

The role of biomarkers in clinical practice

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Abstract

Atherosclerosis is a process that begins intra-arterially and then becomes intraluminal. Imaging is the best method with which to identify and monitor the progression of atherosclerosis; however, until recently, methods have been neither available or practical. Epidemiological studies have shown that biochemical markers, including lipids, glycemia, and renal function, contributed to the risk of cardiovascular events. Later measures of inflammatory processes involved in atherosclerosis and neurohormones (eg, natriuretic peptides) have been added to risk stratification. Biochemical markers are well established, in addition to electrophysiology, for the definition of various grades of myocardial infarction, and biomarker panels now form the core of the diagnostic criteria for definition of acute coronary syndromes. Biomarkers are also used in the development, validation, and safety monitoring of drugs used in the management of atherosclerotic disease. Thus use of biochemical markers is essential to the diagnosis, prognosis, and safety assessment of atherosclerosis.

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Introduction

Atherosclerosis is a process that begins in childhood and is responsible for 35% of mortality. The process begins intra-arterially and only at a late stage begins to obstruct the lumen of the vessel [1]. Imaging of atherosclerosis would be the ideal method of diagnosis and monitoring, but, until recently, methods have been either unavailable or impractical because they involved highly invasive procedures (intravascular ultrasound) for routine use in primary prevention. Therefore surrogate markers such as carotid intima media thickness have been used [2,3]. Biomarkers, defined as biochemical analytes measured in plasma or urine, are used in cardiovascular disease for a number of purposes. The three major uses are for risk assessment in cardiovascular prevention, for the

diagnosis and staging of ischemic heart disease, and for monitoring of the safety of therapies.

Risk assessment

As there is, as yet, no easy method of assessing the burden of atherosclerosis by imaging methods, so the entire basis of cardiovascular risk assessment relies on epidemiological data for cardiovascular disease [4]. In studies such as the Framingham Heart Study, the risk of events is related to demographic and physiological parameters (body mass index, blood pressure) in addition to a series of biochemical markers for risk assessment in the prevention of cardiovascular disease [5]. The best known are total cholesterol and high-density lipoprotein (HDL) cholesterol, which

form part of the core risk-assessment algorithm. Hyperglycemia and diabetes are also risk predictors, but are usually excluded because diabetes is considered to be a cardiovascular risk equivalent [6]. Hyperglycemia and glycated hemoglobin (HbA_{1c}) can also be used to identify higher-risk groups likely to have insulin resistance/metabolic syndrome [7]. Further information has been added in other epidemiological studies through the addition of both triglycerides as a marker of the atherogenic lipoprotein phenotype, and small dense particles (both low-density lipoprotein [LDL] and HDL) [8]. The combination of lipids, blood pressure, hyperglycemia, and waist circumference is used in definitions of the metabolic syndrome, although other markers such as hyperinsulinemia, hyperuricemia, and increased concentrations of inflammatory markers and plasminogen activator inhibitor-1 (PAI-1) also are associated with this syndrome [9]. Cardiovascular risk is also increased in patients with renal dysfunction identified by measurement of plasma creatinine and increasingly expressed as an estimated glomerular filtration rate (eGFR) [10]. When these are combined with the presence of micro- or macroalbuminuria, further increments of risk can be defined. The presence of microalbuminuria in patients with hypertension defines a subset with target-organ damage and requiring extra treatment. The presence of albuminuria allied to eGFR stratifies patients for renal dysfunction and thus can help determine both risk of cardiovascular disease and how drug doses are adjusted.

