Effects of Pioglitazone on Blood Glucose and Inflammatory Markers of Diabetic Kidney Transplant Patients

A Randomized Controlled Trial

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Original Paper

Introduction. The aim of this study was to assess the effects of pioglitazone on blood glucose control and inflammatory biomarkers in diabetic patients receiving insulin after kidney transplantation.
Materials and Methods. In a randomized placebo-controlled trial, 62 diabetic kidney transplant patients were followed for 4 months after randomly assigned to placebo and pioglitazone (30 mg/d) groups. All of the patients continued their insulin therapy irrespective of the group that they were assigned to, in order to evaluate the effects of addition of pioglitazone on blood glucose and inflammation biomarkers including serum C-reactive protein, high-sensitivity C-reactive protein, and interleukin-18 levels, as well as erythrocyte sedimentation rate.
Results. At baseline, there were no significant differences in laboratory studies between the two groups. After 4 months of intervention, along with significant improvement in hemoglobin A1c in the pioglitazone group, daily insulin requirements also decreased and lipid profile improved significantly. In addition, erythrocyte sedimentation rate, C-reactive protein, and high-sensitivity C-reactive protein values were significantly lower in the pioglitazone group ($P = .03$, $P < .001$, and $P = .01$). Interleukin-18 levels were not significantly different at the end of the study between the two groups, but it had a decreasing trend in the pioglitazone group ($P = .002$).
Conclusions. Pioglitazone complementing insulin in diabetic kidney transplant patients not only improved glycemic control, evidenced by hemoglobin A1c, and reduced daily insulin requirement, but also decreased inflammatory markers which may have an impact on overall cardiovascular events and mortalities beyond glycemic control.

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INTRODUCTION

Diabetes mellitus has an important role in long-term patient and graft outcomes of kidney transplant recipients. It is an independent predictor of major cardiovascular events after transplantation,[1] and there is a strong relationship between blood glucose control and graft function and survival after transplantation.[2] Generally, most studies on glycemic control in diabetic patients have focused on new-onset diabetes mellitus (DM) after transplantation.[3]

One study conducted on kidney transplant patients with type 2 DM after 15 years of

follow-up demonstrated that sulfunylureas were rarely effective in controlling blood glucose.[4] Thiazolidinediones are a class of insulin-sensitizing agents currently used in the treatment of DM. Other beneficial effects were demonstrated including anti-inflammatory and nephroprotective effects.[5,6] These compounds may have direct beneficial effects on cardiovascular risks independent of their glucose controlling action.[7] In particular, in patients with type 2 DM, rosiglitazone has a positive effect on cardiovascular risk factors and markers of endothelial dysfunction, including the sensitive marker of vascular inflammation and C-reactive protein (CRP).[8,9] Some researchers have discussed that metabolic syndrome, type 2 DM, and atherosclerosis are multi factorial conditions which appear to have a common inflammatory basis, and it is currently on debate whether a measure of inflammation should be included in definition of the syndrome.[10-12]

Several pieces of evidence suggest that interleukin (IL)-18 is closely correlated with the metabolic syndrome and its consequences with particular emphasis on cardiovascular risk and life style interventions. Interleukin-18 is a potent pro-inflammatory cytokine engaged in the host defense by upregulating both innate and acquired immune responses and may be of particular importance also in mechanisms of kidney allograft rejection.[13-15] Interleukin-18 enhances T-cell and natural killer cell maturation, as well as the production of cytokines, chemokines, and cell adhesion molecules.[16-20] Interleukin-18 may stimulate a T helper 2 response in combination with IL-2, and may act synergistically with IL-12 to stimulate a T helper 1 response with production of interferon, a central feature in the atherosclerotic lesion.[21,22] In various studies, IL-18 has been related with obesity, insulin resistance, hypertension, dyslipidemia, and metabolic syndrome.[23-34]

