

Consolidated and emerging inflammatory markers in coronary artery disease

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Abstract

Coronary artery disease is an event of atherosclerosis characterized by a chronic vascular inflammation. Risk factors like obesity, diabetes mellitus, hypertension, smoking, hypercholesterolemia and positive family history sometimes are not sufficiently adequate to the enhancement of cardiovascular risk assessment. In the past years numerous biomarkers, like C reactive protein, cytokines and adhesion molecules, have been observed to be related to adverse cardiovascular prognosis. Recently, several studies found an association among inflammatory biomarkers and cardiovascular diseases suggesting their utility to identify the risk of an acute ischemic event and the detection of vulnerable plaques. The emerging

inflammatory markers are well divided for diagnosis and prognosis and plaque instability of coronary artery disease. Some of them, the lectin-like oxidized low density lipoprotein receptor-1 can be important both in diagnosis and in the evaluation of plaque instability, other are inserted in the above reported classification. The emerging inflammatory markers in acute-phase include amyloid A, fibrinogen and pentraxin 3 while myeloperoxidase, myeloid-related protein 8/14 and pregnancy-associated plasma protein-A are recognize markers of plaque instability. Lastly, some studies demonstrated that circulating miRNAs are involved in coronary artery disease, acute myocardial infarction and heart failure.

Key words: Coronary artery disease; Plaque instability; Inflammation; Acute phase; Biomarkers

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Core tip: In this review we want to focus the reader's attention on the differences between inflammatory markers of cardiovascular risk already accepted by the scientific community and the emerging markers in order to encourage the healthcare services to improve laboratory techniques in early diagnosis and more precise evaluation of the risk. Is also important to use a classification according to the stage where the patient is located regarding emerging inflammatory markers for diagnosis, prognosis and plaque instability.

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INTRODUCTION

Atherosclerosis is largely recognized as a chronic inflam-

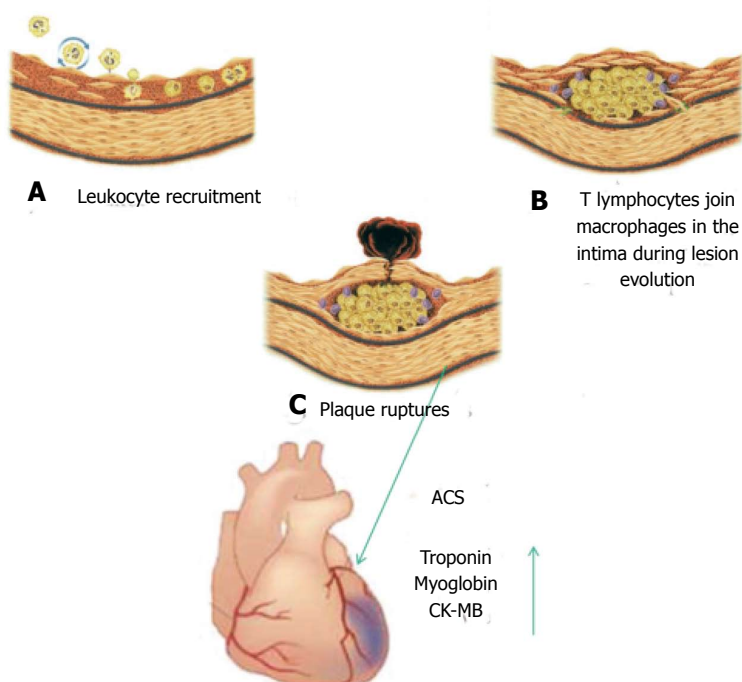


Figure 1 Phases of coronary atherosclerosis. Events implicated in the progression of acute coronary syndrome (ACS).

matory disorder caused by vascular and extravascular factors^[1,2] and coronary artery disease (CAD) is its common manifestation. CAD could result in the development of acute coronary syndrome (ACS), which is often associated with breakage of an atherosclerotic plaque and partial or complete thrombosis of the related artery.

