MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 5306-5311
DOI: 10.12659/MSM.914979

Received: 2019.01.04
Accepted: 2019.03.14
Published: 2019.07.17

Culprit Lesion Characteristics in Young Patients with Hyperhomocysteinemia

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Source of support: This work was supported by a grant from the National Key Research and Development Program of China (2017YFC0908800), the Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (code: ZYLX201303), the National Key Clinical speciality Construction Project (2013-2014), and the "Beijing Municipal Administration of Hospitals" Ascent Plan (Code: DFL20150601)

Background: The relationships between culprit coronary plaque characteristics and hyperhomocysteinemia (HHcy) are not fully understood in young patients. In this study we investigated the relationship between culprit atherosclerotic plaque phenotype assessed by optical coherence tomography (OCT) and hyperhomocysteinemia (HHcy) in young patients.

Material/Methods: We investigated the OCT imaging and HHcy of 123 lesions in 123 young patients (≤45 years of age). According to OCT images, culprit lesions were classified as thin-cap fiber atheroma (TCFA), thrombus, and other. The 123 patients were grouped as: HHcy group (53 cases, HHcy ≥15.5 μmol/l) and control group (70 cases, HHcy <15.5 μmol/l).

Results: Compared with the control group, the HHcy group had a higher proportion of OCT-TCFA (p=0.03), OCT-vasa vasorum (p=0.013), and OCT-thrombus (p=0.012), and a larger lipid arc (p=0.002). HHcy (P=0.037) and metabolic syndrome (MetS) (P=0.016) remained independent predictors of TCFAs. HHcy (P=0.026) and smoking (P=0.005) remained independent determinants of thrombus.

Conclusions: HHcy and MetS are associated with TCFAs, and HHcy and smoking are associated with thrombus in young patients with coronary artery disease.

MeSH Keywords: Coronary Artery Disease • Hyperhomocysteinemia • Optical Coherence Tomography

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/914979

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Background

Coronary artery disease (CAD) is common in middle-aged and elderly people. However, the incidence of CAD in young patients has also increased in recent years [1]. Conventional risk factors such as hypertension, diabetes (DM), hyperlipidemia, and smoking do not explain all CAD cases in young patients. Homocysteine (Hcy) is a disulphide amino acid present at low concentrations in cells (<1 μmol/l) and in plasma at 5–15 μmol/l. It is nonprotein amino acid and an intermediate in methionine metabolism that arises when methionine acts as a donor in methylation reactions. Hcy has been extensively studied and is considered to be an independent CAD risk factor [2].

Hyperhomocysteinemia (HHcy) is an independent risk factor in young CAD patients [3]. Few studies have assessed the relationships between HHcy and culprit coronary plaque phenotypes in young patients.

Optical coherence tomography (OCT) with a resolution of 10–20 μm has become the most accurate instrument for intracoronary evaluation [4]. It is used to a large extent to assess the microstructure of atherosclerotic plaque, which may be a key factor in determining plaque stability. OCT characteristics are validated by histologic evaluation [4,5].

In the present study we evaluated the relationship between culprit atherosclerotic plaque OCT-phenotyping and HHcy in young patients.

Material and Methods

Ethics approval

The study, in accordance with the Declaration of Helsinki, was approved by the local ethics committee of the hospital. Since the retrospective study and data analysis were performed anonymously, the study was exempt from the informed consent requirements.

Study population

This was a single-center study. Between April 2014 and March 2017, 123 consecutive patients (≤45 years of age) who underwent OCT were selected, including patients with stable CHD and acute coronary syndromes (ACS). According to the level of homocysteine, they were divided into a HHcy group (53 cases, Hcy ≥15.5 μmol/l) [6] and a control group (70 cases, Hcy <15.5 μmol/l). We excluded patients with a known history of severe hepatic or renal dysfunction, an ongoing inflammatory condition, familial hypercholesterolemia, or arteritis. Patients with poor OCT images, incomplete follow-up data, or missing data were also excluded.

