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Ischemia-modified albumin, a predictive marker of major adverse cardiovascular events in continuous ambulatory peritoneal dialysis patients

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ABSTRACT

Objectives: The aim of this study was to evaluate the efficiency of ischemia-modified albumin (IMA) for predicting major adverse cardiovascular events (MACE) in continuous ambulatory peritoneal dialysis (CAPD) patients.

Design and methods: A prospective observational study was conducted with 120 CAPD patients and 37 healthy volunteers. Demographic and clinical data were collected. The primary end point is the occurrence of MACE.

Results: A total of 157 participants with a mean age of 43.64 years finally completed this study. The CAPD patients had a significantly high rate of MACE ($P = 0.001$) and high levels of IMA than healthy controls ($P < 0.001$). Compared with CAPD patients with normal levels of IMA, the CAPD patients with high levels of IMA (>85 kU/L) had lower non-MACE survival rate ($P < 0.001$), which indicated that the high IMA CAPD patients may suffer a high rate of MACE. In addition, the high IMA CAPD patients also had a low level of serum albumin ($P < 0.001$) and hemoglobin ($P = 0.018$). The correlation analysis showed that the serum albumin level was the most effective factor influencing IMA ($B = -0.967$, $P < 0.001$).

Conclusions: CAPD patients with high levels of IMA had a high incidence rate of MACE. IMA was a good predictive marker of MACE and might be important in cardiovascular risk stratification of CAPD patients.

Introduction

Continuous ambulatory peritoneal dialysis (CAPD) is an effective replacement therapy for improving the prognosis of end-stage renal disease (ESRD) patients. And it was found that CAPD has lesser hemodynamic stress than hemodialysis [1]. However, more and more evidences currently showed that cardiovascular diseases are the leading cause of death in CAPD patients [2]. So, to find out an early and effective marker for predicting cardiovascular events will be helpful to carry out early intervention and decrease the cardiovascular mortality of CAPD patients.

Ischemia-modified albumin (IMA) was first discovered in the early 1990s, and a great deal of roles of IMA have been gradually identified e.g. early marker of acute coronary syndromes (ACS) and potential biomarker of protein oxidation in hemodialysis [3,4]. In addition, IMA levels were also showed to be increased in thyroid dysfunction patients and obese population [5,6]. Sharma et al. found that IMA levels could predict mortality in patients with ESRD [7]. However, in CAPD patients, the predictive value of IMA for major adverse cardiovascular events (MACE) is still unknown.

In this study, we performed a prospective observational study. During the 2 year follow-up period, the primary end point is MACE. The levels of IMA and survival rate of non-MACE (no occurrence of MACE) among the participants were compared. We aimed to investigate the predictive value of IMA for MACE in CAPD patients and explored the influencing factors of IMA.

Abbreviations: ACS, acute coronary syndromes; CAPD, continuous ambulatory peritoneal dialysis; DBP, diastolic blood pressure; ESRD, end-stage renal disease; hs-CRP, high sensitivity CRP; IMA, ischemia-modified albumin; LDL-c, low density lipoprotein cholesterol; MACE, major adverse cardiovascular events; non-MACE, no occurrence of MACE; SBP, systolic blood pressure; TC, total cholesterol; WBC, white blood cell.

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Materials and methods

Study population

Between January 2009 and January 2012, a total of 165 participants at affiliated Donghua Hospital of Sun Yat-sen University were initially enrolled in this study. 37 were the healthy volunteers, and 128 participants were the CAPD patients. The healthy controls were recruited from the health screening center of our hospital. The mean age was 41.81 ± 2.74 years. They were selected according to their self-reported medical history based on their age and gender distribution. The inclusion criteria for healthy volunteers were as follows: (1) their age and gender were matched with the CAPD patients; (2) no smoke and alcohol addiction and no history of drug abuse; (3) did not have hypertension, diabetes, tumor, etc.; and (4) did not participate in any clinical trials of drugs in recent 3 months. The CAPD patients were on regular dialysis for at least 3 months. Exclusion criteria were age <18 years, acute cardiovascular and cerebrovascular ischemia diseases e.g. acute coronary syndrome and acute cerebral infarction, peripheral vascular disease, shock, severe infection, severe hepatic or heart failure, malignant tumor, and serum albumin level lower than 20 g/L or higher than 55 g/L. All the participants were followed up after 24 months. The study end point was the occurrence of MACE. The primary MACE outcome included cardiovascular death, myocardial infarction, stroke or heart failure, and all-cause mortality [8].

At the end of run period, 157 participants completed this study. 8 CAPD patients were excluded. One patient's age was less than 18 years old. Three patients changed to hemodialysis. Four patients disagreed to follow up. The study protocol was approved by the Sun Yat-sen University Ethics Committee, and written informed consent was obtained from all the participants.

Data collection

Demographic and clinical data were collected: age, gender, body mass index (BMI), primary renal disease, blood pressure, duration of dialysis, and medication history.

Venous blood samples were drawn after overnight fasting. Serum samples were obtained after suitable centrifugation and were stored at −80 °C. The laboratory data were measured from blood samples: (1) calcium, phosphorus, glucose, albumin, creatinine, uric acid, total cholesterol (TC), triglycerides, low density lipoprotein cholesterol (LDL-c) and homocysteine (TBA-120 auto-analyzer); (2) high sensitivity CRP (hs-CRP) (Siemens Healthcare Diagnostics, Inc., Marburg, Germany); and (3) white blood cell (WBC) count, hemoglobin, and platelet (Sysmex, Kobe, Japan).

