Haptoglobin phenotype 2-2 as a potentially new risk factor for spontaneous venous thromboembolism

Rainer Vormittag
Thomas Vukovich
Christine Mannhalter
Erich Minar
Verena Schönauer
Christine Bialonczyk
Mirko Hirschl
Ingrid Pabinger

Background and Objectives. Haptoglobin (Hp) is a plasma protein that binds free hemoglobin and thus prevents catalysis of reactive oxygen species by the Fenton reaction. A genetic polymorphism has been described that leads to the generation of two distinct alleles, Hp1 and Hp2, which define three major haptoglobin phenotypes, denoted Hp1-1, Hp2-1 and Hp2-2. Hp2-2 has been reported to be associated with the risk of atherosclerosis and coronary heart disease. In our study we investigated the association of haptoglobin genotype and phenotype with the risk of spontaneous venous thromboembolism (VTE).

Design and Methods. One hundred and twenty-eight patients with a history of spontaneous deep vein thrombosis (70 women, 58 men), 105 with spontaneous symptomatic pulmonary embolism (58 women, 47 men) and 122 healthy controls (60 women, 62 men) were enrolled. Haptoglobin levels were measured immunonephelometrically and phenotypes were detected by polyacrylamide gel electrophoresis and subsequent immunoblotting.

Results. The Hp2-2 phenotype was significantly more prevalent in patients (42%) than in controls (30%) and significantly increased the risk for VTE in univariable (odds ratio=1.6, 95% confidence interval [1.0-2.6], p=0.04) and multivariable analyses (odds ratio=1.9 [1.0-3.4], p=0.04). Hp2-2 (n=134) was associated with significantly lower haptoglobin levels (median=89.7 mg/dL) than Hp2-1 (n=170, median = 123.5 mg/dL, p<0.001) or Hp1-1 (n=51, median=142.8 mg/dL, p<0.001).

Interpretation and Conclusions. Our study gives the first evidence that Hp2-2 represents a risk factor for spontaneous VTE, presumably through a pathophysiological mechanism similar to that in arterial disease.

Key words: venous thrombosis, pulmonary embolism, haptoglobin, haptoglobin phenotype

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From the Department of Internal Medicine I, Division of Hematology and Hemostaseology, Medical University Vienna, Austria (RV, VS, IP); Institute of Medical and Chemical Laboratory Diagnostics, Medical University Vienna, Austria (TV, CM); Department of Internal Medicine II, Division of Angiology, Medical University Vienna, Austria (EM); Department of Dermatology, Wilhelminenspital Vienna, Austria (CB); Department of Angiology, Hanusch-Krankenhaus, Vienna, Austria (MI).

Correspondence:
Prof. Dr. Ingrid Pabinger-Fasching, Department of Internal Medicine I, Division of Hematology and Hemostaseology, Medical University Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. E-mail: ingrid.pabinger@meduniwien.ac.at

Haptoglobin (Hp) is an acute-phase protein synthesized in the liver and plays an important role in hemoglobin metabolism.[1] The major stimulus for its production is interleukin-6.[2] The Hp gene is located on the long arm of chromosome 16 (16q22.3).[3,4] An allelic polymorphism gives rise to two distinct alleles, Hp1 and Hp2, defining three major phenotypes, denoted Hp1-1, Hp2-1 and Hp2-2.[5] The protein is composed of one α and one β-chain.[6] Hp2-2 can form cyclic multimers, because of a longer α-chain with two instead of one cysteine residues.[7] A spectrum from dimers to oligomers, containing both large and small α-chains, can be found in heterozygous individuals. Only dimers are present in individuals with Hp1-1. The latter phenotype has the highest capacity to inhibit hemoglobin-induced oxidative reactions, Hp2-1 an intermediate capacity and Hp2-2 the lowest capacity.[8] Large multimers have only limited ability to sieve through injured endothelium and to bind to hemoglobin in the extracellular space.[8] Rapid binding of hemoglobin is of great importance because free hemoglobin generates reactive oxygen species by the Fenton reaction.[5] Reactive oxygen species have been shown to cause endothelial damage, to promote atherosclerosis and to favor the development of thrombotic diseases.[9] In this context the different anti-oxidative capacity of the three phenotypes gains importance. An association between Hp2-2 and the risk of gestational diabetes mellitus, atherosclerosis and arterial thrombosis has been described.[10–14] However, data are inconsistent.[15] No data are currently available on haptoglobin genotype and phenotype distributions in individuals with spontaneous venous thromboembolism (VTE). We, therefore, investigated the contribution of these two parameters to the risk of spontaneous VTE.

