Statin use is associated with decreased CD-40 ligand expression on T lymphocytes of coronary atheroma plaque in patients with stable coronary artery disease

Statin kullanımı stabil angina pektorisli olgularda koroner aterom plağı T lenfositlerinde CD-40 ligand ekspresyonunu azaltmaktadır

Uğur Türk, Emin Alioğlu, İstemihan Tengiz, Ertuğrul Ercan, Reşat Mahmudov, Hamza Duygu*, Cüneyt Türkoğlu**

Department of Cardiology, Central Hospital

*Department of Cardiology, Faculty of Medicine, Ege University, İzmir, Turkey

ABSTRACT

Objective: Atherosclerosis is a chronic inflammatory disease. Statins suppress the inflammation in the plaque. This cross-sectional study was planned to evaluate the effect of statins on plaque T cell activation markers in patients with stable angina pectoris undergoing coronary intervention and atherectomy procedures.

Methods: Twenty-six patients with stable angina with suitable for atherectomy coronary lesions were enrolled in the study. Fourteen of 26 patients who had been taking statin treatment for at least six months were assigned to the Group 1 (Statin group) and 12 patients who had not received any lipid lowering treatment comprised the Group 2 (Control group). Atherectomy specimens were studied with single and double immunohistochemical staining (CD25, CD69, and CD40L). Statistical analysis was performed using Student's t-test and Fisher's exact test.

Results: There was no significant difference between the total tissue area of sections (Group 1: 8.4±0.9 mm^2, Group 2: 7.8±0.9 mm^2, $p>0.05$). CD3, CD25, CD69, and CD40L positive cells did not show statistically significant difference between the groups in unit area (mm^2). There was no significant difference between the groups for percentage of T lymphocytes expressing CD25 (Group 1: 7.8±4.6%, Group 2: 7.8±5.9%, p=0.97) and CD 69 (Group 1: 12.9±4.6%, Group 2: 15.5±5.2%, p=0.203). The expression of CD40L was significantly lower in Group 1 than in Group 2 (Group 1: 4.8±3.9%, Group 2: 11.2±8.7%, p=0.034).

Conclusion: We concluded that, statin treatment may decrease the expression of CD40L on plaque T lymphocytes in patients with stable angina pectoris. *(Anadolu Kardiyol Derg 2008; 8: 99-103)*

Key words: Statin, CD40L, T cell activation markers

ÖZET

Amaç: Ateroskleroz kronik inflamatuvar bir hastalıktır. Statinler plak içi inflamasyonu baskılamaktadırlar. Bu kesitsel çalışmada amacımız statinlerin stabil angina pektorisli olgularda aterom plağı T lenfosit aktivasyonu üzerine etkilerini araştırmak idi.

Yöntemler: Çalışmaya koroner aterektomi planlanmış 26 olgu dahil edildi. Statin grubu (Grup 1) en az 6 ay süre ile statin tedavisi almakta olan 14 olgudan oluşmaktaydı. Kontrol grubu (Grup 2) olarak herhangi bir lipid düşürücü tedavi almayan 12 olgu seçildi. Aterektomi örnekleri immunhistokimyasal çalışma ile değerlendirildi (CD25, CD69 ve CD40L). İstatistiksel değerlendirmeler için Student's t-test ve Fisher's exact testleri kullanıldı.

Bulgular: Gruplar arasında total doku alanı açısından anlamlı farklılık yoktu (Grup 1=8.4±0.9 mm2, Grup 2=7.8±0.9 mm^2, $p>0.05$). Birim alandaki (mm^2) CD3, CD25, CD69 ve CD40L pozitif hücreler açısından gruplar arasında anlamlı farklılık saptanmadı. CD25 eksprese eden T lenfositler gruplar arasında benzer oranlarda idi (Grup 1 %7.8±4.6, Grup 2 %7.8±5.9, p=0.97). CD69 ekspresyonu açısından statin grubunda daha az oranda olmak üzere istatistiksel anlama ulaşmayan farklılık sözkonusu idi (%12.9±4.6, %15.5±5.2, p=0.203). Bununla birlikte statin grubunda T lenfositlerin CD40L ekspresyonu anlamlı şekilde daha düşük oranda idi (%4.8±3.9, %11.2±8.7, p=0.034).

