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Elevated Homocysteine Is a Predictor of All-Cause Mortality in a Prospective Cohort of Renal Transplant Recipients

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Key Words
Homocysteine · Renal transplant · Cardiovascular mortality

Abstract
Background: In patients with chronic kidney disease, an elevated homocysteine concentration is associated with an increased incidence of cardiovascular events. ***Aim:*** The aim of this study was to investigate the relationship between homocysteine concentration and all-cause mortality during prospective follow-up of a renal transplant cohort. ***Methods:*** A total of 378 renal transplant recipients were recruited between June 2000 and December 2002. Homocysteine was measured at baseline and mortality data was collected at a median of 2,441 days after enrolment. ***Results:*** In univariate analysis, homocysteine was a significant predictor of mortality ($p < 0.001$). In multivariate analysis, homocysteine remained a significant independent predictor of mortality following adjustment for traditional cardiovascular risk factors ($p = 0.01$), vitamin B_{12} and folate ($p < 0.001$) and estimated glomerular filtration rate ($p = 0.03$). ***Conclusions:*** In the renal transplant recipients enrolled in this study, homocysteine concentration was a significant predictor of mortality in univariate survival analysis and in multivariate survival analysis following adjustment for traditional cardiovascular risk factors and following adjustment for renal function. Assessing the effect of lowering homocysteine concentration on the survival of patients with a renal transplant is therefore worthy of further study.

Introduction

Raised homocysteine levels have been implicated in the pathogenesis of atherosclerosis since the original report highlighting accelerated vascular pathology in patients with homocystinuria [1, 2]. Since then, further evidence has emerged suggesting that an elevated homocysteine level is a biomarker for vascular disease [3–7] and associated with an increased incidence of cardiovascular events in the general population [8].

There are many factors that influence total homocysteine concentrations. Genetic variants of the enzymes involved in homocysteine metabolism can modulate homocysteine levels, e.g. a common C677T polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene, influences MTHFR enzyme activity; individuals homozygous for the TT genotype have higher homocysteine levels [9, 10].

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Folate and vitamin B_{12} are also important determinants of plasma homocysteine concentrations. In the general population, it has been suggested that two-thirds of individuals with elevated homocysteine have inadequate intake of these vitamin cofactors [11].

Although homocysteine concentrations were lower in patients receiving folate and vitamin B supplementation as compared to those receiving placebo, a corresponding reduction in cardiovascular events has not been demonstrated [12–14].

Homocysteine concentrations also rise in progressive chronic kidney disease in parallel with the decline in glomerular filtration rate (GFR) [15–17] and patients with end-stage renal disease are 33 times more likely to have elevated homocysteine levels than matched controls [18]. Although homocysteine concentrations decrease during a session of haemodialysis [19, 20] and following renal transplantation [21], more than 90% of patients on haemodialysis and 60–70% of renal transplant recipients [21] have persistently elevated homocysteine levels. As in the general population, a raised homocysteine concentration is associated with an increased incidence of cardiovascular events in patients with chronic kidney disease [7, 22] and in patients with a renal transplant [23].

We hypothesised that an elevated homocysteine concentration would predict increased risk of mortality in renal transplant recipients. The aim of this study was therefore to assess the relationship between homocysteine concentration and all-cause mortality during prospective follow-up of a renal transplant cohort.

Methods

A total of 378 renal transplant recipients were recruited from the renal transplant clinics at Belfast City Hospital and Antrim Area Hospital in Northern Ireland between June 2000 and December 2002. The study was approved by the Research Ethics Committee of Queen's University Belfast and fully informed written consent was obtained from each participant prior to enrolment. Patients were eligible for entry if they had a functioning renal transplant present and although no formal exclusion criteria were imposed, patients who were unwell or had signs of sepsis at initial assessment were deferred until a subsequent clinic re-assessment.

All the renal transplant patients recruited to this study were >3 months post-renal transplant and 94% were recruited >12 months after transplant surgery. All participants had stable graft function and were on standard immunosuppression regimens.

