cardiac or renal dysfunction or known coronary heart disease, rosiglitazone treatment for 52 weeks elicited a small, although not clinically significant, increase in left ventricular mass and diastolic volume.[65] It is doubtless, even in that study, that a degree of adaptation of cardiac architecture was taking place to compensate for a chronic increase in circulating load.

However, in many patients with type 2 diabetes, left ventricular wall compliance is compromised by an increase in the content of collagen fibres, and more so after acute myocardial infarction, which

invokes a damage repair programme. Presumably, under conditions where blood volume is expanded beyond a critical threshold, perhaps against a background of chronic renal insufficiency and/or raised levels of circulating insulin (induced by a sulfonylurea or exogenous insulin), which itself can cause fluid retention,[47] cardiac function tips into decline, spiralling downwards in the face of a chronically elevated pre-load. It is against this background that in Europe, although not in the US, TZDs are contraindicated in combination with insulin.

However, the interesting point with regard to TZD treatment is that mortality rate was not increased in those high-risk patients developing CHF on pioglitazone,[17] or during the 12 months after discharge with a diagnosis of CHF,[66] or acute myocardial infarction (AMI),[67] and still taking a TZD. In one of these studies,[66] a retrospective cohort study of 16 417 Medicare beneficiaries with diabetes and an in-hospital diagnosis of heart failure, TZD treatment exhibited significant protection against 1-year mortality (hazard ratio [HR] = 0.87; 95% CI 0.80, 0.94), similar to that shown by metformin (HR = 0.86; 95% CI 0.78, 0.97). Remarkably, in combination, the protective effects were additive (HR = 0.76; 95% CI 0.58, 0.99). In a further retrospective cohort study, this time of 24 953 Medicare beneficiaries with diabetes and discharged after hospitalisation for AMI,[67] combined metformin/TZD treatment afforded highly significant protection against 1-year mortality (HR = 0.52; 95% CI 0.34, 0.82), although neither drug alone was influential in this study. In both studies, the re-admission rate for treatment of CHF was slightly raised by maintained TZD treatment, although not by metformin.

At this point, we should also draw attention to the fact that both TZDs and metformin are presently contraindicated in diabetic patients with CHF, and it is counter-intuitive to find protection, even additive protection, against 1-year mortality in such a large cohort of elderly patients with type 2 diabetes rather than a catastrophic increase. Whilst the obvious question is 'why?', it is beyond the scope of this review to speculate on the possible mechanisms of cardiac protection. This point has been addressed in a separate paper.[68]

6. TZDs and Risk Management

Here, we should first emphasise the importance of lifestyle intervention to improve general physical fitness and to pay greater attention to meal choice and size to promote weight loss in patients with type 2 diabetes who are overweight or obese. TZDs do not suppress the appetite and without changes to diet and exercise routines, patients will almost certainly gain weight on these drugs, not least because they promote triglyceride storage in subcutaneous fat depots. With lifestyle intervention, there is ample proof that weight gain on TZDs is not inevitable and, indeed, that highly beneficial weight reduction is possible.[69,70]

Identifying those patients least suitable for TZD treatment is not straightforward, but the American Heart Association (AHA)/American Diabetes Association (ADA) consensus statement remains the most comprehensive step-by-step guide to the safe introduction and use of these drugs.[71] As we have seen in earlier discussion, patients with left ventricular hypertrophy, known macrovascular and/or microvascular disease and significant renal impairment, comprise a high-risk category (and more so if they have had longstanding diabetes, are elderly and are already insulin users). Unsurprisingly, the AHA/ADA consensus statement advises caution about the use of TZDs in cases of known or suspected heart failure, since they may 'unmask' previously asymptomatic cardiac insufficiency by increasing plasma volume. Careful monitoring of any manifestation of fluid retention is needed and TZDs should be initiated at low dosage when there is doubt about the patient's cardiac status. TZDs should be avoided altogether in patients with NYHA class III–IV heart failure.

