The relation between coronary lesion distribution and risk factors in young adults

Genç erişkinlerde koroner lezyon dağılımı ile risk faktörlerinin ilişkisi

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Abstract

Objective: In this cross-sectional, case-controlled study, we aimed to evaluate classical and novel risk factors in young patients with coronary artery disease (CAD), and the relation between coronary risk factors and coronary lesion distribution.

Methods: Fifty-three patients under age of 45 years with severe coronary artery stenosis on angiography (group A) and age matched sixty patients having normal or non-critical stenosis on coronary angiography (group B) comprised the study groups. Conventional (smoking, family history, diabetes, hypertension) and novel risk factors (lipoprotein (a), homocysteine) were compared between the groups. Moreover, the relation between risk factors, and coronary lesions distribution, including left main artery (LMA) or proximal or mid left anterior descending (LAD) artery and remaining coronary lesions was investigated. Logistic regression analysis was used to define confounding factors predicting severe CAD and coronary lesion distribution and ROC curve analysis was performed to determine the cut-off value of independent factors, which were assessed by logistic regression analysis.

Results: Smoking was more prevalent in group A compared to group B. Lipoprotein (a) and homocysteine levels were also higher in group A than group B. For group A and B median (max-min) values of lipoprotein (a) were 34 (2-174) mg/dl and 38 (2-203) mg/dl (p=0.038), respectively and homocysteine levels were 12.3 (5-56.6) µmol/L and 9 (1.4-19) µmol/L (p=0.012), respectively. Smoking and homocysteine were independent predictors of severe CAD in young patients according to logistic regression analysis with an Odds ratio of 3.7 (95% CI=1.572-8.763; p=0.002) and 1.2 (95% CI=1.045-1.341; p=0.008), respectively. For predicting significant CAD the cut-off value of homocysteine was 11.6 µmol/L with a sensitivity and specificity of 53% and 77%, respectively (AUC=0.637; 95% CI=0.542-0.725; p=0.008). Within group analysis in group A patients revealed that only homocysteine was an independent predictor of LMA or proximal or mid-LAD lesion presence with an Odds ratio of 1.2 (95% CI=1.011-1.465; p=0.016). ROC curve analysis revealed a cut-off value of 12 µmol/L in predicting LMA or proximal or mid-LAD lesions with a sensitivity and specificity of 65% and 91%, respectively (AUC=0.735; 95% CI=0.594-0.850; p=0.002).

Conclusion: In our study, we found that young patients with severe CAD had different risk profile with higher frequency of smoking and increased levels of lipoprotein (a) and homocysteine. While smoking status and homocysteine may be used for prediction of severe CAD in young individuals, only homocysteine predicted coronary lesion distribution in LMA and proximal or mid-LAD.

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Key words: Coronary artery disease, coronary risk factors, lesion distribution, homocysteine, lipoprotein (a), young, logistic regression analysis

Özet

Amaç: Kesitsel vaka-kontrol çalışmasında genç koroner arter hastalarında (KAH) klasik ve yeni risk faktörlerini ve koroner risk faktörlerinin koroner arter lezyon dağılımıyla ilişkisini araştırmayı amaçladık.

Yöntemler: Anjiyografik olarak ciddi koroner arter darlığı olan 45 yaş altında 53 hasta (grup A) ile yaş ve cinsiyetleri uyumlu koronerleri normal veya non-kritik lezyonu olan 60 olgu (grup B) çalışmaya alındı. Gruplar arasında konvansiyonel (sigara, aile öyküsü, diyabet, hipertansiyon) ve yeni risk faktörleri (lipoprotein (a), homosistein) karşılaştırıldı. Bunların yanı sıra risk faktörleriyle sol ana koroner (SAK) veya proksimal veya orta segment sol ön inen (SÖİ) koroner arter ile diğer koroner arterlerdeki lezyon dağılımı arasındaki ilişki araştırıldı. Ciddi KAH ve koroner lezyon dağılımını belirleyen faktörler için lojistik regresyon analizi yapıldı ve lojistik regresyon analiziyle saptanan bağımsız risk faktörleri için kesim noktasının belirlenebilmesi için ROC eğrisi çizildi.

