ORIGINAL RESEARCH

What Is the Meaning of Homocysteine in Patients on Dialysis?

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Objective: To evaluate the determinants of total plasma homocysteine levels and their relations with nutritional parameters, inflammatory status, and traditional risk factors for cardiovascular disease in renal failure patients on dialysis treatment.

Design: The study was conducted on 70 clinically stable patients, 50 of them on hemodialysis (70% men; 55.3 ± 14.5 years) and 20 on peritoneal dialysis (50% men; 62 ± 13.7 years). Patients were analyzed in terms of biochemical parameters (serum lipids, creatinine, homocysteine [Hcy], creatine-kinase [Ck], folic acid, and vitamin B_{12}), anthropometric data, markers of inflammatory status (tumor necrosis factor-alpha, C-reactive protein, interleukin-6), and adapted subjective global assessment.

Results: The total prevalence of hyperhomocysteinemia (>15 μmol/L) was 85.7%. Plasma folic acid and plasma vitamin B_{12} were within the normal range. Multiple regression analysis ($r^2 = 0.20$) revealed that the determinants of total Hcy were type of dialysis, creatinine, Ck, folic acid, and total cholesterol. Hcy was positively correlated with albumin and creatinine and negatively correlated with total cholesterol, high density lipoprotein cholesterol, folic acid, and vitamin B_{12}.

Conclusions: The determinants of total Hcy in the study sample were type of dialysis, creatinine, Ck, folic acid, and total cholesterol. Evidently, the small sample size might have had an effect on the statistical analyses and further studies are needed. However, Hcy in patients on dialysis treatment may not have the same effect as observed in the general population. In this respect, the association between malnutrition and inflammation may be a confounding factor in the determination of the true relationship between Hcy, nutritional status, and cardiovascular risk factors in this group.

CHRONIC KIDNEY DISEASE (CKD) is frequently associated with metabolic and nutritional disorders, such as malnutrition and inflammation, which are considered to be important predictors of morbidity–mortality[1,2] in patients submitted to dialysis. Cardiovascular disease (CVD) is a major cause of the high mortality rate in end-stage renal disease patients. Among several CV risk factors, the markedly increased level of plasma total homocysteine (tHcy) in end-stage renal disease patients has been suggested to be an independent risk factor for CVD.[3,4]

In addition to renal dysfunction, the status of vitamins B_6, B_{12}, and folic acid, and the genetic polymorphisms of enzymes involved in Hcy metabolism can also influence total Hcy concentration in patients with CKD.[4,5] Thus, the decline of glomerular filtration rate may be associated with the increased plasma concentrations of Hcy.[6,7]

Hyperhomocysteinemia can be classified as moderate (16 to 30 μmol/L), intermediate (31 to 100 μmol/L), and severe (>100 μmol/L). Normal

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plasma levels range from 5 to 15 μmol/L.[8] The prevalence of hyperhomocysteinemia ranges from 85% to 100% in end-stage CKD patients, with values at least 3 times higher than the normal range.[9] As is also the case for healthy individuals, in uremic patients about 75% of plasma Hcy is protein-bound.[10]

Protein-energy malnutrition (PEM) is a common problem among patients on dialysis, with a 40% to 70% prevalence, and together with inflammation, it represents the main predictor of a poor clinical outcome for these patients. Patients also suffering from CVD have a high prevalence of malnutrition, hypoalbuminemia, and low protein intake.[11] PEM is assumed to predispose to inflammation and CVD, possibly because of the increased risk of infection or to an increased inflammatory response.[12]

The frequent contact with dialysis membranes, catheters, dialysate, or peritoneal fluid may represent a preinflammatory status. The increased release or activation of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) may not only promote catabolism with increased protein degradation and suppression of protein synthesis, but may also inhibit appetite and cause hypoalbuminemia.[11]

Several studies have suggested that decrease, and not an increase in Hcy concentration may be related to the higher prevalence of CVD and to a poor clinical outcome among patients with chronic renal diseases. This might be because of the association between low tHcy and PEM, a fact that, of itself, represents a known risk factor for a poor clinical outcome in patients submitted to dialysis.[13–16] This paradoxical association between tHcy and poor outcome in patients on dialysis is known as "reverse epidemiology."[3,11,17] The effects of malnutrition and inflammation are believed to play a significant role in the inversion of the association between risk factors and clinical outcome,[18] but it is unclear whether there is a significant association between tHcy and inflammation in patients on dialysis. Some studies have shown a positive correlation between tHcy and high mortality rates among patients on dialysis, whereas others have failed to show this association.[3,11,17]

The objective of the present study was to evaluate the relations between Hcy, nutritional parameters, inflammatory state, and serum lipids in patients on dialysis to clarify the real significance of hyperhomocysteinemia in this group.