Sonuç: Statin tedavisinin stabil angina pektorisli olgularda koroner ateroma T lenfositlerinde CD40L ekspresyonunu baskılayabileceği sonucuna varıldı. *(Anadolu Kardiyol Derg 2008; 8: 99-103)*

Anahtar kelimeler: Statin, CD40L, T lenfosit aktivasyon göstergeleri

Address for Correspondence/Yazışma Adresi: Uğur Türk, MD, Department of Cardiology, Central Hospital, İzmir, Turkey
Phone: +90 232 390 40 01 Fax: +90 232 341 68 68 E-mail: droturk@yahoo.com

Introduction

Atherosclerosis is a chronic inflammatory disease of the arterial intima. Various immune competent cells such as macrophages and T cells play a crucial role in this inflammatory process. Activation of these cells promotes plaque instability which results in severe clinical scenarios such as acute coronary syndromes or ischemic stroke (1).

T cells play major role in the immunomodulation and progression of the atherosclerotic lesions. T cells are one of the most common cells presented in human atherosclerotic lesions. These cells secrete several cytokines which further promote the atherosclerotic lesions. Moreover these cytokines contribute to activation of macrophages, smooth muscle cells and endothelial cells (2). Activated T cells stimulate macrophages in atheroma to secrete matrix metalloproteinases, which cause plaque vulnerability. Significant increase in peripheral activated T cells in patients with unstable angina pectoris have been demonstrated previously (3). Furthermore, increased expression of T cell activation markers have been demonstrated in culprit coronary atheroma plaques of patients with acute coronary syndrome (4).

Statin treatment has a proven role in the primary and secondary prevention of cardiovascular diseases (5). Anti-atherosclerotic effects of these agents are not restricted to their lipid lowering effects. Statins produce many of their beneficial effects through plaque stabilization. Immunomodulatory properties of the agents play a crucial role in the anti-atherosclerotic and plaque stabilizing effects. Effects of the agents on T cells may be prominent in their immunomodulatory characteristics. Previous studies suggest that statins have T-cell suppressor effect on various levels (6-8).

Therefore, we aimed to investigate the effect of statin therapy on T cells activation markers in coronary atheroma with stable coronary artery disease.

Methods

Study Population

The study population consisted of 26 consecutive male patients with stable angina pectoris (Canadian Cardiovascular Society Class 2) underwent elective coronary atherectomy (CA). Single culprit coronary lesion suitable (proximally located eccentric lesion in a non-tortuous coronary artery more than 3 mm in diameter) for coronary atherectomy were selected. Twenty-six atherectomy specimens were obtained from patients. Group 1 was consisted of 14 patients.

The exclusion criteria were: the presence of (1) familial dyslipidemia; (2) immunomodulatory and/or immunosuppressive therapy; (3) history of malignancy; (4) renal or hepatic failure; (5) history of acute coronary syndrome within last 6 months; (6) treatment with any lipid-lowering therapy for Group 2; (7) statin treatment shorter than 6 months for Group 1.

The cross-sectional study was approved by the medical ethical committee of center. All patients gave informed consent.

Immunohistochemical Analysis

Retrieved coronary plaque specimens were prepared for light microscopic examination. After formalin fixation, the specimens were embedded in paraffin. Multiple sections were obtained from each specimen. One section of each specimen was stained with hematoxylin and eosin (HE), whereas the other sections were allocated for immunohistochemical examination. Finally, sections were photographed with a charge-coupled device camera (Nikon, SMZ) connected to an IBM personal computer. All examinations were performed by the same pathologist who was unaware of clinical properties of the patients.

Immunohistochemical analyses were performed by using single- and double immunostainings. Paraffin sections of specimens were cut in 3 µm sections and adhered to poly-L-lysine coated slides. Sections were deparaffinized in xylene and rehydrated in graded ethanols. Pressure cooking method was used for antigen retrieval (9).