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Bulgular: Grup A ile B karşılaştırıldığında sigara kullanımı grup A'da daha sıktı. Lipoprotein (a) ve homosistein seviyeleri grup A'da grup B'den daha yüksekti. Grup A ve B için sırasıyla mediyan (minimum-maksimum) değerler lipoprotein (a) için 34 (2-174) mg/dl ve 38 (2-203) mg/dl (p=0.038), homosistein için 12.3 (5-56.6) µmol/L ve 9 (1.4-19) µmol/L (p=0.012) idi. Lojistik regresyon analizinde sigara ve homosistein ciddi KAH olan genç hastalarda sırasıyla 3.7 (%95 CI=1.572-8.763; p=0.002) ve 1.2 (%95 CI=1.045-1.341; p=0.008) odds oranıyla bağımsız belirteçlerdi. Ciddi KAH'nı belirlemede homosistein için kesim değeri %53 duyarlılık ve %77 özgüllükle 11.6 µmol/L bulundu (AUC=0.637; %95 CI=0.542-0.725; p=0.008). Grup A'daki grup içi analizde sadece homosistein SAK veya proksimal veya orta SÖİ koroner arter lezyon varlığının bağımsız belirteciydi ve odds oranı 1.2 (%95 CI=1.011-1.465; p=0.016) idi. ROC eğrisi analizinde SAK veya proksimal veya orta SÖİ arter lezyonları için homosistein'in kesim değeri %65 duyarlılık ve %91 özgüllükle 12 µmol/L (AUC=0.735; %95 CI=0.594-0.850; p=0.002) idi.
Sonuç: Çalışmamızda ciddi KAH olan gençlerde risk profilinin farklı olduğunu ve bunlarda sigara kullanım sıklığıyla lipoprotein (a) seviyesinin yüksek olduğunu saptadık. Sigara ve homosistein genç bireylerde ciddi KAH'nı belirlemede kullanılabilirken sadece homosistein SAK ve proksinal veya orta SÖİ koroner lezyon dağılımını belirlemede kullanılabilir. *(Anadolu Kardiyol Derg 2009; 9: 91-5)*
Anahtar kelimeler: Koroner arter hastalığı, koroner risk faktörleri, lezyon dağılımı, homosistein, lipoprotein (a), genç, lojistik regresyon analizi

Introduction

Cardiovascular diseases are one of the leading causes of death in all over the world (1). Although it is regarded as a disease of advanced age, coronary artery disease (CAD) has high prevalence (2) and higher cardiac mortality in the young (3, 4). Many global risk assessment approaches are available for clinicians including Framingham risk score (5). However, none of them is ideal especially in young individuals (5, 6) who have high CAD mortality rates (3, 4). Novel risk factors for coronary heart disease like hyperhomocysteinemia, lipoprotein (a) (Lp a), apolipoprotein B, apolipoprotein B/A_1 ratio and adiponectin may have the same clinical implications in younger people (7-10) as in adult patients. Moreover, hypercoagulable state (high fibrinogen and D-dimer levels) was shown in premature CAD (11).

Topographic distribution of atherosclerotic lesions in coronary arteries has been investigated in several studies (12-15), however, there is limited data about coronary lesion distribution in young patients, and no knowledge about the relation between coronary risk factors and coronary lesion distribution.

In this cross-sectional case-control study, we aimed to evaluate: 1. conventional and novel cardiovascular risk factors and 2. the lesion topography in coronary arteries, and the relation of the coronary artery lesion topography with conventional and novel risk factors in young patients with CAD.

Methods

The study population composed of 113 consecutive young patients (age below 45 years) who underwent coronary angiography with the suspicion of CAD due to typical chest pain or ischemic findings on treadmill exercise test or myocardial scintigraphy.

The study protocol was reviewed and approved by local Ethics Committee and written informed consent was obtained in all participants. Exclusion criteria were history of previous myocardial infarction or CAD, and non-atheromatous CAD such as congenital coronary artery anomalies, spontaneous coronary artery dissection, and drug abuse or hypercoagulable states such as antiphospholipid syndrome. Participants were grouped as having significant coronary artery stenosis (>70% luminal narrowing) or not. A total of 53 patients with significant coronary artery stenosis constitute the group A, and remaining 60 patients -group B. Moreover, we categorized the group A patients according to coronary lesion distribution as those having left main (LMA) or proximal or mid left anterior descending (LAD) coronary artery lesions (subgroup 1), or having coronary artery lesions in other segments (subgroup 2). The reason for choosing LMA and proximal or mid LAD segments for categorization is having the highest severity coefficient of these lesions in Gensini CAD severity score (16).

