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Asymmetrical dimethylarginine is associated with renal and cardiovascular outcomes and all-cause mortality in renal transplant recipients

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Increased plasma levels of asymmetric dimethylarginine (ADMA) are associated with endothelial dysfunction and predict the progression to dialysis and death in patients with chronic kidney disease. The effects of these increased ADMA levels in renal transplant recipients, however, are unknown. We used the data from ALERT, a randomized, double-blind, placebo-controlled study of the effect of fluvastatin on cardiovascular and renal outcomes in 2102 renal transplant recipients with stable graft function on enrollment. Patients who were initially randomized to fluvastatin or placebo in the 5- to 6-year trial were offered open-label fluvastatin in a 2-year extension of the original study. After adjustment for baseline values for established factors in this *post hoc* analysis, ADMA was found to be a significant risk factor for graft failure or doubling of serum creatinine (hazard ratio 2.78), major cardiac events (hazard ratio 2.61), cerebrovascular events (hazard ratio 6.63), and all-cause mortality (hazard ratio 4.87). In this trial extension, the number of end points increased with increasing quartiles of plasma ADMA levels. All end points were significantly increased in the fourth compared to the first quartile. Our study shows that elevated plasma levels of ADMA are associated with increased morbidity, mortality, and the deterioration of graft function in renal transplant recipients.

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Patient and graft survival after renal transplantation has improved considerably over the recent decades. Current 5- and 10-year patient survival rates are around 85 and 66%, and allograft half-lives have improved from 7.7 years in the mid 1980s to 10.9 years in mid 1990s.[1] However, life expectancy of renal transplant recipients is still shortened and premature graft failure is a major clinical problem.

We have previously shown that atherogenic lipids are risk factors for premature cardiac events in renal transplant recipients, and that this risk is reduced by lipid-lowering therapy.[2,3] However, despite statin treatment, the risk of major cardiac events (MACEs) in this population remains elevated. In addition to traditional cardiovascular (CV) risk factors, numerous modifiable, and non-modifiable risk factors have been proposed to contribute to the excessive CV risk in renal transplant recipients,[4,5] and to the risk of allograft failure.[6] One potential risk factor is asymmetric dimethylarginine (ADMA), an established risk factor for CV events and all-cause mortality in other populations,[7] which has not been investigated in transplant recipients.

Asymmetric dimethylarginine has also been shown in patients with chronic kidney disease (CKD) to be an important risk factor for progression to end-stage renal disease and all-cause mortality.[8]

Asymmetric dimethylarginine is an endogenous competitive inhibitor of nitric oxide synthase and reduces nitric oxide (NO) generation,[9,10] thus inhibiting the beneficial effect of NO on vasodilatation, arterial stiffness, and endothelial function.[11,12] ADMA levels are inversely related to glomerular filtration rate (GFR) in patients with mild-to-moderate CKD,[8,13] and elevated levels have been associated with CV events and death in patients receiving hemodialysis.[14,15] Thus, ADMA may be a predictor for renal graft loss, CV events and all-cause mortality in patients with different stages of CKD. The contribution of ADMA for such events in renal transplant recipients is unknown.

RESULTS

Baseline characteristics

Basic patients and demographic data in Assessment of Lescol in Renal Transplantation (ALERT) and the extension ALERT have been published previously.[2,16] Participants in the ALERT were renal transplant recipients with stable graft function for a mean duration of 4.5 years before randomization into the trail. The treatment arms in the ALERT study were comparable with regard to baseline demographic and clinical characteristic. There were no differences in ADMA values between placebo and fluvastatin arms. In this *post hoc* analysis, we separated the patients into ADMA quartiles according to ADMA levels. Estimated glomerular filtration (ml/min per 1.73 m^2) was calculated by using the formula from the Modification of Diet in Renal Disease study.[17] The demographic data are summarized in Table 1. Patients in the different ADMA quartiles are comparable with regard to age, blood pressure, lipid levels, body mass index, and serum calcium and phosphate values. There was a tendency to increased serum creatinine and decreased estimated GFR with higher ADMA levels, although ADMA was only weakly but significantly correlated with serum creatinine ($r = 0.218$, $P = 0.000$) and as expected inversely correlated with estimated GFR ($r = -0.193$, $P = 0.000$). Hypertension and use of antihypertensive drugs was also more common in patients with higher ADMA levels.

