Original Article
Correlation analysis between serum lipoprotein (a) and the incidence of aortic valve sclerosis

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Abstract: This clinical trial explores the correlation between serum lipoprotein and the severity of aortic valve sclerosis in patients diagnosed with aortic valve sclerosis (AVS). A total of 1260 subjects diagnosed with AVS were enrolled in this study between May 2005 and June 2013 and divided into the young-aged (30-59 years, n=217), middle-aged (60-74 years, n=561) and elderly groups (75-93 years, n=482). In each group, patients were subgrouped into AVS and healthy controls according to angiography findings. Parameters including triglyceride (TG), serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), free fatty acid (FFA), lipoprotein (a) [Lp(a)], apolipoprotein A1 (ApoAl) and apolipoprotein B (ApoB) were accurately measured. Correlation between these parameters and the severity of AVS was statistically evaluated. In the middle-aged and elderly groups, serum Lp(a), TC and LDL-C were significantly higher in patients with AVS compared with healthy counterparts (both $P<0.05$). In the elderly group, serum HDL-C in AVS patients was significantly lower than healthy subjects ($P<0.05$). In the young-aged group, serum Lp(a) and ApoB were significantly increased compared with healthy counterparts (both $P<0.05$). Gemini score in the elderly group was significantly higher than the other groups (both $P<0.01$). No statistical significance was observed in Lp(a) levels among groups I, II and III. The number of coronary stenosis in group III was significantly increased than those in groups I and II ($P<0.01$). Lp(a), LDL-C and aging act as independent risk factors of AVS and promote the incidence and progress of AVS.

Keywords: Correlation, lipoprotein (a), aortic valve sclerosis, aging

Introduction

Aortic valve sclerosis (AVS) is a non-inflammatory chronic degenerative process, which probably leads to life-threatening injuries. Aging, turbulent flow and pressure overload are believed to contribute to the incidence and development of aortic valve sclerosis. Atherosclerosis has been proven to act as the key pathological factor of the incidence and development of aortic valve sclerosis [1, 2]. Serum lipoprotein (a) [Lp(a)] is an independent macromolecular lipoprotein that consists of an Lp(a), which has a high degree of homology and possesses specific antigenicity, which plays a pivotal role in the incidence and development of atherosclerosis and thrombosis by the underling mechanism of interfering lipid metabolism and fibrinolytic system, which is significantly different from the metabolic pathways of alternative apolipoproteins. Several studies have suggest-

ed that Lp(a) is probably an independent risk factor for cardiovascular disease [3, 4]. Previous investigations have demonstrated that Lp(a) levels may be correlated with preclinical atherosclerosis including angiographic coronary atherosclerosis [5], ultrasonographic intima-media wall thickening and calcification in the extracoronary arteries [6]. Previous investigations have hinted that serum Lp(a) level is positively correlated with the incidence of cardiovascular disease, hinting that Lp(a) may serve as one of independent risk factors of aortic valve sclerosis [7]. However, the association between Lp(a) level and aortic valve sclerosis remains elusive. In this study, the clinical outcomes of blood lipid and coronary angiography in 1260 hospitalized patients with aortic valve sclerosis for 8 consecutive years were retrospectively analyzed, aiming to evaluate the diagnostic value of serum Lp(a) and its association with the severity of aortic valve sclerosis in elderly population.

Materials and methods

Study subjects

A total of 1260 patients clinically diagnosed with aortic valve sclerosis underwent coronary angiography at our institution between June 2005 and July 2013, aged 33-90 years, (69.76±9.80) years on average. All participants were assigned into group I (aged 30-59 years and 53.71±5.51 years on average, n=217), group II (aged 60-74 years and 67.86±4.28 years on average, n=561) and group III (75-93 years and 78.94±3.26 years on average, n=482) based upon the classification criteria of population age proposed by World Health Organization (WHO) in 2000. Among them, 535 (42.46%) were male and 725 (57.53%) were female. A total of 783 (62.14%) were complicated with hypertension, 308 (42.45%) accompanied with diabetes, 161 (12.78%) complicated with chronic obstructive pulmonary diseases and 478 (37.94%) accompanied with ischemic stroke. All subjects were examined with conventional electrocardiogram, echocardiogram and routine blood biochemical tests.

