Int J Clin Exp Med 2016;9(12):23605-23611
www.ijcem.com /ISSN:1940-5901/IJCEM0039876

Original Article

Plasma renin activity and low-density lipoprotein cholesterol level: potential risk factors of premature cardiovascular disease in young male people with hypertension

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Received May 14, 2016; Accepted October 15, 2016; Epub December 15, 2016; Published December 30, 2016

Abstract: Background: Hypertension has become prevalent among the young people. Although a variety of risk factors have been identified for cardiovascular diseases (CVD), there have been few reports focusing on the young hypertensive population. Objective: To investigate the potential risk factors of premature CVD (PCVD) in young patients with hypertension. Methods: A total of 261 male hypertensive patients with ages ≤40 years were recruited. The clinical and laboratory data of 161 hypertensive patients with PCVD and 100 hypertensive patients without any visible coronary disease according to angiography were compared. Results: Family history of CVD, drinking, smoking, history of cerebral infarction, BMI and the laboratory tests results of WBC, levels of uric acid, blood urea nitrogen, FPG, TC, TG, VLDL-C, LDL-C, CRP, renin and angiotensin II levels were significant in PVCD and control groups. Multivariate logistic analysis showed high renin activity level and LDL-C had a significant predictive value for the incidence of PCVD, with ORs of 6.35 (P=0.002) and 4.77 (P=0.007), respectively. Receiver operating characteristic (ROC) curve analysis revealed the cut-off values of 1.331 μg mL^{-1} h^{-1} for renin and 3.252 mmol L^{-1} for LDL-C for detection PVCD. Spearman's correlation coefficient between LDL-C level and renin activity was 0.349 (P<0.001). Conclusion: Higher LDL-C level and renin activity are important risk factors for PCVD in young Chinese individuals with hypertension.

Keywords: Hypertension, low-density lipoprotein cholesterol, premature cardiovascular disease, renin

Introduction

Hypertension is an important public health concern given that it is highly prevalent [1]. In European countries the prevalence of hypertension ranges between 28.00% and 44.00% [2]. With the huge economic development, the lifestyles of most Chinese have changed greatly and there was a trend of increasing incidence of hypertension because of the changement in diet and behavior patterns. Recent studies show that, in China, the prevalence of hypertension among men has reached 30.09%, and the prevalence among women is 24.79% [3]. The percentage of young Chinese people with hypertension comprised 4.5% to 5.5% of the total adult hypertension patients [4].

Previous studies have demonstrated that hypertension is highly correlated with stroke mortality, and may cause organ damage and is an important risk factor for cardiovascular events [2]. While the cardiovascular mortality has steadily declined among the elderly population because of the development of primary and secondary prevention measures, the cardiovascular mortality among the young is still increasing [5, 6]. In recent years, the incidence of cardiovascular diseases (CVD) in China has been increasing, especially among the young Chinese population [7]. According to the China's population-monitoring data, CVD is the leading cause of death [8], the cardiovascular death accounted for 40% of all deaths [7]. Data showed that, with a 10 mmHg increase in systolic pressure, the increases in risk of stroke and fatal myocardial infarction are 53% and 31%, respectively [7].

A novel concept of preventing and treating CVD or reducing the cardiovascular mortality has

emerged as a comprehensive therapy targeting various risk factors [9]. Besides hypertension, by correlating clinical data with autopsy studies, investigators related cigarette smoking, elevated lipid levels, and elevated body mass index (BMI) with the severity of CVD [10, 11]. However, to date, few reports have focused on the young population (≤40 y) with hypertension. In the present study, we investigated the potential risk factors in a cohort of young male Chinese hypertensive population, to provide new clues for the prediction and prevention of premature CVD (PCVD) in these patients.