Definition of cardiovascular risk factors

The definition of a smoker was current smoking. Overweight was defined as a body mass index (BMI) >25 kg/m^2. Hypertension referred to systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or treatment of hypertension. DM meant a fasting blood glucose >126 mg/dl or treated DM (adhering to a diabetic diet or prescribed an oral hypoglycemic agent). Total cholesterol >200 mg/dl or being treated for hypercholesterolemia was defined as hypercholesterolemia. Metabolic syndrome (MetS) was defined as an adult meeting 3 or more of the following indicators [7]: waist circumference ≥90 cm for males or ≥80 cm for females; triglycerides ≥150 mg/dL; high-density lipoprotein cholesterol ≤40 mg/dL; systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or treated for hypertension; and fasting blood glucose level ≥100 mg/dL or treated DM. A family history of CAD was defined as an individual with CAD in first-degree relatives.

Coronary angiography and OCT procedure

Diagnostic angiograms were performed via radial access using a 5-Fr catheter. A 5000 IU bolus of heparin was administered. For OCT implementation, a 0.014-inch distal guidewire was placed in the target vessel and 200 mg of nitroglycerin was injected intracoronarilly through a 6-Fr guide catheter. Images of frequency domain OCT were acquired using the C7-XRTM OCT Intravascular Imaging System, (St. Jude Medical, St. Paul, MN, USA), which uses advanced imaging techniques to identify the culprit lesion. During image acquisition, coronary blood flow was replaced by continuous flushing of contrast agent directly from the guiding catheter at a rate of 3–4 ml/s using a power injector, thereby creating an almost blood-free situation at 20 mm/s with the integrated automated pull-back device.

OCT image analysis

Offline OCT images were analyzed by the operator who performed the pull-back and by an independent investigator who was unaware of the clinical presentation; the outcomes of inconsistent OCTs were resolved by consensus. The culprit lesions were classified as thin-cap fiber atheroma (TCFA), thrombus, and other. TCFA refers to a fiber cap-covered plaque with a lipid arc >90° and a thickness <65 μm [8]. Plaque erosion was defined by the presence of preserved vascular integrity (intact fibrous cap), a larger residual lumen, and a platelet-rich thrombus [9]. A vasa vasorum was defined as a small black hole within a plaque with a diameter of 50–300 μm that was present on at least 3 consecutive frames in pull-back images [10].

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Table 1. Baseline characteristics of patients enrolled in this study.

	HHcy (n=53)	Control (n=70)	P
Male, n (%)	49 (92.5)	58 (82.9)	0.176
Family history, n (%)	6 (11.3)	4 (5.7)	0.325
Smoker, n (%)	33 (62.3)	34 (48.6)	0.147
Overweight, n (%)	33 (62.3)	46 (65.7)	0.708
Hypertension, n (%)	28 (52.8)	35 (50.0)	0.856
Diabetes mellitus, n (%)	8 (15.1)	14 (20.0)	0.636
Hypercholesterolemia, n (%)	9 (17.0)	12 (17.1)	1.000
Metabolic syndrome, n (%)	37 (69.8)	45 (64.3)	0.566
Culprit vessel			
Left main, n (%)	0 (0.0%)	4 (5.7)	0.133
Left anterior descending, n (%)	37 (69.8)	46 (65.7)	0.700
Left circumflex, n (%)	2 (3.8)	8 (11.4)	0.185
Right coronary artery, n (%)	14 (26.4)	12 (17.1)	0.266

HHcy – hyperhomocysteinemia.

Table 2. Optical coherence tomography derived plaque characteristics.

	HHcy (n=53)	Control (n=70)	P
TCFA, n (%)	43 (81.1)	44 (62.9)	0.027
Macrophage accumulation, n (%)	37 (68.9)	38 (54.3)	0.095
Calcified nodule, n (%)	4 (7.5)	8 (11.4)	0.552
Vasa vasorum, n (%)	20 (37.7)	12 (17.1)	0.013
Cholesterol crystal, n (%)	12 (22.6)	12 (17.1)	0.495
Erosion, n (%)	4 (7.5)	2 (2.9)	0.401
Plaque rupture, n (%)	8 (15.1)	10 (14.3)	1.000
Thrombus, n (%)	14 (26.4)	6 (8.6)	0.012
Fibrotic plaque, n (%)	28 (52.8)	46 (65.7)	0.193
Maximum lipid arc°	257.3±72.7	203.6±114.1	0.002
% Area stenosis	82.5±15.0	82.6±11.3	0.944

HHcy – hyperhomocysteinemia; TCFA – thin-cap fibroatheromas.

