Original Article

The association between fasting serum insulin, apo-lipoproteins level, and severity of coronary artery involvement in non-diabetic patients

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Abstract

Background: In the previous studies, fasting insulin and apo-lipoproteins are considered as one of the risk-factor of coronary artery disease (CAD) but did not have the same results.

In this study, we attempted to define the association of high fasting insulin and apo-lipoproteins of serum in non-diabetic patients who were afflicted with coronary arteries disease with severity of coronary arteries involvement.

Materials and Methods: This study was conducted between September 2011 and February 2012 on three groups, each one consisting of 100 members while using angiographic scores of Gensini with three equal groups with low, medium, and high stenosis of coronary arteries.

The evaluation of non-diabetic patients afflicted with CADs, included the fasting glucose level less than 126 mg/dl or non-consumption of blood glucose reduction drugs or negativity history of diabetes.

Results: In this study, there were 300 non-diabetic patients afflicted with CAD in three groups of low, medium, and high extremity. Due to attained results, the patients afflicted with high CAD had a higher level of insulin (18.3 ± 0.8) in relation with low and medium groups ($P < 0.001$). As it was observed, the level of serum apo-lipoproteins of A1 (APO-A1) in low group of CAD (175 ± 36.4) is meaningfully higher than its quantity in high-CAD group (158 ± 42.4, $P < 0.001$). Furthermore, the quantity of serum apo-lipoproteins of B (APO-B) in mild CAD group (139 ± 30.4) is meaningfully less than severe CAD group (155.21 ± 29.7, $P < 0.001$).

Conclusion: Our findings show that insulin, APO-A1, APO-B, and total cholesterol measurement is a good case for defining the severity of coronary artery involvement, while high-density lipoprotein, low-density lipoprotein, and triglyceride are not important risk-factors.

Key Words: Apo-lipoprotein A, apo-lipoprotein B, coronary artery disease, fasting serum insulin

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INTRODUCTION

Atherosclerosis of coronary arteries starts in childhood but its symptom shows itself, especially in women, at higher ages.[1] The coronary ischemic diseases are the most common causes of death and risk element of cardiovascular diseases, which intensification with: Cigarette smoking, familial history of early coronary

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diseases, hypertension, familial hyperlipidemia, increase the level of low-density lipoprotein (LDL) and decrease the level of high-density lipoprotein (HDL), diabetes and metabolic syndrome.[2]

Hence, determining these elements and prevent them will decrease the cardiovascular diseases. Study the essential elements in this illness leads to important solutions.

In 2025, the death caused by cardiovascular diseases will exceed from all the other common causes of death.[2]

The clinical studies have shown that the level of lipoproteins (specially HDL and LDL) and apo-lipoproteins (specially decrease of apo-lipoproteins of A [APO-A] and increase of apo-lipoproteins of B [APO-B]) has an essential role in creation of atherosclerosis.[3,4]

The protection effect of HDL on atherosclerosis is accorded with a density higher than 75 mg/dl, which results in age prolonging. Increase in 1% of HDL causes 2-3% decrease of coronary disease.[5] Furthermore, the increase of APO-A1 has a protection effect on atherosclerosis.

APO-A1 is the main apo-lipoprotein of HDL and APO-B is the main protein of LDL — very low-density lipoprotein (VLDL), intermediate density lipoprotein, and residue of chylomicrons. With determination of these two apo-lipoproteins we can predict coronary arteries disease and the severity of coronary artery involvement.[6]

There is a paradoxical result about the role of fasting insulin in non-diabetic patient who were afflicted with atherosclerosis of coronary arteries.[7-9]

Involved mechanism in creation and intensification of atherosclerosis by insulin directly (heart rate increase, sympathetic stimulation, and increase in cardiac output) has shown that hyperinsulinemia has a close association with increase of triglycerides (TGs), decrease of HDL and shrinking and agglomeration of LDL ingredients and the main element of hyperinsulinemia danger is because of lipids change.[10] Also, the increase level of Plasminogen activator inhibitor-1 (PAI-1) (the restrainer of type 1 of plasminogen activation agent) in patient who were afflicted with hyperinsulinemia led to disruption in creation and intensification of coronary artery disease.[11]

The Caerphilly study has showed that hyperinsulinemia is dependent on variables like TG of blood. In addition, the association between hyperinsulinemia and the intensity of coronary artery declines power when the effect of other factors like age and race is considered,[12] wider involvement of coronary artery causes an increase of ischemic cardiomyopaty and myocardial infarction (MI) 1 and increases the death rate.[13] This study has been conducted to determinate the high fasting insulin and apo-lipoproteins in association with severity of coronary artery involvement in non-diabetic patients.

