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Review Article

Association of systemic inflammatory biomarkers with morphological characteristics of coronary atherosclerotic plaque by intravascular optical coherence tomography

S. Koganti [1, 2, 6, *], A. Karanasos [3, 4], E. Regar [3, 5], R.D. Rakhit [2, 6]

[1] Citizens Specialty Hospital, Hyderabad, India
[2] UCL Institute of Cardiovascular Science, London, UK
[3] Erasmus MC, Thoraxcentre, Rotterdam, the Netherlands
[4] Hippokration Hospital, Athens Medical School, Athens, Greece
[5] University Hospital of Zurich, Switzerland
[6] Royal Free Hospital, London, UK

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ABSTRACT

Despite significant advances in preventive, medical, and interventional management, coronary artery disease remains the leading cause of death worldwide. We now know that in the majority of acute coronary syndromes, a thrombotic event is triggered either by the rupture or erosion of the so-called high-risk or 'vulnerable' plaque. However, accurately identifying the individual who is at significant risk of acute event remains the holy grail of preventive cardiology. To better stratify an individual's risk of developing and suffering a cardiovascular event, biomarkers are needed that can accurately predict coronary events and, if possible, monitor disease activity in response to medical or interventional therapies. In order to be able to understand the association of these biomarkers with the morphological substrate of high-risk plaques, intravascular imaging modalities can provide invaluable assistance. Novel imaging tools such as optical coherence tomography (OCT) have not only helped in identifying atherosclerotic plaque characteristics that are unstable but also in estimating global plaque burden. In this study, we provide an overview of our current knowledge of association of various inflammatory markers with atherosclerotic plaque characteristics seen on OCT.

1. Introduction

Ischemic heart disease remains the leading cause of death worldwide, despite advances in medical and interventional therapies.[1] It is now widely accepted that atherosclerosis is an inflammatory process.[2] All the key steps from initiation and progression of atherosclerosis to eventual plaque rupture or erosion and thrombus formation involve inflammatory pathways.[3] Studies from cellular and molecular biology have shown how inflammatory pathways differ in each step of atherosclerosis.[2] It is now well established that molecules such as cytokines and adhesion molecules alter endothelial integrity, through which cells such as monocytes gain entry and alter the structural integrity of the arterial wall. Ensuing lipid accumulation and plaque progression involves degradation of interstitial collagen by matrix metalloproteinase.[4] Both local and systemic inflammation contribute to plaque rupture with a subsequent role of activated platelets in thrombus formation and propagation by binding with monocytes. Yet again, it is the dynamic interplay between cells such as platelets and monocytes with molecules such as tissue factor and P-selectin glycoprotein ligand 1 that mediates thrombus formation and propagation. A greater knowledge of the role played by various inflammatory cells and molecules involved in atherogenesis may translate into the development of biomarkers[5,6] that can be used to screen individuals who are at risk and to monitor interventions aimed at ameliorating atherosclerosis. (see Table 1)

The majority of knowledge regarding the pathophysiology of atherosclerosis is based on histology. A vulnerable plaque is defined as a coronary atherosclerotic plaque that is prone to rupture and

* Corresponding author. Citizens Specialty Hospital, Hyderabad, 500019, India. Tel.: +00919912911177.
E-mail address: sudheerkoganti@hotmail.com (S. Koganti).
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Table 1
Association of inflammatory biomarkers and plaque morphology in patients with ACS.

