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Evaluation of endothelial function and thrombotic system in children whose parents had early onset coronary heart disease

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Summary

Aim: Risk of MI in first-degree relatives of patients who had an acute MI prior to age of 55 years is 2-7 fold higher compared to their peers. The aim of this study was to investigate the levels of some haemostatic and inflammatory markers in children whose parents had early onset (<55 years) coronary artery disease (CAD) and whether those markers were effective in indicating the risk for CAD development.

Material and Method: This study was performed in Pediatric Cardiology Division of Istanbul Medical Faculty. Forty-three healthy children whose parents had early onset CAD were matched for age and sex and tissue factor (TF), tissue factor pathway inhibitor (TFPI), fibrinogen, von Willebrand factor (vWF) and highly sensitive CRP (hsCRP) were analyzed in both groups. The study was approved by Istanbul Medical Faculty ethics committee. Data obtained in the study were assessed using SPSS 10.0 program.

Results: : The study group had higher vWF than the control group (116.3±52.2 vs. 86.8±41.4 ng/mL), $p<0.05$). Tissue factor, total and free TFPI, fibrinogen and hsCRP were not statistically different between the two groups.

Conclusions: Although premature CAD is known to have a particularly strong genetic component, this study showed that haemostatic and inflammatory markers except vWF are not independent risk factors for children with a family history of early onset CAD. *(Turk Arch Ped 2011; 46: 21-6)*

Key words: Early onset coronary heart disease, fibrinogen, high sensitive C-reactive protein, premature coronary heart disease, tissue factor, tissue factor pathway inhibitor, von Willebrand Factor

Introduction

Coronary artery disease (CAD) caused by atherosclerosis in adults is the leading cause of death worldwide, especially in the western countries (1). According to the data of the study conducted with the leadership of the Turkish Cardiology Association since 1990, it is estimated that there are two million CAD cases in Turkey and 65000 of these die annually because of CAD (2). In recent years, genetic and environmental factors involved in the pathogenesis of CAD have become the focus of investigations. Since genetic factors may be more prominent in CAD occurring at an early age, children with a familial history of early onset CAD should be investigated in terms of underlying biochemical or hematologic disorders (3,4). When biochemical or hematologic risk factors are determined, primary and secondary prevention plans will be possible to be designed starting from childhood (5,6).

The aim of this study was to determine levels of hemostatic and inflammatory markers including tissue factor (TF), free and total tissue factor pathway inhibitor (TFPI), fibrinogen, von Willebrand Factor (vWF) and highly sensitive C-reactive protein (hsCRP) which would predict the occurrence of disease in healthy children with a familial history of early onset CAD and to find if these markers are increased in children at risk because of familial CAD history.

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Material and Method

This study was performed prospectively in the Division of Pediatric Cardiology, Istanbul Medical Faculty between September 2005 and September 2007. Forty three subjects between the ages of 5 and 18 whose parents had early onset (≤55 years old) CAD and who were brought to Pediatric Cardiology Outpatient Clinic because of a murmur heard on physical examination and whose echocardiographic examination revealed no anomaly were included in the study. Fourteen of the subjects were male (32.6%) and 29 were female (67%). These subjects were matched with healthy controls for age and sex and TF, total and free TFPI, fibrinogen, vWF and hsCRP levels were measured. Before including in the study, all subjects in the study group and control group and their families were informed about the study in detail and informed consent forms were signed. In addition, the study was approved by the local Ethics Committee.

By detailed history taking it was ensured that the subjects in the study and control group had no chronic disease and did not smoke. Then detailed physical examination was performed and body measurements (weight, height), blood pressure measurements were done. Individuals who had the above-mentioned diseases, who were smokers and who had acute disease on the day the blood sample was taken were not included in the study. Morning blood samples following 10-12 hours of fasting after dinner were taken from all patients included in the study. TF, free and total TFPI were measured using "Imubind-tissue factor" kit (American Diagnostica Inc, US) on ELX-800 Biotech-Instruments Inc. ELISA reader. Serum hsCRP was measured by turbidimetric method with Roche Integra-800 autoanalyser. While these measurements were done in Pediatric Biochemistry Laboratory, plasma fibrinogen and vWF were measured in Pediatric Hematology Laboratory. Fibrinogen was measured using "Fibri-prest automate 2" kit (Diagnostica, Stago Inc, France) with Clauss method and vWF was measured using "vWF ELISA" kit (Diagnostica, Stago Inc, France).

