Oxidized LDL: As a risk factor for cardiovascular disease in renal transplantation

LDL oxidada: Como um fator de risco para doença cardiovascular no transplante renal

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Abstract

Objectives: The mortality rate of chronic kidney disease (CKD) patients that have undergone renal replacement therapy is very high due to cardiovascular diseases (CVD). Some studies have indicated that cyclosporine A, a drug used to prevent transplant rejection, is associated with bone loss following transplantation. Furthermore, it has an oxidative effect on circulating lipids. Its prooxidant effect on cell membranes causes calcium release. This study aimed to examine whether or not renal transplantation result in improvement in oxidative stress and to assess the association between oxidized LDL (ox-LDL) and some variables in the prediction of CVD risk in Renal Transplantation (RT) patients that were compared with the control group. **Material and Methods:** A total number of 30 CKD patients were recruited to evaluate time dependent changes in biomarker of OS before and after RT. The ox-LDL, lipid metabolism parameters, CsA, creatinine, calcium and phosphate were assessed both before RT, 10 days and 6 months after RT in comparison with the control group (n = 30). **Results:** Over 6 months, ox-LDL concentration changed from 79.7 ± 9.7 to 72 ± 7 mU/mL ($p < 0.009$). calcium phosphate level was positively correlated with the concentration of ox-LDL (R = 0.467, $p = 0.011$) and cyclosporine (R = 0.419, $p = 0.024$) 6 months after transplantation. **Conclusion:** The findings indicated that restoring renal function by transplantation, improves uremia induced oxidative stress. calcium phosphate product, as an independent risk factor for CVD, correlates with ox-LDL before RT and 6 months after RT. Calcium phosphate product correlates with cyclosporine in the RT group, too.

Keywords: calcium phosphates; cardiovascular diseases; kidney transplantation; oxidative stress.

Resumo

Objetivos: A taxa de mortalidade de pacientes com doença renal crônica (DRC), que tenham sido submetidos à terapia de substituição renal, é muito elevada devido a doenças cardiovasculares (DCV). Alguns estudos indicaram que a ciclosporina A (CsA), um medicamento utilizado para prevenir a rejeição de transplante, está associada à perda óssea após o transplante. Além disso, ela tem um efeito oxidante sobre os lipídeos circulantes. Seu efeito pró-oxidante nas membranas celulares provoca a liberação de cálcio. Este estudo teve como objetivo analisar se o transplante renal pode ou não resultar em melhora no estresse oxidativo (EO); e avaliar a associação entre a LDL oxidada (LDL-ox) e algumas variáveis na predição do risco de DCV em pacientes transplantados renais (TR), comparados com o grupo controle. **Materiais e Métodos:** Um total de 30 pacientes com DRC foram recrutados para avaliação das alterações dependentes do tempo no biomarcador de EO antes e após TR. Foram avaliados: LDL-ox, parâmetros do metabolismo dos lipídeos, a CsA, creatinina, cálcio e fosfato tanto antes do TR, 10 dias e 6 meses após o TR, em comparação com o grupo controle (n = 30). **Resultados:** após 6 meses, a concentração de LDL-ox mudou de 79,7 ± 9,7-72 ± 7 mU/ml ($p < 0,009$). O nível de fosfato de cálcio foi positivamente correlacionado com a concentração de LDL-ox (R = 0,467, $p = 0,011$) e ciclosporina (r = 0,419, $p = 0,024$) 6 meses após o transplante. **Conclusão:** Os resultados indicaram que a restauração da função renal pelo transplante, melhora o estresse oxidativo induzido pela uremia. O produto de fosfato de cálcio, como um fator de risco independente para DCV, correlaciona-se com o LDL-ox antes do TR e 6 meses após o TR. O produto de fosfato de cálcio também se correlaciona com a ciclosporina no grupo TR.

Palavras-chave: doenças cardiovasculares; estresse oxidativo; fosfatos de cálcio; transplante de rim.