Cholesterol crystals were defined as thin-linear structures with high backscattering without attenuation within the plaque [11]. Thrombus (white or red), plaque rupture, macrophage accumulation, calcified nodules, fibrotic plaques, the maximum lipid arc, and the cross-sectional stenosis area (%) were determined according to the International Working Group for Intravascular Optical Coherence Tomography (IWG-IVOCT) Consensus standards [12].

Laboratory measurements

After overnight fasting, the patient's venous blood sample was taken in an EDTA tube and immediately placed on ice. Samples were kept at –20°C and analyzed within 1 week. Plasma total homocysteine was measured by high-performance liquid chromatography.

Statistical analysis

Categorical data were presented as counts and proportions and were compared using the χ^2 test. Normally distributed data were presented as mean ±SD and were compared using the *t* test. Univariate and multivariate regression analysis were performed for independent predictors. Statistical analysis was performed with SPSS 22 software. P value <0.05 was considered to be a significant difference.

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Table 3. Univariate and multivariate analysis for TCFA and thrombus predictors.

	Univariate analysis			Multivariate analysis		
	OR	95%CI	P	OR	95%CI	P
TCFA						
Smoking	1.771	0.809–3.877	0.153			
Overweight	1.686	0.760–3.739	0.199			
Hypertension	2.026	0.917–4.477	0.081			
Diabetes mellitus	0.671	0.254–1.774	0.421			
Hypercholesterolemia	1.042	0.369–2.942	0.939			
Metabolic syndrome	2.783	1.240–6.246	0.013	2.747	1.203–6.273	0.016
Hyperhomocysteinemia	2.541	1.95–5.896	0.030	2.505	1.059–5.929	0.037
Thrombus						
Smoking	9.918	2.188–44.951	0.003	9.112	1.979–41.951	0.005
Overweight	1.364	0.484–3.847	0.557			
Hypertension	1.199	0.458–3.137	0.712			
Diabetes mellitus	1.181	0.353–3.951	0.788			
Hypercholesterolemia	0.491	0.105–2.299	0.367			
Metabolic syndrome	0.915	0.334–2.504	0.863			
Hyperhomocysteinemia	3.829	1.359–10.789	0.011	3.403	1.154–10.038	0.026

TCFA – thin-cap fibroatheromas.

Results

Baseline clinical data and plaque characteristics

123 patients had previously undergone coronary angiography and OCT. Baseline clinical features and coronary angiography data were not significantly different between the 2 groups (Table 1). Patients in the HHcy group had a higher proportion of TCFA (p=0.027), vasa vasorum (p=0.013), thrombus (p=0.012), and larger lipid arc (p=0.002) compared with the control group (Table 2).

Multivariate analysis

Multivariate regression analyses were performed to assess individual predictors of the presence of TCFAs and thrombus in culprit lesions in these patients. Risk factors (P<0.05) from univariate analysis were included in the multivariate analysis (Table 3). After the other risk factors were adjusted HHcy [odds ratio (OR): 2.505, 95% confidence interval (CI): 1.059–5.929, P=0.037] and MetS (OR: 2.747, 95% CI: 1.203–6.273, P=0.016) were independent predictors of TCFAs for the young CAD patients. HHcy (OR: 3.403, 95% CI: 1.154–10.038, P=0.026) and smoking (OR: 9.112, 95% CI: 1.979–41.951, P=0.005) were independent determinants of thrombus for the young patients with CAD. Figure 1 was a representative OCT image of TCFA (Figure A1, A2), red thrombus (Figure B1, B2), and white thrombus (Figure C1, C2).

Discussion

The main findings of our study were as follows: (1) HHcy and MetS were independent predictors of TCFAs, and (2) HHcy and smoking were independent predictors of thrombus. This is the first OCT study to investigate the relationship between OCT-culprit plaque phenotype and HHcy in young patients.

