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Thiazolidinediones: A novel class of drugs for the prevention of diabetic nephropathy?

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Diabetic nephropathy is the leading cause of end-stage renal disease. Novel preventive measures for diabetic renal complications are urgently needed. Miyazaki *et al.* report that rosiglitazone, a thiazolidinedione insulin sensitizer and a potent peroxisome proliferator-activated receptor γ agonist, not only effectively improves glycemic control but also halts progression of albuminuria in type 2 diabetic patients with early-stage diabetic nephropathy. These findings could offer a new prevention of diabetic nephropathy in insulin-resistant diabetic patients.

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As the prevalence of type 2 diabetes has risen to epidemic proportions worldwide, diabetic renal complications, or diabetic nephropathy (DN), has become a serious public-health concern.[1] The population with type 2 diabetes has risen about 5% annually in the United States since 1990 and shows no sign of slowing down. DN is one of the major complications of diabetes. About half of all diabetic patients have microalbuminuria, and among those, about 50% eventually develop overt DN. Diabetic renal complications in diabetes may not only progress to renal failure but also significantly increase the risk of cardiovascular disease. DN is characterized by sequential pathophysiological events including renal hypertrophy, extracellular matrix accumulation, and renal fibrosis with loss of renal function. The pathogenesis of renal involvement in diabetes has long been thought to be the result of the interplay of metabolic and hemodynamic factors. However, it has also been noticed that intensive control of hyperglycemia and hypertension effectively prevents or slows its progression to ESRD in only a subset of diabetic patients. Therefore research efforts have recently been directed toward preventing the development and slowing the progression of DN.

Among many experimental drugs that have been shown to be effective in attenuating DN in animal models of type 2 diabetes, the thiazolidinedione (TZD) class of insulin-sensitizing agents holds great promise for treating both insulin resistance and diabetic renal complications. TZDs are a group of compounds including rosiglitazone (Avandia) and pioglitazone (Actos), both widely used in diabetes clinic.These agents exert their insulin-sensitizing action via binding and acting on a nuclear receptor transcription factor designated peroxisome proliferator-activated receptor γ (PPARγ), which is expressed in many insulin-sensitive tissues especially in the liver, skeletal muscle, and adipose tissue. Upon activation by TZDs, PPARγ modulates gene expression of many target genes involved in glucose transport and utilization in peripheral tissues, thereby enhancing insulin action and lowering blood glucose.[2] Increasing evidence *in vitro* and in animal models suggests that adipose tissues play an important role in these beneficial metabolic effects. Activation of adipose PPARγ has been shown to improve insulin sensitivity by inhibiting the release of free fatty acids (FFAs), tumor necrosis factor-α (TNF-α), and resistin, all of which have been implicated in the pathogenesis of insulin resistance.[3] On the other hand, TZD treatment has been found to attenuate insulin resistance by stimulating production of several insulin-sensitizing adipokines, including adiponectin and visfatin. The clinical study by Miyazaki *et al.*[4] (this issue) clearly demonstrates that 3-month rosiglitazone treatment resulted in decreased levels of plasma FFAs and TNF-α and increased concentrations of adiponectin in type 2 diabetic patients. This study provides important mechanistic insights into insulin-sensitizing actions of rosiglitazone in this clinical setting and supports an idea that pharmacologic interventions aimed at improving lipid toxicity, low-grade inflammation, and adiponectin may represent novel avenues to treat type 2 diabetes.

In addition to metabolic effects, there is now a considerable amount of evidence suggesting that TZDs can ameliorate microalbuminuria and slow the progression of DN. In type 2 diabetic rodents, the TZDs rosiglitazone and pioglitazone were found to be effective in the prevention and progression of albuminuria and renal fibrosis.[5] Consistently, all available human studies with TZDs have reported a marked reduction in urine albumin-to-creatinine ratio (UACR) or urinary albumin excretion in type 2 diabetes with microalbuminuria.[6] It appears that the favorable renal effect of TZDs in type 2 diabetes is not completely dependent on their insulin-sensitizing action, as metformin produced similar glycemic control but had practically no effect on UACR, as is reported by Miyazaki *et al.*[4]