Staining protocol: Primary antibody in the slide specimen was examined for colored end-product at side of the target antigen. Diaminobenzidine (Lab Vision, TL-012-HDN with anti mouse IgG (H and L), anti rabbit IgG (H and L) yielded a characteristic brown end-product whereas fast red chromogen (DAKO, K 0597 with anti mouse IgG (H and L), anti rabbit IgG (H and L) yielded a red end-product. The presence of these colors was interpreted as a positive staining result. The following antibodies were used; CD69 (MCA 1580R, Serotec), CD40L (RDI-CD154abm-TP, Research Diagnostic), CD25 (MS-203-R7 Lab Vision), Anti-Human Smooth muscle Actin (1A4, DAKO), CD 3 (PS1, Novacastra Laboratories).

Morphometric analysis: The results of immunostaining for T lymphocyte activation markers were quantified planimetrically with image analysis software (ImageWarp 1.5, BitFlow Inc. 300 Wildwood Ave Woburn, MA, USA) (10). Cells that expressed activation markers were counted by using the same software.

Laboratory measurements: Fasting blood samples were drawn from the antecubital vein at 08:00 am and 24 hours after the atherectomy procedure. Automatic analyzer was used for standard laboratory parameters (Olympus AU 5200, Olympus Germany). Fibrinogen was measured using a coagulometric assay according to Clauss Method on an automatic analyzer BioMerieux-Option B (France).

Statistical analysis: Statistical analyses were performed with SPSS 13.0 for Windows (SPSS, Chicago, IL, USA). Sample size calculation was not performed in current pilot study. Demographic and clinical data were expressed as mean ± SD. For comparison of continuous variables of baseline charac teristics Student's t-test was used, for categorical data the Fisher's exact test. A value of $p<0.05$ was considered to indicate statistical significance.

Results

Demographical characteristics of groups are shown in Table 1. Laboratory parameters are summarized in Table 2. There were no significant differences between the groups according to biochemical parameters except triglyceride levels. Triglyceride levels were significantly lower in Group 2 than in Group 1.

There were no significant differences between the total tissue areas of sections (Group 1 -8.42±0.86 mm^2, Group 2 -7.82±0.91 mm^2). The numbers of CD3-, CD25-, CD69-, and CD40L-positive cells of the plaques was similar in both groups in unit area (mm^2) (9.61±8.2 vs 7.43±4.4, p=0.24 for CD3-, 0.61±0.57 vs 1.35±1.94, p=0.186 for CD25-, 1.06±1.02 vs 2.81±2.86 p=0.06 for CD69-, 0.51±0.84 vs 3.33±6.61, p=0.12 for CD40L-expressing cells; respectively) (Fig. 1). There were no statistically significant differences in the percentages of T cells expressing activation

markers to total T cells in unit area between the groups except CD40L expression. The expression of CD40L was lower in Group 1 than in Group 2 (4.84±3.91% vs 11.19±8.68%, p=0.034) (Fig. 2).

Discussion

Inflammation triggers the atherosclerosis related acute vascular events (11, 12). Increased focal inflammatory activity in the arterial wall is one of the main characteristics of atherosclerosis. T lymphocytes play an important role in proceeding inflammatory activity in human atheroma plaques (1). Falk et al. (13) demonstrated that rupture of the plaques frequently occurred where the fibrous cap of the plaque was observed thinnest as well as infiltrated by T lymphocytes and macrophages. T lymphocytes can easily adhere to dysfunctional endothelium and release important cytokines such as IL-1, IL-2, IL-6, IFN-gamma and TNF-alpha exerting key roles in immune-modulation (14). It has been demonstrated that activated T lymphocytes increased in the peripheral blood during the course of acute coronary syndromes (15). T lymphocytes are essential in maintenance of inflammatory response and its acute exacerbation periods in the plaques. It was shown that percentage of activation marker expressing T lymphocytes in atheroma plaques of the patients with acute coronary syndromes is more than in plaques with stable coronary artery disease. It was found that activation level of T lymphocytes in the plaque well correlated positively with the severity of the clinical course (4).