Introduction

Cardiovascular disease (CVD) is the major cause of death in patients with chronic kidney disease (CKD) that undergo renal replacement therapy (RRT). The predicted risk is 3.5-50 times more than normal population that causes about 40% of total deaths among patients who receive RRT.[1-5] Patients with end stage renal disease (ESRD) have a high prevalence of oxidative stress (OS) as a risk factor for cardiovascular events.[3,6-8]

Atherosclerosis progression occurs after starting hemodialysis; therefore, dialysis therapy or uremic factors may be a cause of OS in these patients.[9] Dyslipidemia, such as high levels of low-density lipoprotein (LDL), is another risk factor that accelerates atherogenesis process. Chronic administration of immunosuppressive drugs such as cyclosporine A (CsA) result in altering plasma lipoprotein metabolism. For this reason, atherogenesis is a common problem that is observed after kidney transplantation.[10-13] Reports have shown that CsA has prooxidant effect on cell membranes and promotes oxidation of circulating lipids.[14,15] LDL is easily susceptible to oxidation in OS conditions that results in oxidized LDL (ox-LDL) form, and has some atherogenic features.[16,17]

This study was conducted to determine if there is further improvement in oxidative stress status of kidney transplant recipients with regard to serum ox-LDL levels before and after transplantation. According to Regmi *et al.*,[18] there was a significant association between higher value of $Ca^{2+} \times PO_4$, micro inflammation, and oxidative stress in CKD patients. Threfore, it can be concluded that the medication in transplanted patients is related to oxidative stress and created inflammatory process in CKD patients gradually. The other aim of this study was to assess ox-LDL correlation with serum $Ca^{2+} \times PO_4$.

Materials and methods

Subjects

For this study, thirty eligible patients for kidney transplantation from Shahid Modarres hospital in Tehran were recruited. A control group consisting of 30 healthy participants was used for comparison. The participants of the control group were normolipidemic and did not have any disease.

One day before renal transplantation, induction therapy with CsA was started for all patients according to the protocol of transplant unit. The exclusion criteria that were considered were as follows:

Patients who were on HD less than 6 months

1. History of active infection within recent 3 months
2. History of malignancy
3. History of chronic liver disease
4. Acute rejection after transplantation.

Inclusion criteria in the RT group were patients treated with conventional triple immunosuppressive drugs composed of cyclosporine, mycophenolic acid and Prednisolone with no evidence of acute allograft rejection during the last 3 months before taking part in this study. The causes of renal failure in these patients were diabetic nephropathy, chronic glomerulonephritis, polycystic kidney disease, hypertensive ischemic nephropathy, obstructive nephropathy and unknown etiology. We had no post-transplant diabetes melitus in the RT patients. All of diabetes melitus patients in the RT group were diabetic before RT (during hemodialysis). The patients, before RT, were under regular hemodialysis for at least 6 months 3×4 h/week by synthetic high-flux membranes with Fresenius-2008B hemodialyser.

All participants signed a consent form, which was approved by the Ethical Committee Board of Shahid Beheshti University (IRB approval number is 61825). Age, sex, body mass index (BMI = weight (kg)/ height (m)*2 and smoking habits of both groups were recorded.

Methods

Three blood samples were obtained after 12-hours of fasting from patients: before transplantation, on the discharge day (10 days after transplantation) and 6 months after transplantation. Samples were centrifuged at 3,000×g for 10 minutes at room temperature within 1 hour after collection and stored at – 80°C until the assays were performed.

Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine and urea were measured by a Hitachi 917 analyzer using Roche reagents (Roche, Mannheim, Germany). Low density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula. Very low density lipoprotein (VLDL) cholesterol was computed by dividing triglyceride by 5. Serum total calcium and serum phosphate were measured by using commercial kits (Pars Azmoon Co).

Ox-LDL concentration was measured by a competitive enzyme-linked immuno absorbent assay method, via using a novel commercially available ELISA kit (Cusabio biotech Co, LTD, Wuhan, China), with detection range between 1.56 mU/mL and 100 mU/mL. The intra-assay and inter-assay variations were < 8% and < 10%, respectively. The standard curve concentrations used for the ELISAs were 100 mU/mL, 50 mU/mL, 25 mU/mL, 12.5 ng/mL, 6.25 mU /mL, 3.12 mU/mL, 1.56 mU/ml and 0 mU/ml. The minimum detectable dose of human ox-LDL is < 0.78 mU/mL.

CsA concentration was measured by using RIA kit in whole blood, only in renal transplant recipients (DIA source Immuno Assays S.A. - Rue du Bosquet, 2 - B-1348 Louvain-la-Neuve - Belgium). Intra-assay and inter-assay variation were found below or equal to 9.2 % and 7.3 %. The measurement range of Cs A (from analytical sensitivity to highest calibrator) was 1.61 to approximately 2500 ng/mL.

Statistical analysis

Results were presented as numbers, percentages, and mean with standard deviation (mean ± SD) when appropriate.