In these years a large number of studies permitted a better knowledge of the events implicated in the progression of ACS: here we summarize them (Figure 1). In these processes there is a recruitment of macrophages, that secretes lytic enzymes such as metalloproteinases. The atheroma core is constituted by foam cells and extracellular lipids shrouded by of smooth-muscle cells and collagen matrix. Plaque ruptures release adhesion molecules and soluble factors, such as D-dimers, von Willebrand factor and plasminogen activator inhibitor-1 that have an important role in thrombus formation. In a few hours after thrombus formation, but before the initiation of coronary ischemia, albumin is released. Troponin, myoglobin, and creatine kinase-MB are time-dependent release components associated with myocardial necrosis^[3] (Figure 1). The extent of these events influences the circulating troponin level^[4]. Therefore it is important to identify the fundamental steps leading to atherosclerotic plaque rupture.

Adequate risk assessment remains the most challenging in individuals classified into low or intermediate risk categories. Inflammation is important in the progression of atherosclerosis and in plaque rupture^[1,5]. For this reason, numerous inflammatory markers have been extensively investigated as potential candidates for the enhancement of cardiovascular risk assessment.

Several recent studies have demonstrated the role of inflammation in mediating the stage of CAD, often caused by lipid accumulation.

Moreover the different part of atherogenesis could be related to inflammatory biomarkers that are important for clinical diagnosis, treatment and prognosis of patients with CAD. However, because conventional risk factors do not explain the changes in atherosclerosis, efforts have focused on developing novel biomarkers which identify vulnerable plaques and cardiovascular disease^[6,7].

These new laboratory biomarkers should be standardized in variability, sensitivity and specificity from established risk markers. Finally, the cost of the assays has to be acceptable. In this review we analyze the inflammatory markers now considered valid in the stratification of risk for CAD and those emerging, checking if new ones can express something more than the standardized biomarkers.

CONSOLIDATED MARKERS

C-reactive protein

C-reactive protein (CRP), a pentraxin composed of 5 subunits, is an inflammatory marker that may increase in various pathological situations, synthesized mainly in the liver, but it is also produced by leukocytes and adipocytes^[8,9].

According considerable evidence, during infection or tissue necrosis circulating CRP may increase 50000 times, but it is also regarded as an independent variable of future cardiovascular events^[10].

CRP fosters antigen presentation and phagocytosis attaching to phosphocholine that is usually found in cell membranes and polysaccharides in prokaryotes and fungi and binding to complement C1q complex and factor H^[11,12].

Moreover it can attach low density lipoprotein (LDL), and be identify within the plaque^[13] where it participates to inflammatory atherogenic processes^[14]. CRP is elevated

in patients with acute and chronic coronary syndromes in relation to the composition of the plaque^[15,16] and is related to the complications of heart failure^[17]. Low plasma levels of CRP indicate a good state of health^[18], while increase when the style of life worsens. The MONICA Augsburg Study shows that low quality “Western” diet with low consumption of vegetables, fruit and fiber, extensive use of saturated fat, low physical activity and obesity, are associated with higher CRP levels^[19].

Therefore, increment of CRP plasma concentration reflects not good lifestyle choices that lead to a metabolic disequilibrium and inflammation. The study of a large population has revealed that an increase in the levels of CRP (> 3 mg/L, elevated levels) was associated with mortality of 22962 subjects^[20].

Ridker *et al.*^[21] showed that CRP was a better biomarker of cardiovascular diseases than LDL cholesterol. However when measured together, they give better prognostic detail than measured separately^[21]. A large prospective study documented a strong association between CRP predictive power and the risks for coronary artery disease^[22,23]. Moreover, the Canadian Cardiovascular Society suggested that CRP evaluation in patients at “intermediate risk”, could represent a predictive risk of a cardiovascular event from 10% to nearly 20% within the subsequent 10 years^[24]. In agreement with this observation, the National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines and the American College of Cardiology Foundation-AHA Task Force on Practice Guidelines affirmed that the evaluation of CRP levels was acceptable for patients at intermediate risk^[25,26].

Another study regarding people at intermediate risk for a cardiovascular event showed that the values of CRP and fibrinogen could help to prevent one additional event over a period of 10 years for every 400 to 500 people screened.

Current knowledge, however, suggests that the CRP concentration might reflect the vulnerability of the atheromatous lesion and the prospect of plaque rupture^[5,27,28]. The development of high-sensitivity CRP (hs-CRP) assays has been useful to investigate its role in predicting first cardiovascular events.