Methods

Subjects

The study was conducted at a Nephrology Service in the municipality of Ribeirao Preto, State of São Paulo, Brazil. The sample consisted of 70 patients on dialysis treatment, 50 of them on hemodialysis (HD) and 20 on peritoneal dialysis (PD). Patients were evaluated 3 times, that is, at baseline and on 2 more occasions at 2 month intervals, for a total of 4 months of follow-up. Inclusion criteria were to have been on dialysis treatment for a minimum of 8 weeks and being 18 years old or older. The exclusion criterion was life expectancy of $<$6 months. In all, 12 patients were excluded during the study: 7 due to death, 3 due to renal transplantation, 1 due to a neurogenic tumor, and 1 due to prolonged hospitalization. Thus, 58 patients concluded the study. The study was approved by the Research Ethics Committee of the University Hospital, Faculty of Medicine of Ribeirão Preto, University of São Paulo (HCFMRP-USP); all patients gave written informed consent to participate.

Biochemical Parameters

Blood was collected before the dialysis session from a peripheral vein after a fast of 8 to 12 hours and analyzed by a laboratory on contract for the following routine biochemical data: creatinine, ferritin, iron, albumin, glucose, hemoglobin, hematocrit, urea (before and after dialysis), calcium, phosphorus, and potassium. The remaining analyses, vitamin B_{12}, folic acid, Hcy, creatine-kinase (Ck), IL-6 (reference value: $<$9.9 pg/mL), C-reactive protein (CRP; RV: $\leq$0.9 mg/dL), and TNF-α (RV: $<$8.1 pg/mL) were performed at the Nutrition and Metabolism Laboratory of FMRP/USP using automated chemiluminescence kits (Immulite - Siemens HealthCare Diagnostics, Deerfield, IL, USA). Lipid fractions and Ck were quantitated using colorimetric analysis kits (Labtest). The low density lipoprotein fraction (LDLc) was calculated by the formula of Friedewald et al.[19]: LDL = total cholesterol (TC) $-$ (TG/ 5 + HDLc) for TG values to a maximum of 300 mg/dL. The fraction of urea reduction from the beginning to the end of the HD session was used to calculate percent urea reduction and the Kt/V index.[20]

Nutritional Evaluation

Dry weight, height, arm circumference, abdominal circumference, and skinfolds (tricipital, bicipital, suprailiac, and subscapular folds) were measured. Body mass index (BMI), arm muscle circumference, and arm fat area were calculated and evaluated by the standard method adapted by Frisancho[21] Percent total body fat (% TBF) was estimated from the sum of the skinfolds by the equation of Durnin and Womersley.[22] Subjective global assessment adapted to the dialysis population as proposed by Kalantar-Zadeh et al.[23] was also performed for the classification of nutritional status into 5 groups according to the sum of scores.

Statistical Analysis

Data are reported as means ± standard deviation. Pearson correlation was used to determine associations between Hcy and nutritional parameters, and significant differences between the 2 types of dialysis were determined by a linear mixed effects (random and fixed effects) model. Multiple linear regression models were used to evaluate Hcy in relation to the anthropometric and biochemical parameters. The models were constructed with grouped variables and with those showing the highest association with Hcy being used as the dependent variable for the choice of the best model. The 95% confidence intervals were constructed for each estimate and the *P*-values were calculated for each one.

The analyses were obtained from the unadjusted multiple linear regression models because the small sample size and the large number of confounding variables interfered considerably with the adjusted model. The level of significance was set at $P < .05$. The SAS software (version 9.0. 2002, SAS Institute Inc., Cary, NC) was used for statistical analysis.