Evaluation of coronary arteries

Coronary angiography was performed by a femoral approach using the modified Seldinger technique. Standardized angiographic projections (LMA, LAD and left circumflex arteries were assessed in the right anterior oblique projection with caudal angulations, and for the right coronary artery in the left anterior oblique projection with cranial angulations) were chosen for the assessment of each arterial segment. We used the coronary artery map from the Coronary Artery Surgery Study (CASS) (17) for vessel classification.

Assessing risk factors

A detailed medical and family history and physical examination were performed. Smoking is defined as any tobacco use within last five years. Positive family history defined as having any first-degree relative with known CAD. Hypertension was defined as having a blood pressure above 140 mm Hg systolic or 90 mm Hg diastolic at three consecutive measurements divided by 15 minutes intervals or any antihypertensive agent use. Blood fasting glucose level above 126 mm/dl or under antidiabetic medication were accepted as diabetes mellitus presence. Weight and height measurements were performed with a standardized scale with light clothes and naked feet. Following a 8-12 hours fasting state blood was drawn for each subject in order to determine the serum lipids, lipoprotein (a), apolipoprotein A, apolipoprotein B, and homocysteine. The plasma fractions were transferred to a plastic tube and stored at -80°C until analysis. Plasma samples were drawn into chilled EDTA tubes (1 mg/ml blood) containing aprotinin (500 KIU/ml of blood). The whole blood samples were centrifuged at 1.600 G for 15 min at 20°C. Plasma Lp (a) levels was measured using Macra Terumo Lp (a) ELISA kit. Plasma apolipoprotein A and B levels were measured using CardioCHEK Microwell ELISA kits. Plasma homocysteine levels were measured using Axis Homocysteine ELISA kit.

Statistical analysis

Data were analyzed by SPSS 11.5 (SPSS Inc., Chicago, Il., USA) software. Continuous variables were expressed as mean ± standard deviation, median (min-max) and categorical variables as numbers and percentages. Mann-Whitney U or t test according to normality test results were used for comparison of continuous variables. Chi-square test was used for comparison of categorical

variables. In order to determine predictive factors for assessing coronary artery disease and coronary lesion location logistic stepwise regression analysis was performed. Only parameters, with a p value below 0.2 obtained in comparison of groups, were chosen for logistic regression analysis. Finally, discriminatory power of independent parameters was quantified in terms of area under Receiver Operating Characteristics (ROC) curve analysis. Cut-off value was accepted as the point at highest accuracy in ROC curve analysis. A p value under 0.05 was accepted as significant. For determining sample size statistical software package G*Power (version 3.0.10, Franz Faul, Universität Kiel, Germany) was used. A total of 120 subjects were calculated as a sample size for α=0.05 and 90% power. However, the study had to be completed with 113 participants for technical reasons and because of patient characteristics participants could not be categorized equally.

Results

Group A was composed of 52 males and 1 females with a mean age of 37±5 years, and group B 58 male and 2 female with a mean age of 37±5 years. Conventional and novel risk factors and their comparison are illustrated in Table1. Among these parameters smoking, Lp (a), and homocysteine were found to be significantly higher in group A than in group B (p=0.002, p=0.038 and p=0.012, respectively). Age, smoking, triglyceride, Lp (a) and homocysteine were chosen for logistic regression model. Logistic stepwise regression analysis revealed that smoking (OR=3.7, 95% CI: 1.572-8.762, p=0.002) and homocysteine (OR=1.2, 95% CI: 1.045-1.341, p=0.008) levels were independent predictors of significant CAD. ROC analysis showed that serum value of 11.6 µmol/L for homocysteine had sensitivity of 53% and specificity of 77% in predicting of significant CAD (AUC=0.637, 95% CI 0.542 – 0.726, p=0.008) (Fig. 1).

Of these 53 patients forming group A, 38 (72%) had LMA or proximal or mid-LAD lesions (subgroup 1), and 15 (28%) had lesions at remaining coronary segments (subgroup 2). Coronary risk factors and their comparison between subgroup 1 and 2 is illustrated in Table 2. Among them only homocysteine level was statistically significant higher in subgroup 1 than in subgroup 2 (p=0.029). Hypertension, diabetes and homocysteine were chosen for logistic regression analysis, and logistic stepwise regression analysis identified homocysteine (OR=1.2, 95% CI: 1.011-1.465, p=0.016) as an independent predictor of LMA or proximal or mid-LAD lesions. ROC curve analysis revealed a cut-off value of 12 µmol/L for homocysteine to be predictive for LMA or proximal or mid-LAD lesions with a sensitivity and specificity of 65% and 91%, respectively (AUC=0.735, 95%CI 0.594 – 0.850, p=0.002) (Fig. 2).

