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# Assessment of Diagnostic Efficiency of Lipoprotein (a), Homocysteine, High Sensitive C-Reactive Protein and Fibrinogen in Patients with Coronary Artery Disease

## Koroner Arter Hastalarında Lipoprotein (a), Homosistein, Yüksek Duyarlı C-Reaktif Protein ve Fibrinojen Etkinliğinin Tanısal Değerlendirilmesi

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## ABSTRACT

**Purpose:** To evaluate the diagnostic value of major and other risk factors as lipoprotein (Lp) (a), homocysteine (Hcy), high sensitive C-reactive protein (hs-CRP) and fibrinogen in CAD patients.

**Materials and Methods:** A total of 223 subjects (118 patients and 105 controls) were included in the study according to their coronary angiographic results. Lipoprotein (a), Hcy, hs-CRP and fibrinogen levels were measured using immunoturbidometric, florescent polarization immunoassay and nefelometric methods, respectively. Fasting glucose and lipid parameters, except low density lipoprotein cholesterol (LDL-C), are determined by enzymatic colorimetric methods and the LDL-C levels were calculated by the Fridewald formula.

**Results:** Logistic regression analysis showed that when the biochemical variables in placed in a model, the most important variables were Lp (a), Hcy, hs-CRP and fibrinogen. We showed that each unit of Lp (a), Hcy, hs-CRP and fibrinogen increases the risk of CAD 1.029, 1.177, 1.027 and 1.013 fold, respectively. Among these, fibrinogen level was the most sensitive and efficient parameter in prediction of CAD.

**Conclusion:** Although Lp (a), Hcy, hs-CRP and fibrinogen are independent risk factors for CAD, fibrinogen was the most important one. Fibrinogen can be used as a reliable risk factor for CAD in clinical practice.

**Key Words:** Coronary artery disease, risk factors, Lipoprotein (a), Homocysteine, hs-CRP, fibrinogen.

## ÖZET

**Amaç:** Koroner arter hastalığında (KAH) Lipoprotein (Lp) (a), homosistein (Hcy), yüksek duyarlıklı C-reaktif protein (hs-CRP) ve fibrinojen gibi majör ve diğer risk faktörlerinin tanısal değerini araştırmak amaçlanmıştır.

**Materyal ve Metod:** Çalışmaya koroner anjiyografi sonucuna gore 118'i KAH ve 105'i KAH olmadığı belirlenen toplam 223 kişi dahil edildi. Lipoprotein (a), Hcy, hs-CRP ve fibrinojen düzeyleri sırasıyla, immünoturbidometrik, flöresan polarizasyon immünoassay ve nefelometrik yöntemlerle ölçüm yapıldı. Açlık glukoz ve düşük dansiteli lipoprotein kolesterol (LDL-K) dışındaki lipid parametrelerine enzimatik kolorimetrik yöntemlerle bakılmış olup, LDL-K düzeyleri Fridewald formülüne göre hesaplanmıştır.

**Bulgular:** Lojistik regresyon modelinde biyokimyasal değişkenlerden en önemlileri göre Lp (a), Hcy, hs-CRP ve fibrinojen olarak belirlenmiştir. Lipoprotein (a), Hcy, hs-CRP ve fibrinojenin herbir ünitesinin sırasıyla, 1.029, 1.177, 1.027 ve 1.013 kat KAH riskini artırdığı gösterilmiştir. Bu parametrelerden KAH için öngörüsü en hassas ve etkili olanın fibrinojen olduğu gösterilmiştir.

**Sonuç:** Lipoprotein (a), Hcy, hs-CRP ve fibrinojen KAH için bağımsız risk faktörleri olması yanında bunların arasında en önemlisinin fibrinojen olduğu belirlenmiştir. Fibrinojen, klinik uygulamada KAH için güvenilir bir risk factör olarak kullanılabilir.