Serum IMA was measured by a colorimetric assay developed by Bar-Or et al. [9]. This method is based on the principle of quantitative scanning of free cobalt present after cobalt binding has taken place. According to the manufacturer (Yi Kang, Co. Ltd., Changsha, China), the IMA upper limit of normal is 85 kU/L [10].

Statistical analysis

All data are expressed as mean ± standard error (SEM). Statistical analyses were done using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Differences of continuous variables between groups were determined by unpaired *t*-test, while categorical variables were compared by using chi-square analysis. The non-MACE survival related to IMA levels was analyzed in a Kaplan–Meier model. Pearson's correlation coefficient was calculated for the correlation of continuous variables with IMA levels. A P value <0.05 (two-tailed) was considered to be significant.

Results

Demographic and clinical characteristics of the total participants at baseline

A total of 157 participants with a mean age of 43.64 years finally completed this study. 8 CAPD patients were excluded. One patient's age was less than 18 years old. Three patients changed to hemodialysis. Four patients disagreed to follow up. The baseline demographic and clinical characteristics of these participants are presented in Table 1. As seen from the table, the CAPD patients had a significantly higher rate of MACE (38 vs. 2, P = 0.001), and significantly elevated levels of IMA (87.56 ± 0.84 vs. 75.21 ± 2.27 kU/L, P < 0.001). In addition, it was found that the systolic blood pressure and diastolic blood pressure (SBP and DBP) were significantly increased in these patients (P < 0.001). As for other indicators, the CAPD patients also had higher levels of serum phosphorus, creatinine, uric acid, hs-CRP, and homocysteine and lower levels of hemoglobin (P < 0.05).

Demographic and clinical characteristics of two IMA groups in CAPD patients

To explore the characteristics of CAPD patients with high levels of IMA, we grouped the CAPD patients based on the serum IMA levels. The value of IMA more than 85 kU/L was defined a high level of IMA. Table 2 showed that compared with the CAPD patients with low levels of IMA (81.99 ± 0.68 kU/L), the high IMA (95.94 ± 0.10 kU/L) CAPD patients had a significantly higher rate of MACE (28 vs. 10, P < 0.001), and significantly lower levels of albumin, uric acid, TC, and hemoglobin (P < 0.05).

Predictive value of IMA for MACE in CAPD patients

To analyze the predictive value of IMA for MACE in CAPD patients, the Kaplan–Meier survival curve analysis was performed. Fig. 1 showed that the CAPD patients with high levels of IMA had a significantly lower non-MACE survival rate (P < 0.001), which indicated that the high IMA CAPD patients may suffer a high rate of MACE.

Table 1
Demographic and clinical characteristics of healthy controls and CAPD patients.

	Control (n = 37)	CAPD (n = 120)	P
Age (year)	41.81 ± 2.74	44.22 ± 1.32	0.40
Sex ratio (male/female)	22/15	74/46	0.81
No. of MACE	2	38	0.001
BMI (kg/m^2)	21.63 ± 0.30	21.47 ± 0.26	0.75
SBP (mm Hg)	123.03 ± 2.26	151.58 ± 1.98	<0.001
DBP (mm Hg)	77.73 ± 1.33	90.26 ± 1.19	<0.001
Calcium (mmol/L)	2.04 ± 0.023	2.40 ± 0.025	0.43
Phosphorus (mmol/L)	1.01 ± 0.033	1.61 ± 0.054	<0.001
Glucose (mmol/L)	5.33 ± 0.19	5.13 ± 0.054	0.55
Albumin (g/L)	34.68 ± 1.18	33.62 ± 0.43	0.38
Creatinine (μmol/L)	72.39 ± 3.30	1000.95 ± 29.33	<0.001
Uric acid (μmol/L)	339.42 ± 19.67	420.57 ± 6.84	<0.001
TC (mmol/L)	4.30 ± 0.14	4.58 ± 0.029	0.56
Triglycerides (mmol/L)	1.23 ± 0.086	1.34 ± 0.029	0.93
LDL-c (mmol/L)	2.39 ± 0.072	2.73 ± 0.027	0.55
WBC count (10^9/L)	7.65 ± 0.46	7.48 ± 0.26	0.44
Hemoglobin (g/L)	127.97 ± 3.29	108.12 ± 2.19	<0.001
Platelet (10^9/L)	212.95 ± 12.44	215.84 ± 5.76	0.83
IMA (kU/L)	75.21 ± 2.27	87.56 ± 0.84	<0.001
hs-CRP (mg/L)	0.90 ± 0.076	13.39 ± 3.42	0.045
Homocysteine (μmol/L)	13.54 ± 1.48	27.80 ± 0.84	<0.001

All values are expressed as mean ± SEM.
Abbreviations: BMI, body mass index; CAPD, continuous ambulatory peritoneal dialysis; DBP, diastolic blood pressure; hs-CRP, high sensitivity C-reactive protein; IMA, ischemia modified albumin; LDL-c, low density lipoprotein cholesterol; MACE, major adverse cardiovascular events; SBP, systolic blood pressure; TC, total cholesterol; WBC, white blood cell.