Although there is at least 1 cardiovascular risk factor in most CAD patients, 20% of CAD patients have no conventional risk factors [13]. Studies showed that HHcy is an independent, modifiable risk factor in patients with ischemic heart diseases and thrombosis [14,15]. A meta-analysis revealed a positive correlation between plasma homocysteine concentration and ischemic heart disease [16]. HHcy is believed to promote atherogenesis and atherothrombosis through several mechanisms [17,18]. Enzyme genetic defects involved in homocysteine metabolism, including 5,10-methylenetetrahydrofolate reductase, methionine synthase, and cystathionine-β-synthase, may cause HHcy [19]. It can also be caused by nutritional deficiencies of folate, vitamin B6, and vitamin B12 [19]. The blood concentrations of folate, vitamin B12, and vitamin B6 are inversely

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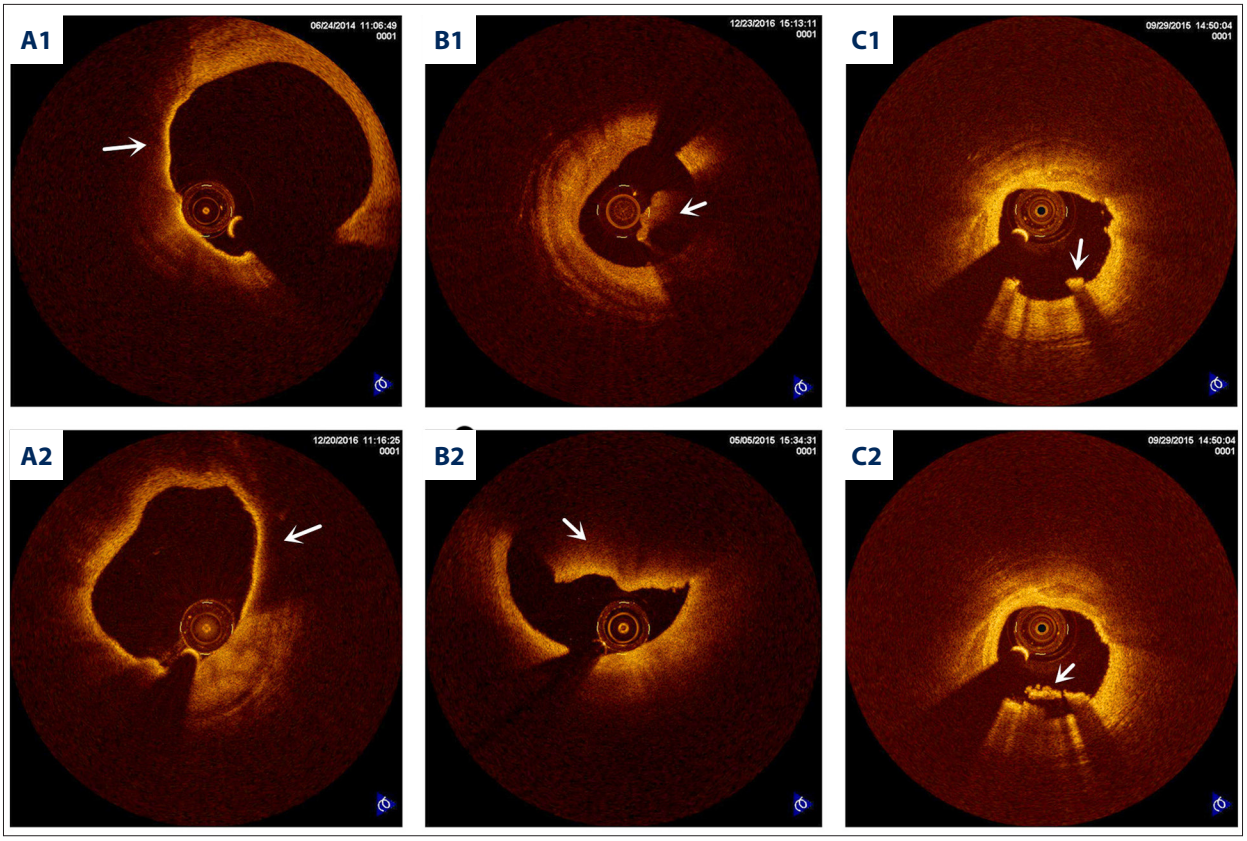

Figure 1. The optical coherence tomography images of thin-cap fibroatheroma (TCFA) and thrombus. Arrows in images **A1** and **A2** showed TCFA, **B1** and **B2** showed red thrombus, and **C1** and **C2** showed white thrombus.