Cytokines

Interleukin 1 (IL-1), IL-6, IL-10, monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor alpha (TNF- α) are the main investigated cytokines among those which predict cardiovascular events involved in vascular inflammation and atherosclerosis^[29,30]. IL-1 and IL-6, regulate CRP production *via* direct stimulation of the hepatocytes^[31]. IL-6 may increase plaque instability modulating the expression of TNF- α , and MCP-1^[32]. Elevated IL-6 levels in healthy men correlated with increased risk for future MI independently from hs-CRP^[33]. According to some author IL-6 seems to be a marker more sensitive and specific than CRP in vascular inflammation and CRP studies show a weaker association with cardiovascular disease than cytokines^[34,35]. In the Framingham study (FRISC-II), IL-6 increment above 5 ng/L

was related with a mortality from 6- to 12-mo without a relationship with troponin and hs-CRP^[36].

Therefore, IL-6 plasma concentration results as an effective independent index of increased mortality in unstable CAD and characterizes subjects who advantages of an initial invasive strategy. In addition, the intensity of plaque inflammation and its vulnerability seems to be linked with plasma IL-6 levels^[36].

Some studies showed that IL-1 could have a regulatory function in the atherosclerotic development suggesting its modulation in vascular smooth muscle cell mitogenesis^[37,38], in leukocyte adherence to vascular wall^[39,40], in LDL metabolism^[41,42], in extracellular matrix proteins^[43] and in vascular permeability^[44]. Moreover, IL-1 has been found to suppress vascular contractility^[45] and induce pro-coagulant activity^[46].

Several years ago, increased levels of IL-1 α and IL-1 β were detected in human atherosclerotic plaque, suggesting their local synthesis^[47]. Moreover, IL-1 protein has been detected in macrophages from damaged carotid arteries^[48]. In the macrophages IL-1 β secretion seems to be induced by the cholesterol crystals present into the plaque^[49].

The presence of increased IL-1 β plasma concentration in patients affected by unstable angina indicates its important role in the acute stage^[50]. However, in mouse models conflicting roles have been reported for IL-1 β : on the one hand the absence of IL-1 β is associated with a reduction of atherosclerotic severity^[51], on the other hand, IL-1 β inactivation seems to be related to atherosclerotic plaque stability^[52].

TNF- α plays a role in myocardial dysfunction and remodeling after acute coronary events^[53]. On behalf of this effect, the CARE study showed that TNF-levels increased in recurrent coronary events after a MI compared with controls^[54].

The chemokine MCP-1 recruits monocytes into the arterial wall activating these cells to induce endothelial injury^[55]. In addition, a positive correlation between MCP-1 levels and the extent of coronary atherosclerosis was found in the coronary circulation of patients with unstable angina^[56,57]. Moreover, MCP-1 levels have been found to correlate with older age^[58], hypertension^[59], hypercholesterolemia^[60], and kidney failure^[61], while an inverse correlation has been observed with estrogen replacement^[62] and HMG-CoA reductase inhibitor therapy^[60]. In several studies with small number of subjects, plasma MCP-1 levels were highest among patients with acute coronary syndromes (ACS), intermediate with stable coronary disease, and lowest among healthy control subjects.

IL-10 is an important factor for its anti-atherogenic property. In fact patients with high IL-10 levels had a reduced mortality compared with those that have only elevated CRP^[63].

In 158 patients affected by stable CAD, during a 7-year follow-up period, the multivariate analysis of 10 cytokines showed IL-8 as the only independent marker for cardiovascular diseases^[64]. In summary, even if the results are still controversial, in our opinion among consolidated