The 378 renal transplant recipients enrolled in this study represented 98% of all renal transplant recipients attending the renal transplant clinics at Belfast City Hospital and Antrim Area Hospital and 71.7% of all patients with a functioning renal transplant in Northern Ireland at the end of 2002. The 2% of patients not enrolled either did not consent to participate in the study or, more commonly, were attending renal transplant clinics at other geographically distant hospitals in the Northern Ireland region.

At enrolment, with the assistance of a research nurse, patients completed a cardiovascular risk assessment questionnaire. This recorded the presence of traditional cardiovascular risk factors (age, gender, diabetes and smoking history) and previous history of vascular disease (stroke, myocardial infarction, coronary artery bypass grafting, angioplasty, amputation for peripheral vascular disease or angiographic evidence of atherosclerotic vascular disease). Each participant's prescribed drug therapy, including the immunosuppression regimen, was also recorded.

Each patient had a measurement of blood pressure recorded. This was the average of the last 3 blood pressure measurements (measured using a Disytest sphygmomanometer, Welch-Allyn, Buckinghamshire, UK) assessed at the renal transplant clinic.

A fasting blood sample was obtained from each participant and stored at –70°C until biochemical analysis.

Biochemical Analyses

Homocysteine was measured using a high-performance liquid chromatography method with fluorescence detection [24]. The laboratory reference range for homocysteine was 5–15 μmol/l. Serum B_{12} and folate were measured using a radioassay technique (ICN Pharmaceuticals, Costa Mesa, Calif., USA). The normal laboratory range for serum B_{12} was 14–650 ng/l and >1.8 μg/l for serum folate.

Serum total cholesterol and high-density lipoprotein (HDL) cholesterol were measured using VITROS slides and analysed using a VITROS 700 System (Ortho Clinical Diagnostics, Rochester, N.Y., USA).

Serum creatinine was measured using the VITROS Slide System and the VITROS 950 analyser system (Ortho Clinical Diagnostics, Rochester, N.Y., USA). The detection range for creatinine was 4–1,238 μmol/l.

The estimated GFR (eGFR) was calculated for all patients using the 4-variable Modification of Diet in Renal Disease (MDRD) equation [25]: eGFR (ml/min/1.73 m^2) = 186 × (serum creatinine [μmol/l]/89)$^{-1.154}$ × age$^{-0.203}$ × (0.742 if female) × (1.21 if African American).

The 24-hour urinary protein was measured using a dye binding technique (Microprotein PR, Sigma, Poole, UK). Analysis was performed on a Roche Cobas Fara analyser (Roche, Basel, Switzerland).

High-sensitivity C-reactive protein (hsCRP) was measured using a high-sensitivity immunoturbidimetric assay (Randox, Crumlin, UK). Samples were analysed using a Roche Cobas Fara (Roche, Basel, Switzerland).

Prospective Data Collection

The collection of prospective follow-up data was completed in April 2008 at a mean of 2,243 days and a median of 2,441 days after enrolment. The shortest period of follow-up after recruitment to the study was 82 days and the longest period of follow-up was 2,844 days.

Mortality data, including date of death, where applicable, was available for all participants. This information was obtained from the mortality data recorded on the Regional Nephrology Database at Belfast City Hospital and via letter and direct telephone

Table 1. Biological characteristics of the renal transplant recipients enrolled in this study

Characteristic	
Male	243 (64%)
Age, years	47.3 ± 14.3
Diabetic	54 (14%)
Smokers	72 (19%)
Systolic blood pressure, mm Hg	132 ± 14
Diastolic blood pressure, mm Hg	79 ± 8
Body mass index	26.5 ± 4.5
Creatinine, μmol/l	130 (106, 160)
eGFR, ml/min/m^2	52.5 ± 20.2
Time since transplant, years	7 (3, 13)
Homocysteine, μmol/l	15.6 (12, 20.5)
Vitamin B_{12}, ng/l	408 (287, 568)
Folate, μg/l	5.8 (4.2, 8.8)