Specifically, the signs of an impending problem that patients and their physicians should be advised to take heed of are: a rapid gain in bodyweight of >3kg, the sudden appearance of pedal oedema and the development of breathlessness at rest or during mild exercise.

In the absence of such sudden changes in physical status, a more insidious development of CHF is difficult to exclude without further non-invasive tests, such as detailed clinical examination, an ECG, chest x-ray, measurement of plasma brain natriuretic peptide (BNP) and other standard laboratory tests. These and more elaborate tests, such as echocardiography or radionuclide assessment of left ventricular function, tend to be pursued only after TZD treatment has been discontinued, remedial diuretic therapy commenced or completed, and a revised antihyperglycaemic treatment regimen prescribed.

One pertinent question to arise from this usual sequence of events is: might it be pragmatic to requisition a plasma BNP assay, together with detailed clinical examination, chest x-ray and an ECG, prior to discontinuation of a TZD or even before a TZD is started in doubtful cases, as a means of assessing cardiac status and future risk? In the case of prior screening, the information gleaned could be used to determine patient suitability for these drugs.

BNP is certainly one emergent diagnostic tool since it accurately reflects end-diastolic wall stress in both systolic and diastolic heart failure, although levels are higher in the former.[72] Furthermore, BNP levels in patients with type 2 diabetes reliably predict future cardiac and all-cause mortality.[73] However, values do tend to be lower in subjects with obesity than in those who are overweight or in those of a lean phenotype,[74] and this relationship persists even in patients with advanced heart failure.[75] By contrast, renal insufficiency (estimated GFR [eGFR] <60 mL/min), by reducing the clearance of BNP, results in a higher plasma BNP level than that seen in subjects with an eGFR of >60 mL/min for the same degree of heart failure.[76]

Perhaps, at present, we do not have sufficient information to answer this question with enough certainty, but there seems little doubt that TZDs do increase BNP in patients with type 2 diabetes, and that the baseline level is not only a determinant of the treatment-related increment, but also a predictor of those patients who are at risk of developing clinically significant fluid retention, including that leading to left ventricular dysfunction.[77,78] However, what is not known with sufficient precision, is the threshold level of BNP that would guide the clinical decision to continue/discontinue TZD therapy for those on treatment already, or whether to start/avoid TZD therapy when options for improving glycaemic control are being considered.

Whether research leading to a genetic test of absolute suitability or unsuitability of patients for TZD therapy is any nearer to fruition is a moot point. A population-attributable risk for oedema of approximately 50% has been assigned to the Pro12Ala polymorphism in the PPARγ gene,[79] although whether this polymorphism also correlates with a susceptibility to CHF is, as yet, unknown.

Table I shows the factors that may predispose patients to develop TZD-associated fluid retention. Predicting the susceptibility of patients with type 2 diabetes to TZD-induced fluid retention, oedema and CHF, if it can be accomplished with greater accuracy than has been possible to date, would be a great step forward in the application of these drugs and would save on the resources (often deployed in association with hospitalisation) that are needed to manage these adverse effects, as well as the stress, inconvenience and potential harm inflicted on those patients affected.

Of course, one might also surmise that if fluid retention can be prevented or reversed by an effective diuretic agent or some other strategy, such as

Table I. Patient factors predisposing to thiazolidinedione-induced fluid retention

Age
Female gender
LVH on ECG
Elevated BNP
Past medical history of IHD or CHF
Macrovascular and/or microvascular disease
Renal impairment
Sulfonylurea therapy
Insulin therapy
PPARγ polymorphisms
Concomitant use with other drugs known to induce peripheral oedema

BNP = brain natriuretic peptide; **CHF** = congestive heart failure; **IHD** = ischaemic heart disease; **LVH** = left ventricular hypertrophy; **PPARγ** = peroxisome proliferator-activated receptor γ.

salt restriction, then to a large extent, this particular cascade of events might be blocked and the problem essentially resolved. In this context, is there an effective diuretic agent presently available?