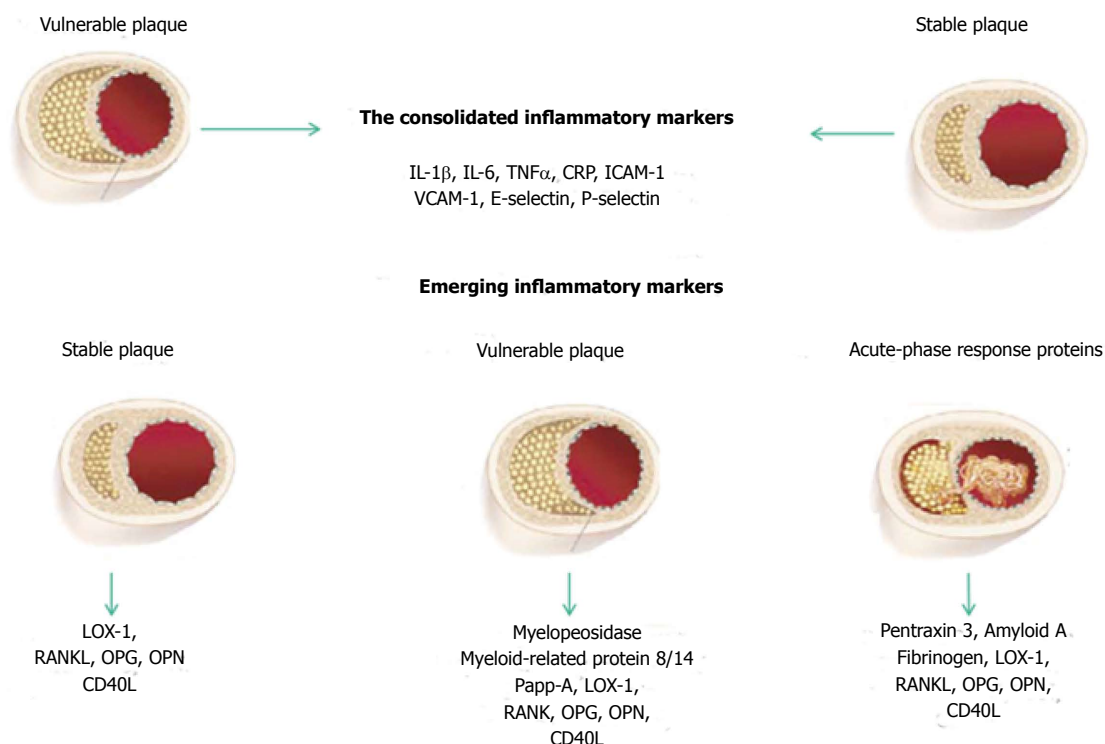


Figure 2 Consolidated and emerging inflammatory markers. A new approach to establish the risk for coronary artery disease. Today new inflammatory markers are studied and classified according to their role in the development of coronary artery disease. TNF- α : Tumor necrosis factor alpha; IL: Interleukin; CRP: C-reactive protein; CAM: Adhesion molecules; OPG: Osteoprotegerin; OPN: Osteopontin. PAPP-A: Pregnancy-associated alpha plasma protein A; LOX-1: Lectin-like oxidized low-density lipoprotein receptor-1.

cytokine, IL-6 represents the best prognostic biomarker in CAD.

Adhesion molecule

Although very broad, adhesion molecules (CAMs) may be regarded as inflammatory markers of cardiovascular risk. Soluble CAMs (ICAM-1, VCAM, P and E selectins) are released from the surface of the cell and reflect cellular activation^[65]. CAMs induce the bind between leucocytes, platelets and vascular wall^[66]. After the adherence to the endothelium, the leucocytes transmigrate into the arterial wall determining the first phase of atherosclerosis^[66].

Several studies reported an association between the increase of plasma CAM concentration and the risk of cardiac events^[34,67,68], but their role in CAD prognosis have not been established because their finding are still quite confused.

In patients with stable CAD, CAMs plasma concentrations were measured and informations on cardiovascular events were collected for some years. Among CAMs, only VCAM-1 resulted independently significant with future cardiovascular events^[69].

In agreement with this study, other authors observed that the concentrations of sVCAM-1 > 780 ng/mL and CRP > 3 mg/L corresponded to a sensitivity > 90% for predicting future events in patients affected by acutely ACS^[70].

On the contrary, other studies did not confirm these findings for sVCAM-1; instead, they suggested that CRP and sICAM-1 were useful for identifying the risk of a cardiac event in patients with unstable angina

who underwent coronary stenting^[71]. Finally, another prospective study showed that only P-selectin and cardiac troponin I, but not the other CAMs, were significantly higher among patients who had a serious cardiac event during the subsequent 3 mo^[72].

EMERGING INFLAMMATORY MARERS

The lack of “traditional” risk factors cannot make totally free of the disease and new emerging markers of inflammation have been studied in the effort to identify biomarkers predicting the risk, and at the same time reflecting plaque instability in the early or in the acute phase. On the bases of these studies, we must point out that today is also in use a classification according to the stage where the patient is located (Figure 2).

