Serum Lipoprotein-A in Patients with Aortic Valve Sclerosis as A Predictor for Severity of Coronary Artery Disease

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Abstract: Objective: The aim of this study was to assess the association of serum level of lipoprotein (a) [Lp (a)] with severity of coronary artery disease (CAD) in aortic valve sclerosis (AVS) patients. **Background**: The relation between AVS on one hand and severity of CAD and complexity of coronary lesions on the other hand, was not clearly established by previous investigators. Also the correlation between Lp (a) and severity of CAD in AVS using SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) score was not tested before. **Methods**: In this study, a total of 50 eligible patients with AVS were divided into 2 groups: high and normal Lp (a) with cut off level (30 mg /dl). We included assessment of all major cardiovascular risk factors, transthoracic echocardiography and coronary lesion characteristics by angiography. SYNTAX scoringwas used. **Results**: There was significant relation between severity and number of diseased coronaries on one hand and Lp (a) levels on the other hand in AVS patients. **Conclusions**: Serum Lp (a) is an independent predictor for severity of coronary lesions among AVS patients.

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1. Introduction

Aortic sclerosis was until recently considered a benign degenerative process of the elderly. But, it was observed that aortic sclerosis has a higher incidence of myocardial infarction (MI) and cardiovascular deaths. (**1**)

Because aortic valve sclerosis (AVS) does not itself cause sufficient hemodynamic perturbations to affect cardiovascular function, the mechanisms of its association with poor cardiovascular outcomes are not well established. But, as it is the site of frequent turbulence and mechanical shear stress from blood flow, the aortic valve, acts as a focus for the deposition of lipids implemented in the atherosclerosis process. (**2**)

Histopathologic similarities were found between degenerative aortic valve disease and atherosclerotic coronary artery disease (CAD) (**3**), with evidence of inflammation common to both conditions. Inflammation is an important underlying mechanism for the pathophysiology of chronic atherosclerotic process and has also been implicated in the initiation of coronary plaque rupture. (**4**)

Several studies have linked aortic valve sclerosis with astherosclerotic risk factors, systemic and coronary astherosclerosis as well as cardiovascular morbidity and mortality, but these data are conflicting.

Coronary artery disease is the largest leading cause of death worldwide. 25% of all deaths in the developed countries subjects aged 35 years and older owing to CAD and more than half of acute coronary syndromes especially acute myocardial infarctions occur without previous history or symptoms of CAD. Similarities between developed and developing countries in life style and food habits made these figures to be equal. (**5**)

Serum lipoprotein (a) [Lp (a)] is an independent macromolecular lipoprotein with a high degree of homology and specific antigenicity, which plays an important role in the incidence and development of atherosclerotic and thrombotic processes by interfering with lipid metabolism and fibrinolytic system, and this is significantly different from the metabolic pathways of alternative apolipoproteins. (**6, 7**)

Many investigators have suggested that Lp (a) may be an independent risk factor for cardiovascular disease (**8,9**) and have observed that serum Lp (a) level is positively correlated with both incidence and severity of cardiovascular disease. (**10**) We, therefore aimed to determine the association lof serum level of Lp (a) with the severity and complexity of coronary lesions in AVS patients using SYNTAX scoring (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery).

2. Patients and method

Study group

This prospective study was performed including 50 eligible ischemic heart disease (IHD) patients presenting with chest pain and /or dyspnea. Informed consents were taken from all patients with approval of

Ethics Committee of Menoufia University. Patients were subdivided into 2 groups; Group I (high risky LP (a) level) included 29 patients and Group II (normal non risky level) included 21 patients with cut off level of serum Lp (a) of 30 mg /dl.

Inclusion criteria included IHD patients with different grades of AVS submitted to coronary angiography. Exclusion criteria included aortic valve stenosis (peak velocity ≥ 2 m/s.), prosthetic aortic or mitral valves, age below18 years, chronic steroid use, immunosuppressive therapy and chronic inflammatory diseases (such as inflammatory bowel disease, rheumatoid arthritis and systemic lupus erythematosus).

