A Prothrombotic State is Associated with Early Arterial Damage in Hypertensive Patients

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**Aim:** A prothrombotic state is associated with organ damage in hypertensive patients. Carotid intima-media thickness (IMT) is an early marker of vascular damage that anticipates the development of atherosclerotic plaques. The aim of the present study was to investigate the relationships between subclinical carotid damage and markers of the prothrombotic state in hypertension.

**Methods:** In 258 essential hypertensive patients who were consecutively recruited at a hypertension clinic an ultrasound carotid scan was performed with assessment of the IMT and plasma levels of C-reactive protein, fibrinogen, fibrin D-dimer, prothrombin fragment 1+2, homocysteine, and lipoprotein(a) were measured.

**Results:** Patients with an IMT above the median of the distribution (800 μm) were older and had greater BMI, pulse pressure, duration of hypertension, and prevalence of coronary heart disease than patients with an IMT below the median. Patients with higher IMT had also greater levels of C-reactive protein, fibrinogen, fibrin D-dimer, and homocysteine. Regression analysis showed a direct relationship of IMT with age, waist circumference, pulse pressure, fibrinogen, fibrin D-dimer, and number of cigarettes smoked per day, and an inverse relationship with creatinine clearance. On multivariate analysis, age, pulse pressure, and fibrin D-dimer were independently related with IMT.

**Conclusion:** In hypertensive patients, subclinical carotid damage is related with evidence of activated coagulation system suggesting a prothrombotic state. This might contribute to the development of hypertensive arterial damage even in the earliest stages.

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**Key words:** Carotid arteries, Intima-media thickness, Fibrinogen, Fibrin D-dimer

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**Introduction**

The early stages of atherosclerosis are associated with subtle structural changes of arterial vessels, such as thickening of the intima-media complex. Carotid intima-media thickness (IMT) is a reproducible marker of early arterial disease and is easily detected by ultrasonography. Carotid IMT is increased in subjects with multiple risk factors and, as established in cross-sectional and prospective studies, the thickness of the inner carotid layer is predictive of major cardiovascular events. This is why measurement of the IMT can provide useful information for stratification of the cardiovascular risk in asymptomatic patients.

In addition to the classical cardiovascular risk factors, many emergent conditions, including abnormalities of some components of the hemostatic system, are possibly involved in the occurrence of atherosclerosis-related events. Epidemiological evidence indicates that the coagulation system plays an important role in the pathogenesis of atherosclerotic vascular disease and increased incidence of cardiovascular events has been associated with higher circulating levels of fibrinogen, D-dimer, and plasminogen activator inhibitor-1 (PAI-1). In patients with hypertension we have previously demonstrated that a prothrombotic state is associated with the presence and severity of organ damage and a significant association of
thrombin generation with carotid IMT has been reported in middle-aged subjects without clinically overt atherosclerotic disease. The aim of the present study was to investigate the relationship of the carotid IMT with markers of activity of the hemostatic and fibrinolytic system in a large group of patients with arterial hypertension.

**Methods**

**Patients**

In a cross-sectional protocol, we included 258 essential hypertensive patients (139 men, 119 women, age 57 ± 12 yr) who were referred to the Hypertension Unit of our clinic. The patients seen at our clinic include individuals with all grades of hypertension who live in north-eastern Italy and are representative of hypertensive patients in this geographical area. Patients in either primary or secondary prevention were included: 22 patients (8%) had a history of ischemic heart disease and 10 patients (4%) had a history of cerebrovascular disease. Patients were defined as smokers if they had smoked for more than ten years before enrolment in the study and smoking was quantified by the number of cigarettes smoked per day. At the time of the study, 192 patients (74%) were being treated with antihypertensive agents, 38 (15%) with lipid-lowering drugs, and 65 (25%) with antiplatelet drugs. The cardiovascular status was assessed in all patients by a complete case history, physical examination, and electrocardiogram (ECG). Additional laboratory tests, including echocardiography, treadmill exercise stress testing, myocardial perfusion scan, coronary angiography, ultrasound examination of abdominal aorta, iliac and femoral arteries were performed when appropriate. The retrospective diagnosis of myocardial infarction was confirmed by a documented history, ECG changes, and significant increase of troponin C levels. The neurological diagnosis of transient ischemic attack and atherothrombotic stroke was confirmed by a documented history, clinical signs, and computerized cerebral axial tomography.