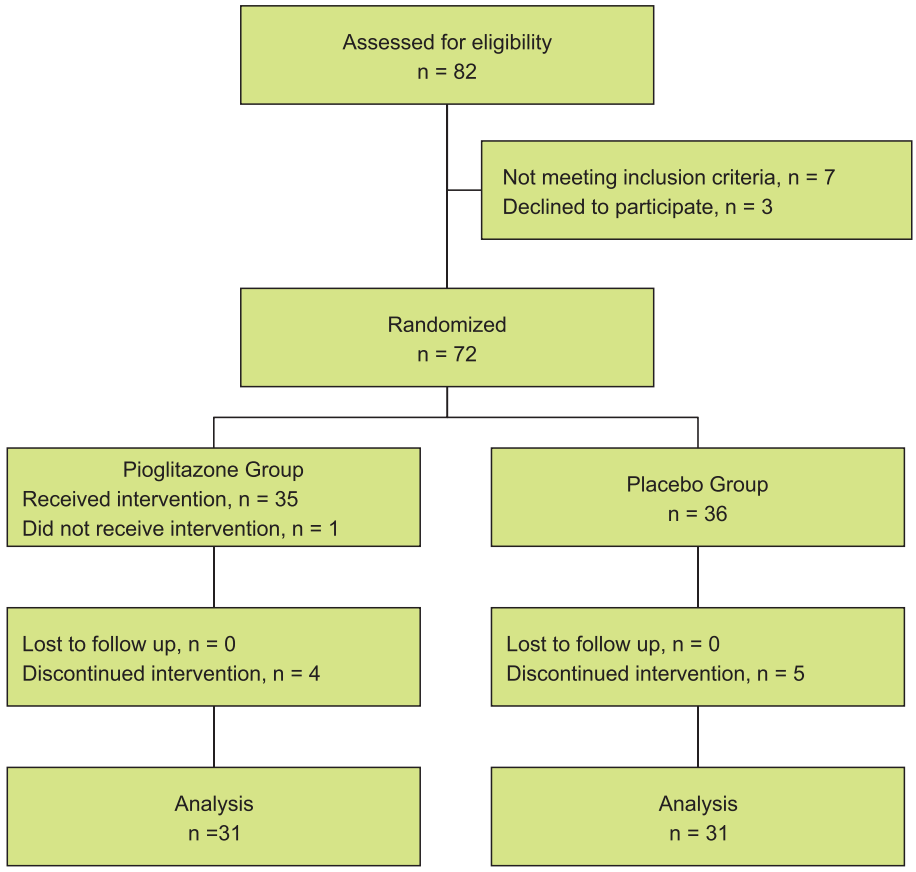
Furthermore, several large-scale prospective studies have indicated that high levels of Hemoglobin A1c increase all-cause mortality and cardiovascular disease risk.[35-38] This indicates a feasible utility of Hemoglobin A1c as a marker of prognostic prediction in patients with and without DM. The correlation between lipid abnormalities (higher levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides, and lower level of high-density lipoprotein cholesterol) and increased mortality is appointed firmly in general population,[39,40] and a number of studies have illustrated the association between hypercholesterolemia and development of graft vessel disease.[41,42] There is little experience on glycemic control with thiazolidinediones after kidney transplantation . The aim of the present study was to assess the effects of pioglitazone on blood glucose control and inflammatory biomarkers including in diabetic patients receiving insulin after kidney transplantation in a double-blind randomized placebo-controlled trial.

MATERIALS AND METHODS

Study Design

We conducted a double-blind randomized placebo-controlled trial to evaluate effects of pioglitazone on blood glucose and inflammation biomarkers including high-sensitivity CRP (HSCRP), erythrocyte sedimentation rate (ESR), and IL-18 levels in diabetic kidney transplant patients. From September 2012 till May 2013, patients were recruited from the Transplantation Center of Shahid Labbafinejad Medical Center (Shahid Beheshti University of Medical Sciences, Tehran, Iran). Kidney transplant recipients were included in the study if they had received a kidney transplant at least 1 month prior to the study, with stable graft function within the past 2 weeks. Patients were excluded if they had any history of febrile episodes, hepatitis B or C infection, a glomerular filtration rate less than 30 mL/min based on the Modification of Diet in Renal Disease equation at baseline, history of congestive heart failure (New York Heart Association class II-IV), and pregnancy during the study. Those who received steroid pulse or had acute episodes of allograft dysfunction (decrement of glomerular filtration rate by at least 30 mL/min) during the follow-up period were also excluded. Eighty-two kidney transplanted diabetic patients were assessed for eligibility. Ten of 82 patients were excluded as mentioned in the flowchart (Figure).