Study	Population	Inflammatory marker	Association with plaque morphology
Inflammatory biomarkers			
Raffel et al. [17]	32 ACS and 11 SA patients	WBC count	• WBC count correlated with cap thickness and macrophage density of the plaque • CRP levels higher in TCFA versus non-TCFA lesions
Kashiwagi et al. [20]	47 ACS patients	CRP	• CRP levels higher in TCFA versus non-TCFA lesions
Fujii et al. [21]	35 AMI and 20 SA patients	CRP	• CRP independent predictor of multiple TCFA in the coronary tree in AMI
Bouki et al. [18]	32 ACS and 14 SA patients	CRP, IL-18	• CRP and IL-18 levels higher in TCFA versus non-TCFA lesions • CRP and IL-18 levels higher in ruptured plaques versus non-ruptured plaques • IL-18 levels lower in plaques with calcification • CRP levels independent predictor of ruptured plaque
Li et al.	12 AMI, 23 UA and 11 SA patients	WBC count, CRP, IL-18, TNFα	• Cap thickness inversely correlated with WBC count and CRP, IL-18, and TNFα levels • WBC count and CRP, IL-18, and TNFα levels higher in TCFA versus non-TCFA lesions • No association for any factor with plaque rupture • CRP levels independent predictor of TCFA
Nicolli et al. [19]	50 non-ST elevation ACS patients	CRP, MPO, MMP-9, MMP-2, Cystatin-C	• CRP and MMP-9 levels higher in plaque rupture compared to erosion and severe stenosis without thrombus • MPO levels higher in plaque erosion compared to rupture and severe stenosis without thrombus • Cystatin-C levels higher in severe stenosis without thrombus compared to plaque rupture or erosion • No association of MMP-2 with plaque morphology
Ferrante et al. [47]	25 AMI patients	CRP, MPO	• No difference in CRP levels for plaque rupture versus plaque erosion • Elevated MPO levels in plaque erosion versus plaque rupture
Koga et al. [22]	28 ACS and 47 SA patients	CRP, pentraxin-3	• Levels of pentraxin-3, but not CRP, were higher in TCFA versus non-TCFA lesions, both in ACS and SA lesions
Ozaki et al. [34]	25 AMI and 20 UA patients	PSGL-1 expression in circulating monocytes	• Increased PSGL-1 expression in circulating monocytes in lesions with plaque rupture
Matsuo et al.[36]	53 ACS and 49 SA patients	MDA-LDL, CRP	• Higher CRP levels but no difference in MDA-LDL levels in TCFA versus non-TCFA lesions in ACS • Significantly higher MDA-LDL levels in ruptured TCFA versus non-ruptured TCFA in ACS
Teraguchi et al. [31]	37 AMI patients	MAGE, circulating monocytes	• Increased MAGE in plaque rupture compared to non-ruptured plaque • Increased circulating monocytes in plaque rupture
Sun et al. [25]	81 CAD patients	Neopterin	• Higher levels of Neopterin in non-culprit plaque that have TCFA, smaller FCT, and more macrophages
Wakabayashi et al. [41]	59 ACS patients	Eicosapentaenoic acid/Arachidonic acid	• Low EPA/AA ratio in ACS patients with TCFA
Lee et al. [43]	206 SA patients	Troponin	• Elevated cTnI group has frequent TCFAs, a greater lipid arc, and longer lipid length
Gu et al. [46]	24 ACS patients	Lp-PLA2	• Positive correlation between Lp-PLA2 activity, FCT, and plaque volume

Abbreviations: ACS = Acute coronary syndrome, SA= Stable angina, AMI = Acute myocardial infarction, CAD = Coronary artery disease, UA = unstable angina, WBC = white blood cells, TCFA = Thin cap fibroatheroma, CRP=C-reactive protein, IL = interleukin, TNFα = tumor necrosis factor alpha, MPO = myeloperoxidase, MMP = Matrix metalloproteinase, PSGL-1 = P-selectin glycoprotein ligand-1, MDA-LDL = malondialdehyde-modified low-density lipoprotein, MAGE = mean amplitude of glycemic excursion, FCT − Fibrous cap thickness, Lp-PLA2 = Lipoprotein-associated phospholipase A2.