In earlier discussion, we reviewed the literature pertaining to TZD-induced salt and water retention not only via the renal proximal tubule by virtue of an indirect, homeostatic mechanism, but also via a direct effect on the medullary collecting duct cell epithelial sodium channel, ENaCα. Whilst the contribution of this latter action to overall fluid retention is by no means clear in patients with type 2 diabetes, it might conceivably be of major significance in some individuals, perhaps those most at risk of intolerable oedema and/or CHF during TZD therapy.

Thus, an obvious clinical strategy to emerge from the animal and *in vitro* data would seem to be to try to tackle this adverse effect of TZDs with amiloride, an inhibitor of ENaCα itself,[45] or spironolactone, a specific antagonist of aldosterone, which regulates the expression of both ENaCα and SGK1.[49]

The critical test is to establish whether either of these drugs might reduce TZD-induced fluid retention and/or oedema. Indeed, our group has recently attempted to address this issue.[38] We studied the effect of three mechanistically distinct diuretics (furosemide, hydrochlorothiazide and spironolactone) on TZD-induced fluid retention, using haematocrit as a surrogate for an increase in plasma volume.[80,81] A total of 381 patients with type 2 diabetes, who were inadequately controlled on their existing oral antidiabetic therapy, were included in this multicentre study. Following 12 weeks of add-on rosiglitazone therapy, 260 patients (68%) exhibited a decrease in haematocrit of ≥0.5%, the cut-off point used to define plasma volume expansion. Baseline values of HbA_{1c} were comparable in patients with or without volume expansion, and improved similarly in both groups.

In the patients with fluid retention, the fall in haematocrit was accompanied by significant reductions in total haemoglobin and plasma albumin levels. Moreover, the reduction in haematocrit was correlated with the fall in haemoglobin and this was inversely correlated with the changes in ECF volume. TBW and ECF volume increased significantly, consistent with plasma volume expansion.

Those patients who did not volume expand had a mean increase in haematocrit and no significant changes in total haemoglobin level or plasma electrolytes. Plasma aldosterone levels remained unchanged and plasma levels of atrial natriuretic peptide (ANP) tended to fall. TBW and ECF volume (measured in 69 patients only) were unaltered.

In patients with fluid retention, reductions in plasma aldosterone levels and increases in plasma ANP levels were consistent with increased sodium reabsorption and central venous volume. Therefore, salt and water balance was reset to a new equilibrium and maintained by a slight, but significant, increase in serum sodium.

The allocation of patients with fluid retention to withdrawal of rosiglitazone treatment or to different types of diuretic therapy for 7 days provided data consistent with the notion that at least part of the bodyweight gain with rosiglitazone is due to salt and water retention.

Patients who received spironolactone exhibited, numerically, the greatest reversal of fluid retention, as indicated by a significant increase in haematocrit and a fall in ECF volume. Bodyweight also fell to the largest extent in the spironolactone group.

Hydrochlorothiazide treatment was also partially effective in reducing fluid retention, whilst furosemide had a more limited effect. Of note, withdrawal of rosiglitazone treatment had no significant effect in reversing fluid retention over 7 days, suggesting a persistent action of rosiglitazone and implying that drug withdrawal alone is not a rapid means of reversing volume expansion.

The secondary analyses, which compared the effectiveness of the three diuretics in reversing rosiglitazone-induced changes in haematocrit and ECF, indicated that spironolactone was most probably superior to furosemide, and that furosemide might also be less effective than hydrochlorothiazide. However, the numerical differences between drugs were not statistically significant. Studies with a larger sample size would be required to investigate

these possible differences between diuretic drugs with greater precision.

