FREQUENCY OF DYSLIPIDEMIA AMONG PATIENTS WITH DEEP VEIN THROMBOSIS PRESENTED TO A TERRIARY CARE HOSPITAL, PESHAWAR

Nowsherwan, M. Bilal, Syed Athar, M. Yaseen Khan, M. Amjad Taqweem

ABSTRACT

Objective: To determine the frequency of dyslipidemia among patients with deep vein thrombosis presented to a terriary care hospital Peshawar.

Materials And Methods: The study was conducted in Medical unit, Lady Reading hospital Peshawar. Through a Descriptive cross sectional study design, consecutive 157 patients were included in the study between Janauary to December 2015. All the patients diagnosed on DVT were asked to come fasting next early morning. On their revisit 5cc of blood was obtained under strict aseptic techniques to detect dyslipidemia (on serum cholesterol and HDL). Results were noted on a proforma specially designed for the purpose.

Results: In this study, a total of 157 patients with deep vein thrombosis were included, with a male to female ratio of 3:1. The study included age ranged from 16 up to 67 years. Average age was 46.70 years + 1.42 SD. Dyslipidemia was observed in 32 (20.38%) patients having deep vein thrombosis.

Conclusion: Dyslipidemia was observed in deep vein thrombosis patients which can be compared to other national and international studies. Male were found in majority than females.

Key Words: *Frequency, Dyslipidemia, Deep Vein Thrombosis, Pulmonary Embolism.*

INTRODUCTION

Deep vein thrombosis is a serious and potentially fatal event. Deep vein thrombosis (DVT) and pulmonary embolism (PE), known collectively as venous thromboembolism (VTE) occurs in approximately 1-2 per 1000 persons per year,[1] and affects an estimated 900,000 people in the U.S. each year, resulting in several hundred thousand hospitalizations and about 300,000 deaths.[2] The estimated overall age-adjusted incidence rate is higher for men (114 per 100,000) than it is for women (105 per 100,000).[3]

In Pakistan the incidence of deep venous thrombosis is generally not known because of the lack of epidemiological data but the relative high prevalence in certain clinical setups and its potentially harmful consequences cannot be denied.[4]

There is significant inverse association between high-density lipoprotein cholesterol (HDL-c) and VTE in a study of twenty-one case-control and cohort studies with a total of 63552 patients met the inclusion criteria. Compared with control subjects, the risk of VTE was 2.33 for obesity, 1.51 for hypertension, 1.42 for diabetes mellitus, 1.18 for smoking and 1.16 for hypercholesterolemia (95% CI, 0.67 to 2.02). Weighted mean high-density lipoprotein cholesterol levels were significantly lower in VTE patients.[5]

However another study showed no association between dyslipidemia and VTE. In this study during a median of 10.8 years of follow-up, there were 341 VTE events. Blood pressure, high levels of triglycerides and total cholesterol, low HDL cholesterol, self-reported diabetes, and smoking were all associated with increased risk of MI but not associated with VTE.[6]

Other studies demonstrated an association between hypercholesterolemia and objectively verified VTE. However further studies are needed to identify those patients who could eventually benefit maximally from treatment with statins for prevention of VTE.[7]

One of the study showed that in VTE patients 44% of patients had total cholesterol level more than 200 mg/dl while 17.8% of patients having high density lipoprotein levels less than 60mg/dl.[8]

Anticoagulation is the usual treatment for deep venous thrombosis in general patients are initiated on brief course (less than a week) of heparin treatment while they start on 3 to 6 months course of warfarin. Low molecular weight heparin (LMWH) is preferred Standard treatment for acute venous thromboembolism is limited by the need for parenteral heparin initially, with overlapping administration of a vitamin K antagonist. This presents a challenge to outpatient management, since treatment with a vitamin K antagonist requires

Department of Medicine, PGMI Lady Reading Hospital Peshawar

Address for correspondence:
Dr. Nowsherwan
Assistant Professor Department of Medicine, PGMI Lady Reading Hospital Peshawar
E-mail: Nowsherwan@yahoo.com

laboratory monitoring and dose adjustment and may be complicated by drug and food interactions.[9]

Rationale of the study was to provide us with local statistics about magnitude of dyslipidemia among patients with DVT. As much of the literature failed to show any significant relation between dyslipidemia and DVT, therefore, this descriptive study was designed to determine the frequency of dyslipidemia among patients with DVT and if found to be significantly high in our population, we will recommend more research work on its association with DVT before coming on to conclusions and recommendation for future. interaction between host mucosal defense