The patients were divided into 2 groups by computerized random number method. Clinician researchers, participants, and data analysts remained blinded to the random allocations during the study. Concealment of randomization was adhered. All 72 eligible patients were randomly assigned to the placebo and pioglitazone groups. All



Flow diagram of the progress through the phases of the randomized trial.

of the participants continued their insulin therapy irrespective of the group that they were assigned to and the cyclosporine-based immunosuppressive protocol which consisted of mycophenolate mofetil and prednisolone were used in all of them. Pioglitazone, 30 mg/d, and placebo were administered in the study groups for 4 months. Both pioglitazone (Glutazone) and placebo were manufactured by the Osveh Pharmaceutical Co (Tehran, Iran). All of the patients were followed for 4 months and laboratory studies were done at baseline and monthly up to the end of the study period.

The study was carried out according to the principles of the Declaration of Helsinki and was approved by the ethics institutional committee of Shahid Beheshti University of Medical Sciences. This trial was registered in the Iranian Registry of Clinical Trials (IRCT2012121811807N1). Written informed consent was obtained from all participants. The patients were closely observed by regular monthly visits and also by telephone for 4 months. At each visit, data were collected for the outcome events, compliance, and side effects. All clinical and laboratory variables were documented and dose of insulin was adjusted based on the American Diabetes Association guideline. According to the guideline, preprandial plasma glucose of 90 mg/dL to 130 mg/dL and hemoglobin A1c less than 7% were considered as treatment goals for adults with DM.

Laboratory Studies

We measured concentrations of fasting blood glucose (FBS), hemoglobin A1c, and serum levels of lipid profile, kidney function markers, CRP, HSCRP, ESR, and IL-18 at the beginning of the study and monthly during the 4 months of the follow-up period. In each visit, 5 mL of whole blood was collected to assess these parameters. After centrifuging the samples and measurement of the mentioned parameters, serum component was separated and frozen at -20°C for measurements of the IL-18 level with enzyme-linked immune sorbent assay kits (Boster's Human IL-18 ELISA

Kit was based on standard sandwich enzyme-linked immune-sorbent assay technology) at the initiation and the end of study.

Outcomes

The primary outcome of the study was changes in blood glucose level and secondary outcomes were changes in lipid profile and inflammatory markers including CRP, HSCRP, ESR, and IL-18 level.

Statistical Analyses

Results were expressed as means ± standard deviation, or as proportion (percentage). The *t* test was used for comparisons of parametric data when normal distribution and equal dispersion were recognized. The Mann-Whitney U test and the Wilcoxon signed-rank test were used when the variance was unequal. Differences in the categorical data were analyzed by chi-square test, and the Fisher exact test was used when appropriate. Repeated measure analysis of variance was used to compare the two groups with consecutive measurements. A *P* value less than .05 was considered significant.

RESULTS

Basic Characteristics of Participants

Of the 72 patients, 1 in the pioglitazone group and 5 in the control group were excluded from the study due to nonadherence to study protocol and 4 dropped out in the pioglitazone group due to side effects. The baseline characteristics of the 62 patients who completed the study are shown in Table 1. The two groups were comparable in terms of all variables examined at baseline.

