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A Case-Control Study of Risk Factors of Abdominal Aortic Aneurysm

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ABSTRACT

Objective: To explore the potential risk factors of abdominal aortic aneurysm (AAA) in the Chinese population.

Methods: A matched case-control study was designed for the study. Patients with AAA administrated in the First Affiliated Hospital of Zhengzhou University from January 2005 to December 2007 were included in the study. Sex and age-matched volunteers were selected for the case-control in the same period. A uniform questionnaire was sent to patients and volunteers to collect demographic data, past medical history, and behavioral factors. General physical examination, ultrasound examination of the abdominal aorta, and serological testing were used to collect clinical data. Environmental risk factors of abdominal aortic aneurysms were analyzed by conditional logistic regression.

Results: A total of 465 subjects including 155 patients were enrolled in the study. Multivariate regression analysis found that people with high blood pressure have high risk of AAA (OR = 1.88, 95% CI 1.12-3.18; P = .02). Smoking is a significant independent risk factor for AAA; the morbidity of AAA in smokers is 5.23-fold of non-smokers (95% CI 2.44-11.23). Dyslipidemia (OR = 2.61, 95% CI 1.45-4.70), serum high sensitivity C-reactive protein (OR = 2.43, 95% CI 1.37-4.31), and homocysteine (OR = 2.73, 95% CI 1.61-4.65) were valuable parameters in detecting AAA.

Conclusion: Hypertension and smoking are risk factors of abdominal aortic aneurysms; dyslipidemia, high-sensitivity C-reactive protein, and homocysteine levels are associated with AAA.

INTRODUCTION

Abdominal aortic aneurysm (AAA) is a localized enlargement of the abdominal aorta such that the diameter is greater than 3 cm or more than 50% larger than normal [Khashram 2015]. AAAs occur most commonly in males over 50 years old. Those people with a family history have high risk of AAA [Bird 2015]. AAA can seriously threaten the lives of patients and lead to society with heavy financial burdens. Screening for AAA in high-risk groups can effectively reduce AAA-related mortality in European and American countries [Jacob 2015]. Therefore, identification of risk factors for AAA has important significance for early prevention and treatment of AAA.

Few studies are ongoing that focus on epidemiology of AAA, and risk factors of AAA are still unknown in the Chinese population. In this study, we investigate the risk factors, providing the basis for identifying high-risk groups.

MATERIALS AND METHODS

The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. All patients and control subjects gave their written informed consent.

Patients Inclusion and Exclusion Criteria

Inclusion criteria: (1) older than 40 years; (2) the abdominal aorta ultrasound or abdominal computed tomography (CT) scan diagnosed infrarenal aortic aneurysm; and (3) complete survey data can be obtained with signed informed consent. Exclusion criteria: (1) diagnosed with infectious disease; (2) secondary abdominal aortic aneurysm (such as trauma); (3) serious mental illness, difficult to cooperate with the investigation and physical examination; (4) severe infections or autoimmune diseases; (5) pregnant women; (6) patients with malignant tumor.

Volunteer Inclusion and Exclusion Criteria

Volunteer inclusion criteria: (1) sex matched with patients, the age difference less than 3 years; (2) not suffering from any location, any cause of abdominal aortic aneurysm screening with abdominal aortic ultrasound or abdominal CT; and (3) complete survey data can be obtained with signed informed consent. Exclusion criteria: (1) suffering from aortic dissection, aortic aneurysm thoracic aortic disease; (2) symptomatic peripheral arterial occlusion; (3) severe infection or autoimmune diseases; (4) the body or spirit has major shortcomings, cannot cope with the questionnaire and blood test persons; (5) pregnant women; (6) malignant tumor.