MATERIAL AND METHODS

This descriptive cross-sectional study was done at the department of medicine, Lady Reading Hospital Peshawar, a total of 157 consecutive patients were included in the study between Janauary to December 2015. All adult patients > 12 years of age of either gender diagnosed as deep venous thrombosis were included in this study. Patients with bilateral leg swelling but difference in circumference (10 cm below tibial tuberosity) is less 3cm and patients with diabetes and/or hyperlipidaemias under pharmological treatment, like taking simvastatin, rosuvastatin, atorvastatin were excluded from the study.

After approval from hospital ethical review committee, the data for this study was compiled from indoor and outdoor patients full filling the inclusion criteria visiting medicine department of Lady Reading Hospital Peshawar and diagnosed with the deep vein thrombosis. The purpose and benefits of the study were explained to all patients included in the study and if agreed upon a written informed consent was obtained.

All the patients diagnosed on DVT were asked to come fasting next early morning. On their revisit 5cc of blood was obtained under strict aseptic techniques to detect dyslipidemia (on serum cholesterol and HDL). All investigations including total cholesterol and High Density Lipoproteins were carried out in laboratory of Lady Reading Hospital Peshawar under supervision of an expert pathologist having minimum of five years of experience.

All the above mentioned information including name, age, gender and address were recorded on a pre designed proforma. Strictly exclusion criteria were followed to control confounders and bias in the study results.

The collected data was analyzed by SPSS statistical package version 10. Mean ± SD was calculated for continuous variables like age, serum cholesterol and HDL. Frequencies and percentages were calculated for categorical variables like gender, dyslipidemia. All collected data was represented by using charts, tables and graphs.

RESULTS

In this study, 157 patients with deep vein thrombosis were included, in which 95 (60.51%) were male and 62 (39.49%) were female patients. Male to female ratio was 3:1 (Figure No. 1).

Patient's age was divided in five categories, out of which most common age group for deep vein thrombosis was 51–65 years, of which majority of the 51 (32.5%) patients. Thirty four (21.7%) patients were in the age range of 21-35 years, 50 (31.8%) were of age range 36-50 years, 51 (32.5%) presented at age 51-65 years while 17 (10.8%) lies in age group of more than 60 years and 5 (3.2%) belongs to less than 20 years of age. The study included age ranged from 16 up to 67 years. Average age was 46.70 years + 1.42SD (Table 1).

Dyslipidemia was observed in 32 (20.38%) patients having deep vein thrombosis while 125 (79.62%) have not face the dyslipdemia during the study period. (Figure No. 2) Age wise distribution of dyslipidemia shows that majority of the dyslipidemia 12 (23.5%) were found in 51-65 years of age while 39 (76.5%)were non dyslipidemia, no patients have age groups of less than 20 years were dyslipidemia while 5 (100%) were non dyslipidemia, 6 (17.6%) have age range of (21-35) years were dyslipidemia while 28 (82.4%) were non dyslipidemia, 11 (22%) have age range of 36-50 years

