JMB 2008; 27 (2) DOI: 10.2478/v10011-008-0008-1

UDK 577.1 : 61 **ISSN 1452-8258**

JMB 27: 148–153, 2008

Review article
Pregledni članak

BIOCHEMICAL MARKERS OF ATHEROSCLEROSIS

BIOHEMIJSKI MARKERI ATEROSKLEROZE

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Summary: This paper is a brief review of some lipid parameters and serum markers of inflammation in a view of their predictive relevance for the atherosclerotic disease. A discourse on the importance of measuring different lipids and lipoproteins, concentration of LDL particles and apolipoprotein levels is still underway. Also, the recommendations for apolipoprotein (a), phenotypization and other lipid markers have not yet been established. In recent years the recommendations imply simultaneous measuring of multiple markers and calculating the lipid index values such as lipid tetrad index (LTI), lipid pentad index (LPI) and atherogenic index of plasma (AIP). Several circulating markers of inflammation such as C-reactive protein, serum fibrinogen and elevated leukocyte number, are consistently associated with atherosclerosis. In spite of a lack of evidence on measuring the C-reactive protein in a wide population, the guidelines for its application in diagnostics and therapy of coronary heart disease were developed. Some proinflammatory cytokines, adhesion molecules and markers of leukocyte activation are promising markers, requiring, however, more detailed prospective evaluation. The question to be elucidated is if these inflammatory markers are directly involved in the pathogenic process.

Keywords: atherosclerosis, biochemical markers, lipids, lipoproteins

Kratak sadržaj: U ovom radu razmatrani su samo neki lipidni parametri i serumski markeri inflamacije u pogledu njihove prediktivne povezanosti s aterosklerotskom bolešću. Nastavlja se debata o značaju merenja različitih lipida i lipoproteina, uključujući koncentraciju LDL čestica i nivoe apolipoproteina. Takođe, nisu uspostavljene preporuke za apolipoprotein (a) fenotipizaciju i druge lipidne markere. Poslednjih godina preporučuje se simultano merenje nekoliko markera i izračunavanje lipidnih indeksa kao što su lipid tetrada index (LTI), lipid pentada index (LPI) i aterogeni indeks plazme (AIP). Nekoliko cirkulišućih markera inflamacije, npr. C-reaktivni protein, serumski fibrinogen i povišenje broja leukocita, dosledno su udruženi s aterosklerozom. Iako nema dokaza za korisnost merenja C-reaktivnog proteina u široj zajednici, formirane su preporuke za njegovu upotrebu u dijagnostici i lečenju koronarne bolesti srca. Neki proinflamatorni citokini, adhezioni molekuli i markeri leukocitne aktivacije su obećavajući markeri, ali zaslužuju dalja prospektivna ispitivanja. Pitanje koje zahteva odgovor je i da li su ti inflamatorni markeri direktno uključeni u patogeni proces.

Ključne reči: ateroskleroza, biohemijski markeri, lipidi, lipoproteini

Introduction

Coronary heart disease (CHD) is one of the major causes of morbidity and mortality worldwide. Its increasing prevalence is nowadays also recorded in the East European countries (1). The need for identifying risk factors and serum markers of atherosclerosis in the process of early detection and prediction of risk for cardiovascular disease has gained much attention in recent years.

Correlation between atherosclerosis and levels of total-, LDL and HDL cholesterol has well been confirmed and widely accepted in diagnostic practice. This approach is recommended by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) as a basis for screening and treatment of patients with CHD (2). Though principles and recommendations are based on abundant clinical trials, patients with intermediary risk rate make one-third of

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all cases of myocardial infarction (3). Furthermore, higher prevalence of CHD in some populations could only partly be explained by traditional lipid risk factors (4). Therefore, numerous authors focus on elaborating lipid algorithms of high diagnostic accuracy, as well as identifying novel CHD markers (5).

In that respect, the view that atherosclerosis is a disease characterized by low-level vascular inflammation is gaining much attention recently (6). It is well established that local inflammation occurs not only as the formation of plaques, but it plays an important role in the weakening of the fibrous cap of the developed lesions and plaque rupture. The majority of studies investigating the role of markers for systemic inflammation and inflammatory markers of vascular origin established elevated concentrations in patients with atherosclerosis, particularly in those with an unstable coronary disease (7–9). In that respect, there are two questions of outmost clinical importance. First, if circulating markers of inflammation could differentiate between healthy subjects and those with atherosclerotic manifestations. Second, if those markers could differentiate between patients with a stable atherosclerotic disease and those prone to unstable manifestations of atherosclerosis. The question whether the different inflammatory markers are simply markers, or if they actively contribute to the development and progression of an atherosclerotic disease, still remains unclear (9–11).