Investigation Methods

All patients and volunteers were given a uniform study questionnaire, receiving standardized physical examination and serological testing. The questionnaire included demographic characteristics, chronic disease history, treatment history, and behavioral factors. Standardized physical examination including measurement of height, weight, waist and hip circumference, blood pressure, abdominal aortic ultrasound or abdominal CT; fasting peripheral venous blood collected for serological testing, indicators, including serum

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Table 1. Histories of Chronic Diseases of Patients with AAA and Controls

	Case group (n = 155)	Control group (n = 310)	*P*	95% CI
Hypertension	108	143	<.01	2.73 (1.79-4.16)
Dyslipidemia	76	61	<.01	3.78 (2.45-5.85)
2DM	18	46	.34	0.75 (0.42-1.35)
CAD	53	80	.06	1.5 (0.98-2.29)
Ischemic stroke	29	31	.01	1.97 (1.16-3.35)
PAD	51	51	<.01	2.64 (1.64-4.27)

2DM indicates type 2 diabetes mellitus; CAD, cardiovascular disease; PAD, peripheral arterial disease.

glucose (GLU), glycerol three Rouge (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), Apo lipoprotein A1 (ApoA1), Apo lipoprotein B (ApoB), high-sensitivity C-reactive protein (hsCRP), and homocysteine (Hcy).

Lifestyle

Smoking is defined as the total amount of smoking over 100; regular drinking is defined as drinking at least six months and each amount of alcohol intake of 50 mL wine alcohol; physical activity is defined as the average of once a week, each more than 30 min and continued more than six months, conscious, non-working and physical exercises housework content. Barefoot measuring height and weight with light clothes and body mass index (body mass index, BMI), 24 ≤ BMI <28 were overweight, BMI ≥28 as obese. Waist and hip measurements and calculation of the waist-hip ratio (WHR), male WHR >1.0, women WHR >0.9 is defined as abdominal obesity. Abdominal aorta ultrasound by two experienced vascular surgeons operating independently, infrarenal abdominal aortic aneurysm, infrarenal aorta is defined as the maximum diameter of more than adjacent normal diameter of the abdominal aorta 1.5-fold or greater than 3 cm. Blood lipid abnormality was defined as TC ≥1.7 mmol/L, or TG ≥5.7 mmol/L, or HDL-C ≤1.0 mmol/L, or LDL-C ≥3.4 mmol/L, or subjects taking lipid-lowering drugs.

Statistical Analysis

Sample size calculations are applying PASS. 2008 v8.0.3 software, based on previous literature, and the parameters were set as follows: matching ratio 1:2, P0 = 0.40, OR = 2.0, Phi = 0.0, power = 0.90, α = 0.05. Epidata 3.1 was used to establish a database, and parallel double entry error detection. Statistical analysis was performed using SAS 9.13 software. Distribution of continuous variables are presented as mean ± standard deviation. Deviation between the groups was compared using non-parametric Wilcoxon paired test. Disaggregated data are presented as distribution frequency and percentage. Independent risk factors of abdominal aortic aneurysm were analyzed using multivariate logistic regression model. Out level of the model was set at $P = .25$. Different exposure levels of factors are valued through OR values and 95% confidence intervals.

Table 2. Association of AAA and Behavioral Factors

	Case group (n = 155)	Control group (n = 310)	*P*	95% CI
Smoking				
Yes, n (%)	132	167	<.01	7.72 (3.95-15.06)
No, n (%)	23	143		
Drinking				
Yes, n (%)	79	131	.02	0.75 (0.42-1.35)
No, n (%)	76	179		
Physical activity, n (%)	94	181	.63	0.9 (0.60-1.36)

RESULTS

Characteristics of Subjects

A total of 465 subjects were enrolled in the study including 155 AAA patients and 310 volunteers (Table 1). The AAA patients were administrated in the First Affiliated Hospital of Zhengzhou University from January 2005 to December 2006 and the 310 volunteers were sex and age-matched in the study.

Among the patients, 138 (138/155, 89.0%) were male, 17 (17/155, 11.1%) were female with a mean age of 69.2 ± 10.0 years. The mean age of the control group was 69.6 ± 10.9 years old.

