High prevalence and risk factors for kidney dysfunction in patients with atherosclerotic cardio-cerebrovascular disease

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Summary

**Background:** Patients with atherosclerotic cardio-cerebrovascular disease are at high risk of kidney dysfunction because of the overlap of several risk factors. The purpose of this study is to examine the prevalence and characteristics and risk factors for kidney dysfunction in the cardio-cerebrovascular disease population.

**Methods:** Renal functions of 1012 patients with the cardio-cerebrovascular disease were evaluated with the purpose of evaluating characteristics of the incidence, risk factors for kidney dysfunction in the cardio-cerebrovascular disease population.

**Results:** In the univariate analysis, the major risk factors for kidney dysfunction in the patients with the cardio-cerebrovascular disease were age, gender, hypertension, diabetes mellitus, dyslipidemia and serum uric acid. In the patients with both hypertension and diabetes mellitus the percentages of significantly decreased eGFR were 25.6%. Results of multivariable analysis showed that diabetes mellitus (odds ratio (OR) 1.609, 95% confidence intervals (CI) 1.08–2.398, \( P = 0.019 \)), hypertension (OR 1.547, 95% CI 1.049–2.281, \( P = 0.028 \)) and serum uric acid (OR 1.009, 95% CI 1.007–1.010, \( P < 0.001 \)) were independent risk factors for reduced kidney function.

**Conclusions:** In the context of the cardio-cerebrovascular disease kidney dysfunction is common and has a high prevalence. Patients with both cardio-cerebrovascular disease and kidney dysfunction at any stage should be recognized as high-risk population.

Introduction

Atherosclerotic cardio-cerebrovascular disease remains one of the leading causes of morbidity and mortality around the world.\(^1,2\) Over a third of the first myocardial infarctions and strokes are lethal. Decreased kidney function has been associated with cardiovascular disease in cross-sectional studies for a long time.\(^3\) Kidney dysfunction is a strong independent predictor of mortality and poor outcome in patients with acute stroke.\(^4\) The incidence of ischemic stroke is much higher in patients with chronic kidney disease than in the general population.\(^5\) The dialysis population suffers a 5-to-10-fold higher risk of hospitalized stroke in comparison with population without end-stage renal disease (ESRD).\(^6\) Therefore, kidney dysfunction is an important predictor of clinical outcomes in patients with atherosclerotic cardio-cerebrovascular disease. The presence of kidney dysfunction increases the risk of death in cases of atherosclerotic cardio-cerebrovascular disease.\(^7,8\) Many patients with kidney dysfunction will eventually develop ESRD and need renal replacement therapy. Thus, it is important to detect and measure potential kidney dysfunction in patients with atherosclerotic cardio-cerebrovascular disease. There are many common risk factors in patients with renal disease and atherosclerotic cardio-cerebrovascular disease. In the general population traditional risk factors for kidney dysfunction are also associated with...
atherosclerotic cardio-cerebrovascular disease. So, some patients may simultaneously suffer from both kidney dysfunction and atherosclerotic cardio-cerebrovascular disease. These patients have a worse prognosis than those with atherosclerotic cardio-cerebrovascular disease only. There is evidence that treatment of kidney dysfunction at the earliest possible stage is effective for preventing progression to ESRD and exacerbation of cardio-cerebrovascular disease.\cite{9} In the clinical setting, many patients are unaware of their kidney dysfunction, leading to delays in implementing treatment that can potentially result in more effective prevention of ESRD and decreased morbidity and mortality from kidney dysfunction. Therefore, it is important to test this group of patients who are at high-risk status of developing early-stage renal dysfunction. The purpose of this study is to describe the prevalence of kidney dysfunction and characteristics of risk factors in the populations with atherosclerotic cardio-cerebrovascular disease.

