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# Impact of Homocysteinemia on Long-Term Renal Transplant Survival

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ABSTRACT

Aim. We prospectively followed a cohort of 202 renal transplant recipients for 5 years to examine the impact of fasting homocysteinemia on long-term patient and renal allograft survival.

Methods. Cox proportional hazards regression analysis was used to identify independent predictors of all-cause mortality and graft loss.

Results. Hyperhomocysteinemia (tHcy >15 μmol/L) was present in 48.7% of the 202 patients, predominantly among men (55.8%) as opposed to women (37.1%). At the end of the follow-up period, 13 (6.4%) patients had died including 10 from cardiovascular disease, and 23 had (11.4%) had lost their grafts. Patient death with a functioning allograft was the most prevalent cause of graft loss (13 recipients). Levels of tHcy were higher among patients who died than among survivors (median 23.9 vs 14.3 μmol/L; $P = .005$). Median tHcy concentration was also higher among the patients who had lost their allografts than those who did not (median 19.0 vs 14.1 μmol/L; $P = .001$). In a Cox regression model including gender, serum creatinine concentration, transplant duration, traditional cardiovascular risk factors, and associated conditions, such as past cardiovascular disease, only tHcy concentration (ln) (HR = 5.50; 95% CI, 1.56 to 19.36; $P = .008$) and age at transplantation (HR = 1.07; 95% CI, 1.02 to 1.13; $P = .01$) were independent predictors of patient survival. After censoring data for patient death, tHcy concentration was not a risk factor for graft loss.

Conclusions. This prospective study shows that tHcy concentration is a significant predictor of mortality, but not of graft loss, after censoring data for patient death.

SHORT- AND LONG-TERM GRAFT and patient survivals after renal transplantation have improved considerably over the past three decades. However, life expectancy beyond 10 years is still considerably less than in the general population, mainly due to cardiovascular events. In fact, an accelerated form of atherosclerosis commonly occurs in these patients. Cardiovascular disease is the leading cause of morbidity and mortality in renal transplant recipients, accounting for approximately 40% of all deaths.[1,2]

Classic cardiovascular risk factors (eg, dyslipidemia, hypertension, and diabetes) as well as nonmodifiable risk factors such as age, gender, and family history do not fully explain the cardiovascular disease. Among other predictors of atherosclerotic disease, attention has been drawn to the association between homocysteine and cardiovascular events. Clinical and epidemiological studies have shown that homocysteine measured in serum or plasma is a strong predictor of cardiovascular risk.[3,4] The results of early cross-sectional and case-control studies strongly support this hypothesis.[5,6] Prospective studies of patient populations known to be at high risk of cardiovascular events, including renal patients, consistently report strong associations between homocysteine and cardiovascular as well as all-cause mortality.[7–16]

Elevated levels of fasting total plasma homocysteine (tHcy) are prevalent in patients who underwent kidney

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transplantation. Some studies suggest as well that hyperhomocysteinemia is a cardiovascular risk factor in these recipients.[17–22]

In the present study, we prospectively followed a cohort of 202 recipients for 5 years to examine the impact of fasting homocysteinemia on long-term patient and renal allograft survival.

## PATIENTS AND METHODS

### Subjects

This investigation was conducted based on a cross-sectional study in 1999 among 202 renal recipients sought to assess the prevalence and determinants of hyperhomocysteinemia in stable patients.[22] The study population was selected from 633 cadaveric kidney transplants with functioning allografts, which had been performed between June 1983 and April 1997. Inclusion criteria were age over 18 years, first renal allograft, posttransplant time of at least 6 months, and stable plasma creatinine values for the prior 3 months. Patients who had been diagnosed with any kind of cancer, liver disease or chronic alcoholism were excluded, as were those taking folic acid or B vitamins. After the inclusion and exclusion criteria had been fulfilled, the remaining 413 patients were stratified into systematic random sample of 220 subjects using a two-by-two sequential selection from our computerized patient base. Among the 220 selected patients, 202 were included in our analysis. The other 18 were excluded because of death, transfer to other hospitals, intake of vitamin supplements containing folic acid or complex B vitamins, and nonappearance at blood draws.

