

Anti-inflammatory Effects of Pioglitazone in Diabetic Kidney Transplant Recipients

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The adverse effects of oxidative stress and inflammation on kidney transplants have been shown by investigational studies in animal models and a number of controlled clinical trials. Oxidative stress plays a major role in the pathogenesis of systemic inflammation.¹ Chronic inflammation at 1 and 5 years after transplantation is related to the higher rates of graft loss and lower kidney function. Inflammation and oxidative stress are the most important reasons of cardiovascular morbidity and mortality in patients with chronic kidney disease.¹

Inflammatory markers and oxidative stress biomarkers such as high-sensitivity C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and 8-isoprostaglandin F₂ α (inflammatory marker) are utilized in several studies as a predictor of short- and long-term graft function, and there is a significant relationship between levels of these markers and the transplant kidney function.² Interleukin-6, TNF- α , and CRP, the proinflammatory cytokines, are significantly elevated in end-stage renal disease patients before transplantation in comparison with healthy individuals, and transplantation considerably reduces inflammation in 2 to 3 months if kidney function becomes normal.³⁻⁵ Levels of inflammatory and oxidative stress markers are reduced slowly following kidney transplantation. These biomarkers were at their maximum levels 4 hours after transplantation, but then declined to or even below their preoperative levels on the 4th day posttransplantation.⁶

Studies demonstrate that posttransplant diabetes mellitus enhances the rate of cardiovascular disease and infection.^{7,8} Diabetes mellitus is invariably associated with inflammation and oxidative stress. Inflammation and oxidative stress are significantly greater in diabetic patients after transplantation

and are associated with poorer kidney allograft function in the diabetic recipients with higher hemoglobin A1c.^{9,10} Inflammation also appears to play a role in chronic allograft nephropathy and serum level of CRP, IL-6, IL-10, TNF- α , IL-2R, and IL-4 are noticeably elevated in chronic allograft nephropathy.¹¹ Hepatic glucose production is increased and insulin-stimulated glucose removal is decreased as an effect of steroids in transplanted insulin-dependent diabetes mellitus patients. Steroids induce both hepatic and peripheral insulin resistance and amplify insulin requirement in transplant patients.¹²

Pioglitazone is a prescription drug of the class thiazolidinedione with hypoglycemic (antihyperglycemic and antidiabetic) characteristics to treat diabetes mellitus. Pioglitazone selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor- γ (PPAR- γ). Prior studies in animal models had described the valuable roles for PPARs in reducing kidney injury and dysfunction; they exert anti-inflammatory and anti-oxidant properties via the downregulation of inflammatory cytokines and reduction of oxidative stress.¹³ Nondiabetic kidney disease model in rats demonstrated that pioglitazone provides renoprotection to a similar extent as an angiotensin-converting enzyme inhibitor by anti-inflammatory mechanisms. In vitro study on rat mesangial cells randomly assigned to control group, high glucose group, and pioglitazone group after 48-hour exposure, demonstrated that pioglitazone could inhibit oxidative stress through suppressing NADPH oxidase expression and p38MAPK phosphorylation.¹⁴

In this issue of the *Iranian Journal of Kidney Diseases*, Kharazmkia and colleagues¹⁵ reported the efficacy of pioglitazone in 62 insulin-dependent transplant

patients. Transplantation was performed because of kidney failure due to different reasons, but insulin was being administered because of diabetes mellitus. Fifty percent of the included patients were set in the pioglitazone group. At baseline, no significant differences in glycemic control levels and inflammatory mediator levels and lipid levels were detected between two arms of the study. After 4 month of treatment, hemoglobin A1c decreased significantly ($1.21 \pm 1.2\%$) in the study group in comparison with placebo group. Daily neutral protamine Hagedorn insulin requirements may be as an indicator of insulin resistance also decreased considerably (4.48 ± 9.5 IU/d) in the pioglitazone group although in placebo arm daily dose of neutral protamine Hagedorn insulin increased from baseline. Pioglitazone also significantly improved transplanted patients serum lipid profile. Interleukin-18 levels declined from 354.12 ± 156.24 pg/mL to 210.05 ± 144.52 pg/mL after 4 months of pioglitazone administration (statistically significant). Furthermore, serum level of inflammatory markers (erythrocyte sedimentation rate, CRP and high-sensitivity CRP) were significantly lower in the pioglitazone group at the end of the trial.¹⁵

In conclusion, pioglitazone may be a useful and attractive therapy of diabetic transplant recipients. In these patients, it represents a suitable property as an adjunctive therapy to insulin. Pioglitazone improve long-term glucose control (lower hemoglobin A1c) and also leads to a significant decline of inflammatory markers such as erythrocyte sedimentation rate, CRP, high-sensitivity CRP, and IL-18. Therefore, a randomized controlled trial with a larger sample size evaluating biomarkers of stress oxidative such as malondialdehyde and insulin resistance level are recommended for future studies.

CONFLICT OF INTEREST

None declared.

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