Edema and Congestive Heart Failure from Thiazolidone Insulin Sensitizers—Excess Sodium Reabsorption in the Collecting Duct

Collecting Duct-Specific Deletion of Peroxisome Proliferator-Activated Receptor γ Blocks Thiazolidinedione-Induced Fluid Retention

Thiazolidinediones Expand Body Fluid Volume through PPARγ Stimulation of ENaC-Mediated Renal Salt Absorption

Thiazolidiones are peroxisome proliferator-activated receptor γ (PPARγ) agonists that enhance insulin sensitivity and are increasingly used as oral antidiabetic agents. The two currently available agents are pioglitazone and rosiglitazone. Their use has dramatically increased recently and this year the results of major outcome trials are expected. Of interest to nephrologists, the thiazolidinediones have, among others, beneficial effects on BP (1), proteinuria (2), and potentially atherogenesis (3). The downside is the propensity to cause fluid retention and congestive heart failure—a matter of such concern and clinical importance that the unusual step had been taken to publish simultaneously in *Circulation* and *Diabetes Care* a consensus statement from the American Heart Association and the American Diabetes Association dealing with the issue of edema caused by thiazolidinediones (4).

What is the magnitude of the risk?
In the pioneer studies documenting the efficacy and safety of thiazolidinediones, patients with heart disease NYHA (New York Heart Association) class III and class IV had been excluded and cardiac events were rare. In the target population of elderly type 2 diabetics, however, risk factors for or presence of asymptomatic or symptomatic heart disease are common. This may explain why, in some studies including patients closer to real life (5–7) or in reports on clinical practice experience (8), weight gain and congestive heart failure were seen with considerable frequency, although some new observations suggest that some of the risk estimates may have been exaggerated by confounding factors (9,10). Furthermore, the ability of thiazolidones to cause a positive sodium balance is supported by the fact that a positive sodium balance has also been observed in Sprague-Dawley rats treated with rosiglitazone (11).

In the US placebo-controlled trials, edema had occurred in 4.8% of subjects on pioglitazone monotherapy compared with 1.2% on placebo (4). In double-blind trials with rosiglitazone, the incidence of edema was 4.8% compared with 1.3% on placebo (4). The risk is apparently particularly elevated when the glitazones are used in combination with insulin, which by itself causes sodium retention (12). In the study of Raskin et al. (6), the incidence of edema in patients on 8 mg rosiglitazone was 16.2% compared with 4.7% in patients taking insulin alone.

In contrast to edema, congestive heart failure was seen much less frequently. When rosiglitazone was administered as monotherapy or when it was added to sulfonylurea or metformin, the rate of congestive heart failure did not differ from what was seen on placebo. In contrast, when added to insulin therapy the incidence was 3% compared with 1% on insulin alone (4). Similar data were reported for pioglitazone. In a retrospective, 8.5-mo, observational study based on health insurance claims, the risk of heart failure, even when corrected for confounders, was higher (4.5%) in patients exposed to thiazolidinediones than in patients not exposed to these drugs (2.6%). More recently, however, the data of the Kaiser Permanente Medical Care Program Diabetes Registry failed to show that short-term use of pioglitazone was associated with an elevated risk of hospitalization for congestive heart failure relative to standard first line diabetes therapy (10).

Nevertheless, the consensus statement (4) recommended that doctors check patients for
edema and heart disease before starting treatment with thiazolidinediones and to monitor body weight and watch for dyspnea and other signs of congestive heart failure in patients at high risk.

The reason for the sodium-retaining effect of thiazolidinediones had long remained enigmatic. Vasodilatation with compensatory fluid retention, sympathetic overactivity (13), alterations of endothelial permeability (14), and others were proposed. Because insulin has been known for decades to increase tubular reabsorption and to cause sodium retention (12), as in the edema of refeeding, it had also been proposed that the positive sodium balance was the result of an enhanced renal tubular response to insulin.

This issue has now been definitively settled by the recent publication of two papers (15,16), both of which used genetic and molecular techniques to provide incontrovertible evidence that thiazolidinediones, i.e., PPARγ agonists, upregulate the collecting duct sodium channel (ENaC) and stimulate active sodium transport in this nephron segment.

