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The influence of estimated creatinine clearance on plasma homocysteine in hypertensive patients with normal serum creatinine

Yen-Hung Lin [a,d], Kuan-Yin Pao [c], Vin-Cent Wu [a,d], Yu-Li Lin [f], Yu-Fen Chien [b], Chi-Sheng Hung [a,d], Yu-Jen Chen [b], Chung-Pin Liu [g], I-Jung Tsai [e], Churn-Shiouh Gau [c], Kwan-Dun Wu [d], Juey-Jen Hwang [a,d,*]

[a] *Department of Internal Medicine, National Taiwan University Hospital Yun-Lin Branch, Yun-Lin, Taiwan*
[b] *Division of clinical pathology, National Taiwan University Hospital Yun-Lin Branch, Yun-Lin, Taiwan*
[c] *Graduate Institution of Clinical Pharmacy, National Taiwan University College of Medicine, Taipei, Taiwan*
[d] *Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*
[e] *Pediatrics, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*
[f] *Department of Business Administration, Chihlee Institute of Technology, Taipei, Taiwan*
[g] *Department of Internal Medicine, Yuan's General Hospital, Kaoshung, Taiwan*

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Abstract

Objectives: To examine the relation of estimated creatinine clearance (eCrCl) and plasma total homocysteine (tHcy) in hypertensive patients with a normal serum creatinine level.

Design and methods: A total of 137 hypertensive patients (mean age 66.6 years, 69 men) with serum creatinine level ≤1.5 mg/dL gave 10-h fasting blood samples for measurement of tHcy, serum folic acid, and serum vitamin B_{12}.

Results: 95 patients fell into a chronic renal insufficiency (CRI) group (eCrCl ≤ 60 mL/min/1.73 m^2) and 42 into a normal renal function (NRF) group (eCrCl > 60 mL/min/1.73 m^2). The CRI group was older ($p<0.001$), had higher tHcy ($p<0.001$), higher serum urea nitrogen ($p<0.001$), higher serum creatinine ($p<0.001$), lower eCrCl ($p<0.001$), and lower diastolic blood pressure ($p=0.001$). In univariate analysis, eCrCl had the strongest correlation with tHcy ($r=-0.453$, $p<0.001$). Significant correlations, ranging in decreasing order from $r=-0.418$, $p<0.001$ to $r=-0.170$, $p=0.047$, were also noted between tHcy and twelve other variables. In multivariate analysis, only eCrCl ($p<0.001$), usage of fibrate ($p<0.001$), serum level of vitamin B_{12} ($p=0.002$), serum level of folic acid ($p=0.009$), and smoking ($p=0.027$) were independent predictors of tHcy.

Conclusion: eCrCl is a strong independent predictor of tHcy in hypertensive patients with normal serum creatinine.

Keywords: eCrCl; Folic acid; Homocysteine; Serum creatinine; Vitamin B_{12}

Introduction

Hypertension is a major risk factor for both renal disease and cardiovascular disease (CVD) [1]. Several large trials have demonstrated a renal–cardiovascular association in hypertensive patients with mild to moderate renal insufficiency [2–6]. In the Hypertension Detection and Follow-up Program study, the baseline serum creatinine level had a significant prognostic value for 8-year mortality, even in patients with a normal serum creatinine [4]. Although the underling mechanism is still unknown, the increased cardiovascular risk for patients with mild renal insufficiency is probably contributed by higher tHcy, increased systemic inflammation and hypercoagulability, and nephrosclerosis [7–10].

Elevated tHcy has been implicated recently as a potential atherogenic agent and a risk factor for CVD [11–14]. The

* Corresponding author. Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, No. 7, Chung-Shan South Road, Taipei, Taiwan. Fax: +886 2 23224263.
E-mail address: juey@ha.mc.ntu.edu.tw (J.-J. Hwang).

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kidneys play a major role in homocysteine clearance and metabolism [15]. In animal studies, it has been confirmed that homocysteine is taken up and metabolized by the renal tubular cells [16–18]. Patients with mild to moderate renal disease also have significantly but moderately higher tHcy [15,19]. The hyperhomocysteinemic state of patients with decreased renal function involves the reduced clearance of tHcy more than increased delivery to plasma [15,20]. The reduction of clearance involves either a defect of intrarenal metabolism or a defect of uraemia-induced extrarenal metabolism [15].