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and many other groups.[6] At present, the underlying mechanisms by which TZDs exert their renal-protective effects in diabetic patients remain only partially characterized. In addition to their anti-hyperglycemic, anti-hyperinsulinemic, and anti-hypertensive effects, TZDs may also directly act on renal PPARγ in the glomeruli and proximal tubules in type 2 diabetic patients.[2] The most intriguing and important finding of the study by Miyazaki *et al.*[4] might be that two adipocyte-derived cytokines, TNF-α and adiponectin, were differentially affected by rosiglitazone treatment. The authors show for the first time that reduction in the proinflammatory adipokine TNF-α and increase in anti-inflammatory adiponectin were independently associated with the regression of UACR in type 2 diabetic patients after rosiglitazone treatment, suggesting that inhibition of TNF-α release and stimulation of adiponectin production in adipose tissues may represent a novel mechanism contributing to the renal-protective effect of TZDs (Figure 1).

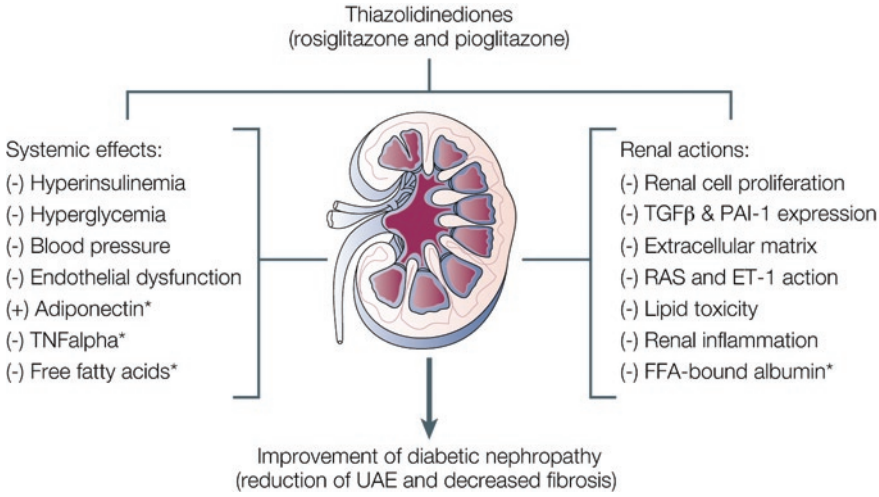

Figure 1 | Mechanisms by which thiazolidinediones attenuate albuminuria and improve diabetic nephropathy. TNF-α, tumor necrosis factor-α; TGFβ, transforming growth factor-β; PAI-1, plasminogen activator inhibitor-1; RAS, renin–angiotensin system; ET-1, endothelin-1; FFA, free fatty acid; UAE, urinary albumin excretion. Asterisks indicate evidence from the study by Miyazaki *et al.*[4]

To date, it remains only partially understood how TNF-α and adiponectin affect renal function in diabetic conditions. Although in their discussion Miyazaki *et al.*[4] claim that increased circulating TNF-α was of adipocyte origin, it is also possible that this cytokine could be produced and secreted in diabetic kidneys, where TNF-α acts on its receptors to stimulate the production of other proinflammatory factors, recruit inflammatory cells, and induce cell apoptosis, resulting in renal damage. Adiponectin, as an insulin-sensitizing, anti-inflammatory, and vasculo-protective cytokine, has been proved to ameliorate insulin resistance, low-grade inflammation, and endothelial-cell dysfunction, which frequently occur in type 2 diabetes. Its levels were also directly correlated with renal disease progression.[7] The close association between plasma adiponectin levels and UACR found by Miyazaki and colleagues[4] has now advanced our understanding of this relationship between the adipocyte factor adiponectin and albuminuria in type 2 diabetic patients. Although the mechanisms mediating renoprotection remain incompletely understood, increased adiponectin production by TZD treatment may attenuate albuminuria via both systemic (insulin-sensitizing) and direct renal action (improving endothelium function). This issue warrants further investigation.

In the report by Miyazaki and colleagues,[4] treatment of diabetic patients with rosiglitazone, but not with metformin, also significantly lowered the levels of FFAs in parallel with reduced albuminuria. This finding is important and implies that FFA-bounded albumin might be ameliorated by TZD treatment. An increasing body of evidence has emerged that it is the FFAs bound to albumin, rather than albumin itself, that cause severe tubulointerstitial damage by being reabsorbed into the proximal tubule.[8] If this is proved true, decreased FFA-depleted albuminuria may also contribute to the protective effect of TZDs on DN in type 2 diabetic patients (Figure 1).

