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Anti-Inflammatory Effect of Atorvastatin on the Kidney Graft of Living Donor Transplants

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Background: Recent studies have demonstrated that statins have anti-inflammatory and immunomodulatory properties, which could be considered beneficial in kidney transplantations. This study assesses the anti-inflammatory effect of atorvastatin on the kidney grafts of living donor transplants.

Material/Methods: In a randomized clinical trial, kidney donors were divided into 2 groups. The study group constituted 24 donors who received 40 mg atorvastatin, and 24 donors who received a placebo control, 4 weeks prior to transplantation. Serum C-reactive protein (CRP) levels were measured before and after atorvastatin administration. CRP and renal function of kidney recipients were measured at baseline and 1, 6, and 24 hours after transplantation.

Results: After 4 weeks of treatment, the CRP level was 5.62±3.82 mg/dL in the control group and 3.27±0.62 mg/dL in the study group (P=0.007). Upon reperfusion, CRP levels in recipients at 1 hour were, 5.8±3.9 and 3.8±1.0 mg/dL, respectively (P=0.04). Twenty-four hours after the kidney transplantations, serum creatinine levels were 2.5±1.5 mg/dL in the study group and 3.7±2.4 mg/dL in the control group (P=0.04).

Conclusions: Our study suggests that the use of atorvastatin prior to allograft procurement of kidney transplant, reduces the acute kidney inflammatory burden profile, and promotes an improved kidney function recovery following transplantation.

MeSH Keywords: **Anti-Inflammatory Agents • Hydroxymethylglutaryl-CoA Reductase Inhibitors • Kidney Transplantation • Living Donors**

Abbreviations: **CG** – control group; **CRP** – C-reactive protein; **e-GFR** – estimated glomerular filtration rate; **HDL** – high-density lipoprotein; **HIV** – human immunodeficiency virus; **HLA** – human leukocyte antigen; **IL** – interleukin; **LDL** – low-density lipoprotein; **SG** – study group; **TC** – total cholesterol; **TC** – total cholesterol

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Background

Despite the strong compatibility of human leukocyte antigen (HLA) from deceased donors with recipients, grafts from living donors have a superior survival rate due to the longer ischemic time of deceased donors' organs, which results in greater damage during tissue reperfusion [1].

Ischemia-reperfusion injury, a major cause of acute renal injury in a transplanted kidney, leads to a proinflammatory state and raises graft immunogenicity. Ischemia also contributes to the release of free radicals and proinflammatory cytokines and activates innate immunity [2]. Therefore, pharmacological options like statins have been tested to reduce this inflammatory cascade and improve kidney graft survival [3].

There is experimental and clinical evidence indicating that statins, in addition to their lipid-lowering action, possess strong anti-inflammatory and immunomodulatory effects, decreasing C-reactive protein (CRP) and proinflammatory cytokines such as interleukin (IL)-6 and IL-8. Statins also promote the repair of damaged endothelium, and its function by mobilizing endothelial cells, increasing cell proliferation and releasing nitric oxide; which together decreases the incidence of acute transplant rejection [1,3,4]. Therefore, this non-lipid-lowering effect could be considered beneficial in living donor kidney transplants.

The objective of this study was to evaluate the anti-inflammatory effect of atorvastatin on the kidney grafts from living-related donors on their recipients.

Material and Methods

Study design

We performed a randomized, double-blind, placebo-controlled clinical trial between January 2012 and January 2014 at a single institution of the Mexican Institute of Social Security. Study variables of the recipients included age, sex, etiology, cold and warm ischemia times, and serum CRP levels.

The inclusion criteria for donors were: age >18 years old, both genders, compatibility by blood group, body mass index (BMI) less than 30 kg/m^2, glomerular filtration rate (GFR) higher than 80 mL/min/1.73 m^2 body surface area calculated using the formula of CKD-EPI, and creatinine clearance higher than 80 mL/min calculated using the Cockcroft-Gault formula. Exclusion criteria included any comorbid conditions such as arterial hypertension, diabetes mellitus, active infection or history of tuberculosis, high risk for thromboembolism, chronic lung/heart disease, tobacco use, history of neoplasia with propensity to recurrence, history of bilateral urolithiasis, HIV positive, pregnancy, psychiatric disease or complex kidney abnormalities, and haplotype or HLA disparities. In addition, donors were excluded in the presence of proteinuria (>300 mg/24 hours), GFR <80 mL/min/1.73 m^2 body surface area, hematuria, or BMI >30 kg/m^2.