Based on data distribution, repeated measures ANOVA were applied to compare variables of groups, followed by Tukey post-hoc to analyze the data. Pearson's correlation test was performed to examine the correlation between all variables. Multiple regression analysis was used to investigate the relationships between the concentration of ox-LDL and lipid, lipoprotein, $Ca^{2+} \times PO_4$ and CsA. p values ≤ 0.05 were considered statistically significant. Analyses were adjusted for age, gender, current cigarette smoking, regular physical activity and BMI, and were carried out using GraphPad Prism software (Version 5).

Results

Thirty healthy adults (17 males; 13 females) and 30 patients (16 males; 14 females) took part in the study. The mean age of patients was 42 ± 16 years. Results are shown in Table 1, and Figures 1, 2, and 3.

Table 1 shows mean with standard deviation of demographic data and laboratory findings of the patients and the control group. The groups were matched according to age, gender and BMI. As can be seen, the total plasma ox-LDL concentration was significantly higher among the patients before RT as compared to the amount recorded 6months after RT and the control group (79.7 ± 9.7 mu/ml *versus* 72 ± 7 mu/ml and 68.9 ± 4 mu/ml; $p = 0.009$, $p = 0.001$). In addition, the values of lipid metabolism are summarized here.

Ox-LDL levels had no correlation with gender, age, type of dialysis membrane, smoking status, physical activity, appetite, dialysis duration before RT and primary cause of CKD.There were no statistical differences between ox-LDL levels before RT and 10 days after RT ($p = 0.958$), (Fig. 1). There was a significant decrease in ox-LDL following RT, which was marked significant after 6 months ($p < 0.009$).

As expected, urea and creatinine concentration decreased after a successful RTT. As can be seen, $Ca^{2+} \times PO_4$ before transplantation is higher compared to the control group and 10 days and 6 months after RT ($p < 0.0001$). The Pearson correlation analysis showed that $Ca^{2+} \times PO_4$ level was positively correlated with the concentration of ox-LDL (R = 0.467, $p = 0.011$) and cyclosporine (R = 0.419, $p = 0.024$) 6 months after transplantation (Figs. 2,3). Also this correlation analysis showed ox- LDL was correlated with $Ca^{2+} \times PO_4$ before RT (R = 0. 467, $p = 0.011$).

In the model of multiple stepwise regression analysis, ox-LDL was selected as the dependent variable, and lipid, lipoproteins, calcium, $Ca^{2+} \times PO_4$ and CsA were considered as independent variables. This model demonstrated that ox-LDL concentration in RT group was associated positively with $Ca^{2+} \times PO_4$ level ($R_2 = 0.219$, $\beta = 0.456$, $p = 0.013$).

Discussion

In this study, the researchers hypothesized that transplantation would improve oxidative stress marker, ox-LDL, that is also proposed as a risk factor for the development of atherosclerosis and kidney failure in renal transplantation.[19-23] The researchers also investigated its correlation with other variable such as ca^{+2}, p, $Ca^{2+} \times PO_4$ and lipid profile.

The result of this study showed that serum Ox-LDL significantly decreased after RT and Serum Ox-LDL correlated with $Ca^{2+} \times PO_4$ in serum before and 6 months after RT.

RT is the choice treatment for patients with ESRD that results in better survival and quality of life rather than dialysis (before RT). However, cardiovascular (CV) events remain considerably high in these

Table 1 Demographic data and laboratory parameters for patients and controls

Parameters	Pre-Tplt	Post-Tplt after 10 days	Post-Tplt after 6 months	Control
Number/sex	30 (16M, 14F)	30 (16M, 14F)	30 (16M, 14F)	30 (17M, 13F)
Age (year)	42.0 ± 16.0	42.0 ± 16.0	42.6 ± 16.0	40.0 ± 8.0
BMI (kg/m^2)	25.5 ± 5.0	24.5 ± 3.0	25.0 ± 2.0	25.0 ± 3.0
Urea (mg/dl)	128.0 ± 40.0***	56.0 ± 19.0*	55.0 ± 19.0*	35.0 ± 5.5
Creatinine (mg/dl)	7.7 ± 2.0***	1.2 ± 0.1	1.2 ± 0.1	0.98 ± 0.1
Total Chol (mg/dl)	152.0 ± 32.0	186.0 ± 17.0	192.0 ± 20.0^	177.0 ± 23.0
LDL- Chol (mg/dl)	78.0 ± 36.0***	104.0 ± 17.0	110.0 ± 22.0^^	105.0 ± 19.0
HDL-Chol (mg/dl)	43.0 ± 12.0	44.0 ± 7.0	44.0 ± 6.0	45.5 ± 3.0
Triglyceride (mg/dl)	157.0 ± 86.0***	187.7 ± 36.0	189.0 ± 26.0^^^	133.0 ± 27.0
VLDL- Chol (mg/dl)	31.4 ± 17.0	37.5 ± 7.0	38.0 ± 5.0***	26.7 ± 9.0
Calcium (mg/dl)	9.1 ± 1.2*	9.4 ± 0.3	9.4 ± 0.3	9.6 ± 0.5
Phosphorus (mg/dl)	6.4 ± 1.7**	4.2 ± 0.8	4.1 ± 0.7	4.5 ± 0.7
CyclosporineA (ng/dl)	N/A	263.0 ± 57.0	154.0 ± 47.0	N/A
Ox-LDL (mU/ml)	79.7 ± 9.7**	81.2 ± 8.0**	72.0 ± 7.0^^	68.9 ± 4.0
$Ca^{2+} \times PO_4$ (mg^2/dL^2)	58.3 ± 17.0***	39.5 ± 8.1	38.8 ± 6.3	43.4 ± 7.4

