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Plasma High-Sensitivity C-Reactive Protein Level is Associated with Impaired Estimated Glomerular Filtration Rate in Hypertensives

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Background: Both inflammation and chronic kidney disease (CKD) are related to cardiovascular disease. Whether inflammatory biomarkers are associated with impaired glomerular filtration rate (GFR) is unclear in hypertensives.
Methods: We recruited hypertension patients from the cardiovascular clinic of a tertiary medical center in Taiwan. GFR was calculated using the 7-item Modification of Diet in Renal Disease (MDRD) study equation and impaired GFR (IGFR) was defined as GFR less than 60 ml/min/1.73 m^2. High-sensitivity C-reactive protein (hsCRP) kits were used for the measurement of the CRP levels.
Results: In our study, 572 consecutive hypertensive patients were enrolled. The range of patient age was 26-91 years (mean 60.5 $\pm$ 11.7), and hsCRP and GFR ranged from 0.01 to 9.99 mg/L and 16.6 to 239.6 ml/min//1.73 m^2, respectively. HsCRP levels were correlated with GFR ($p = 0.01$) and the presence of IGFR ($p = 0.009$). Multivariate regression analysis showed hsCRP ($p = 0.03$), age ($p < 0.001$) and urinary albumin-to-creatinine ratio (UACR) ($p = 0.002$) are independent factors associated with GFR. Furthermore, hsCRP levels [odds ratio (OR) = 1.16, 95% CI = 1.03-1.31, $p = 0.02$], age (OR = 1.09, 95% CI = 1.07-1.12, $p < 0.001$), and UACR (OR = 1.02, 95% CI = 1.01-1.04, $p < 0.001$) independently predicted the presence of IGFR using binary logistic regression analysis.
Conclusions: Information obtained from our study showed that hsCRP is associated with IGFR in hypertensives.

Key Words: Chronic kidney disease • C-reactive protein • Glomerular filtration rate • Hypertension • Inflammation

INTRODUCTION

Chronic kidney disease (CKD) is a global public health problem.[1] Patients with CKD have a higher risk of progression to end-stage renal disease (ESRD) and a poor cardiovascular prognosis.[2] Taiwan has been recognized as an endemic area for kidney disease, with the highest incidence and prevalence rates of ESRD in the world.[3] Taiwan has undertaken a nationwide CKD prevention effort incorporating a multidisciplinary care program,which has proven effective in decreasing the incidence of dialysis, mortality, and medical costs. However, the number of CKD patients in Taiwan and the rest of the world continues to rise in addition to an increasing prevalence of comorbidities such as hypertension.[4]

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Therefore, the development of an effective risk stratification strategy is crucial for high-risk populations such as hypertensives.[5-7]

High-sensitivity C-reactive protein (hsCRP) has been introduced as a predictor of cardiovascular events in cardiovascular medicine.[8] It has been noted that hsCRP can bind to damaged endothelial cells, activate the complement system, promote foam cell formation, aggregate low-density lipoprotein, and stimulate tissue factor production by monocytes.[9-12] HsCRP can also induce adhesion molecules in endothelial cells and deposit along the walls of glomerular capillaries, suggesting that hsCRP may participate in the pathogenesis of glomerulosclerosis and atherosclerosis.[13]

Previous studies have investigated the relationship between hsCRP and renal outcomes with conflicting results.[14,15] A limited numbers of studies discussed the role of hsCRP in risk stratification for renal parameters in hypertensive patients. We therefore examined the association between hsCRP and the estimated glomerular filtration rate (GFR) in hypertensives.