Inclusion criteria for recipients were patients older than 18 years with an appropriate attachment to renal dialysis treatment, blood group matching, compatibility of HLA with the donor, and administration of immunosuppressive therapy to prevent early rejection with cyclosporine or tacrolimus, depending on the condition of each patient.

Exclusion criteria included any morbid condition developed just before the scheduled surgery for a renal transplant, such as infection, stroke, cardiac ischemia, or any major vascular disease.

Treatment assignment and intervention

Assignment to the treatment or placebo group was provided with random numbers in sealed envelopes conducted by a physician of the outpatient clinic. Atorvastatin 40 mg or homologated placebo was assigned orally every 24 hours for 4 weeks to the study group (SG) and the control group (CG), respectively. Adherence to the treatment or placebo was assessed through a daily intake survey and with the return of the blisters with quantification of tablets taken from the drug or placebo packages.

Biochemical measurements

Blood and urine samples from donors were taken at the beginning of the protocol and 24 hours before the kidney procurement to evaluate the blood count, glucose, serum urea, serum creatinine, serum potassium, prothrombin time, 24-hour urine protein and creatinine clearance, and CRP serum levels.

Blood samples of the kidney recipients were taken to evaluate the CRP levels prior to the surgical procedure, after reperfusion of the grafts, and 6 and 24 hours after the transplantation. Renal function was also measured 24 hours before and after the intervention. Recipients' renal function and graft survival were assessed during the following year.

Surgical intervention

Donors were submitted to a general balanced anesthesia. Depending on the age and hemodynamic condition of the patient, propofol 2–2.5 mg/kg of weight and cisatracurium 0.2 mg/kg per weight were intravenously administered for anesthesia and neuromuscular blockade. During the anesthesia, patients received isoflurane, fractionated doses of fentanyl

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Table 1. Preoperative clinical and laboratory features of living-donors.

Features	Study group n=24	Control group n=24	*P* value
Age (years)	37±9.8	34.7±9.5	0.42
Gender (M/F)	11/13	12/12	0.50
BMI (kg/m^2)	25.6±2.9	25.8±2.4	0.80
Hemoglobin (g/dL)	14.4±1.2	14.4±1.5	0.92
White blood cells (10^3/µL)	7.7±1.8	7.7±1.8	0.50
Neutrophils (%)	54.2±6.9	58.1±7.7	0.74
Platelet (10^3/µL)	242.4±44	242.3±5	0.99
Serum glucose (mg/dL)	91.2±11.5	87.4±11.3	0.25
Serum urea (mg/dL)	28.3±7.1	26.6±5.6	0.39
Serum creatinine (mg/dL)	0.7±0.1	0.7±0.1	0.53
Serum potassium (meq/L)	4.2±0.3	4.1±0.4	0.96
Prothrombin time (seg)	11.9±0.5	11.9±0.4	0.88
24-hour urine protein (g/24 h)	0.2±0.1	0.2±0.1	0.65
Creatinine clearance (mL/min)	116.9±24.7	113.7±20.2	0.63
Living donor related	18/24	22/24	0.22

citrate, and inhaled 100% oxygen to maintain a minimum of 95% peripheral oxygen saturation.

Open nephrectomy was performed in all kidney donors. Warm ischemia time was obtained, and grafts were washed with Wisconsin preservation solution.

Sample size

Sample size was obtained based on the decrease of CRP levels in the early postoperative period in the living kidney donor, according to the protocol observed by Hampel et al. [5]. The sample size was calculated with an α error of 0.05 and β of 0.20, to obtain a sample size of 24 donors and 24 recipients per group.

Statistical analysis

SPSS for IBM statistical software (version 20 for Windows; IBM Corp., Armonk, NY, USA) was used for data analysis. The data are expressed as frequencies and percentages and means and standard deviations. To compare results, the Student's *t* test was used for continuous variables, and the chi-square or Fisher's exact test was used for qualitative data when appropriate. The relationship between age, gender, body mass index, pre and post-transplant median blood pressure, operative bleeding, creatinine clearance, cold and warm ischemia times, cholesterol serum levels, pre and post-transplant glomerular filtration rate and the post reperfusion C-reactive protein levels were studied using multivariate regression analysis. Statistical significance from 2-tailed tests was assumed when $P<0.05$.

Ethical considerations

Ethical aspects of this study are based on the Regulations of the General Law of Health, regarding Health Research, and with the Helsinki Declaration of 1989 and its amendments. It was authorized with the registration number: 2011-1301-78 by the Local Committee for Research and Ethics in Health Research. In addition, the protocol was registered at ClinicalTrials.gov with the identifier number NCT02355704. The protocol was financially supported by a grant of the Health Research Coordination of the Mexican Institute of Social Security FIS/IMSS/PROT/MD11/996.

