Atherosclerosis in Diabetes: Pathogenesis

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CHAPTER OUTLINE

Introduction
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Pathology of Atherosclerosis
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Adhesion Molecules and Chemotactic Proteins
Early Atherosclerotic Changes in Diabetic Subjects
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INTRODUCTION

Atherosclerosis, a complicated multifactorial pathological process, affects mainly large and medium sized arteries resulting in macrovascular disease. Virtually all large vessels are involved, and clinical manifestations result from the narrowing and thrombosis of coronary, cerebral and some peripheral arteries. Though the consequential end points of atherosclerosis are well defined, there is no clear explanation for the pathophysiology leading to atherosclerosis. Further the pathophysiology in diabetic subjects is even more complicated, as several cardiovascular risk factors are triggered due to metabolic alterations resulting in increased risk for atherosclerosis (Figure 1). In the past few decades, accelerated development of atherosclerosis in diabetes, both causative factors and pathophysiology have been the subject of intense study.[1] These studies have improved the knowledge on the pathogenic mechanisms of atherosclerosis and the triggering factors that lead to acute clinical events.

ARTERIAL VESSEL WALL STRUCTURE

Endothelial cells, smooth muscle cells and extracellular matrix like elastic elements, collagen and proteoglycans are the basic constituents of the walls of arterial blood vessels. The vessel wall has three layers: the innermost layer, the tunica intima, middle layer, the tunica media and the outer layer, the tunica adventitia.

PATHOLOGY OF ATHEROSCLEROSIS

The pathological sequence of atherosclerosis involves macrophages that develop into foam cells and get deposited at the junction of the tunica intima and tunica medial layers of the artery and later progress into a fibrous atheroma.[2]

Important factors in the initiation and growth of plaques are:

1. Endothelial dysfunction and injury
2. Sub endothelia, monocyte / macrophage accumulation
3. Lipoprotein infiltration
4. Smooth muscle cell proliferation
5. Influx of T lymphocytes and other inflammatory cells and progressive lipid accumulation in foam cells, finally leading to plaque formation, erosion, platelet aggregation and adhesion thrombosis.

FIBRINOLYSIS AND COAGULATION

Endothelium helps to regulate homeostasis of the cardiovascular system by releasing antithrombotic, fibrinolytic factors, and vasodilators. Diabetes is associated with several disorders of coagulation and