Data obtained in the study were assesses using SPSS 10.0 program. In evaluation, student's t test was used for comparison of TF, TFPI and vWF measurements compatible with normal distribution and Mann Whitney U test was used for comparison of fibrinogen and hsCRP measurements not compatible with normal distribution in addition to definitive statistical methods. In addition, the effect of free and total TFPI, fibrinogen, vWF and hsCRP on having a history of early onset coronary heart disease was examined using multi-variant, retrospective, stepwise logistic regression method. Data were expressed as mean±standard deviation. A p value below 0.05 was considered to be statistically significant.

Results

In both groups, 14 of the subjects were male (32.6%) and 29 were female (67.4%). The ages of the subjects in the study and control groups varied between 5 and 18 years. Mean age in the study and control group was 13.3±3.6 years (the youngest: 5, the oldest: 18, median: 14 years). No statistically significant difference was found between the study and control groups in terms of body measurements and blood pressure values (summarized in Table 1). When body weight and body mass index were calculated, 4 subjects (9.3%) in the study group and 3 subjects (6.9%) in the control group were found to be overweight or obese. When systolic blood pressure and diastolic blood pressure were assessed according to age, hypertension (>95% percentile) was found in 3 subjects (6.9%) in the study group and in 2 subjects (4.6%) in the control group. While no statistically significant difference was found between the study and control groups in terms of TF, TFPI, fibrinogen and hsCRP, vWF values in the study group (116.3±52.2 ng/mL) were found to be higher than the values measured in the control group (86.8±41.4 ng/mL) ($p<0.05$). Levels and comparisons of TF, free and total TFPI, fibrinogen and vWF in the study and control groups and the normal values for these markers are summarized in Table 2. vWF value determined in plasma samples taken in our study was found to be 116±52.2 ng/mL (the lowest: 31, the highest 283 ng/mL) in the study group

Table 1. Body measurements and blood pressure values in the study and control groups

	Grup	n	Value	p
Weight (kg)	Study Control	43 43	50.2±15.9 (17-86, 49) 50.7±3.6 (15.4-85, 51)	NS
Height (cm)	Study Control	43 43	153±17 (106-179, 159) 154±19 (103-179, 159)	NS
Body mass index (kg/m^2)	Study Control	43 43	21.0±4.14 (13.5-30.8, 21.2) 20.6±4.1 (12.8-30.5, 21.6)	NS
Systolic blood pressure (mmHg)	Study Control	43 43	115.3±12.2 (89-149, 114) 115.8±10.0 (89-138, 120)	NS
Diastolic blood pressure (mmHg)	Study Control	43 43	69.4±8.6 (54-84, 70) 70.1±8.1 (54-85, 75)	NS

Results are given as mean±Standard deviation (minimum-maximum, median). NS: Not significant

and 86.8±41.4 ng/mL (the lowest: 11, the highest: 197 ng/mL) in the control group. vWF values in the study group were found to be higher than the values measured in the control group ($p<0.05$). vWF values were found to be high in 12 samples in the study group and in 5 samples in the control group. In addition, the effect of free and total TFPI, fibrinogen, vWF and hsCRP on having a history of early onset coronary heart disease was examined using multi-variant, retrospective, stepwise logistic regression method. It was found that tissue factor, free and total TFPI, fibrinogen and hsCRP did not affect having a familial history of early onset CAD as an independent factor and high vWF was found to be effective as an independent risk factor [OR: 1.017 (95% confidence interval 1.005-1.0029)]. These statistical data mean that an increase of 1 ng/mL in vWF increases the possibility of familial history of early onset CAD by 1.7%.