Subjects and methods

Subjects: The population-based study was conducted in the city of Taizhou, a city-level division of Zhejiang Province of East China. Subjects included in the present study were recruited from the department of cardiology of Taizhou Hospital, and complained of chest pain or were suspected to have CVD from July 2000 to July 2015. Subjects were eligible to be recruited if they had hypertension and were young male patients with the age ≤40 years old (the cutoff of 40 years old was used to identify young patients based on previously accepted nomenclature [12, 13]). According to the World Health Organization (WHO) criteria, participants were classified as hypertensive if two of their results of systolic blood pressure (BP) were ≥140 mmHg or diastolic BP were ≥90 mmHg or if they were currently taking anti-hypertensive medications for longer than one month. Based on the results of coronary angiography, subjects were divided into a PCVD group and a normal coronary group (the control group). Exclusion criteria were: incomplete clinical data; a history of chronic hepatitis, chronic kidney disease or severe renal artery stenosis; serious infections, connective tissue disease, cancer or blood disease; currently pregnant or lactating, or long-term treatment with contraceptive drugs; severe vascular heart disease; and secondary hypertension or endocrine diseases such as thyroid dysfunction or adrenal cortical dysfunction. Participation in the study was voluntary, and informed consent was obtained from each person who agreed to participate in the study. The study was approved by the Ethics Committee of Taizhou Hospital.

Coronary angiography: Judkins method was used for angiography as has been described previously [14]. Two professional physicians assessed the angiography results. Patients with the luminal diameter of the main coronary artery or its main branches narrowed >50% were diagnosed with CVD. Normal coronary arteries were defined as those with no obvious stenosis of the main branches according to angiography.

Laboratory tests and clinical data

The levels of fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C) and albumin, globulin, high-sensitivity C-reactive protein (CRP), renin, angiotensin II and aldosterone were measured. The testing of the renin-angiotensin-aldosterone system (RAAS) was conducted in strict accordance with the instructions in the kit manual.

Body mass index (BMI) was computed as weight (kg)/height (m^2) and classified according to the World Health Organization's Asian criteria [15] as overweight (BMI ≥23 kg m^{-2}). A detailed record of age and history of hypertension, diabetes mellitus, smoking and family history of CVD was recorded. Diabetes was diagnosed by demonstrating corresponding symptoms, plasma glucose level ≥11.1 mmol/L, fasting glucose level ≥7.0 mmol/L, blood glucose level ≥1 mmol/L at 2 h glucose tolerance testing or a clear history of diabetes. Patients who smoked at least one cigarette daily for more than one year or long-term smokers who had quit less than six months previously were defined as smoking positive. Family history of PCVD was defined first-degree relatives with an age of onset of CVD ≤55 years old in men and ≤65 years old in women. Drinking was defined as alcohol consumption ≥25 g/d or ≥100 g/week for more than one year. According to the Chinese guidelines on prevention and treatment of dyslipidemia in adults [16], hypercholesterolemia was defined as TC >5.18 mmol/L, hypertriglyceridemia as TG >1.70 mmol/L, low HDL-C as HDL-C <1.04 mmol/L and high LDL-C as LDL-C >3.37 mmol/L.

Statistical analysis

All statistical analyses were carried out using SPSS version 16.0 for Windows (SPSS Inc.,

Table 1. Demographic characteristics of the total study participants at the baseline examination

Demographic data	Groups		*p*-value
	PCVD (n=161)	Control (n=100)	
Age, years	35±4.89	35±3.99	0.890[a]
Smoking habit, n (%)	101 (63.0)	15 (15.0)	<0.001[b]
Family history of CVD, n (%)	41 (25.5)	10 (10.0)	0.002[b]
Has diabetes, n (%)	58 (36.0)	28 (28.0)	0.179[b]
Body mass index, kg m^{-2}	25.48±3.06	24.65±2.19	0.018[c]
Systolic blood pressure, mmHg	142.9±21.8	140±24.2	0.317[a]
Diastolic blood pressure, mmHg	85.8±12.9	86.2±14.1	0.814[a]
Taking antihypertensive drugs, n (%)	128 (79.5)	79 (79.0)	0.922[b]
ACEI or ARB, n (%)	23 (14.3)	14 (14.0)	0.948[b]
Beta-blockers, n (%)	48 (29.8)	26 (26.0)	0.506[b]
Ca^{2+} channel blockers, n (%)	44 (27.3)	24 (24.0)	0.551[b]
Diuretics, n (%)	21 (13.0)	14 (14.0)	0.825[b]
Alcohol drinking, n (%)	46 (28.5)	13 (13.0)	0.003[b]
History of cerebral infarction, n (%)	23 (16.8)	5 (5.0)	0.004[b]
Taking statins, n (%)	35 (21.7)	26 (26.0)	0.429[b]

Data presented as mean ± SD unless otherwise indicated. [a]values were tested by independent t-test, [b]values were tested by χ^2 test, and [c]values values were tested by Mann-Whitney U test. ACEI Angiotensin-converting enzyme inhibitors, ARB angiotensin II receptor blockers.