These patients were prospectively followed for 5 years for longitudinal associations between tHcy levels and patient overall mortality/graft failure. None of the 202 study patients received folic acid, vitamin $B_{12}$, or vitamin $B_6$ supplementation during the 5-year follow-up period.

### Biochemical Determinations

Blood samples were collected from each participant after an overnight fast. Total homocysteine levels were determined between January and June 1999, by polarized immunofluorescence on an automated Abbott IMx analyser. Two measurements of tHcy were made in each patient at an interval of 3 months to evaluate fluctuations in tHcy values. No significant differences were found between the two determinations of tHcy levels.[23] The second measurement was used to perform all subsequent study analyses. Plasma pyridoxal 5′-phosphate was determined by high performance liquid chromatography with fluorescence detection. Plasma vitamin $B_{12}$ and plasma and erythrocyte folate were measured on automated analyzer ACS: Centaur (Chiron Diagnostics) by chemioluminescence. At the time of the second measurement of tHcy, the laboratory tests included serum measurements of creatinine, urea, uric acid, albumin, total protein, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and total cholesterol, apolipoproteins A and B-100, lipoprotein(a), fibrinogen, and plasminogen activator inhibitor-1 (PAI-1).

### Study Variables

Medical records were reviewed to obtain information regarding demographic status, body weight, past dialysis time, surgical and initial postoperative transplant procedures, coexistent and previous medical illnesses, including individual and familial history of clinical cardiovascular disease. Because the time from the transplant procedure to tHcy determination varied among patients, transplant duration before tHcy measurement was also considered in the analysis. All cardiovascular risk factors were ascertained at the time of the second tHcy determination. We analyzed risk factors including age, hypertension, cigarette smoking history, diabetes mellitus, and obesity, as well as LDL and HDL cholesterol, triglycerides, lipoprotein(a), fibrinogen, and PAI-1 levels.

### Statistical Analyses

Kolmogorov-Smirnov test was used to assess significant departures from normality. The concentration of tHcy showed a marked, positively skewed distribution. Thus, tHcy and all variables with a skewed distribution, such as creatinine, folic acid, and vitamin $B_{12}$, were natural log transformed (ln) before statistical analysis.

Results are expressed as mean values ± standard deviations. In specific cases, geometric means (due to the log-normal distribution of variable), median, and interquartile range (IQR) are also presented. For continuous variables significance of differences between groups were assessed using Student *t* test for independent samples, or Mann-Whitney test when appropriate; for categorical variables we used the $\chi^2$ test, or Fisher exact test wherever appropriate. Unadjusted correlations between continuous variables were calculated by Pearson's correlation coefficient.

Cox proportional hazards regression model was used to assess the independent effects of the risk factors on patient and graft survival and to calculate the hazard ratios of death, after controlling for gender, serum creatinine concentration, and traditional risk factors for cardiovascular disease, such as cigarette smoking, diabetes mellitus, hypertension, obesity, and past history of cardiovascular events. Transplant duration was also included in the model, because time since the procedure to tHcy measurement varied among patients. Primary outcome analyses focused on patient and graft survivals. In a first analysis, graft loss was defined as the loss of graft function, resulting in the need to restart dialysis, need for retransplantation, or death (graft survival without censoring data for patients who died with functioning grafts). An additional analysis was performed after censoring data on patients who died with a functioning allograft (graft survival censored for patient death). The proportionality assumption for the Cox regression models was tested and met in this study (the log-log survival curves were compared for categorical variables, and the significance of covariate time interaction terms for continuous variables). All skewed continuous variables included in the univariate or multivariate Cox proportional-hazard models were (natural log) transformed. Multivariate Cox regression analysis was performed using backward, stepwise selection. The results are reported as hazard ratios (HR), with 95% confidence intervals (95% CI), and *P* values.