Discussion

Main results of our study are: 1-smoking, and homocysteine are independent predictors of significant CAD in young individuals; 2-the most common coronary lesions are found in the LMA coronary artery or proximal or mid-LAD segments in young CAD patients; 3-homocysteine is an independent predictor for determining the LMA or proximal or mid-LAD lesions in young patients with significant CAD.

Several studies have demonstrated that smoking is strongly associated with premature CAD (18-21). Framingham Heart Study

Table 1. Clinical and laboratory characteristics of patients with and without significant coronary artery disease

Parameters	Group A (n=53)	Group B (n=60)	p*
Age, years	37±5	37±5	0.161
Gender, n(%)			
Male	52 (98)	58 (97)	0.635
Female	1 (2)	2 (3)	
Smoking, n(%)	39 (74)	27 (45)	0.002
Hypertension, n(%)	8 (15)	5 (8)	0.263
Diabetes, n(%)	1 (2)	1 (2)	0.930
Family history, n(%)	15 (28)	18 (30)	0.844
BMI, kg/m^2	26.4±3.0	26.5±4.4	0.492
Total cholesterol, mg/dl	192±49	200±45	0.404
LDL-cholesterol, mg/dl	119 (61-1006)	137 (63-1292)	0.689
HDL-cholesterol, mg/dl	41±7	43±8	0.210
Triglyceride, mg/dl	134 (43-466)	163 (59-597)	0.123
Lipoprotein (a), mg/dl	34 (2-174)	38 (2-203)	0.038
Apolipoprotein A-1, mg/dl	126±29	121±28	0.534
Apolipoprotein B-100, mg/dl	115±37	110±34	0.429
Homocysteine, µmol/l	12.3 (5-23)	9 (1.4-19)	0.012

Continuous normally distributed data are presented as Mean±SD, not normally distributed data are expressed as Median (min-max) values and categorical variables are presented as numbers/percentages
*Unpaired t test for independent samples, Chi-square test and Mann Whitney U test
BMI - body mass index, HDL - high density lipoprotein, LDL - low density lipoprotein

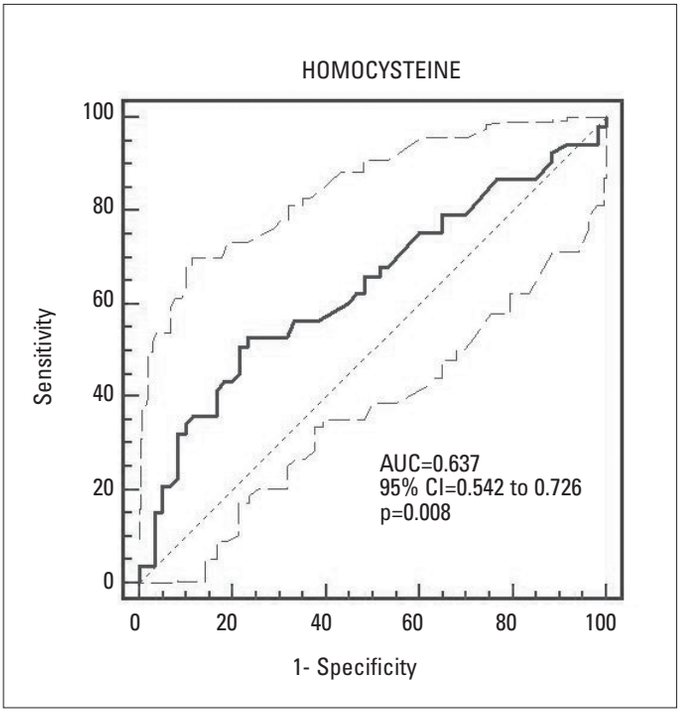

Figure 1. ROC curve of homocysteine for predicting significant coronary artery disease
AUC - area under curve, CI - confidence interval

Table 2. Clinical and laboratory characteristics of patients with significant coronary artery disease