Results

Twenty-four donors were included in each of the 2 groups; of whom, 23 were male donors and 25 were female donors. The kinship in the CG corresponds to 22 living-related donors and 2 living-unrelated donors. In the SG, 18 were living-related donors and 6 were living-unrelated donors. Clinical features and preoperative studies are described in Table 1.

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Table 2. C-reactive protein and serum lipids in kidney donors between groups.

	At inclusion to the protocol		*P* value	1 hour before donor nephrectomy		*P* value
	Study group n=24	Control group n=24		Study group n=24	Control group n=24	
CRP	4.3±2.8	3.5±1.4	0.21	3.27±0.62	5.62±3.82	0.007
Total cholesterol	263.6±55.8	266.6±50.2	0.84	212.6±51.6	264.6±47.3	0.001
Low-density lipoprotein cholesterol	122.5±17.9	125.6±10.2	0.45	103.5±12.4	121.7±9.4	0.00
High-density lipoprotein cholesterol	44.3±10.4	41.5±11.4	0.39	55.7±5.1	43.6±7.4	0.00
Triglycerides	144.3±20.2	159.2±22.4	0.02	127.4±16.4	157±27.8	0.00

CRP – C-reactive protein.

Table 3. Intragroup values of C-reactive protein and serum lipids in kidney donors.

	Study group		*P* value	Control group		*P* value
	At inclusion n=24	At nephrectomy n=24		At inclusion n=24	At nephrectomy n=24	
CRP	4.3±2.8	3.27±0.62	0.05	3.5±1.4	5.62±3.82	0.02
Total cholesterol	263.6±55.8	212.6±51.6	0.00	266.6±50.2	264.3±47.3	0.88
Low-density lipoprotein cholesterol	122.5±17.9	103.5±12.4	0.00	125.6±10.2	121.7±9.4	0.16
High-density lipoprotein cholesterol	44.3±10.4	55.7±5.1	0.00	41.5±11.4	43.6±7.4	0.36
Triglycerides	144.3±20.2	127.3±16.4	0.002	159.2±22.4	157±27.8	0.77

CRP – C-reactive protein.

Before group allocation, CRP, total cholesterol (TC), and low-density lipoprotein (LDL) cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were not significantly different between donors. After treatment with atorvastatin, CRP levels decreased significantly (*P*=0.007). The results of C-reactive protein and serum lipids in kidney donors between groups are shown in Table 2. The results of C-reactive protein and serum lipids in kidney donor intra groups are shown in Table 3

Concerning operative events, mean warm ischemia times were 3.23±1.18 min in the SG, and 3.01±1.36 in the CG (*P*=0.74); cold ischemia times were 43.69±31.82 (SG) and 46.62±35.66 min, (CG) (*P*=0.76). The mean arterial pressure before clamping the renal artery was 107.66±10.18 mm Hg for the CG, and 108.83±7.11 mm Hg for the SG (*P*=0.68), postreperfusion values were 107.17±10.18 mm Hg and 105.08±6.63 mm Hg, respectively (*P*=0.40). The average intraoperative bleeding was 327.92±152.4 mL for the CG and 285.42±211.35 mL for the SG (*P*=0.42).

Regarding kidney recipients, 14 patients were female and 34 were male. Clinical features and preoperative test results showed no significant difference between groups (Table 4).

Renal function was evaluated 24 hours after surgery showing significant changes in the recipients of the SG since serum urea and creatinine levels were significantly lower in this group as shown in Table 5.

CRP baseline values had similar patterns in both groups, with a mean of 5.2±4.0 mg/dL in the CG and 3.9±1.1 mg/dL in the SG (*P*=0.16). These values showed significant differences after graft reperfusion and 6 hours later as shown in Table 6.

In the multivariate regression analysis, three variables were identified as independent predictors for decrease in CRP basal values. They were age (odds ratio OR –0.292, 95% confidence interval CI, –0.581 to 0.138, p=0.001), creatinine clearance (OR –0.0132, 95% CI, –1.311 to 0.807, p=0.004) and glomerular filtration rate (OR 0.408, 95% CI, –0.557 to 2.070, p=0.009). Regarding CRP reperfusion values, no variable was found with statistical significance,

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Table 4. Preoperative clinical and laboratory features in recipients.