Results

Male patients predominated in the sample (64.3%) and 70% of the patients were on HD and 50% on PD. There was a significant difference between groups in terms of age (HD: 55.3 ± 14.5 years; PD: 62 ± 13.7 years) and time of dialysis (HD: 27.03 ± 21.9 months; PD: 36.65 ± 30.58 months). The cause of renal failure was unknown in 47.1% of the subjects and was reported to be caused by diabetic nephropathy in 27.1% and hypertensive nephrosclerosis in 17.1% of the subjects. HD showed good dialytic efficiency, with mean percent urea reduction values of 68.3% ± 7.2% and Kt/V 1.5 ± 0.3.

The anthropometric data of PD patients were significantly higher than those of HD patients (Table 1), except for the tricipital skinfold (TSF) and arm fat area, which were similar for the 2 groups (data not shown). Regarding BMI, there was a significant percentage of eutrophy (54.3%) and overweight/obesity (37.1%) in the sample as a whole. In the HD group, 10% of the patients were malnourished (vs. 5% of PD patients) and 30% were overweight or obese (vs. 55% of PD patients). However, on the basis of SGA, 97.1% of all patients presented nutritional risk (mild malnutrition).

Regarding the biochemical evaluation, the prevalence of hypoalbuminemia (<3.5 mg/dL) was 62% in HD patients and 75% in PD patients. Mean plasma Hcy concentration was significantly higher in HD than in PD patients and the prevalence of hyperhomocysteinemia was 87.7% for the sample as a whole (in the moderate form in 60% of cases and in the intermediate form in 25.7%). Mean plasma concentrations of folic acid and vitamin B_{12} were adequate, although the PD group had significantly higher folic acid and Ck values (Table 2). The plasma concentrations

Table 1. Anthropometric Parameters of Patients According to Dialysis Modality

Variables	HD	PD	Total	*P*-Value
Dry weight (kg)	60.8 ± 10	66.9 ± 17.6	62.5 ± 12.9	.01
BMI (kg/m^2)	22.8 ± 3.7	27.1 ± 6.7	24.1 ± 5.1	<.01
AC (cm)	87.5 ± 11.4	98 ± 14.7	90.5 ± 13.2	<.01
TBF (%)	26.5 ± 16	32.4 ± 11	28 ± 15.1	.04
AMC (cm)	22 ± 2.5	22.8 ± 2.9	22.2 ± 2.6	.01
AFA (cm^2)	30 ± 8.9	33.6 ± 10.5	31 ± 9.4	<.01

BMI, body index mass; AC, abdominal circumference; % TBF, percent total body fat; AMC, arm muscle circumference; AFA, arm fat area.

Values are mean ± standard deviation.

Table 2. Routine Biochemical Parameters of Patients According to Dialysis Modality

Variables	HD	PD	HD + PD	*P*-Value
Iron (mg/dL)	86.6 ± 4.47	105.5 ± 6.2	96.1 ± 5.3	.02
Albumin (g/dL)	3.6 ± 0.04	3.3 ± 0.06	3.3 ± 0.3	<.01
Glucose (mg/dL)	82.6 ± 3.2	100.4 ± 4.6	91.5 ± 3.9	<.01
Calcium (mg/dL)	9.2 ± 0.1	8.9 ± 0.1	9.1 ± 0.1	.02
Potassium (mEq/L)	5.8 ± 0.1	3.8 ± 0.2	4.8 ± 0.2	<.01
Hcy (μmol/L)	28.1 ± 11.9	22.2 ± 7.3	15.2 ± 1.6	.01
Folic acid (nmol/L)	19.5 ± 3.8	47.5 ± 5.4	33.5 ± 4.6	<.01
CK (U/l)	58.5 ± 9.7	125.6 ± 13.6	92.1 ± 11.7	<.01

Hcy, homocysteine; CK, creatine kinase.
Values are mean ± standard deviation.

of vitamin B_{12}, creatinine and total cholesterol did not differ between the 2 modalities of dialysis (data not shown).