Efficiency of statins in the prevention of cardiovascular events has been proved by several studies. They have antiinflammatory and immune-modulator effects both at the systemic and atheroma plaque levels (16-18). It has been shown that treatment with statins reduces the size of atheroma plaques and decreases cellular content of the plaques concurrently (20-22).

It is believed that immune-modulator effects of statins are mainly due to their effects on.

T lymphocytes (23, 24). Therefore, we aimed to study the effects of the statins on the activation of T lymphocytes in the coronary atheroma plaques in patients with stable coronary artery disease. CD25, CD40L and CD69 were studied as the T lymphocyte activation markers.

CD25 is expressed on the cell surface within a period of 2 to 24 hours following the stimulation of T lymphocytes and is an alpha subunit of trimeric IL-2 receptor (25). In the present study, there was no significant difference between two groups in the percentage of T lymphocytes expressing CD25 (p=0.97).

Previous studies using single (25) and double (4) immunohistochemical staining showed that percentage of T lymphocytes expressing CD25 was significantly higher in the coronary atheroma plaques of the patients with acute coronary syndromes compared to those with stable angina pectoris.

A study by Caspar-Baugil et al. (26) showed that oxidized low density lipoprotein (LDL) suppresses the expression of CD25. Statins are known to inhibit oxidation of LDL in the circulation as well as in the atheroma plaques (27, 28). Thus, it may be possible that treatment with statins increases CD25 expression indirectly. Alleviation of CD25 suppression diminished by LDL oxidation can explain why statins are not suppressive for CD25 expression. The present study found no statistically significant difference between the groups for CD25 expression. This finding explained that different mechanisms might play a role in the effect of the statins on CD25 expression.

CD69 was also studied as an activation marker. CD69 is the earliest surface antigen expressed on T lymphocytes following IL-2- or TCR-mediated activation during the course of acute coronary syndrome (4). However, in the present study, no significant difference was found between two groups in the

Table 1. Demographic characteristics

Parameters		Statin Group (n=14)	Control Group (n=12)	p*
Age, years		61.2±11.3	58.5±8.4	>0.05
Hypertension, n (%)		9 (64.3)	5 (41.7)	>0.05
Current Smoker, n (%)		9 (64.3)	7 (58.3)	>0.05
Diabetes Mellitus, n (%)		4 (28.6)	2 (16.7)	>0.05
Peripheral Arterial Disease, n (%)		1 (7.1)	2 (16.7)	>0.05
History of MI, n (%)		4 (28.6)	3 (25)	>0.05
LVEF, %		51.0±7.5	54.0±8.2	>0.05
Treatment	ACE-inhibitor, n (%)	10 (71.4)	5 (41.7)	>0.05
	Beta-Blocker, n (%)	9 (64.3)	6 (50)	>0.05
	Aspirin, n (%)	13 (92.9)	11 (91.7)	>0.05
	Nitrate, n (%)	9 (64.3)	7 (58.3)	>0.05
	Clopidogrel, n (%)	1 (7.1)	1 (8.3)	>0.05
Target Vessel	LAD, n (%)	10 (71.4)	8 (66.6)	>0.05
	Cx, n (%)	1 (7.1)	0 (0)	
	RCA, n (%)	3 (21)	4 (33.3)	

Data presented as mean±SD, proportions/percentages.
*Student's t test and Fisher's exact test.
ACE- angiotensin converting enzyme, Cx- circumflex Artery, LAD- left anterior descending artery, LVEF- left ventricular ejection fraction, MI- myocardial infarction, RCA- right coronary artery

percentages of CD69 expression (p=0.203). Possible explanation of this finding may be the selection of the study population from the patients with stable angina pectoris who have a relatively lower inflammatory activity.