Chicago, IL, USA). Data were expressed as mean ± standard deviation (SD). Normally distributed measurement data were compared between PVCD and control group using independent t tests; data incompatible with normal distribution were compared between the two groups using the Mann-Whitney U test. The measurement data between groups were compared with χ^2 test. Risk factors were analyzed using multivariate logistic regression; Stepwise method was used for variables selection. Receiver operating characteristic (ROC) curve analysis was performed to determine the cutoff value of LDL-C level and renin activity detecting the PVCD. The significance level was set at 0.05.

Results

A total of 261 patients were recruited into the present study, after coronary angiography, 161 were diagnosed with PCVD and 100 were assigned to the control group. The characteristics of the total study participants at the baseline examination are presented in **Tables 1**, **2**. The two groups exhibited no statistically significant difference in age, years of hypertension, systolic and diastolic blood pressure at admission, or proportion taking antihypertensive drugs. There were also no differences in the proportion of patients taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, Ca^{2+} channel blockers, diuretics or statins, or in the number of diabetic patients. However, the groups were significantly different with regard to family history of CVD (P=0.002), drinking (P=0.003), percentage of smokers (P<0.001), history of cerebral infarction (P=0.004) and BMI (P=0.018).

According to the laboratory examination results, The PCAD group and the control exhibited no significant difference in the number of peripheral blood platelets, creatinine, albumin, globulin, HDL-C and aldosterone. However, statistically significant differences in white blood cells (WBC) (P=0.002), levels of uric acid (P=0.024), blood urea nitrogen (P=0.008), FPG (P<0.001), TC (P=0.048), TG (P=0.001), VLDL-C (P=0.002), LDL-C (P<0.001), CRP (P=0.031) were observed. Of all the tested renin-angiotensin system (RAS) components, renin and angiotensin II levels in the PCAD group were significantly higher than in the control group (P<0.001 and P=0.011, respectively), but aldosterone level (P=0.294) was not significantly different.

The existence of coronary disease was considered as a dependent variable in the present study, while family history of CVD, drinking, smoking, history of cerebral infarction, BMI and the laboratory tests results of WBC, levels of uric acid, blood urea nitrogen, FPG, TC, TG, VLDL-C, LDL-C, CRP, renin and angiotensin II were considered as independent variables. After analysis using the multivariate logistic regression, results revealed renin and LDL-C level had a significant predictive value for the incidence of PCVD, with ORs of 6.35 (P=0.002) and 4.77 (P=0.007), respectively (**Table 3**).

ROC curve analysis revealed a cut-off value of 1.331 μg mL^{-1} h^{-1} for renin, with 83.7% sensitiv-

Table 2. Laboratorial characteristics of the total study participants at the baseline examination

Laboratory test results	Reference value	Groups		*p*-value
		PCVD (n=161)	Control (n=100)	
White blood cells, $\times 10^9$	4-10	6.76±2.16	5.95±1.89	0.002[a]
Platelets, $\times 10^9$	100-300	216.83±50.92	221.34±60.23	0.517[a]
Uric acid, μmol/L $\times 10^5$	1.50-4.16	3.77±1.16	3.45±1.02	0.024[c]
Blood urea nitrogen, mmol/L	3.2-7.1	6.39±2.02	5.79±1.31	0.008[c]
Creatinine, μmol/L	53-106	93.16±30.88	89.23±43.11	0.392[a]
FPG, mmol L^{-1}	3.9-6.4	7.21±2.57	5.90±1.21	<0.001[a]
TG, mmol L^{-1}	<1.70	2.28±2.11	1.57±0.86	0.001[c]
TC, mmol L^{-1}	<5.02	5.30±0.85	5.08±0.91	0.048[a]
LDL-C, mmol L^{-1}	<3.12	4.50±1.37	2.99±1.05	<0.001[a]
VLDL-C, mmol L^{-1}	<0.41	0.91±0.36	0.79±0.21	0.002[a]
HDL-C, mmol L^{-1}	>1.04	1.28±0.44	1.31±0.32	0.554[a]
Albumin, g L^{-1}	40-55	38.43±5.18	38.75±6.21	0.653[c]
Globulin, g L^{-1}	20-30	26.99±4.34	27.43±3.36	0.387[a]
CRP, mg L^{-1}	<10	0.71±1.34	0.38±0.93	0.031[c]
Renin, μg mL^{-1} h^{-1}	1.0-2.5	1.59±0.27	1.15±0.16	<0.001[a]
Angiotensin, pg mL^{-1}	10-30	62.23±15.93	56.65±19.28	0.011[c]
Aldosterone, nmol mL^{-1}	1.38-4.15	2.81±0.86	2.68±1.13	0.294[c]

Data presented as mean ± SD. [a]values were tested by independent t-test and [c]values were tested by Mann-Whitney U test. FPG fasting plasma glucose, TG triglycerides, TC total cholesterol, LDL-C low-density lipoprotein cholesterol, VLDL-C very low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, CRP C-reactive protein.