METERIALS AND METHODS

Patient characteristics

This cross-sectional retrospective study was conducted from January 2007 to December 2009. A total of 572 consecutive patients with hypertension were followed at the cardiovascular clinic of a tertiary medical center in Taiwan and were invited to participate. They were enrolled in the study if they met the following inclusion criteria: (1) diagnosis of hypertension, and (2) regular cardiovascular outpatient clinic follow-up for at least 6 months. Study exclusion criteria were as follows: (1) hsCRP > 10 mg/dL, or (2) presence of an acute inflammatory or infectious illness at the time of enrollment.[16]

Measurements

We reviewed in detail the subjects' medical histories, including height, weight, and blood pressure. The biochemistry laboratory measurements obtained from these patients included levels of fasting glucose, blood urea nitrogen (BUN), creatinine, albumin, and a complete lipid profile comprising low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), total cholesterol, and triglycerides. All tests were performed at the central laboratory of Kaohsiung Medical University Hospital. CRP levels were measured using hsCRP kits. Patients with hsCRP levels > 10 mg/dL were excluded. Obesity was defined as a body mass index ≥ 27 kg/m^2. Hyperlipidemia was defined as a cholesterol or triglyceride level ≥ 200 mg/dL or current treatment with a lipid-lowering agent.

Calculations and definitions

Hypertension was diagnosed when systolic blood pressure was ≥ 140 mmHg or diastolic blood pressure was ≥ 90 mmHg, in accordance with hypertension guidelines. The estimated GFR was calculated using the 7-item Modification of Diet in Renal Disease (MDRD) study equation [GFR = $170 \times (\text{creatinine})^{-0.999} \times (\text{age})^{-0.76} \times (\text{urea})^{-0.170} \times (\text{albumin})^{+0.318} \times 0.762$ if female].[17] Impaired GFR (IGFR) was defined as a GFR < 60 ml/min/1.73 m^2. This range corresponds to stage 3 or higher CKD according to the National Kidney Foundation's classification scheme and assists in the identification of individuals with clinically significant CKD.[18] The urinary albumin-to-creatinine ratio (UACR) in mg/g was calculated as the urinary albumin concentration divided by the creatinine concentration, and microalbuminuria was defined as a UACR between 30 and 300 mg/g.

Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD), and the Student's t-test and chi-square test were used to analyze continuous variables and categorical data, respectively. Correlations between continuous variables were determined using Pearson's test. A multivariable logistic regression analysis was used to identify independent factors associated with GFR and the presence of IGFR, respectively. Significant variables from the univariate analysis were further tested in the multivariate regression analysis. Calculations were performed with SPSS 10.0 software (SPSS, Chicago, IL, USA). All tests were 2-sided, and the level of significance was established as $p < 0.05$.

RESULTS

The study group consisted of 572 consecutive hy-

pertensive patients, 309 (54%) of whom were men. Ages ranged from 26 to 91 years (mean, 60.5 ± 11.7 years). BUN levels ranged from 5.8 to 138 mg/dL (mean, 16.1 ± 8.5 mg/dL), creatinine levels ranged from 0.34 to 3.80 mg/dL (mean, 0.95 ± 0.34 mg/dL), and albumin levels ranged from 3.44 to 5.10 g/dL (mean, 4.29 ± 0.26 g/dL).

GFR values ranged from 16 to 239 mL/min/1.73 m^2, with a mean GFR of 85 ± 24 mL/min/1.73 m^2. The numbers of patients with a GFR ≥ 90, 60-89, 30-59, and 15-29 mL/min/1.73 m^2 were 243 (42.5%), 253 (44.2%), 70 (12.2%), and 6 (1.1%), respectively. Overall, 76 (13.3%) of the patients had IGFR. Twenty-five (4.4%) patients had microalbuminuria, and the rest were normoalbuminuric. No subjects had macroalbuminuria, defined as a UACR greater than 300 mg/g.

