JMB 2007; 26 (1) DOI: 10.2478/v10011-007-0008-6

UDK 577.1 : 61 **ISSN 1452-8258**

JMB 26: 42–45, 2007

Original paper
Originalni naučni rad

HYPERHOMOCYSTEINEMIA IN CHRONIC RENAL INSUFFICIENCY

HIPERHOMOCISTEINEMIJA U HRONIČNOJ BUBREŽNOJ INSUFICIJENCIJI

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Summary: Hyperhomocysteinemia is an independent risk factor for premature cardiovascular disease. Since the homocysteine level is elevated in patients with advanced chronic renal insufficiency, it has been presented as an important factor contributing to the development of cardiovascular complications in these patients. In this study we examined the level of homocysteine in patients with mild-moderate degree of glomerular filtration rate reduction (creatinine clearance >40 mL/min and <80 mL/min/1.73 m^2). Thirty patients (f=15, m=15) were compared with healthy subjects (n=32, f=17, m=15). Blood samples were collected and subjected to assays for homocysteine, creatinine, creatinine clearance. The results show that homocysteine levels of patients were significantly higher than those of healthy subjects (12.75 ± 3.9 vs. 8.5 ± 1.75 μmol/L, p<0.001). The obtained results also show a significant negative relationship between the level of homocysteine and creatinine clearance (r=–0.8). In conclusion, hyperhomocysteinemia is a common finding not only in advanced chronic renal insufficiency, but also in patients with mild-moderate reduction of glomerular filtration rate, and may significantly contribute to premature development of cardiovascular complications.

Keywords: homocysteine, chronic renal insufficiency

Kratak sadržaj: Hiperhomocisteinemija je nezavistan faktor rizika za razvoj kardiovaskularnih bolesti. Povišen nivo homocisteina nalazi se i u bolesnika sa uznapredovalim stadijumima hronične bubrežne insuficijencije i predstavlja jedan od značajnih doprinosnih faktora za nastanak učestalih kardiovaskularnih komplikacija u ovih bolesnika. U ovoj studiji ispitivan je nivo homocisteina u bolesnika sa blagim odnosno umerenim stepenom redukcije jačine glomerulske filtracije (klirens kreatinina 40–80 mL/min/1,73 m^2). Trideset bolesnika (ž=15, m=15) upoređeno je sa kontrolnom grupom zdravih ispitanika (n=32, ž=17, m=15). Određivani su sledeći parametri: homocistein, kreatinin, klirens kreatinina. Rezultati pokazuju da je nivo homocisteina u bolesnika sa hroničnom bubrežnom insuficijencijom značajno viši u odnosu na kontrolnu grupu (12,75 ± 3,9 vs. 8,5 ± 1,75 μmol/L, p<0,001). Rezultati takođe pokazuju značajnu inverznu korelaciju između homocisteina i klirensa kreatinina (r=–0,8). Može se zaključiti da se hiperhomocisteinemija nalazi ne samo u bolesnika sa uznapredovalom hroničnom bubrežnom insuficijencijom, već i u bolesnika sa blagim-umerenim stepenom redukcije jačine glomerulske filtracije, što može značajno doprineti ranom razvoju kardiovaskularnih komplikacija.

Ključne reči: homocistein, hronična bubrežna insuficijencija

Introduction

Hyperhomocysteinemia is considered an independent risk factor for atherosclerosis in patients with normal renal function (1) and defined as a plasma total homocysteine level above 12 μmol/L.

Endothelial dysfunction contributes to the complex changes that occur within the vessel wall during hyperhomocysteinemia. Many studies have suggested that the bioactivity of endothelium-derived NO is reduced during hyperhomocysteinemia and that increased oxidative stress and levels of reactive oxygen species play a key role in the vascular changes elicited by hyperhomocysteinemia (2). Impaired endothelial vasomotor responses have been ascribed to reduced bioavailability of nitric oxide due to autooxidation of homocysteine in plasma which leads to oxidative inactivation of nitric oxide (3). Other potential consequences of hyperhomocysteinemia include general hypomethylation due to inhibition of the

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transmethylation pathway, posttranslational protein modification and/or damage by homocysteine-thiolactone, a highly reactive compound formed by methionyl-tRNA synthetase, and enhanced endoplasmic reticulum stress, which involves disruption of the folding and the processing of the newly synthesized proteins in the endoplasmic reticulum (4).