Table 2. Biological and biochemical differences in renal transplant recipients with a homocysteine concentration ≤15 μmol/l (group 1) as compared to those with a homocysteine concentration >15 μmol/l (group 2)

	Group 1 (n = 169)	Group 2 (n = 210)	Significance
Age, years	45.8 ± 13.5	48.6 ± 14.7	0.053
Male	95	148	0.004
Diabetic	26	28	0.570
Smokers	21	51	0.003
eGFR, ml/min/m^2	60.9 ± 20.1	45.6 ± 17.7	<0.001
Vitamin B_{12}, ng/l	444 (321, 600)	387 (264, 529)	<0.001
Folate, μg/l	7.2 (4.9, 10.0)	5.0 (3.6, 7.4)	<0.001
hsCRP, mg/l	1.7 (0.8, 3.7)	2.0 (0.9, 5.4)	0.117

Results expressed as arithmetic mean ± standard deviation or median (inter-quartile range).

contacts with the primary care physicians of the renal transplant recipients enrolled in this study. No patients were lost to follow-up.

Statistical Analyses

Data analysis was performed using SPSS (version 11.0 Chicago, Ill., USA). Kolmogorov-Smirnoff analysis was used to test if variables were normally distributed. Logarithmic transformation was performed for variables that did not conform to a normal distribution. For normally distributed variables data is expressed as arithmetic mean ± standard deviation. For those variables that were not normally distributed data is expressed as median with the interquartile range in brackets. The significance of differences between 2 groups was assessed using independent samples t test for normally distributed variables. A 2-tailed $p < 0.05$ was considered to be statistically significant.

Kaplan-Meier analysis with log-rank test was used for univariate survival analysis. Homocysteine concentration was banded into thirds prior to survival analysis.

A Cox regression model was used for multivariate survival analysis. Given the size of the study population, traditional cardiovascular risk factors were banded into thirds prior to inclusion as co-variates in the Cox regression model. As there are no established cutoffs for either vitamin B_{12} or folate, these variables were also banded into thirds prior to inclusion in survival analysis.

Results

The characteristics of the renal transplant recipients enrolled in this study are shown in table 1. All participants were white. No participants were taking B vitamin or folate supplements at enrolment. All 378 participants had measurements for homocysteine, creatinine, total cholesterol and HDL cholesterol. A total of 375 participants had a measurement for hsCRP, 359 had a measurement for vitamin B_{12} and folate and 354 had a measurement for 24-hour urinary protein excretion.

Homocysteine concentration was significantly lower in females as compared to males [14.8 (10.7, 19.8) vs. 16.1 (12.6, 20.7) μmol/l, p = 0.014] and smokers had a significantly higher homocysteine concentration than non-smokers [18.4 (13.5, 24.3) vs. 15.2 (11.3, 19.9) μmol/l, p < 0.001]. There was no significant difference in homocysteine concentration between diabetics and non-diabetics [15.1 (11.2, 20.0) vs. 15.7 (12.0, 20.4) μmol/l, p = 0.064].

A total of 168 renal transplant recipients had a homocysteine concentration within the laboratory reference range (≤15 μmol/l). The differences between those renal transplant recipients with a homocysteine concentration ≤15 μmol/l as compared to those renal transplant recipients with a homocysteine concentration >15 μmol/l are shown in table 2.

As participants were transplanted between 1968 and 2001, their immunosuppression mainly reflected the drug therapy available at the time of transplantation. Consequently, wide combinations of immunosuppression regimens were in use in this study population. However, 258 renal transplant recipients were prescribed a calcineurin inhibitor and these renal transplant recipients had a significantly higher homocysteine concentration as compared to those transplant recipients who were not prescribed a calcineurin inhibitor [16.3 (12.7, 21.4) vs. 14.3 (11.0, 17.8) μmol/l respectively, p = 0.004].