EMERGING INFLAMMATORY MARERS FOR DIAGNOSIS, PROGNOSIS AND PLAQUE INSTABILITY

Lectin-like oxidized low-density lipoprotein receptor-1

Clinical studies have demonstrated that well-known coronary risk factors, including metabolic diseases, hypertension, obesity and smoking, are associated with oxidative stress. When the LDL are exposed to oxidative stress, they are caught in the vessel and oxidized (ox-LDL). Oxidized LDL promotes the synthesis of a large variety of cytokines and chemokines by the endothelium. Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1)

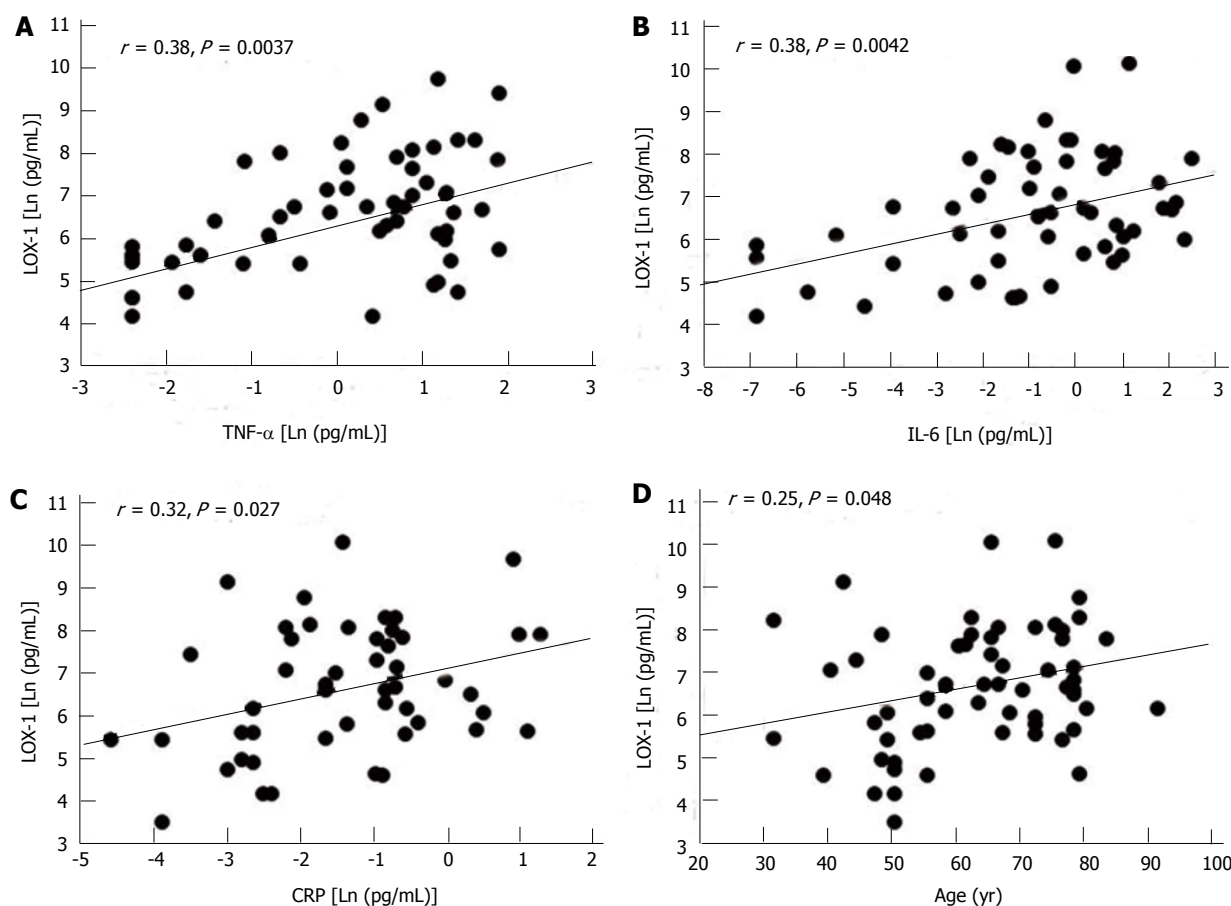


Figure 3 Regression analysis of LOX-1. From Lubrano *et al.*^[76], 2008. Positive association between circulating levels of LOX-1 and inflammatory markers. TNF- α : Tumor necrosis factor alpha; IL: Interleukin; CRP: C-reactive protein; LOX-1: Lectin-like oxidized low-density lipoprotein receptor-1.

appears to be an important receptor for ox-LDL in endothelial cells^[73]. LOX-1 not only allows the passage of oxidized lipids in the cells, but as already described, may cause endothelial dysfunction/apoptosis, inflammation, and the increase smooth muscle cell number favoring the formation of atheroma^[74-76].