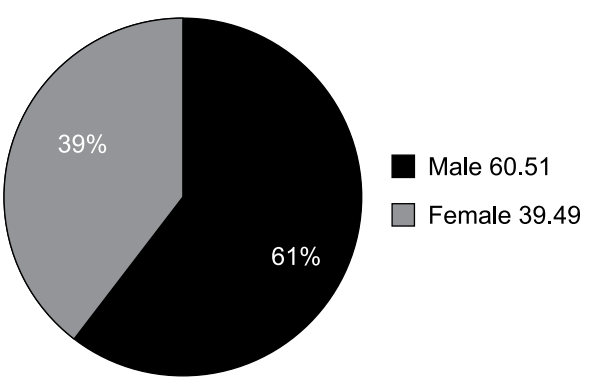

Figure No: 1 Gender Distribution

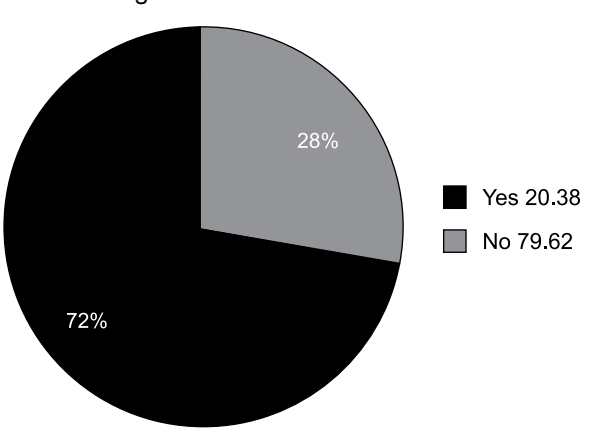

Figure No: 2 Distribution of Dyslipidemia

Table No: 1. Age Wise Distribution of Patients

Age Ranges	No. of Patients	Age
<= 20 Year	5	3.2
21 – 35 Years	34	21.7
36 – 50 Years	50	31.8
51 – 65 Years	51	32.5
66 + Years	17	10.8
Total	157	100.0

Table No:2. Age Wise Distribution of Dyslipidemia

Age Ranges	Dyslipidemia		Total
	Yes	No	
<= 20 Years	0 (0%)	5 (100%)	5 (100%)
21 – 35 Years	6 (17.6%)	28 (82.4%)	34 (100%)
36 – 50 Years	11 (22.0%)	39 (78.0%)	50 (100%)
51 – 65 Years	12 (23.5%)	39 (76.5%)	51 (100%
66+ Years	3 (17.6%)	14 (82.4%)	17 (100%)
Total	32 (20.4%)	125(79.6%)	157(100%)

Table No:3 Gender Wise Distribution of Dyslipidemia

Gender	Dyslipidemia		Total
	Yes	No	
Male	16 (16.8%)	79 (83.2%)	95(100%)
Female	16 (25.8%)	46 (74.2%)	62(100%)
Total	32 (20.4%)	125(79.6%)	157(100%)

were dyslipidemia while 39 (78%) were non dyslipidemia and 3 (17.6%) cases have age range of more than 66 years of age were dyslipidemia while 14 (82.4%) were non dyslipidemia (Table 2).

The majority of females i.e. 16 (25.8%) presented with deep vein thrombosis were dyslipidemia while 79 (83.2%) were non dyslipidemia and 16 (16.8%) male patients were dyslipidemia while 46 (74.2%) were non dyslipidemia. Which shows that the female patients are found in minority as that of female with dyslipidemia having deep vein thrombosis (Table 3).

DISCUSSION

Deep venous thromboembolic disease (DVT) is a polygenic disease with pathogenic contributions from both genetic and environmental risk factors.[10,11] Various molecular dysfunctions in the protein C pathway, including factor V Leiden[12,13] are among the currently most common identifiable genetic risk factors for DVT.[14] Although dyslipoproteinemia is associated with arterial thrombosis, especially in men, little is known about the relationships between DVT and plasma lipids or lipoprotein subclasses.[15-18] Several observations suggest a relationship between DVT and dyslipidemia. Spontaneous DVT is associated with clinically silent atherosclerotic vascular disease. The use of lipid-lowering statins reduces DVT.[19,20]

Subnormal plasma levels of glucosylceramide, a glycosphingolipid that circulates in lipoproteins, are found in DVT patients.[21] Because glucosylceramide and HDL enhance the anticoagulant activity of activated protein C,[22-24] It has been speculated that glucosylceramide and HDL may help protect against DVT.[25]

HDL cholesterol levels in particular are significantly lower in patients who experience DVT.[5] Diabetes mellitus has been associated with a 42% increase in the risk of DVT or PE.[26] A case-control study of 208 DVT patients and 300 control subjects from Korea demonstrated that both low levels of HDL cholesterol and elevated fasting glucose correlated with a doubling in the risk of VTE.[27]

Lipoprotein subclass analyses show that these differences reflect lower levels of large HDL particles and higher levels of small LDL particles. Confirming the NMR based demonstration of dyslipoproteinemia in DVT patients, antigenic assay data for the major apolipoprotein of HDL showed lower apoAI levels. The difference in the apoB/ apoAI ratio between DVT patients and controls was statistically stronger than differences in either apolipoprotein alone. DVT was associated with low levels of HDL particle concentration and appeared to be associated specifically with reduced plasma levels of large HDL particles and not with differences in medium and small HDL particles.