Exclusion criteria: Those subjects with severe heart failure, severe bacterial infection, thyroid gland lesions, malignant tumors, hemopathy, rheumatism and severe liver and renal dysfunctions were excluded from this clinical trial.

Study methods

Measurement of blood lipid index: A total of 1260 patients were subjected to coronary arteriography examination. In the morning, they were fasting and received approximately 3 ml sampling of intravenous blood. Blood lipid content was detected by using Hitachi 7600 automated chemistry analyzer (Hitachi, Japan). The parameters including triglyceride (TG), serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and free fatty acid (FFA) were measured by using biochemical methods. The levels of lipoprotein a (Lp(a)), apolipoprotein AI (ApoAI), apolipoprotein B (ApoB) were detected by using immunoturbidimetric assay.

Coronary angiography: All patients underwent multi-position coronary angiography by adopting Seldinger via femoral artery or oar arterial puncture. ST-DDSs medical imaging workstation v3.1 quantitative computer analysis sys-

tem (QCA) was utilized to analyze quantitatively the degree of coronary stenosis. Those subjects with at least one branch blood vessel among left main coronary artery (LM), Left anterior descending coronary artery (LAD), left circumflex artery (LCX) and right coronary artery (RCA) having an inside diameter stenosis ≥50% were clinically diagnosed with aortic valve sclerosis. In each group, the patients were subdivided into CHD and control subgroups on the basis of coronary angiography results.

Evaluation of aortic valve sclerosis severity: All subjects diagnosed with aortic valve sclerosis by coronary angiography to evaluate the degree of aortic valve sclerosis. The number of vascular branches affected by aortic valve sclerosis: the lesions affecting LAD, LCX or RCA were counted as one branch. For LM pathological lesions, LAD involvement and LCX stenosis were regarded as two branches. The sum of stenosis vascular branches represented the quantity of aortic valve sclerosis-affected vessels. Gensini score [8]: the degree of coronary stenosis was quantitatively analyzed by coronal arteries imaging partition evaluation criteria proposed by American Heart Association and Gemini score system. The degree of angiostenosis for each branch (LM, LAD, LCX and RCA) was quantitatively evaluated, respectively. No sign of stenosis was counted as 0, stenosis degree <25% was deemed as one point, 25%-50% as two points, 50%-75% as four points, 75%-90% as eight points, 90%-99% as 16 points and ≥99% as 32 points. The stenosis scores of each branch were multiplied by the following coefficients. LM lesions ×5.0; LAD proximal lesions ×2.5, LAD middle lesions ×1.5, LAD distal lesions ×1.0. Pathological changes of the opposite branch: the first opposite branch lesions ×1.0, the second opposite branch lesions ×0.5, LCX proximal lesions ×2.5, LCX distal lesions ×1.0, descending posterior branch lesions ×1.0, posterior collateral branch lesions ×0.5; RCA proximal, middle and distal lesions all ×1.0. The sum of the scores of all branches equated to the total score of the severity of aortic valve sclerosis.

Statistical analysis

SPSS 17.0 statistical software was utilized for data analysis (SPSS, Chicago, IL, USA). Descriptive continuous variables were statistically analyzed by mean $\overline{x}$ ± standard deviation (SD).