Parameters	LMA or proximal or mid-LAD lesion (n=38)	non-LAD lesion (n=15)	p*
Age, years	37±5	38±5	0.450
Gender, n(%)			
Male	37 (97)	15 (100)	0.530
Female	1 (3)	-	
Smokers, n(%)	28 (74)	11 (73)	0.979
Hypertension, n(%)	4 (11)	4 (27)	0.143
Diabetes, n(%)	-	1 (7)	0.111
Family history, n(%)	10 (26)	5 (33)	0.613
BMI, kg/m2	26.7±3.4	25.6±1.7	0.384
Total cholesterol, mg/dl	194±47	189±57	0.921
LDL-cholesterol, mg/dl	125 (64-1006)	119 (61-1042)	0.401
HDL-cholesterol, mg/dl	41±6	41±9	0.897
Triglyceride, mg/dl	132 (43-331)	139 (67-466)	0.471
Lipoprotein (a), mg/dl	35 (10-174)	31 (2-112)	0.228
Apolipoprotein A-1, mg/dl	124±27	129±34	0.664
Apolipoprotein B-100, mg/dl	116 (52-222)	107 (63-161)	0.874
Homocysteine, µmol/l	13.8±3.8	10±3.3	0.029

Continuous normally distributed data are presented as Mean±SD, not normally distributed data are expressed as Median (min-max) values and categorical variables are presented as numbers/percentages
*Unpaired t test for independent samples, Chi-square test and Mann Whitney U test
BMI - body mass index, HDL - high density lipoprotein, LAD - left anterior descending coronary artery, LDL - low density lipoprotein, LMA - left main coronary artery

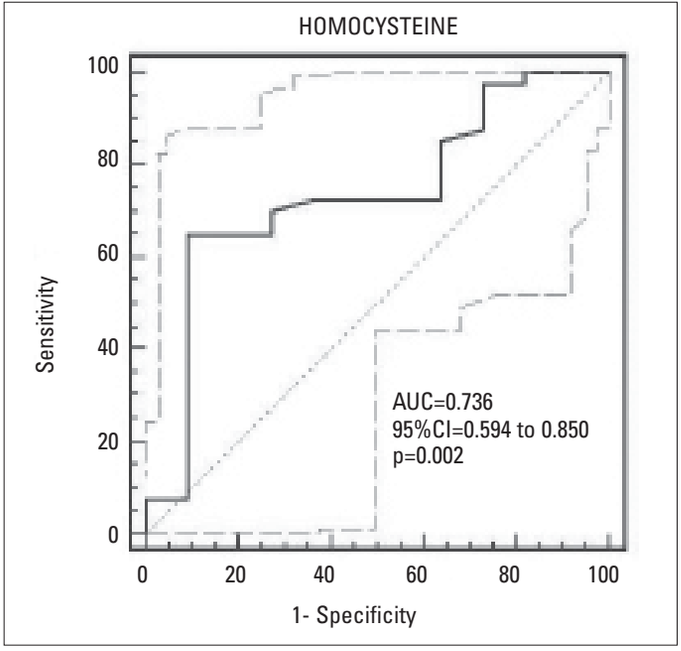

Figure 2. ROC curve of homocysteine for predicting LMA or proximal or mid-LAD segment lesions

AUC - area under curve, CI - confidence interval, LAD - left anterior descending coronary artery, LDL - low density lipoprotein, LMA - left main coronary artery

has reported that the risk of CAD was approximately three-fold higher in young smokers compared with nonsmokers (22). It is well known that increased plasma Lp (a) levels is associated with a high risk for premature CAD (23-26). In this study, we also found high Lp (a) levels in young patients having significant lesions. Results of our study are in line with above mentioned previous findings. Moreover, we also showed homocysteine level as an independent marker of significant CAD in young patients.

While there are several articles focused on topographic lesion distribution of coronary arteries and their severity (27-30), especially in adults, our study results implied that young CAD patients have coronary lesions mainly affecting LMA or proximal or mid-LAD, which was also observed by Yıldırım et al. (31). This type of distribution is generally accepted as a strong indication for surgical revascularization because of higher mortality with medical or interventional therapy (32).

Among conventional and novel coronary risk factors, only homocysteine had a significant relation between significant LMA or proximal or mid-LAD lesions according to our study findings. Although, there were some previous reports showing the relation between homocysteine and premature CAD (33, 34), none of them investigated the relation between homocysteine and coronary lesion topography. It was thought that the oxidative stress caused by homocysteine may be responsible for premature coronary artery disease (35).