On the basis of clinical laboratory serum cholesterol data, HDL-C was lower in DVT cases than controls, and the ratio of LDL-C/HDL-C was higher in DVT patients than controls. Although LDL-C data were not particularly striking, the OR for DVT in subjects with LDL-C level, suggesting that elevated LDL-C is associated with DVT. When the quartile-based OR for VTE associated with elevated LDL-C was calculated. To identify genetic factors contributing to the observed dyslipoproteinemia, we assessed genetic variation in 3 genes regulating HDL metabolism.[28-33]

Compared with controls, the B2 allele of the CETP TaqI polymorphism was less frequent in male VTE cases. CETP plays a pivotal role in cholesteryl ester transfer from HDL to apoB-containing lipoproteins, and CETP deficiency or CETP inhibitors increase HDL levels.[34,35] The TaqI B2 allele is linked to decreased CETP plasma levels of antigen and activity that results in larger HDL and LDL particle size[36] and in higher HDL-C levels.[37]

Thus, the lower B2 allelic frequency observed in VTE patients is predicted to cause lower HDL and higher LDL levels. Of note, the CETP TaqI locus is in

strong linkage disequilibrium with other polymorphisms in the CETP gene that may directly affect CETP activity and concentration.[38] The allele frequencies of hepatic lipase and endothelial lipase polymorphisms that were studied did not differ, thus reducing the likelihood that these genes contribute to dyslipoproteinemia in DVT. Relevant to this analysis is the comparability between the VTE and control groups for clinical conditions that are associated with changes in lipid metabolism. Such conditions include BMI, smoking, diabetes, hypertension, and atherosclerotic coronary artery disease. BMI was different for DVT patients compared with controls.

However, after adjustments for known venous thrombosis risk factors including BMI, statistically significant OR values and trend for DVT were maintained, with few exceptions. The overall finding of dyslipoproteinemia involving both lower HDL levels and elevated LDL levels associated with DVT was strongly supported by the statistical analysis after adjustments. The prior and current smoking rates diabetes, hypertension, and atherosclerotic coronary artery disease in DVT patients were similar to those in controls and thus cannot explain the observed dyslipoproteinemia. As reviewed elsewhere,[25] elevated LDL or oxidized LDL can promote thrombin formation, whereas HDL can enhance the protein C anticoagulant pathway and reduce thrombin generation.

An increased ratio of LDL to HDL, reflected in apoB/ apoAI or LDL-C/HDL-C values, could be prothrombotic by contributing to an imbalance in thrombin generation, resulting in hypercoagulability. Thus, there is substantial biological plausibility for mechanisms by which the observed dyslipoproteinemia might be prothrombotic for VTE. Additional protective effects of HDL and/or harmful effects associated with elevated LDL might also be relevant for understanding mechanisms whereby dyslipoproteinemia might help cause venous thrombosis. Dyslipidemia and dyslipoproteinemia are distinct but related entities. Although this is the first report to assess dyslipoproteinemia in VTE, a few limited studies of VTE and dyslipidemia based purely on lipid measurements have appeared.[39-41]

Among those studies, the association of dyslipidemia with DVT was not as strong as observed for cardiovascular diseases, and this association was controversial. Gonzalez-Ordonez et al[41] reported an association of dyslipidemia with DVT that was stronger in men than women. In our study, we also found a modest association of VTE with dyslipidemia in men, i.e. with low HDL-C or with elevated LDL-C. However, our data show stronger correlations between DVT and dyslipoproteinemia than between VTE and dyslipidemia, emphasizing the importance of apolipoproteins and lipoprotein particles compared with bulk plasma lipid levels, consistent with the concept that certain HDL particles may be protective for VTE and/or that certain LDL particles directly contribute to increase DVT risk.

More research on dyslipoproteinemia and VTE is clearly needed. Although less convenient than serum lipid assays, ELISA assays to determine apoB and apoAI levels and apoB/ apoAI ratios might prove useful. Lipoprotein subclass analysis by NMR technology might not be a practical laboratory test for routine clinical care. However, further clinical research studies using NMR spectroscopy to quantify lipoprotein subclass levels in DVT patients are well warranted, as are studies of SNPs in genes that regulate HDL and LDL metabolism, notably the CETP TaqI B1/B2 polymorphism. Other genetic factors that influence lipoprotein metabolism might also contribute to dyslipoproteinemia in VTE. The role of gender in risk analysis for venous thrombosis is very important because hormone use increases risk for female subjects,[42] whereas male gender per se increases risk.[43-45]

CONCLUSION

Deep venous thromboses have many similar pathogenetic mechanisms. Endothelial injury, platelet activation, elevated levels of intrinsic clotting factors and inflammatory markers, increased fibrinogen, and impaired fibrinolysis are characteristic of the two disorders. In addition, older age, dyslipidemia, and gender in our study also predispose to deep venous and arterial thrombosis.