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has morphological resemblance to ruptured plaques.[7] The thin cap fibroatheroma (TCFA), a plaque with thin fibrous cap (<65 μm), macrophage infiltration, and large necrotic core, is currently considered the main phenotype of vulnerable plaque.[8] Autopsy studies from patients who have suffered sudden cardiac death revealed the substrate for atherothrombosis to be plaque rupture in 60-70% of the cases, plaque erosion in 20-30% of the cases, and calcified nodules in the rest.[9] Autopsy studies have, however, several limitations in that they represent the far-end of the clinical spectrum and ex vivo specimens need heavy processing and fixation with formalin which lead to some degradation.[10] Intracoronary imaging modalities such as optical coherence tomography (OCT) can be used for the in vivo imaging of coronary arteries and studying the atherosclerotic plaque characteristics due to high-resolution images (15 μm) obtained by near-infrared light.[11-13] In their seminal study, Jang et al visualized the atherosclerotic plaque characteristics of culprit lesions by OCT in a cohort of 57 patients presenting with ST segment elevation myocardial infarction (STEMI, n = 20), non STEMI (NSTEMI, n = 20), and stable angina (SA, n = 17).[14] OCT-identified TCFA and disrupted plaques were more prevalent in acute coronary syndromes (ACS), in contrast to plaques from stable coronary artery disease patients that had a higher incidence of calcifications. These findings were concordant with an ex vivo study conducted by the same group[15] and previously reported autopsy studies.[16]

As new data showing associations between biomarkers and cardiovascular events emerge, the finding of an association between the circulating levels of biomarkers and plaque morphology by OCT can provide new insights into the role of these biomarkers and the implicated mechanisms, thus providing more effective risk stratification.

The aim of this manuscript is to review the literature on the relationship between inflammatory markers and plaque vulnerability using OCT.

2. Association with White blood cells (WBC)

Raffel et al conducted one of the first studies that correlated inflammatory markers with plaque characteristics using OCT.[17] The relationship between the peripheral WBC count, local macrophage density over the fibrous cap, other morphological features, and presence of TCFA was evaluated in 43 patients undergoing angiography for ACS or SA. Patients with lipid-rich plaques had higher WBC counts in comparison to those with non−lipid-rich plaques, and there was a significant linear relationship between WBC count and plaque fibrous cap macrophage density irrespective of the presenting syndrome. Moreover, there was a strong linear relationship between WBC count and macrophage density in culprit plaque when compared to remote plaque. Further, an inverse linear relationship between WBC count and plaque macrophage density with fibrous cap thickness was found. Patients having culprit plaque with TCFA morphology had a higher median WBC count compared with those with culprit plaque without TCFA. Although this study revealed a strong association between WBC and the presence of vulnerable plaque, it did not provide answers with respect to a mechanistic role of WBC in plaque destabilization.

3. Association with C- reactive protein (CRP), high sensitivity (hs) CRP, & Interleukins

Bouki et al evaluated OCT-derived plaque characteristics between ACS and SA and correlated with hs-CRP and Interleukin (IL18) in 46 patients (32 ACS and 14 SA).[18] They noted more ruptured plaques and TCFA and lipid-rich plaques in patients presenting with ACS and more calcific plaques in patients presenting with SA. IL18 and hs-CRP were significantly elevated in patients presenting with ACS when compared to those with SA and correlated with presence of TCFA. Furthermore, on multivariate analysis, hs-CRP was found to independently predict the presence of plaque rupture and detect it with a high degree of sensitivity and specificity. Niccoli et al sought to evaluate the relationship between hs-CRP, Matrix metalloproteinase (MMP)-9, MMP-2, Myeloperoxidase (MPO), and Cystatin−C with the presence of plaque rupture, plaque erosion, and significant stenosis with no thrombus.[19] Their cohort of 84 patients consisted of 50 NSTE-ACS and 34 SA patients. Additionally, there was no difference in plaque characteristics between ACS and SA in culprit artery only OCT. However, hs-CRP and MMP9 were associated with the presence of plaque rupture, MPO was associated with the presence of plaque erosion, and cystatin−c was associated with the presence of significant stenosis without any superimposed thrombosis. Kashiwagi et al evaluated the relationship between coronary arterial remodeling, fibrous cap thickness (FCT), and hs-CRP levels in 47 consecutive patients presenting with ACS. In this culprit plaque only study, arterial remodeling was assessed by intravascular ultrasound (IVUS), and FCT was measured by OCT.[20] In total, positive remodeling (PR) was observed in 17 out of 47 patients, and negative or intermittent remodeling was observed in the remainder. Lipid-rich plaques and TCFA were more frequent in the PR group. Furthermore, high levels of hs-CRP were observed in the group with PR, as well as in those with documented TCFA. In a 3-vessel OCT study involving 35 AMI and 20 SA patients, Fujii et al showed hs-CRP levels to be associated with the presence of multiple TCFAs in ACS patients.[21]