One of the activation markers studied was CD40L (CD154). CD40L, a member of TNF family, is a glycoprotein with immune regulatory properties. It's found in free forms in the plasma and in bound form on the cell surface. CD40L expression on the surface of T lymphocytes may be detected within 1 to 2 hours following TCR-mediated activation and continues for 24 hours (29). More than 90% of soluble form of CD40L (sCD40L) is secreted by platelets. Remaining is secreted into plasma by T lymphocytes, macrophages, endothelial cells and smooth muscle cells. CD40 is a receptor of this molecule and is expressed mainly by platelets, macrophages, T lymphocytes, smooth muscles and endothelial cells. Interactions of CD40 and CD40L molecules substantially increase the inflammatory response. These interactions lead to activation of platelets and platelet-leukocyte adhesion (14) and increase the expression of tissue factor in the macrophages. These processes lead to pro-thrombotic conditions in the plaque (30). This study revealed that the expression of CD40L on T cells was significantly lower in group 1 than in Group 2. (p=0.034).

Plasma level of soluble CD40L is considered to be a good indicator of inflammatory activity and a strong predictor for the possible cardiovascular events in future (31). Furthermore, it has been shown that T lymphocytes in atheroma plaques of the patients with acute coronary syndromes expressed high percentages of CD40L (4).

CD40-CD40L system is in the center of the interaction between thrombosis, inflammation and atherosclerosis processes (14). So this system considered to be chosen as a new target in fight against cardiovascular diseases. Statins, glitazones, clopidogrel and GpIIb/IIIa inhibitors were shown to decrease CD40L expression in vivo and in vitro (32).

Limitations of the study

This study has several potential limitations: (1) Our study groups were small, due to very limited number of patients underwent coronary atherectomy in our centre at the time interval (July 2002-September 2004) of the study. (2) Because of same reason, we were not able to standardize statin therapy. (3) Enough atherectomy materials for histopathologic examination

Table 2. Biochemical parameters

Parameters	Statin Group (n=14)	Control Group (n=12)	p*
Total Cholesterol, mg/dl	194.0±26.9	198.7±34.1	>0.05
LDL-Cholesterol, mg/dl	108.5±22.6	124.1±24.9	>0.05
HDL-Cholesterol, mg/dl	39.2±6.8	38.4±6.3	>0.05
Triglyceride, mg/dl	180.8±44.8	141.0±38.1	0.024
Lipoprotein (a), mg/dl	39.9±18.9	50.0±43.6	>0.05
Fibrinogen, mg/dl	392.2±121.9	398.4±160.0	>0.05
Homocysteine, μmol/l	15.4±3.7	19.3±5.7	>0.05
Uric Acid, mg/dl	6.6±1.5	6.6±1.3	>0.05
Sedimentation rate, mm/h	15.7±8.7	15.1±8.7	>0.05
hsCRP, mg/l	0.79±0.53	0.81±0.44	>0.05

Data presented as mean±SD
*Student's t test
HDL- high density lipoprotein, hsCRP- high sensitive C reactive protein, LDL- low density lipoprotein

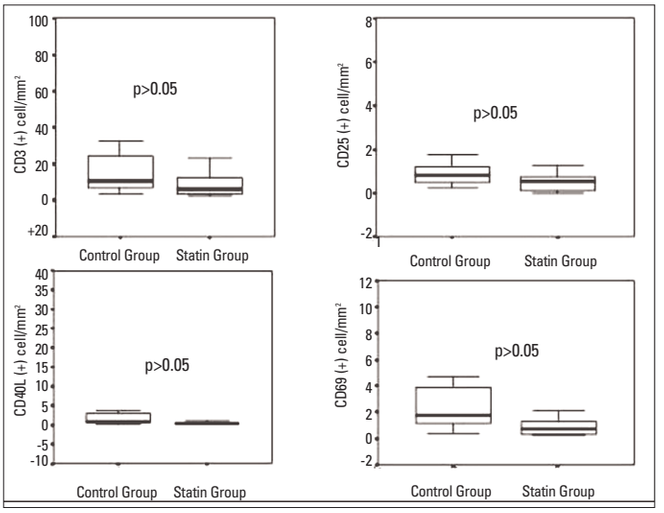

Figure 1. The numbers of CD3, CD25, CD69 and CD40L-positive cells in per mm² of the sections