Design and Methods

Patients

Between July 1999 and December 2002 consecutive outpatients with a history of spontaneous VTE, who were referred for an assessment of thrombosis risk factors, were recruited. Spontaneous VTE was defined as VTE without a triggering event (surgery, relevant trauma causing immobilization, pregnancy, delivery or malignancy). The study protocol was approved by the Ethics Committee of the University Hospital Vienna. Patients received detailed written information about the study, and were only included if written informed consent was obtained. Patients' medical histories were collected by a standardized questionnaire and from medical records on the day of study inclusion. The diagnosis of VTE was verified by at least one objective method, either duplex sonography or venography for deep venous thrombosis, either angiography, computerized spiral tomography or combined ventilation-perfusion scanning (high probability) for pulmonary embolism. Enrollment took place at least three months after the thrombotic event.

Events occurring during hormone-replacement therapy or during oral contraceptive use were considered spontaneous. Only a small number of patients (n = 11) were under treatment with hormone replacement or oral contraceptives (n=30) at the time of VTE. In these women, treatment was terminated at the time of diagnosis of VTE and enrollment took place at least three months later. Exclusion criteria were current pregnancy, malignancy, diabetes mellitus, chronic renal, liver or pancreatic disease, rheumatic disease necessitating pharmacological treatment, inflammatory bowel disease, continuation of hormone replacement therapy after VTE or delivery. In patients with recent surgery or trauma and a history of spontaneous VTE that had occurred months before, enrollment into the study was delayed for at least 6 weeks.

Two hundred and thirty-three patients fulfilled the enrollment criteria. Patients were included irrespective of treatment with oral anticoagulants (29%) or aspirin (7%) or the presence of established risk factors for VTE. One-hundred and twenty-eight individuals had had spontaneous deep vein thrombosis without clinical signs of pulmonary embolism, 105 had had spontaneous symptomatic pulmonary embolism and in 48 (46%) of these simultaneous deep vein thrombosis was confirmed. The remaining 57 patients with pulmonary embolism did not present clinical signs of deep vein thrombosis. Only objectively confirmed events were considered. Healthy controls (n=122) comprised individuals without a medical history of VTE or arterial thrombosis from the same geographic region and ethnic background as the patients. Women in the control group had never received hormone replacement therapy. Individuals in this reference group were genetically unrelated to the patients and were either spouses or acquaintances of the patients, hospital staff, or friends or relatives of hospital staff. Control individuals were not related to each other. Matching for age and sex was not performed pair-wise, but for the whole group. Following commonly used definitions, individuals with a body mass index above 30 kg/m^2 are referred to as obese, those with a body mass index between 25 and 30 kg/m^2 as overweight and those with a body mass index below 25 kg/m^2 as normal-weight.

Blood sampling and laboratory methods

Venous blood samples were obtained after overnight fasting at study inclusion. Plasma was snap frozen and stored at -80°C until performance of the assay in series. Haptoglobin phenotype was determined essentially following a method described previously by Yang and coworkers,[16] using 5 µL plasma samples mixed with 500 µL sodium dodecyl sulfate glycerin Tris buffer (pH 8.6). A 10–15% polyacrylamide gradient gel at 250 V and 80 AVh was used to separate the haptoglobin phenotypes electrophoretically on a Pharmacia Phast System (Pharmacia Biotech, Uppsala, Sweden). Samples were blotted on nitrocellulose and blocked with 3% milk powder in Tris-buffered saline. Rabbit anti-human haptoglobin IgG antibodies were used for detection and, subsequently, goat anti-rabbit IgG antibodies conjugated to alkaline phosphatase (Dako, Glostrup, Denmark) and a phosphatase developing solution (Technoclone, Vienna, Austria) were used for visualization of the bands. Two experienced investigators independently analyzed the electropherograms. Faintly stained samples were reanalyzed using the 10-fold plasma volume (50 µL).