**Carotid B-Mode Ultrasonography**

The right and left carotid arteries were examined with a duplex scanner (Aplio CV; Toshiba Japan) using a 7 MHz linear array transducer. The same trained operator performed all examinations. Carotid IMT was measured with an electronic caliper on the far wall of the distal segment of the common carotid arteries, 1.0 cm proximal to the beginning of the carotid bulb. IMT image was frozen in end-diastole by means of ECG triggering. The mean value of three IMT measurements in wall segments free from plaques was calculated. The IMT was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo. Intraobserver variability was 5.6% and the correlation coefficient of duplicate measurements of IMT was 0.830.

**Analytical Methods**

A venous blood sample was taken between 8:00 and 9:00 am after an overnight fast without venous stasis. Total cholesterol and triglycerides were assayed enzymatically by an automated method (International Laboratory, Milan, Italy). HDL-cholesterol was assayed after magnesium chloride-dextran sulphate precipitation of apolipoprotein B containing lipoproteins. The concentration of LDL-cholesterol was calculated with the formula of Friedewald et al. Plasma fibrinogen was measured by a functional assay in an automatic coagulometer autoanalyser (Instrumentation Laboratory, Lexington, MA, USA) (inter- and intra-assay coefficients of variation were 6.8% and 5.1%, respectively, and the lower limit of detection was 0.35 g/L). Prothrombin fragment 1 + 2 (F1 + 2) plasma levels were evaluated by enzyme-linked immunosorbent assay according to the method of Pelzer et al. Plasma fibrinogen was measured by a functional assay in an automatic coagulometer autoanalyser (Instrumentation Laboratory, Lexington, MA, USA) (inter- and intra-assay coefficients of variation were 11.2% and 5.5%, respectively, and the lower limit of detection was 20 pMol/L). D-dimer was measured immuno-enzymatically according to the method of Rylatt et al. (inter- and intra-assay coefficients of variation were 7.1% and 5.3%, respectively, and the lower limit of detection was 150 ng/mL). Antithrombin III was determined by a functional chromogenic assay (Instrumentation Laboratory) (inter- and intra-assay coefficients of variation were 8.6% and 7.4%, respectively, and the lower limit of detection was 10%). The lipoprotein(a) [Lp(a)] concentration was determined with a double-antibody enzyme-linked immunosorbent assay (Strategic Diagnostic, Newark, NJ, USA) using a mouse monoclonal anti-Lp(a) antibody for coating and a horseradish peroxidase-conjugated polyclonal goat anti-Lp(a) antibody for detection (inter- and intra-assay coefficients of variation were 8.6% and 6.3%, respectively). Plasma homocysteine was determined by means of high-performance liquid chromatography. Plasminogen activator inhibitor-1 (PAI-1) was measured in citrate-anticoagulated plasma using an immuno-functional method (inter- and intra-assay coefficients of variation were 6.0% and 4.6%, respectively). Plasma level of tissue-plasminogen activator (t-PA) was determined by an enzyme-linked immuno-sorbent assay (inter- and intra-assay
Clinical characteristics of the patients according to the median value of IMT

| Patients (258) | IMT < 800 μm | ≥ 800 μm | P |
|---------------|--------------|----------|---|
| Male sex, n (%) | 139 (54) | 63 (51) | 76 (56) | 0.290 |
| Age, yr | 57 ± 12 | 51 ± 11 | 63 ± 10 | < 0.001 |
| Systolic BP, mm Hg | 144 ± 16 | 142 ± 14 | 146 ± 18 | 0.089 |
| Pulse BP, mm Hg | 57 ± 13 | 52 ± 9 | 61 ± 14 | < 0.001 |
| Duration of hypertension, yr | 11 ± 9 | 9 ± 8 | 13 ± 9 | < 0.001 |
| BMI, kg/m² | 28.3 ± 4.7 | 27.6 ± 4.3 | 29.0 ± 5.1 | 0.018 |
| Waist circumference, cm | 96 ± 12 | 93 ± 12 | 99 ± 12 | < 0.001 |
| Diabetes, n (%) | 32 (12) | 9 (7) | 23 (18) | 0.017 |
| Cigarettes/day | 2 [0-20] | 0 [0-15] | 10 [0-30] | 0.002 |
| Creatinine clearance (ml/min/1.73 m²) | 89 ± 24 | 97 ± 22 | 81 ± 24 | < 0.001 |
| Ischemic heart disease, n (%) | 22 (8) | 4 (3) | 18 (13) | 0.003 |
| Cerebrovascular disease, n (%) | 10 (4) | 2 (2) | 8 (6) | 0.063 |