Baseline characteristics of patients with and without IGFR

Table 1 shows the baseline characteristics of pa-

Table 1. Baseline characteristics of IGFR and Non-IGFR patients

Characteristics	Total (n = 572)	Non-IGFR (n = 496)	IGFR (n = 76)	p-value
Male sex (%)	309 (54.0)	272 (54.8)	37 (48.7)	0.32
Age (years)	60.45 ± 11.72	58.98 ± 11.26	70.01 ± 10.13	< 0.001
HT duration (years)	7.1 ± 4.7	7.03 ± 4.8	7.6 ± 4.6	0.35
HT grade (I/II)	109/463	100/396	9/67	0.09
Smoking (%)	110 (19.2)	93 (18.8)	17 (22.4)	0.46
Height (meter)	161.20 ± 8.28	161.47 ± 8.18	159.50 ± 8.77	0.53
Weight (kg)	69.60 ± 12.08	69.73 ± 11.94	68.79 ± 12.99	0.53
BMI (kg/m^2)	26.90 ± 3.94	26.95 ± 3.85	26.55 ± 4.48	0.47
Obesity (%)	260 (45.5)	228 (46.2)	32 (42.1)	0.50
Diabetes (%)	178 (31.1)	155 (31.3)	23 (30.3)	0.86
Hyperlipidemia (%)	401 (70.1)	345 (69.6)	56 (73.7)	0.46
Fasting glucose (mg/dL)	115.64 ± 26.06	115.94 ± 25.79	113.68 ± 27.90	0.48
HbA1C (%)	6.16 ± 0.95	6.15 ± 0.93	6.20 ± 1.02	0.68
Albumin	4.29 ± 0.26	4.29 ± 0.25	4.24 ± 0.26	0.10
BUN (mg/dL)	16.07 ± 8.53	14.70 ± 7.79	25.00 ± 7.82	< 0.001
Creatinine (mg/dL)	0.95 ± 0.34	0.86 ± 0.19	1.51 ± 0.51	< 0.001
Total cholesterol (mg/dL)	187.92 ± 41.41	188.55 ± 41.01	183.78 ± 44.06	0.35
Triglyceride (mg/dL)	139.34 ± 83.74	139.25 ± 82.65	139.89 ± 91.16	0.95
LDL-cholesterol (mg/dL)	111.87 ± 34.35	112.88 ± 34.00	105.30 ± 36.08	0.07
HDL-cholesterol (mg/dL)	42.74 ± 18.96	42.83 ± 19.90	42.15 ± 11.08	0.77
HsCRP (mg/L)	1.81 ± 1.87	1.71 ± 1.75	2.48 ± 2.43	0.009
UACR (mg/g)	5.50 ± 15.55	4.45 ± 12.59	12.40 ± 27.17	0.01
CHD (%)	165 (28.8)	137 (27.6)	28 (36.8)	0.10
CVA (%)	23 (4.0)	15 (3.0)	8 (10.5)	0.002
PAOD (%)	6 (1.0)	5 (1.0)	1 (1.3)	0.58
Medication				
Aspirin (%)	184 (32.2)	154 (31.0)	30 (39.5)	0.14
Clopidogrel (%)	16 (2.8)	13 (2.6)	3 (3.9)	0.51
ACEI (%)	113 (19.8)	99 (20)	14 (18.4)	0.75
ARB (%)	399 (69.8)	337 (67.9)	62 (81.6)	0.02
β-blocker (%)	368 (64.3)	314 (63.3)	54 (71.1)	0.19
Diuretic (%)	279 (48.8)	233 (47.0)	46 (60.5)	0.03
CCB (%)	278 (48.6)	237 (41.4)	41 (53.9)	0.32
Statin (%)	204 (35.7)	176 (35.5)	28 (36.8)	0.82

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CHD, coronary heart disease; CVA, cerebrovascular accident; HsCRP, high-sensitive C-reacting protein; HT, hypertension; IGFR, impaired glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

tients with and without IGFR. Compared to those without IGFR, patients with IGFR were significantly older (70.01 ± 10.13 vs. 58.98 ± 11.26 years, p < 0.001) and had higher levels of BUN, creatinine, UACR, and hsCRP (25.00 ± 7.82 vs. 14.70 ± 7.79 mg/dL, 1.51 ± 0.51 vs. 0.86 ± 0.19 mg/dL, 12.40 ± 27.17 vs. 4.45 ± 12.59 mg/g, and 2.48 ± 2.43 vs. 1.71 ± 1.75 mg/L, respectively; all p < 0.02). Diuretic use (60.5% vs. 47.0%, p = 0.03) was also significantly higher in the IGFR group.