Of the 378 renal transplant recipients recruited in this study, 84 had a known history of cardiovascular disease

Table 3. Biological and biochemical differences in the renal transplant recipients who had died at follow-up as compared to the renal transplant recipients who were still alive at follow-up

	Deceased (n = 73)	Survivors (n = 305)	Significance
Age, years	57.4 ± 14.1	45.5 ± 13.5	<0.001
Male	45	198	0.773
Cardiovascular disease at enrolment	33	51	<0.001
Systolic blood pressure, mm Hg	135 ± 14	131 ± 14	0.031
Total cholesterol, mmol/l	5.2 ± 1.1	5.3 ± 1.0	0.478
HDL cholesterol, mmol/l	1.4 ± 0.5	1.4 ± 0.4	0.717
Diabetic	17	37	0.014
Smokers	13	59	0.764
eGFR, ml/min/m^2	45.9 ± 24.2	53.9 ± 19.0	0.009
hsCRP, mg/l	3.8 (1.9, 9.9)	1.7 (0.8, 3.9)	<0.001
Homocysteine, μmol/l	18.8 (14.2, 22.4)	15.1 (11.3, 19.5)	<0.001
Vitamin B_{12}, ng/l	412 (298, 651)	406 (286, 561)	0.251
Folate, μg/l	5.8 (4.5, 8.9)	5.7 (4.1, 8.8)	0.956

Results expressed as arithmetic mean ± standard deviation or median (inter-quartile range).

at enrolment (defined as a history of coronary artery disease and/or peripheral vascular disease and/or cerebrovascular disease). However, although the homocysteine concentration was greater in the participants with a known history of cardiovascular disease at enrolment as compared to those individuals without known cardiovascular disease, this did not reach statistical significance [16.2 (11.9, 21.2) vs. 15.4 (12.0, 20.1) μmol/l, p = 0.250]. There was no significant difference in vitamin B_{12} levels or serum folate levels in those renal transplant recipients with a known history of cardiovascular disease at enrolment compared to those individuals without known cardiovascular disease [395 (275, 539) vs. 409 (292, 580) ng/l, p = 0.672 and 5.4 (4.3, 8.9) vs. 5.9 (4.2, 8.8) μg/l, p = 0.951, respectively].

Mortality data was available for all participants. At follow-up, 305 participants were alive and 73 participants had died. Patients were divided into 2 groups based on survival at follow-up. Significant differences, as shown in table 3, included that those who had died during follow-up were older, more likely to be diabetic, have had a history of cardiovascular disease at enrolment, had lower eGFR, higher systolic blood pressure, and higher homocysteine concentrations as compared to those who were still alive at follow-up. However, as shown, there was no significant difference in vitamin B_{12} or serum folate concentrations in those renal transplant recipients who had died at follow-up as compared to those who were still alive at follow-up.

Of the 73 renal transplant recipients who had died, 27 had died of a cardiovascular cause, 36 from a non-cardiovascular cause and for 10 participants cause of death could not be accurately established. There was no significant difference in homocysteine concentration between those participants who had died from a cardiovascular cause as compared to those participants who had died of a non-cardiovascular cause [18.2 (14.0, 21.7) vs. 15.3 (11.4, 19.9) μmol/l, p = 0.342]. Similarly, there was no significant difference in vitamin B_{12} or serum folate concentrations in those who had died of a cardiovascular death as compared to those who had died of a non-cardiovascular death (p = 0.187 and p = 0.567, respectively).

In univariate analysis, as shown in figure 1, homocysteine concentration banded into thirds was a significant predictor of mortality (p < 0.001). However, neither vitamin B_{12} nor serum folate banded into thirds were significant predictors of all-cause mortality in Kaplan-Meier analysis (p = 0.827 and p = 0.919, respectively).

