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# The Relationship between Micro Albuminuria and Plasma Homocysteine Level in Chinese Patients with Hypertension

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## Abstract

**Objective:** To explore the relationship between plasma homocysteine (Hcy) and micro albuminuria in Chinese patients with hypertension.

**Methods:** 150 Chinese patients with hypertension were enrolled from October 2012 to April 2013 in Zhabei Central Hospital and Tongji hospital in Shanghai. Plasma level of Hcy, micro albuminuria, total cholesterol, triglyceride, low density lipoprotein, high density lipoprotein and fasting blood-glucose were measured, meanwhile possible related risk factors such as smoking, alcohol drinking were assessed. The enrolled patients were divided into two groups according to the plasma level of Hcy: hyperhomocysteinemia (Hcy) group (Hcy>15 μmol/L, male 41 cases, female 39 cases) and non- Hcy group (Hcy ≤ 15 μmol/L, male 32 cases, female 38 cases).

**Results:** The level of microalbuminuria was increased with the level of plasma Hcy .Microalbuminuria were higher in Hcy group (30.34 ± 8.85 mg/L) than in non- Hcy group (16.65 ± 3.28 mg/L, P<0.05); 2.Correlation analysis showed that the levels of plasma Hcy related positively with micro albuminuria (r=0.946, P<0.01). There were no significant correlation between Hcy and total cholesterol, triglyceride, low density lipoprotein, high density lipoprotein, fasting blood glucose (P>0.05).

**Conclusion:** Hcy is associated with a higher incidence of microalbuminuria in patients with hypertension.

**Keywords:** Hypertension; Homocysteine; Micro albuminuria

## Introduction

Chronic Kidney Disease (CKD) and its associated morbidity pose a worldwide health problem. Cardiovascular disease is the leading cause of premature death among the CKD population [1]. Microalbuminuria is a marker of renal injury that can often be detected earlier than any tangible decline in glomerular filtration rate. As well as being a risk marker of renal dysfunction, micro albuminuria is now widely accepted as an independent risk factor for cardiovascular morbidity and mortality [2]. The elevation of homocysteine (Hcy) level is now known as an independent risk factor for vascular diseases and hyperhomocysteinemia (Hcy) is more common in Chinese patients with hypertension due to their special genetic background [3]. It can promote oxidant injury to the vascular endothelium, impairs endothelium-dependent vasomotor regulation, and may also alter the coagulant properties of the blood [4-5]. Whether Hcy has any effect on microalbuminuria in patients with hypertension has not been clarified as yet. The aim of this study was to assess the influence of Hcy on micro albuminuria in Chinese hypertension patients.

## Methods

### Participants

150 patients with hypertension were enrolled consecutively from October 2012 to April 2013 in Zhabei Central Hospital and Tongji hospital in Shanghai. The study participants consisted of 70 hypertensive patients without Hhcy, 80 hypertensive patients with Hhcy. All data were prospectively collected. Resting blood pressure (BP) values were obtained at a physician's office. Patients were advised to refrain from smoking or consumption of coffee or tea, and physical exercise, 30 min prior to the measurement. Before measurement, patients were seated to rest for 5 min. Two separate measurements were averaged to determine office blood pressure [6]. Hhcy was defined as a serum Hcy concentration higher than 15 μmol/l according to recommendations of Centers for Diseases Control [6-7]. Patients with previous coronary artery disease (CAD), diabetes mellitus, hyperuricemia, severe renal dysfunction, left ventricular systolic dysfunction, secondary HT, moderate-severe valve disease, atrial fibrillation, symptoms of CAD and equivalent findings on exercise electrocardiography and perfusion scan, or 24-h rhythm electrocardiography were excluded. All participants gave their informed consent.

### Laboratory measurements

Blood samples were drawn by venipuncture to measure routine blood chemistry parameters after fasting for at least 8 h. Fasting blood glucose, serum creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were recorded. Glucose, creatinine, and lipid profile were determined by standard methods. Hcy levels were determined with an assay kit (MAKER, China) based on an enzymatic cycling method.