**Materials and methods**

**Study participants**

The present retrospective study included 1012 patients aged 40–80 years old who were diagnosed with atherosclerotic cardio-cerebrovascular disease at the Department of Neurology and Cardiology of the First Affiliated Hospital of Harbin Medical University from October 2010 to December 2012. Atherosclerotic cardio-cerebrovascular disease included coronary heart disease and cerebrovascular disease at inclusion or in history. The diagnosis of coronary heart disease was based on the history of myocardial infarction or definite history of angina with documented electrocardiographic findings, or the findings of the lumen narrowing of at least one coronary artery or its branches by coronary angiography. Cerebrovascular disease included transient ischaemic attack and cerebral infarction, which was diagnosed on the basis of neurological symptoms, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the brain. Patients with history of renal disease before atherosclerotic vascular disease, immune system diseases or acute kidney failure are excluded. The study was approved by the Ethical Committee of the First Affiliated Hospital of Harbin Medical University. Written informed consent was obtained from all participants.

**Data collection**

Detailed medical history, complete physical examination and laboratory parameters were collected from the hospital electronic database. The collected parameters include age, gender, serum uric acid, serum urea, serum creatinine, total cholesterol, HDL and LDL cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, smoking, diabetes mellitus, hypertension and medications history. Diabetes mellitus was defined as history of diabetes or use of medications to treat diabetes mellitus. Hypertension was defined as history of hypertension or use of medications to treat hypertension, or blood pressure levels \( \geq 140/90 \) mmHg (mean of three measurements) in the supine position. Dyslipidemia was defined as presence of abnormal cholesterol and/or triglycerides or use of lipid lowering agents.

**Ascertainment of level of kidney function**

Kidney function was assessed by estimated glomerular filtration rate (eGFR). eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) study equation, as suggested by the National Kidney Foundation (NKF) guidelines.\cite{10} In accordance with the clinical data, the serum creatinine and eGFR of all the patients did not deteriorate rapidly, and the patients did not suffer from acute renal failure. All members of the study were allotted to a group based on their eGFR levels. Group 1 included patients with eGFR \( \geq 90 \) ml/min/1.73 m\(^2\). Group 2 corresponded to GFR values from 60 to 89 ml/min/1.73 m\(^2\), and Group 3 to GFR values from 15 to 59 ml/min/1.73 m\(^2\). Patients with eGFR<15 ml/min/1.73 m\(^2\) were not included in this study.

**Statistical analysis**

Continuous variables and categorical variables were expressed as mean \pm standard deviation (SD) and percentage, and were evaluated with one-way analysis of variance (ANOVA) test and the Chi-square test, respectively. The Kolmogorov–Smirnov test was used to test the normality of the distribution of each variable. In the multivariable models, smoking, diabetes mellitus, hypertension, serum uric acid and dyslipidemia were adjusted for. eGFR was calculated using MDRD study equation which employs age and gender. Therefore, the multivariable analysis was performed after exclusion of age and gender. Stepwise backward logistic regression analysis was used to determine the independent predictors of kidney dysfunction and to calculate odds ratios (ORs) in patients with atherosclerotic cardio-cerebrovascular disease. ORs were estimated with 95% confidence intervals (CIs). All \( P \)-Values were two-tailed, and a value of \( \leq 0.05 \) was considered statistically significant. SPSS 10.0 Statistical
package Program was used to complete all statistical analyses.

Results

The study population consisted of 1012 patients with atherosclerotic cardio-cerebrovascular disease, of whom 55.1% had cerebrovascular disease and 44.9% had coronary heart disease. Baseline characteristics of the 1012 patients with atherosclerotic cardio-cerebrovascular disease are shown in Table 1. Using eGFR as an indicator, a distribution of kidney dysfunction is presented in Figure 1. The mean eGFR was $81.86 \pm 24.55$ ml/min/1.73 m² ($n = 1012$). Three hundred and fifty-seven (35.3%) patients had an eGFR $\geq 90$ ml/min/1.73 m². Four hundred and eighty-seven (48.1%) patients had mildly reduced eGFR in the range 60–89 ml/min/1.73 m². One hundred and fifty-two (15%) patients had moderately reduced eGFR in the range 30–59 ml/min/1.73 m². Sixteen (1.6%) patients had significantly reduced eGFR in the range of 15–29 ml/min/1.73 m².