Values are expressed as the mean ± SD. Interquartile ranges [IQR] for variables with skewed distribution are shown in parentheses. Abbreviations: BP, blood pressure; BMI, body mass index.

Statistical Analysis

For statistical analysis, hypertensive patients were divided according to the median value of IMT (800 μm) and the clinical characteristics are listed in Table 1. Patients with higher IMT were older and had higher pulse pressure, duration of hypertension, BMI, and waist circumference. In addition, patients with higher IMT had greater daily consumption of cigarettes, were more often diabetics, and had a greater prevalence of coronary heart disease and cerebrovascular disease, although the latter difference did not reach statistical significance. In addition, patients with higher IMT had more frequent use of antihypertensive drugs (P = 0.0032), angiotensin-receptor antagonists (P = 0.024), diuretics (P = 0.014), lipid-lowering drugs (P = 0.004), and antiplatelet drugs (P < 0.001).

Table 2 shows the lipid and carbohydrate metabolism variables in the two groups. Patients with higher IMT had comparable plasma lipid values and greater levels of plasma glucose at fasting and in response to the oral glucose load, but no significant differences were found in fasting insulin and C-peptide levels and coefficients of variation were 10% and 8%, respectively. Plasma glucose was assayed by the glucose oxidase method. Plasma insulin and C-peptide levels were measured by radioimmunoassay (Behring, Marburg, Germany). These parameters were measured at baseline and after (30, 60, 90, 120, 180 min) a standard 75 g oral glucose load, and the area under the response curve (AUC) was calculated by the trapezoidal rule. The Homeostatic Model Assessment (HOMA) index was calculated from fasting plasma glucose (mmol/L) and insulin (μU/mL) using the formula: [(glucose μmol/L) × insulin (μU/mL) / 22.5].
in the HOMA index. Patients with higher IMT values had significantly greater levels of D-dimer, fibrinogen, C-reactive protein, and homocysteine than patients with lower IMT values, whereas no differences between the two hypertensive groups were found in the other hemostatic variables and in Lp(a) (Table 3).

On univariate regression analysis, IMT was significantly and directly related with age ($r=0.578$, $P<0.001$), waist circumference ($r=0.215$, $P<0.001$), pulse pressure ($r=0.379$, $P<0.001$), number of cigarettes smoked per day ($r=0.259$, $P<0.001$) (Fig. 1), and plasma D-dimer ($r=0.394$, $P<0.001$) and fibrinogen ($r=0.203$, $P=0.003$) levels (Fig. 2), and inversely related with creatinine clearance ($r=-0.309$; $P<0.001$). Stepwise multivariate analysis was performed entering variables that were related with IMT on univariate regression analysis according to the strength of the relationship, with the addition of gender and presence of diabetes. Multivariate analysis indicated that the relationship of plasma D-dimer with IMT values occurs independently of age, gender, number of cigarettes smoked per day, presence of diabetes, waist cir-

