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Original article

Hyperhomocysteinemia in patients with mild chronic renal failure

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Abstract

Background: The aim of this study was to evaluate the prevalence of high plasma levels of homocysteine in patients with mild renal failure.
Methods: Forty-six chronic renal failure patients (25 males and 21 females, mean age 55.6 ± 14.4 years) were recruited for the study. Mean plasma creatinine was 2.1 ± 1.0 mg/dl and mean creatinine clearance was 50.6 ± 26.3 ml/min. Patients with severe renal failure were excluded. Patients were compared with a control group with normal renal function ($n = 35$, 22 men and 13 women, mean age 50.0 ± 11.5 years). Plasma homocysteine values were measured in both groups at baseline and after an oral overload of methionine.
Results: Baseline homocysteine levels of patients were higher than those of controls (16.5 ± 7.3 vs. 10.4 ± 4.2 μmol/l, $p < 0.0001$). Some 34 patients and 4 controls had increased plasma homocysteine levels at baseline. After the oral overload, 4 more patients had abnormally increased homocysteine levels, meaning that 83% of the patients with chronic renal failure had hyperhomocysteinemia.
Conclusions: Hyperhomocysteinemia is a very common finding among patients with mild renal failure. The need for vitamin supplementation should be evaluated in the first stage of chronic renal failure.

Keywords: Homocysteinemia; Chronic renal failure

1. Introduction

Retrospective and prospective studies have demonstrated that hyperhomocysteinemia is a risk factor for premature cardiovascular disease [1,2] independent of other classical risk factors, such as smoking, hypercholesterolemia, arterial hypertension, and diabetes [3]. Chronic renal failure is another important risk factor, not only for premature atherosclerosis but also for its rapid progression, because the risk of cardiovascular and peripheral vascular disease is associated with the metabolic abnormalities involved in uremia [4]. Moderate hyperhomocysteinemia is common in the general population and has been linked to cardiovascular disease [5]. The combined presence of two risk factors for atherosclerosis, such as diabetes and hyperhomocysteinemia, strongly increases the risk of cardiovascular disease [6,7].

Hyperhomocysteinemia has a high prevalence among patients with end-stage renal disease, which may contribute to the very high cardiovascular risk in these patients [8]. The prevalence of hyperhomocysteinemia among patients with mildly impaired renal failure is less well known, although it has been demonstrated that homocysteine levels are closely related to plasma creatinine [9]. Moreover, some studies of end-stage renal failure and of diabetic patients have shown that the glomerular filtration rate is a strong determinant of plasma homocysteine and cysteine concentrations [10–12].

There is a considerable amount of information on homocysteine levels among patients receiving renal replacement therapy [13–30] including kidney graft recipients [31,32]. Less information has been published about patients with end-stage renal failure [8,9,21,33], and there are few

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Table 1
Causes of chronic renal failure

Vascular nephropathy	17
Interstitial nephropathy	11
Glomerulonephritis	8
Diabetic nephropathy	5
Other/unknown	5
Total	46

reports on earlier stages of renal failure (creatinine clearance < 50 ml/min) [34–36]. Only one report demonstrated higher blood homocysteine levels in mild renal failure (creatinine clearance 35–70 ml/min). This does not necessarily imply a greater prevalence of pathological homocysteine values in this group of patients. The question that needs to be answered is whether an increase in plasma homocysteine due to mild renal failure exceeds the threshold value for diagnosis and treatment of hyperhomocysteinemia. The aim of the present study was to assess the prevalence of true hyperhomocysteinemia in a group of patients with mild chronic renal failure.

2. Methods

2.1. Patients and controls

Forty-six patients (25 males and 21 females, mean age 55.6±14.4 years) with established mild renal failure (creatinine clearance ≥ 40 ml/min and < 80 ml/min) were studied. The causes of renal failure are summarized in Table 1. Thirty-five normal controls (22 men and 13 women, mean age 50.0±11.4 years) were selected and recruited in the outpatient clinic after renal disease or failure was excluded. Plasma creatinine, creatinine clearance, total cholesterol, and plasma triglycerides were recorded. There were 11 smokers in the patient group and 14 in the control group. Seventeen patients and four controls were diabetics. Thirty-seven patients were hypertensive, as were 31 controls.

2.2. Determination of total plasma homocysteine

Total fasting plasma homocysteine was measured in samples drawn at the time of the study by fluorescence polarization immunoanalysis. All forms of plasma homocysteine were determined in this analysis, including reduced (homocysteine) and oxidized (homocysteine, homocysteine–cysteine mixed disulfide, and protein-bound homocysteine mixed disulfide) forms. These forms are collectively referred to as total plasma homocysteine. A total plasma homocysteine level of 10.4 μmol/l for men and 11.4 μmol/l for women was used as a threshold value to diagnose hyperhomocysteinemia. Patients were given an oral overload of methionine (100 mg/kg) and blood samples were taken 5 h after intake. The test was considered positive when total plasma homocysteine after overload was greater than 25 μmol/l.

2.3. Statistical analysis

Results are expressed as mean±1 standard deviation. The Kolmogorof-Lilliefors test showed that plasma homocysteine levels did not follow a normal distribution. Consequently, these values were compared using the Mann–Whitney test for non-paired data and the Wilcoxon rank test for paired data. Other continuous values were compared using the non-paired Student's *t*-test. The chi-square test was used to challenge discrete data. All statistical tests were two-sided. Pearson coefficients were used to assess linear correlations. *P* values below 0.05 were considered to be significant. Analysis was done with the G-Stat statistical package.

3. Results

Total blood homocysteine levels of patients at baseline were nearly twice those of controls (16.5±7.3 μmol/l vs. 10.4±4.2 μmol/l, respectively; $p<0.0001$, Mann–Whitney test). After the oral overload, the mean plasma homocysteine levels did not differ between the two groups (patients 37.4±18.1 μmol/l; controls 31.6±13.2 μmol/l; $p=0.165$, not significant, Mann–Whitney test); however, the increment was highly significant for both groups (patients $p<0.0001$; controls $p=0.00002$ Wilcoxon rank test; Fig. 1). The mean increment of plasma homocysteine levels after the methionine overload did not differ between the two groups (patients 20.3±18.5 μmol/l, controls 21.1±10.9 μmol/l, not significant, Mann–Whitney test).

Plasma creatinine and total plasma homocysteine levels showed a statistically significant correlation by single linear regression (Pearson coefficient 0.72, $p<0.0001$; Fig. 2). Creatinine clearance and homocysteine also showed a negative significant relationship (Pearson coefficient − 0.51, $p=0.000002$).

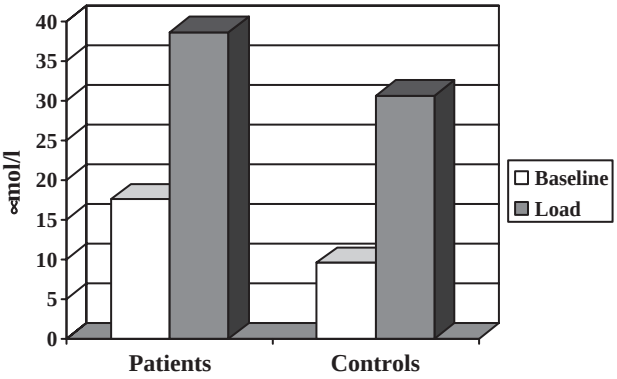

Fig. 1. Plasma homocysteine levels are significantly higher in patients than in controls, both at baseline and 5 h after an oral methionine load.