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ controls *versus* patients; ^ $p < 0.05$,^^ $p < 0.01$,^^^ $p < 0.001$ Pre-Tplt *versus* Post-Tplt. Data are shown as mean ± SD; Tplt: transplantation; BMI: body mass index; M: male; F: female; Chol: cholesterol; LDL: low-density lipoprotein; HDL: high-density lipoprotein; VLDL: very low density lipoprotein; Ox-LDL: oxidized LDL; N/A: not applicable.

Figure 1. Comparison of ox-LDL level before transplant, 10 days after transplant and 6 months after it with control group. *= significant difference between before renal transplantation and controls, **= significant difference after 6 months compare to control group.

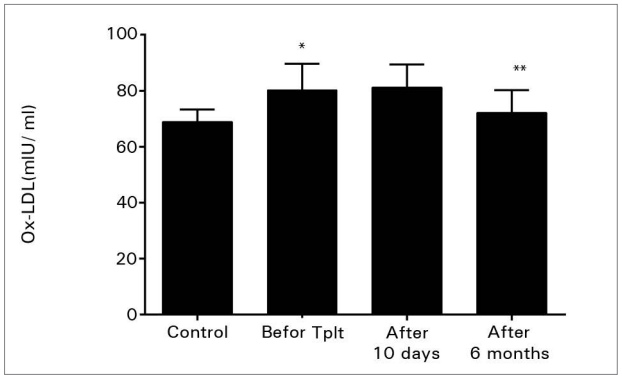
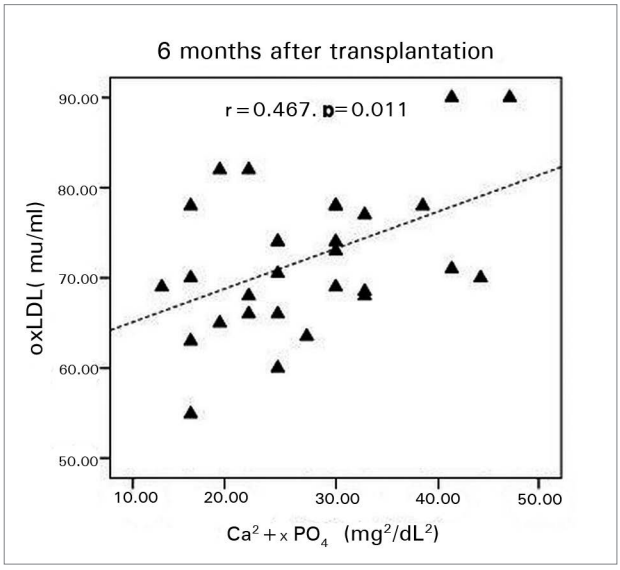


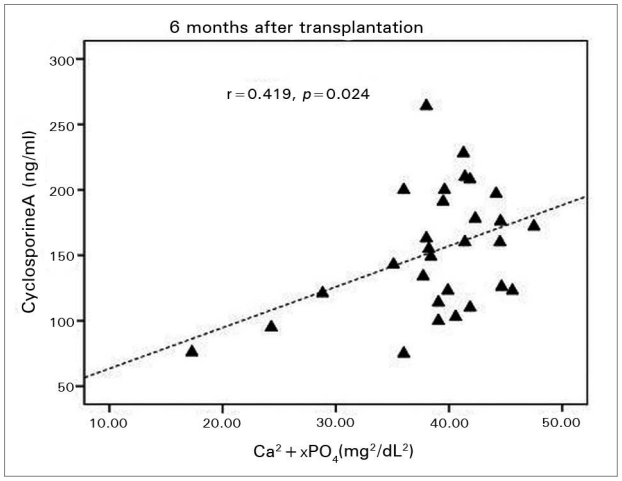
Figure 2. Scatter plot showing the positive relationship between oxidized LDL (ox-LDL) and $Ca^{2+} \times PO_4$ after 6 months.