| Table 2. Lipid and carbohydrate metabolism variables in the study patients |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | Patients (258)  | IMT < 800 µm    | IMT ≥ 800 µm    | $P$              |
| Total cholesterol, mmol/L | 5.32 ± 1.01     | 5.34 ± 0.93     | 5.30 ± 1.08     | 0.766            |
| HDL cholesterol, mmol/L    | 1.52 ± 0.41     | 1.54 ± 0.40     | 1.50 ± 0.43     | 0.474            |
| LDL cholesterol, mmol/L    | 3.16 ± 0.98     | 3.18 ± 0.96     | 3.15 ± 1.00     | 0.832            |
| Triglycerides, mmol/L      | 1.35 ± 0.76     | 1.29 ± 0.80     | 1.41 ± 0.73     | 0.239            |
| Glucose, mmol/L            | 5.64 ± 1.18     | 5.39 ± 1.17     | 5.87 ± 1.50     | 0.005            |
| Insulin, pmol/L            | 75.6 ± 51.3     | 74.9 ± 60.4     | 76.2 ± 41.4     | 0.859            |
| C-Peptide, nmol/L          | 0.81 ± 0.42     | 0.77 ± 0.45     | 0.85 ± 0.40     | 0.149            |
| HOMA index                 | 2.72 ± 2.36     | 2.64 ± 2.64     | 2.81 ± 2.08     | 0.600            |
| AUC glucose, mmol/L/min    | 21.4 ± 5.4      | 20.5 ± 4.7      | 22.3 ± 6.0      | 0.042            |
| AUC insulin, pmol/L/min    | 1442 [897-2662] | 1510 [882-2439] | 1442 [954-2776] | 0.898            |

Values are expressed as the mean ± SD. Interquartile ranges [IQR] for variables with skewed distribution are shown in parentheses.

| Table 3. Hemostatic variables, CRP, homocysteine, and lipoprotein(a) in the study patients |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | Patients (258)  | IMT < 800 µm    | IMT ≥ 800 µm    | $P$              |
| Partial thromboplastin time, sec | 28 ± 4         | 28 ± 4         | 28 ± 4         | 0.205           |
| Prothrombin time, INR     | 1.02 ± 0.22     | 1.00 ± 0.08     | 1.04 ± 0.29     | 0.232           |
| Fibrinogen, g/L          | 3.64 ± 0.84     | 3.48 ± 0.73     | 3.79 ± 0.91     | 0.003           |
| D-dimer, mg/L            | 0.43 ± 0.41     | 0.31 ± 0.23     | 0.55 ± 0.51     | <0.001          |
| Prothrombin factor F1 + 2, pmol/L | 197 ± 113      | 189 ± 140      | 204 ± 81       | 0.448           |
| PAI-1, ng/mL             | 9.7 [6.0-15.7]  | 9.9 [5.8-15.6]  | 9.2 [9.1-15.2]  | 0.969           |
| t-PA, ng/mL              | 4.5 [2.7-6.6]   | 4.2 [2.5-6.8]   | 4.6 [2.8-5.7]   | 0.938           |
| Antithrombin III, %      | 101 ± 13        | 103 ± 12        | 100 ± 14        | 0.109           |
| Protein C, %             | 109 ± 24        | 112 ± 22        | 107 ± 26        | 0.131           |
| Protein S, %             | 95 ± 22         | 97 ± 19         | 93 ± 25         | 0.187           |
| CRP, mg/L                | 2.3 [1.0-3.7]   | 1.7 [1.0-3.0]   | 3.0 [1.2-4.7]   | 0.005           |
| Lipoprotein(a), mg/dL    | 12.2 [4.6-24.3] | 12.1 [5.8-22.3] | 12.2 [4.4-25.9] | 0.926           |
| Homocysteine, μmol/L     | 12.4 ± 4.9      | 11.7 ± 4.5      | 13.0 ± 5.3      | 0.030           |

Values are expressed as the mean ± SD. Interquartile ranges [IQR] for variables with skewed distribution are shown in parentheses.
cumference, pulse pressure, duration of hypertension, and creatinine clearance (Table 4).

**Discussion**

Because arterial disease is the major underlying factor leading to the most clinically relevant cardiovascular events and these events are usually due to the formation of a thrombus at the site of an atherosclerotic plaque, research on the mechanisms of vascular damage in hypertensive patients has concentrated on the hemostatic pathways. In this study, we investigated the relationship between subclinical carotid damage and markers of prothrombotic state in a large group of patients with essential hypertension. Results demonstrate that fibrinogen and fibrin D-dimer levels are directly related with carotid IMT in these patients and that the relationship of D-dimer with early arterial damage occurs independently of age, anthropometric variables, frequency of diabetes, and renal function. This finding indicates that the thickening of the inner layer of carotid arteries in hypertension is under the influence of a prothrombotic state. In addition to an activated hemostatic system, hypertensive patients with greater IMT are older, heavier smokers, and have higher pulse pressure levels, longer duration of hyper-
vascular index and higher levels were detected in patients with more severe atherosclerosis. No conclusive studies on the relationships between the hemostatic/fibrinolytic system and carotid IMT in patients with hypertension are available in the literature.