	Study group n=24	Control group n=24	*P* value
Age (years)	31±12	27.1±7	0.17
Gender (M/F)	16/8	18/6	0.37
Time evolution (years)	3.3±2.6	2.7±1.1	0.33
Etiology of renal failure			
Unknown	15/24 (62.5%)	16/24 (66.6%)	0.50
Renal hypoplasia	6/24 (25%)	4/24 (16.6%)	0.36
No-specified glomerulonephritis	2/24 (8.3%)	0/24 (0%)	0.24
Polycystic kidney disease	1/24 (4.1%)	3/24 (12.5%)	0.30
Other etiology	0/24 (0%)	1/24 (4.1%)	NC
Hemoglobin (g/dL)	10.7±2.0	9.9±1.8	0.19
White blood cells (10^3/µL)	6.6±2.1	6.1±1.9	0.42
Neutrophils (%)	60.4±9.7	61.3±11.4	0.77
Platelet (10^3/µL)	233.7±61.8	199.1±61.4	0.06
Serum glucose (mg/dL)	85.8±13.9	91.6±34.8	0.45
Serum urea (mg/dL)	112.3±37	116.5±37.8	0.70
Serum creatinine (mg/dL)	11.3±4.9	11.9±4.2	0.63
Serum potassium (meq/L)	5.1±0.5	4.9±0.7	0.59

NC – not calculable.

Table 5. Renal function 24 hours after kidney transplant in recipients.

	Study group n=24	Control group n=24	*P* value
Serum urea (mg/dL)	44.9±15.6	64.8±30.7	0.01
Serum creatinine (mg/dL)	2.5±1.5	3.7±2.4	0.04
Serum potassium (meq/L)	4.0±0.3	4.2±0.4	0.38

Table 6. C-reactive protein in kidney transplant recipients (mg/dL).

	Study group n=24	Control group n=24	*P* value
Basal	3.9±1.1	5.2±4.0	0.16
1 h	3.8±1.0	5.8±3.9	0.04
6 h	4.7±2.4	6.4±5.1	0.04
24 h	22.9±9.8	24.4±13.4	0.73

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Table 7. Long-term renal function in the kidney recipients.

	6 months			1 year		
	Study group	Control group	*P* value	Study group	Control group	*P* value
e-GFR	89.05±15.2	86.16±14.8	0.50	89.5±15.8	86.3±16.3	0.49
Serum creatinine (mg/dL)	1.08±0.1	1.16±0.2	0.76	1.12±0.1	1.18±0.2	0.31

as age (OR –0.382, 95% CI, –0.362 to 0.190, p=0.128), gender (OR 0.097, 95% CI, –3.16 to –5.17, p=0.82), BMI (OR 0.23, 95% CI, –0.30 to 0.06, p=0.06), post-transplant medial arterial pressure (OR 0.30, 95% CI, –0.04 to 0.40, p=0.07), operative bleeding (OR 0.07, 95% CI, –0.01 to 0.01, p=0.63) and post-transplant glomerular filtration rate (OR –0.16, 95% CI, –0.16 to –0.70, p=0.67) failed to demonstrate any significant difference. During the long-term follow-up, 2 patients from the SG lost the kidney graft during the first 6 months and one patient in the CG lost the kidney graft during the first year, for reasons attributable to rejection and lack of adherence to the immunosuppressive treatment. The loss of the kidney graft was not attributed to the use of atorvastatin in the donor. The renal function (e-GFR and creatinine) of the remaining recipients is described in Table 7.

Discussion

Living donor kidney transplantation is a better replacement therapy for end-stage kidney failure over deceased donor kidney transplantation, owing to the absence of secondary kidney injury, shorter ischemia time, and the possibility of an early transplantation. In addition, it allows individualization of immunosuppression, and the possibility of starting the immunosuppressive therapy days before the transplantation, preventing acute rejection, and enhancing the survival and quality of life of the kidney recipients [6].

Recently, evidence has emerged that statins and their pleiotropic properties have additional clinical uses through anti-inflammatory and immunomodulatory effects [7]. It has been observed that patients who are treated with statins decrease their levels of inflammatory markers as the CRP levels in patients who did not receive statins has shown [8]. In the "Jupiter trial" 20 mg of rosuvastatin was administered in healthy patients. In the follow-up of 1.9 years, patients who were treated with rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity CRP levels by 37%. These results propose an inflammatory modulation of the renal graft with statin administration in healthy kidney donors [9].