**Anahtar Kelimeler:** Koroner arter hastalığı, risk faktörleri, Lipoprotein (a), Homosistein, hs-CRP, fibrinojen.

## INTRODUCTION

Many major risk factors as age, gender, family history, smoking, obesity, hyperlipidemia, hypertension (HT) and diabetes mellitus (DM) have been described in patients with coronary artery disease (CAD). However, atherosclerosis can also develop at the absence of major risk factors[1]. It has been documented that the risk factors other than major ones can also cause the development of CAD. Lipoprotein (a) [(Lp (a)], homocysteine (Hcy), high sensitive C-reactive protein (hs-CRP) and fibrinogen can be counted among these risk factors. Lipoprotein (a) is formed by linkage of a low density lipoprotein cholesterol (LDL-C) particle with apolipoprotein (a) and accepted as a kind of modified form of LDL-C. Lipoprotein (a) may play a role in the development of atherosclerosis by inhibiting fibrinolysis, and also binding to macrophages and promotes foam cell formation[1]. Much evidence has accumulated that Lp(a) is a proatherogenic particle[2]. High plasma total homocysteine (tHcy) level has been proposed as another important risk factor[3]. The mechanism by which high tHcy levels leading to CAD remains unclear[3,4]. In many studies it was shown that inflammation also had an important role in the formation of atherosclerosis at an increasing rate. High-sensitive C-reactive protein is secreted from the liver in response to inflammation. Patients with CAD have elevated hs-CRP levels[5,6]. Fibrinojen is a 340-kDa glycoprotein produced in the liver. It has a direct effect on the vascular wall and blood viscosity. An association between increased circulating levels of fibrinogen and the development of acute myocardial infarction (AMI) has been demonstrated[7].

In this study, we investigated the diagnostic value of major and other risk factors as Lp (a), Hcy, hs-CRP and fibrinogen in patients with CAD.

## MATERIAL and METHODS

**Patients.** A total of 223 patients (141 males and 82 females aged between 34-75 years) who underwent coronary angiography and admitted to the department of cardiology during 1 year period were included in the study. An informed consent from each patient was obtained and the study protocol was approved by local ethical committee. A positive family history was defined as CAD in a parent or sibling noted under the age of 55 for men and 65 for women. We calculated body mass index (BMI). A sustained blood pressure ≥140 mmHg systolic and ≥90 mmHg diastolic or using antihypertensive drug at the time of investigation was defined as HT[8]. Hyperlipidemia was defined as serum total cholesterol (TC) level ≥200 mg/dL and/or LDL-C level ≥130 mg/dL or using lipid lowering drugs at the time of investigation and hypertriglyceridemia was defined as trygliseride (TG) level ≥150 mg/dL and high-density lipoprotein cholesterol (HDL-C) was considered present if the concentration of HDL-C was <40 mg/dL according to The Third Report of The National Cholesterol Education Program guidelines[9]. Diabetes mellitus was considered to be present if there was a history of diabetes, fasting blood glucose ≥126 mg/dL or the use of an antidiabetic medication[10]. Patients who had cancer, hepatic or renal failure (serum creatinine >1.5 mg/dL) or using drugs which affect plasma Hcy level such as multivitamin and anticancer agents were excluded.

**Coronary Angiography.** Coronary angiography was performed by the Judkins technique. Angiograms were interpreted by two cardiologists. Coronary artery disease was defined as ≥50% reduction of internal diameter of left anterior descending, right or circumflex coronary artery or their primary branches. Patients without angiographic lesions were considered as without CAD.

**Biochemical Analysis.** Blood samples were drawn from the antecubital vein with minimal venous occlusion and collected into non-anticoagulant tubes after a rest period of ≥30 minutes in supine position following 12 hours fasting prior to the coronary angiography. Following coagulation of the samples for 1 hour in the room temperature the sera were immediately separated by centrifuging at 3000 rpm and stored at -70$^{o}$C until analysis. Levels of Lp (a), Hcy and, hs-CRP were quantified by using a immunoturbidometric technique in modular Roche analyzer (Roche Diagnostics, USA), a florescent polarization immunoassay method (FIPA) in Abbott IMX analyzer (Abbott Diagnostics, USA) and, immunonephelometric technique in Dade Behring BN II analyzer (Siemens Diagnostics, USA), respectively. Furthermore, routine analyses as measurement of glucose, TC, HDL-C, TG, and creatinin were performed in Olympus AU5200 autoanalyzer (Olympus Diagnostic Systems, USA). Low density lipoprotein cholesterol was also calculated by Friedewald formula[11].