Table 1. Comparison of all parameters among different age and control groups

Parameters	Young-aged group (30-59 years)			Middle-aged group (60-74 years)			Elderly group (75-93 years)		
	Aortic valve sclerosis subgroup (n=72)	Control subgroup (n=145)	t	Aortic valve sclerosis subgroup (n=331)	Control subgroup (n=230)	t	Aortic valve sclerosis subgroup (n=275)	Control subgroup (n=160)	t
Age	55.13±4.32	54.01±5.66	-2.997b	68.55±4.25	67.11±4.15	-3.824b	79.21±3.33	78.55±3.12	-0.377
Gender			4.137a***			4.460a***			4.852a***
Male	33 (41.77%)	46 (58.23%)		149 (64.22%)	83 (35.78%)		161 (71.88%)	63 (28.12%)	
Female	39 (28.26%)	99 (77.34%)		182 (55.32%)	147 (44.68%)		161 (62.40%)	97 (37.60%)	
TG	2.27±1.27	1.98±1.02	-0.819	1.87±1.55	1.73±1.06	-1.130	1.87±0.42	1.63±0.51	-0.667
TC	5.10±1.15	5.01±1.16	-0.474	5.85±1.16	4.85±1.26	0.087a	4.91±1.22	3.78±1.03	-1.062a
HDL-C	1.29±0.63	1.26±0.19	-0.271	1.31±0.54	1.29±0.48	-0.352	1.26±0.47	1.38±0.58	-2.321a
LDL-C	3.06±0.85	2.97±1.35	-0.439	3.88±1.05	2.72±0.92	-1.758b	3.94±1.24	2.73±1.12	0.989b
Lp(a)	227.00	107.00	-4.415b**	159.00	130.60	-2.856b**	213.50	134.10	-4.566
ApoAI	1.56±0.79	1.43±0.22	-0.975	1.38±0.26	1.42±0.27	1.500	1.42±0.27	1.43±0.24	0.244
ApoB	1.07±0.11	0.84±0.23	-1.958a	0.86±0.22	0.83±0.22	-1.348	0.94±0.83	0.82±0.23	-1.610
FFA	0.62±0.33	0.67±0.39	0.834	0.79±0.47	0.78±0.40	-0.325	0.78±0.41	0.80±0.46	0.389
Aortic valve sclerosis branches	1.67±0.98			1.89±1.02			2.36±1.14		
Gensini score	16.75±7.48			22.28±13.12			29.44±18.25		

Note: *denotes median (interval of quartile and percentage); **denotes Z value; ***denotes χ^2; Comparison between different age and control groups, a denotes $P<0.05$; b denotes $P<0.01$.

Table 2. Comparison of aortic valve sclerosis and Gensini score among different age groups

Groups	Aortic valve sclerosis branches		Gensini score	
	Mean value	P	Mean value	P
Groups I-II	-0.259	0.060	-6.324	0.056
Groups II-III	-0.212	0.010b	-5.742	0.004b
Groups III-I	1.471	<0.001b	12.067	<0.001b

Categorial variables were expressed as the median, interval of quartile and percentage. Statistical comparison among different groups was conducted using normal distribution. Measurement data were analyzed using *t*-test and one-way ANOVA. Paired-comparison was conducted by LSD. *P*<0.05 was considered as statistical significance.

Results

Prevalence of aortic valve sclerosis

In the young-aged group, 33.18% (72/217) of patients suffered from aortic valve sclerosis, mean aged (55.13±4.35) years, including 33 males (45.83%) and 39 females (54.17). In middle-aged group, 331 of 561 patients (59%) were clinically diagnosed with aortic valve sclerosis, aged (68.71±3.83) years on average, including 149 males (45.02%) and 182 females (54.98%). In the elderly group, 322 among 482 subjects (66.80%) were diagnosed with aortic valve sclerosis, aged (78.88±3.24) years on average, 161 males (50%) and 161 females (50%).

Comparison of age, gender and blood lipid levels

In all groups, the percentage of male subjects was significantly higher compared with that of female counterparts (all *P*<0.05). For the young- and middle-aged groups, patients in the aortic valve sclerosis subgroup was significantly older compared with those in the control subgroup (*P*<0.01). In the middle-aged and elderly groups, Lp(a), TC and LDL-C levels in the aortic valve sclerosis subgroups were elevated or significantly higher compared with those in the control subgroup (all *P*<0.05). Serum HDL-C level in aortic valve sclerosis patients in the elderly group was significantly lower than that in the control subgroup (*P*<0.05). In the young-

aged group, Lp(a) level in middle-aged patients was significantly enhanced (*P*<0.01) and ApoB level was significantly increased (*P*<0.05) than the healthy counterparts (**Table 1**).

Comparison of blood lipid levels between two subgroups within each group

FFA level in the young-aged group was significantly higher compared with those in the middle-aged and elderly groups (*P*<0.05). No statistical significance was observed in Lp(a), TG, TC, HDL-C, LDL-C, ApoAI and ApoB levels of CHD patients among the young-, middle-aged and elderly groups.

