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Original Article

High Serum Lipoprotein (a) as an Independent Risk Factor for Premature Coronary Artery Disease in the Iranian Population

Behshad Naghshtabrizi, *[1] MD; Shahram Homayounfar, [1] MD; Manoochehr Karami, [2] MS, PhD; Maryam Tazang, [1] MD

ABSTRACT

Background: The predisposing factors of coronary artery disease (CAD) include hypertension, diabetes mellitus, hyperlipidemia, smoking, and positive family history. Yet, new risk factors that can lead to CAD in early ages have been investigated in recent studies. The present study aimed to evaluate the role of a number of suggested risk factors in the previous studies—including serum levels of homocysteine, fibrinogen, and lipoprotein (a)—in patients suffering from early CAD in Iran.

Methods: This descriptive cross-sectional study was conducted on 50 patients with the 1st presentation of CAD without any previous treatment. CAD was confirmed by selective coronary angiography, and all the major risk factors were negative. The serum levels of the above-mentioned factors were measured. Then, the data were analyzed using SPSS, version 20. A *P* value less than 0.05 was considered statistically significant.

Results: The study participants comprised 34 males aged 45 years or below and 16 females aged 55 years or below. The mean serum levels of homocysteine, fibrinogen, and lipoprotein (a), which were measured and compared to normal levels, were 13.22 mg/dL (P=0.305), 4.019 g/L (P=0.305), and 2.341 µmol/L (P<0.001), respectively.

Conclusions: The findings of this study revealed lipoprotein (a) as an independent risk factor in premature CAD in the Iranian population. However, this was not the case regarding homocysteine and fibrinogen. The acceptance or rejection of this hypothesis requires more extensive studies with larger sample sizes. ***(Iranian Heart Journal 2017; 18(2):17-22)***

Keywords: Coronary artery disease, Homocysteine, Fibrinogen, Serum Lp(a)

[1] Farshchian Heart Center, Hamadan University of Medical Sciences, Hamadan, I.R. Iran.
[2] Social Determinants of Health Research Center, Hamadan University of Medical Sciences, Hamadan, I.R. Iran.

*** Corresponding Author:** Behshad Naghshtabrizi, MD; Farshchian Heart Center, Hamadan University of Medical Sciences, Hamadan, I.R. Iran.
E-mail: behshadnaghshtabrizi@yahoo.com **Tel:** 09123493924

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Coronary artery disease (CAD) occurs due to the accumulation of atheromatous plaques consisting of cholesterol on the walls of the coronary vessels. Since coronary vessels are responsible for transmitting oxygen and nutrients to the myocardium, the accumulation of atheromatous plaques in the lumens of these vessels results in a decrease in their diameter and, consequently, shortage

of oxygen and nutrients in cardiac cells. This tightness occurs either as a chronic (by increase in the size of atheromatous plaques) or an acute process (by tearing atheromatous plaques and activating coagulative process). [1]

The incidence of CAD in young adults is terms "early onset CAD". This disease has been referred to by various terms such as early onset CAD and young CAD, in different articles. [2] The maximum age of patients suffering from early onset CAD is 45 years or less in males and 55 years or less in females. [3]

Several processes such as lipid disorder, platelet activation, thrombosis, endothelial dysfunction, inflammation, oxidative stress, smooth muscle cell proliferation, matrix metabolism changes, and genetic factors are involved in the creation of atherosclerotic plaques. [4] These risk factors play a significant role in creating and increasing the speed of the atherosclerosis process. These risk factors include hypertension, hyperlipidemia, smoking, diabetes mellitus, obesity, and non-modifiable risk factors such as age, sex, and positive family history. [4] These major risk factors comprise only 50% of CAD cases. [5] It should be noted that smoking is the most prevalent risk factor among the youth. [6]

To date, a few new atherosclerosis risk factors have been suggested to detect individuals with a high risk of developing premature CAD, including high levels of lipoprotein (a). Among high lipoprotein (a) levels, high homocysteine levels, thrombotic pathologic risk factors, plasminogen activator inhibiter-1 (PAI-1), and thromboxane, [5] high levels of lipoprotein (a), homocysteine, and fibrinogen are more likely to be related to CAD and were investigated in the current study.