We have previously investigated the possible involvement of the coagulation system as a risk factor for the development and progression of organ damage in patients with hypertension. Fibrinogen, fibrin D-dimer, and prothrombin fragment $1 \, + \, 2$ were associated with the presence and severity of hypertensive organ damage at the cardiac, renal, and vascular level, with a relationship that for the former two variables was independent of age, blood pressure levels, duration of hypertension, and smoking status. The present study suggests the possible contribution of the hemostatic system to the thickening of inner arterial layers and extends our previous observation to the earliest stages of hypertensive vascular disease.

Fibrinogen has been identified as a major independent risk factor for coronary artery disease, cerebrovascular disease, and peripheral vascular disease in the general population. Fibrinogen increases blood viscosity, promotes arterial fibrogenesis, and its degradation products are chemotactic for mononuclear cells and mitogenic for smooth muscle cells. Fibrin D-dimer is the major breakdown fragment of fibrin and a good biochemical marker of an existing thrombophilia. In fact, measurement of plasma D-dimer provides a reliable estimation of the overall state of activation of the coagulation system. Prospective epidemiological studies have demonstrated that D-dimer is independently associated with the risk of myocardial infarction, cerebrovascular accidents, and peripheral artery disease. Both increased fibrinogen and D-dimer levels reflect the existence of a prothrombotic state that might contribute to the development and progression of atherosclerotic vascular disease in hypertension.

Some potential limitations of this study should be discussed. First, the cross-sectional design and possible interference of confounders does not permit evidence of a causal relationship between coagulation abnormalities and the early stages of hypertensive vascular damage. Although the strength of the relationship between D-dimer and IMT might suggest causality, it cannot be excluded that higher D-dimer is just a marker of a more severe atherosclerotic burden in patients with greater IMT. Second, the use of a clinic sample might limit the extrapolation of the conclusions to the general population because of a possible bias in the referral of patients to the source of care. Third, in our study patients, treatment with antihypertensive, lipid-lowering, and antiplatelet drugs that

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**Table 4. Multivariate regression analysis with IMT as the dependent variable**

| Variable                  | $\beta$ standard coefficient | $P$  |
|---------------------------|-----------------------------|------|
| Age                       | 0.400                       | $<$0.001 |
| Pulse pressure            | 0.204                       | 0.001 |
| Log D-dimer               | 0.152                       | 0.022 |
| Number of cigarettes/day  | 0.116                       | 0.058 |
| Diabetes mellitus         | 0.090                       | 0.128 |
| Duration of hypertension  | 0.067                       | 0.291 |
| Waist circumference       | 0.049                       | 0.463 |
| Creatinine clearance      | $-$0.036                    | 0.575 |
| Male                      | $-$0.013                    | 0.840 |
might affect the activity of the hemostatic system could represent an important confounder; however, the frequency of the use of drugs that might favourably affect the fibrinolytic system, such as angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, or the carotid wall was more frequent in patients with higher IMT and therefore it is unlikely that the difference in drug use could explain our findings. Finally, ultrasonography cannot distinguish between intima and media thickness because of insufficient axial resolution; therefore, the measurement of IMT in the distal common carotid artery is unable to assess whether increased IMT represents atherosclerosis (intimal thickening) or vascular hypertrophy (medial thickening).

**Conclusion**

The results of this study could have some relevant implications for the identification of organ damage in patients with hypertension and for the management and prognosis of these patients. The strength of the relationship between carotid IMT and D-dimer levels implies that these parameters might be useful in the diagnostic evaluation of hypertensive patients to identify those who have probably developed or will develop vascular damage. Detection of the activated hemostatic system in hypertensive patients might be useful in guiding the physician towards more aggressive antihypertensive treatments and better control of additional risk factors. Also, correction of the prothrombotic state by the use of drugs that interfere with coagulation might reduce the incidence of cardiovascular events in hypertension. This hypothesis will have to be tested in future studies.