Serum creatinine levels are frequently used as a screening test for renal dysfunction although the true glomerular filtration rate (GFR) is more accurate and precise [21]. Patients with normal serum creatinine level were identified by some laboratories as having abnormal renal function [22,23]. Estimation of creatinine clearance using the Cockroft–Gault formula is easy and clinically valuable [24,25]. However, the association between estimated creatinine clearance (eCrCl) and tHcy in hypertensive patients with a normal serum creatinine level is still unclear. Therefore, we conducted this study to examine these associations in hypertensive patients with a normal serum creatinine level.

Material and methods

Study population

In this cross-sectional study, we enrolled 137 medically treated ambulatory, hypertensive patients (69 men, mean age 66.6 years) who had a serum creatinine level ≤1.5 mg/dL and who received medical treatment or follow-up from September 2003 to April 2004 at the National Taiwan University Hospital in Taipei, Taiwan. The study was approved by the ethics committee of the National Taiwan University Hospital and all subjects gave informed consent.

We assessed eCrCl, which was calculated by using the Cockroft–Gault formula. Patients whose eCrCl was less than 60 mL/min/1.73 m^2 by the Cockroft–Gault formula [24] were defined as the chronic renal insufficiency (CRI) group and those with eCrCl>60 mL/min/1.73 m^2 as the normal renal function (NRF) group.

Coronary artery disease (CAD) was defined as at least 50% stenosis in one or more of the three coronary arteries or their primary branches as determined by coronary angiogram. Hyperlipidemia was defined as a total cholesterol level ≥240 mg/dL or total triglyceride ≥200 mg/dL, or under medication for hyperlipidemia. Diabetes mellitus was defined as blood glucose level of 126 mg/dL after an overnight fast or under medication for diabetes mellitus. Body mass index (BMI) was calculated by the computer as weight divided by height squared (kg/m^2).

Measurements of tHcy, serum folic acid, and serum vitamin B_{12}

Venous blood samples were collected in serum separation tubes and EDTA tubes after overnight fasting. After clotting and centrifugation, the serum was stored at −70 °C until analysis. Plasma was obtained immediately by centrifugation of the EDTA blood at 2000 rpm for 10 min, and stored at −70 °C until analysis. Total homocysteine concentrations were measured by fluorescence polarization immunoassay (Abbott AXSYM System). The normal range of tHcy is 4.5–7.9 μmol/L in 30- to 59-year-old females, 6.3–11.2 μmol/L in 30- to 59-year-old males, and 5.8–11.9 μmol/L in >60-year-old persons. Elevated plasma tHcy level is defined as plasma tHcy level above the upper limit of the reference level according to their age and sex. Serum folic acid and vitamin B_{12} levels were measured by immunoassay with an IMMULITE 2000 analyzer and the corresponding kits (DPC, Los Angeles, CA). The normal range for folic acid was 3–17 ng/mL, and that for vitamin B_{12} was 193–982 pg/mL. Blood urea nitrogen and creatinine were measured by a TBA-200 FR automatic analyser (Toshiba, Tokyo, Japan).

Statistical analysis

Results were expressed as mean±SD (standard deviation) unless otherwise specified. Unpaired Student's *t* test was used to analyze continuous data, and either the Chi-square or the Fisher's exact test was used to analyze categorical data. The Spearman non-parametric correlation test was used to analyze the association between tHcy and its determinants. Significant determinants in the Spearman non-parametric correlation test were then tested by the multivariate linear regression test with stepwise subset selection to identify independent factors predicting tHcy. Statistical analyses were performed with SPSS for Windows version 10.0 (SPSS Inc, Chicago, IL). A value of $p<0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics of patients

For all study participants, the serum creatinine level was 1.0±0.2 mg/dL, the eCrCl was 56.1±16.0 mL/min/1.73 m^2, and the plasma tHcy was 10.6±3.7 μmol/L. There were 42 patients (30.7%) with elevated plasma tHcy. There were 95 patients in the CRI group and 42 patients in the NRF group. The baseline characteristics of patients are listed in Table 1. Patients in the CRI group were older ($p<0.001$), had higher tHcy ($p<0.001$), a higher serum urea nitrogen level ($p<0.001$), a higher serum creatinine level ($p<0.001$), lower eCrCl ($p<0.001$), and lower diastolic blood pressure ($p=0.001$) than patients in the NRF group. Besides, the percentage of patients with elevated plasma tHcy was borderline high in the CRI group ($p=0.05$). There were no differences in gender, serum vitamin B_{12}, serum folic acid, BMI, prevalence of diabetes mellitus, hyperlipidemia, smoking, coronary artery disease, systolic blood pressure, pulse pressure, usage of anti-hypertensive agents, and usage of lipid-lowering agents between these two groups.