Haptoglobin levels were measured immunonephelometrically (Dade Behring®, Wilmington, Germany) on a Behring Nephelometer II. Factor VIII activity was measured on a Sysmex CA 7000 analyzer using factor VIII deficient plasma (Hyland Baxter Immuno, Vienna, Austria) and Dade® Actin®-FS (Dade Behring, Marburg, Germany).[17] The cut-off of elevated factor VIII activity was set at 230% for practical reasons by the Institute of Medical and Chemical Laboratory Diagnostics of the Medical University Vienna. This represented the 95th percentile (233% factor VIII activity) and thus the upper limit of the normal range in the reference cohort of healthy individuals (n=220) of the Institute. Deficiencies of protein C, protein S and antithrombin as well as factor V Leiden and prothrombin G20210A variation were diagnosed as described previously.[17]

Statistical methods

Binary logistic regression analysis was applied to cal-

culate univariable and multivariable odds ratios for spontaneous VTE, for idiopathic VTE and spontaneous symptomatic pulmonary embolism without clinical signs of deep vein thrombosis (dependent variables) and corresponding 95% confidence intervals (CI). The multivariable model included the following independent variables: haptoglobin phenotype (categorized in two levels: Hp2-2 versus Hp2-1 or Hp1-1), haptoglobin, age, sex, body mass index, factor V Leiden and prothrombin G20210A variation (categorized in two levels: heterozygous or homozygous mutation carrier or carrier of normal variant) and factor VIII (categorized in two levels: activity above or below 230%). Correlation of metric parameters was analyzed by the non-parametric Spearman's-test. χ^2-tests were applied for comparison of categorical variables and Mann-Whitney tests for metric variables, respectively. A two-tailed p-value of less than 0.05 was considered to indicate statistical significance. All tests were performed with the statistical package SPSS 12 for Windows®.

Results

The demographic characteristics of patients and controls and risk factors for VTE in both groups are displayed in Table 1. Six patients (3%) also had a history of arterial thrombosis. Factor V Leiden and prothrombin G20210A variation were more prevalent in patients than in controls. Nine patients (4%) had protein C deficiency, three (1%) had protein S deficiency, one (0.4%) had antithrombin deficiency and one (0.4%) had a lupus anticoagulant.

Hp2-2 phenotype was significantly more prevalent in patients (42%) than in controls (30%) and significantly increased the risk of VTE in univariable and multivariable analyses (OR=1.6 and 1.9, respectively, Table 2). In comparison with Hp1-1, Hp2-1 did not show any association with an increased risk of spontaneous VTE (OR=1.0 [0.5-2.0]), whereas an odds ratio of 1.7 [0.9-3.3] was found for Hp2-2 in a stepwise univariable analysis. Among the 233 individuals with spontaneous thrombosis, 30 women were taking oral contraceptives and 11 were under hormone replacement therapy at the time of thrombosis. If these women were excluded from the analysis and the remaining 192 individuals with idiopathic VTE were compared to the 122 healthy controls a univariable odds ratio of 1.8 [1.1-2.9] and a multivariable odds ratio of 2.1 [1.1-3.9] were found. The proportion of individuals with Hp2-2 phenotype was especially high in patients with symptomatic spontaneous pulmonary embolism without clinical signs of deep vein thrombosis (n=57, Hp1-1=8.2%, Hp2-1=42.1%, Hp2-2=50.9%). For the comparison of this subgroup with controls a univariable odds ratio of 2.4 [1.2-4.5] (p=0.009) and a multivariable odds ratio of 3.4 [1.5-8.0] (p=0.009) were calculated. The haptoglobin phenotype distribution did not significantly deviate from the Hardy-Weinberg equilibrium in patients (Hp1-1 13%, Hp2-1 45%, Hp2-2 42%, p=0.76) or controls (Hp1-1 16%, Hp2-1 53%, Hp2-2 30%, p=0.34). Similar haptoglobin phenotype distributions were observed in patients with a single event of VTE (Hp1-1=12.7%, Hp2-1=45.7%, Hp2-2=41.6%) and those with recurrent events (Hp1-1=16.7%, Hp2-1=41.7%, Hp2-2=41.7%).