As shown in table 4, in multivariate analysis homocysteine remained a significant predictor of mortality following adjustment for traditional cardiovascular risk factors, i.e. age, gender, smoking, diabetes, systolic blood pressure, total cholesterol and HDL cholesterol (p = 0.01) and following adjustment for vitamin B_{12} and folate (p < 0.001). Interestingly, homocysteine also remained a significant predictor of mortality following adjustment for eGFR (p = 0.03) and 24-hour urine protein excretion (p = 0.002).

Table 4. Kaplan-Meier and Cox regression survival analysis for homocysteine concentration banded into thirds

	Kaplan-Meier significance	Cox regression analysis significance	exp(B)[a]	confidence interval
Homocysteine adjusted for traditional risk factors[b]				
<13.1 µmol/l	<0.001	0.01	1	
13.1–18.5 µmol/l			2.12	1.0, 4.2
>18.5 µmol/l			3.6	1.8, 7.1
Homocysteine adjusted for folate and vitamin B_{12}				
<13.1 µmol/l	<0.001	<0.001	1	
13.1–18.5 µmol/l			2.2	1.1, 4.5
>18.5 µmol/l			4.3	2.2, 8.5
Homocysteine adjusted for eGFR				
<13.1 µmol/l	<0.001	0.03	1	
13.1–18.5 µmol/l			1.7	0.8, 3.3
>18.5 µmol/l			2.5	1.2, 4.9
Homocysteine adjusted for proteinuria				
<13.1 µmol/l	<0.001	0.002	1	
13.1–18.5 µmol/l			2.2	1.0, 4.6
>18.5 µmol/l			3.6	1.8, 7.4

[a] Exp(B), or the odds ratio, is the predicted change in odds for a unit increase in homocysteine.

[b] Homocysteine adjusted for age, gender, diabetes, smoking, systolic blood pressure, total cholesterol and HDL cholesterol.

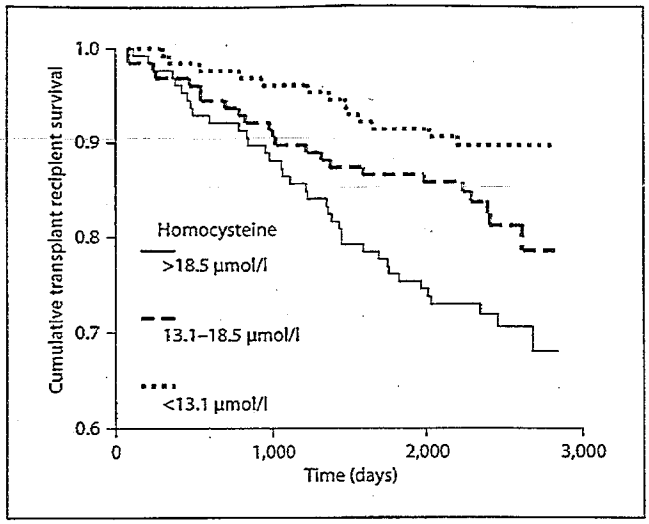

Fig. 1. Kaplan-Meier survival curve for renal transplant recipients stratified by homocysteine concentration banded into thirds.

Discussion

A raised homocysteine concentration is reported to be an independent risk factor for cardiovascular disease in the general population [5]. Prospective studies of patients with renal disease suggest that individuals with higher homocysteine levels are at increased risk of cardiovascular events and death [22, 26, 27].

In the renal transplant recipients enrolled in this study, homocysteine tended to be higher in those with a history of vascular disease at enrolment and was significantly higher in those renal transplant recipients who had died at follow-up as compared to those who were still alive at follow-up. Similarly, in Kaplan-Meier analysis those renal transplant recipients with an elevated homocysteine concentration had a significantly increased risk of mortality. However neither vitamin B_{12} nor serum folate was a significant predictor of all-cause mortality. Similar results have recently been reported in an older population [28].

