TEHRAN HEART CENTER

Original Article

# Do C-Reactive Protein and Lipoprotein (a) Have Different Impacts on the Severity of Coronary Artery Disease in Diabetic and Non-Diabetic Patients?

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## Abstract

***Background:*** *The potential role of lipoprotein (a) changes and also inflammation in coronary artery disease (CAD) have rendered these processes one of the most interesting objects of study in patients affected by type 2 diabetes mellitus. The aim of the current study was to evaluate lipoprotein (a) and other lipid profiles and also C-reactive protein (CRP) as the predictors of cardiovascular disease severity in non-insulin dependent diabetic subjects in comparison with non-diabetic CAD patients.*

***Methods:*** *Between June and September 2004, 372 patients with CAD were enrolled at Tehran Heart Center. Non-insulin dependent diabetics accounted for 102 of the cases, and the remaining 270 were non-diabetics. The severity of CAD was evaluated using the Gensini score, and the effect of patient variables such as serum lipid concentrations and CRP on CAD severity in the diabetics was investigated and compared with that of the non-diabetics.*

***Results:*** *The mean of the Gensini score, CRP, and serum concentrations of all the lipid profiles were similar between the diabetic and non-diabetic patients. In the diabetic group, a high CRP concentration (β=0.200, Rs= 0.040; P=0.046) was effective on the Gensini score, whereas lipoprotein (a) and lipid profiles did not influence CAD severity. In the non-diabetics, no significant relationships were found between the Gensini score and all the studied laboratory indices.*

***Conclusion:*** *A high CRP level is an important predictor of the severity of CAD in diabetic patients with CAD.*

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***Keywords:*** *Diabetes mellitus • Coronary artery disease • Lipoprotein(a) • Inflammation*

## Introduction

Several studies have shown that the incidence of coronary artery disease (CAD) related to atheroma in patients with type 2 diabetes mellitus is higher than that of the general population and is accompanied with an increased total mortality rate.[1,2] The greater mortality in these patients cannot be explained only by the presence of the classic risk factors

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for CAD such as smoking, hypertension, and an increased plasma cholesterol concentration.[3] However, recent studies have presented hypotheses about a positive relationship between the occurrence of CAD and the changes in serum lipoprotein concentrations, especially high and low density lipoprotein and lipoprotein (a). Previous in vitro studies supported a pathophysiological role for lipoprotein (a) in the development of atherosclerosis and in some prospective studies; lipoprotein (a) concentrations were higher in the subjects who later developed ischemic heart disease than those in the control groups.[4] In the Iranian population, high levels of serum lipoprotein (a) have been associated with increased risk of CAD in diabetic patients.[5] It has also been indicated that the abnormalities in high density lipoprotein (HDL) might contribute to the well-established high risk of atherosclerosis in non-insulin dependant diabetes mellitus (NIDDM).[6] Indeed, low HDL cholesterol has been found to be predictive of CAD events in a prospective study of NIDDM patients.[7] Nevertheless, another study reported that the predictive value of HDL cholesterol was relatively weak.[8] Recent research has shown that the inflammatory processes play an important role in CAD and other manifestations of atherosclerosis.[9] that has been more highlight than in diabetic patients.[10]

Given the potential role of lipoprotein (a) and other lipid profile changes and also inflammation in CAD, these processes have recently become one of the most interesting topics of study in patients affected by type 2 diabetes mellitus. Be that as it may, the data in the existing literature are still controversial, not least those on the Iranian population. Furthermore, most of the recent studies have demonstrated factors effective on CAD severity in diabetics and non-diabetics and confirmed significant differences between the two groups. In the present study, we sought to study the impact of these factors in CAD patients with and without diabetes mellitus so that we could determine the difference in CAD severity between diabetics and non-diabetics and also the main predictors of this severity in the two groups with the approach to the effects of lipoprotein (a) and the inflammatory index.

## Method

We retrospectively searched the special angiography database for patients aged between 25 and 90 years who were candidates for angiography at Tehran Heart Center between June and September 2004. A total of 372 patients met these criteria and were, thereafter, divided into a group of 102 (27.4%) diabetics and a group of 270 (72.6%) non-diabetics. The patients were treated with insulin, and those undergoing valvular surgeries or non-cardiac procedures were excluded.