Discussion

Presence of familial history of early onset CAD is considered to be a greater risk factor for occurence of this disease (6). Although the exact mechanism for this increase in risk is not known, tendency to atherosclerosis, tendency to thrombosis and inflammation are possible causes (7). Endothelial damage occuring before angiopathy in atherosclerosis leading to coronary artery disease is the earliest sign of subclinical atherosclerosis and the critical step (8). Circulatory signals regulating inflammation, growth factors, cell adhesion, thrombosis and vascular tonus of the underlying smooth muscle are produced by endothelial cells. Increase in hemostatic variables which are released from the endothelium and which regulate thrombosis and fibrinolysis is considered to be an indicator of endothelial damage and dysfunction (9). Therefore, many investigators have searched for special markers indicating endothelial dysfunction leading to atherosclerosis and thus CAD. Thrombomodulin, vWF, TF and TFPI are some of these markers (9-11). In this study, TF, TFPI, vWF and fibrinogen were investigated as a marker of endothelial demage and hsCRP as a marker of inflammation in children with a familial history of early onset CAD.

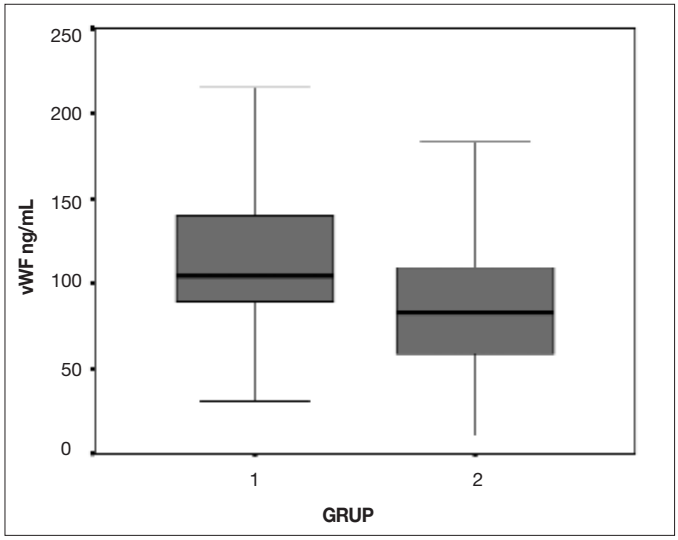

Figure 1. vWF values in the study and control goups

The most important result of this study is the fact that vWF is high in children with a familial history of CAD at an age younger than 55 and this marker can be used as a predictor for CAD. vWF is an important element in the blood necessary for hemostasis in capillaries with high flow stress. Its deficiency leads to bleeding diathesis in the mucosa. High levels of vWF in the blood leads to thrombosis. In addition, high vWF is considered to be an important independent marker for atherosclerosis. vWF has been shown to accelerate the formation of atherom plaques in arterial junctions with high flow stress (12). In addition to this important role of vWF in the formation of thrombosis and atherosclerosis, high levels of vWF found in children with a familial history of early onset CAD in our study may mean that this marker is one of the first markers of the process of atherosclerosis starting at an early age. Postmortem studies have shown that atherosclerosis starts in childhood, fatty streaks in the arteries are seen at the end of the first decade and fatty streaks are seen even in intrauterine period when maternal hypercholesterolemia is present (13). Based on the results of our study, it was concluded that vWF can be used as an early marker of atherosclerosis. However, Makris et al. (14) did not find a difference in vWF in children with a paternal history of myocardial infarction (MI) before the age of 55 in the patient group which was created in a way similar to our study compared to controls in their study. The difference in the results of the two studies may be explained by the facts that children only with paternal history of MI were included and the control group was not selected appro-

Table 2. TF, free and total TFPI, fibriogen and vWF levels in the study and control groups and comparison

	Study group	Control group	P	Normal values
DF (pg/mL)	137.9±59.6	131.8±47.4	AD	0-150
Toplam DFYI (ng/mL)	64.0±15.0	68.2±15.8	AD	0-100
Serbest DFYI (ng/mL)	19.2±4.5	20.5±4.7	AD	0-20
Fibrinojen (mg/L)	251.8±71.1	243.0±56.0	AD	200-400
vWF (ng/mL)	116.3±52.2	86.8±41.4	<0.05	0-100
hsCRP (mg/L)	1.1±1.2	1.2±1.2	AD	0-0.5