4. Association with other novel inflammatory markers

4.1. Pentraxin 3

Pentraxin 3 (PTX3) is an acute phase reactant and member of the pentraxin superfamily along with CRP. High levels of PTX3 are locally expressed in vascular endothelial and smooth muscle cells in human atherosclerotic lesions. Previously, PTX-3 has been shown to be an early indicator of acute myocardial infarction.[22] Koga et al evaluated the association of PTX-3 with the presence of TCFA and arterial remodeling index in 75 patients with CAD, of which 28 were diagnosed to have ACS and the remaining had SA. Intravascular imaging was carried out with OCT and IVUS. The levels of PTX3 were significantly higher in patients with TCFA and correlated inversely with FCT and positively with the remodeling index. Multivariate logistic regression analysis showed that a higher PTX3 level was the most powerful predictor of TCFA with receiver operating curve analysis showing that PTX-3 levels >3.24 ng/ml could predict the presence of TCFA with 84% sensitivity and 86% specificity.

4.2. Neopterin

Neopterin, a pteridine derivative, is an intermediate metabolite in guanosine triphosphate metabolism and in tetrahydrobiopterin biosynthesis. Neopterin which is secreted by activated macrophages has previously been shown to be elevated in patients with ACS than SA.[23] Furthermore, Kaski et al showed that elevated neopterin levels at baseline in a cohort of patients with NSTE-ACS were independently associated with cardiac death, acute myocardial infarction, and unstable angina after six months.[24] More recently, Sun et al evaluated the levels of neopterin from peripheral venous blood in patients presenting with NSTE-ACS and SA, and evaluated a possible association with vulnerable plaque features from non−culprit plaques.[25] Higher levels of neopterin were detected in non-culprit plaques with vulnerable features such as

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presence of TCFA, low FCT, and high macrophage infiltration. However, a possible association of neopterin levels with culprit lesion morphology remains elusive, as it was not evaluated in the context of this study.

4.3. Myeloperoxidase

MPO, a hemoprotein released upon neutrophil activation, has been shown to predict the outcome of patients with ACS[26,27] and is considered to be a marker of plaque vulnerability.[27] A study evaluating the association of MPO with plaque erosion or rupture in patients presenting with ACS has shown significantly higher MPO blood levels in eroded plaques. Furthermore, overlying thrombus in eroded plaques had significantly higher MPO levels when compared to thrombus from ruptured plaques in postmortem coronary samples of sudden death cases. Moreover, MPO levels were not elevated in the fibrous cap near the rupture or the interface between thrombus and artery in eroded plaques but were significantly elevated in the thrombus overlying eroded plaques, suggesting a role in thrombus formation. This could be explained by a mechanism including hyaluronan-mediated loss of endothelial layer followed by platelet adhesion and subsequent thrombus formation.[28] Further, in line with previous studies, MPO levels were elevated in smokers when compared to non-smokers,[29] although this could be a confounder given the high percentage of smokers in the group with plaque erosion. In the same study, investigators showed no such discriminatory role for CRP.