Homocysteine transsulfuration and remethylation enzymes are present in human kidney tissue, indicating that metabolism is possible. Studies in the rat have shown that homocysteine is taken up and metabolized by the kidney (5). Plasma homocysteine is increased in patients with chronic renal failure and could be linked to their high cardiovascular morbidity and mortality (6). Hyperhomocysteinemia has high prevalence among patients with end-stage renal disease (7), but the prevalence of hyperhomocysteinemia among patients with mildly impaired renal failure is less well known (8). There are few reports on the earlier stages of renal failure (9).

As for the cause of hyperhomocysteinemia in renal insufficiency, it was previously thought that impaired renal excretion could be responsible, but it has been ascertained that homocysteine excretion is negligible. The association between hyperhomocysteinemia and renal dysfunction may therefore be causal, i.e. renal failure causes elevated plasma homocysteine levels, but the relationship may also be due to other confounding factors, which, on the one hand lead to renal dysfunction and, on the other hand, cause hyperhomocysteinemia by different mechanisms. Two, not mutually exclusive hypotheses for the first possibility are: (i) homocysteine disposal in the kidneys themselves is disturbed, and (ii) extrarenal homocysteine metabolism is impaired (4).

The aim of the present study was to assess the prevalence of true hyperhomocysteinemia in a group of patients with mild-moderate chronic renal insufficiency.

Material and Methods

In this cross-sectional study thirty patients (15 females and 15 males, mean age 52.9 ± 11.6 years) with established mild-moderate chronic renal insufficiency (creatinine clearance between 40–80 mL/min/ 1.73 m^2) were studied. We can consider renal insufficiency as chronic if the decline of glomerular filtration rate lasts 3–6 months (10). Patients with folic acid and vitamin B_{12} supplementation were excluded.

The control group included thirty two healthy subjects (17 females and 15 males, mean age 46 ± 12.2 years).

Total plasma homocysteine, creatinine and creatinine clearance were recorded. Total fasting plasma homocysteine was measured in samples drawn at the time of the study by fluorescence polarization immunoanalysis (AxSYM analyzer, Abbott reagents). All forms of plasma homocysteine were determined in this analysis, including reduced and oxidized forms. These forms are collectively referred to as total plasma homocysteine. Plasma creatinine and creatinine clearance were examined by standard biochemical methods (Jaffe method with deproteinization of serum using Boehringer reagents).

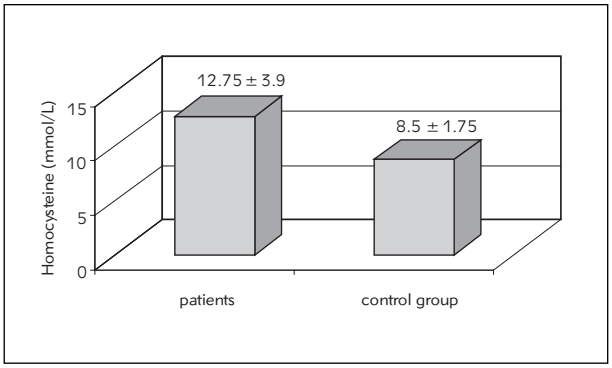
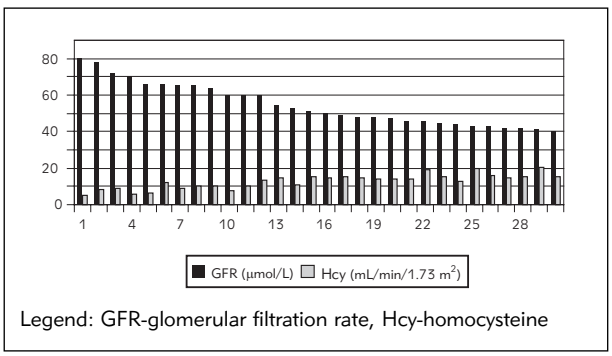


Figure 1 Mean values of plasma homocysteine ± SD in both groups.



Legend: GFR-glomerular filtration rate, Hcy-homocysteine

Figure 2 Link between homocysteinemia and glomerular filtration rate.