Hp2-2 (n=134) was associated with significantly lower haptoglobin levels (median=89.7 mg/dL) than Hp2-1 (n=170, median=123.5 mg/dL, p< 0.001) or Hp1-1 (n=51, median=142.8 mg/dL, p< 0.001) (Figure 1). Individuals with Hp2-1 had about 37% higher median haptoglobin levels (p<0.001) and those with Hp1-1 about 59% higher levels (p< 0.001) than those with Hp2-2.

Haptoglobin levels were significantly higher in patients (median=120.2 mg/dL, interquartile range

Table 1. Basic characteristics and risk factors for VTE in patients and controls and p values in univariable analysis (χ^2-test and Mann-Whitney test, respectively).

	Patients n=233	*Controls n=122*	*p*
Women, n (%)	128 (55)	60 (49)	0.3
Age at study entry, median [IQR], years	45 [35-59]	44 [31-55]	0.054
Age at (first) VTE, median [IQR], years	42 [30-56]	–	–
Body mass index, median [IQR], kg/m^2	26.6 [23.6-29.6]	23.8 [21.4-26.3][§]	< 0.001
Factor V Leiden*, n (%)	72 (31)	12 (10)	< 0.001
Prothrombin G20210A,[†] n (%)	19 (8)	2 (2)°	0.03
Factor VIII activity above 230%	35 (16)	1 (1)[#]	< 0.001

*IQR: interquartile range; *All heterozygous except six patients (3 %) who were homozygous; [†]all heterozygous except one homozygous (1 %) patient; [§]data missing for 6 individuals; °analysis not done in 17 individuals; [#]analysis not done in 7 patients and 4 controls.*

Table 2. Odds ratios for VTE according to haptoglobin phenotype.

	Patients n (%)	*Controls n (%)*	*Univariable OR [95% confidence interval]*	*Multivariable OR1 [95% confidence interval]*
Hp2-2	97 (42)	37 (30)	1.6 [1.0-2.6], p=0.04	1.9 [1.0-3.4], p=0.04
Hp2-1/Hp1-1	136 (58)	85 (70)	*	*

**Adjusted for haptoglobin, age, sex, body mass index, factor V Leiden, prothrombin G20210A variation, elevated factor VIII.*