Association of Lifestyle and AAA

Distribution of smoking and drinking behavior between the case and control group was statistically significantly different, but the difference between the exercise groups was not statistically significant (Table 2). Risk for AAA in smokers was 7.72-fold of nonsmokers (95% CI 3.95-15.06; $P < .01$). Alcohol is a risk factor for AAA. The morbidity of AAA in drinking was 1.61-fold of drinkers (95% CI 1.07-2.43; $P = .02$)

Association of Serum Parameters and AAA

There were no significant differences in terms of obese and overweight between the two groups ($\chi^2 = 1.27$, $P = .26$). The same results were found in abdominal obesity ($\chi^2 = 0.05$, $P = .83$). Dyslipidemia was higher in AAA patients than the control group (OR = 2.92, 95% CI 1.96-4.36; $P < .01$). The level of ApoA1, ApoB was significantly different between the two groups ($P < .01$). High-sensitivity CRP reflecting the state of systemic inflammation in AAA patients was higher than that of the control group (OR = 3.69, 95% CI 2.41-5.64; $P < .01$). The level of Hcy was associated with AAA (OR = 4.06, 95% CI 2.65-6.23; $P < .01$) (Table 3).

Table 3. Association of AAA with Physical and Blood Biochemical Parameters

	Status	Case group (n = 155)	Control group (n = 310)	*P*	95% CI
BMI					
	<24	71	126	.26	0.86 (0.66-1.12)
	24-27.9	61	129		
	≥28	23	55		
Abdominal obesity	>0.9-1.0	17	32	.83	1.08 (0.56-2.05)
GLU	>6.1 μmol/L	18	50	.21	0.68 (0.38-1.22)
Dyslipidemia		118	138	<.01	2.92 (1.96-4.36)
ApoA1	≤1.0 g/L	49	51	<.01	2.35 (1.49-3.69)
ApoB	≥1.1 g/L	38	17	<.01	5.60 (3.04-10.3)
hsCRP	≥0.3 g/L	72	59	<.01	3.69 (2.41-5.64)
Hcy	≥15 μmol/L	116	131	<.01	4.06 (2.65-6.23)

Multiple Variants Analysis

Association of AAA and multivariates including hypertension, lack of hemorrhagic stroke, peripheral arterial occlusive, smoking, drinking, dyslipidemia, serum high sensitivity C-reactive protein eight variables, and serum homocysteine excessive rates were analyzed by logistic regression analysis (Table 4). In the sex and age-matched pairs, high blood pressure significantly increased the risk of AAA (OR = 1.88, 95% CI 1.12-3.18; *P* = .02). Smoking was a significant independent risk factor for AAA. Morbidity of AAA in smokers was 5.23-fold than non-smokers (95% CI 2.44-11.23). Dyslipidemia was also a risk factor of AAA (OR = 2.61, 95% CI 1.45-4.70). High-sensitivity C-reactive protein and homocysteine had a high association with abdominal aortic aneurysm (OR = 2.43, 95% CI 1.37-4.31; OR = 2.73, 95% CI 1.61-4.65). Ischemic stroke, peripheral arterial occlusive, and alcohol consumption were not associated with AAA when all other factors matched.

DISCUSSION

In this study, we investigated the risk factors of AAA. We explored by a matched case-control study in order to reduce selection bias and improve research efficiency. Patients and the control group were included in the study from the same hospital. There were no differences in term of sex, age, and disease between the two groups. The two group could represent the population, respectively.

The results of this study showed that hypertension is an independent risk factor of AAA. This finding is consistent with previous studies on American, European, and other Asian populations. The morbidity of AAA inpatients with hypertension is 1.25 to three times that of patients with normal blood pressure [Vardulaki 2002; Agroyannis 2002]. But, when concerning the multivariate analysis, results showed that no other cardiovascular and cerebrovascular diseases were associated with AAA [Basso 2015; Bath 2015].