Lipoprotein (a) is similar to low-density lipoprotein (LDL), which is created by linkage of glycosylated apolipoprotein (a) and polymorph to B-100 lipoprotein. [7] High serum levels of lipoprotein (a) have been approximately observed in one-third of patients suffering from CAD. Further, the results of several clinical and epidemiological studies have proved lipoprotein (a) as a risk factor for CAD. [8]

Thus far, many studies have revealed that high levels of lipoprotein (a) (> 1.07 µml/lit or > 30 mg/dL) are related to CAD, premature CAD, myocardial infarction, restenosis after percutaneous coronary intervention, and cerebrovascular disease. [9] Furthermore, high lipoprotein (a) levels have an adverse effect on the outcome of patients undergoing coronary revascularization. [10]

Homocysteine is an amino acid bearing sulfur, which is produced as a medium product during methionine amino acid metabolism. The hypothesis of the influence of homocysteine on atherosclerosis was mentioned in 1969 for the 1st time by observing peripheral coronary and cerebrovascular atherothrombosis in children suffering from homocystinuria. Hyperhomocysteinemia causes athero-thrombosis through unknown mechanisms. In this regard, various theories have been mentioned, including the impact on platelet activity and endothelial and smooth muscle cell function. In fact, homocysteine increases the production of thromboxane A2, platelet hyperaggregability, and amount of lipoprotein (a) binding to fibrin and decreases the protecting influence of relaxing factors extracted from the endothelium. It has pre-coagulative effects, as well. [11] Hyper-homocysteinemia is considered for amounts more than 12.84 µml/lit. [12]

Fibrinogen is a glycoprotein activated at the final stage of coagulation cascade. Fibrinogen stimulates smooth muscle cell proliferation and platelet hyperaggregability and increases blood viscosity and mitogenic effects. Hyperfibrinogenemia may be a sign of an inflammatory process related to atherosclerosis. [13] High fibrinogen levels are also allied to aging, female sex, high triglyceride and LDL levels, low high-density lipoprotein (HDL) levels, obesity, smoking,

physical inactivity, family history of premature CAD, diabetes, and hypertension. [14] The normal fibrinogen level is 3.55 ± 0.63 gr/lit. The results of a previous study demonstrated that this level was 3.82 ± 0.68 gr/lit among young patients with premature CAD. [15]

The present study aimed to assess the above-mentioned risk factors for CAD among patients suffering from premature CAD in Iran. It seems that genetic susceptibility may affect these risk factors in different populations.

METHODS

This descriptive cross-sectional study was performed on 50 patients admitted with premature CAD detected by angiography with physicians' confirmation between January and September 2015. The corresponding criteria were 50% or more obstruction in the diameter of the left main vessels and 70% or more obstruction in the diameter of the other coronaries. Written informed consent was obtained from the participants prior to the study. The inclusion criteria of the study were comprised of suffering from premature CAD as the 1st presentation of CAD and having no major risk factors—including hypertension, hyperlipidemia, diabetes mellitus, cigarette smoking, obesity, and positive family history. Accordingly, the patients included were not treated for CAD before.

First, 10cc blood was drawn from the participants and then, the serum levels of homocysteine, fibrinogen, and lipoprotein (a) were measured. The serum homocysteine level was measured using enzymatic TIC, serum fibrinogen level via the coagulate method, and serum lipoprotein (a) level via immuno TIC. The fibrinogen and homocysteine levels were measured up to 1 hour after drawing blood to reduce pseudo-positive results.

The data were collected using the patients' laboratory reports and were recorded in a related checklist. Accordingly, serum homocysteine levels more than 12.84 mg/dL, serum lipoprotein (a) levels more than 1.07 mμ/L, and serum fibrinogen levels more than 4.18 g/L were considered abnormal. The patients' ages were recorded, as well. It is worthy of note that the records were investigated anonymously and each patient was given a code.

Finally, the data were analyzed using SPSS, version 20. Descriptive statistics such as mean (SD) and other central tendency indices were used to describe the study population. To assess the statistical significance between the serum levels of homocysteine, fibrinogen, and lipoprotein (a) in comparison to hypothesized values, we employed 1-sample *t*- tests. A *P* value less than 0.05 was considered statistically significant.

RESULTS

This descriptive study was conducted on 50 patients (34 [68%] males aged ≤45 y and 16 [32%] females aged ≤55 y) referred to Farshchian Heart Center in Hamedan. The study participants encompassed patients suffering from premature CAD with 50% or more obstruction in the diameter of the left main vessel and 70% or more obstruction in the diameter of the other coronary vessels proved through angiography. The patients had no major risk factors such as hypertension, hyperlipidemia, diabetes mellitus, cigarette smoking, obesity, and positive family history. All the data gathered in the present study are illustrated in tables 1 to 4. The mean serum levels of homocysteine, fibrinogen, and lipoprotein (a) were measured and compared to their respective normal mean levels. The mean serum level of homocysteine was 13.22 mg/dL (*P*=0.305), mean serum level of fibrinogen was 4.01 g/L (*P*=0.305), and mean serum level of lipoprotein (a) was 2.34 μmol/L (*P*<0.001) in the study population.