All analyses were performed using SPSS statistical analysis software, version 12.0 for Windows (SPSS Inc, Chicago, Ill, USA). Results were considered statistically significant when $P < .05$.

## RESULTS

### Cross-Sectional Study

The mean age of the 202 patients (113 men and 89 women) was 44 ± 11 years (range, 21 to 71), and the mean time after renal transplantation was 58.5 ± 37.2 months (range, 17 to 192). Diabetes was present in 21 (10.4%) recipients with 10 of them having developed diabetes after renal transplantation. Twenty-five (12.4%) patients had a history of vascular disease: 17 and 10 patients had a vascular event before and after kidney transplantation, respectively.

As we previously reported,[22] hyperhomocysteinemia (tHcy > 15 μmol/L) was present in 48.7% of the 202 study patients, predominantly in male (55.8%) compared with female recipients (37.1%). Hyperhomocysteinemia was mild (≤30 μmol/L) in 93 patients (96.9%) and moderate (between 31 and 100 μmol/L) in the remaining three patients (2.9%). The geometric mean of tHcy was 14.9 μmol/L and tHcy levels were significantly higher among male than female patients (16.2 vs 13.4 μmol/L; $P < .001$). Levels of tHcy were modestly correlated with transplant duration ($r = .21$, $P = .003$). No significant correlations were observed between tHcy concentration and age, or age at the time of kidney transplantation.[23] None of the evaluated risk factors for atherosclerosis was significantly associated with hyperhomocysteinemia, either using univariate or multivariate analysis, namely, the presence of hypertension, obesity, smoking, and dislipidemia. No correlation was also found between tHcy levels and plasma fibrinogen or PAI-1.[23]

Multiple regression analysis showed that about 46.7% of the variation in tHcy concentrations was predicted by gender, serum creatinine and uric acid, presence of previous vascular events, erythrocyte folate, and therapy with central α-adrenergic receptor blockers.[23]

### Prospective Study (Patient Survival)

During the 5-year follow-up period, 13 recipients died (6.4%) with 10 deaths attributed to cardiovascular events. Cardiovascular causes of death included cardiac arrest (five patients), myocardial infarction (three patients), and stroke (two patients). Other causes of death included: malignancy (one patient), gastrointestinal bleeding (one patient), and unknown (one patient).

Age at the time of transplantation was significantly greater among those who died [median 44.8 (IQR 39.6 to 56.7) vs 38.7 (IQR 31.0 to 48.4) years; $P = .002$], as well as among recipients of greater age at the time of tHcy measurement [median 54.3 (IQR 45.6 to 62.3) vs 42.8 (IQR 35.6 to 52.3) years; $P = .01$]. Time since transplantation was also significantly higher among those who died [median 71.9 (IQR 49.7 to 96.4) vs 49.4 (IQR 29.0 to 71.5) months; $P = .039$], but no significant differences were observed in graft function, evaluated by serum creatinine concentration [median 1.4 (IQR 1.1 to 1.8) vs 1.5 (IQR 1.4 to 2.3) mg/dL; $P = .49$).

Fasting homocysteine concentrations were significantly higher among patients who died than the survivors [median 23.9 (IQR 14.1 to 25.4) vs 14.3 (IQR 11.5 to 18.1) μmol/L, $P = .005$]. No significant differences were found between levels of LDL and HDL cholesterol, triglycerides, lipoprotein(a), fibrinogen, and PAI-1. No significant differences were also found among the remaining cardiovascular risk factors, namely, diabetes, hypertension, obesity, and cigarette smoking.

Univariate Cox analysis only showed age at time of transplantation (HR = 1.09; 95% CI, 1.03 to 1.15; $P = .003$), tHcy concentration (ln) (HR = 4.60; 95% CI, 1.49 to 14.23; $P = .008$), and previous cardiovascular events (HR = 3.45; 95% CI, 1.00 to 11.84; $P = .049$) to be significantly associated with all-cause patient mortality.