In this study, 85.2% of AAA patients had a history of smoking. Smoking can increase the mortality of AAA significantly with other confounding factors matched. Previous studies have found that smoking has high relevance with AAA occurrence, development, rupture, and postoperative recovery [Badger 2009; Meijer 2012; Johansson 2015]. There is a dose-response association between smoking and AAA diameters [Koole 2012]. The mechanisms of tobacco inducing AAA are complex. Nicotine and other harmful substances can increase blood flow and stimulate blood vessel contraction. Those will increase shear stress of blood vessels [Maegdefessel 2012]. Results of animal studies showed that long-term nicotine exposure can increase inflammatory cytokines such as interleukin -1β and tumor necrosis factor-α in the vascular wall [Kaneko 2011]. Smoking can strengthen the matrix metalloproteinase (MMPs) hydrolysis through inhibiting expression of metalloproteinasesinhibitor-3 (tissue inhibitor of metalloproteinase 3, TIMP-3) [Eugster 2005; Wiernicki 2013]. These biological changes will break the balance of the protein hydrolysis process, thus promoting the formation and expansion of AAA.

In this study, we found no correlation between alcohol consumption and AAA with other factors matched. In previous studies, the impact of alcohol on AAA did not result in a unified conclusion [Wong 2007]. Some studies show that there is no association between alcohol consumption and AAA [Stackelberg 2014], but others found that an average intake of 30 grams or more alcohol per day can increase the risk of AAA. In this study, we found that 76.1% patients with AAA had high blood lipid levels. Studies showed the association of

Table 4. Results of Multivariable Regression Analysis for AAA

Risk factors	χ^2	*P*	OR (95% CI)
Hypertension	5.60	.02	1.88 (1.12-3.18)
PAD	2.38	.12	1.65 (0.87-3.01)
Smoke	18.04	<.01	5.23 (2.44-11.23)
Dyslipidemia	10.17	<.02	2.61 (1.45-4.70)
High hsCRP	9.18	<.03	2.43 (1.37-4.31)
High Hcy	13.75	<.04	2.73 (1.61-4.65)

abnormal lipid levels and AAA, and this has been confirmed by multiple studies [Parmar 2013]. Forsdahl et al found that TC and HDL-C are independent risk factors of AAA in 2009 in a population cohort study in Norway [Forsdahl 2009]. The study also showed that TC and HDL levels and risk of AAA have a dose-response relationship. A cohort study found that cholesterol-lowering statin drugs can significantly reduce the risk of AAA, and slow the rate of expansion of AAA (OR = 0.76, 95% CI 0.63-0.91). Dyslipidemia is an important risk factor of AAA and it is necessary to control the level of lipids in blood. Morbidity and mortality were higher in people with high blood lipid levels.

Documents show that high C-reactive protein levels and hyperhomocysteinemia are risk factors of cardiovascular disease [Sharif 2013]. Also, they have an effect on the occurrence and development of AAA. More than 20 years ago, Powell et al explored the potential relationship between CRP levels and AAA for the first time [Powell 1987]. They found that hsCRP was higher in AAA patients than in that of closed artery disease. HsCRP is an independent risk factor of AAA. Populations with higher levels of hsCRP have higher morbidity of AAA. High HsCRP levels increase the size of the aneurysm. This study found that HsCRP levels were excessive in 46.5% of patients with AAA. The results showed that chronic inflammation may be one reason for abdominal aortic aneurysm formation. Hyper homocysteinemia is a marker of cardiovascular disease and endothelial injury. It is associated with AAA. Previous studies have found a dose-response association between serum Hcy levels and AAA diameter [Liu 2012]. The study found that 74.8% of the case group subjects had elevated levels of Hcy (OR = 2.73, 95% CI 1.61-4.65). Studies have found that Hcy can cause dysfunction of endothelial cells of the blood vessel wall, resulting in endothelial damage and degradation of elastic fibers, causing the vessel wall to weaken [Sun 2015]. Also, hyper homocysteinemia can directly increase the activity of MMP-2 and MMP-9, and make elastin and fibrin degrade. This causes AAA.

There are some limitations in this case-control study. First, some of the variables in the study were obtained through self-reported subjects, which may induce recall bias. Second, the sequence of research variables and disease is difficult to determine. A cohort study is needed to elucidate this.

In summary, the results of the case-control study showed that smoking, hypertension, dyslipidemia, serum high sensitivity C-reactive protein, and homocysteine levels are risk factors of AAA. The results of this study call for high frequent screening in high-risk groups. The results provide a scientific basis for further research on the etiology of AAA.

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