Table 3. Multivariate logistic regression analysis of risk factors associated with PVCD

	Odds ratio	95% CI	*p*-value
Demographic data			
Smoking habit	1.30	0.91-1.84	0.143
Family history of CVD	1.01	0.82-1.63	0.953
Body mass index	1.02	1.00-1.04	0.091
Alcohol drinking	1.48	1.05-2.03	0.063
History of cerebral infarction	1.55	1.33-1.89	0.075
Laboratory test results			
White blood cells	1.00	0.98-1.01	0.891
Uric acid	1.00	0.98-1.02	0.747
Blood urea nitrogen	1.17	0.93-1.48	0.171
FPG	2.11	1.61-2.92	0.052
TG	1.39	1.09-1.78	0.079
TC	0.36	0.27-0.48	0.063
LDL-C	6.35	1.99-9.60	0.002
VLDL-C	1.60	1.21-2.11	0.684
CRP	0.94	0.76-1.15	0.575
Renin	4.77	1.22-7.01	0.007
Angiotensin	1.16	0.87-1.54	0.289

CI confidence interval, FPG fasting plasma glucose, TG triglycerides, TC total cholesterol, LDL-C low-density lipoprotein cholesterol, VLDL-C very low-density lipoprotein cholesterol, CRP C-reactive protein.

ity (95% CI: 76.4-88.5) and 94.0% specificity (95% CI: 87.4-97.7; AUC=0.911, P< 0.001), and 3.252 mmol L^{-1} for LDL-C, with 80.7% sensitivity (95% CI: 73.8-86.5) and 68.0% specificity (95% CI: 57.9-76.9; AUC= 0.807, P<0.001), for PVCD detection (**Figure 1**). Spearman's correlation coefficient between LDL-C level and renin activity was 0.349 (P<0.01).

Discussion

CVD, in terms of coronary heart disease (CHD), ischemic stroke, and peripheral artery disease, are the leading cause of morbidity and mortality worldwide, although optimal medical therapy has been prescribed for primary and secondary preventions [17]. It has been estimated that significantly less than 10% of all individuals presenting with documented CVD are under the age of 40 years [18]. However, this group of patients may be disproportionately significant because CVD that does appear in young adults can lead to devastating outcomes for these patients, their families, and society. Hypertension is one of the most significant risk factors for CVD [19].

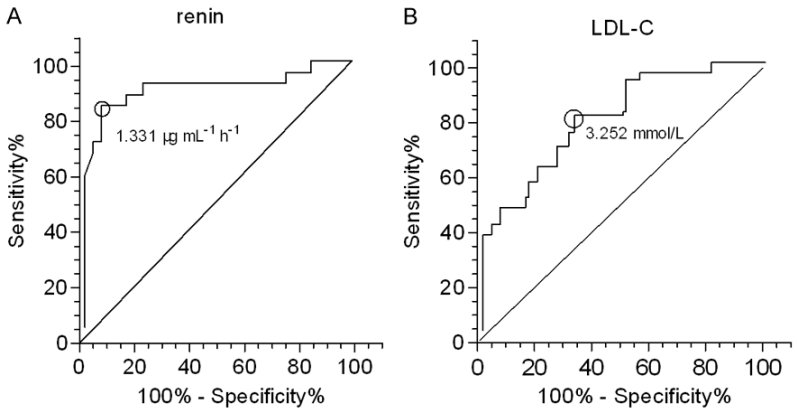

Figure 1. Receiver operating characteristics curves (ROC) of renin activity (A) and LDL-C (B) level for predicting PVCD. For the renin of 1.331 μg mL^{-1} h and LDL-C of 3.252 mmol L^{-1}, the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were demostrated as follows:

	Cutoff value	AUC (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Renin	1.331 μg mL^{-1} h^{-1}	0.911	83.75	94.00	95.74	78.33	87.74
LDL-C	3.252 mmol L^{-1}	0.807	80.75	68.00	80.36	69.39	76.24

However, there are also many other factors influencing the CVD progression in the high-risk population of already with hypertension. To our best of knowledge, this is the first time to report the risk factors of PCVD in the young male hypertensive population.