5. Impact of glucose fluctuation, monocyte subsets, & P-selectin glycoprotein ligand 1 (PSGL-1)

Elevated blood glucose levels are commonly seen in patients presenting with AMI secondary to excessive sympathetic drive[30]*. This pattern is seen in both diabetics and non-diabetics. However, it is not known if there is any correlation between glucose levels at the time of presentation with AMI or during recovery with atherosclerotic plaque characteristics. In a small study involving 37 consecutive patients with AMI that underwent OCT, Teraguchi et al showed that glycemic variability, expressed as the mean amplitude of glycemic excursion (MAGE), was significantly higher in patients with plaque rupture than non-rupture patients.[31] It is important to note that variability in glucose measurements was carried out prospectively up to 7 days, not allowing the evaluation of a possible prospective association of fluctuation in glucose levels with a future AMI. Furthermore, MAGE correlated positively and significantly with levels of CD14-bright CD16fl-monocytes, which in turn were higher in patients with plaque rupture than in non-rupture patients. Whilst this suggests that glucose fluctuation is pro-inflammatory, no other correlation with traditional inflammatory markers such as WCC, CRP, or cytokines was shown. Thus, this study at best hypothesizes that dynamic glucose fluctuation in diabetic and non-diabetic patients is potentially associated with plaque rupture.

The role of monocytes in atherosclerosis is well established.[32] Monocytes play a crucial role in the formation and propagation of thrombus in ACS patients. Activated platelets in ACS express P−selectin, which is an adhesion molecule to which monocytes bind through PSGL-1 resulting in platelet-rich arterial thrombi.[33] In another monocyte-based study, the expression of PSGL-1 in circulating peripheral CD14++CD16+ monocytes was significantly elevated in AMI patients with plaque rupture and intracoronary thrombus by OCT. Interestingly, similar levels of PSGL-1 were not seen in plaque rupture associated with SA. Considering that thrombus formation secondary to plaque rupture or erosion is pathognomonic of ACS and that the culprit lesion in SA is usually obstructive in nature, plaque rupture in SA seen on OCT is usually an incidental finding that may have happened in the past with no clinical sequelae. Therefore, at the time of identification, plaque rupture is probably no longer acute, and as a result there is no thrombus, thus explaining the normal PSGL-1 levels.[34]

6. Oxidized low density lipoproteins (Ox-LDL)

Malondialdehyde-modified LDL (MDA-LDL) is an oxLDL that was shown to be elevated in patients with ACS.[35] Matsuo et al evaluated the relationship between coronary plaque vulnerability assessed by OCT and circulating MDA-LDL in stable and unstable CAD. The circulating levels of MDA-LDL were significantly higher in patients with ACS, in SAP patients with TCFA and in ACS patients with ruptured TCFA.[36] Similarly, experimental studies in mice have shown a transient increase in plasma Ox-LDL during the progression of atherosclerosis; however, they do not allow to discriminate whether the observed elevated MDA-LDL levels in patients with vulnerable plaque are due to association or causation.[37]

7. N3 and n6 polyunsaturated fatty acids (PUFA)

Eicosapentaenoic acid (EPA), a member of n3 PUFA family, is derived from fish oil and has a role in preventing cardiovascular events.[38] Arachidonic acid (AA), a member of n6 PUFA, is known to promote CAD. Chronic imbalance of EPA & AA is known to promote CAD.[39] A low EPA/AA ratio has been shown to be associated with thin cap fibroatheroma and wide lipid arc as seen on OCT in patients with stable angina.[40] Similarly, in ACS patients, EPA/AA ratio was noted to be significantly lower in patients with TCFA than in those without TCFA.[41] Addressing this imbalance through means such as higher consumption of oily fish or fish oil supplements may impart stability to atherosclerotic plaque but this has to be confirmed by larger studies.