NS: Not significant, hsCRP: Highly sensitive C-reactive protein, TF: Tissue factor, TFPI: Tissue factor pathway inhibitor, vWF: von-Willebrand factor.

priatly and sufficiently in the study of Makris et al. Two other studies conducted in recent years found higher vWF along with FVII and FXII, fibrinogen and tPAI in children with a familial history of MI compared to controls. However, in the method of these studies, the time of CAD in the parents was not considered (15). The normal blood level of vWF is between 40% and 200%. vWF level was reported to be lower in individuals with a blood type of 0 by 25% (16). Blood level increases as the age grows older. vWF level has been shown to be increased with beta-adrenergic stimuli, with steroid treatment, in inflammatory diseases, in atherosclerosis, in diabetes mellitus, in renal and hepatic diseases and in vasculitis (12). An important limitation of our study was the fact that we did not get blood type records of the subjects in the study and control groups. None of the children in the study and control group had a history of chronic disease or drug use.

In our study, no difference was found in fibrinogen levels between the groups with and without a familial history of early onset CAD. Fibrinogen is one of the most important constituents of coagulation. It binds to activated thrombocytes and facilitates aggregation, initiates the formation of fibrin and increases plasma viscosity. In addition, fibrinogen is high in inflammatory states (17). High fibrinogen has been determined as a risk factor for CAD, repeated cardiac events and death in MI. A positive corelation between fibrinogen and risk factors of CAD including smoking, obesity, DM and dyslipidemia has been found (18). In contrast to our study, Makris et al.(14) found fibrinogen to be higher in children with a paternal history of MI before the age of 55 compared to controls in their study. However, Shea et al. (19) and Pitsavos et al.(20) did not find fibrinogen to be higher in children with a positive familial history compared to controls which was compatible with the results of our study.

Studies have shown that acute coronary thrombosis occurs with rupture of the weak fibrous cap of the vulnerable atherosclerotic plaque in the coronary artery. In this case, TF enters the blood, binds to FVII/VIIa and initiates coagulation (21). Fat-rich necrotic center of the plaque which is the most thrombogenic element of the coronary lesion is a region where abundant TF is present. Binding of TF to FVIIa causes the formation of thrombin, stimulates thrombocyte activation and CAD, MI or unstable angina occur as a result of partial or full obstruction in coronary arteries with the formation of fibrin (22). Thrombosis occurring with increased circulatory TF is considered to be a cardiovascular risk factor along with DM, smoking, hyperlipidemia and hypertension (23). In our study, we did not find any difference in TF and TFPI levels between the children with a familial history of early CAD and the healthy controls. Increase in release of TF or expression of TF on specific cell surfaces is the base of the current view about the activation of coagulation. Therefore, inhibition of TF pathway is very important for the balance of blood flow. The first activation of coagulation starting by TF and ending with the formation of a small amount of fibrin is inhibited by TFPI released from the endothelium. Thus, TFPI is the main inhibitor of coagulation which occurs by TF. Tissue factor pathway inhibitor inhibits TF-FVIIa binding irreversibly in the presence of FXa in addition to inhibiting FXa directly (24,25). Vascular endothelium is the main source of TFPI and 50-80% of TFPI circulating in vessels is kept in the endothelium. In humans and in in vitro studies, decreased TFPI in the atherosclerotic plaque has led to the conclusion that TFPI is rather successful in local inhibition of TF pathway decreasing arterial thrombosis in the atherosclerotic lesion (25).

It was investigated if tissue factor pathway inhibitor is also effective in lipoprotein biochemistry beyond inhibiting TF. TFPI was found to increase lipoprotein lipase activity and to increase triglyceride hydrolysis by this way (26). Brodin et al. (26) concluded that TFPI RNA started to increase 10 minutes after VLDL stimulus and TFPI was released in response to lipoprotein lipase and VLDL bound to endothelial cell.