Direct atherogenic features of insulin have been observed in many experimental and clinical studies.[14,15]

Various clinical studies on patients afflicted with coronary artery disease have shown that the quantity of apo-lipoproteins in regard to other lipoproteins measured is a good indicator for coronary artery disease[16,17] and is the best criteria for CAD groups identification. The other studies have also shown that the ratio of total cholesterol/HDL is the strongest predictor of CAD risk and shows the outcome of patients' disease better than lipoproteins.

MATERIALS AND METHODS

The present cross-sectional study was conducted at Shahid Mostafa Chamran Hospital, Noor and Ali-Asghar Hospital, in 2011 on non-diabetic patients afflicted with CAD, which come to these centers for angiography. Initially, the patients had announced their consent for doing survey in filled forms.

Three groups consisting of 100 people afflicted with low, medium, and severe stenosis of coronary arteries were chosen by random sampling and altogether constitute a community of 300 non-diabetic patients afflicted with coronary arteries diseases. The qualification criteria for patients entry is the positive exercise test and existence of stenosis in angiography of coronary arteries.

Those patients who had the record of heart valve disease or artificial heart valve, congenital heart disease, bacterial endocarditis, chronic renal and liver disease, cardiomyopathy, patients afflicted with a fasting glucose equal with or higher than 126 mg/dl or using drugs with blood lipid reduction effect and severe infarct of myocardial muscle or angioplasty background in the past 2 months or record of cerebrovascular or peripheral-vascular diseases were removed from this study.

The clinical data, previous disease records and used drugs were collect by a questionnaire 1 day before

angiography. When sampling in one group was completed, we started sampling in the other two groups.

In this study, variables like age, sexuality, and race were ignored and metabolic syndrome was statistically removed.

Clinical information includes hypertension, cigarette smoking background, early and familial coronary artery disease and usage of beta-blocker and diuretics.

Hypertension is defined along with the background of high blood pressure and anti-hypertensive drugs usage. Blood pressure of higher than 125/85 is nominated as hyper-tension, based on JNC V (diastolic blood pressure [DBP] >85 mmHg, systolic blood pressure [SBP] >125 mmHg).

There are two kinds to smoking cigarette: (1) Those who have never smoked cigarette and (2) those that were or currently smoking cigarette.

The quantities of cholesterol and serum TG are measured by commercial kits (Pars-azmoon, Iran). HDL-cholesterol (HDL-C) was measured after sedimentation with phosphor tungstic acid.

Then APO-a and APO-b were measured by commercial kits (Pars-azmoon, Iran) using the immunoro-bidometric method.

The serum insulin was measured by DSL kits, using the radio immunoassay method.

The whole data was analyzed in Statistical Package for the Social Sciences (SPSS) application (ver. 19) using the statistical test of Chi-square, analysis of variance, and logistic regression. The results of quantitative variables were in (standard deviation ± average) format and the results of qualitative variables were expressed in percentage format.

The logistic regression was used accompanied with clinical and laboratory variables and the variable of outcome was defined as the indicator of stenosis of coronary artery. The quantity of $P < 0.05$ is statistically significant.