Table 1. Basal Characteristics of Participants

Characteristic	Pioglitazone Group	Placebo Group	*P*
Number of patients	31	31	…
Mean age, y	50.2 ± 12.6	54.8 ± 8.7	.24
Male sex (%)	24 (77.4)	16 (51.6)	.06
Body weight, kg	74.4 ± 14.4	76.5 ± 3.7	.68
Time since transplantation, mo	40 ± 28	51 ± 50	.45
Secondary transplant	1	1	> .99
Cigarette smoking	0	0	> .99
Cadaveric transplant	10	7	.57
Treatment			
Angiotensin-converting enzyme inhibitors (%)	2 (6.5)	3 (9.7)	> .99
Angiotensin receptor blockers (%)	13 (41.9)	10 (32.3)	.43
Aspirin (%)	11 (35.5)	15 (48.4)	.30
Allopurinol (%)	6 (19.4)	5 (16.1)	.74
Statins (%)	19 (61.2)	17 (54.8)	.46
Vitamins E and C (%)	0	0	> .99
Mean insulin neutral protamine Hagedorn dose, IU/d	38.2 ± 23.7	34.1 ± 14.3	.78
Mean insulin regular dose, IU/d	18.0 ± 12.4	17.3 ± 14.3	.67
Mean prednisolone dose, mg/d	6.0 ± 1.9	5.9 ± 2.8	.39
Mean cyclosporine dose, mg/d	138.4 ± 33.0	139.8 ± 48.1	.90
Mean cyclosporine dose, mg/kg/d	2.04 ± 0.75	1.84 ± 0.74	.23
Mean values for laboratory studies			
Fasting blood glucose, mg/dL	136.0 ± 61.6	145.5 ± 84.8	.82
Hemoglobin A1c, %	8.6 ± 1.9	7.8 ± 1.6	.19
Erythrocyte sedimentation rate, mm/h	25.7 ± 18.0	17.5 ± 15.0	.06
C-reactive protein, mg/L	7.1 ± 11.6	3.4 ± 6.1	.28
High-sensitivity C-reactive protein, mg/L	6.4 ± 18.0	4.3 ± 10.2	.18
Interleukin-18, pg/mL	354.12 ± 156.24	349.14 ± 221.02	.68
Serum creatinine, mg/dL	1.59 ± 0.31	1.38 ± 0.45	.34
Blood urea nitrogen, mg/dL	30.48 ± 12.41	29.97 ± 13.61	.99
Serum total cholesterol, mg/dL	189.6 ± 40.0	193.8 ± 54.1	.98
Serum low-density lipoprotein cholesterol, mg/dL	104.6 ± 28.9	102.5 ± 39.3	.39
Serum high-density lipoprotein cholesterol, mg/dL	47.7 ± 10.2	51.2 ± 17.1	.76
Serum triglyceride, mg/dL	161.7 ± 56.1	181.3 ± 95.8	.92
Hemoglobin, g/dL	13.4 ± 1.7	13.4 ± 1.3	.64

Transplantation was performed because of kidney failure due to different reasons, but all patients were using insulin because of DM. There were no significant differences in the administration of various medications (Table 1).

Outcomes

Changes in measured parameters after intervention are depicted in Tables 2 and 3. The mean hemoglobin A1c at baseline was 8.6 ± 1.9% in the pioglitazone group and 7.8 ± 1.6% in the placebo group. Although changes in the fasting blood glucose did not demonstrate any significant differences among the groups, changes of hemoglobin A1c during the 4 months of follow-up showed improvement in the pioglitazone group,

Table 2. Trend of Laboratory Data

Parameter	Pioglitazone Group	Placebo Group	*P*
Fasting blood glucose, mg/dL			
Baseline	132.6 ± 57.2	131.4 ± 45.5	.75
Month 2	122.4 ± 47.4	126.2 ± 42.7	.72
Month 3	112.3 ± 30.1	137.3 ± 59.0	.19
Month 4	118.6 ± 48.9	131.1 ± 50.0	.14
P for trend	.11	.82	…
Erythrocyte sedimentation rate, mm/h			
Baseline	21.8 ± 15.3	19.5 ± 17.3	.41
Month 2	16.6 ± 17.4	18.8 ± 14.3	.34
Month 3	12.9 ± 10.6	17.1 ± 14.2	.24
Month 4	11.8 ± 11.1	20.3 ± 15.7	.03
P for trend	0.0001	0.12	…
C-reactive protein, mg/dL			
Baseline	3.3 ± 4.8	3.4 ± 5.3	.32
Month 2	2.9 ± 3.4	5.4 ± 9.2	.40
Month 3	1.8 ± 1.8	6.7 ± 8.1	.002
Month 4	2.1 ± 4.2	5.7 ± 7.8	< .001
P for trend	.001	.004	…
High-sensitivity C-reactive protein, mg/dL			
Baseline	3.6 ± 6.1	4.2 ± 9.5	.49
Month 2	2.1 ± 4.5	3.7 ± 9.1	.66
Month 3	1.8 ± 3.8	5.2 ± 13.4	.30
Month 4	1.1 ± 2.3	4.8 ± 10.7	.01
P for trend	.001	.02	…
Interleukin-18, pg/mL			
Baseline	354.12 ± 156.24	349.14 ± 221.01	.68
Month 4	210.05 ± 144.52	328.47 ± 275.10	.15
P for trend	.002	.75	…
Mean changes*			
Hemoglobin A1c, %	-1.21 ± 1.2	0.39 ± 1.0	< .001
Serum low-density lipoprotein cholesterol, mg/dL	-15.3 ± 16.6	0.16 ± 32.6	.002
Serum high-density lipoprotein cholesterol, mg/dL	4.23 ± 7.02	-0.45 ± 11.60	.007
Serum triglyceride, mg/dL	-28.6 ± 8.2	3.9 ± 13.0	.04
Serum total cholesterol, mg/dL	-18.0 ± 28.3	4.2 ± 30.4	.004
Serum creatinine, mg/dL	0.04 ± 0.17	0.12 ± 0.21	.53
Blood urea nitrogen, mg/dL	-2.84 ± 14.90	3.16 ± 5.65	.91
Hemoglobin, g/dL	-0.14 ± 1.32	-0.06 ± 1.50	.72
Prednisolone dose, mg/d	-0.48 ± 1.20	-0.58 ± 2.00	.51
Cyclosporine dose, mg/d	-12.1 ± 28.0	-12.41 ± 7.5	.13
Cyclosporine dose, mg/kg/d	-0.19 ± 0.42	-0.47 ± 0.36	.63
Insulin neutral protamine Hagedorn dose, IU/d	4.48 ± 9.50	0.32 ± 3.48	.001
Insulin regular dose, IU/d	1.74 ± 4.90	0.16 ± 2.20	.05
Body weight, kg	0.61 ± 2.63	0.60 ± 2.16	.73