The different point in our study was that TF and TFPI which had been investigated in CAD in many studies before were evaluated in children who had no complaints and who had a familial history of early onset CAD for the first time. The fact that there was no difference between the study and control groups may be explained by the possibility that TF and TFPI had not changed yet in the pathophysiologic changes which might have occurred in these patients in the developing atherosclerotic process. In new studies, anticoagulant activity of TF can be measured and it has been reported that anticoagulant activity of TFPI and free TFPI show a strong correlation in healthy individuals (27). This new measurement is continued to be investigated in CAD and in individuals with a high risk of CAD.

Full elucidation of the relationship between atherosclerosis and inflammation in recent years has led to the conclusion that some inflammatory markers may be used to determine the risk of development of cardiovascular events (28). Among these markers, the strongest evidences are related to CRP. There is abundant evidence suggesting CRP can be used to determine cardiac events which might develop in patients presenting with CAD and in individuals who have no known cardiac disease. Moderately high or high CRP levels accompany increased risk of cardiovascular event independent of the presence of other risk factors. C-reactive protein is produced also by macrophages and smooth muscle cell inside the atherosclerotic plaque and this causes the atherosclerotic plaque to become vulnerable and to rupture. In addition, C-reactive protein draws the circulatory monocytes near the plaque by activating them, contributes to dysfunction of entothelium, provides cytokine release and activation of complement system and facilitates remodeling of extracellular matrix. CRP also provides inititation of thrombotic events by stimulating tissue factor synthesis. Like CRP, interleukin 1, 6, 18 and CD40/CD40 complex play important roles in weakening of atherosclerotic plaque and thrombosis. These cytokines act locally or systemically. As a result of this complicated puzzle, the amount of TF in plasma increases via release from

monocytes and neutrophils, circulatory platalets, endothelial cells or atherosclerotic plaque itself against the inflammatory response (28,29).

Increase in C-reactive protein is an indicator of increased inflammatory state in the vascular wall. Increase in CRP is a marker of recurring ischemia, MI and sudden cardiac death in patients with CAD (29). Increase in highly sensitive CRP indicates increased inflammatory state in the vascular wall (28). In our study, we did not find any difference in hsCRP between the children with a familial history of early onset CAD and healthy controls. This migth have suggested that hsCRP had not increased yet in the newly developing atherosclerotic process, so inflammation in the vascular wall had not contributed to atherosclerosis yet.

In this study conducted in children with a familial history of early onset CAD, the limit of early age was selected to be 55 years. In many studies performed on this subject, the limit of early age was selected to be 55 years (30-32) like in our study, but Mansur et al. (5) selected 45 years, Jomini et al (33) selected 50 years in men and 55 years in women, Hauser et al. (34) selected 51 years in men and 56 years in women and American Cholesterol Education program selected 55 years in men and 65 years in women (17). A threshold age lower than 55 years is not appropriate, since familial hypercholesterolemia may be present in most patients with CAD occuring at an age of 45 or earlier. At older ages, early onset state which increases the risk loses its property. Therefore, we also considered 55 years as the limit compatible with the literature.

A limitation of our study is the fact that only familial history was used as a risk factor. It may be beneficial to measure the same markers in individuals with multiple risk factors including obesity, hyperlipidemia and diabetes in further studies and to determine the total risk (35).

In our study, we did not find any difference in hemostatic markers including TF, free and total TFPI, fibrinogen and in inflammatory markers including hsCRP between the children with a familial history of early onset CAD and healthy controls. This suggested that these markers had not yet increased and thus inflammation and thrombotic process in the vascular wall had not yet contributed to atherosclerosis. However, vWF can be used as a marker to predict atherosclerotic disease. Further large-scale, prospective, randomized studies are needed on this subject. In the future, when new risk markers are found in studies similar to our study, development of CAD will be able to be predicted beforehand and prevented by changing the lifestyle of children at risk and applying treatment options.