CAD was considered significant if there was a 75% or greater stenosis in the cross-sectional diameter and 50% or greater stenosis in the luminal view.[11] The severity of coronary atherosclerosis was also quantified using the Gensini score.[12] The following data were included for analysis: 1) General characteristics: age and gender; 2) Risk factors for CAD: current smoking history (patient regularly smokes a tobacco product/products one or more times per day or has smoked in the 30 days prior to admission),[13] hyperlipidemia (total cholesterol $\geq$5.0 mmol/l, HDL-cholesterol $\leq$1.0 mmol/l in men, or $\leq$1.1 mmol/l in women, and triglycerides $\geq$2.0 mmol/l),[14] hypertension (systolic blood pressure $\geq$140 mmHg and/or diastolic $\geq$90 mmHg and/or on anti-hypertensive treatment),[15] and diabetes mellitus (symptoms of diabetes plus plasma glucose concentration $\geq$11.1 mmol/l or fasting plasma glucose $\geq$7.0 mmol/l or 2-hpp $\geq$11.1 mmol/l)[16]; 3) Homodynamic status: number of defected coronary vessels and severity of defected coronary vessels according to the Gensini scoring;[17] and 4) serum C-reactive protein (CRP) level. Plasma glucose concentrations were assessed by means of a glucose hexokinase method (Pars Azmoon kits accredited by Bioactiva Diagnostica, Germany). Serum total cholesterol, HDL cholesterol, and triglycerides were measured via enzymatic techniques (Pars Azmoon kits accredited by Bioactiva Diagnostica, Germany). The Friedewald formula was used to calculate low density lipoprotein (LDL) cholesterol, except when the triglyceride level was >4.52 mmol/l. Blood pressure was calculated as the mean of two measurements, performed in the sitting position after 5 minutes of rest, using a random-zero sphygmomanometer (Hawksley-Gelman, Lancing, Sussex, UK.). CRP level was measured by immunoturbidometry (Pars Azmun, Iran), and lipoprotein(a) was measured using Tint ELIZA (Biopool, USA).

The results were reported as mean±standard deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups were compared using the Student's t-test for the continuous variables and the chi-square test or Fisher's exact test if required for the categorical variables. Predictors exhibiting a statistically significant relationship with the Gensini score in the univariate analysis were taken for a multivariable linear regression analysis to investigate their independence. The data analyzer was anonymous, and data collection and processing were approved by the institutional review board of our heart center. P values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

## Results

The general characteristics and hemodynamic status of the patients are summarized in Table 1.

Table 1. Characteristics of diabetic and non-diabetic patients with coronary artery disease*

| Characteristics | Diabetics (n=102) | Non-diabetics (n=270) | P value |
|---|---|---|---|
| Male | 54.9 | 76.7 | <0.001 |
| Age (y) | 60.0±10.1 | 57.4±10.6 | 0.026 |
| Family history of CAD | 50.0 | 45.6 | 0.448 |
| Hyperlipidemia | 68.6 | 35.9 | <0.001 |
| Hypertension | 53.9 | 34.4 | 0.001 |
| Smoking | 76.5 | 58.9 | 0.002 |
| Recent MI | 46.1 | 54.1 | 0.168 |
| History of CVA | 5.9 | 2.3 | 0.082 |
| History of PVD | 38.2 | 20.7 | <0.001 |
| Previous PCI | 3.9 | 3.7 | 0.928 |
| Gensini score | 66.5±42.2 | 60.6±46.4 | 0.244 |
| Number of coronary artery involvement: | | | 0.038 |
| One | 13.7 | 24.4 | |
| Two | 30.4 | 32.2 | |
| Three | 55.9 | 43.3 | |

*Data are presented as percentage or mean±SD
CAD, Coronary artery disease; MI, Myocardial infarction; CVA, Cerebrovascular accident; PVD, Peripheral vascular disease; PCI, Percutaneous coronary intervention

The mean age of the diabetic patients was higher than that of the non-diabetic patients (P=0.026). A history of cigarette smoking (P=0.002), hyperlipidemia (P<0.001), and hypertension (P=0.001) were also found more among the diabetics. Although a history of recent myocardial infarction and cerebrovascular disease was similar between the two groups, peripheral vascular disease had occurred more often in the diabetics. There was a significant difference in the number of defected vessels between the two groups (P=0.038). Single-vessel disease was more frequent in the non-diabetic patients, whereas three-vessel disease was detected more in the diabetics. However, the mean of the Gensini score was similar between the diabetics and non-diabetics (P=0.244), and so were the serum concentrations of lipoprotein (a) and lipid profiles (Table 2). The mean of CRP was not different between the two study groups.