As a whole, our findings may explain the higher mortality rate of myocardial infarction in young patients by showing the majority of young patients with significant CAD having proximal left coronary artery system lesions. In addition, homocysteine plays a significant role in causing these high risk lesions.

Limitations of the study

There were some limitations in our study. First of all, the study population was divided into two groups, one of them included patients having significant lesions. However, other group included patients having non-significant lesions and normal coronary arteries. Hence, mild cases of CAD were also included in our control group that may attenuate the observed differences between the groups, especially for conventional and novel risk factors. The majority of participants were male, and there were only two patients with diabetes. We thought that it could not represent general population. Although the discriminatory power of our study is sufficient, large-scale multi-center studies are needed to reach a definitive conclusion.

Conclusion

Results of our study imply that, smoking, homocysteine and Lp (a) are independent predictors of premature CAD. Homocysteine also has an incremental value in these patients because it may provide important information about coronary lesion distribution.

References

1. Gaziano JM. Global burden of cardiovascular disease. In: Zipes DP, Libby P, Bonow RO, Braunwald E, editors. Braunwald's Heart Disease. A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia: Elsevier Saunders; 2005. p 1-19.
2. McGill HC Jr, McMahan CA, Zieske AW, Tracy RE, Malcolm GT, Herderick EE, et al. Association of coronary heart disease risk