REFERENCE

1. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost. 2007;5:692-9.
2. Raskob GE, Silverstein R, Bratzler DW, Heit JA, White RH. Surveillance for deep vein thrombosis and pulmonaryembolism:ecommendations from a national workshop Am J Prev Med. 2010;38:502-9.
3. Heit J. The epidemiology of venous thromboembolism in the community. ArteriosclerThrombVascBio.2008;28:370.
4. Sheikh.MS,Rehman MF. DVT prophylaxis role of low molecular weight heparin. Professional Med J. 2011;18:275-9.
5. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation. 2008;117:93-102.
6. Chamberlain AM, Folsom AR, Heckbert SR, Rosamond WD, Cushman M. High-density lipoprotein cholesterol and venous thromboembolism in the Longitudinal Investigation of Thromboembolism Etiology (LITE). Blood. 2008;112:2675-80.
7. Poredos P, Jezovnik MK. Dyslipidemia, statins, and venous thromboembolism. Semin Thromb Hemost. 2011;37:897-902.
8. Deguchi H, Pecheniuk NM, Elias DJ, Averell PM, Griffin JH. High density lipoprotein deficiency and

dyslipoproteinemia associated with venous thrombosis in men. [Online] [cited on: 2012 jan 2]. Available on: http://www.circulationaha.org

9. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. (8th edition). Chest. 2008;133:454-5.

10. Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet. 1999;353:1167-73.

11. Lensing AW, Prandoni P, Prins MH, Buller HR. Deep-vein thrombosis. Lancet. 1999;353:479-85.

12. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature. 1994;369:64-7.

13. Greengard JS, Sun X, Xu X, Fernandez JA, Griffin JH, Evatt B. Activated protein C resistance caused by Arg506Gln mutation in factor Va. Lancet. 1994;343:1361-2.

14. Goodnight SH, Griffin JH. Hereditary Thrombophilia. In: Beutler E, Lichtman MA, Coller BA, Kipps TJ, Seligsohn U, eds. Williams Hematology. New York, NY: McGraw-Hill; 2001;1697-714.

15. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837-47.

16. Grundy SM. Primary prevention of coronary heart disease: integrating risk assessment with intervention. Circulation. 1999;100:988-98.

17. Fuster V, Gotto AM Jr. Risk reduction. Circulation. 2000;102:94-102.

18. Freedman DS, Otvos JD, Jeyarajah EJ, Shalaurova I, Cupples LA, Parise H, et al. Sex and age differences in lipoprotein subclasses measured by nuclear magnetic resonance spectroscopy: the Framingham Study. Clin Chem. 2004;50:1189-200.

19. Prandoni P, Bilora F, Marchiori A, Bernardi E, Petrobelli F, Lensing AW, et al. An association between atherosclerosis and venous thrombosis. N Engl J Med. 2003;348:1435-41.

20. Herrington DM, Vittinghoff E, Lin F, Fong J, Harris F, Hunninghake D, et al. Statin therapy, cardiovascular events, and total mortality in the Heart and Estrogen/Progestin Replacement Study (HERS). Circulation. 2002;105:2962-7.

21. Ray JG, Mamdani M, Tsuyuki RT, Anderson DR, Yeo EL, Laupacis A. Use of statins and the subsequent development of deep vein thrombosis. Arch Intern Med. 2001;161:1405-10.

22. Deguchi H, Fernandez JA, Pabinger I, Heit JA, Griffin JH. Plasma glucosylceramide deficiency as potential risk factor for venous thrombosis and modulator of anticoagulant protein C pathway. Blood. 2001;97:1907-14.

23. Deguchi H, Fernandez JA, Griffin JH. Neutral glycosphingolipid dependent inactivation of coagulation factor Va by activated protein C and protein S. J Biol Chem. 2002;277:8861-5.

24. Griffin JH, Kojima K, Banka CL, Curtiss LK, Fernandez JA. High density lipoprotein enhancement of anticoagulant activities of plasma protein S and activated protein C. J Clin Invest. 1999;103:219-27.

25. Griffin JH, Fernandez JA, Deguchi H. Plasma lipoproteins, hemostasis and thrombosis. Thromb Haemost. 2001;86:386-94.

26. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation. 2008;117:93-102.