Given the strong correlation between renal function and homocysteine, some commentators have likened measuring plasma homocysteine to an 'expensive creatinine' [29]. However, the results of this study demonstrated that homocysteine remained a significant predictor of mortality following adjustment for renal function.

Similarly, Winkelmayer et al. [27] also demonstrated an increased risk of mortality with increasing homocysteine concentration, independent of GFR, in a prospective study of renal transplant recipients. However, in patients with chronic kidney disease, Menon et al. [30] found no association between total homocysteine and all-cause mortality after adjustment for GFR.

Of interest, in our study, homocysteine concentration was significantly higher in the renal transplant recipients prescribed a calcineurin inhibitor as compared to those who were not prescribed a calcineurin inhibitor. The proposed mechanisms for this association include postglomerular vasoconstriction and consequent reduction in renal blood flow [31] and impaired remethylation of homocysteine to methionine [16].

However, whatever the association or mechanism for elevated homocysteine levels in patients with renal disease, the effect of reducing homocysteine concentration on cardiovascular outcome has not been established.

As in the general population [32], several studies have demonstrated that folic acid and vitamin B_{12} decreases

homocysteine levels in renal transplant recipients [21, 31, 33–35].

Interestingly however, the results of the Norwegian Vitamin Trial NORVIT found that although homocysteine levels were reduced in patients with an acute myocardial infarction treated with B vitamins, there was no significant effect on the primary composite endpoint of recurrent myocardial infarction, stroke and sudden death attributed to coronary artery disease as compared to those participants randomised to placebo [36]. Similar results have recently been reported by Albert et al. [14]. Despite significant lowering of homocysteine concentration, there was no reduction in cardiovascular events during a follow-up of 7.3 years in high-risk women receiving folic acid, vitamin B_6 and vitamin B_{12} as compared to those women receiving placebo [14].

Therefore, despite the association between homocysteine and vascular disease, the role of lowering homocysteine concentration as a method to reduce or prevent cardiovascular disease has not been proven.

The Folic Acid for Vascular Outcome Reduction in Transplantation FAVORIT trial has completed recruitment of several thousand renal transplant recipients into a randomized trial of folic acid, vitamin B_6 and vitamin B_{12} supplementation [37]. This trial is designed to assess whether there is a clinically relevant change in cardiovascular endpoints following reduction in total homocysteine in renal transplant recipients receiving high or lower dose folic acid multivitamins during a 4-year follow-up period.

Nevertheless our prospective cohort study, representative of the renal transplant recipients in Northern Ireland has yielded significant results. Confounding factors were limited by analysing a fasting sample for homocysteine, recruiting patients with stable graft function who were clinically well, more than 3 months post-transplant, and on standard immunosuppression regimens. In addition, factors known to influence homocysteine concentration were included as co-variates in the multivariate Cox regression survival analysis. Selection bias was minimised by the lack of formal exclusion criteria.

We acknowledge that there are some limitations to our study. This study was performed in a white renal transplant population in a single geographical region of the United Kingdom, so the applicability or generalisability of the results of this study to other geographical regions or ethnic groups is not established. Also, although data on history of cardiovascular disease was recorded, information on other comorbidities which could impact on mortality was not recorded at enrolment. We also acknowledge that despite our efforts to limit confounding, there may be residual confounding factors.

Nevertheless, this prospective study generated interesting results identifying elevated homocysteine concentration as an independent risk factor for increased mortality in a cohort of renal transplant recipients.

In summary, homocysteine is an intriguing biomarker for vascular disease. It correlates with many traditional cardiovascular risk factors and demonstrates a tight relationship with renal function. However, in the renal transplant recipients enrolled in this study, homocysteine was a significant predictor of mortality following adjustment for traditional cardiovascular risk factors and following adjustment for renal function. As the results of this prospective study of renal transplant recipients support the findings of Winkelmayer et al. [27], further research is needed to assess whether lowering homocysteine concentration will have an impact on the incidence of cardiovascular events or improve the survival of patients with a renal transplant.

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