Table 2. Laboratory indices of diabetic and non-diabetic patients with coronary artery disease*

| Indices | Diabetics (n=102) | Non-diabetics (n=270) | P value |
|---|---|---|---|
| Final FBS | 174.5±71.0 | 98.0±19.1 | <0.001 |
| Triglyceride | 199.8±95.6 | 184.7±103.5 | 0.190 |
| Cholesterol | 209.1±47.2 | 208.3±49.1 | 0.882 |
| LDL | 129.9±41.1 | 134.1±41.1 | 0.397 |
| HDL | 38.4±10.4 | 39.2±9.0 | 0.506 |
| Lipoprotein a | 39.2±34.5 | 42.1±39.2 | 0.491 |
| CRP | 12.5±9.0 | 12.6±14.2 | 0.966 |

*Data are presented as mean±SD mg/dl
FBS, Fasting blood sugar; LDL, Low density lipoprotein; HDL, High density lipoprotein; CRP, C-reactive protein

Our multivariate linear regression analysis showed that in the diabetic group, among all the studied patients' laboratory indices, only a high CRP concentration was effective on the Gensini score adjusted for confounders and lipoprotein (a) and lipid profiles did not influence CAD severity (Table 3). In the non-diabetics, CRP concentration was a predictor of the severity of CAD (Table 4).

Table 3. Impact of laboratory indices on Gensini score in diabetic patients adjusted for confounders

| | Univariate P value | Multivariate P value | Beta | 95% Confidence Interval | |
|---|---|---|---|---|---|
| Female | <0.001 | 0.001 | 26.535 | 41.615 | 11.455 |
| Age | 0.350 | 0.341 | 0.328 | -0.351 | 1.007 |
| Hypertension | 0.143 | 0.631 | -3.294 | -16.794 | 10.206 |
| Smoking | 0.254 | 0.236 | -10.826 | -28.794 | 7.142 |
| Triglyceride | 0.383 | 0.205 | -0.042 | -0.107 | 0.023 |
| Cholesterol | 0.380 | 0.172 | 0.143 | -0.063 | 0.350 |
| LDL | 0.995 | 0.708 | -1.369 | -8.569 | 5.830 |
| HDL | 0.062 | 0.056 | -0.927 | -1.877 | 0.024 |
| Lipoprotein a | 0.994 | 0.287 | 0.118 | -0.100 | 0.335 |
| CRP | 0.046 | 0.005 | 1.208 | 0.365 | 2.050 |

LDL, Low density lipoprotein; HDL, High density lipoprotein; CRP, C-reactive protein

Table 4. Impact of laboratory indices on Gensini score in non-diabetic patients adjusted for confounders

| | Univariate P value | Multivariate P value | Beta | 95% Confidence Interval | |
|---|---|---|---|---|---|
| Female | <0.001 | <0.001 | -21.026 | -29.590 | -12.462 |
| Age | <0.001 | <0.001 | 1.069 | 0.725 | 1.412 |
| Hypertension | 0.194 | 0.160 | 5.727 | -2.268 | 13.722 |
| Smoking | 0.146 | 0.383 | 3.814 | -4.774 | 12.401 |
| Triglyceride | 0.832 | 0.457 | 0.014 | -0.023 | 0.052 |
| Cholesterol | 0.716 | 0.006 | 0.129 | 0.037 | 0.221 |
| LDL | 0.898 | 0.543 | -0.136 | -0.574 | 0.303 |
| HDL | 0.269 | 0.552 | -0.124 | -0.533 | 0.285 |
| Lipoprotein a | 0.685 | 0.554 | 0.033 | -0.076 | 0.142 |
| CRP | 0.167 | 0.039 | 0.310 | 0.016 | 0.604 |

LDL, Low density lipoprotein; HDL, High density lipoprotein; CRP, C-reactive protein