Lipid markers of atherosclerosis

Plasma levels of lipids and lipoproteins have been well established as strong predictors of CHD. Hence, NCEP ATP III recommends determination of the lipoprotein profile on empty stomach at 5-year intervals in adults aged 20 years and above, i.e. total serum cholesterol, LDL cholesterol, HDL cholesterol and triglyceride contents (2).

Along with the abundant evidence on a stronger positive correlation of apolipoproteins (apo) with atherosclerosis and coronary events than that of the plasma lipoproteins, there still are some opposing attitudes on preferable quantifications to be taken – either cholesterol carried by lipoprotein particles or their actual concentration expressed as apo B and apo AI (12).

Lipoproteins are spherical molecules that transport different amounts of cholesterol and triglycerides in the bloodstream. LDL and HDL particles are rich in cholesterol, while VLDL and chylomicron particles predominantly transport triglycerides The apoB is present on the surface of LDL, VLDL and chylomicrons (one molecule at each particle), while apo A-I resides on HDL particles. Though small amounts of apo A-I are present on apoB-containing lipoproteins, apo B is never a constituent of HDL (13).

Conventional lipid tests determine the amount of cholesterol and triglycerides transported by all particles within the lipoprotein classes or in total plasma. Thus, cholesterol and triglycerides may be regarded as surrogate markers for their carrier-lipoprotein particles. Rationale in support of quantifying the cholesterol level, however, implies the fact that cholesterol esters are the main lipid components responsible for the development of atherosclerosis, hence are present in the foam cells and extracellular plaque matrix, and susceptible to oxidation that could increase their atherogenic potential (14).

There is strong evidence supporting the apolipoprotein concept, stating that the concentration of atherogenic particles, to which the arterial wall is exposed, is a more important parameter that is assessed using apoB concentration. Moreover, apoB adheres these particles to proteoglycanes in endothelial cells, as well as in plaque matrix, thus its plasma concentrations are directly associated with the amount of particles entering and remaining in the plaque (12, 13, 15). The view that apolipoproteins are of better predictive value than LDL and HDL cholesterol is supported by the fact that there is an active exchange of lipid components between the lipoprotein particles, which results in a wide variation in cholesterol level in these molecules and corresponding LDL and HDL alterations (15). Besides, it has been suggested that the metabolic »fate« of lipoproteins is determined by protein content rather than the lipid content, which is due to multiple roles of apolipoproteins in lipid metabolism (4).

Relative significance of the level of LDL cholesterol and apo B-containing lipoprotein particles is partly determined by the measurement method. Apo B is measured directly, mostly by immunonephelometric analysis of the plasma, on empty stomach or postprandially (16), whereas LDL cholesterol is mostly calculated indirectly as the difference of total cholesterol minus HDL-cholesterol and VLDL-cholesterol. Thereat, the quantity of VLDL cholesterol is also calculated by dividing the triglyceride value by 2.2, and it is accurate only for concentrations below 4.5 mmol/L (17). Contrary to those limitations, apo B offers not only a good approximation of LDL particles level, but also of the total concentration of atherogenic lipoproteins. In that respect, apo B can be considered a superior indicator of the global atherogenic risk over the sole quantification of LDL cholesterol and triglyceride levels, particularly in conditions of hypertriglyceridaemia characterized by high VLDL and low LDL levels (12).

Several prospective studies demonstrated that the concentration of lipoprotein particles, rather then their cholesterol content, is strongly correlated with increased risk for fatal myocardial infarction, even after long-term statin treatment; however, these studies also revealed that LDL-cholesterol is a target lipid variable, which corresponds with the recommendations of international therapeutic guidelines (12, 13, 18). Measuring of apo B and A-I, however, sig-

nificantly improves the prediction of prospective cardiac death, particularly in the elderly population, in whom the conventionally quantified cholesterol shows reduced predictive value (18), as well as in children and adolescents originating from parents with premature atherosclerosis (4).

Another approach to the measurement of atherogenic lipoproteins is the use of non-HDL cholesterol, which is easily calculated by deducting the HDL cholesterol from the total cholesterol value, with no need for previous fasting of the patient. This is the cholesterol contained in VLDL and LDL particles, atherogenic triglyceride-rich lipoproteins, cholesteryl ester-enriched remnants of triglyceride-rich lipoproteins, and lipoprotein(a). Consequently, the non-HDL cholesterol is essentially the cholesterol analogue to an apo B level, having a higher correlation coefficient in comparison with the LDL cholesterol concentration, even after statin treatment (19). Though apo B is a superior predictor of CHD, the non-HDL cholesterol content is easily available within the primary screening of the lipid profile, and according to the recommendations of NCEP ATP III it is identified as a secondary therapeutic target after achieving the target levels of LDL cholesterol (2).