This study shows that, whereas patients treated with placebo had an approximately 18% increase in urinary albumin excretion, patients receiving rosiglitazone treatment exhibited an approximately 50% reduction in albuminuria. Although the finding is encouraging, one should be cautious in drawing a conclusion based on current data, as this was a relatively short-term study with small samples. Because only 20% of type 2 diabetics develop chronic kidney disease and DN, usually 10 years after the onset of diabetes, it would be essential to conduct a long-term study with a large patient population to determine the benefit of TZDs in DN prevention. Clinically, the development and progression of DN occur in several sequential stages, including glomerular hyperfiltration, microalbuminuria (UACR 30–300 μg/mg), macroalbuminuria (UACR >300 μg/mg), and renal failure. It is of note that glomerular filtration rate was not accurately determined in patients in this study. However, data from the measurement of creatinine clearance appeared to indicate that a few patients in both groups might have glomerular hyperfiltration. Furthermore, only a small proportion of patients seems to develop microalbuminuria with a UACR greater than 30 μg/mg. Therefore, it would be important to revisit the data after identifying these patients. Finally, a decrease or increase in urine albumin excretion within the normal range may not be as valuable as we thought in defining the degree of renal injury or function deterioration. Although the study by Miyazaki *et al.*[4] was the first placebo-controlled study and provides valuable information, a long-term clinical trial with a large population is required to define the beneficial role of TZDs in DN

prevention. It is also worth mentioning that rosiglitazone treatment has recently been shown to cause severe side effects, such as weight gain as seen in this study, fluid retention, and increased cardiovascular risk.[9,10] Thus, it becomes important to determine whether the benefit of using TZDs would outweigh the risks.

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Research in HIV-related renal diseases lags behind their burden to the 'positive' community

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Although outcomes for persons with HIV infection and renal disease have improved, the analysis by Choi *et al.* suggests that they remain similar to or worse than outcomes for persons with diabetes mellitus. This study should be used to frame the research resources that we devote to furthering knowledge in this area.

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It has been my individual perception that HIV-related kidney diseases were not and are not getting the appropriate quantity of dedicated clinical research, given the risk of morbidity and mortality associated with them. I have often wondered why.

In the 1980s, when the possibility that the HIV virus could be associated with the kidney disease HIV-associated nephropathy became apparent,[1] patient outcomes were swift and devastating. The average patient was on dialysis 3 months after the recognition of his or her kidney disease,[2] and the mortality rate was a striking 50% for those who survived to dialysis.[3–5] I remember the problems that we faced with graft infections among persons with HIV and even early discussions of whether or not it was appropriate to offer dialysis to this group of patients.

The development of effective antiretroviral medications was clearly among the most amazing and rapid births of therapeutic regimens in the history of modern medicine. The early 1990s brought the availability of effective nucleoside reverse transcriptase inhibitors and their now familiar codes of AZT, d4T, ddI, and so on. The mid-1990s saw the introduction of the first protease inhibitors. The subsequent development of new drug classes—non-nucleoside reverse transcriptase inhibitors and fusion inhibitors—and the practice of combining different drug classes into exceptionally effective and complementary regimens (highly active antiretroviral therapy) have cumulatively improved outcomes at an astonishing rate.[6] With this improvement, it is estimated that the relative proportion of persons with HIV who begin dialysis has also been positively affected.[7]

So have we won the battle against HIV-related renal disease? Absolutely not. The article by Choi *et al.*[8] (this issue) provides that reality check.

In this analysis of patients receiving their care within the Veterans Administration Health System, Choi *et al.*[8] demonstrate that the risk of end-stage renal disease (ESRD) among African Americans is twice as high in those with HIV infection as it is in those with diabetes mellitus. Given that the rate of decline of kidney function and the rate of death are also almost twice as high among African Americans with HIV infection as they are among those with diabetes, arguably, it is likely that a significant proportion of African Americans with HIV and chronic kidney disease are dying before developing ESRD and that the actual risk of ESRD is therefore even higher than Choi *et al.*[8] estimate.

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