## *Discussion*

We studied the role of some laboratory indices such as CRP and lipoprotein (a) as predictors of CAD severity in type 2 diabetic patients and found a relation between the CRP level and CAD severity. Inflammation plays an essential role in the development of insulin resistance and type 2 diabetes mellitus, the initiation and progression of atherosclerotic lesions, and plaque disruption. CRP is a marker of low-grade inflammation and has a role in the pathogenesis of atherosclerotic lesions in humans.[17] Pai et al. found a significant association between CRP levels and the risk of CAD. These findings are consistent with the role of these inflammatory markers in the elevated risk of

cardiovascular events associated with type 2 diabetes.[18] The association with the duration of diabetes mellitus supports the hypothesis that one of the mechanisms for the increased CRP in diabetic subjects may be a chronic inflammatory state. This state could result from endothelial damage and dysfunction caused by the diabetic state.[19] Higher levels of CRP seem to be also associated with low levels of PON1 activity (an anti-inflammatory enzyme located on HDL, which protects against the development of atherosclerosis), providing a mechanistic link between inflammation and the development of atherosclerosis.[19] Furthermore, the effects of high levels of CRP and both complications and mortality due to the progression of diabetes mellitus have been indicated. In a study by Machness et al. on patients with type 1 diabetes, CRP concentration was significantly higher in the presence of any complication, neuropathy, nephropathy, and retinopathy; whilst in the population with type 2 diabetes, a higher CRP concentration was found in the presence of any complication and CAD.[20] Also, in another study, in patients with type 2 diabetes who had acute coronary syndrome, CRP seemed to be an independent predictor of cardiovascular death.[21]

We also found that lipoprotein (a) was not an effective indicator of the severity of CAD in both diabetic and non-diabetic groups. Similarly, Govindaraju et al. in a study among the Indian population showed that in diabetics, there was a trend toward increased lipoprotein (a) levels compared to the controls, but the difference was not statistically significant. They also found no relationship between lipoprotein (a) levels and number of stenosed coronary arteries.[22] In the Solfrizzi et al. study, elevated lipoprotein (a) levels did not appear to be an independent predictor of CAD among elderly patients, but high serum lipoprotein (a) was a CAD risk factor dependent on type 2 diabetes mellitus and the combined effect of high lipoprotein (a) and high LDL cholesterol increased coronary risk.[23] However, in a cohort study by Tsimikas et al., Lp (a) lipoprotein levels showed a strong and graded association with the presence and extent of CAD.[24] It has been demonstrated that a 10% reduction in LDL cholesterol during a lipid-lowering trial eliminates lipoprotein (a) as a predictor of subsequent angiographic progression of CAD.[25] It seems that lipoprotein (a) is a CAD risk factor dependent on total cholesterol or LDL cholesterol, suggesting a direct atherogenic action of Lp (a) for its high affinity binding to glycosaminoglycans and fibronectin.[25] Also, it seems that the atherogenicity of Lp (a) lipoprotein may be mediated in part by associated proinflammatory oxidized phospholipids.[24] It has even been suggested that serum analysis for Lp (a) lipoprotein may become a useful tool for the identification in early life of members of a subpopulation particularly at risk of developing CHD.[26]

In our study, no significant difference in terms of serum Lp (a), LDL, HDL, and cholesterol concentrations was observed between the diabetic and non-diabetic patients. Similarly, Pedreno et al. found that serum Lp (a) levels were increased in patients with angiographically documented CAD, but there were no significant differences between the diabetic and non-diabetic patients, which indicated that elevated Lp (a) levels were specifically associated with CAD but not with type-2 diabetes mellitus.[27] Also, in the Abdella et al. study, Lp (a) was not an independent risk factor for CAD in patients with diabetes mellitus. Serum Lp (a), a risk factor for coronary heart disease in some non-diabetic populations, is largely under genetic control and varies among ethnic and racial groups.[28] Nonetheless, in the Solfrizzi et al. study, in the elderly, elevated Lp (a) levels did not appear to be an independent predictor of CAD, whereas this lipoprotein was a risk factor only in the subjects with type 2 diabetes mellitus and elevated LDL cholesterol.[5]

## Conclusion

The higher rate of main CAD risk factors, higher incidence of cardiovascular disease, and the effects of inflammatory factors on the progression of CAD complications in diabetic patients require multifactorial control for CAD risk reduction in this group of patients. Our findings indicate that a high CRP level could be an important predictor of CAD severity in diabetic patients with CAD and underscore the role of inflammatory processes in the progression of coronary lesions in these patients.

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