*Values are the mean of differences between baseline and month 4.

Table 3. Mean Hemoglobin and Lipid Profile Values at the End of Study

Parameter	Pioglitazone Group	Placebo Group	*P*
Hemoglobin A1c, %	7.6 ± 0.8	7.2 ± 1.3	.05
Serum total cholesterol, mg/dL	171.7 ± 37.6	198.6 ± 42.1	.01
Serum low-density lipoprotein cholesterol, mg/dL	89.4 ± 28.2	102.8 ± 28.4	.003
Serum high-density lipoprotein cholesterol, mg/dL	51.97 ± 11.82	50.74 ± 13.30	.002
Serum triglyceride, mg/dL	133.1 ± 38.8	185.2 ± 91.0	.001

whereas it increased by 0.3% in the placebo group (Table 2). The total dose of neutral protamine Hagedorn insulin at the end of the study decreased in the pioglitazone group, while it slightly increased in the placebo group. There was no significant difference in regular insulin total dose at the end of the study between two groups.

The declining trend in ESR in the pioglitazone group was significant, whereas in the placebo group, ESR did not show such a decline, leading to a significant difference of ESR levels between the two group at the end of the study (Table 2). Compared to baseline, levels of CRP and HSCRP did not show any significant difference between the two groups, but at the end of the study, the levels of these parameters were significantly lower in the pioglitazone group ($P < .001$ and $P = .01$), although serum CRP and HSCRP levels both had a decreasing trend in both groups. Regarding the IL-18 level, the changes were not significantly different at baseline and also at the end of the study between the two groups, but there was a decreasing trend in the pioglitazone group ($P = .002$) that could not be seen in the control group ($P = .75$).

Improvements of lipid profile variables were shown in the pioglitazone group (Table 2). The changes of blood urea nitrogen and serum creatinine levels and doses of hemoglobin, prednisolone, and cyclosporine were not significantly different between the two groups at the end of the study. In addition, a small amount of weight gain was observed in both groups, which was not significant.

Safety of Treatment

There were 4 dropouts in the pioglitazone group due to drug adverse effects (3 had mild to moderate lower extremity edema and 1 had insomnia, which led to discontinuation of treatment). Pioglitazone was well tolerated in all other patients who continued the trial and none of the patients had transient elevation of liver enzyme levels 2 or more times the upper limits or severe congestive heart failure.