**Statistical Analysis.** The results of descriptive analysis in the samples were defined as mean ± standard deviation and range. Student's *t*-test was used to compare means of the biochemical parameters in CAD and the non-CAD group. Chi-square test was used to analyze other risk factors. In order to establish cut-off values of conventional risk factors, ROC (receiver-operating characteristic curve) analysis were applied to the samples. Multiple logistic regression analysis was used to determine the relationship between the risk factors, biochemical parameters and CAD. *P* value <0.05 was considered as significant.

## RESULTS

Clinical Characteristics and Laboratory Findings: Among the study population, 118 patients had CAD and 105 had normal coronary arteries (non-CAD). The mean age of patients were significantly higher than the non-CAD group (56.3 ± 9.7 vs 52.3 ± 10.2 p= 0.003). The other risk factors such as smoking, family history, HT and DM were also higher in the CAD group compared to non-CAD. Serum TC, LDL-C, TG, levels and TC/HDL-C ratio were significantly higher in CAD group than the non-CAD group. The mean serum Lp (a) level was also higher in the CAD group (60.5 ± 46.8 vs 29.5 ± 16.6 p< 0.001). Patients Hcy, hs-CRP and fibrinogen levels were found to be significantly higher in CAD group than the non-CAD group (Table 1).

**Table 1. Clinical characteristics and the laboratory findings of patients and the controls**

| Variable | Controls (%) n=105 | Patients (%) n=118 | *p* value |
|---|---|---|---|
| Age (years) | 52.3±10.2 | 56.3±9.7 | 0.003 |
| Male/Female | 64/41 | 77/41 | NS |
| Smoking | 30 (31.6) | 65 (68.4) | 0.000 |
| Family History | 4 (8) | 46 (92) | 0.000 |
| BMI (kg/m$^2$) | 27.2±4.4 | 27.3±3.9 | NS |
| Hypertension | 19 (32.7) | 40 (67.3) | 0.006 |
| Diabetes Mellitus | 4 (14.3) | 24 (85.7) | 0.000 |
| Glucose (mg/dL) | 98.1 ± 21.2 (63-247) | 115.9 ± 48.0 (60-318) | 0.001 |
| TC (mg/d.L) | 181.5 ± 36.5 (96-395) | 203.9 ± 49.0 (112-362) | <0.001 |
| HDL-C (mg/dL) | 45.5 ± 9.7 (26-72) | 43.0 ± 8.8 (21-61) | 0.049 |
| LDL-C (mg/dL) | 105.8 ± 31.2 (41-297) | 120.6 ± 41.7 (46-274) | 0.003 |
| TG (mg/dL) | 150.7 ± 60.3 (20-272) | 201.2 ± 140.0 (64-1045) | 0.006 |
| TC/HDL-C | 4.11 ± 0.94 (1.9-7.5) | 4.85 ± 1.27 (2.4-8.4) | <0.001 |
| Lp (a) (mg/dL) | 29.5 ± 16.6 (0-96) | 60.5 ± 46.8 (0-268) | <0.001 |
| Hcy (µmol/L) | 12.7 ± 2.9 (5.5-23.8) | 17.3 ± 10.6 (5.6-99.7) | <0.001 |
| Hs-CRP (mg/L) | 17.3 ± 15 (1.7-116) | 43.7 ± 39.7 (2.5-142) | <0.001 |
| Fibrinogen (mg/dL) | 324.4±60.9 (214-529) | 437.6±142.7 (212-1080) | <0.001 |

(+): present; (-): absent; CAD: coronary artery disease; BMI: body mass index; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; Lp (a): lipoprotein (a); Hcy: homocysteine; hs-CRP: high sensitivity C-reactive protein
NS: nonsignificant, Data presented as mean ± standard deviation

Predictors of Coronary Artery Disease: Logistic regression analysis showed that when the variables in Table 1 placed in a model, the most important variables were Lp (a), Hcy, hs-CRP and fibrinogen (Table 2). Our results showed that each unit of Lp (a), Hcy, hs-CRP and fibrinogen increases the risk of CAD 1.029, 1.177, 1.027 and 1.013 fold, respectively.