This pharmacodynamic feature suggests the use of statins in some inflammatory, immunologic, and cell proliferative disorders. However, in most studies, the administration of this therapy starts after the ischemia-reperfusion injury has been triggered; thereby, it has been suggested that the use of statins should occur before the transplantation to reduce adverse events [9,10].

Bayes et al. found that atorvastatin at a dose of 10 mg/day administered to kidney transplant recipients does not modify the levels of CRP or alter the inflammatory markers after 12 weeks of treatment. They found a 19% decrease in the levels of CRP at 3 months compared with baseline; however, there was no statistically significant difference [11].

Another study published by Pérez et al. measured the levels of CRP after a treatment with low doses of atorvastatin of 10 mg/day in kidney recipients after 12 weeks of treatment. They found a decrease of 21.2% in CRP levels in kidney recipients at 3 months compared with baseline, but without statistical significance [12].

Yazbek et al. [13] studied renal transplant recipients treated with atorvastatin at doses of 10 mg for 12 months and compared them with a control group; they reported that levels of CRP remained stable (*P*=0.52) in the statin group but increased in the control group (*P*=0.01) [13]. At the time, there was no evidence of the use of statins in kidney donors with a focus on improving kidney status prior to transplantation or its impact on the ischemia-reperfusion injury and the associated inflammation post-transplantation. Several researchers have demonstrated (in experimental models of renal IRI in rat and mice) that pretreatment with statins before injury, improves kidney function, prevents tubular cell damage, and reduces inflammation [14–17].

Palin et al. [18], in an experimental model in rats, demonstrated that donor and recipient simvastatin pretreatment combined with daily recipient treatment reduced graft inflammation and chronic allograft injury. Treatment using only statins started after transplantation reduced inflammation to some extent but did not affect chronic kidney allograft injury. Pretreatment using only donor statins impaired graft function and increased proteinuria.

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These interesting findings led us to conduct this study with atorvastatin in living donor kidney transplants as well as determine its impact on the kidney status after recipients received the transplant.

It is now known that there is a significant increase in the endothelial vasodilator response after a month of treatment with statins, although the decrease in cholesterol levels was not evident at that time [19]. A favorable response has also been demonstrated in the endothelium in patients with heart failure and an improved vascular flow mediated by cyclooxygenase-2 [20]. This pathway of prostacyclin synthesis (specifically, prostaglandins I_2 and E_2) enables statins to present vasodilator, antiplatelet, and anti-inflammatory effects [21].

In rats, Wu et al. [22] reported that atorvastatin significantly reduces protein oxidation products, limiting structural damage, and reducing post ischemic acute tubular necrosis, in addition to lower serum creatinine levels by an increased creatinine clearance. Moreover, this protective effect can be generated due to the inhibition of intrarenal atherosclerosis as result of the lipid-lowering effect.

The inhibition of lipoprotein storage in the mesangium can reduce the number of LDL particles that bind to recipients expressed by mesangial cells and restricts the production of the matrix.

Additionally, it has been shown that statins can reduce proteinuria, and increase renal blood flow and glomerular filtration [23].

Vascular compliance has emerged as a predictor of mortality in patients on hemodialysis, and after renal transplantation. Therefore, statins may exert beneficial effects on blood vessels and endothelial function in patients with chronic kidney disease [20].

The proposed beneficial effects of atorvastatin include antithrombotic effects, protecting endothelial functions, changing thrombus formation, altering platelet aggregation, and enhancing fibrinolysis. In addition, other benefits have also been observed with the administration of atorvastatin including an improvement of the homocysteine levels in renal recipients [24].

Conclusions

The administration of atorvastatin to donors (40 mg orally every 24 hours for 4 weeks) prior to kidney transplantation decreased CRP levels. The reduction in CRP levels was maintained in the recipients following the transplantation procedure. That is, the data suggest that anticipatory treatment of donors with atorvastatin prior to transplantation ameliorated the potential deleterious response of the donated kidney (ischemia-reperfusion injury) once it was transplanted to a recipient. Overall, this study also supports that donors administered atorvastatin prior to kidney transplantation ("preventive" approach) represents a different strategy to reduce inflammatory burden from a proposed protective effect of atorvastatin (or other statin) post-transplantation that in addition to not overlapping with the period of most kidney stress (that is, during the ischemia-reperfusion injury intrinsic to the transplantation procedure), is also dependent of the dose and duration of treatment post-transplantation. With these results, it is mandatory to design protocols that evaluate the effect of long-term administration of atorvastatin on renal function in recipients from living and deceased donors.

Conflicts of interest

None.

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