In the univariate analysis, characteristics of the study cohort were analyzed across all three groups. The major risk factors for kidney dysfunction in patients with the cardio-cerebrovascular disease are age, gender, smoking, hypertension, diabetes mellitus, dyslipidemia and serum uric acid. Patients with lower eGFR were older, and were more likely to be women. All patients in the lowest eGFR category had the higher rates of hypertension, diabetes mellitus, dyslipidemia, and had higher levels of serum uric acid compared with those with normal kidney function. Based on the level of eGFR, the correlation between risk factors and kidney dysfunction were shown in Table 2.

In the context of the cardio-cerebrovascular disease, morbidity of kidney dysfunction was significantly higher among patients who had hypertension or diabetes mellitus. In the present study 72 (7.1%) patients had diabetes mellitus only, 425 (42%) patients had hypertension only, 160 (15.8%) patients had hypertension and diabetes mellitus simultaneously, and others had none of the two diseases. In patients with both hypertension and diabetes mellitus the percentage of markedly decreased eGFR was 25.6%, which is significantly greater than those without these two diseases and those with one disease only (Figure 2, $P = 0.001$).

To further analyze the independent contribution of risk factors to kidney dysfunction, multivariate logistic regression analysis was performed in this population. Candidate variables for multivariate analysis were diabetes duration, hypertension,
smoking, dyslipidemia and serum uric acid. Results showed that diabetes mellitus (OR 1.609, 95% CI 1.08–2.398, \( P = 0.019 \)), hypertension (OR 1.547, 95% CI 1.049–2.281, \( P = 0.028 \)), and serum uric acid (OR 1.009, 95% CI 1.007–1.010, \( P < 0.001 \)) were identified as independent risk factors for reduced kidney function in the patients with the cardio-cerebrovascular diseases (Table 3).

### Discussion

The present study showed a high prevalence of kidney dysfunction in the population with

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**Table 2** Univariate analysis for risk factors of kidney dysfunction in patients with cardio-cerebrovascular disease

<table>
<thead>
<tr>
<th>characteristics</th>
<th>Patients with normal eGFR</th>
<th>Patients with 90–60 ml/min eGFR</th>
<th>Patients with &lt;60 ml/min eGFR</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n (%)</td>
<td>357 (35.3%)</td>
<td>487 (48.1%)</td>
<td>168 (16.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.18 ± 9.07</td>
<td>63.94 ± 9.8</td>
<td>70/98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>223/134</td>
<td>291/196</td>
<td>82 (48.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>161 (45.1)</td>
<td>192 (39.4)</td>
<td>82 (48.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>82 (23.0)</td>
<td>99 (20.3)</td>
<td>51 (30.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>186 (52.1)</td>
<td>281 (57.7)</td>
<td>118 (70.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>224 (62.7)</td>
<td>285 (58.5)</td>
<td>116 (69.0)</td>
<td>0.046</td>
</tr>
<tr>
<td>Serum uric acid (mmol/l)</td>
<td>282.93 ± 78.88</td>
<td>321.96 ± 86.11</td>
<td>387.89 ± 110.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>61.24 ± 9.91</td>
<td>81.28 ± 12.54</td>
<td>122.80 ± 38.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²body)</td>
<td>107.65 ± 15.26</td>
<td>75.22 ± 8.41</td>
<td>46.33 ± 11.20</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 3** Multivariable logistic regression analysis for risk factors associated with kidney dysfunction in patients with cardio-cerebrovascular disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>OR</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>1.25</td>
<td>0.867–1.802</td>
<td>0.231</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.547</td>
<td>1.049–2.281</td>
<td>0.028</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.609</td>
<td>1.08–2.398</td>
<td>0.019</td>
</tr>
<tr>
<td>Serum uric acid</td>
<td>1.009</td>
<td>1.007–1.010</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.174</td>
<td>0.802–1.718</td>
<td>0.410</td>
</tr>
</tbody>
</table>