**Table 2. Multiple logistic regression analysis for the prediction of CAD.**

| Variable | Odds Ratio* | 95% CI | p value |
|---|---|---|---|
| Lp (a) (mg/dL) | 1.029 | 1.014-1.045 | <0.001 |
| Hcy (µmol/L) | 1.177 | 1.072-1.292 | 0.001 |
| hs-CRP (mg/L) | 1.027 | 1.004-1.050 | 0.021 |
| Fibrinogen (mg/dL) | 1.013 | 1.007-1.018 | <0.001 |

*Age-adjusted ORs were given, $R^2$= 0.44
Lp (a): lipoprotein (a); Hcy: homocysteine; hs-CRP: high sensitivity C-reactive protein

Predictive Value of Lp (a), Hcy, Hs-CRP and Fibrinogen for CAD: According to the cut-off levels, positive and negative predictive values of Lp (a), Hcy, and hs-CRP are shown in Table 3. Among these findings fibrinogen levels were the most sensitive and efficient parameter in prediction of CAD.

**Table 3. Sensitivity, specificity and predictive value of Lp (a), Hcy, hs-CRP and fibrinogen**

| Variable | Cut-off value | Diagnostic Sensitivity (%) | Diagnostic Specificity (%) | Positive Predictive Value (%) | Negative Predictive Value (%) | Efficiency of the Test (%) |
|---|---|---|---|---|---|---|
| Lp (a) (mg/dL) | 35 | 67 | 69 | 71 | 65 | 68 |
| Hcy (µmol/L) | 13.5 | 59 | 72 | 71 | 61 | 65 |
| hs-CRP (mg/L) | 2.0 | 61 | 71 | 74 | 63 | 68 |
| Fibrinojen (mg/dL) | 350 | 78 | 70 | 74 | 74 | 74 |

Lp (a): lipoprotein (a); Hcy: homocysteine; hs-CRP: high sensitivity C-reactive protein

The Data of ROC Curve of Lp (a), Hcy, Hs-CRP and Fibrinogen: The ROC curve analysis of Lp (a), Hcy, hs-CRP and fibrinogen variables showed that the most important predictor for CAD was also fibrinogen (Figure 1).