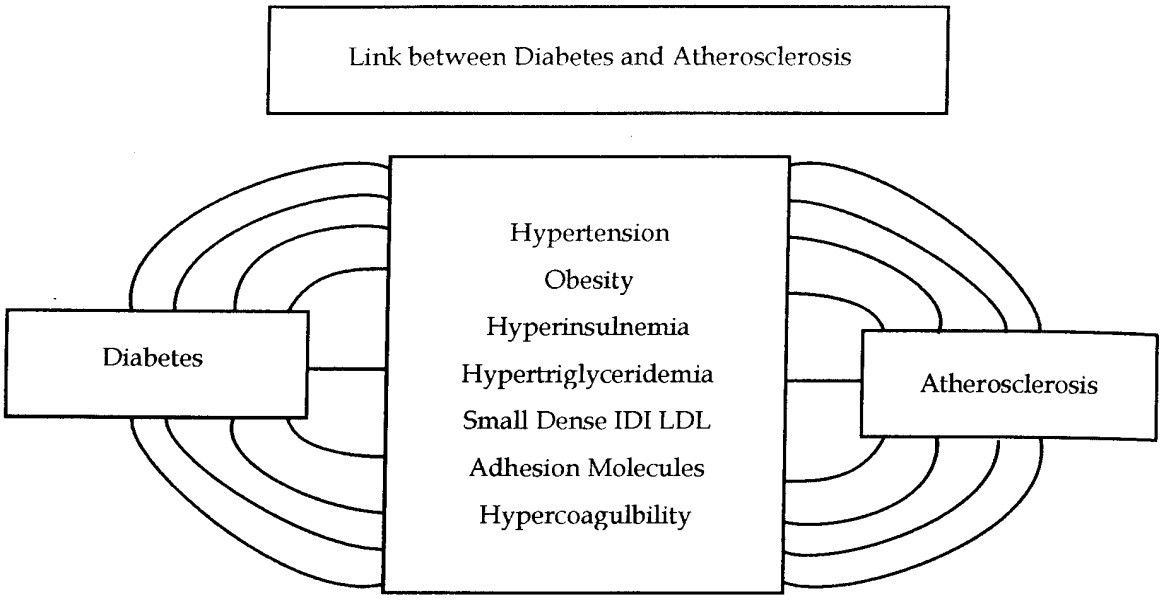

Fig. 1. Link between Diabetes and Atherosclerosis

fibrinolysis. Patients with diabetes mellitus tend to have increased Plasminogen Activator Inhibitor [PAI-1] levels, decreased fibrinolysis, increased tissue plasminogen activator [tPA] and increased fibrinogen levels in common with metabolic syndrome.[3] Recent studies from Chennai have shown levels of fibrinogen and PAI-1 to be associated with angiographically proven coronary artery disease [CAD][4] that the relative odds ratios for CAD increased with increase in quartiles of fibrinogen and plasminogen activator inhibitor.[4] These imbalances in fibrinolysis and coagulation increase atherosclerotic progression in diabetic subjects.

LOW DENSITY LIPOPROTIEN

Increase in plasma cholesterol and its main transporter LDL is an important risk factor in atherosclerosis. In diabetic subjects, LDL tend to get modified due to hyperglycemia, oxidative stress and other metabolic abnormalities. Small dense LDL is considered to be more prone to oxidation and conformational changes[5], which results in the lowering of LDL clearance by its receptors, triggering immunological changes (Figure 2).[6] Some studies have shown the oxidizability of LDL to be associated with early structural changes.[7] Studies have shown that diabetic subjects had higher small dense LDL compared to normals.[8] Modified LDL stimulates endothelial cells to release adhesion molecules.

ADHESION MOLECULES AND CHEMOTACTIC PROTEINS

There is enhanced endothelial production of vascular cell adhesion molecules-1 (VCAM-1) and monocyte chemotactic protein-1 (MCP-1) in diabetic subjects, all of which are known to enhance the atherosclerotic process. The chemokine MCP-1 recruits and activates monocytes from the circulation to inflammatory site and this activation is stimulated by VCAM-1.[9]

Damage to the endothelium triggers adherence and aggregation of platelets at the site of damage. This enhances monocytes to further enter the tunica intima,

and proliferate within the tunica-media junction of the artery. This combination of biochemical and anatomical alterations contributes to oxidative stress and increased vascular damage and the vicious cycle continues.

EARLY ATHEROSCLEROTIC CHANGES IN DIABETIC SUBJECTS

Basically the atherosclerotic process could be categorized into functional and structural changes in the artery. The first to occur would be functional changes in the arteries leading to the loss of elasticity. This is followed by structural changes like lipid infiltration and foam cell formation, leading to intimal thickening, plaque formation and finally narrowing of the lumen of the artery interfering with blood flow. The plaque eventually ruptures with consequent intraluminal thrombosis with blockage.

Functional changes can be studied by looking at flow mediated dilatation or arterial stiffness. These pre-clinical atherosclerotic markers have gained wide recognition as they are useful surrogate markers for CAD and can also be used in studies on prevention and intervention of CAD.[10,11] In a population-based study, the mean IMT values among diabetic subjects were found to be higher compared to normal subjects.[12] More recently, IMT values were reported to increase progressively with increasing glucose intolerance. In subjects with normal glucose tolerance the mean IMT values were lowest followed by those with impaired glucose tolerance and highest among the diabetic subjects.[13] Endothelial dysfunction measured as flow