Correlation between baseline characteristics and GFR

GFR negatively correlated with age (r = -0.41, p < 0.001), BUN (r = -0.45, p < 0.001), creatinine (r = -0.76, p < 0.001), UACR (r = -0.13, p = 0.001), and hsCRP (r = -0.10, p = 0.01). The albumin level was positively associated with GFR (r = 0.13, p = 0.002). The GFR also correlated with gender (p < 0.001) and aspirin use (p = 0.001), but not with the use of other medications (Table 2).

Independent predictors of GFR in the multivariate regression analysis

Variables included in the multivariate linear regression were age, gender, UACR, aspirin use, and hsCRP. The multivariate models showed that hsCRP (p = 0.03), age (p < 0.001), and UACR (p = 0.002) were independent predictors of GFR. The percentage of GFR variance explained by these variables was 20.1%.

Table 2. Correlation between baseline characteristics and GFR

Characteristic	r	p-value
Age (years)	-0.41	< 0.001
Height (meter)	0.04	0.30
Weight (kg)	-0.25	0.55
BMI (kg/m^2)	0.02	0.62
Fasting glucose (mg/dL)	0.05	0.26
HbA1C (%)	-0.2	0.63
BUN (mg/dL)	-0.45	< 0.001
Creatinine (mg/dL)	-0.76	< 0.001
Total cholesterol (mg/dL)	0.04	0.40
Triglycerides (mg/dL)	-0.34	0.41
LDL-cholesterol (mg/dL)	0.08	0.06
HDL-cholesterol (mg/dL)	0.05	0.27
UACR (mg/g)	-0.13	0.001
HsCRP (mg/L)	-0.10	0.01
Albumin	0.13	0.002

BMI, body mass index; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HsCRP, high-sensitive C-reacting protein; LDL, low-density lipoprotein; UACR, urinary albumin-to-creatinine ratio.

Independent predictors of IGFR in the binary logistic regression analysis

Variables included in the regression analysis were age, UACR, use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and diuretics, a history of cerebrovascular accident, and hsCRP. The binary logistic regression analysis found that age [odds ratio (OR): 1.09, 95% confidence interval (CI): 1.07 to 1.12, p < 0.001], UACR (OR: 1.02, 95% CI: 1.01 to 1.04, p < 0.001), and hsCRP (OR: 1.16, 95% CI: 1.03 to 1.31, p = 0.02) were significant independent predictors of IGFR in hypertensive patients (Table 3). The percentage of IGFR variance explained by these variables was 26.9%.

DISCUSSION

There were two major findings in this cross-sectional study. First, hsCRP is a significant predictor of IGFR in hypertensive patients. Second, UACR is also an independent predictor of the presence of IGFR in hypertensives without macroalbuminuria.

HsCRP and the kidney

HsCRP can deposit along the walls of glomerular capillaries and may participate in the pathogenesis of glomerulosclerosis.[13] Elevated CRP levels were found in hemodialysis patients or elderly persons with renal

Table 3. Predictors of IGFR in the binary logistic regression analysis

Characteristic	OR	95% CI	p-value
HsCRP (mg/L)	1.16	1.03-1.31	0.02
Age (years)	1.09	1.07-1.12	< 0.001
UACR (mg/g)	1.02	1.01-1.04	< 0.001
CVA	2.45	0.82-7.31	0.11
Diuretic use	1.28	0.72-2.29	0.40
ACEI use	1.27	0.54-2.99	0.59
ARB use	2.23	0.96-5.16	0.06

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; CVA, cerebrovascular accident; HsCRP, high-sensitive C-reacting protein; IGFR, impaired glomerular filtration rate; OR, odds ratio; UACR, urinary albumin-to-creatinine ratio.