factors with microscopic qualities of coronary atherosclerosis in youth. Circulation 2000; 102: 374-9.
3. Klag MJ, Ford DE, Mead LA, He J, Whelton PK, Liang KY, et al. Serum cholesterol in young men and subsequent cardiovascular disease. N Engl J Med 1993; 328: 313-8.
4. Mukherjee D, Hsu A, Moliterno DJ, Lincoff AM, Goormastic M, Topol EJ. Risk factors for premature coronary artery disease and determinants of adverse outcomes after revascularization in patients <or=40 years old. Am J Cardiol 2003; 92: 1465-7.
5. Wierzbicki AS, Reynolds TM, Gill K, Alg S, Crook MA. A comparison of algorithms for initiation of lipid lowering therapy in primary prevention of coronary heart disease. J Cardiovasc Risk 2000; 7: 63-71.
6. Zarich S, Luciano C, Hulford J, Abdullah A. Prevalence of metabolic syndrome in young patients with acute MI: does the Framingham Risk Score underestimate cardiovascular risk in this population? Diab Vasc Dis Res 2006; 3: 103-7.
7. Foody JM, Milberg JA, Robinson K, Pearce GL, Jacobsen DW, Sprecher DL. Homocysteine and lipoprotein (a) interact to increase CAD risk in young men and women. Arterioscler Thromb Vasc Biol 2000; 20: 493-9.
8. Isser HS, Puri VK, Narain VS, Saran RK, Dwivedi SK, Singh S. Lipoprotein (a) and lipid levels in young patients with myocardial infarction and their first-degree relatives. Indian Heart J 2001; 53: 463-6.
9. Köz C, Uzun M, Yokuşoğlu M, Baysan O, Erinç K, Sağ C, et al. Evaluation of plasma adiponectin levels in young men with coronary artery disease. Acta Cardiol 2007; 62: 239-43.
10. Köz C, Baysan O, Haşimi A, Cihan M, Uzun M, Yokuşoğlu M, et al. Conventional and non-conventional coronary risk factors in male premature coronary artery disease patients already having a low Framingham risk score. Acta Cardiol 2008; 63: 623-8.
11. Pineda J, Marín F, Marco P, Roldán V, Valencia J, Ruiz-Nodar JM, et al. Premature coronary artery disease in young (age <45) subjects: Interactions of lipid profile, thrombophilic and haemostatic markers. Int J Cardiol 2008 Jul 12. [Epub ahead of print]
12. Schmermund A, Möhlenkamp S, Baumgart D, Kriener P, Pump H, Grönemeyer D, et al. Usefulness of topography of coronary calcium by electron-beam computed tomography in predicting the natural history of coronary atherosclerosis. Am J Cardiol 2000; 86: 127-32.
13. Davies PF, Shi C, Depaola N, Helmke BP, Polacek DC. Hemodynamics and the focal origin of atherosclerosis: a spatial approach to endothelial structure, gene expression, and function. Ann N Y Acad Sci 2001; 947: 7-16.
14. Farmakis TM, Soulis JV, Giannoglou GD, Zioupos GJ, Louridas GE. Wall shear stress gradient topography in the normal left coronary arterial tree: possible implications for atherogenesis. Curr Med Res Opin 2004; 20: 587-96.
15. Molloi S, Wong JT. Regional blood flow analysis and its relationship with arterial branch lengths and lumen volume in the coronary arterial tree. Phys Med Biol 2007; 52: 1495-503.
16. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol 1983; 51: 606.
17. Killip T, Fisher L, Mock M, for the CASS Investigators. National Heart, Lung, and Blood Institute Coronary Artery Surgery Study (CASS): a multicenter comparison of the effects of randomized medical and surgical treatment of mildly symptomatic patients with coronary artery disease, and a registry of consecutive patients undergoing coronary angiography. Circulation 1981; 63 (suppl I, pt II): I-1-I-81.
18. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 1998; 338: 1650-6.
19. McGill HC Jr, McMahan CA, Malcom GT, Oalmann MC, Strong JP. Effects of serum lipoproteins and smoking on atherosclerosis in young men and women. The PDAY Research Group. Pathobiological Determinants of Atherosclerosis in Youth. Arterioscler Thromb Vasc Biol 1997; 17: 95-106.
20. Zimmerman FH, Cameron A, Fisher LD, Ng G. Myocardial infarction in young adults: angiographic characterization, risk factors and prognosis (Coronary Artery Surgery Study Registry). J Am Coll Cardiol 1995; 26: 654-61.
21. Chen L, Chester M, Kaski JC. Clinical factors and angiographic features associated with premature coronary artery disease. Chest 1995; 108: 364-9.
22. Kannel W, McGee D, Castelli W. Latest perspectives on cigarette smoking and cardiovascular disease: the Framingham Study. J Card Rehabil 1984; 4: 267-77.
23. von Eckardstein A, Schulte H, Cullen P, Assmann G. Lipoprotein (a) further increases the risk of coronary events in men with high global cardiovascular risk. J Am Coll Cardiol 2001; 37: 434-9.
24. Sandkamp M, Funke H, Schulte H, Köhler E, Assmann G. Lipoprotein (a) is an independent risk factor for myocardial infarction at a young age. Clin Chem 1990; 36: 20-3.
25. Bostom AG, Cupples LA, Jenner JL, Ordovas JM, Seman LJ, Wilson PW, et al. Elevated plasma lipoprotein (a) and coronary heart disease in men aged 55 years and younger. JAMA 1996; 276: 544-8.
26. Hopkins PN, Wu LL, Hunt SC, James BC, Vincent GM, Williams RR. Lipoprotein (a) interactions with lipid and nonlipid risk factors in early familial coronary artery disease. Arterioscler Thromb Vasc Biol 1997; 17: 2783-92.
27. Ackerman RF, Dry TJ, Edwards JE. Relationship of various factors to the degree of coronary atherosclerosis in women. Circulation 1950; 1: 1345-54.
28. Montenegro MR, Eggen DA. Topography of atherosclerosis in the coronary arteries. Lab Invest 1968; 18: 586-93.
29. Tuzcu EM, Kapadia SR, Tutar E, Ziada KM, Hobbs RE, McCarthy PM, et al. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: evidence from intravascular ultrasound. Circulation 2001; 103: 2705-10.
30. Halon DA, Sapoznikov D, Lewis BS, Gotsman MS. Localization of lesions in the coronary circulation. Am J Cardiol 1983; 52: 921-6.
31. Yildirim N, Arat N, Doğan MS, Sökmen Y, Ozcan F. Comparison of traditional risk factors, natural history and angiographic findings between coronary heart disease patients with age <40 and >or=40 years old. Anadolu Kardiyol Derg 2007; 7: 124-7.
32. Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation 2004; 110: e340-437.
33. Guo H, Lee JD, Ueda T, Shan J, Wang J. Plasma Homocysteine Levels in Patients With Early Coronary Artery Stenosis and High Risk Factors. Japanese Heart Journal 2003; 44: 865-87.
34. Pinto X, Vilaseca MA, Garcia-Giralt N, Ferrer I, Pala M, Meco JF, et al. Homocysteine and the MTHFR 677C->T allele in premature coronary artery disease. Case control and family studies. Eur J Clin Invest 2001; 31: 24-30.
35. Maron BA, Loscalzo J. Homocysteine. Clin Lab Med 2006; 26: 591-609.