Moreover LOX-1 increment was observed to be associated with cardiovascular risk factors like hypertension and metabolic disorder. In a population of patients affected by CAD, our previous studies showed a positive relationship between circulating levels of LOX-1 and inflammatory markers: this work suggested also that LOX-1 levels increased with the severity of the disease^[76] (Figure 3). Other authors underlined the importance of this novel biochemical marker for the stratification risk of the population and therapeutic strategy for CVD.

Overt cardiovascular disease is typically preceded by a long period of sub-clinical cardiovascular disease and sub-clinical atherosclerosis can be present for decades before the occurrence of a myocardial infarct event. Soluble LOX (sLOX-1) has shown to be informative either early or late in the process disease^[77-79].

Recent study observed that the circulating levels of sLOX-1 are very high in acute coronary syndrome and that the plateau value is reached before troponin T, highlighting the instability of the plaque^[80].

It has been reported that serum levels of sLOX-1 are also specifically elevated in acute coronary syndrome and the peak value has been reported to rise before troponin T^[80]. In conclusion, sLOX-1 levels are related to the prognosis of acute coronary syndrome and reflect the instability of plaque^[78].

Nuclear factor-kappa B, osteoprotegerin, osteocalcin, osteopontin, CD40

Receptor activator of nuclear factor Kappa-B ligand (RANKL) is the ligand of the receptor inducer factor- κ B (NF- κ B) and belongs to the family of cytokines TNF-related. It is synthesized by T cells and stromal/osteoblastic cells and is a strong chemotactic factor for human monocytes^[81]. RANKL-stimulated microvascular endothelial cells favor monocyte adhesion and trans endothelial migration thus increasing the recruitment of osteoclast- and osteoblast like cell precursor^[81,82].

Osteoprotegerin (OPG) synthesized in osteoblasts is part of the TNF super-family. It binds to RANKL thereby preventing interaction with its transmembrane receptor^[83].

RANKL and OPG have been shown to be potentially valuable markers for a better assessment of coronary calcification and cardiovascular risk associated with it. It has been observed that RANKL and OPG may play a key role in maturation and calcification of atherosclerotic

plaque^[84,85]. In fact these factors increased in serum of post-infarction of atherosclerotic animal models and of humans with unstable angina^[86,87].

Osteocalcin, a protein found in bone and dentin and also synthesized in mononuclear cells, has been related with the severity of aortic calcification^[88].

Osteopontin (OPN), an extracellular matrix protein and pro inflammatory cytokine, facilitates the recruitment of monocytes/macrophages through its adhesive domain^[89] and promotes the inhibition of vascular calcification. In fact it is increased in patients with vascular calcification resulting more like a marker than a mediator of atherosclerosis progression^[90].

CD40, a member of TNF family, is also a stimulatory receptor on antigen-presenting cells of the immune system that induces inflammatory processes through the binding of the CD40 ligand (CD40L). Elevated levels of soluble CD40L (sCD40L) have been found in patients with hypercholesterolemia, ACS and cardiovascular disease. sCD40L is also associated with atherosclerosis and plaque instability^[91]. In the CAPTURE trial, increased sCD40L (> 5 g/L) was related to a 6-mo mortality or nonfatal MI suggesting that sCD40L may be an independent risk marker of cardiovascular events. Statins, antihypertensive drugs, and antiplatelet agents have been shown to modulate it^[92]. Moreover, sCD40L was found to be increased in smokers and positively associated with both total cholesterol and biomarkers of inflammation. However, it was not reported as an independent biomarker for the risk of MI^[93].

ACUTE-PHASE RESPONSE PROTEIN

Quantitative and qualitative changes of inflammatory markers are able to identify the acute stage of the disease. The plaque ruptures cause the consequent platelet aggregation and subsequent thrombosis, the final stage in which atherosclerosis leads to acute ischemic syndromes of AMI and sudden death^[5].