Zhang et al. generated mice with collecting duct-specific conditional disruption of the PPARγ gene (15). They found that, compared with wild-type mice, the knockout mice gained less body weight and had less pronounced antinatriuresis when treated with rosiglitazone. Some minor reduction of sodium excretion was still noted in the knockout mice. Incomplete PPARγ gene deletion in the collecting duct is an unlikely explanation, given the demonstration of the nearly complete absence of the respective PCR products in the inner medulla. It is therefore possible that other renal sites make a minor contribution to fluid retention as well. Within the kidney, PPARγ is highly expressed in renal medullary collecting duct, but low-level expression, as detected by reverse transcription–PCR and in situ hybridization, does also occur in glomeruli, proximal tubules, and microvasculature (17–19). The physiologic role of such low-level expression remains uncertain, particularly because in past studies PPARγ agonists had failed to affect renal hemodynamics and glomerular filtration (20,21).

The molecular mechanism of sodium retention was further clarified by generating primary cultures from the collecting ducts of PPARγ knockout mice and wild-type mice. In the latter, rosiglitazone stimulated sodium transport as assessed by transepithelial resistance and trans-epithelial flux of radiolabeled sodium (22Na); such stimulation was virtually absent in the cultures obtained from PPARγ knockout mice. Furthermore, the rosiglitazone-stimulated 22Na flux in the wild-type collecting duct primary cultures was abrogated by amiloride.

These conclusions are in line with previous observations that in the renal medulla PPARγ agonists increase the expression of the ENaC and molecules further downstream in the transcellular sodium transport such as SGK1 and Na,K-ATPase (22).

These results are impressively complemented by the study of Guan et al. (15), which investigated the effects of pioglitazone and amiloride on weight gain and sodium retention again in knockout mice and in collecting-duct cultures. The similar effects of rosiglitazone and pioglitazone illustrate that stimulation of sodium transport in the collecting duct is a class effect of glitazones.

This nice piece of translational research raises a number of interesting issues. First, because no abnormalities of sodium balance were seen in the PPARγ knockout mice under basal conditions, it is unlikely that this mechanism of control of sodium reabsorption in the collecting duct contributes to “normal” sodium homeostasis. The findings suggest, however, that activation of the PPARγ receptor, presumably by the endogenous ligands such as 15-deoxy-delta(12,14)prostaglandin J2 and potentially others, comes into play when sodium homeostasis is stressed by situations such as refeeding, i.e., provision of carbohydrates after a prolonged fast.

Second, after the site of sodium reabsorption has been pinpointed to the collecting duct, edema during treatment with thiazolidiones should logically be treated with amiloride, which in the collecting duct monolayer preparation had selectively inhibited the increase in sodium transport in response to thiazolidiones (22).

Third, amiloride may have to be considered not only in the edema of diabetic patients treated with PPARγ agonists, but also in edema of refeeding, which is not infrequently seen in the intensive care unit (22).

Finally, after the recognition that some angiotensin receptor blockers are partial PPARγ
agonists (23,24), it will be of interest whether they share the antinatriuretic action and the underlying molecular mechanisms with classic PPAR\textgamma agonists.

References
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ever since the seminal review of Russell Ross (1), the atherosclerotic plaque has been regarded as a highly dynamic lesion exhibiting inflammatory activity (2) as postulated by R. Virchow in 1856 (3). Although originally it had been thought that progression—and potential reversal—of the plaque was brought about by residential cells, it has recently been increasingly recognized that circulating, bone marrow–derived, mononuclear, endothelial precursor cells (4–7) participate in endothelial, and hence vascular, repair. These circulating progenitor cells express specific markers, e.g., CD34\(^+\)KDR\(^+\), which allow their identification using standardized techniques (8), i.e., flow cytometry and in vitro culture using morphologic characteristics or expression of marker molecules as a read-out. Poorly characterized signals allow such precursors to specifically home in on sites of endothelial lesions and denudation (9–11), where they operate apparently not only by local proliferation, but, more importantly, by secreting cytokines and other factors, thus providing a micromilieu favoring repair.

In apparently healthy subjects without manifest atherosclerosis, the number and, according to preliminary studies (12), the function of endothelial precursor cells correlate to the number of cardiovascular risk factors (13,14). Furthermore, a correlation exists between the number of endothelial precursor cells and endothelial dysfunction (13,15–17).