Figure 2. The percentages of patients with hypertension or/and diabetes mellitus in the various groups. In patients with decreased kidney function (eGFR values from 15 to 59 ml/min/1.73 m²) the percentages of patients with both hypertension and diabetes mellitus were significantly greater than those with one disease only and those without these two diseases \( (P=0.001) \).
Kidney dysfunction and atherosclerotic cardio-cerebrovascular disease. Reduced eGFR is frequent and strongly influences the long-term outcome in the general population. Patients with low baseline eGFR had increased risk of overall and cardiovascular mortality. Additionally, the present study demonstrates that kidney dysfunctions of the patients with cardio-cerebrovascular disease mostly are in the mild and moderate stages of renal failure, with the majority in the mild stage. Previous epidemiological study has shown that even mild kidney dysfunction independently predicted increased cardiovascular mortality and elevated incidence of myocardial infarction and stroke. Therefore, clinicians should not ignore mild renal impairment in high risk patients with atherosclerotic cardio-cerebrovascular disease.

Prospective and retrospective studies have shown that kidney dysfunction is an independent risk factor for cardiovascular disease with an estimated doubling of the cardiovascular and total mortality. The reasons for the increased risk of kidney dysfunction in persons with cardio-cerebrovascular disease are not fully understood. In the past decades, a number of risk factors have been investigated and proven to be effective predictors of atherosclerosis and its related diseases. Furthermore, the pathophysiology of kidney dysfunction involves several risk factors that are analogous to cardio-cerebrovascular disease, including dyslipidemia, hypertension, endothelial dysfunction, oxidative stress, nitric oxide homeostasis and inflammatory markers. All of these risk factors may play an important role in accelerated atherosclerosis in the arteries of the kidney, heart and brain. Meanwhile, reduced eGFR results in lower clearance and higher plasma levels of some inflammatory factors. These factors, as well as increased inflammation and oxidative stress, aggravate the risk of chronic kidney dysfunction. Therefore, patients with cardio-cerebrovascular disease are at a higher risk of kidney dysfunction.

In this study, age is a risk factor associated with kidney dysfunction in the cardio-cerebrovascular disease population. Aging is associated with structural and functional changes in the kidneys, and might reflect the progressive development of atherosclerosis, resulting in impaired renal function. Age and atherosclerosis are associated with cerebrovascular disease. Prior studies indicated that with advanced age the prevalence of kidney dysfunction is increasing. Consistent with previous reports, results of those studies elucidated the high prevalence of kidney dysfunction in elderly patients with cardio-cerebrovascular disease.

Furthermore, when comparing the prevalence of kidney dysfunction in the cardio-cerebrovascular disease population with or without diabetes mellitus and hypertension, the results demonstrated that diabetes mellitus and hypertension are associated with an two-fold increased risk of kidney dysfunction. Microalbuminuria with normal eGFR is the most common renal abnormality in the diabetes mellitus, followed by reduced eGFR. In the present study, to concentrate the evaluation on eGFR the microalbuminuria is not included in the definition of kidney dysfunction and patients are assigned according to eGFR only. In a previous study, an increased risk of reduced eGFR with diabetes mellitus has been observed among patients with existing cardiovascular disease. Epidemiologic studies have also clearly demonstrated that an elevated risk associated with decreased estimated GFR in the population with diabetes mellitus. Furthermore, diabetes mellitus and hypertension are strong risk factors for early decline in kidney function and stroke. Consistent with previous studies, the present study shows that 30.4% of patients with eGFR 15-69 ml/min/1.73 m² had diabetes mellitus, and 25.6% of patients with both diabetes mellitus and hypertension had marked reduction in eGFR, which highlights the strong associations between kidney dysfunction and these two diseases. These results indicate that cardio-cerebrovascular disease and the kidney dysfunction are intercorrelated. If patients with cardio-cerebrovascular disease have diabetes mellitus and hypertensive, the renal dysfunctions quickly get worse.