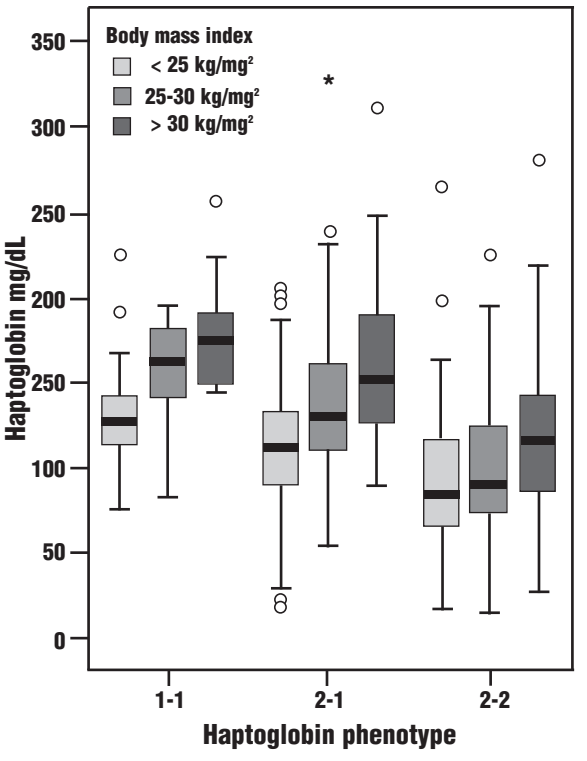

Figure 1. Box plot of haptoglobin levels in clusters of haptoglobin phenotype and body mass index in patients and controls. The margins of the rectangles depict the 25th and 75th percentiles, the line within the rectangles the median level. The whiskers represent the largest and smallest observed values that are within 1.5 box lengths from the end of the box. Outliers are illustrated as circles, extremes as asterisks.

=89.7-157.1) than in controls (median=104.8 mg/dL, interquartile range=78.2–133.3, p=0.003). In univariable but not in multivariable analysis haptoglobin statistically significantly increased the odds for VTE. A 25 mg/dL increase of haptoglobin increased the odds for VTE by 1.2 [95% CI: 1.0 to 1.3, p=0.01] in univariable analysis. However, this association lost its statistical significance in multivariable analysis (OR=1.1, [0.97-1.3], p=0.13).

We found a positive correlation between body mass index and haptoglobin (correlation coefficient=0.3, p<0.001). Overweight individuals (n=134) had about 10% (p<0.06) and obese (n=63) about 33% higher median haptoglobin levels than normal-weight persons (n=152, Figure 1). Haptoglobin levels were not significantly different between women and men (median: 118 mg/dL and 113 mg/dL, respectively, p=0.1). Age and factor VIII were weakly correlated with haptoglobin (correlation coefficient=0.12, p=0.02 and correlation coefficient=0.20, p<0.001, respectively). Patients treated with oral anticoagulants (n=67) did not have significantly different haptoglobin levels (median=116 mg/dL) from those without treatment (n=288, median=118 mg/dL, p=0.5). The median time interval between blood collection and the preceding thrombotic event was 254 days [interquartile range: 210-475] and was not significantly correlated with haptoglobin (correlation coefficient = –0.08, p=0.2). The median time interval between termination of hormone replacement therapy or termination of oral contraception and consecutive blood collection was 366 days (25th-75th percentile: 238-574) and 258 days (25th-75th percentile: 216-434), respectively.

Discussion

In our study the Hp2-2 phenotype was associated with spontaneous VTE. To our knowledge, no data on haptoglobin phenotypes and VTE have been published up to now. However, haptoglobin phenotype has been investigated in patients with atherosclerosis and arterial thrombosis. In the majority of studies persons with Hp2-2 were found to be at increased risk. This phenotype is associated with the accumulation of atherosclerotic lesions in essential hypertension, is overrepresented in patients below the age of 45 who undergo coronary artery bypass grafting and is associated with a lower age at infarction and shorter graft survival time.[14] Furthermore, Hp2-2 was associated with an increased risk for coronary heart disease in diabetics in the Strong Heart Study[12] and showed a significant association with the risk for re-stenosis after peripheral and coronary angioplasty.[11] On the other hand a Belgian Study reported an increased risk for coronary heart disease in persons with Hp1-1 that was independent of haptoglobin concentration.[18] A lower capacity of Hp2-2 compared to Hp2-1 and Hp1-1 to inhibit hemoglobin-induced oxidation at equal concentrations has been convincingly demonstrated.[8] Free hemoglobin catalyses the generation of reactive oxygen species, which directly injure cell membranes, impair vasodilatation and lead to formation of oxidized low density lipoprotein.[19] Oxidized low density lipoprotein is cytotoxic and an important mediator of atherosclerosis. Increased levels of reactive oxygen species have been observed in varicose veins, especially in those with thrombophlebitis[20] and increased levels of circulating lipoperoxidative markers have been reported in patients with acute deep vein thrombosis.[21] These mechanisms and findings give a plausible explanation for an association of Hp2-2 with the risk of VTE, as observed in our study. Our data confirm an earlier finding that haptoglobin levels are remarkably correlated with phenotypes.[5] Individuals with Hp2-2 had the lowest levels of haptoglobin, those with Hp2-1 had intermediate levels and those with Hp1-1 had the highest levels. The phenotype had a stronger influence on haptoglobin levels than did other factors that showed a significant correlation, such as the body mass index. Although Hp2-2 was more frequent among our