7.1. Troponin I

High sensitivity troponins at low levels were noted not only to be present in a great majority of patients with stable CAD but were also associated with the incidence of cardiovascular death and heart failure.[42] Lee et al compared clinical and atherosclerotic plaque characteristics in patients undergoing PCI for stable CAD by dividing them into two groups: one with cTnI $\geq$0.03 ng/ml and one with cTnI <0.03 ng/ml.[43] The group in which cTnI was elevated was noted to have frequent TCFAs, a greater lipid arc, and longer lipid length. Furthermore, periprocedural myocardial injury occurred more frequently in the group with elevated cTnI, with OCT-identified TCFA being an independent predictor. This study suggests the presence of low levels of high sensitivity troponins in some patients with CAD, which are associated with vulnerable plaque and an adverse outcome. However, large-scale studies have to be carried out to assess the feasibility of incorporating high sensitivity troponin levels into traditional risk scoring systems to see if it has a good discriminator value.

7.2. Lipoprotein-associated phospholipase A2 (Lp-PLA2)

Lp-PLA2 is an enzyme known to hydrolyze ox-LDL particles leading to the production of byproducts that have been shown through in vitro experiments to cause plaque instability.[44] Prior studies have shown association between higher levels of Lp-PLA2 mass and coronary events.[45] Gu et al studied FCT and plaque volume in non-culprit lipid-rich plaques at baseline and after 12 months by using OCT and IVUS in 24 patients presenting with ACS. A significant positive correlation was noted between Lp-PLA2

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activity, FCT, and plaque volume. Despite the potential role of Lp-PLA2 measurement as a biomarker for progression of CAD, the lack of any therapeutic benefit of direct inhibition of Lp-PLA2 activity in the SOLID-TIMI52 study suggests that this is not a suitable target for intervention.[46]

8. Summary

In summary, several studies, though limited by their relatively small numbers of participants, have shown a good correlation between inflammatory markers and OCT-derived atherosclerotic plaque characteristics. However, the causation or association is still unclear, as predicting the levels of inflammatory markers and their association with vulnerable plaque in the run-up to an acute event is difficult. Furthermore, with the exception of traditional markers such as CRP, hs-CRP, WBC, and Troponin, measuring novel inflammatory markers is cumbersome and is still at an experimental level. These observations highlight the fact that research in this field is still in its infancy and any conclusions are preliminary.

9. Conclusion

Prospective long-term and larger studies with a simplified means of assaying biomarkers are required before they can be adopted into risk stratification models. Until then, the debate on and pursuit of how best to predict the next acute coronary event goes on.

Conflict of interest

There is No conflict of interest.