Studies have shown that serum uric acid is an independent risk factor for the development of kidney injury in the general population. Consistent with previous studies, the serum uric acid is identified as an independent risk factor for kidney dysfunction in patients with cardio-cerebrovascular disease in the present study. Serum uric acid promotes macrophage infiltration in atherosclerotic vessels with increased production of oxygen free radicals, inhibits the production of nitric oxide and promotes the development arteriolosclerosis. Therefore, serum uric acid participates in the progression of atherosclerosis and the effect of it on the organs was associated with kidney, heart and brain simultaneously. Furthermore, epidemiological studies have demonstrated that elevated serum uric acid levels may anticipate an increased risk of vascular disease, including cardiovascular events and stroke. Therefore, serum uric acid influences the development of kidney dysfunction in the cardio-cerebrovascular disease population.

Although many studies suggest that dyslipidaemia is involved in the progression of kidney injury, the complexity of the lipid disorders in kidney disease and the strong relationship with
another risk factor for progression of kidney dysfunction are not fully understood. Current studies indicate that dyslipidaemia can potentially accelerate progression of kidney injury by several mechanisms. First, dyslipidemia promotes accelerated vascular atherosclerosis in the kidney. Secondly, tubular epithelial cells reabsorb fatty acids, phospholipids and cholesterol, which results in tubulointerstitial inflammation, foam cell formation and tissue injury. In addition, accumulation of lipoproteins in glomerular mesangium can promote matrix production and glomerulosclerosis. Meanwhile, dyslipidemia which promotes accelerated atherosclerosis is a common risk factor for cardio-cerebrovascular disease. However, in the multivariate analysis of the present study, result could not demonstrate the significance of an association between dyslipidaemia and kidney dysfunction in the cardio-cerebrovascular disease population. A possible reason is that the composition or function of blood lipids was abnormal but not serum levels. Furthermore, some patients use lipid lowering agents.

Limitations

There are several limitations in the present study. First of all, this study is a retrospective single center analysis. A multiple center prospective study on the development of kidney dysfunction in the population with cardio-cerebrovascular disease may warrant the results. Additional analysis in a multiple center prospective cohort will further elucidate the importance of kidney dysfunction in the population with cardio-cerebrovascular disease. Second, as to the kidney injury, two different manifestations should be considered. One manifestation is the albuminuria because of vascular endothelial dysfunction, and the other is the decreased eGFR. In the present study albuminuria is not included because of different mechanism and patients are assigned to eGFR only. The combined effects of these manifestations in patients with cardio-cerebrovascular disease need to be examined in future studies. In addition, the estimation of GFR from serum creatinine also has several limitations, including variation in creatinine production based on muscle mass and other factors. To minimize these effects, we used the recommended MDRD formula which decreases bias.\(^{10}\)

Conclusions

In conclusion, the results of this study demonstrate the high epidemiology of kidney dysfunction in the cardio-cerebrovascular disease populations. The patients with cardio-cerebrovascular disease are at high risk of the kidney dysfunction as a result of the overlap of several risk factors for cardio-cerebrovascular and renal disease. The increasing attention to kidney dysfunction is fully justified, because it has a considerable impact on cardio-cerebrovascular disease. Therefore, in the context of the cardio-cerebrovascular disease estimation of renal function should be systematically carried out. Patients with both cardio-cerebrovascular disease and kidney dysfunction at any stage should be recognized as high-risk populations and have access to the most effective prevention and treatment.

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References