Conflict of interest: None declared

References

1. Starc GTJ. Management of hyperlipidemia in children. Ped Card 2001; 12: 205-13. (Abstract) / (Full Text) / (PDF)
2. Onat A, Keleş İ, Çetinkaya A, ve ark. On yıllık TEKHARF çalışması verilerine göre Türk erişkinlerinde koroner kökenli ölüm ve olayların prevalansı yüksek. TKD 2001; 29: 8-19.
3. Reis EC, Kip KE, Marroquin OC, et al. Screening children to identify families at increased risk for cardiovascular disease. Pediatrics 2006; 118: 1789-97. (Abstract) / (PDF)
4. Murabito JM, Nam BH, D'agostino RB, Lioyd-Jones DM, O'Donnell CJ, Wilson WF. Accuracy of offspring reports of parental cardiovascular disease history: The Framingham offspring study. Ann Intern Med 2004; 140: 434-40. (Abstract)
5. Mansur AD, Mattar APL, Rolim AL, et al. Distribution of risk factors in parents and siblings of patients with early coronary artery disease. Arq Bras Cardiol 2003; 80: 582-4. (Abstract) / (Full Text)
6. Nasir K, Michos ED, Rumberger JA, et al. Coronary artery calcification and family history of premature coronary heart disease. Sibling history is more strongly associated than parental history. Circulation 2004; 110: 2150-6. (Abstract) / (PDF)
7. Gaeta G, De Michele M, Cuomo S, et al. Arterial abnormalities in the offspring of patients with premature myocardial infarction. N Engl J Med 2000; 343: 840-6. (Abstract) / (Full Text) / (PDF)
8. Chara M, Tousoulis D, Stefanadis C. Early atherosclerosis in children. Diagnostic approaches and therapeutic strategies. Intern J Cardiol 2005; 109: 152-9. (Abstract) / (Full Text) / (PDF)
9. Rigla M, Mateo J, Fontjuberta J, Souto JC, Leiva A, Perez A. Normalization of tissue factor pathway inhibitor activity after glycemic control optimization in type 1 diabetic patients. Thromb Haemost 2000; 84: 223-7. (Abstract)
10. Onat A, Hergenç G, Yıldırım B, ve ark. Türk erişkinlerde kanda fibrinojen düzeyleri ve bazı risk parametreleri ile ilişkileri. TKD 2000; 28: 115-20. (Abstract)
11. Al-Nozha MM, Abdel-Gader AM, Arafah MR, Al-Maatouq MA, Al-Shahid MS, Al-Harthi SS. Tissue factor pathway inhibitor, natural coagulation inhibitors and hemostatic activation markers in patients with acute coronary syndromes. Saudi Med J 2005; 26: 937-42. (Abstract)
12. Gürsel T. Von willebrand hastalığı Türk toplumundaki prevalansı, kliniği ve genetik özellikleri. II. Ulusal Tromboz, Hemostaz ve Anjioloji Kongresi. Kasım, Türkiye, İstanbul; özet kitabı: 2001:29-32.
13. Napoli C, Glass CK, Witztum JL, et al. Influence of maternal hypercholesterolaemia during pregnancy on progression of early atherosclerotic lesions in childhood: fate of early lesions in children (FELIC) study. Lancet 1999; 354: 1234-41. (Abstract) / (Full Text) / (PDF)
14. Makris TK, Hatzizacharias AN, Krespi PG, et al. Markers of risk in young offspring with paternal history of myocardial infarction. Intern J Cardiol 2003; 89: 287-93. (Abstract) / (Full Text) / (PDF)
15. Pankow JS, Folsom AR, Province MA, et al. Family history of ischemic heart disease and hemostatic variables in middle aged adults. Thromb Haemost 1997; 77: 87-93.
16. Nathan DG, Orkin SH. Nathan and Oski's Hemotology of Infancy and Childhood. 5th edition, volume 2. Philedelphia: WB Saunders Company, 2002; 1631-59.
17. Robinson DM, Schwahn C, Alte D, John U, Felix SB, Völzke H. Plasma fibrinogen levels are associated with a strong family history of myocardial infarction. Blood Coagul Fibrinolysis 2004; 15:4 97-502. (Abstract)
18. Wilhemsen L, Svardsudd K, Korsan-Bengtien K, Larson B, Welin L, Tibblin G. Fibrinogen as a risk factor for stroke and myocardial infarction. New Engl J Med 1984; 311: 501-5. (Abstract)
19. Shea S, Isasi CR, Couch S, et al. Relations of plasma fibrinogen level in children to measures of obesity, the (G-455-->A) mutation in the beta-fibrinogen promoter gene, and family history of ischemic heart disease: the Columbia University BioMarkers Study. Am J Epidemiol 1999; 150: 737-46. (Abstract) / (PDF)
20. Pitsavos C, Skoumas J, Dernellis J, et al. Influence of biological factors on lipid and fibrinogen measurements in young men. An epidemiological study in 2009 recruits. Eur Heart J 1998; 19: 1642-7. (Abstract) / (Full Text) / (PDF)