Among the traditional risks for CVD, hypercholesterolemia and increased LDLc levels were present in 37.1% and 30% of the patients as a whole, respectively. Particularly important was the 70% prevalence of elevated LDLc in the PD group. Regarding the inflammatory markers, all HD patients had inflammation, as shown by TNF-α values higher than 81 pg/mL, by IL-6 levels higher than 9.9 pg/mL in 42% of patients, and by CRP levels higher than 0.9 mg/mL in 50% of patients. A similar situation was observed in the PD group, with all patients presenting inflammation according to TNF-α levels, 45% of them according to IL-6, and 40% according to CRP. There was no significant difference between modalities of dialysis.

The correlations detected between Hcy and other parameters at baseline showed that TSF and % TBF presented a significant inverse correlation with Hcy. Among the biochemical parameters, only creatinine showed a positive correlation with Hcy, whereas TC and folic acid presented a significant inverse correlation (Table 3).

Table 4 presents the correlation between Hcy and the other parameters evaluated at the 3 time points considered. It can be seen that only albumin showed a significant positive correlation with Hcy ($P = .008$) (Fig. 1), whereas vitamin B_{12}, folic acid, and HDLc showed a significant inverse correlation. The mean plasma concentrations of Hcy at the 3 time points studied were as follows: T0: 16.94 ± 7.67 μmol/L; T1: 17.52 ± 11.84 μmol/L, and T2: 15.04 ± 7.7 μmol/L; and T0 = T1 >72 ($P = .02$).

Multiple regression analyses between Hcy and the anthropometric variables were conducted in 3 models according to the group of variables, that is, anthropometric, biochemical, and inflammatory. When the best model was considered regarding all of these variables, an evident contribution of type of dialysis, creatinine, Ck, folic acid, and TC was observed (Table 5), but for patients with hypoalbuminemia (<3.5 g/dL), only the dialysis, creatinine, and folic acid variables continued to be determinants (Table 6).

Discussion and Conclusions

Hyperhomocysteinemia was detected in 85.6% of the total sample, with a predominance of the moderate form (60%) and with a higher prevalence in the HD group. The concentrations of vitamin B_{12} and folic acid were adequate and

Table 3. Correlations Between Homocysteine and Nutritional Parameters at Baseline

Variables	Coefficient	*P*-Value
Total cholesterol	−0.254	.034
Folic acid	−0.314	.009
Creatinine	0.241	.044
TSF	−0.251	.04
TBF	−0.24	.05

TSF, triceps skinfold tickness; TBF, percent total body fat.

Table 4. Analysis of the Correlations Between Homocysteine and Nutritional Parameters Obtained at 3 Different Times of Evaluation

Variables	Coefficient	*P*-Value
Vitamin B_{12}	−0.212	.003
Folic acid	−0.251	.001
HDLc	−0.231	.001
Albumin	0.193	.008

HDLc, high-density lipoprotein cholesterol.

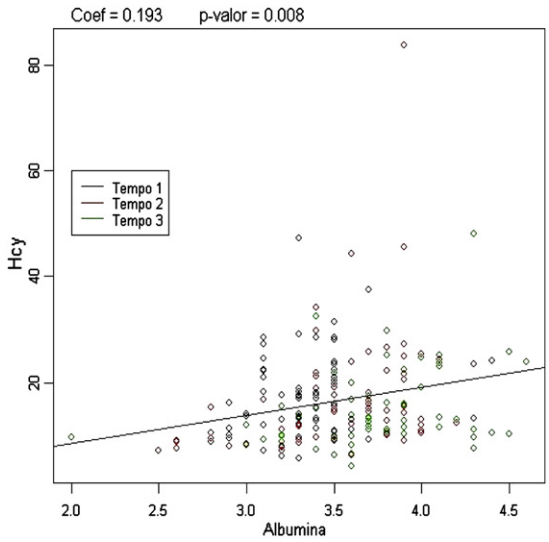

Figure 1. Correlation between homocysteine and albumin, considering the 3 evaluations. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

agreed with other studies[7,24] and were also inversely correlated with Hcy.