We used multivariate Cox proportional hazards regression analysis to better define independent risk factors for mortality. In a Cox regression model including gender, serum creatinine concentration, transplant duration, traditional cardiovascular risk factors (smoking, hypertension, diabetes, and dyslipidemia) and associated conditions, such as past cardiovascular disease, stepwise elimination of nonsignificant variables only left "tHcy concentration" and "age at transplantation" as significant, independent predictors of patient survival. Cox regression analysis showed that tHcy (ln) was a risk factor for overall patient mortality (HR = 5.50; 95% CI, 1.56 to 19.36; $P = .008$), adjusted for transplant duration between the transplant and tHcy measurement. Age at transplantation (HR 1.07; 95% CI, 1.02 to 1.13; $P = .01$) was also an independent predictor of mortality, corresponding to a 7% per year increase in HR for mortality.

### Prospective Study (Graft Survival)

In relation to graft failure, 23 renal transplant patients (11.4%) lost their grafts during this 5-year follow-up. Patient death with a functioning allograft was the most prevalent cause of graft loss, namely, 13 of the 23 renal transplant patients.

Median tHcy concentration was higher among patients who had versus had not lost their allografts [median 19.0 (IQR 15.2 to 25.1) vs 14.1 (IQR 11.5 to 18.0) μmol/L, $P = .001$]. However, after excluding allograft loss due to patient death no significant differences were found [17.4 (IQR 15.2 to 20.7) vs 14.3 μmol/L (IQR 11.5 to 18.7), $P = .123$]. By univariate Cox analysis, tHcy levels were a significant predictor of graft failure (HR = 3.47; 95% CI, 1.36 to 8.80; $P = .009$), but after the censoring of that data for patients who died with a functioning allograft no significant association was found between tHcy levels and graft loss (HR = 1.85; 95% CI, 0.38 to 9.13; $P = .448$).

## DISCUSSION

In this longitudinal study, we investigated the impact of tHcy levels on long-term patient and graft survivals. The analysis revealed that tHcy levels were an independent predictor of patient mortality but not of kidney allograft loss after censoring for patient death.

Evidence from the general population suggests that even mild elevations in tHcy levels might confer an increased risk for all-cause mortality and particularly cardiovascular disease-related mortality, which is the major cause of death among patients with kidney transplants.[8,10,12] A smaller literature in renal transplantation also points a substantial risk of hyperhomocysteinemia contributing to the increased risk of early cardiovascular disease.[17–21]

Whereas small retrospective studies are often subject to various biases, prospective studies generally provide a more robust estimate of association. Data from prospective stud-

ies among populations with primary and secondary cardiovascular risk have shown that tHcy concentrations are inversely related with survival.[10,11,24] To our knowledge, only three prospective cohort studies have evaluated the potential relationship between homocysteinemia and cardiovascular events or survival in the kidney transplant population.

Ducloux et al followed 207 patients over a period of about 19 months to evaluate the association between baseline tHcy levels and subsequent development of cardiovascular disease. There were 30 new cardiovascular events during that follow-up period. In a multivariable proportional hazards model, after adjustment for age, gender, prior cardiovascular disease, creatinine, cyclosporine use, smoking, hypertension, diabetes, dyslipidemia, and tHcy, only age, serum creatinine, and tHcy levels were significant predictors of cardiovascular events during follow-up.[25] A study from Hagen et al examined the prospectively influence of 5, 10-methylene-tetrahydrofolate reductase genotypes and tHcy concentrations on all causes of mortality and graft outcomes of 189 patients. During the follow-up period of 2.26 ± 0.66 years, nine patients died and 22 returned to dialysis. In the Cox multivariate model tHcy concentration was unrelated to patient or graft survival.[26] A recent study performed by Winkelmayer et al prospectively followed 733 stable patients for a median of 6.7 years to evaluate the associations between tHcy levels and patient and graft survival in kidney transplant patients. During this follow-up, 164 patients died (22.4%) and 279 lost their allograft (38.1%). By multivariate analysis, the authors reported that patients with elevated levels of tHcy had a 75% higher mortality rate and a 50% increased risk of graft loss. They concluded that elevated tHcy levels were an independent risk factor for both mortality and allograft loss in kidney transplant recipients.[27]