21. Mackman N. Role of tissue factor in hemostasis thrombosis and vascular development. Athroscler Thromb Vasc Biol 2004; 24: 1015-22. (Abstract) / (Full Text) / (PDF)
22. Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high risk plaque. J Am Coll Cardiol 2005; 46: 937-54. (Abstract) / (PDF)
23. Sambola A, Osende J, Hathcock J, et al. Role of risk factors in the modulation of tissue factor activity and blood thrombogenicity. Circulation 2003; 107: 973-7. (Abstract) / (Full Text) / (PDF)
24. Morange PE, Blankenberg S, Alessi MC, et al. Atherogene Investigators. Prognostic value of plasma tissue factor and tissue factor pathway inhibitor for cardiovascular death in patients with coronary artery disease: the AtheroGene study. J Thromb Haemost 2007; 5: 475-82. (PDF)
25. Caplice NM, Mueske CS, Kleppe LS, Simari RD. Presence of tissue factor pathway inhibitor in human atherosclerotic plaques is associated with reduced tissue factor activity. Circulation 1998; 98: 1051-7. (Abstract) / (Full Text) / (PDF)
26. Brodin E, Iversen N, Hansen JB. Impact of native VLDL on tissue factor pathway inhibitor in endothelial cells and interactions between TFPI and lipoprotein lipase. J Lab Clin Med 2006; 147: 167-73. (Abstract) / (Full Text) / (PDF)
27. Dahm AE, Andersen TO, Rosendaal F, Sandset PM. A novel anticoagulant activity assay of tissue factor pathway inhibitor I (TFPI). J Thromb Haemost 2005; 3: 651-8. (Abstract) / (Full Text) / (PDF)
28. Rost NS, Wolf PA, Kase CS, et al. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study. Stroke 2001; 32: 2575-9. (Abstract) / (Full Text) / (PDF)
29. Margaglione M, Cappucci G, Colaizzo D, Vecchione G, Grandone E, Di Minno G. C-reactive protein in offspring is associated with the occurrence of myocardial infarction in first-degree relatives. Arterioscler Thromb Vasc Biol 2000; 20: 198-203. (Abstract) / (Full Text) / (PDF)
30. Samani NJ, Burton P, Mangino M, et al. A genomewide linkage study of 1933 families affected by premature coronary artery disease. The British Heart Foundation (BHF) Family Heart Study. Am J Hum Genet 2005; 77: 1011-20. (Abstract)
31. Antal M, Regoly-Merei A, Mesko E, et al. Incidence of risk factors in parents with acute myocardial infarction at young age and in their children. Orv Hetil 2004; 145: 2477-83. (Abstract)
32. Kelishadi R, Zadegan NS, Nadery GA, Asgary A, Bashardoust N. Atherosclerosis risk factors in children and adolescents with or without family history of premature coronary artery disease. Med Sci Monit 2002; 8: 425-9. (Abstract)
33. Jomini V, Oppliger-Pasquali S, Wietlisbach V, et al. Contribution of major cardiovascular risk factors to familial premature coronary artery disease: the GENECARD Project. J Am Coll Cardiol 2002; 40: 676-84. (Abstract) / (PDF)
34. Hauser ER, Crossman DC, Granger CB, et al. Genomewide scan for early-onset coronary artery disease in 438 families. The GENECARD Study. Am J Hum Genet 2004; 75: 436-47. (Abstract) / (Full Text) / (PDF)
35. Guran O, Akalın F, Ayabakan C, Dereli FY, Haklar G. High sensitivity C-reactive protein in children at risk for coronary artery disease. Acta Paediatr 2007; 96: 1214-9. (Abstract) / (Full Text) / (PDF)