The literature well documented the association between serum concentrations of acute phase proteins and the onset of coronary heart disease and myocardial infarction^[94,95]. The emerging inflammatory markers in the acute-phase include pentraxin 3 (PTX3), amyloid A, and fibrinogen^[96-102].

Pentraxin-3

Pentraxins are a superfamily of soluble proteins with cyclic multimeric structure^[103]. Among these, PTX3 a protein characterized by a long N-terminal domain, results as an important player in immunity and inflammation^[104]. Dendritic cells, macrophages and endothelial cells produce PTX3 in response to IL-1 and TNF^[105]. Moreover increased plasma PTX3 levels were observed in patients with cardiovascular disease and resulted also more closely related than CRP levels in acute phase of cardiac damages^[106] suggesting that it could be a sensitive and specific prognostic indicator^[107].

It has been also hypothesized an association of PTX3 in individuals with stable coronary artery disease and kidney dysfunction. However, an adjustment for the

estimated glomerular filtration rate modestly attenuated these associations^[108]. By immune histochemical staining PTX3 was strongly expressed on the surface of lumen and within the atherosclerotic plaque in humans and animal models^[96,97,109]. Moreover, in the same experimental models, soluble PTX3 increased in the early phase after ischemic heart events and PTX3 mRNA and protein expression enhanced in the ischemic area of the heart^[110].

In a prospective study of patients with myocardial infarction and ST elevation, PTX3 predicted 3-mo mortality while other markers such as the liver-derived short pentraxin CRP or NT-proBNP, TnT, CK did not^[107]. In patients with unstable angina pectoris within the six hours of the chest pain, PTX3 resulted to be more specific for ACS than neutrophil activating peptide-2 and cardiac troponin I (cTnI)^[111,112].

Amyloid A

Serum amyloid A (SAA) proteins are a family of apolipoproteins associated with high-density lipoprotein (HDL) and are now considered emerging markers of inflammation. In fact elevated SAA levels are present in coronary artery disease and indicate worse prognosis in CAD. Therefore actions involved to reduce SAA levels could improve the conditions of patients with acute CAD^[113].

A study of Kosuge *et al*^[99] reported that, in patients with ACS, increased SAA levels were associated with cardiovascular events within 30 d, without any relationship with CRP level. Therefore these data indicated SAA more useful predictor than CRP in these patients.

In the high serum SAA group the left ventricular ejection fraction, measured during follow-up, was significantly lower than in the low serum SAA group and more frequent complications, such as cardiac rupture, carcinogenic shock, subacute thrombosis, and cardiac death, were also present^[100].

Furthermore SAA levels were quite well associated with coronary artery disease with a predictive risk for cardiovascular events within 3 years, while this did not happen with hs-CRP^[114]. In a substudy of TIMI 11A, elevated SAA levels predicted increased risk of 14-d mortality in patients with ACS^[115]. In a Women Ischemia Syndrome Evaluation study, in which women were referred for coronary angiography because of suspected ischemia, elevated SAA values were correlated with angiographic severity of CAD and 3-year risk for cardiovascular events^[114]. At the same time, no relationship was observed between SAA levels and recurrent Coronary Events^[116].

Fibrinogen

Several studies have indicated fibrinogen as a predictive marker in CAD^[117]. Fibrinogen is involved in platelet aggregation, endothelial injury, plasma viscosity and plays a central role in the formation of thrombus.

Epidemiological data have shown the important predictive role of fibrinogen in CAD, identifying it as an emerging risk factor because its measurement may improve the estimation of absolute risk obtained by conventional

risk factor for CV^[117].

Although it is still discussed the role of fibrinogen as inflammatory markers of risk, many studies indicated an association of hyperfibrinogenemia with atherothrombosis.

Already in the past, some authors have demonstrated that the risk estimation for CAD could be double when fibrinogenemia was also evaluated^[118].

Emerging Risk Factors Collaboration showed that, the measurement of fibrinogen level in patients at risk for CAD, could prevent an additional event in the next 10 years for every 400-500 people studied^[119].

However, also recent results show that the evaluation of fibrinogen during MI may be useful in identifying patients at high risks for future acute events^[102].