insufficiency.[19,20] In a large non-diabetic population, elevated CRP levels were positively associated with loss of renal function and traditional cardiovascular risk factors including blood pressure, serum cholesterol level, smoking, and plasma glucose level.[15] However, some studies found that higher serum levels of CRP are not related to renal parameters in patients with non-diabetic kidney disease.[14,21,22] Few studies investigated the impact of CRP on renal parameters in hypertensive patients. Our study found that hsCRP is an independent factor associated with GFR and IGFR, and could be considered in the risk assessment of renal target organ damage in hypertensive patients as well as in metabolic syndrome patients, as suggested in the hypertension treatment guidelines.[8]

Albuminuria in the kidney

Several previous studies also showed urinary albumin excretion (UAE) to be associated with functional renal abnormalities. The UACR was associated with the risk of mortality.[23] These may be partially explained by the association between UACR and the presence of endothelial dysfunction, an early marker of atherosclerosis. Therefore, hypertension guidelines strongly recommend measurement of UAE or UACR in Taiwan, which has the highest prevalence of ESRD in the world.[8] Our study found that UACR is correlated with IGFR in hypertensive patients, which further supports the guideline recommendation to measure UACR as a risk stratification parameter in CKD-endemic areas such as Taiwan.

Diuretic use in hypertensives with renal impairment

Diuretics are an old but effective class of antihypertensive agents. Thiazide and loop diuretics are used for hypertension control because fluid retention is a common problem in CKD patients. According to the ALLHAT trial, thiazide-type diuretics are superior in preventing primary or more major forms of cardiovascular disease and are less expensive.[24] They should be preferred for first-step antihypertensive therapy if no compelling indications exist, as suggested by the JNC VII hypertension guideline.[25] For those patients with a poor response to antihypertensive treatment, an adequate diuretic dose should be prescribed before diagnosing resistant hypertension.[26] Because of the ineffectiveness of thiazide-type diuretics in patients with poor renal function, loop diuretics are preferred in hypertensive patients with estimated GFRs < 30 mL/min/1.73 m^2. In our study population, IGFR subjects received more diuretics than non-IGFR subjects, in line with the hypertension guidelines.

Aspirin use in hypertensives with renal dysfunction

In our study, we found that hypertensive patients treated with aspirin had lower GFRs. Accelerated atherosclerosis is frequently found in subjects with renal disease. Therefore, subjects with chronic renal failure are exposed to increased morbidity and mortality as a result of cardiovascular events.[27] The benefit of aspirin in people with CKD and hypertension was demonstrated in a post hoc analysis of the Hypertension Optimal Treatment (HOT) trial.[28] Major cardiovascular events were reduced by 9%, 15%, and 66% in patients with baseline GFRs of ≥ 60, 45 to 59, and < 45 ml/min/1.73 m^2, respectively. Aspirin therapy produces greater absolute reductions in major cardiovascular events in hypertensive patients with CKD than in those with normal kidney function. Among every 1000 persons with a GFR < 45 ml/min/1.73 m^2 treated for 3.8 years, 76 major cardiovascular events will be prevented. However, the 2012 KDIGO guidelines still recommend aspirin for secondary prevention but not primary prevention.[29]

Limitations

Our study has several limitations. First, because 572 hypertension patients were recruited from a tertiary medical center, selection bias could exist and our patients may therefore not represent the general hypertensive population. Second, in this cross-sectional study, it was possible to demonstrate the correlation between IGFR and inflammation, but not the causal relation. We could not determine whether inflammatory activity is one of the causes of IGFR or if poor renal function leads to increased inflammation. Therefore, further longitudinal studies are needed to confirm the causal relation between inflammation and IGFR. Third, hypertension patients in this study were not medication-naive. However, we tried to adjust for drugs affecting markers of inflammation such as aspirin and statins. Fourth, we did not routinely assess levels of uric acid, calcium, and phosphate, which are related to renal impairment in hypertensives.

CONCLUSIONS

Because hsCRP is an independent factor associated with GFR and renal impairment, it could be considered in the risk assessment of renal target organ damage in hypertensive patients. Further longitudinal studies are warranted to confirm these findings.

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