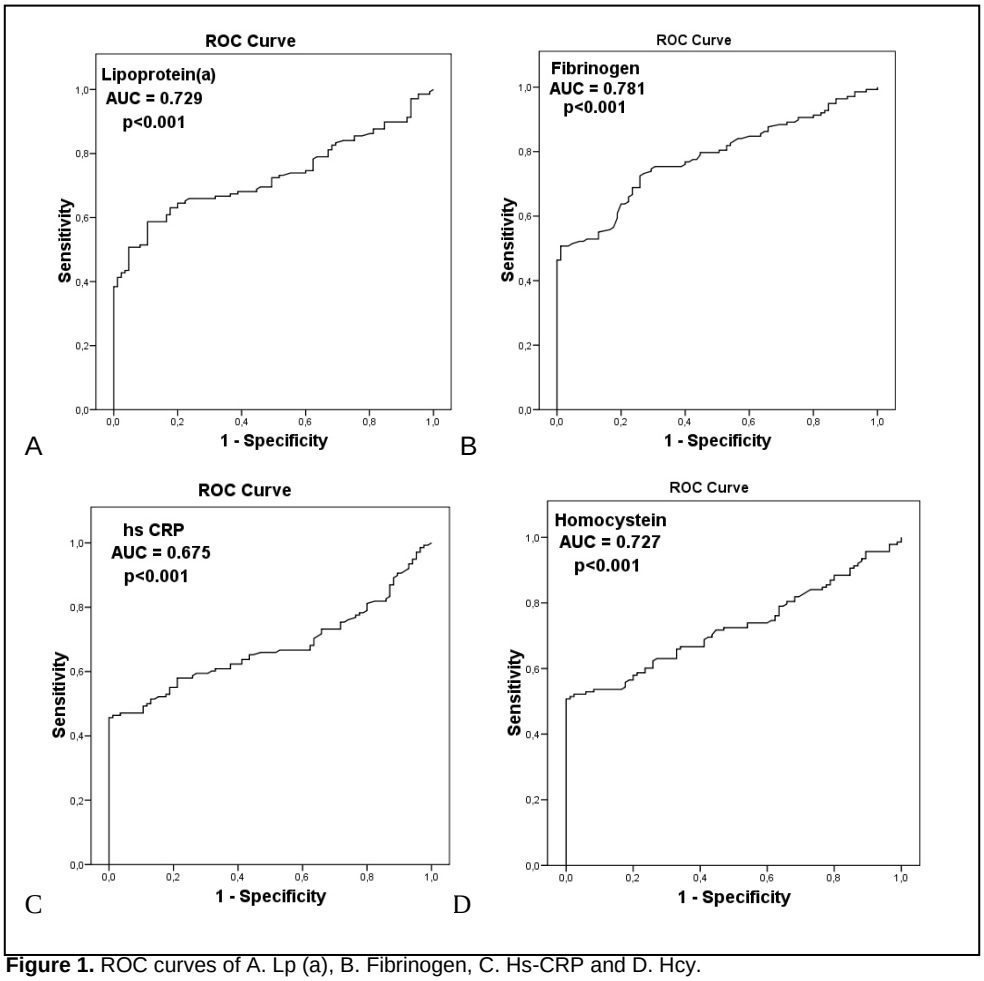


**Figure 1.** ROC curves of A. Lp (a), B. Fibrinogen, C. Hs-CRP and D. Hcy.

## DISCUSSION

This study demonstrated that, Lp (a), Hcy, hs-CRP and fibrinogen were to be the predictors of CAD. Among these the most important factor was fibrinogen. It has been found that the role of age, gender, smoking, family history, HT, DM and hyperlipidemia were important in the progression of CAD[12]. In our study the mean age, the frequency of smoking, family history, HT and DM were found to be higher in CAD group compared to the non-CAD group. Levels of TC, LDL-C, TG and the TC/HDL-C ratio were also higher in CAD group. These findings were compatible with the other studies[13].

Numerous epidemiological studies have identified elevated serum Lp (a) concentrations as a risk factor for atherosclerotic vascular disease[14,15]. The results of prospective follow-up studies that investigate the relationship between Lp (a) levels and CAD progression are controversial[16]. It was reported that elevated Lp (a) levels may promote atherosclerosis via Lp(a)-derived cholesterol entrapment in the intima, via inflammatory cell recruitment, and/or via the binding of pro-inflammatory-oxidized phospholipids[16]. The prothrombotic, anti-fibrinolytic actions of apolipoprotein (a) are expressed on the one hand as inhibition of fibrinolysis with enhancement of clot stabilization and on the other

as enhanced coagulation via the inhibition of tissue factor pathway inhibitor[15,16]. The case control studies showed that Lp (a) levels were significantly higher in CAD group than the non-CAD group[15]. We also found the Lp (a) levels were significantly higher in CAD group. Our result also showed that the Lp (a) level was an independent risk factor for CAD.

The plasma Hcy is also a controversial risk factor. Nikfardjam et al. demonstrated that hyperhomocysteinemia was not related with the anatomical extent of CAD in young patients and could be indicated a less important role of Hcy for the long-term development of significant coronary atherosclerosis17. Some studies have shown an increase in plasma concentration of Hcy as an independent risk factor for the development of arterial thrombosis[7,18,19]. In different studies, Hcy cut-off values were found between 9-18 µmol/L19,20. In our study Hcy levels were found significantly higher in CAD group. We obtained the threshold value of Hcy was 13.5 µmol/L. Our cut-off value was also between the previously given values. There are many possible reasons for different levels of Hcy in every population. Factors like nutrition habits, genetic factors, life styles and race can affect Hcy levels21. Some of the suggested mechanisms are the damaging effects of tHcy on endothelium, platelets, coagulation factors, and smooth muscle of the vessel wall, and oxidative modification of the LDL-C[3,4].

Injury of vessel wall and the associated inflammatory response are now generally recognized as essential components of atherogenesis. Inflammatory markers are independent predictors of cardiovascular events[14]. Serum hs-CRP has been reported by many studies to be an independent predictor of angiographically defined CAD[13,22]. We found also hs-CRP as an independent predictor for CAD. Some studies demonstrated that hs-CRP cut-off values were between 2-3 mg/L[23,24]. Our threshold value of hs-CRP was 2.0 mg/L. In our study the test sensitivity, specificity, positive predictive value, negative predictive value and efficiency were 61%, 71%, 74%, 63% and 66%, respectively. Yun et al. found their test sensitivity and specificity 61.7% and 69.7%[23]. Guran et al. indicated that the sensitivity, the specificity and positive predictive value of their hs-CRP test as 58%, 92% and 93%, respectively$_{24}$. Our findings were compatible with Yun et al. We found that for each hs-CRP unit the risk of CAD increases 1.027 fold.