related to total homocysteine content; therefore, malnutrition leads to an increased risk of HHcy in people with low blood concentrations of these components [19,20]. Hcy triggers proliferation of vascular smooth muscle cells, and it also helps to increase the activity of 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase, which in turn increases cholesterol synthesis [21]. High serum cholesterol can promote atherosclerosis and is a risk factor for CAD. Hcy inhibits nitric oxide synthase activity, leading to endothelial dysfunction [22]. The Hcy metabolism generates reactive oxygen species that can directly injure the endothelium. Moreover, Hcy is a potent procoagulant with a high level of Hcy, and can cause endothelial injury by oxidative modification of LDL-cholesterol, influence coagulation factors such as platelets, and arterial smooth muscle. These eventually lead to arterial mural thrombosis and fibrin deposition. A prospective randomized placebo-controlled intervention study evaluating coronary endothelial function in CAD patients with HHcy found that coronary endothelial function was improved after treatment with folic acid and cobalamin [6]. Another randomized double-blind placebo-controlled trial showed folic acid reduced the level of plasma homocysteine and was associated with improved endothelial function in CAD patients [23].

A meta-analysis showed that TCFA is a strong predictor of culprit plaque rupture in all ACS scenarios [24]. Our study is the first to show that HHcy is a TCFA independent risk factor. Three-vessel virtual histology-intravascular ultrasound (VH-IVUS) analysis showed that DM and MetS patients had a larger plaque-plus-media burden, larger necrotic core, and more frequent VH-IVUS-derived TCFA in coronary arterial trees compared to patients without DM or MetS, suggesting that there is more plaque vulnerability in DM and MetS patients (59±9 years of age) [25]. Compared with control subjects, coronary plaques in patients with MetS (60±11 years) contain more lipid, as identified using OCT [26].

We also found that MetS is an independent predictor of TCFA; this result is in contrast to an earlier report that the presence of MetS was not associated with VH-derived TCFA in patients (64.7±9.5 years) with stable angina pectoris (SAP) [27].

Case-control and cross-sectional studies clearly indicated that mild-to-moderate HHcy is associated with increased risk of arterial and venous thrombosis. However, additional studies are required to unequivocally determine whether HHcy is a causal risk factor of thrombosis, especially of the venous circulation [28]. Cigarette smoking promotes thrombotic changes by

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platelet activation and enhancing the effects of clotting factors, and both play a prominent role in formation of thrombi [29]. Prior observational studies have found a positive association between cigarette smoking and thrombus [30].

Conclusions

We demonstrated that HHcy and MetS are independent risk factors of OCT-TCFAs, and HHcy and smoking are related to thrombosis in young patients with CAD.

Conflicts of interest

None.

References:

1. Kalantzi K, Korantzopoulos P, Tzimas P et al: The relative value of metabolic syndrome and cardiovascular risk score estimates in premature acute coronary syndromes. Am Heart J, 2008; 155: 534–40
2. Veeranna V, Zalawadiya SK, Niraj A et al: Homocysteine and reclassification of cardiovascular disease risk. J Am Coll Cardiol, 2011; 58: 1025–33
3. Wu Y, Huang Y, Hu Y et al: Hyperhomocysteinemia is an independent risk factor in young patients with coronary artery disease in southern China. Herz, 2013; 38: 779–84
4. Rathore S, Terashima M, Matsuo H et al: Association of coronary plaque composition and arterial remodelling: A optical coherence tomography study. Atherosclerosis, 2012; 221: 405–15
5. Jang IK, Bouma BE, Kang DH et al: Visualization of coronary atherosclerotic plaques in patients using optical coherence tomography: Comparison with intravascular ultrasound. J Am Coll Cardiol, 2002; 39: 604–9
6. Willems FF, Aengevaeren WR, Boers GH et al: Coronary endothelial function in hyperhomocysteinemia: improvement after treatment with folic acid and cobalamin in patients with coronary artery disease. J Am Coll Cardiol, 2002; 40: 766–72
7. Alberti KGMM, Eckel RH, Grundy SM et al: Harmonizing the metabolic syndrome: A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation, 2009; 120: 1640–45
8. De Rosa R, Vasa-Nicotera M, Leistner DM et al: Coronary atherosclerotic plaque characteristics and cardiovascular risk factors – insights from an optical coherence tomography study. Circ J, 2017; 81: 1165–73
9. Jia H, Dai J, Hou J et al: Effective anti-thrombotic therapy without stenting: intravascular optical coherence tomography-based management in plaque erosion (the EROSION study). Eur Heart J, 2017; 38: 792–800
10. Tian J, Hou J, Xing L et al: Significance of intraplaque neovascularisation for vulnerability: Optical coherence tomography study. Heart, 2012; 98: 1504–9
11. Nishimura S, Ehara S, Hasegawa T et al: Cholesterol crystal as a new feature of coronary vulnerable plaques: An optical coherence tomography study. J Cardiol, 2017; 69: 253–59
12. Tearney GJ, Regar E, Akasaka T et al: Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies. J Am Coll Cardiol, 2012; 59: 1058–72
13. Smith SC Jr.: Current and future directions of cardiovascular risk prediction. Am J Cardiol, 2006; 97: 28A–32A
14. Selhub J: Homocysteine metabolism. Annu Rev Nutr, 1999; 19: 217–46
15. Mattson MP, Shea TB: Folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. Trends Neurosci, 2003; 26: 137–46
16. Clarke R, Collins R, Lewington S et al: Homocysteine and risk of ischemic heart disease and stroke: A meta-analysis. JAMA, 2002; 288: 2015–22
17. Ma Y, Li L, Geng XB et al: Correlation between hyperhomocysteinemia and outcomes of patients with acute myocardial infarction. Am J Ther, 2014; 23: 1464–68
18. Thambyrajah J, Townend JN: Homocysteine and atherothrombosis – mechanisms for injury. Eur Heart J, 2000; 21: 967–74
19. Curro M, Gugliandolo A, Gangemi C et al: Toxic effects of mildly elevated homocysteine concentrations in neuronal-like cells. Neurochem Res, 2014; 39: 1485–95
20. Loscalzo J, Handy DE: Epigenetic modifications: Basic mechanisms and role in cardiovascular disease (2013 Grover Conference Series) Pulm Circ, 2014; 4: 169–74
21. Shenov V, Mehendale V, Prabhu K et al: Correlation of serum homocysteine levels with the severity of coronary artery disease. Ind J Clin Biochem, 2014; 29: 339–44
22. Basu A, Jenkins AJ, Stoner JA et al: DCCT/EDIC Research Group.15: Plasma total homocysteine and carotid intima-media thickness in type 1 diabetes: A prospective study. Atherosclerosis, 2014; 236: 188–95
23. Thambyrajah J, Landray MJ, Jones HJ et al: A randomized double-blind placebo-controlled trial of the effect of homocysteine-lowering therapy with folic acid on endothelial function in patients with coronary artery disease. J Am Coll Cardiol, 2001; 37: 1858–63
24. Iannaccone M, Quadri G, Taha S et al: Prevalence and predictors of culprit plaque rupture at OCT in patients with coronary artery disease: A meta-analysis. Euro Heart J – Card Imag, 2016; 17: 1128–37
25. Zheng M, Choi SY, Tahk SJ et al: The relationship between volumetric plaque components and classical cardiovascular risk factors and the metabolic syndrome: A 3-vessel coronary artery virtual histology – intravascular ultrasound analysis. JACC Cardiovasc Interv, 2011; 4: 503–10
26. Yonetsu T, Kato K, Uemura S et al: Features of coronary plaque in patients with metabolic syndrome and diabetes mellitus assessed by 3-vessel optical coherence tomography. Circ Cardiovas Imag, 2013; 6: 665–73
27. Lee MG, Jeong MH, Kim DH et al: Can metabolic syndrome predict the vulnerable plaque in patients with stable angina pectoris? Virtual histology-intravascular ultrasound analysis. J Cardiol, 2012; 59: 66–274
28. Gatt A, Makris M: Hyperhomocysteinemia and Venous Thrombosis. Semin Hematol, 2007; 44: 70–76
29. Al Rifai M, DeFilippis AP, McEvoy JW et al: The relationship between smoking intensity and subclinical cardiovascular injury: The Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis, 2017; 258: 119–30
30. Bakhru A, Erlinger TP: Smoking cessation and cardiovascular disease risk factors: Results from the third national health and nutrition examination survey. PLoS Med, 2005; 2: 528–36

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