27. Jang MJ, Choi WI, Bang SM, Lee T, Kim YK, Ageno W, et al. Metabolic syndrome is associated with venous thromboembolism in the Korean population. Arterioscler Thromb Vasc Biol. 2009;29:311-5.

28. Guerra R, Wang J, Grundy SM, Cohen JC. A hepatic lipase (LIPC) allele associated with high plasma concentrations of high density lipoprotein cholesterol. Proc Natl Acad Sci USA. 1997;94:4532-7.

29. Grundy SM, Vega GL, Otvos JD, Rainwater DL, Cohen JC. Hepatic lipase activity influences high density lipoprotein subclass distribution in normotriglyceridemic men: genetic and pharmacological evidence. J Lipid Res. 1999;40:229-34.

30. Ma K, Cilingiroglu M, Otvos JD, Ballantyne CM, Marian AJ, Chan L. Endothelial lipase is a major genetic determinant for high-density lipoprotein concentration, structure, and metabolism. Proc Natl Acad Sci USA. 2003;100:2748-53.

31. Brousseau ME, O'Connor JJ Jr, Ordovas JM, Collins D, Otvos JD, Massov T, et al. Cholesteryl ester transfer protein TaqI B2B2 genotype is associated with higher HDL cholesterol levels and lower risk of coronary heart disease end points in men with HDL deficiency: Veterans Affairs HDL Cholesterol Intervention Trial. Arterioscler Thromb Vasc Biol. 2002;22:1148-54.

32. Couture P, Otvos JD, Cupples LA, Lahoz C, Wilson PW, Schaefer EJ, et al. Association of the C-514T polymorphism in the hepatic lipase gene with variations in lipoprotein subclass profiles: the Framingham Offspring Study. Arterioscler Thromb Vasc Biol. 2000;20:815-22.

33. Barter PJ, Brewer HB Jr, Chapman MJ, Hennekens CH, Rader DJ, Tall AR. Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis. Arterioscler Thromb Vasc Biol. 2003;23:160-7.

34. Brousseau ME, Schaefer EJ, Wolfe ML, Bloedon LT, Digenio AG, et al. Effects of an inhibitor of cholesteryl ester transfer protein on HDL cholesterol. N Engl J Med. 2004;350:1505-15.

35. Ordovas JM, Cupples LA, Corella D, Otvos JD, Os-

good D, Martinez A, et al. Association of cholesteryl ester transfer protein-TaqIB polymorphism with variations in lipoprotein subclasses and coronary heart disease risk: the Framingham Study. Arterioscler Thromb Vasc Biol. 2000;20:1323-9.

36. Boekholdt SM, Thompson JF. Natural genetic variation as a tool in understanding the role of CETP in lipid levels and disease. J Lipid Res. 2003;44:1080-93.

37. Klerkx AH, Tanck MW, Kastelein JJ, Molhuizen HO, Jukema JW, Zwinderman AH, et al. Haplotype analysis of the CETP gene: not TaqIB, but the closely linked _629C3A polymorphism and a novel promoter variant are independently associated with CETP concentration. Hum Mol Genet. 2003;12:111-23.

38. Kawasaki T, Kambayashi J, Ariyoshi H, Sakon M, Suehisa E, Monden M. Hypercholesterolemia as a risk factor for deep-vein thrombosis. Thromb Res. 1997;88:67-73.

39. Lippi G, Brocco G, Manzato F, Guidi G. Relationship between venous thromboembolism and lipid or lipoprotein disorders. Thromb Res. 1999;95:353-4.

40. Gonzalez-Ordonez AJ, Fernandez-Carreira JM, Fernandez-Alvarez CR, Venta OR, Macias-Robles MD, Gonzalez-Franco A, et al. The concentrations of soluble vascular cell adhesion molecule-1 and lipids are independently associated with venous thromboembolism. Haematologica. 2003;88:1035-43.

41. Rosendaal FR, Van HV, Tanis BC, Helmerhorst FM. Estrogens, progestogens and thrombosis. J Thromb Haemost. 2003;1:1371-80.

42. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. Arch Intern Med. 2002;162:1182-9.

43. Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. N Engl J Med. 2004;350:2558 -63.

44. Baglin T, Luddington R, Brown K, Baglin C. High risk of recurrent venous thromboembolism in men. J Thromb Haemost. 2004;2:2152-5