CAD is the atherosclerosis of coronary arteries results from atherosclerotic plaques in the walls of coronary arteries, which is stenosis higher than 50% of diagonal of one coronary arteries in any part of the vessel or a diagonal more than 0.3 mm of collaterals.[18] Therefore, the diagnosis of CAD is done based on angiography findings and defining the intensity and wideness of CAD on the basis of Gensini score.[19]

The division of CAD angiography findings include: (1) First group: None of them had the stenosis of more than 50% that is usually called "non-significant." (2) Mild CAD: Only one of their coronary arteries had a stenosis of more than 50%. (3) Moderate CAD: Are those that had the stenosis of more than 50% in two coronary arteries. (4) Severe CAD: Are those had the stenosis of more than 50% in more than two coronary arteries.[18]

In the Gensini score method, the coronary arteries were divided into 11 segments and their score are from 0 to 72 based on the intensity of stenosis which includes: (1) Normal coronary arteries (0 score), (2) mild CAD (0-15 scores), (3) moderate CAD (16-30 scores), and (4) severe CAD (31-72 scores).[19]

And the score of each segment is defined based on stenosis: Score 1 (25% stenosis), score 2 (60% stenosis), score 4 (75% stenosis), score 8 (90% stenosis), score 16 (99% stenosis), and score 32 (100% stenosis).

The score of involved piece based on Gensini score: LAD (proximal: 2.5, median: 1.5, distal: 1); LMD (5); LCX (proximal: 2.5, median: 1, vital: 1); RCA (proximal: 1, median: 1, distal: 1), the marginal branches of LCX, D1, and sepral (LAD): Score 1 and (LAD) D2: Score 0.5.

Gensini method gives a score to each segment and sums up the total profile of stenosis. For example, the 100% stenosis in the middle part of LAD and the75% stenosis in the proximal LCX And the stenosis of 90% in the distal RCA are calculated in this way:

LAD: 32 × 1.5 = 48; LCX: 4 × 2.5 = 10; RCA: 8 × 1 = 8

Genisi score = 66, which means severe CAD.

Hyperinsulinemia is the excessive increase of insulin because of production increase or decrease in absorption liver cells that has the normal cut point of 15 Ulμ/ml.

There exists two types of apo-lipoproteins: Namely A (APO-A) and B (APO-B) that their normal cut points are 190 and 140 mg/dl, respectively.

Cardio-angiography was done by using judkins percutaneous femoral artery method and 35 × 5 mm Diagnostic Philips, video tape with the video recording speed of 25 frame per second. All the videos were analyzed by three specialists.[20]

RESULTS

In this study, based on Genisi score, 300 patients were placed into three groups of low, medium, and severe

with the Genisi score of 14. 7 ± 1.7, 28.3 ± 2.3, and 49.4 ± 3.1, respectively.

The average of systolic blood pressure (SBP) and diastolic blood pressure (DBP) with the intensity of Gensini score did not show any significant statistical difference (P = 0.169 and P = 0.063), while there was a significant statistical difference between cigarette smoking and Genisi Score. The number of cigarette smoking patients in severe CAD group was more than mild CAD (P = 0.002). There was not significant statistical relation between familial background and atherosclerosis intensity (Gensini score, P = 0.815) [Table 1].

In Table 2, the average serum insulin and APO-B in severe atherosclerosis (Gensini score = 49.4 ± 3.1) was meaningfully higher than the low atherosclerosis (Gensini score = 14.7 ± 1.7) (P < 0.001 and P < 0.001, respectively]. The average APO-A1 and the ratio of A1 to B apo-lipoproteins in severe atherosclerosis (Gensini score = 49.4 ± 3.8) was less than mild atherosclerosis (P < 0.001 and P < 0.001, respectively), but the average of TG, HDL, and the ratio of LDL to HDL had no meaningful statistical difference in patients with different atherosclerosis intensities and Gensini scores. The average of total cholesterol and ratio of it to HDL in severe atherosclerosis group (Gensini score = 49.4 ± 3.1) was meaningfully more than the mild group (Gensini score = 14.7 ± 1.7).