The patients avoid strenuous activity in the 2 days prior to the urine test and keep fasting for at least 12 hours. Each patient provided 10 ml spot midstream urine sample that was collected aseptically into separate sterile bottles and submit for censorship immediately. The samples were assayed immuno-turbidometrically for urinary albumin

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concentration (UAC) using Gama radioimmunoassay counter (Anhui USTC ZONKIA Scientific Instrument Co Ltd, China) with intra- and inter-assay coefficients of variation of 2.17-4.78 at 11.6-142.8 mg/L UAC. Each assay was run in duplicates and results obtained were averaged. Normo-albuminuria was defined as UAC <19 mg/L, Microalbuminuria as UAC 19-174 mg/L.

### Statistical analysis

Continuous variables were given as mean ± standard deviation; categorical variables were defined as percentages. Group differences were compared using analysis of variance (ANOVA). Correlation testing by Pearson's method was used to assess univariate relationships between Hcy level and parameters related to hypertension. Probability values of $p<0.05$ were considered significant. All statistical analyses were carried out using statistical software (SPSS, version 17.0 for Windows; SPSS Inc., St. Louis, MO).

## Results

The basic characteristics of the groups are given in Table 1. 70 hypertensive without Hhcy (Hcy ≤ 15 μmol/L, 32 males, 38 females), and 80 hypertensive with Hhcy (Hcy>15 μmol/L, 41males, 39 females) were included in the study. The mean age was similar in the two groups (59.3 vs 59.5, p = 0.709). There were no significant differences between the two groups regarding 24h mean systolic/diastolic blood pressure and prevalence of main cardiovascular risk factors, such as smoking, age and blood lipids. There were no differences in their anti-hypertensive drug use, and theoretically those drugs have no effect on patients' Hcy levels.

The results of the urine micro albumin examination in the two groups are summarized in Table 2. We can see that with the increase of serum Hcy level, the patients' urinary micro albumin gradually increased (Figure 1). There were significant differences between the two groups regarding the urinary micro albumin level (16.65 mg/L vs 30.34 mg/L, $p<0.01$).

We also use Pearson correlation analysis to analysis the correlations between Hcy and parameters related to hypertension. The results are shown in Table 3. After corrections for age and body mass index, Hcy was significantly correlated with urine micro albumin but there were no significant correlation with total cholesterol, triglyceride, low density lipoprotein, high density lipoprotein and fasting blood glucose.

| | Hypertension without Hhcy (n=70) | Hypertension with Hhcy (n=80) | *p* value |
|---|---|---|---|
| Age, years | 59.3 ± 7.2 | 59.5 ± 7.5 | NS (0.709) |
| Female sex, n (%) | 38 (54.2) | 39 (48.8) | NS (0.517) |
| Smoking, n (%) | 24 (34.3) | 31 (38.8) | NS (0.613) |
| Drinking, n (%) | 37 (52.9) | 42 (52.5) | NS (1.000) |
| Disease's duration, months | 127 ± 122 | 136 ± 144 | NS (0.712) |
| Serum Total cholesterol (mmol/l) | 4.62 ± 0.72 | 4.63 ± 0.77 | NS (0.982) |
| Serum Triglyceride (mmol/l) | 2.19 ± 0.95 | 2.36 ± 1.09 | NS (0.374) |
| Serum glucose (mmol/l) | 4.86 ± 0.23 | 4.78 ± 0.26 | NS (0.510) |

**Table 1:** Baseline conditions.

| | Hypertension without Hhcy (n=70) | Hypertension with Hhcy (n=80) | *p* value |
|---|---|---|---|
| Serum homocysteine (μmol/L) | 10.83 ± 2.54 | 24.69 ± 6.84 | <0.01 |
| urine microalbumin (mg/L) | 16.65 ± 3.28 | 30.34 ± 8.85 | <0.01 |