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**Conflicts of Interest**

None.

**References**

1) Simon A, Megnien JL, Levenson J: Coronary risk estimation and treatment of hypercholesterolemia. Circulation, 1997; 96: 2449-2452

2) Aminbakhsh A, Mancini GB: Carotid intima-media thickness measurement: what defines an abnormality? A systematic review. Clin Invest Med, 1999; 22: 149-157

3) Irie Y, Sakamoto K, Kubo F, Okusu T, Katura T, Yamamoto Y, Umahara Y, Katakami N, Kaneto H, Kashiyama T, Ueda Y, Kosugi K: Association of coronary artery stenosis with carotid atherosclerosis in asymptomatic type 2 diabetic patients. J Atheroscler Thromb, 2011; 18(4): 337-344

4) Ohnishi H, Sawayama Y, Furusyo N, Maeda S, Tokunaga S, Hayashi J: Risk factors for and the prevalence of peripheral arterial disease and its relationship to carotid atherosclerosis: the Kyushu and Okinawa population Study (KOPS). J Atheroscler Thromb, 2010; 17: 751-758

5) Kablak-Ziembicka A, Przewlocki T, Sokolowski A, Traczyk W, Podolec P: Carotid intima-media thickness, hs-CRP and TNF-α are independently associated with cardiovascular event risk in patients with atherosclerotic occlusive disease. Atherosclerosis, 2011; 214: 185-190

6) The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC): 2007 Guidelines for the management of arterial hypertension. J Hypertens, 2007; 25: 1105-1187

7) Simon A, Gariepy J, Chironi G, Megnien JL, Levenson J: Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. J Hypertens, 2002; 20: 159-169

8) Catena C, Novello M, Lapenna R, Baroselli S, Colussi GL, Nadalini E, Favret G, Cavarape A, Soardo G, Sechi LA: New risk factors for atherosclerosis in hypertension: focus on the prothrombotic state and lipoprotein(a). J Hypertens, 2005; 23: 1617-1631

9) Folsom AR: Hemostatic risk factors for atherosclerotic disease: an epidemiologic view. Thromb Haemost, 2001; 86: 366-373

10) Koenig W: Fibrinogen in cardiovascular disease: an update. Thromb Haemost, 2003; 89: 601-609

11) Riddler PM, Hennekens CH, Cerskus A, Stumper MJ: Plasma concentrations of cross-linked fibrin degradation product (D-dimer) and the risk of future myocardial infarction among apparently healthy men. Circulation, 1994; 90: 2236-2240

12) Cushman M, Lemaire RN, Kuller LH, Psaty BM, Macy EM, Sharrett AR, Tracy RP: Fibrinolytic activation markers predict myocardial infarction in the elderly. The Cardiovascular Health Study. Arterioscler Thromb Vasc Biol, 1999; 19: 493-498

13) Sechi LA, Zingaro L, Catena C, Casaccio D, De Marchi S: Relationship of fibrinogen levels and hemostatic abnormalities with organ damage in hypertension. Hypertension, 2000; 36: 978-985

14) Páramo JA, Orbe J, Beloqui O, Benito A, Colina I, Martínez-Vila E, Diez J: Prothrombin fragment 1 + 2 is associated with carotid intima-media thickness in subjects free of clinical cardiovascular disease. Stroke, 2004; 35: 1085-1089