Table 1: The quantity of clinical variables in the studied population based on the intensity of atherosclerosis in coronary arteries (Gensini score)

Variables	Mild (%)	Moderate (%)	Severe (%)	*P* value
Gensini score	1.7±14.7	2.3±28.3	3.1±49.4	
Systolic blood pressure (SBP)	22±133	17±128	24±125	0.169
Diastolic blood pressure (DBP)	8±82	9±82	9±78	0.069
Smoking	32 (33.3)	20 (20.8)	44 (45.8)	0.002
Family history CAD+	14 (30.4)	18 (39.1)	15 (30.5)	0.815

In Table 3, according to clinical and laboratory variable and their effect upon the atherosclerosis intensity of coronary arteries and utilizing the processed model of proportional odds regression model (logistics) and in regard to ARIC criterion, it was shown that insulin and diastolic blood pressure are the indicators of intensification of atherosclerosis of coronary arteries (intensification of stenosis of coronary artery).

DISCUSSION

In the present survey, the role of hyperinsulinemia and APO-A1 and B (APO-B) (that both are the components of HDL and LDL cholesterol, respectively) in the intensity of coronary artery disease was investigated so that the association of these three variables with the intensity of coronary artery stenosis was observed.

The relationship between the serum insulin level and coronary artery diseases has been investigated in different studies so that following the 22-year investigation of Finland police personnel, hyperinsulinmia was observed to be the risk factor of coronary arteries diseases and brain stroke[21] In this study, no association was observed between fasting insulin and CAD but after glucose prescription insulin was associated with coronary arteries diseases.

The studies of Kaplan[22] and others[23-27] have shown that hyperinsulinemia is an independent risk-factor of coronary arteries stenosis intensity that was consistent with the present study. Furthermore, the Cups study has shown that hyperinsulinemia is aggravating of coronary artery stenosis intensity even when there exist no metabolic disorder that was consistent with the present study.

The cardiovascular health[28] study considers hyperinsulinemia as a strong predictor of stenosis

Table 2: Quantity of laboratory variables in the population under study according to the severity of coronary atherosclerosis (Gensini score)

Variables	Mild (average ± standard deviation)	Moderate (average ± standard deviation)	Severe (average ± standard deviation)	*P* value
Insulin	13.21±5.7	9.7±15.75	10.8±18.13	<0.001
APO-A1	175±36.4	±163.02	42.4±158	<0.001
APO-B	139±30.4	23.1±146	29.7±155.21	<0.001
HDL	42±11.7	12±41.5	14±40	0.12
LDL	118±35	42±120	48±121	0.06
Total cholesterol	37±185.32	40±202.45	43±207.3	<0.001
TG	178±134	121±180	104±181	0.08
APO-A/APO-B	1.30±33%	1.14±27%	1.04±27%	<0.001
Total cholesterol/HDL	4.26±1.01	5.01±0.9	6.00±1.52	<0.001
LDL/HDL	2.71±0.44%	2.74±0.23%	2.83±0.55%	<0.009

APO-A1: Apo-lipoproteins of A1; APO-A: Apo-lipoproteins of A; APO-B: Apo-lipoproteins of B; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglyceride

Table 3: Intensification of stenosis of coronary artery

Variable	*b*	SE	Exp(*b*)	Confidence interval		*P* value
				Lower	Upper	
Moderate and severe						
Intercept 1	−2.87	3.35				0.39
Intercept 2	−0.68	3.34				0.83
APO-B (mg/dl)	−0.002	0.02	0.997	0.96	1.04	0.88
APO-A1 (mg/dl)	−0.004	.0.01	1.00	0.97	1.03	0.97
APO-A/APO-B	2.05	2.11	7.77	1.22	488.1	0.33
FBS (mg/dl)	0.009	0.009	1.01	0.99	1.02	0.28
Insulin (Ulμ/dl)	0.09	0.01	1.9	1.88	2.95	*P*<0.001
Systolic blood pressure (mmHg)	−0.02	0.009	1.02	1.00	1.04	0.11
Diastolic blood pressure (mmHg)	0.04	0.02	1.97	1.93	2.02	0.03
LDL-C (mg/dl)	−0.01	0.007	0.98	0.97	1.00	0.08
HDL-C (mg/dl)	−0.16	0.02	1.08	1.03	1.41	0.54
Cholesterol (mg/dl)	0.06	0.004	1.98	0.97	2.09	*P*<0.06
TG (mg/dl)	−0.01	0.004	0.99	0.90	0.99	0.63
Smoking	0.49	0.28	0.60	0.35	1.05	0.07
No smoking	Reference	–	–	–	–	–
CAD+	0.55	0.37	1.75	0.83	3.63	0.14
CAD−	Reference	–	–	–	–	–

APO-A1: Apo-lipoproteins of A1; APO-A: Apo-lipoproteins of A; APO-B: Apo-lipoproteins of B; FBS: Fasting blood sugar; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; CAD: Coronary artery disease

intensity of coronary arteries in regard to those who had normal level of insulin.