What had been lacking so far was prospective, controlled evidence that a diminished number of endothelial precursor cells indeed predicted hard endpoints, e.g., the occurrence of cardiovascular events, thus providing some indirect evidence for a potential causal role.

In the recent study of Schmidt-Lucke et al. (12), 44 patients with stable coronary artery disease, 33 patients with acute coronary syndromes, and 43 controls were followed for a median period of 10 mo. At baseline the authors measured circulating endothelial precursor cells as defined by expression of the surface marker CD34\(^+\)KDR\(^+\) using flow cytometry. Cardiovascular events were defined as cardiovascular death, unstable angina, myocardial infarction, percutaneous
transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG), or ischemic stroke. The number of endothelial precursor cells was significantly lower in patients developing cardiovascular events (0.0067 ± 0.0097 per 100 peripheral mononuclear cells versus 0.02 ± 0.02 in patients without events). By Kaplan-Meier analysis, reduced numbers of endothelial precursor cells were associated with a significantly higher incidence of cardiovascular events (P < 0.0009). By multivariate analysis, reduced numbers of endothelial precursor cells were significant independent predictors of adverse prognosis, even when the data were corrected for traditional cardiovascular risk factors and disease activity (hazard ratio, 3.9).

The remarkable results document that low numbers of endothelial precursor cells are strong, independent predictors of atherosclerotic events. This finding provides strong support for the hypothesis that these cells contribute to ongoing vascular repair. Indeed, recent experimental studies documented endothelial precursor cells homing into arterial segments denuded of endothelial cells after balloon injury (9,10), and they may even replace dysfunctional endothelial cells.

Whether endothelial cell precursors are beneficial only by their action on plaque remodeling or whether effects on vasodilatation (13) and coronary collateral support (18) also play a role is currently undecided.

The mechanism causing reduced numbers of endothelial cell precursors is currently unknown, but exhaustion of the cell pool in the bone marrow, impeded mobilization, or reduced survival and maturation in the circulation are potential explanations. In view of the fact that uremia can be regarded as a form of premature, accelerated aging (19), it is of interest that the capacity to react to stress-induced mobilization of precursor cells declines with increasing age (20). This has also been specifically shown in the atherosclerosis model of the apoE knockout mouse (21), a model that has been widely used to study accelerated atherogenesis in uremia (22–24).

Why are the above findings of interest to nephrologists? In a seminal report, Lindner et al. (25) reported excess cardiovascular death in the dialyzed patient and postulated that in uremia atherosclerosis was accelerated. It had remained uncertain for a considerable time, however, whether excess cardiac death is not simply explained by the high prevalence of classic risk factors or whether truly uremia-specific acceleration of atherosclerosis occurs. This issue has meanwhile been settled by the demonstration of accelerated plaque growth in apoE knockout mice with reduced renal function (22–24), and even accelerated coronary calcification is suggested by studies in patients with early renal disease (26).

Are there abnormalities of endothelial precursor cells in uremia (27)? Uremia with or without hemodialysis is associated with a deficient number of endothelial progenitor cells (28–30). After renal transplantation, numbers were decreased when the graft function was not normal (31). The capability of endothelial progenitor cells to migrate and form tubes was reduced, and the serum of uremic patients inhibited their capacity to differentiate in vitro. Amelioration of uremia after institution of renal replacement therapy increased their number (28).

Are there perspectives for intervention to repair these defects? Several interventions increase endothelial precursor cells. In nonuremic patients it has been shown that physical training increases their number (32), and the same has been shown for statins (33–35) and for angiotensin receptor blockers (36). Finally, erythropoietin (EPO) has been identified as a potent physiologic stimulus of endothelial progenitor cell mobilization (37,38).

These beneficial effects are not restricted to nonuremic patients. Even at concentrations that were subtherapeutic with respect to correction of anemia, EPO regulated endothelial progenitor cell concentrations (39).

On the one hand, endothelial cells, presumably sloughing off the vascular wall, can be demonstrated in the circulation of uremic patients (40) and are associated with future vascular events (41). On the other hand, the numbers of the endothelial cell progenitor cells are diminished (28). These cells predict cardiovascular events, at least in nonuremic patients (12). It is not unreasonable to assume that the balance between vessel injury and repair is deranged in uremia. The above possibilities of intervention on the horizon give cause for cautious optimism.
References