patients, slightly higher haptoglobin levels were observed in the patient population than in the control group. Other factors may have contributed to an increase of haptoglobin levels in patients. Patients in our study had a significantly higher body mass index than controls, which definitely accounted for some of the observed difference in haptoglobin levels between the two groups. Moreover, we cannot exclude acute phase reactions in some individuals, although we chose a study design intended to minimize inclusion of individuals with transient inflammation. Although haptoglobin levels were slightly higher in patients than in controls, they did not independently increase the risk of VTE. A similar observation has been made for the inflammatory marker high sensitivity-C-reactive protein: higher levels were found in patients with thrombosis than in controls, but a significantly increased risk for VTE was not described.[22-24] According to our data increased haptoglobin levels do not seem to be associated with VTE. The decreased capacity of Hp2-2 to inhibit hemoglobin-induced oxidative reactions[8] appears to increase thrombosis risk compared to Hp2-1 and Hp1-1 even at a slightly higher absolute concentration. There are currently no data available on haplotype phenotype distribution in Austria, but this phenotype distribution was analyzed in the Swiss population.[25] In a very large population-based study (n=4004) Hp2-2 was found in 33%, Hp2-1 in 48% and Hp1-1 in 19%. This phenotype distribution was not significantly different from that observed in the control group of our study (p=0.5) and the frequency of established risk factors for VTE in our control group was in very good accordance with data from the literature. A slightly higher proportion of Hp2-2 phenotype (35%) was observed in another large study (n=1000) that investigated healthy Belgian blood donors.[26] Therefore, our data need to be confirmed in a large, preferably prospective population-based study.

In conclusion, our study introduces a potentially new risk factor for spontaneous VTE, presumably acting through the same pathophysiological mechanism as in arterial disease. Our findings merit intensified basic and clinical research on the role of haptoglobin phenotypes in arterial as well as venous vascular disease.

RV: designed and performed the research, analyzed data and wrote the manuscript; TV: designed the research, provided vital analytical tools, analyzed the data and wrote the manuscript; CM: analyzed data and wrote the manuscript; EM, VS, CB and MH: performed the research and wrote the manuscript; IP: designed and performed the research, analyzed the data, and wrote the manuscript. All the authors approved the final version to be published. The authors also declare that they have no potential conflicts of interest.