The ARIC[29] study, after 6-8 years investigation of 12,000 people, showed the association of hyperinsulinemia and the length of waist as one of the risk-generating factors of brain stroke[30] and the NBC study showed that CAD causes the disruption in the function of glucose metabolism and hyperinsulinemia. In addition to that, degrees of resistance to insulin and dyslipidemia and the history of hypertension cause 30% increase of intensification risk of coronary artery diseases[31] that was consistent with the present study.

The Caerphilly study showed that hyperinsulinemia is dependent on variables like TG density. Furthermore, the association and stenosis intensity of coronary arteries, gain less power when the effect of other factors like age and race is considered.[31] The results of futuristic and epidemiologic[32-38] surveys did not show the association of hyperinsulinemia and intensity of stenosis of coronary arteries but the relationship of hyperinsulinemia with coronary arteries diseases was weak.

Miller *et al*. showed that in those people with normal level of blood glucose but with impaired glucose tolerance, hyperinsulinemia causes the risk of cardiovascular factor.[23] The studies of Khadem-Ansari showed the association of decrease of APO-A and increase of APO-B with the intensity of stenosis of coronary arteries, although there was no association between the lipoproteins (LDL and HDL) with the intensity of stenosis in coronary arteries[38] that was consistent with the present study.

Yamada *et al*. showed the association between high blood pressure, low HDL due to age and sexuality and body mass index and manifested that the decreased insulin control level or resistance to insulin causes the reduction of risk of CAD or coronary arteries diseases. Also showed that deferred hyperinsulinemia, after the meal, is associated with intensity of CAD.[39]

Other studies showed the association between CAD intensity, although hyperinsulinemia had no relationship with CAD intensity.[40,41]

D'Agostino *et al* showed the relationship of decrease in APO-A and increase in APO-B and the ratio of APO-A1/APO-B with the intensity of coronary arteries stenosis and these were of higher priority than Total Cholesterol, LDL and HDL[1] that was consistent with the present study.

Goswami has shown the association of the ratio of APO-B/APO-A to be important in defining fatalness and non-fatalness MI as strong predictors of CAD intensification in relationship with HDL-C and LDL-C when the ratio of APO-b/APO-a had defined its treatment to be usage of lipid reduction drugs.[42]

Willson showed that higher levels of insulin and APO-B and decrease of HDL and lesser APO-A independently increase the risk of heart caesura (MI).[43]

Rasouli[44] also showed the association of low APO-A, high APO-B and high-level of total cholesterol with the intensity of CAD and they manifested that the ratio of APO-B/APO-A, can be used as the cholesterol risk stratification of CAD that is consistent with our study too.

In regard to findings of current study in people who were afflicted with coronary arteries diseases and the increase of APO-B and decrease of APO-A and increase of total cholesterol can be regarded as CAD risk stratification. In addition to that, the ratios of APO-A/APO-B and total cholesterol/HDL showed the CAD intensification much better than LDL and HDL. The diastolic blood pressure and cigarette smoking are related to the intensity of stenosis of coronary arteries and effectiveness of these factors is in line with the investigation of other researchers.[45]

The results of the present study cannot be considered as the final conclusion and the predictive quantities of insulin and lipid is not applicable to the whole community due to fact that it has been achieved in a community consisting of patients afflicted with CAD or coronary artery disease while still applicable to those with CAD. Therefore, it is suggested that in CAD patients, the measurement of probable predictive agents, like apo-lipoproteins and insulin, made providentially.

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