**Table 2:** Serum homocysteine level and urine micro albumin.

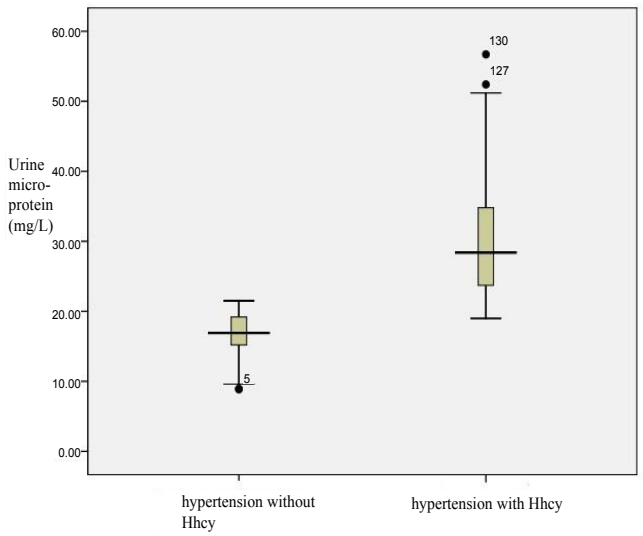


**Figure 1:** Distribution of symptoms and diagnosis of stroke by socio-demographic characteristics, Kingdom of Saudi Arabia, 2013.

| | r | p |
|---|---|---|
| urine microalbumin (mg/L) | 0.946 | 0.001 |
| total cholesterol (mmol/L) | -0.025 | 0.763 |
| Triglyceride (mmol/L) | -0.051 | 0.533 |
| low density lipoprotein (mmol/L) | 0.062 | 0.499 |
| high density lipoprotein (mmol/L) | 0.044 | 0.596 |
| fasting blood glucose (mmol/L) | -0.199 | 0.515 |

**Table 3:** Correlations of parameters related to hypertension with homocysteine level.

## Discussion

In the present study, it was demonstrated that there were strong relationship between Hcy level and urine micro albumin.

Hhcy has been linked to hypertension for the past decades. Even mild Hhcy is a major risk factor for arterial vascular disease, independent of conventional risk factors, such as diabetes mellitus, cigarette smoking, or hyperlipidemia. The mechanism may be related to impairment of vascular endothelial and smooth muscle cell function [8-12]. It has been suggested that Hhcy diminishes vasodilatation by nitric oxide, increases oxidative stress, alters the elasticity of the vascular wall, and contributes to elevate the blood pressure [13]. Human studies have shown that high levels of Hcy are associated with impaired endothelial-dependent vasodilatation in essential hypertension. It has been thought that an interaction between Hcy and endothelium in hypertensive patients may promote thrombogenesis and thermogenesis, leading to adverse cardiovascular events [14-16]. Leakage of small amounts of proteins in urine has been considered since 1980s a crucial sign of early kidney disease, especially in diabetic and hypertension patients. Microalbuminuria was shown to be a concomitant factor of several metabolic and no metabolic cardiovascular risk factors in patients with essential hypertension [17-19]. Yet the relationship between microalbuminuria and Hhcy has been inadequately studied. Our study aimed to assess microalbuminuria in hypertensive patients with or without Hhcy.

In our study, it was observed that the level of microalbuminuria increased with the level of serum Hcy. Micro albuminuria were higher

in Hhcy group (30.34 ± 8.85 mg/L) than in non-Hhcy group (16.65 ± 3.28 mg/L, P<0.05). Correlation analysis also showed that the levels of plasma Hcy had positive relationship with micro albuminuria (r=0.946, P<0.01). Several mechanisms have been proposed to explain the reason for the results. Recent studies suggested that Hcy is toxic to kidney tissues. Diet induced chronic Hhcy could induce arterial and arteriolar thickening, and tubulointerstitial and podocyte injury in the kidney [20,21]. Regarding the mechanism of Hcy-induced glomerular injury, Hcy was shown to activate MAP kinases and to induce endoplasmic reticulum stress in cultured meningeal cells [22]. It was also shown that Hcy stimulates ceramide-mediated redox signaling [23], and increases monocyte chemo attractant protein-1 expression in the kidney via nuclear factor-kappaB activation [24]. These studies suggest that Hhcy may play a causative role in early renal injury, in addition to being a marker of impaired renal function [25,26]. Since Hcy has been shown to cause cardiovascular disease and endothelial damage [27-30], Hhcy in hypertension patients may lead to endothelial dysfunction in systemic and renal blood vessels, and predispose these patients to increased risks of microalbuminuria.

In summary, it was shown that Hhcy associated with a higher incidence of microalbuminuria in patients with hypertension. Further studies in larger populations are needed to confirm these findings, and to test whether lowering of plasma Hcy by dietary manipulation [31] is helpful for patients at risk for hypertensive nephropathy.

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