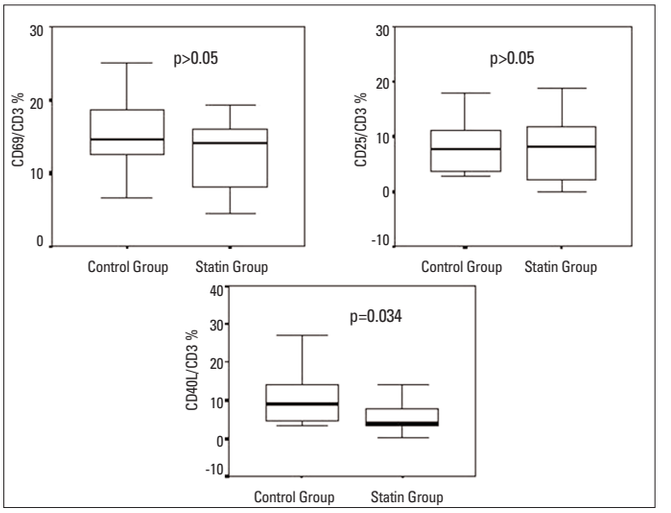

Figure 2. Percentages of activated T cells

were derived from male patients only. (4) Owing to the limited sample size and follow-up period and lack of standardization of statin therapy, we were not able to evaluate the net impact of statin therapy on morphometric results and clinical end points such as acute coronary syndrome, death, revascularization, and hospitalization (5). Measurement of all inflammatory markers was performed on samples that were stored deep-frozen until analysis. We, therefore, cannot exclude the possibility of protein degradation.

Conclusion

New therapeutic approaches to prevent activation of T lymphocytes which play important role in maintaining chronic inflammatory process in the plaque and structuring of atheroma plaque may protect the plaque from inflammatory exacerbations. In the present study CD40L expression as a strong activation marker of T lymphocytes was lower in the patients receiving statin treatment. Although statins are known to decrease sCD40L levels, there is no information about their effects on the expression of CD40L at the atheroma plaque. Inhibition of CD40-CD40L system at the tissue level may provide a stronger control on the inflammatory response at the level of plaque and may prevent formation of prothrombotic conditions.