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References

1. Wang Y, Kinzie E, Berger FG, Lim SK, Baumann H. Haptoglobin, an inflammation-inducible plasma protein. Redox Rep 2001;6:379-85.
2. Oliviero S, Cortese R. The human haptoglobin gene promoter: interleukin-6-responsive elements interact with a DNA-binding protein induced by interleukin-6. Embo J 1989;8:1145-51.
3. Robson EB, Polani PE, Dart SJ, Jacobs PA, Renwick JH. Probable assignment of the alpha locus of haptoglobin to chromome 16 in man. Nature 1969; 223:1163-5.
4. Magenis RE, Hecht F, Lovrien EW. Heritable fragile site on chromosome 16: probable localization of haptoglobin locus in man. Science 1970;170:85-7.
5. Langlois MR, Delanghe JR. Biological and clinical significance of haptoglobin polymorphism in humans. Clin Chem 1996; 42: 1589-600.
6. Bowman BH, Kurosky A. Haptoglobin: the evolutionary product of duplication, unequal crossing over, and point mutation. Adv Hum Genet 1982; 12:189-261.
7. Wejman JC, Hovsepian D, Wall JS, Hainfeld JF, Greer J. Structure and assembly of haptoglobin polymers by electron microscopy. J Mol Biol 1984; 174:343-68.
8. Melamed-Frank M, Lache O, Enav BI, Szafranek T, Levy NS, Ricklis RM, et al. Structure-function analysis of the antioxidant properties of haptoglobin. Blood 2001; 98:3693-8.
9. Touyz RM, Schiffrin EL. Reactive oxygen species in vascular biology: implications in hypertension. Histochem Cell Biol 2004; 122:339-52.
10. Mustafa S, Vukovich T, Prikoszovich T, Winzer C, Schneider B, Esterbauer H, et al. Haptoglobin phenotype and gestational diabetes. Diabetes Care 2004; 27:2103-7.
11. Roguin A, Koch W, Kastrati A, Aronson D, Schomig A, Levy AP. Haptoglobin genotype is predictive of major adverse cardiac events in the 1-year period after percutaneous transluminal coronary angioplasty in individuals with diabetes. Diabetes Care 2003; 26:2628-31.
12. Levy AP, Hochberg I, Jablonski K, Resnick HE, Lee ET, Best L, et al. Haptoglobin phenotype is an independent risk factor for cardiovascular disease in individuals with diabetes: the Strong Heart Study. J Am Coll Cardiol 2002;40:1984-90.
13. Chapelle JP, Albert A, Smeets JP, Heusghem C, Kulbertus HE. Effect of the haptoglobin phenotype on the size of a myocardial infarct. N Engl J Med 1982;307:457-63.
14. Delanghe J, Cambier B, Langlois M, De Buyzere M, Neels H, De Bacquer D, et al. Haptoglobin polymorphism, a genetic risk factor in coronary artery bypass surgery. Atherosclerosis 1997; 132:215-9.
15. Golabi P, Kshatriya GK, Kapoor AK. Association of genetic markers with coronary heart disease (myocardial infarction) - a case-control study. J Indian Med Assoc 1999; 97:6-7.
16. Yang SE, Min WK, Park H, Chun S, Nah J, Kim JQ. Distribution of haptoglobin phenotypes in a Korean population, using the semi-automated PhastSystem. Ann Clin Biochem 2000; 37:205-9.
17. Pabinger I, Grafenhofer H, Kaider A, Ilic A, Eichinger S, Quehenberger P, et al. Preeclampsia and fetal loss in women with a history of venous thromboembolism. Arterioscler Thromb Vasc Biol 2001;21: 874-9.
18. De Bacquer D, De Backer G, Langlois M, Delanghe J, Kesteloot H, Kornitzer M. Haptoglobin polymorphism as a risk factor for coronary heart disease mortality. Atherosclerosis 2001; 157:161-6.
19. Gutteridge JM. The antioxidant activity of haptoglobin towards haemoglobin-stimulated lipid peroxidation. Biochim Biophys Acta 1987;917:219-23.
20. Glowinski J, Glowinski S. Generation of reactive oxygen metabolites by the varicose vein wall. Eur J Vasc Endovasc Surg 2002; 23:550-5.
21. Re G, Lanzarini C, Vaona I, Pazzaglia M, Palareti G, Bassein L, et al. Systemically circulating oxidative species in human deep venous thrombosis. Eur J Emerg Med 1998; 5:9-12.
22. Vormittag R, Vukovich T, Schönauer V, Lehr S, Minar E, Bialonczyk C, et al. Basal high-sensitivity-C-reactive protein levels in patients with spontaneous venous thromboembolism. Thromb Haemost 2005; 93: 488-93.
23. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997; 336:973-9.
24. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Tracy RP, Aleksic N, et al. Coagulation factors, inflammation markers, and venous thromboembolism: the longitudinal investigation of thromboembolism etiology (LITE). Am J Med 2002; 113:636-42.
25. Scheil HG, Scheffrahn W. Haptoglobin (HPA)-Subtypen in schweizerischen Populationen. Anthrop Anz 1998; 56:25–30.
26. Delanghe J, Langlois M, Duprez D, De Buyzere M, Clement D. Haptoglobin polymorphism and peripheral arterial occlusive disease. Atherosclerosis 1999; 145:287-92.