patients even after RT. CV events in RT recipients arise earlier and are along with rapid progression and calcification; CKD patients and healthy population experience these processes differently. For RT recipients, modification in CV risk factors such as oxidative stress may partially lead to better survival after renal transplantation.[3,7,19]

The initial finding indicated that ox-LDL decreased after RT in comparison with its serum level before transplantation. After 6 months, these values were in agreement with those of the control group. In line with this result, Simmons *et al.*[7] reported significant decline in plasma Free F_2 Isoprostane content, an oxidative biomarker, after transplantation that persisted for 2 months. In addition, Kimak *et al.*[11] reported that Ox-LDL decreased in RT patients compared to HD group after 6 and 12 months. However, this reduction was not as much as the control group. Simmons *et al.*[7] reported that ox-LDL level decreased even one week after RT. However, in this study, its increase was observed after 10 days. Its higher level compared to the results of this study may be due to the kind

Figure 3. Scatter plot showing the positive correlation between cyclosporine A and $Ca^{2+} \times PO_4$ after 6 months.



of immunosuppression drug. The patients in this study consumed just Cs A and in Simmons *et al.* [7] study half of patients were treated with Tacrolimus. Venkiteswaran *et al.*[17] showed that LDL was isolated from recipients' plasma treated with Cs A showed significantly higher susceptibility to oxidation as compared to tacrolimus.

The results of this study also indicated increased levels of cholesterol, LDL, VLDL and triglyceride, while HDL concentration was normal. Immunosuppressive drugs are necessary to prevent allograft rejection. It seems that these medications could exacerbate dyslipidemia or hyperlipidemia.[24-26]

The concentration of $Ca^{2+} \times PO_4$ 6 months after transplantation was lower than that of the control group and before transplantation. Both calcium and phosphate absorptions were impaired in patients with CKD. Calcium absorption improved dramatically after successful renal transplantation, while phosphate absorption remained the same. The interaction of various drugs with intestinal transport mechanisms for phosphate could be an important factor in this regard, and long-term steroid administration and cyclophosphamide treatment reduced phosphate absorption. Also, the increased secretion of gastric acid produced by prednisolone may possibly have a role in reducing phosphate absorption in transplant recipients.[27]

The concentration of $Ca^{2+} \times PO_4$ was higher before transplantation compared to the control group. The elevation in serum phosphate leads to the increase of $Ca^{2+} \times PO_4$. Thus, the increase in phosphorus, directly and indirectly, leads to an increase in parathyroid cells and increased synthesis and secretion of PTH. Increased secretion of PTH increases blood level of calcium ions, which increases the level of $Ca^{2+} \times PO_4$ product.[28]

Based on the results obtained in this study, there is a positive correlation between ox-LDL and $Ca^{2+} \times PO_4$ (as the predictor of CVD risk in CKD patients) and also between $Ca^{2+} \times PO_4$ and cyclosporine. The multiple stepwise regression analysis demonstrated that in RT group ox-LDL concentration was associated positively with $Ca^{2+} \times PO_4$ level after 6 months. Regmi *et al.*[18] also found a significant association between higher value of $Ca^{2+} \times PO_4$, micro inflammation and oxidative stress in CKD patients. They showed that oxidative stress and inflammation markers such as anti-oxLDL and hsCRP were associated with higher serum $Ca^{2+} \times PO_4$ levels. So, it can be concluded that the medication in transplanted patients is related to oxidative stress, and created the inflammatory process in patients gradually.

In conclusion, the findings indicate that restoration of renal function by transplantation improves uremia induced oxidative stress. $Ca^{2+} \times PO_4$ product, as an independent risk factor for CVD, correlates with ox-LDL (before RT and 6 months after RT) and serum level of cyclosporine (in the RT group).

The present study has certain limitations such as the small sample size and the absence of 25(OH) vitamin D levels. The cross sectional design did not clearly elucidate the cause-and-effect of results. However, it is anticipated that this work can contribute to detecting populations with cardiovascular risk factors.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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