DISCUSSION

The primary endpoint in the study was looking at changes of glycemic control indexes such as fasting blood glucose and hemoglobin A1c levels and insulin requirements. As mentioned in various studies, pioglitazone is an effective agent for the treatment of DM, as evidenced by the significant improvement in hemoglobin A1c levels. This occurred despite an overall decrease in total daily insulin requirements[43]; we showed a reduced requirement of total daily dose of insulin at the end of study in the pioglitazone group, while it slightly increased in placebo group, despite no significant changes in regular insulin total dose in both groups. There was a significant improvement in hemoglobin A1c level in this group. In this study, fasting blood glucose did not reach a significantly difference level, but tended to decrease after pioglitazone treatment. This can be in part due to active adherence to glycemic targets in both groups, because in both groups, an improvement trend in fasting blood glucose could be observed.

Insulin-resistant state may be associated with the higher production of cytokine as a consequence of reduction in anti-inflammatory effect of insulin.[6] The major finding of this study was that pioglitazone caused a reduction in inflammatory markers CRP, HSCRP, and ESR. The significant changes of variables were prominent at the end of the 4th month. Our study confirmed the data of Luther and Baldwin and Parulkar and colleagues, who measured serum inflammatory biomarkers in patients with type 2 DM who completed 26- and 16-week randomized trials with glitazones to assess the safety and efficacy of these agents.[43,44] In their study, the reduction in ESR, CRP, and HSCRP were comparable with our study.

In subgroup analysis, we observed a significant decline in inflammatory markers in those reached

the best controlled blood glucose level irrespective of the group they were assigned to. In other words, it can be claimed that glycemic control and reducing inflammatory biomarkers are aligned. On the other hand, when a subgroup analysis was performed among those with most impressive reduction of inflammatory markers in both groups, decrement of hemoglobin A1c was only significant in the pioglitazone group ($P < .001$). This can be due to the specific property of pioglitazone beyond its anti-inflammatory effect that needs further clarifications.

In this study, serum level of IL-18 was declined in the pioglitazone group ($P = .002$), but IL-18 decrement during the 4 months of follow-up in the placebo group was not significantly different ($P = .75$), although when compared 2 groups from beginning of the study to the end, this reduction was not leading to a difference, that maybe due to limited sample size or the duration of observation in this trial. Several lines of evidence support a cardinal role of IL-18 in the pathogenesis of the metabolic syndrome. Importantly, IL-18 has been shown to be closely associated with the metabolic syndrome and its components,[33] to predict cardiovascular events and cardiovascular mortality in populations with the metabolic syndrome,[45,46] and to precede the development of DM.[47] This decrement of IL-I8 in our pioglitazone group may have a positive impact in reduction of cardiovascular mortality.

We found that pioglitazone therapy did not have a relevant effect on cyclosporine level or doses as was shown formerly.[43] In our study, we did not find any changes in blood urea nitrogen, creatinine, hemoglobin in each groups, and no episode of liver toxicity was detected in pioglitazone group. Thiazolidinediones have many other beneficial nonglycemic properties such as increased high-density lipoprotein cholesterol, decreased low-density lipoprotein cholesterol, decreased triglycerides, decreased vascular resistance and inflammation, and improved endothelial cell function.[47,48] Our study revealed improvement in lipid profile, as secondary outcomes, with the initiation of pioglitazone.