Methods

Each patient was subjected to full history taking, thorough clinical examination, 12-lead ECG and:

2D echocardiography with Vivid 9 GE: M-mode and doppler examination were performed to determine aortic valve structure and function, increase thickness, increase echogenicity, calcification, pressure gradient, peak v and the degree of AVS (from 1-3).

Full laboratory investigations including measurement of serum lipoprotein-a (determined by Enzyme Linked Immunosorbent Assay {ELISA} technique using kits provided from DRG International Inc., USA).

Coronary angiography (CA) using SYNTAX score to analyze the number and severity of coronary lesion in the main epicardial coronary arteries.

Statistical analysis

Data were collected, tabulated, and statistically analyzed with an IBM compatible personal computer with SPSS statistical package version 17Chicago 2008: SPSS Inc.

Descriptive statistics: such as percentage (%), mean (x), and standard deviation (SD) were determined.

Analytical statistics: these were ascertained using the X2 -test, Fisher's exact test, the Mann-Whitney U-test, the Kruskal-Wallis test, and analysis of variance (F), with a level of significance as follows: p-value less than 0.05 was considered significant, p-value less than 0.001 as highly significant, and p-value greater than 0.05 as non-significant.

3. Results:

Out of 63 patients, 50 patients were eligible and highly selected: Group I (29 patients) with high serum Lp (a) <30 mg /dl and group II (21 patients) with Lp (a)>30 mg /dl.

Regarding the age and gender of the studied population, it was shown that the age of all patients 60.76 years with SD (standard deviation) ± 5.39 and 16 patients were females with a percentage of 32 % of all patients and 34 were males with a percentage of 68 % of all patients. (Table 1)

As regard risk factors distribution among studied population: 58% (29 patients) of all studied population had high risky Lpa level and 42 % (21 patients) had normal or non-risky levels. Also 50% (25 patients) of all patients were smokers, 26% (13 patients) were ex-smokers and 24% (12 patients) were nonsmokers. Laboratory findings showed high total cholesterol <200 mg/dl and total leucocytic count (TLC)<11 mg/dl in 54% (27 patients) of all population versus 46% (23 patients) with normal or low levels. Hypertension and diabetes were found in 56% (28 patients) versus 44% (22 patients) who were non hypertensives or diabetics. Moreover, 76% (38 patients) had clear family history of IHD versus 24% (12 patients) with no family history of IHD. (Table 2)

Table1: Age and gender of the studied population:

Variable	Summary statistics
Age/years	
Mean ± SD*	60.76±5.39
Median (range)	60 (54-73)
Gender	
Females	16 (32.00%)
Males	34 (68.00%)

*SD= standard deviation

Table 2: Risk factors distribution of the studied population:

Risk factor	Number n (%) 50 patients
Smoking	
Non-smoker	12 (24.00%)
Smoker	25 (50.00%)
Ex-smoker	13 (26.00%)
Family history of IHD*	
No	12 (24.00%)
Yes	38 (76.00%)
LPa†	
Normal level	21 (42.00%)
High level	29 (58.00%)
Hypertension	
No	22 (44.00%)
Yes	28 (56.00%)
Diabetes	
No	22 (44.00%)
Yes	28 (56.00%)
Total cholesterol	
Normal	23 (46.00%)
high	27 (54.00%)
TLC ‡	
Normal	23 (46.00%)
high	27 (54.00%)

* IHD=Ischemic heart disease, † LPa = Lipoprotein-a, ‡TLC= Total leucocytic count.