BIOMARKERS OF PLAQUE INSTABILITY

The main cause of the acute myocardial infarction (AMI) is the plaque rupture, so that it is important to investigate new markers for early diagnosis of plaque instability.

Due to its sensitivity and specificity, troponin is commonly used in the diagnosis of ACS, even if it provides only indirect details on myocardial necrosis induced by embolization of atherothrombotic material, late event of ACS.

Inflammation is a process that is intensified in plaque instability, so that the markers of inflammation may provide indications of cellular processes related to its formation before it occurs myocardial necrosis^[120].

Myeloperoxidase

Myeloperoxidase (MPO) is an enzyme produced by leukocytes that induces the formation of oxygen free radicals and is considered to be one major contributor in the formation and rupture of the plaque^[121].

In patients with ACS, MPO produced by neutrophils, is considered a marker of plaque vulnerability as noted by several studies^[122, 123].

Yunoki *et al*^[124], 2013 observed that the plasma levels of MPO have a significant inverse correlation with levels of paraoxonase-1 bound to HDL, especially, in patients with stable and unstable angina pectoris, suggesting that a mismatch between pro oxidants and anti-oxidants may contribute to the progression of coronary plaque instability^[124].

Myeloid-related protein 8/14

Myeloid-related protein 8/14 (MRP8/14), is a heterodimer consisting of two proteins that bind calcium, calgranulin A and B, which play an important role in the signaling pathways of calcium, in cell cycle progression, cell differentiation, and in the interaction between the cytoskeleton and membrane^[125]. MRP-8/14, also called calprotectin, is synthesized by activated monocytes and neutrophils, and is a pro-inflammatory protein expressed in atherosclerotic plaques.

High concentrations of MRP8/14 in the systemic circulation may reveal the presence of plaques before

necrosis markers suggesting it as a good candidate for the management of ACS unstable.

PAPP-A

PAPP-A is a high-molecular-weight zinc-binding metalloproteinase. PAPP-A was independently associated with recurrent cardiovascular events in patients with ACS. This finding supported the potential usefulness of PAPP-A as a biomarker in patients with ACS^[126]. Moreover as described by Mahto *et al*^[127] PAPP-A is the reliable marker which can discriminate the cases of MI from unstable angina and controls^[127]. Another study has suggested PAPP-A to be a predictor of mortality or myocardial infarction in patients with ACS^[128].

Role of microRNAs in CAD

MicroRNAs (miRNAs) are short non-coding RNA molecules that regulate gene expression post-transcriptionally through suppression or degradation of target messenger RNA (mRNA).

MiRNAs were found in the circulating blood and are differently induced in patients with CAD, AMI, and heart failure^[129-132].

Of interest is miR-155, which proved to be a new component of inflammatory signal transduction pathways in the pathogenesis of atherosclerosis. In fact the expression of miR-155 is considered to be a prospective marker for predicting the prognosis of CAD since it is found to be expressed mainly in patients with CAD compared to healthy subjects^[133].

CONCLUSION

Inflammatory biomarkers appear to have an important prognostic value in patients with cardiovascular disease and may be useful in the diagnosis of apparently healthy subjects without known CAD who cannot be assessed with conventional risk factors.

Inflammatory biomarkers may have prognostic value for future cardiovascular risk among those at high risk or with documented cardiovascular disease. They also may be useful for identifying apparently healthy individuals, without known CAD, who may be at a higher risk than estimated by traditional risk factors.

Although recent data demonstrate that there is a close association between inflammatory biomarkers and coronary artery disease, further studies must be carried out taking into account also some important criteria typically used in the selection of a new biomarker: discrimination, calibration and reclassification, i.e. the ability of a test to discern between those that will face the disease from those that will be free, the assessment of the risk factor predicted and observed, classification in categories of low, intermediate and high risk for CAD^[134].

In our opinion the best candidate for this role is LOX-1; it was observed to be associated with cardiovascular risk factors like hypertension and metabolic disorder, showing its positive relationship with inflammatory markers and

its increment with the severity of the disease^[76] (Figure 3). Moreover it was elevated in acute coronary syndrome and the peak value has been reported to rise before troponin T reflecting the instability of plaque^[80].

In conclusion, the findings observed in a decade showed that LOX-1 could represent an important marker for clinical characterization of coronary artery disease and a target for new drugs to reduce its expression and production.

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