References

1. *World Health Organisation (2011) Global status report on noncommunicable diseases 2010*. 2011.
2. Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2012;32:2045–2051.
3. Libby P, Ridker PM, Hansson GK, Leducq Transatlantic Network on A. Inflammation in atherosclerosis: from pathophysiology to practice. *J Am Coll Cardiol*. 2009;54:2129–2138.
4. Sukhova GK, Schonbeck U, Rabkin E, et al. Evidence for increased collagenolysis by interstitial collagenases-1 and -3 in vulnerable human atheromatous plaques. *Circulation*. 1999;99:2503–2509.
5. Tousoulis D. Novel biomarkers in heart failure. What they add in daily clinical practice? *Hellenic J Cardiol HJC : HJC = Hellenike kardiologike epitheorese*. 2018;59:193–195.
6. Lovic MB, Djordjevic DB, Tasic IS, Nedeljkovic IP. Impact of metabolic syndrome on clinical severity and long-term prognosis in patients with myocardial infarction with ST-segment elevation. *Hellenic J Cardiol HJC : HJC = Hellenike kardiologike epitheorese*. 2018;59:226–231.
7. Toutouzas K, Benetos G, Karanasos A, Chatzizisis YS, Giannopoulos AA, Tousoulis D. Vulnerable plaque imaging: updates on new pathobiological mechanisms. *Eur Heart J*. 2015;36:3147–3154.
8. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med*. 1997;336:1276–1282.
9. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 2000;20:1262–1275.
10. Toutouzas K, Karanasos A, Tsiamis E, et al. New insights by optical coherence tomography into the differences and similarities of culprit ruptured plaque morphology in non-ST-elevation myocardial infarction and ST-elevation myocardial infarction. *Am Heart J*. 2011;161:1192–1199.
11. Yabushita H, Bouma BE, Houser SL, et al. Characterization of human atherosclerosis by optical coherence tomography. *Circulation*. 2002;106:1640–1645.
12. van der Sijde JN, Karanasos A, van Ditzhuijzen NS, et al. Safety of optical coherence tomography in daily practice: a comparison with intravascular ultrasound. *Eur Heart J Cardiovasc Imag*. 2016.
13. Karanasos A, Ligthart J, Witberg K, van Soest G, Bruining N, Regar E. Optical Coherence Tomography: Potential Clinical Applications. *Curr Cardiovasc Imag Rep*. 2012;5:206–220.
14. Jang IK, Tearney GJ, MacNeill B, et al. In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography. *Circulation*. 2005;111:1551–1555.
15. 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;39:604–609.
16. Kolodgie FD, Burke AP, Farb A, et al. The thin-cap fibroatheroma: a type of vulnerable plaque: the major precursor lesion to acute coronary syndromes. *Curr Opin Cardiol*. 2001;16:285–292.
17. Raffel OC, Tearney GJ, Gauthier DD, Halpern EF, Bouma BE, Jang I-K. Relationship between a systemic inflammatory marker, plaque inflammation, and plaque characteristics determined by intravascular optical coherence tomography. *Arterioscler Thromb Vasc Biol*. 2007;27:1820–1827.
18. Bouki KP, Katsafados MG, Chatzopoulos DN, et al. Inflammatory markers and plaque morphology: an optical coherence tomography study. *Int J Cardiol*. 2012;154:287–292.
19. Niccoli G, Montone RA, Cataneo L, et al. Morphological-biohumoral correlations in acute coronary syndromes: pathogenetic implications. *Int J Cardiol*. 2014;171:463–466.
20. Kashiwagi M, Tanaka A, Kitabata H, et al. Relationship between coronary arterial remodeling, fibrous cap thickness and high-sensitivity C-reactive protein levels in patients with acute coronary syndrome. *Circ J*. 2009;73:1291–1295.
21. Fujii K, Masutani M, Okumura T, et al. Frequency and predictor of coronary thin-cap fibroatheroma in patients with acute myocardial infarction and stable angina pectoris a 3-vessel optical coherence tomography study. *J Am Coll Cardiol*. 2008;52:787–788.
22. Koga S, Ikeda S, Yoshida T, et al. Elevated levels of systemic pentraxin 3 are associated with thin-cap fibroatheroma in coronary culprit lesions: assessment by optical coherence tomography and intravascular ultrasound. *JACC Cardiovasc Interv*. 2013;6:945–954.
23. Liu ZY, Li YD. Relationship between serum neopterin levels and coronary heart disease. *Genet Mol Res*. 2013;12:4222–4229.
24. Kaski JC, Consuegra-Sanchez L, Fernandez-Berges DJ, et al. Elevated serum neopterin levels and adverse cardiac events at 6 months follow-up in Mediterranean patients with non-ST-segment elevation acute coronary syndrome. *Atherosclerosis*. 2008;201:176–183.
25. Sun Y, He J, Tian J, Xie Z, Wang C, Yu B. Association of circulating levels of neopterin with non-culprit plaque vulnerability in CAD patients an angiogram, optical coherent tomography and intravascular ultrasound study. *Atherosclerosis*. 2015;241:138–142.
26. Baldus S, Heeschen C, Meinertz T, et al. Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. *Circulation*. 2003;108:1440–1445.
27. Brennan ML, Penn MS, Van Lente F, et al. Prognostic value of myeloperoxidase in patients with chest pain. *N Engl J Med*. 2003;349:1595–1604.
28. Kolodgie FD, Burke AP, Farb A, et al. Differential accumulation of proteoglycans and hyaluronan in culprit lesions: insights into plaque erosion. *Arterioscler Thromb Vasc Biol*. 2002;22:1642–1648.
29. Burke AP, Farb A, Malcom GT, Liang Y, Smialek J, Virmani R. Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. *Circulation*. 1998;97:2110–2116.
30. Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol*. 1995;26:57–65.
31. Teraguchi I, Imanishi T, Ozaki Y, et al. Impact of glucose fluctuation and monocyte subsets on coronary plaque rupture. *Nutr Metabol Cardiovasc Dis*. 2014;24:309–314.
32. Gu L, Okada Y, Clinton SK, et al. Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low density lipoprotein receptor-deficient mice. *Mol Cell*. 1998;2:275–281.
33. Rinder HM, Bonan JL, Rinder CS, Ault KA, Smith BR. Activated and unactivated platelet adhesion to monocytes and neutrophils. *Blood*. 1991;78:1760–1769.
34. Ozaki Y, Imanishi T, Teraguchi I, et al. Association between P-selectin glycoprotein ligand-1 and pathogenesis in acute coronary syndrome assessed by optical coherence tomography. *Atherosclerosis*. 2014;233:697–703.
35. Holvoet P, Vanhaecke J, Janssens S, Van de Werf F, Collen D. Oxidized LDL and malondialdehyde-modified LDL in patients with acute coronary syndromes and stable coronary artery disease. *Circulation*. 1998;98:1487–1494.
36. Matsuo Y, Kubo T, Okumoto Y, et al. Circulating malondialdehyde-modified low-density lipoprotein levels are associated with the presence of thin-cap fibroatheromas determined by optical coherence tomography in coronary artery disease. *European Heart J Cardiovasc Imag*. 2013;14:43–50.
37. Kato R, Mori C, Kitazato K, et al. Transient increase in plasma oxidized LDL during the progression of atherosclerosis in apolipoprotein E knockout mice. *Arterioscler Thromb Vasc Biol*. 2009;29:33–39.
38. Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med*. 1985;312:1205–1209.
39. Booyens J, van der Merwe CF, Katzeff IE. Chronic arachidonic acid eicosanoid imbalance: a common feature in coronary artery disease, hypercholesterolemia, cancer and other important diseases. Significance of desaturase enzyme inhibition and of the arachidonic acid desaturase-independent pathway. *Med Hypotheses*. 1985;18:53–60.