References

1. Ross R. Atherosclerosis-an inflammatory disease. New Engl J Med 1999; 340: 115-26.
2. Jonasson L, Holm J, Skalli O, Bondjers G, Hansson GK. Regional accumulations of T cells, macrophages, and smooth muscle cells in the atherosclerotic plaque. Arteriosclerosis 1986; 6: 131-8.
3. Tanaka T, Soejima H, Hirai N, Sakamoto T, Yoshimura M, Kajiwara I, et al. Comparison of frequency of Interferon-γ-positive CD4 T cells before and after percutaneous coronary intervention and the effect of statin therapy in patients with stable angina pectoris. Am J Cardiol 2004; 93: 1547-9.
4. Hosono M, de Boer OJ, van der Wal AC, van der Loos CM, Teeling P, Piek JJ, et al. Increased expression of T cell activation markers in atherectomy specimens of patients with unstable angina and acute myocardial infarction. Atherosclerosis 2003; 168: 73-80.
5. Maron DJ, Fazio S, Linton MF. Current perspectives of statins. Circulation 2000; 101: 207-13.
6. Kwak B, Mulhaupt F, Veillard N, Pelli G, Mach F. The HMG-CoA reductase inhibitor simvastatin inhibits INF-gamma induced MHC class II expression in human vascular endothelial cells. Swiss Med Wkly 2001; 131: 41-6.
7. Kwak B, Mulhaupt F, Myit S, Mach F. Statins as newly recognized type of immunomodulator. Nat Med 2000; 6: 1399-402.
8. Horimoto H, Nakai Y, Nakahara K, Nomura Y, Mieno S, Sasaki S. HMG-CoA reductase inhibitor cerivastatin prolonged rat cardiac allograft survival by blocking intercellular signals. J Heart Lung Transplant 2002; 21: 440-5.
9. Neves JI, Begnami MD, Arias V, Santos GC. Antigen retrieval methods and estrogen receptor immunoexpression using 1D5 antibody: a comparative study. Int J Surg Pathol 2005; 13: 353-7.
10. De Melo MR Jr, Araújo Filho JL, Patu VJ, Machado MC, Mello LA, Carvalho LB Jr. Langerhans cells in cutaneous tumours: immunohistochemistry study using a computer image analysis system. J Mol Histol 2006; 37: 321-5.
11. Van der Wal AC, Becker AE, van der Loss CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation 1994; 89: 36-44.
12. Kaartinen M, Penttila A, Kovanen PT. Accumulation of activated mast cells in the shoulder region of human coronary atheroma, the predilection site of atheromatous rupture. Circulation 1994; 90: 1669-78.
13. Falk E, Shah PK, Fuster V. Coronary Plaque Disruption. Circulation 1995; 92: 657-71.
14. Cipollone F, Mezzetti A, Porreca E, Di Febbo C, Nutini M, Fazia M, et al. Association between enhanced soluble CD40L and prothrombotic state in hypercholesterolemia: Effects of statin therapy. Circulation 2002; 106: 399-402.
15. Neri Serneri GG, Prisco D, Martini F, Gori AM, Brunelli T, Poggessi L. Acute T-cell activation is detectable in unstable angina. Circulation 1997; 95: 1806-12.
16. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383-9.
17. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. West of Scotland Coronary Prevention Study Group. Prevention coronary heart disease with Pravastatin in men with hypercholesterolemia. N Eng J Med 1995; 333; 1301-7.
18. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Eng J Med 1996; 335: 1001-9.
19. MRC/BHF Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering therapy and of anti-oxidant vitamin supplementation in a wide range of patients at increased risk of coronary heart disease death: early safety and efficacy experience. Eur Heart J 1999; 20: 725-41.
20. Liao JK. Endothelium and acute coronary syndromes. Clin Chem 1998; 44: 1799-808.
21. Tamia O, Matsukoa H, Itabe H, Wada Y, Kohno K, Imaizumi T. Single LDL apheresis improves endothelium-dependent vasodilatation in hypercholesterolemic humans. Circulation 1997; 95: 76-82.
22. Vaughan CJ, Murphy MB, Buckley BM. Statins do more than just lower cholesterol. Lancet 1996; 348: 1079-82.
23. Okopien B, Krysiak R, Kowalski J, Madej A, Belowski D, Zielinski M, et al. The effect of statins and fibrates on interferon-α and interleukin-2 release in patients with primary type II dyslipidemia. Atherosclerosis 2004; 176: 327-35.
24. Ehrenstein MR, Jury EC, Mauri C. Statins for Atherosclerosis-As Good as It Gets? N Engl J Med 2005; 352: 73-5.
25. Van der Wal AC, Piek JJ, de Boer OJ, Koch KT, Teeling P, van der Loos CM, et al. Recent activation of the plaque immune response in coronary lesions underlying acute coronary syndromes. Heart 1998; 80: 14-8.
26. Caspar-Bauguil S, Saadawi M, Negre-Salvayre A, Thomsen M, Salvayre R, Benoist H. Mildly oxidized low-density lipoproteins suppress the proliferation of activated CD4 T lymphocytes and their interleukin 2 receptor expression in vitro. Biochem J 2001; 330: 659-66.
27. Rabbani R, Topol EJ. Strategies to achieve coronary arterial plaque stabilization. Cardiovasc Res 1999; 41: 402-17.
28. Koh KK. Effects of statins on vascular wall: vaso-motor function, inflammation, and plaque stability. Cardiov Research 2000; 47: 648-57.
29. Castle BE, Kishimoto K, Stearns C, Brown ML, Kehry M. Regulation of expression of the ligand for CD40 on T helper lymphocytes. J Immunol 1993; 151: 1777-88.
30. Patwari P, Weissman NJ, Boppart SA, Jesser C, Stamper D, Fujimoto JG, et al. Assessment of coronary plaque with optical coherence tomography and high frequency ultrasound. Am J Cardiol 2000; 85: 641-4.
31. Saygı S. Atrial fibrillation and CD40 Ligand system. J Card Res 2006; 3: 36-41.
32. Vishnevetsky D, Kiyanista Va, Gandhi PJ. CD40 Ligand: A novel target in the fight against cardiovascular disease. Ann Pharmacother 2004; 38: 1500-8.