Comparison of aortic valve sclerosis severity among different age groups

The number of coronary stenosis vessels in the elderly group was significantly higher compared with those in the young- and middle-aged groups (*P*<0.01). The count of coronary vascular stenosis in the middle-aged group was increased compared with that in the young-aged group, whereas no statistical significance was observed (**Table 2**).

Comparison of Gemini scores among different age groups

Gensini score in aortic valve sclerosis patients from the middle-aged group was elevated than that from the young-aged group with no statistical significance. Gensini score in aortic valve sclerosis patients from the elderly group was significantly higher compared with those from the young- and middle-aged groups (*P*<0.01), as illustrated in **Table 3**. Among 725 patients with aortic valve sclerosis, the severity of aortic valve sclerosis (Gemini score) as dependent variable (Gemini score of 1-10=1, 10.5-40>2, >40=3) and patients' age, gender and blood lipid as independent variables assessed by ordered logistic regression analysis. Lp(a), age and LDL-C were integrated into the regression equation. Lp(a), aging and LDL-C were independent risk factors of aggravating severity of aortic valve sclerosis (β=0.012=0.043 and 0.072, both *P*<0.05) (**Table 3**).

Correlation among age, blood lipid and aortic valve sclerosis

Aortic valve sclerosis branch was defined as a dependent variable (branch =0 denotes 1,

Table 3. Logistic regression analysis of Gensini score

	Regression coefficient (β)	Standard error	Wald value	P	Regression co-efficient 95% CI	
					Lower limit	Upper limit
Lp(a)	0.012	0.003	8.289	0.004	0.004	0.019
LDL-C	0.072	0.025	9.451	0.042	0.014	0.247
Age	0.043	0.010	17.409	<0.001	0.023	0.063

Table 4. Ordered logistic regression analysis of CHD branches

	Regression coefficient (β)	Standard error	Wald value	P	Regression co-efficient 95% CI	
					Lower limit	Upper limit
Lp(a)	0.011	0.039	7.259	0.007	0.002	0.018
LDL-C	0.222	0.102	4.717	0.003	0.022	0.423
Age	0.040	0.010	16.091	<0.001	0.021	0.060

branch=1 denotes 2 and branch ≥2 denotes 3) and patients' age, gender and blood lipid as independent variables analyzed by using logistic regression analysis. Three variables including Lp(a), LDL-C and age were included into the regression equation. Lp(a), LDL-C and aging were all regarded as risk factors of aortic valve sclerosis (β=0.011=0.222 and 0.040, both *P*<0.01) (**Table 4**).

Discussion

As a special macromolecule lipoprotein containing abundant cholesterol with similar structures to LDL, Lp(a) comprises LDL and Apo (a) components with surface cholesterol and phospholipid mixed with hydrophilicity apolipoprotein. Lp(a) shares the structural homology with profibrinolysin (PLG). Lp(a) is correlated with As and thrombosis [9, 10], and the concentration is mainly determined by hereditary factors [11]. The concentration of serum Lp(a) significantly varies among different populations. However, the individual concentration of serum Lp(a) remains relatively stable and is not affected by the use of statins medications. In addition, it is not influenced by patients' age, gender, smoking habit, diet, environment or lipid metabolism [12]. Previous studies [13] have indicated that serum Lp(a) level is positively correlated with the spots within coronary artery. Danesh J, et al [14] analyzed the correlation between serum Lp(a) level and aortic valve sclerosis and demonstrated that elevated concentration of serum Lp(a) is an independent risk factor of the incidence of aortic valve sclerosis.

Scholars found that serum Lp(a) and LDL-C level play a synergistic effect with aortic valve sclerosis. Under the influence of high level of LDLC alone, the incidence of aortic valve sclerosis may be enhanced. The underlying mechanism is probably because Lp(a) is able to enhance the oxidation stress. Consequently, the correlation between serum Lp(a) level and atherosclerosis of coronary artery degree was statistically analyzed in this clinical trial, aiming to investigate whether serum Lp(a) serves as an independent risk factor of the incidence of aortic valve sclerosis.