Our study also confirms that tHcy concentration is an independent predictor of mortality in renal transplantation. The renal transplant recipients who died showed significantly higher tHcy levels than survivors. By multivariate analysis, after adjustment for gender, serum creatinine concentration, and traditional risk factors for cardiovascular disease, tHcy levels remained a significant independent predictor for overall patient mortality.

In the current study, after censoring data for patient death, tHcy levels were not a risk factor for graft loss. Patient death with a functioning allograft was the major cause of graft loss in our patients. Thirteen of the 23 lost grafts were functioning at the time of recipient death. Therefore, censoring death with graft function seems to be more accurate to analyze the impact of tHcy levels on long-term allograft survival. Considering this, tHcy levels did not predicted allograft loss in our patients. We do not know if the endpoint of graft survival analyzed by Winkelmayer et al[27] was graft loss from all causes or death-censored graft loss.

Since the relation between tHcy levels and the risk for cardiovascular disease and mortality appears to be graded, and since there is no definitive evidence suggesting a sudden increase in the risk for vascular disease above a certain threshold level of tHcy,[10,24] we opted to include homocysteine as a continuous variable in the regression model. Since the cutoff values for high tHcy levels are not well defined, not only in these patients but also in the general population, and to avoid bias, we did not choose any arbitrary cutoff points for tHcy levels in the Cox regression analysis.

Our study also confirmed that cardiovascular disease continues to be a major complication after renal transplantation. It was the main cause of death in our patients: 10 of the 13 recipients died due to cardiovascular events. Several studies reported that serum cholesterol level after renal transplantation is associated with cardiovascular mortality.[28,29] In our study, despite cardiovascular disease as the main cause of death, total and LDL cholesterol were not associated with patient mortality, either by univariate or multivariate Cox analysis. Sixty-five of the patients (32.2%) received antilipemic agents, mainly 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. It is possible that the reduction in total and LDL cholesterol levels achieved among these patients confounded the relationship between these lipid parameters and patient survival.

Diabetes, a major cardiovascular risk factor, is associated with an increased risk of graft failure.[30] In this study, no significant association was found between diabetes and patient death. It is possible that the small number of diabetic patients in our study population (21 recipients, 10.4%) did not permit clear conclusions to be made about the real influence of diabetes.

Although this study reveals that homocysteinemia is a significant predictor of overall mortality in chronic stable renal transplant recipients, it does not suggest that tHcy causes mortality. The issue of causality cannot be resolved by observational studies. To confirm a causal relation between tHcy levels and survival or the occurrence of cardiovascular events requires randomized, placebo-controlled trials examining the effect of total homocysteine-lowering therapy on survival.

Cardiovascular disease is the most common cause of death among patients with a functioning renal allograft. To address the pressing challenge in renal transplantation of improving patient survival and long-term graft function, potentially reversible risk factors must be managed, without putting graft function at risk. Homocysteine is one of the potentially modifiable risk factors that could be targeted for intervention. Levels of tHcy can be reduced by simple treatment with folic acid, vitamin $B_{12}$, and/or vitamin $B_6$ even in the absence of deficiencies of these vitamins. And since therapies for primary and secondary prevention are successful in the general population,[31] efforts should be made to prevent or limit the progression of cardiovascular disease and reduce the cardiovascular burden in transplant recipients.

In conclusion, we found that tHcy level was an independent predictor of overall mortality among patients with a

kidney transplant. This prospective study does not prove a causal relation between homocysteine and mortality, but since long-term graft survival depends on long-term patient survival, our findings provide an additional incentive to perform intervention trials with homocysteine-lowering therapy to evaluate the effects of decreasing tHcy levels in the renal transplant population.

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