15) Sechi LA, Kronenberg F, De Carli S, Falleti E, Zingaro L, Catena C, Uttermann G, Bartoli E: Association of serum lipoprotein(a) and size apolipoprotein(a) polymorphism with target-organ damage in arterial hypertension. JAMA,
1997; 277: 1689-1695
16) Stein JH, Korcarz CE, Todd Hurst R, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS: Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a Consensus Statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. J Am Soc Echocardiogr, 2008; 21: 93-111
17) Friedewald WT, Levi RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative centrifuge. Clin Chem, 1972; 18: 499-502
18) Rossi E, Mondonico P, Lombardi A, Preda L: Method for determination of functional (clottable) fibrinogen by the new family of ACL coagulometers. Thromb Res, 1988; 52: 453-468
19) Pelzer H, Schwarz A, Stuber W: Determination of human prothrombin activation fragment 1+2 in plasma with an antibody against a synthetic peptide. Thromb Haemost, 1991; 65: 153-159
20) Rylatt DB, Blake AS, Cottis LE, Massingham DA, Fletcher WA, Maspi PP, Whitaker AN, Elms M, Bunce I, Webber AJ: An immunoassay for human D-dimer using monoclonal antibodies. Thromb Res, 1983; 31: 767-778
21) Sechi LA, Catena C, Zingaro L, Melis A, De Marchi S: Abnormalities of glucose metabolism in patients with early renal failure. Diabetes, 2002; 51: 1226-1232
22) Salomaa V, Stinson JD, Kark JD, Folsom AR, Davis CE, Wu KK: Association of fibrinolytic parameters with early atherosclerosis. The ARIC study. Circulation, 1995; 91: 284-290
23) De Maat MDM, Bladbjerg EM, Drivsholm T, Borch-Johnsen K, Moller L, Jespersen J: Inflammation, thrombosis and atherosclerosis: results of the Glostrup study. J Thromb Haemost, 2003; 1: 950-957
24) Lee AJ, Mowbray PI, Lowe GDO, Rumley A, Fowkes GR, Allan PL: Blood viscosity and elevated carotid intima-media thickness in men and women. The Edinburgh Artery Study. Circulation, 1998; 97: 1467-1473
25) Grebe MT, Luiu B, Sedding D, Heidt MC, Kemkes-Matthes B, Schaefer CA, Tillmans HH, Gunduz D: Fibrinogen promotes early atherosclerotic changes of the carotid artery in young, healthy adults. J Atheroscler Thromb, 2010; 17: 1003-1008
26) Corrado E, Rizzo M, Muratori I, Coppola G, Novo S: Association of elevated fibrinogen C-reactive protein levels with carotid lesions in patients with newly diagnosed hypertension or type II diabetes. Arch Med Res, 2006; 37: 1004-1009
27) Brzosko S, Hryszo T, Lebkowska U, Malyzszko JS, Mysliwiec M: Plasma tissue-type plasminogen activator, fibrinogen, and time on dialysis prior to transplantation are related to carotid intima-media thickness in renal transplant recipients. Transplant Proc, 2003; 35: 2931-2934
28) Faintuch J, Marques PC, Bortolotto LA, Faintuch JJ, Cecconello I: Systemic inflammation and cardiovascular risk factors: are morbidly obese subjects different? Obes Surg, 2008; 18: 854-862
29) Haashy S: Significance of plasma D-dimer in relation to the severity of atherosclerosis among patients evaluated by non-invasive indice of cardio-ankle vascular index and carotid intima-media thickness. Int J Hematol, 2010; 92: 76-82
30) Meade TW, Mellows S, Brozovic M: Haemostatic function and ischemic heart disease: principal results of the Northwick Park Heart Study. Lancet, 1986; ii: 533-537
31) Wilhelmsen L, Svardsson K, Koran-Bengtsen K, Larsson B, Weilin L, Tibblin G: Fibrinogen as a risk factor for stroke and myocardial infarction. N Engl J Med, 1984; 11: 501-505
32) Fowkes FGR, Housley E, Cawood EHH, Macintyre CCA, Ruckley CV, Prescott RJ: Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int Epidemiol, 1991; 20: 384-392
33) Koenig W, Ernst E: Fibrinogen and atherothrombogenesis. Curr Opin Lipidol, 1993; 4: 471-476
34) Graeff H, Hafter R: Detection and relevance of cross linked fibrin derivatives in blood. Semin Thromb Haemost, 1982; 8: 57-68
35) Smith FB, Lee AJ, Fowkes FG, Price JF, Rumley A, Lowe GD: Hemostatic factors as predictors of ischemic heart disease and stroke in the Edinburgh Artery Study. Atheroscler Thromb Vasc Biol, 1997; 17: 3321-3325
36) Fowkes SG, Lowe GD, Housley E, Rattray A, Elton RA: Cross-linked fibrin degradation products, progression of peripheral arterial disease, and risk of coronary heart disease. Lancet, 1993; 342: 84-86