Fibrinogen is also an acute phase reactant and possibly an indicator of chronic inflammation associated with atherosclerosis7. Fibrinogen contributes to blood viscosity, platelet aggregation, fibrin formation, modulates subsequent coagulation activation and fibrinolysis and directly participates in atherogenesis[25]. Fibrinogen is also associated primarily with acute forms of CAD. Previous studies have shown a relationship between fibrinogen levels and coronary atherosclerosis[25,26]. De Luca et al. reported that high fibrinogen level is an independent predictor of presence of CAD26. Meta-analyses reported that increased concentrations of fibrinogen were associated with the development or presence of atherothrombic disease[27]. It was shown that elevated fibrinogen levels might affect the occurrence of cardiovascular events by thrombotic complications rather than the development or progression of CAD[26]. In some large population studies elevated levels of fibrinogen in persons were associated with an increased prevalence of coronary artery calcification[28,29]. Opposite findings were reported in a smaller population study[30]. We found that the mean fibrinogen levels in CAD group were above the upper reference value than the non-CAD group. Fibrinogen was also the most important predictor of CAD.

**Limitations**

1. The first problem is the Lp (a) levels may show important differences among the individuals. The second, there is not a reliable method to measure the Lp (a). On the other hand, standardization about storage of collected samples, analyze type and data notification

are difficult15. Due to the standardization deficiency in Lp (a) measurement and insufficiency of the prospective epidemiologic studies of Lp (a) levels have not been determined in general population.

2. Homocysteine levels may show variations in different measurements. We have done only one measurement for each sample.
3. The number of the samples was not large enough in our study group.

In conclusion, although Lp (a), Hcy, hs-CRP and fibrinogen are independent risk factors for CAD, fibrinogen was the most important one. Fibrinogen can be used as a reliable risk factor for CAD in clinical practice.

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**Ethical approval** Received from the Ethics Committee of Çukurova University, Faculty of Medicine.

**Abbrevations**

**CAD:** Coronary artery disease. **HT:** Hypertension. **DM:** Diabetes mellitus. Lp (a): Lipoprotein (a). **Hcy:** Homocysteine. **Hs-CRP:** High sensitive C-reactive protein**. LDL-C:** Low density lipoproteine cholesterol. **AMI:** Acute myocardial infarction. **BMI:** body mass index. **TC:** Triglyceride. **HDL-C:** High density lipoprotein cholesterol. **TC:** Total cholesterol.

## REFERENCES

1. Robinson K, Mayer EL, Miller D, Green R, van Lente F, Gupta A et al. Hyperhomocysteinemia and low pyridoxal phosphate: common and independent reversible risk factors for coronary artery disease. Circulation. 1995; 92: 2825-30.
2. Ridker PM. Novel risk factors and markers for coronary disease. Adv in Intern Med. 2000; 45: 391-418.
3. McCully KS. Homocystein and vascular disease. Nat Med. 1996; 2: 386-9.
4. Thambyrajah J, Townend JN, Homocysteine and atherotrhrombosis mechanisms for injury. Eur Heart J. 2000; 21: 967-73.
5. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men published erratum appears in N Engl J Med. 1997; 337: 356.
6. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med. 2000; 342: 836-43.
7. Isordia-Salas I, Mendoza-Valez L, Almeida-Gutierrez E, Borrayo-Sanchez G. Genetic factors of hemostatic system in young patients with myocardial infarction. Cir Ciruj. 2010; 78:87-91.
8. 1999 World Health Organization-International Society of Hypertension Guidelines for the management of Hypertension. J Hypertens. 1999; 17: 151-183.
9. Executive summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Cholesterol in Adults (Adult Treatment Panel III). JAMA.2001; 285, 2486-97.
10. American Diabetes Association, The Expert Committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 1999; 22: 5-19.
11. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the Concentration of Low-Density Lipoprotein Cholesterol in Plasma, Without Use of the Preparative Centrifuge. Clin Chem. 1972; 18: 499-500.
12. Ridker PM, Genest J, Libby P. Risk factors for atherosclerotic disease. In: Heart Disease: A Textbook of Cardiovascular Medicine W.B. Saunders, Philadelphia, PA. 2001: 1010–39.
13. Vahdat K, Jafari SM, Pazoki R, Nabipour I. Current increased high sensitivity C-reactive protein and chorionic infections are associated with coronary artery disease: A population-based study. Indian J Med Sci. 2007; 61: 135-43.
14. Koschinsky M L, Marcovina S M. Structure-function relationships in apolipoprotein(a): insights into lipoprotein(a) assembly and pathogenicity. Curr Opin Lipidol. 2004; 15: 167–74.
15. Bozbaş H, Yıldırır A, Pirat B, Eroğlu S, Korkmaz ME, Atar İ. et al. Increased lipoprotein (a) in metabolic syndrome: Is it a contributing factor to premature atherosclerosis? Anat Cardiol J. 2008; 8: 111-5.