The results of the present study revealed that renin and LDL-C level were important factors associated with the risk of PCVD in young hypertensive patients. ROC curve analysis revealed the cut-off values of 1.33 μg mL^{-1} h^{-1} for renin and 3.25 mmol L^{-1} for LDL-C for detection of PVCD. However, we did not find a satisfied correlation coefficient between LDL-C and renin (r=0.349), which indicated a relative independence between the two variables for detection of PCVD.

RAS is a complex signaling pathway and hormonal cascade and implicated in the pathophysiology of CVD at a number of levels. And unregulated RAS is important in the pathogenesis of atherosclerosis and hypertension [20]. Our results showed that, of all the tested RAS components, renin activity was a significant factor associated with the risk of PCVD in young hypertensive patients. The renin activity was significantly different between the PCVD and the control groups (**Table 2**). Although angiotensin II has not been shown to be a significant factor for the development of PCVD after multivariate analysis, the angiotensin II level is higher in the PCVD than in the control group (**Table 2**, P=0.011).

Renin is converted from proenin by juxtaglomerular cells in the kidneys, and Tsecreted directly into the circulation. Plasma renin then carries out the conversion of angiotensinogen released by the liver to angiotensin I. Angiotensin I is subsequently converted to angiotensin II by the enzyme angiotensin-converting enzyme (ACE) found in the lungs. Renin is the upstream molecule in the RAS, and previous reports have found plasma renin concentration was associated with long-term cardiovascular mortality in patients who received coronary angiography [21]. Renin can be inhibited directly by aliskiren, thus preventing the generation of Angiotensin I from angiotensinogen. Studies have showed that aliskiren may offer the additional opportunity to inhibit progression of atherosclerosis at tissue level to reduce the risk of PCVD.

As mentioned above, angiotensin (especially Ang II) is the most important molecules of RAS, and indeed, the final mediator of most effects of the RAS produces pro-inflammatory, proliferative and vasoconstrictor effects on the vasculature [22] that can contribute to initiation and progression of atherosclerosis, including the atherosclerotic plaques found in CVD. Several clinical trials have examined effects of angiotensin inhibition for primary and secondary prevention of CVD. Among patients receiving ramipril (ACE inhibitor) when compared to placebo, there was a 22% relative risk reduction in the primary endpoint of myocardial infarction, stroke, or death from CVD [23]. Therefore, the RAS might be an essential therapeutic target for both prevention and therapy for patients at high risk of adverse cardiovascular events.

The relationship between LDL-C levels and the risk of CVD is clear. In the present study, the patients of PCVD had higher LDL-C level than the controls. According to previous studies [17], plasma level of LDL-C is causally associated with atherosclerosis and CVD. That plasma LDL-C level diminished by hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statins) leads to incident CVD reduction further supports the notion that LDL-C plays an important role on atherosclerosis initiation and progression. In line with the outcomes of published clinical trials, American Heart Association/American College of Cardiology (AHA/ACC) and European Society of Cardiology (ESC) guidelines have recommended a target plasma LDL-C level, based on cardiovascular risk stratification, for each individual.

Observational studies show that there is a continuous positive relation between CVD risk and blood cholesterol concentrations [24], so larger reductions in LDL-C might well produce larger reductions in the risk. This is indirectly supported by the positive association identified in the previous meta-analysis between the absolute reduction in LDL-C in a trial and the proportional reduction in major vascular events in that trial [25]. Further reductions in LDL-C safely produce definite further reductions in the incidence of heart attack, of revascularisation, and of ischaemic stroke, with each 1.0 mmol/L reduction reducing the annual rate of these major vascular events by just over a fifth and a reduction of LDL-C by 2-3 mmol/L would reduce risk by about 40-50% [26].

In conclusion, higher renin activity and LDL-C level were associated with an increased risk of developing PCVD among young Chinese individuals with hypertension. Therefore, combined therapy with lipid-regulating and RAS inhibitors may be important in the development of optimal management strategies to prevent PCVD in young patients with hypertension.

Disclosure of conflict of interest

None.

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