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40. Hasegawa T, Otsuka K, Iguchi T, et al. Serum n-3 to n-6 polyunsaturated fatty acids ratio correlates with coronary plaque vulnerability: an optical coherence tomography study. *Heart Ves*. 2014;29:596–602.
41. Wakabayashi Y, Funayama H, Ugata Y, et al. Low eicosapentaenoic acid to arachidonic acid ratio is associated with thin-cap fibroatheroma determined by optical coherence tomography. *J Cardiol*. 2015.
42. Omland T, de Lemos JA, Sabatine MS, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med*. 2009;361:2538–2547.
43. Lee T, Murai T, Yonetsu T, et al. Relationship between subclinical cardiac troponin I elevation and culprit lesion characteristics assessed by optical coherence tomography in patients undergoing elective percutaneous coronary intervention. *Circ Cardiovasc Intervent*. 2015;8.
44. Hsieh CC, Yen MH, Liu HW, Lau YT. Lysophosphatidylcholine induces apoptotic and non-apoptotic death in vascular smooth muscle cells: in comparison with oxidized LDL. *Atherosclerosis*. 2000;151:481–491.
45. Mallat Z, Lambeau G, Tedgui A. Lipoprotein-associated and secreted phospholipases A(2) in cardiovascular disease: roles as biological effectors and biomarkers. *Circulation*. 2010;122:2183–2200.
46. Gu X, Hou J, Yang S, et al. Is lipoprotein-associated phospholipase A2 activity correlated with fibrous-cap thickness and plaque volume in patients with acute coronary syndrome? *Coron Artery Dis*. 2014;25:10–15.
47. Ferrante G, Nakano M, Prati F, et al. High levels of systemic myeloperoxidase are associated with coronary plaque erosion in patients with acute coronary syndromes: a clinicopathological study. *Circulation*. 2010;122:2505–2513.

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