CONCLUSIONS

In kidney transplant recipients, poiglitazone not only improves glycemic control (evidenced by lower hemoglobin A1c), but also leads to a significant decrement of inflammatory markers such as ESR, CRP, HSCRP, and IL-18 as documented in our trial.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Chadban S, Chan M, Fry K, et al. The CARI guidelines. Nutritional management of diabetes mellitus in adult kidney transplant recipients. Nephrology (Carlton). 2010;15 Suppl 1:S37-S39.
2. Savaj S, Abdi E, Nejadgashti H, et al. Posttransplant diabetes mellitus in kidney allograft recipients at Shaheed Hasheminejad Hospital. Iran J Kidney Dis. 2008;2:46-9.
3. Khalili N, Rostami Z, Kalantar E, Einollahi B. Hyperglycemia after kidney transplantation: frequency and risk factors. Iran J Kidney Dis. 2013;7:226-30.
4. Han SJ, Hur KY, Kim YS, et al. Effects of pioglitazone on subclinical atherosclerosis and insulin resistance in nondiabetic renal allograft recipients. Nephrol Dial Transplant. 2010;25:976-84.
5. Stumvoll M, Haring HU. Glitazones: clinical effects and molecular mechanisms. Ann Med. 2002;34:217-24.
6. Agarwal R. Anti-inflammatory effects of short-term pioglitazone therapy in men with advanced diabetic nephropathy. Am J Physiol Renal Physiol. 2006;290:F600-F605.
7. Martens FM, Visseren FL, Lemay J, de Koning EJ, Rabelink TJ. Metabolic and additional vascular effects of thiazolidinediones. Drugs. 2002;62:1463-80.
8. Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. Circulation. 2002;106:679-84.
9. Esposito K, Ciotola M, Carleo D, et al. Effect of rosiglitazone on endothelial function and inflammatory markers in patients with the metabolic syndrome. Diabetes Care. 2006;29:1071-6.
10. Pradhan AD, Ridker PM. Do atherosclerosis and type 2 diabetes share a common inflammatory basis? Eur Heart J. 2002;23:831-4.
11. Haffner SM. The metabolic syndrome: inflammation, diabetes mellitus, and cardiovascular disease. Am J Cardiol. 2006;97:3A-11A.
12. Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? Circulation. 2004;109:2818-25.
13. Okamura H, Tsutsi H, Komatsu T, et al. Cloning of a new cytokine that induces IFN-gamma production by T cells. Nature. 1995;378:88-91.