In this investigation, the serum Lp(a) level in aortic valve sclerosis subgroup was significantly higher compared with that in control subgroup. No statistical significance was noted in terms of serum Lp(a) levels in aortic valve sclerosis patients among different age groups. Ordered logistic regression analysis revealed that the increases in serum Lp(a) level remains an independent risk factor of aortic valve sclerosis branches and severity after adjustment of TG, TC, HDL-C and LDL-C. It is concluded that serum Lp(a) level plays a pivotal role in the incidence and development of aortic valve sclerosis by interfering lipid metabolism and fibrinolytic system. Underlying mechanisms: (1) Lp(a) is able to accelerate the oxidation of endothelial cells and smooth muscle cells o form Lp(a) ox-Lipoprotein(a) [ox-Lp(a)], which may increase the uptake rate of macrophage and the ox-Lp(a) phagocytosis evolves into foam cells [15], providing a prerequisite for the spot formation and smooth muscle cell proliferation. Meanwhile, Lp(a) possesses the function of osmosism deposits on the vascular wall, penetrates through endothelial, disrupts endothelial diastole function and causes endothelial dysfunction. (2) Lp(a) can accelerate the spot inflammation and influence spot stability [16]. (3) Lp(a) shares structural homology with PLG [11], therefore competitively binding with PLG receptor and interferes the transformation from profibrinolysin into plasmin. Hence, it decreases the plasma content of plasmin, reduces the incidence

of thrombolysis and is involved in thrombosis. In addition, the present study also demonstrated that aging, high level of LDL-C, aortic valve sclerosis branches and Gensini score are significantly correlated.

No effective means have been developed to maintain serum Lp(a) level [17]. Recent studies [18] revealed that nicotinic acid preparation is able to reduce serum Lp(a) level by approximately 20%, decreases the levels of LDL-C,TG and ApoB whereas increases HDL-C concentration. Serum Lp(a) level in individuals is relatively stable and is not influenced by diet, environment and use of hypolipidemic drugs. Consequently, the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) proposed that nicotinic acid supplement should be considered besides the reduction of LDL-C level for patients with a high risk of aortic valve sclerosis. However, whether clinical benefits of intake of nicotinic acid preparation result from LDL-C, TG and ApoB reduction, HDL-C level elevation or serum Lp(a) level declining remain to be investigated by more clinical researches.

Much evidence has demonstrated that LDL-C is an independent risk factor of aortic valve sclerosis. LDL-C permeates beneath the endangium and is absorbed by macrophage and evolves into foam cells. These cells fuse to form the core of lipid spots, which accelerates inflammatory response and promotes the incidence of aortic valve sclerosis. The low level of HDL-C damages the function of reverse cholesterol transport, resists lipid oxidation modification, improves endothelial function and averts the incidence of thrombosis. In this study, serum HDL-C level in aortic valve sclerosis patients was lower compared with control subgroup in senile population. Aortic valve sclerosis branches increased and the degree of pathological changes was aggravated over age. Aging not only significantly enhanced the incidence of aortic valve sclerosis, but also serves as a factor of poor prognosis of aortic valve sclerosis. No statistical significance was observed regarding HDL-C level between the aortic valve sclerosis and healthy controls in the young- and middle-aged groups, which is possibly associated with HDL-C oxidation modification by a variety of factors and loss of atherosclerosis effect due to HDL-C oxidation formation (ox-HDL). Previous studies [19-24] indicat-

ed that the actual protective effect of HDL is not only determined by the quantity alone (HDL-C level), but also by the quality of resisting aortic valve sclerosis. Aging, high level of LDL-C and low level of HDL-C play a synergistic effect in the incidence of aortic valve sclerosis and collectively accelerate the incidence and progress of aortic valve sclerosis along with Lp(a).

Taken together, aging and serum Lp(a) elevation are independent risk factors of aortic valve sclerosis, which accelerate the incidence of aortic valve sclerosis and play a vital role in predicting the incidence and progress of aortic valve sclerosis. No convincing evidence supports that medical drugs may reduce serum Lp(a) level and bring about favorable clinical benefits. Consequently, much attention should be paid to the primary and secondary prevention of aortic valve sclerosis in senile population with high level of Lp(a).

Disclosure of conflict of interest

None.

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