16. Nordestgaard BG, Chapman MJ, Ray K, Bore´n J, Andreotti F, Watts GF. et al. Lipoprotein(a) as a cardiovascular risk factor. Eur Heart J. 2010; 31: 2844-53.

17. Nikfardjam M, Graf S, Hornykewycz S et al. Homocysteine plasma levels in young patients with coronary artery disease. Relation to history of acute myocardial infarction and anatomical extent of disease. Thromb Res. 2001; 103:35-9.

18. Cleopas TJ, Hornstra N, van Hoogstraten B, Van der Meulen J. Homocysteine, a risk factor for coronary artery disease or not? A Meta analysis. Am J Cardiol. 2000; 86: 1005-9.

19. Yan J, Liao JK, Wang D. Elevated homocysteine and C-reactive protein levels independently predict worsening prognosis after stroke in Chinese patients. Journal of Huazhong University of Science and Technology Med Sci. 2010; 30:643-7.

20. Kazemi MBS, Eshraghian K , Omrani GR, Lankarani KB, Hosseini E. Homocysteine Level and Coronary Artery Disease. Angiology. 2006; 57: 9-14.

21. Senaratne MP, MacDonald K, DeSilva D. Possible ethnic differences in plasma homocysteine levels associated with coronary artery disease between South Asian and East Asian immigrants. Clin Cardiol. 2001; 24: 730-4.

22. Lin T, Liu JC, Chang LY, Shen CW. Association of C-reactive protein and homocysteine with subclinical coronary plaque subtype and stenosis using low-dose MDCT coronary angiography. Atherosclerosis 2010; 212: 501-6.

23. Yun KH, Jeong MH, Oh SK, Rhee SJ, Park EM, Lee EM. et al. Response of high-sensitivity C-reactive protein to percutaneous coronary intervention in patients with acute coronary syndrome. Heart Vessels. 2009; 24:175–80.

24. Guran O, Akalin F, Ayabakan C, Dereli FY, Haklar G. High-sensitivity C-reactive protein in children at risk for coronary artery disease. Acta Pædiatrica. 2007; 96: 1214–9.

25. Kim PY, Stewart RJ, Lipson SM, Nesheim ME. The relative kinetics of clotting and lysis provide a biochemical rationale for the correlation between elevated fibrinogen and cardiovascular disease. J Thromb Haemost. 2007; 5:1250–6.

26. Luca GD, Verdoia M, Casetti E, Schaffer A, Cavallino C, Bolzani V. et al. Novara Atherosclerosis Study Group (NAS). High fibrinogen level is an independent predictor of presence and extent of coronary artery disease among Italian population. J Thromb Thrombol. 2010; DOI 10.1007.

27. Ernst E, Resch KL. Fibrinogen as a cardiovascular risk factor: a meta-analysis and review of the literature. Ann Intern Med. 1993; 118: 956–63.

28. Green D, Foiles N, Chan C, Schreiner PJ, Liu K Elevated fibrinogen levels and subsequent subclinical atherosclerosis: the CARDIA Study. Atherosclerosis. 2009; 202: 623–31.

29. Rodrigues TC, Snell-Bergeon JK, Maahs DM, Kinney GL, Rewers M. Higher fibrinogen levels predict progression of coronary artery calcification in adults with type 1 diabetes. Atherosclerosis. 2010; 210: 671–3.

30. Taylor AJ, Bindeman J, Le TP et al Progression of calcified coronary atherosclerosis: relationship to coronary risk factors and carotid intima–media thickness. Atherosclerosis. 2008; 197: 339–45.

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