Taking these trends at face value, how are we to rationalise the findings? Overall, the data are consistent with the notion that rosiglitazone increases Na^+ reabsorption in the collecting duct of the nephron by increasing ENaCα activity and this increased salt and water absorption results in plasma volume expansion. In this respect, the data also provide a partial rationale for the exaggerated fluid retention that may occur when rosiglitazone and insulin are used together, since insulin also stimulates ENaCα activity.[49]

Interestingly, hydrochlorothiazide also significantly reversed rosiglitazone-induced fluid retention. Although the major site of action of thiazide diuretics is the early distal convoluted tubule, these drugs can also inhibit salt and water reabsorption via a NaCl co-transporter in the medullary collecting duct,[82] a site of expression of PPARγ in the nephron. Thereby, these observations provide a logical basis for an interaction between a TZD and hydrochlorothiazide at this location. Of further interest is the fact that the NaCl co-transporter is itself an aldosterone-inducible protein.[83]

By contrast, furosemide, a loop diuretic, which had no significant effect on haematocrit or ECF in our study, acts exclusively on the thick ascending limb of the loop of Henle, where it inhibits the luminal $Na^+K^+2Cl^-$ co-transporter,[84] a segment of the nephron that shows little or no expression of PPARγ.

In summary, these data suggest that diuretic agents that inhibit sodium reabsorption in the renal medullary collecting duct, such as spironolactone and hydrochlorothiazide (as well as amiloride, which was not tested in our study), may be effective agents to ameliorate TZD-induced fluid retention.

At the present time, and in accordance with present AHA/ADA guidelines,[71] we would advise that whenever patients present with symptoms of CHF, TZD therapy should be discontinued, alternative additional antihyperglycaemic treatment prescribed and remedial diuretic therapy commenced. From the present drugs available, it seems to us that on theoretical grounds and supported by our own pilot study, spironolactone (or amiloride) and/or hydrochlorothiazide might provide the most effective means of reversing the volume overload. We also speculate that these agents, alone or in combination, might represent an effective strategy to address early manifestations of TZD-induced fluid retention, thereby reducing their future risk of causing an intolerable oedema and/or CHF. Persuading patients to consume less salt in their diet is also seen as a potential means of lowering the risk of significant fluid retention with TZDs, although this strategy requires formal clinical testing.

However, a note of caution is warranted in those patients taking RAS-blocking drugs (ACE inhibitors and/or angiotensin I receptor antagonists) for their hypertension. Here, we advise careful monitoring of serum potassium, since there is an enhanced risk of hyperkalaemia with potassium-sparing diuretics. In our own study, there were no patients who developed hyperkalaemia, despite the commonplace use of RAS inhibitors. That said, the test cohort had normal renal and preserved cardiac function and diuretic treatment was given for only 7 days, probably insufficient time for hyperkalaemia to develop in those randomised to spironolactone.

Finally, a recent publication suggested that fenofibrate prevented the weight gain and fluid retention associated with rosiglitazone use.[85] However, these findings need to be interpreted with caution due to several factors[86] and, not least, the small number of patients (n = 13) in the study, which was not designed to test strategies for prevention of fluid retention. In fact, because fenofibrate is a PPARα agonist, rosiglitazone and fenofibrate together would be expected to act as a combined PPARγ/PPARα agonist. Since recent data suggest that dual PPAR agonists are significantly more likely to cause fluid retention, oedema and possible adverse renal and cardiovascular outcomes, particularly CHF,[87] we believe that the use of fibrates in combination with glitazones should not be advocated as a strategy to prevent TZD-induced fluid retention.

7. Conclusion

Fluid-retention, a common accompaniment to TZD therapy, appears to provide the essential trigger that precipitates or exacerbates CHF, although there is no evidence to connect this event with increased mortality. TZD-induced oedema is largely peripheral and remains the preponderant manifestation of TZD-induced fluid retention even in those with existing heart failure. Preclinical and pilot clinical data attest to the fact that at least part of the fluid retention derives from a direct effect of TZDs on sodium reabsorption via the renal medullary collecting duct, a mechanism that is sensitive to diuretic agents that have this nephron segment as their site of action, in whole or in part (spironolactone, amiloride, hydrochlorothiazide). Our review suggests potential clinical strategies by which TZD-induced fluid retention might be effectively monitored and addressed.

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