There was highly significant increase of number of diseased epicardial coronary vessels by CA in group I with high risky level of Lp (a) compared to group II with normal level with p-value (>0.001). (Table 3)

Also SYNTAX score was high (35.07 ±6.08SD) in group I with high Lp (a) level compared to group II with low Lp (a) (14.76 ±4.5 SD) with significant p-value (>0.01). (Table 4)

Table 3: Comparison of the number of diseased epicardial vessels in relation to Lp (a) level

Number of diseased vessels	Lp (a) *levels		P. value
	Normal level N=21	High level N=29	
One vessel	14 (66.66%)	1 (3.45%)	
Two vessels	6 (28.57%)	13 (44.82%)	
Three vessels	1 (4.77%)	15 (51.73%)	
Total	21 (100%)	29 (100%)	<0.001

*Lp (a)=Lipoprotein-a

Table 4: Comparison between Lpa levels according to SYNTAX score

SYNTAX score	Normal Lp (a) * level N=21	High Lp (a) level N=29	P. value
Mean ± SD†	14.76 ±4.5	35.07 ±6.08	<0.01

*Lp (a)= Lipoprotein-asis, †SD= standard deviation.

4. Discussion

Our study was conducted on 63 patients presented to Menofiya University Hospitals with IHD. 13 of them were not eligible for the study, the remaining 50 eligible patients were highly selected and subdivided into 2 groups according to the level of Lp (a) with cut off level of 30 mg/dl. Full laboratory investigations were done to reveal associating cardiovascular risk factors. C.A. lastly was performed to all patients to evaluate the severity of coronary artery lesionsand the possibility of intervention (SYNTAX score was used).

In this current study, wefound a very highly significant increase in the prevalence and severity of coronary atherosclerosis detected by CA among patients having high serum level of Lp (a) > 30 mg/dl compared to those with normal level < 30mg/dl. This result was similar to that conducted by Lima et al (**11**) and other previous studies (**12-14**) who found that serum levels of Lp (a) is increasing progressively according to severity of coronary atheromatosis.

In the same context, CA revealed very highly significant increase in the number of diseased epicardial coronary arteries in patients with high serum Lp (a) compared to those with normal Lp (a) levels (with cut off value: 30 mg/dl). This is in agreement with Rajasekhar et al (**15**) who observed that serum Lp (a) levels were higher significantly in triple vessel than single vessel disease but not in two vessel disease which may be due to small sample size and these were similar to other studies. (**16, 17**)

On the other hand, Schwartzman et al (**18**) did not find any significant difference between plasma Lp (a) levels in different classes of coronary artery disease patients according to the number of diseased vessels or the extent of coronary disease angiographically. These findings were similar to those of other investigators. (**19, 20**)

SYNTAX score which is the most recent and reliable angiographic tool for quantification of severity and complexity of coronary artery disease and prediction of outcomes of coronary intervention based on anatomical complexity, was used in our present study and was significantly higher in those with high Lp (a) compared to those with normal Lp (a) levels with cut off value 22 for mild and 34 for high risk scores. (**21, 22**) To our knowledge, it is the first time to implement SYNTAX score as to correlate the severity of AVS with CAD severity.

Gender difference in relation to Lp (a) level was observed in our present study as female gender was significantly correlated with high serum Lp (a) unlike that observed by Pedreno et al (**23**) who showed no gender differences in Lp (a) levels in both patients and controls. This is possibly explained by the lowering

effect of testosterone in males andpresence of menopausal status in women with CHD.

Regarding serum total cholesterol, it was significantly increased in patients with severe coronary lesions and those with severe AVS (grade III) compared to non-severe coronary lesions or mild AVS respectively, and this was co-incident with many previous studies which also suggested the role of statins in decreasing the progression of aortic valve calcification. (**24-26**).

Also, Age and serum Lp (a) were found to be independent risk factors for severity of stenotic lesion (s) in the main epicardial arteries in patients with severe AVS compared with those with mild grades. And these results were similar to that of Bhatt et al (**27**) and others. (**28-30**)

Conclusions:

Serum Lp (a) is an independent predictor factor for the severity and complexity of coronary artery lesions by coronary angiography in AVS patients. Also it is associated with more severe grade of AVS in those patients.

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