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Special Article

Coronary Atherosclerosis: Pathophysiologic Basis for Diagnosis and Management

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ABSTRACT

Coronary atherosclerosis is a long lasting and continuously evolving disease with multiple clinical manifestations ranging from asymptomatic to stable angina, acute coronary syndrome (ACS), heart failure (HF) and sudden cardiac death (SCD). Genetic and environmental factors contribute to the development and progression of coronary atherosclerosis. In this review, current knowledge related to the diagnosis and management of coronary atherosclerosis based on pathophysiologic mechanisms will be discussed. In addition to providing state-of-the-art concepts related to coronary atherosclerosis, special consideration will be given on how to apply data from epidemiologic studies and randomized clinical trials to the individual patient. The greatest challenge for the clinician in the twenty-first century is not in absorbing the fast accumulating new knowledge, but rather in applying this knowledge to the individual patient.

"TA PANTA REI"… "Everything is changing"
[Heraclitus 540-480 B.C.]

Introduction

In the middle of the last century, it was almost impossible to imagine the progress that would be made over the next several decades for the diagnosis and management of coronary atherosclerosis. Compared to the remarkable technology at present, the electrocardiogram and chest x-ray were the only available diagnostic tools for coronary atherosclerosis. Likewise, compared to multiple sophisticated therapeutic modalities available today, only nitroglycerin, morphine and bed rest were used for the management of coronary atherosclerosis at that time.[1]

Coronary atherosclerosis is a complex, long lasting and continuously evolving inflammatory disease characterized by remodeling of the coronary arteries, which supply oxygen

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Abbreviations and Acronyms

ACS = acute coronary syndrome

CABG = coronary artery bypass grafting

CKD = chronic kidney disease

CRP = C-reactive protein

CVD = cardiovascular disease

DAPT = dual antiplatelet therapy

DM = diabetes mellitus

HDL-C = high density lipoprotein cholesterol

HF = heart failure

HTN = hypertension

LDL-C = low density lipoprotein cholesterol

LV = left ventricular

MI = myocardial infarction

OMT = optimal medical therapy

PCI = percutaneous coronary intervention

SCD = sudden cardiac death

STEMI = ST elevation myocardial infarction

to the myocardium. It has various clinical manifestations ranging from asymptomatic to stable angina, acute coronary syndromes (ACS), sudden cardiac death (SCD) or heart failure (HF). Development and progression of coronary atherosclerosis is related to genetic and environmental factors that modulate disease risk individually and through different interactions. Due to the nature of the disease, the majority of the patients may live with coronary atherosclerosis for many years and often decades.[2–5] In this brief review, current knowledge related to the diagnosis and management of coronary atherosclerosis based on pathophysiologic mechanisms will be discussed. In addition to general concepts related to coronary atherosclerosis, special considerations will be given on how to approach the individual patient.

Development of coronary atherosclerosis

Genetic and environmental factors that contribute to the development of the atherosclerotic lesion and progression of the disease are shown schematically in Fig 1.

Genetic factors

Genome-wide association studies have shown that more than 55 loci are related to coronary atherosclerosis. Each individual inherits genetic variants (i.e., minor alleles, polymorphisms, mutations), but only individuals who inherit a combination of multiple variants are at the greatest risk for the development of the disease.[6–10] It should be mentioned that most of these genetic variants related to coronary atherosclerosis are located at DNA sequences that do not code proteins. Only 15 of the genetic variants are related to known risk factors [7 to low density lipoprotein cholesterol (LDL-C), 4 to arterial hypertension (HTN), 2 to triglycerides, 1 to high density lipoprotein cholesterol (HDL-C) and 1 to thrombosis]. The first described genetic variant found to be associated with coronary atherosclerosis is located on the short arm of chromosome 9 (chromosome 9p21) with yet unknown function; it appears that this genetic variant increases the risk of a first coronary heart disease event, but not subsequent events. Of interest, this variant is associated with periodontitis and gout, both conditions that are associated with increase inflammation, but not with C-reactive protein (CRP).[9,10]

For years it has been known that the incidence of myocardial infarction (MI) is related to the ABO blood type; having alleles for blood type A or B is associated with a greater risk for MI compared to blood type O. Group A or B are also associated with higher levels of von Willebrand factor complex.[9,10]

Evidence that LDL-C plays an important role in the development and progression of coronary atherosclerosis has been known for decades. One of the major observations that demonstrated the genetic link between LDL-C and coronary atherosclerosis was by Brown and Goldstein discovering a mutation in the LDL-C receptor in patients with familial hypercholesterolemia, premature coronary atherosclerosis and early death.[11] This observation was crucial for the development of statins, a pharmacologic agent that has been widely used in primary and secondary prevention of atherosclerosis, resulting in a significant decrease in cardiovascular disease (CVD) events and CVD death. Another significant discovery with a genetic link is the enzyme PCSK9 and its effects on LDL-C and coronary atherosclerosis. The enzyme PCSK9 (chromosome 1p32.3) increases the degradation of LDL-C receptors. Mutations that increase the function of PCSK9 are associated with high levels of LDL-C and increase incidence of coronary atherosclerosis. In contrast, mutations that result in loss of function of PCSK9 are associated with low levels of LDL-C and decrease incidence of coronary atherosclerosis. These observations resulted in the development of monoclonal antibodies that inhibit the function of the PCSK9 enzyme[12] (see later). Administration of these agents to patients with hypercholesterolemia who were treated with a statin produced a dramatic decrease in LDL-C (this decrease was in addition to that obtained with statins) and to a significant decrease in CVD events. More recently, a mutation in ANGPL4 has been identified. ANGPL4 is known to inhibit lipoprotein lipase increasing triglyceride levels; carriers with a loss of function mutation were shown to have lower blood levels of triglycerides and lower incidence of coronary atherosclerosis compared to non-carriers. The data suggest that lipoprotein lipase pathway plays an important role in the development of coronary atherosclerosis; it follows that new drugs modulating these pathways can be developed in the near future potentially decreasing the incidence of coronary atherosclerosis.[13] Although low levels of HDL-C are associated with coronary atherosclerosis, therapeutic interventions that increase HDL-C currently have not demonstrated any effect on survival or reduction in CVD events.[9,13–15]

Environmental factors

In addition to cholesterol, other risk factors for coronary atherosclerosis are shown in Fig 1. HTN and diabetes mellitus (DM) are major risk factors contributing to the development of coronary atherosclerosis. Even isolated systolic HTN in young and middle age adults has been shown to be associated with a higher incidence of coronary atherosclerosis. It follows that optimal medical management of HTN and DM, as recent data