Outcomes

Incident rates for renal, cardiac, cerebrovascular (CBV) events and for all cause of death in each quartile of ADMA are summarized in Table 2. Differences between second and fourth ADMA quartiles versus first quartile were tested using log-rank test. *P*-values are given versus first quartile. Kaplan–Meier curves for survivors in each quartile of ADMA are shown in Figure 1. Figure 2 shows relative risk for study outcomes within the asymmetric dimethylarginine (ADMA) quartiles compared with the first quartile.

Renal end points. The number of graft failure or doubling of serum creatinine increased in higher ADMA quartiles, and was highly significant when the third and fourth quartile was compared with the first quartile. The number of graft failure and doubling of serum creatinine almost doubled (79 (16.6%) to 137 (29.8%), $P < 0.001$) from the first to the fourth quartile.

Cardiac end points. The number of MACE and cardiac death or non-fatal myocardial infarction increased in higher ADMA quartiles. These differences were statistically significant between the first and the fourth quartile.

Cerebrovascular events. Rate of CBV events increased with increasing ADMA quartiles and the number of CBV events were more than doubled (3–4 to 11.0%) from the first to the fourth quartile.

All-cause mortality

Number of all cause of death increased also by ADMA quartiles and the number of events was almost doubled (13.9 to 26.8%) in the fourth quartile compared with the first quartile.

Risk factor analysis

The results from the Cox risk factor analyses are summarized in Table 3. The hazard ratios (HR) with 95% confidence intervals (95% CI) and corresponding *P*-values are shown for all study outcomes. The univariate model included continuous ADMA values and study outcomes as dependent variable. The multivariate model was adjusted for potentially important baseline covariates such as age, gender, systolic blood pressure, previous CHD, diabetes mellitus, low-density lipoprotein cholesterol, smoking, and estimated GFR.

In both univariate and multivariate analysis, ADMA is associated with all study end points. ADMA is an independent predictor of GFDSC (graft failure and doubling of serum creatinine): HR 2.78 (95% CI: 1.22–5.82, $P = 0.009$), MACE: HR 2.61 (95% CI: 1.03–6.61, $P = 0.042$), cardiac death or non-fatal myocardial infarction: HR 4.90 (95% CI: 1.70–14.10, $P = 0.003$), CBV events: HR 7.63 (95% CI: 2.52–23.13, $P < 0.001$), and all-cause death: HR 4.87 (95% CI: 2.12–11.18, $P < 0.000$).

DISCUSSION

This study is the first to report that plasma levels of ADMA are associated with increased incidence of MACE, cardiac death or non-fatal myocardial infarction, CBV events, all-cause mortality, and deterioration of graft function in renal transplant recipients. Our findings in this population mirror previous reports in patient with non-transplanted patients with or without CKD.[18]

Epidemiological studies have suggested association between ADMA and hypertension,[19] hypercholesterolemia,[20] diabetes mellitus,[21] and increased CV risk in CKD.[7,9,22,23]

Impaired endothelial function is thought to primarily reflect decreased bioavailability of NO, and an endothelium-derived vasodilator with anti-atherosclerotic properties.[24]

In renal transplant recipients, endothelial dysfunction is well documented, and leads to functional and structural changes that influence arterial stiffness.[25,26] Arterial stiffness, assessed by pulse wave velocity, is present in renal transplant recipients, and is enhanced by the use of calcineurin inhibitors.[27,28] Owing to the pre-existing endothelial dysfunction, renal transplant recipients are at high risk for deleterious effect of inhibitors of NO, such as ADMA. There is no established therapy for elevated ADMA, although rosiglitazone, amlodipine, and valsartan decrease ADMA level.[28,29]

Renal transplant recipients have numerous traditional and non-traditional risk factors for CV events, and although dyslipidemia-dependent CV events, such as myocardial infarction,[2] are reduced by lipid-lowering therapy, there is a considerable residual risk for cardiac mortality and morbidity in these patients.

Although the procedure of renal transplantation may decrease the raised level associated with hemodialysis, ADMA is still increased in renal transplant recipients compared with healthy controls.[30] A raised level of ADMA in our study was associated with a higher incidence of CV events. In the highest quartile of ADMA, the incidence was approximately doubled