Statistics

Statistical analyses were performed using Microsoft Office Excel program package 2003. Results are expressed as mean ± SD. The following statistic methods were performed: f-test, t-test, correlation and single linear regression.

Results

Our group of patients had mean plasma creatinine value of 124.2 ± 24.5 µmol/L and mean creatinine clearance 56.8 ± 11.2 mL/min/1.73 m^2/L. Total blood homocysteine levels of patients were higher than those of controls ($p<0.001$) (*Figure 1*).

Most of the patients with glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 had homocysteine

levels above 12 μmol/L and most of the patients with GFR≥60 mL/min/1.73 m^2 had homocysteine levels below 12 μmol/L. One patient with hyperhomocysteinemia had homocysteine over 20 μmol/L. The other hyperhomocysteinemic patients had homocysteine below 20 μmol/L. These data show that moderate hyperhomocysteinemia has high prevalence in mildly-moderate renal insufficiency (*Figure 2*).

Creatinine clearance and total plasma homocysteine levels showed a statistically significant inverse correlation by linear regression ($r=-0.8$, $p<0.0001$).

Discussion

In patients with chronic renal insufficiency, the risk of cardiovascular morbidity and mortality is substantially increased (11). In addition to the well-known cardiovascular risk factors such as diabetes mellitus, hypertension, obesity, and dyslipidemia, parameters such as elevated serum levels of CRP, fibrinogen, and total Hcy have been defined as cardiovascular risk factors. Only recently has the high prevalence (~10%) of mild to moderate renal insufficiency in the population been recognized (12, 13). Moreover, renal insufficiency itself appears to be a major predictor of cardiovascular mortality, in the general population as well as in subjects with cardiovascular disease (14, 15).

In mild renal insufficiency risk factors are already highly prevalent (16). A moderate increase of plasma homocysteine occurs in the early stages of chronic kidney disease and increase as renal function decreases, indicating the important role of the kidney in the homocysteine metabolism (17, 18). In the present study we found high prevalence of hyperhomocysteinemia in a sample of patients with mild-moderate renal insufficiency. Similar results have been observed in the study of Robles et al. (8), but mean values of homocysteine in our patients were lower than in the study of Robles et al. (12.75 ± 3.9 *vs.* 16.5 ± 7.3 μmol/L). In this study, the highest value of homocysteine in patients was about 20 μmol/L. It suggests that mild-moderate hyperhomocysteinemia is characteristic of mild-moderate chronic renal insufficiency. Bostom et al. (19) found moderately elevated plasma homocysteine level in patients with diagnosed chronic kidney disease.

Our study showed that hyperhomocysteinemia occurs at GFR about 60 mL/min/1.73 m^2, and that levels of homocysteine strongly depend on GFR. Van Guldener (4) has reported that hyperhomocysteinemia occurs at GFR about 60 mL/min, and when end-stage renal disease has been reached, the prevalence of hyperhomocysteinemia is 85–100%. We found that homocysteine levels and GFR showed a negative significant relationship ($r=-0.8$, $p<0.0001$). In their study, Leskinen et al. (20) showed the strong relation between creatinine clearance and total homocysteine ($r=-0.79$, $p<0.01$). Robles et al. also found a significant negative relationship ($p=0.00002$). Recent study of Ninomiya et al. (21) has linked higher homocysteine levels to a greater decline in GFR. Nerbass et al. (22) found high prevalence of hyperhomocysteinemia in patients with moderate to severe renal impairment, and the determinants of total homocysteine levels were creatinine clearance, plasma folate, and plasma vitamin B_{12}. These evidence suggest that the kidney plays a prominent role in the homocysteine metabolism, although the pathogenesis of hyperhomocysteinemia in renal disease remains still unclear.

To summarize, the homocysteinemia rise in mild-moderate chronic renal insufficiency and the levels of homocysteine are higher in patients with lower glomerular filtration rate. Monitoring of the mentioned parameters in these patients is necessary to evaluate the risk for cardiovascular disease and to determine the need to implement vitamin supplementation therapy. In patients with chronic renal failure, possible tools conducive to the reduction of homocysteine levels are folate therapy and therapy with betaine, serine, *N*-acetylcysteine, or B vitamins (vitamin B_6, B_{12}, and B_2) (23).

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Received: January 10, 2007

Accepted: January 29, 2007