According to the NCEP ATP III guidelines, Lp(a) lipoprotein and predomination of small dense LDL particles (sdLDL) are classified as emerging lipid risk factors for cardiovascular diseases (2). Their importance compared to other diagnostic markers is still controversial, and yet there are no recommendations concerning apo(a) phenotyping and other lipid markers (4, 15).

Having in mind the highly complex etiology of CHD, some recent recommendations have implied simultaneous quantification of several markers and calculation of the lipid index values. Lipid tetrad index (LTI) and lipid pentad index (LPI) are emphasized, incorporating several lipids, lipoproteins, including Lp(a)-lipoprotein and apolipoproteins into their calculation schemes (4, 5, 20). The atherogenic index of plasma (API), defined as a logarithm of triglyceride-HDL cholesterol ratio, closely correlates with the size of lipoprotein particles, which makes it particularly suitable in the diagnostics of atherogenic lipoprotein profile characterized by the predominance of sdLDL (4, 21). Moreover, some studies suggest the formulation of models with increased prognostic value in screening for CHD in comparison with the analysis of single biomarkers, not only of lipid origin (5).

There is a strong belief that the use of such novel bioindexes defining overall atherogenic risk associated with dyslipidemia could enable a more precise evaluation of the atherogenic risk in certain ethnic and geographic areas, where the prevalence of CHD could not be explained by traditional lipid risk factors (20, 22).

Circulating markers of inflammation and atherosclerosis

Epidemiologic and prospective studies evaluating the predictive value of the variety of circulating markers of vascular inflammation focused their attention on a number of them, such as C-reactive protein (CRP), fibrinogen, serum amyloid A (SAA), leukocyte count in peripheral blood, immunoglobulins, adhesion molecules, cytokines and chemokines and leukocyte activation markers (7).

C-reactive protein is a hepatic acute-phase reactant, released as a response to intermediary inflammatory cytokines, interleukin-6 (IL-6), IL-1 and, most probably, tumor necrosis factor-α (TNF-α) (7, 9, 11). As a non-specific biochemical marker of inflammation it is used in assessing different inflammatory stages of the disease, as well as in the diagnostics and therapy of the infection (8).

The association between circulating levels of CRP and numerous cardiovascular risk factors has been well established (7, 8, 23). Moreover, the CRP level is a potent predictor of hypertensia, type 2 diabetes and metabolic syndrome (8, 23).

The prospective association between this marker of systemic inflammation and cardiovascular prognosis was first illustrated in patients with acute coronary syndrome and next (somewhat less consistently) among stable patients after myocardial infarction (8). Several prospective studies in healthy individuals revealed that basal CRP levels are to be considered an independent risk factor for future myocardial infarction, sudden cardiovascular death, stroke and peripheral artery disease, indicating its role in evaluating the global vascular risk in primary and secondary prevention (7, 24). CRP seems to be a more powerful predictor than LDL cholesterol, offering additional prognostic information to that obtained by applying the Framingham risk score (8, 9, 24).

It has been demonstrated that statins, along with their hypolipidemic effects, positively affect the inflammation within the plaque, its stability and the CRP level (8). There are some results suggesting that aspirin, fibrates, niacin and ACE inhibitors, which reduce the incidence of vascular events, also downregulate the CRP level, implicating its potential role in therapeutic guidelines (8, 9).

Guidelines for the application of CRP in the diagnostics and therapy of CHD are defined by The Center for Disease Control and the American Heart Association (CDC/AHA) (25). For the purpose of detecting subclinical inflammation that may reflect vascular inflammation, CRP must be quantified using highly sensitive assays (hsCRP) enabling an accurate measurement of the concentration within the reference interval (26). At least two measurements at two-week intervals must be performed (9). To categorize the risk, cut points according to approximate tertiles

in the adult population have been suggested, i.e. low risk <1.0 mg/L, average 1.0–3.0, and high risk >3.0 (25). Levels above 10 mg/L generally implicate the presence of an acute phase response, requiring a repeated testing (23, 27).

CDC/AHA guidelines do not recommend screening of the general population. For the purpose of risk stratification an additional measurement of hsCRP is suggested, which is an independent risk factor in individuals with intermediary risk and patients with known stable coronary disease and/or acute coronary syndrome (25).