The main alterations in lipid profile were the presence of hypercholesterolemia and elevated LDL in both groups, with emphasis on PD. The lipid abnormalities arise when renal function starts to deteriorate and their prevalence is estimated to be approximately 45% to 50% in patients on dialysis.[25,26]

As expected, again, the inverse correlation between Hcy and vitamin B_{12} and folic acid was detected in these patients.[7,24] The patients showed a deficient nutritional status (according to SGA), hypoalbuminemia, and high plasma concentrations of inflammatory cytokines and CRP, suggesting an association between malnutrition and inflammation. A chronic

Table 5. Multiple Linear Regression Analysis with Homocysteine as the Dependent Variable ($r^2 = 0.20$)

Variables	Coefficient	95% CI	*P*-Value
Dialysis	7.15	3.46; 10.84	<.01
Creatinine	0.77	0.02; 1.51	.04
Creatine kinase	0.01	0.00; 0.03	.12
Folic acid	−0.10	−0.17; −0.03	.01
Total cholesterol	−0.04	−0.07; 0.00	.03

CI, confidence interval.

Table 6. Multiple Linear Regression Analysis with Homocysteine as the Dependent Variable in the Group of Patients with Hypoalbuminemia ($r^2 = 0.20$)

Variables	Coefficient	95% CI	*P*-Value
Dialysis	6.77	2.36; 11.17	<.01
Creatinine	1.12	0.06; 2.17	.04
Folic acid	−0.08	−0.16; 0.00	.04

CI, confidence interval.

inflammatory state is common in patients on dialysis, and markers such as CRP may be more than the reference values in 30% to 50% of them.[27]

The changes in plasma lipid profile were quite significant and were marked by the presence of dyslipidemia in both groups, especially in PD patients. Lipid abnormalities arise when renal function starts to deteriorate and their prevalence among patients on dialysis is estimated at approximately 45% to 50%.[25,26]

It is well known that there is no gold standard method for the evaluation of nutritional status,[2] and therefore it is interesting to use several indicators. In the present study, there was a significant positive correlation between classification according to SGA, BMI, and albumin. The patients presented hypoalbuminemia, elevated plasma concentrations of inflammatory markers, and deficient nutritional status (according to SGA), thereby suggesting a possible association between malnutrition and inflammation, which are considered to be indicators of a poor prognosis in HD.[28]

However, it is important to remember that, since albumin is a negative acute phase protein, its plasma concentration can be influenced by inflammation.[15] In patients maintained on dialysis, the presence of a chronic inflammatory state is common and markers such as CRP may be increased in a maximum of 50% of cases.[27] We did not detect any association between anthropometric parameters or inflammatory markers and total Hcy, in agreement with other reports.[16,29,30]

Kalantar-Zadeh et al.[16] observed that low Hcy levels were associated with hospitalization and mortality. However, this result is in contrast to that observed in the general population, in which high, rather than low, Hcy levels are associated with a poor clinical outcome.

Ducloux et al.[31] observed that Hcy was inversely correlated with all causes of mortality in

malnourished HD patients with inflammation. However, this association was not inverse in HD patients who did not present malnutrition or inflammation, suggesting that a potential interaction between Hcy and malnutrition and inflammation parameters may mask an independent role of Hcy in the survival rate.[32]

In the present study, Hcy was positively correlated with albumin and creatinine, as also reported by Akgul et al.[28] and Suliman et al.,[13] and negatively correlated with folic acid, vitamin B_{12}, TC, HDLc, TSF, and % TBF. Because 70% of body Hcy is bound to proteins, mainly albumin, this protein is a strong determinant of Hcy concentration. Singhal et al.[33] observed that Ck was elevated both in patients on HD and on PD and that its levels were positively correlated with muscle mass and negatively correlated with age, in addition to suggesting renal dysfunction as a contributing agent.

Considering simple correlations, Hcy was positively associated with albumin and creatinine and negatively associated with TC and folic acid. The regression analyses showed that the determinants of Hcy in the group as a whole were type of dialysis, creatinine, folic acid, Ck, and TC. It is clear that the small sample size may have had an effect on the statistical analyses and that further studies are needed. However, Hcy may not have the same significance in patients on dialysis, as observed for the general population. In this respect, the association between malnutrition and inflammation may be a confounding factor in the determination of the true relation between Hcy, nutritional status, and cardiovascular risk factors in this group of patients.

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