14. Gerdes N, Sukhova GK, Libby P, Reynolds RS, Young JL, Schonbeck U. Expression of interleukin (IL)-18 and functional IL-18 receptor on human vascular endothelial cells, smooth muscle cells, and macrophages: implications for atherogenesis. J Exp Med. 2002;195:245-57.
15. Striz I, Krasna E, Honsova E, et al. Interleukin 18 (IL-18) upregulation in acute rejection of kidney allograft. Immunol Lett. 2005;99:30-5.
16. Ghayur T, Banerjee S, Hugunin M, et al. Caspase-1 processes IFN-gamma-inducing factor and regulates LPS-induced IFN-gamma production. Nature. 1997;386:619-23.
17. Wang HN, Wang YR, Liu GQ, et al. Inhibition of hepatic interleukin-18 production by rosiglitazone in a rat model of nonalcoholic fatty liver disease. World J Gastroenterol. 2008;14:7240-6.
18. Dinarello CA. The IL-1 family and inflammatory diseases. Clin Exp Rheumatol. 2002;20:S1-13.
19. Dinarello CA. Interleukin-18 and the pathogenesis of inflammatory diseases. Semin Nephrol. 2007;27:98-114.
20. Skurk T, Kolb H, Muller-Scholze S, Rohrig K, Hauner H, Herder C. The proatherogenic cytokine interleukin-18 is secreted by human adipocytes. Eur J Endocrinol. 2005;152:863-8.
21. Dinarello CA. Interleukin 1 and interleukin 18 as mediators of inflammation and the aging process. Am J Clin Nutr. 2006;83:447S-55S.
22. Gracie JA, Robertson SE, McInnes IB. Interleukin-18. J Leukoc Biol. 2003;73:213-24.
23. Ahn HJ, Maruo S, Tomura M, et al. A mechanism underlying synergy between IL-12 and IFN-gamma-inducing factor in enhanced production of IFN-gamma. J Immunol. 1997;159:2125-31.
24. Yoshimoto T, Takeda K, Tanaka T, et al. IL-12 up-regulates IL-18 receptor expression on T cells, Th1 cells, and B cells: synergism with IL-18 for IFN-gamma production. J Immunol. 1998;161:3400-7.
25. Bruun JM, Stallknecht B, Helge JW, Richelsen B. Interleukin-18 in plasma and adipose tissue: effects of obesity, insulin resistance, and weight loss. Eur J Endocrinol. 2007;157:465-71.
26. Evans J, Collins M, Jennings C, et al. The association of interleukin-18 genotype and serum levels with metabolic risk factors for cardiovascular disease. Eur J Endocrinol. 2007;157:633-40.
27. Zirlik A, Abdullah SM, Gerdes N, et al. Interleukin-18, the metabolic syndrome, and subclinical atherosclerosis: results from the Dallas Heart Study. Arterioscler Thromb Vasc Biol. 2007;27:2043-9.
28. Bosch M, Lopez-Bermejo A, Vendrell J, Musri M, Ricart W, Fernandez-Real JM. Circulating IL-18 concentration is associated with insulin sensitivity and glucose tolerance through increased fat-free mass. Diabetologia. 2005;48:1841-3.
29. Fischer CP, Perstrup LB, Berntsen A, Eskildsen P, Pedersen BK. Elevated plasma interleukin-18 is a marker of insulin-resistance in type 2 diabetic and non-diabetic humans. Clin Immunol. 2005;117:152-60.
30. Straczkowski M, Kowalska I, Nikolajuk A, et al. Increased serum interleukin-18 concentration is associated with hypoadiponectinemia in obesity, independently of insulin resistance. Int J Obes (Lond). 2007;31:221-5.
31. Rabkin SW. The role of interleukin 18 in the pathogenesis of hypertension-induced vascular disease. Nat Clin Pract Cardiovasc Med. 2009;6:192-9.
32. Van Guilder GP, Hoetzer GL, Greiner JJ, Stauffer BL, Desouza CA. Influence of metabolic syndrome on biomarkers of oxidative stress and inflammation in obese adults. Obesity (Silver Spring). 2006;14:2127-31.
33. Hung J, McQuillan BM, Chapman CM, Thompson PL, Beilby JP. Elevated interleukin-18 levels are associated with the metabolic syndrome independent of obesity and insulin resistance. Arterioscler Thromb Vasc Biol. 2005;25:1268-73.
34. Troseid M, Seljeflot I, Arnesen H. The role of interleukin-18 in the metabolic syndrome. Cardiovasc Diabetol. 2010;9:11.
35. de VF, Dekker JM, Ruhe HG, et al. Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. Diabetologia. 1999;42:926-31.
36. Khaw KT, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of european prospective investigation of cancer and nutrition (EPIC-Norfolk). BMJ. 2001;322:15-8.
37. Park S, Barrett-Connor E, Wingard DL, Shan J, Edelstein S. GHb is a better predictor of cardiovascular disease than fasting or postchallenge plasma glucose in women without diabetes. The Rancho Bernardo Study. Diabetes Care. 1996;19:450-6.
38. Qiao Q, Dekker JM, de VF, et al. Two prospective studies found that elevated 2-hr glucose predicted male mortality independent of fasting glucose and HbA1c. J Clin Epidemiol. 2004;57:590-6.
39. Kannel WB, Castelli WP, Gordon T. Cholesterol in the prediction of atherosclerotic disease. New perspectives based on the Framingham study. Ann Intern Med. 1979;90:85-91.
40. Pekkanen J, Linn S, Heiss G, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. N Engl J Med. 1990;322:1700-7.
41. Eich D, Thompson JA, Ko DJ, et al. Hypercholesterolemia in long-term survivors of heart transplantation: an early marker of accelerated coronary artery disease. J Heart Lung Transplant. 1991;10:45-9.
42. Sharples LD, Caine N, Mullins P, et al. Risk factor analysis for the major hazards following heart transplantation--rejection, infection, and coronary occlusive disease. Transplantation. 1991;52:244-52.
43. Luther P, Baldwin D, Jr. Pioglitazone in the management of diabetes mellitus after transplantation. Am J Transplant. 2004;4:2135-8.
44. Parulkar AA, Pendergrass ML, Granda-Ayala R, Lee TR, Fonseca VA. Nonhypoglycemic effects of thiazolidinediones. Ann Intern Med. 2001;134:61-71.
45. Troseid M, Seljeflot I, Hjerkinn EM, Arnesen H. Interleukin-18 is a strong predictor of cardiovascular events in elderly men with the metabolic syndrome:

synergistic effect of inflammation and hyperglycemia. Diabetes Care. 2009;32:486-92.

46. Espinola-Klein C, Rupprecht HJ, Bickel C, et al. Impact of inflammatory markers on cardiovascular mortality in patients with metabolic syndrome. Eur J Cardiovasc Prev Rehabil. 2008;15:278-84.
47. Baldwin D Jr, Duffin KE. Rosiglitazone treatment of diabetes mellitus after solid organ transplantation. Transplantation. 2004;77:1009-14.
48. Villanueva G, Baldwin D. Primary management of post-transplant diabetes with rosiglitazone. Am J Transplant. 2004;4(Suppl 8):1599.

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