The use of such marker panels allows a identification of 70–80% of cardiometabolic risk [11]. Further specificity can be added through the addition of markers of inflammation, including C-reactive protein (CRP), fibrinogen, or sialic acid [12]. Some of these markers (eg, CRP) respond to drug therapies such as statins or fibrates. Recently, the use of CRP as a risk marker has been validated in the JUPITER (Justification for the use of statins in Primary prevention an Intervention Trial Evaluating Rosuvastatin) trial [13]. Another inflammation-associated marker that seems to mark an oxidative phenotype is lipoprotein-associated phospholipase A₂ (LpPLA₂), which adds information about cardiovascular risk over and above that provided by CRP [14]. The limited relationship of LpPLA₂ to markers of oxidation such as oxidized LDL and isoprostanes is unclear, but a possibly stronger association with sialic acid and electronegative LDL species means its role has not been fully clarified. Another indirect marker of oxidative stress involves the nitric oxide system, in which asymmetric dimethylarginine (ADMA) has been shown to mark the degree of established atherosclerosis [15]. ADMA is correlated with endothelial vascular dysfunction, given its close relationship to low concentrations of nitric oxide, but

– in contrast to nitric oxide – it is stable. Whether the principal source is vascular or renal is uncertain, but it does mark established atheroma; however, in contrast to many biomarkers, it does not respond to common therapies (eg, antihypertensive agents or statins). Natriuretic peptides are also potential markers of cardiovascular risk, as they may identify patients with left ventricular dysfunction and thus low-grade ischemia, as may other markers of tissue hypoxia such as ischemia-modified albumin [16]. Which risk markers will be added to the basic profile remains, as yet, unclear.

Established cardiovascular disease

Cardiac biomarkers are well established in the diagnosis of acute coronary disease. The release of cardiomyocyte proteins includes (in approximate temporal sequence): myoglobin or fatty acid binding protein 4, glycogen phosphorylase B, creatine kinase MB fraction (CK-MB) and, finally, troponin (T, I or C) [17,18]. The concentrations of troponins are used in conjunction with clinical and electrocardiographic criteria to define the extent of myocardial necrosis and to stratify patients into those with unstable angina, non-Q-wave myocardial infarction, or ST-segment-elevation myocardial infarction, which determine treatment strategies. The availability of newer, more sensitive troponin assays is likely to result in further redefinition between these clinical categories.

None of the above markers is functionally significant. In contrast, the natriuretic peptides are released in response to left ventricular cardiac dysfunction [19]. The most commonly used is brain natriuretic peptide (BNP), which is used as a diagnostic marker of non specific cardiac dysfunction (including pulmonary dysfunction and pericarditis), but is better known as a definitive test to exclude the presence of heart failure [20]. Early studies have not shown a benefit from using BNP to guide management in heart failure, but more sophisticated strategies correcting more accurately for age and sex may prove more useful.

The reliability of cardiac biomarkers for ischemia is such that many are now used in semiquantitative assay formats in point-of-care panels. Typically, these combine hyperacute (myoglobin, fatty acid binding protein) or functional (BNP) markers with intermediate markers (CK-MB), and a late definitive myolytic marker of necrosis (troponin) [17]. There is controversy about the specificity, accuracy and utility of different panels and how they should be integrated with clinical signs and electrocardiographic data, but their convenience is such that usage for triage in emergency rooms is increasing rapidly.

Safety monitoring

Biomarkers are used to monitor drug therapies. The best known are markers of hepatic microsomal induction (γ -glutamyl transferase) and hepatocyte necrosis (transaminases) [21,22]. These are commonly measured to track the toxicity of drug therapies. More specific biomarkers are used to track tissue toxicities. In the severe case of myositis and rhabdomyolysis, the association of statin therapy with myopathy can be tracked by increases in creatine kinase (MM) and myoglobinuria [23]. Nowadays, even subtle toxicities detectable only by changes in transaminases and creatine kinase concentrations, from baseline, allied to genetic biomarkers of statin acid uptake (organic anion transporter), can be used to predict future myositis [24].

Conclusions

Biomarkers are central to the diagnosis and risk stratification of coronary heart disease. Although older biomarkers are well established, newer markers are offering the possibility of further risk stratification, quantification of the underlying atheroma burden, and even marking the correction of cardiac dysfunction by demonstrating the reappearance of normal physiology. ■

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