Reports on the predictive value of minor elevations of the serum CRP in atherosclerotic events gave rise to certain controversies and confusions, as those concentrations were detected in about 1/3 of the American population (23). An exhaustive population research confirmed the relatedness with numerous genetic polymorphisms, pertaining to particular demographic and socioeconomic groups, specific dietary habits, minor inflammatory conditions, prevalent minor irritants from the environment, as well as with numerous non-inflammatory medical conditions (23, 27). Concurrently, such a mild elevation of CRP carries generally bad prognostic implications for various conditions, particularly ageing-associated diseases, indicating mortality in ill individuals, as well as in apparently healthy ones. A possible explanation to this view could be that CRP is only an indicator for wide range of conditions that present the risk factors in their own (23).

The association of other acute-phase proteins, mainly fibrinogen and serum amyloid A, the leukocyte count in the peripheral blood with the CHD and numerous traditional risk factors has been well documented (7, 28, 29). Population studies consistently demonstrated a moderate elevation of serum fibrinogen and leukocyte count in peripheral blood in individuals that subsequently developed atherosclerotic disease (8, 28–30). Increased fibrinogen levels were identified as strong predictors of stroke (28).

Several clinical studies demonstrated an association between elevated levels of major proinflammatory cytokines (IL-1, IL-6 and TNF-α) and chemokynes (monocyte chemoattractant protein-1, MCP-1) and increased cardiovascular risk (31). Similar predictive value of IL-6, the main determinant of the acute-phase proteins in the liver, was established with regard to the unfavorable outcome, as that of the CRP (7, 29). Apparently, these inflammation biomarkers, primarily the IL-6, are promising markers of atherosclerosis. The measurement of these molecules still entails certain methodological limitations, thus its use in the routine clinical practice is yet infeasible (31).

Research was also done on the predictive role of soluble adhesion molecules: membrane-bound vascular cell adhesion molecule 1 (VCAM-1), intracellular adhesion molecule (ICAM-1), endothelial leukocyte adhesion molecule (ELAM-1), P-selectin and E-selectin. Their serum levels directly reflect the cell expression of the molecules playing a pivotal role in the adherence of circulating leukocytes to endothelium and their transmigration into the arterial wall. The association between these specific parameters of endothelial activation and the progression of atherosclerotic plaques, especially the carotid ones, has been well established, independently of the traditional factors and hsCRP (1, 20), where ICAM-1 and VCAM-1 show predictive value (7). Aside from certain methodological shortcomings and ambiguities concerning the clearance mechanisms of those molecules, their importance as markers for increased risk in unstable angina is under exhaustive investigation (29).

Table I Proatherogenic and proinflammatory properties of C-reactive protein and other inflammatory markers (9–11).

Properties
a. Complement activation
b. Interaction with cell surface receptors
c. Thrombosis – enhancement of the procoagulant activity/ reduction of fibrinolysis
d. Cellular modulation, recruitment and activation
e. Expression of inflammatory mediators: cytokines, chemokines and adhesive molecules
f. Decrease of the expression and bioactivity of endothelial nitric oxide
g. Interaction with lipids and lipoproteins
h. Enhancement of apoptosis

The activation of leukocytes and/or the immune system can be assessed by the expression of different cell surface antigens (CD11b/CD18, CD40) and receptors in different cell types (CD163 macrophages), by detection of numerous substances excreted from the leukocytes (elastase, myeloperoxidase, secretory type-II phospholipase A2, defensins, cathelicidins and neopterin), and by determining leukocyte aggregation, as well as flow resistance (7, 32, 33). Increase in number of markers of leukocyte activation has mainly been established in case-control studies, by comparing CHD patients with healthy control individuals, whereas some of them were identified in the atherosclerotic lesions, independently correlating with the atherosclerosis grade (7).

The connection of diverse circulating biomarkers of inflammation with atherosclerotic disease could, however, suggest their active involvement in the process of atherogenesis (9, 11). Multiple regression analysis of those markers in the framework of numerous prospective studies revealed their independent effects, i.e. they are likely to act through a variety of different pathological mechanisms (10) (*Table I*).

Conclusion

The evaluation of an absolute clinical applicability of some new marker requires not only its direct

comparison with the LDL cholesterol or with the Framingham risk score, but taking into account other lipid parameters, as well as non-traditional risk factors such as homocistein (34), leptin (35), insulin resistance and hypofibrinolysis (29). Moreover, it is clearly evident that only one common pathway is not likely to contribute to the development of all cardiovascular diseases on its own, and that the interaction between novel biomarkers and traditional and non-traditional risk factors could be of minor or major importance for each particular patient (24).

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Received: April 19, 2008

Accepted: May 9, 2008