Table 1. Mean (standard deviation), maximum, minimum, and mode of the 3 factors under investigation

Factors	Mean	SD	Max	Min	Mode
Lipoprotein(a)	2.341	1.46	5.940	0.285	2.320
Fibrinogen	4.019	1.16	7.900	1.580	4.340
Homocysteine	13.222	4.99	32.546	6.509	9.616

Table 2. Mean (standard deviation), maximum, minimum, and mode of the 3 study factors among the male patients

Factors	Mean	SD	Max	Min	Mode
Lipoprotein(a)	2.124	1.35	5.940	0.318	0.678
Fibrinogen	3.905	1.18	6.500	1.580	4.340
Homocysteine	13.357	4.09	23.670	7.397	11.465

Table 3. Mean (standard deviation), maximum, minimum, and mode of the 3 study factors among the female patients

Factors	Mean	SD	Max	Min	Mode
Lipoprotein(a)	2.804	1.63	5.533	0.285	2.927
Fibrinogen	4.261	1.1	7.900	3.060	4.510
Homocysteine	12.935	6.67	32.546	6.509	9.616

Table 4. Mean difference of the risk factors compared to their normal levels in the study population

Factors	Mean	Normal Amount	Variance	*P*
Lipoprotein(a)	2.341 µml/L	1.35µm.l/L	1.271	<0.001
Fibrinogen	4. 019 µml/L	4.18 g/L	0.161	0.305
Homocysteine	13.222 mg/dL	12.84 mg/dL	0.382	0.305

DISCUSSION

Findings have indicated that age at the development of CAD has decreased during the recent years. Cardiovascular diseases are the main cause of fatality in both developed and developing countries. Risk factors such as hypertension, diabetes mellitus, hyperlipidemia, cigarette smoking, obesity, and positive family history have been definitely proved to cause cardiovascular diseases. Nonetheless, cardiovascular incidents occur in patients without these risk factors at younger ages. Therefore, these main risk factors were eliminated before investigating the impact of homocysteine, fibrinogen, and lipoprotein (a), as peripheral risk factors, in patients suffering from premature CAD. Herein, the study results are compared to those of other similar studies conducted in this field.

Shenoy et al [16] measured the homocysteine level before performing angiography. The results revealed that the homocysteine level was significantly higher in the patients suffering from CAD than in those without CAD (P<0.001). [16] In that study, the patients were aged between 31 and 65 years and CAD was defined as any degree of coronary artery stenosis, which is different from the population in our study. On the other hand, one of the strong points of our study is the elimination of other risk factors, which might justify the difference between the results.

Yusuf et al [17] conducted a similar study in which the serum level of lipoprotein (a) was measured in 150 patients suffering from CAD (1-, 2-, or 3-vessel disease) and compared to the control group. The authors reported that a lipoprotein (a) serum level greater than 40 mg/dL was an independent risk factor for CAD. According to their results, increased

lipoprotein (a) levels were accompanied by an increase in acute coronary syndrome and CAD with the involvement of more coronary arteries. Approximately similar results were also obtained in the current study. Yet, the advantage of our study is age factor elimination by selecting the samples among younger individuals with similar conditions with respect to the main risk factors.

Another similar study was done by Van loon et al [14] on 353 young patients with their 1st cardiac event (males aged 18–45 y and females aged 18–55 y). The study findings demonstrated that during the average follow-up of 4.2 years, high C-reactive protein (CRP) and fibrinogen levels were related to fatality. Indeed, recurrent events, including all-cause mortality, were related to high levels of CRP and fibrinogen. The difference between the results of that study and those of the present one might be attributed to the difference in patient selection methods.

Banos-Gonzales et al [12] carried out a research on 222 male patients hospitalized to undergo selective coronary angiography. The findings revealed the synergistic effects of high lipoprotein (a) and homocysteine levels on each other and their impact on CAD development. In comparison to that study, the strong points of our study are the selection of the samples out of both male and female patients, elimination of the main risk factors, and investigation of the impact of fibrinogen along with 2 other factors.

Manocha et al [18] suggested that high serum lipoprotein (a) levels were an independent risk factor for CAD and that the upper limits of normal lipoprotein (a) levels were possibly different among different ethnicities. For example, the authors suggested 20 mg/dL for Indians and 30 mg/dL for Caucasians.

Along the same line, Habib et al [19] showed that lipoprotein (a) levels were significantly higher in their patients with CAD than in their healthy individuals, which was associated with more severe and diffused stenosis of the coronary arteries. The result of that study is comparable to ours.

The limitations of our study included its small sample size, its descriptive design, failure to investigate the synergistic effects of the factors, and failure to examine the factors when the patients were fasting. The external validity of our findings is possible. However, given the entity of the study hypothesis, the study findings can be generalized with caution. It is deserving of note that since the main risk factors were not eliminated in any of the previous studies, their results could have been influenced by these factors.

In conclusion, high serum lipoprotein (a) levels constituted an independent risk factor for premature CAD in our sample of the Iranian population.

Conflict of Interest: The authors have no conflict of interests.

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