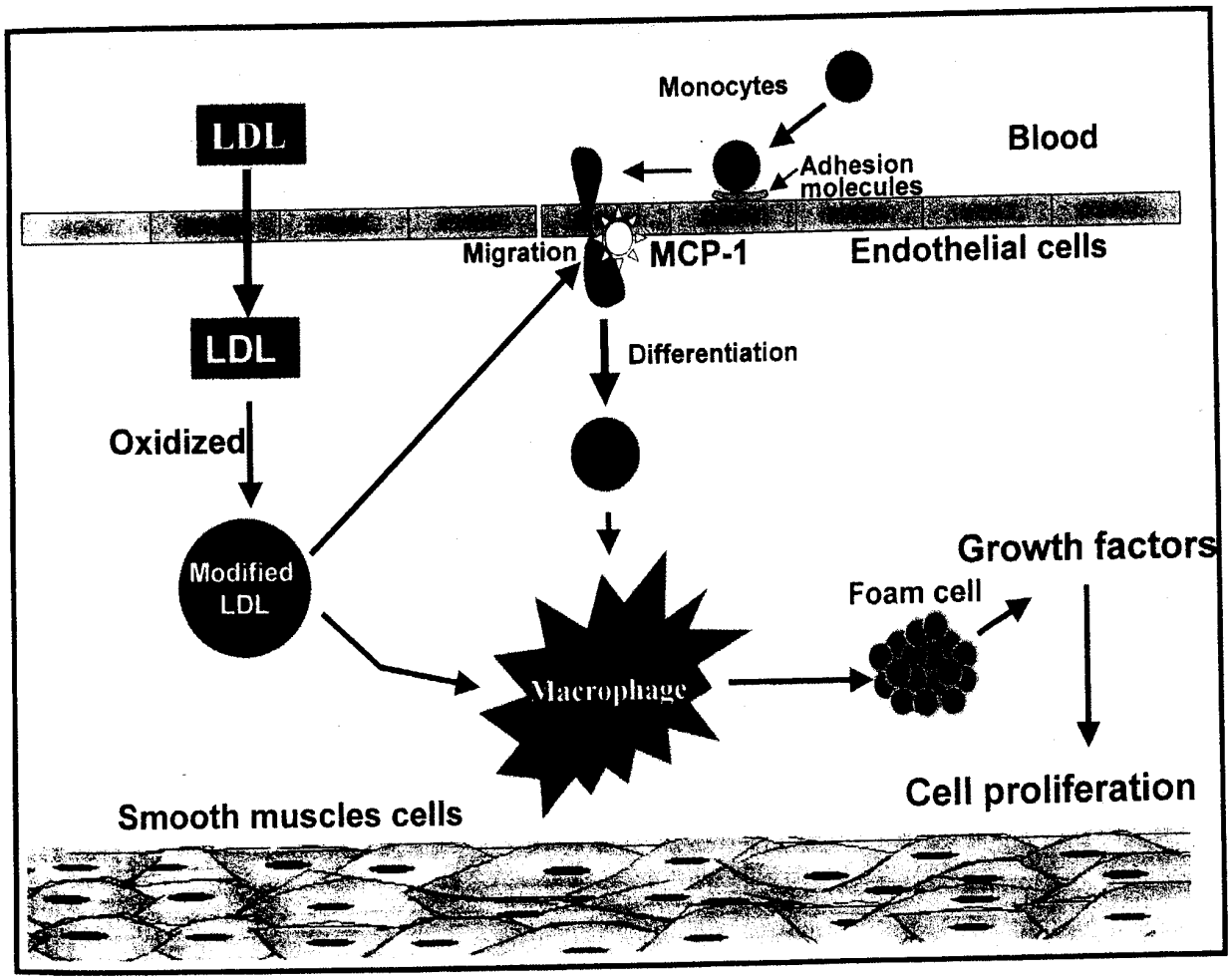

Fig. 2. LDL induced atherosclerotic process

mediated dilatation (FMD) of the brachial artery using high-resolution B mode ultrasonography was also found to be reduced in diabetic patients compared to age and sex matched non-diabetic subjects.[14]

INFLAMMATION

Recent work suggests that coronary occlusion could be an inflammatory process, in which inflammation causes the plaque to rupture. Several studies have shown an association between inflammatory markers with diabetes. Inflammatory changes could take place near the rupture of the plaque, leading to instability of the fibrous tissue in the plaque, thus facilitating thrombosis. Studies on proinflammatory makers have revealed that cytokines like Tumour Necrosis Factor - α [TNF - α], C-reactive protein [CRP] and interleukin – 6 [IL – 6] are strongly associated with CAD. Recent studies suggest that raised CRP plays a key role in mediating insulin resistance and coronary artery disease.[15,16] In a study on 150 South Indians, CRP levels were found to be higher among diabetic subjects with and without CAD compared to non-diabetic subjects without CAD.[17]

PLAQUE RUPTURE

The artery responds to the intimal hyperplasia with efforts for a protective action such as enlargement, thereby increasing the lumen area. This protective process continues until the atheromatous material leads to 40% stenosis. Thereafter, compromise in the lumen area causes hemodynamically significant obstructions.

Acute manifestations of coronary atherosclerosis viz unstable angina, acute myocardial infarction, or sudden cardiac death are considered to share a common pathophysiologic phenomenon: thrombosis or a plaque rupture. Plaques need not necessarily block the arteries, rather, much like an abscess, they are ingrained within the arterial wall and may remain asymptomatic. Some plaques called "vulnerable plaques" could be eroded or may rupture. Such plaques are more dangerous than those that cause anginal pain. Several post-mortem, retrospective studies have shown that plaque disruption plays a key role in the pathophysiology of acute coronary syndromes.[18,19] The fragility of atheromatous plaques has been related to their irregular formation and high lipid content with propensity to rupture. Unstable atheromatous plaques have an increased tendency to rupture. Studies have documented that diabetic subjects have more vulnerable plaques than non-diabetic subjects.[20]

To conclude, numerous factors and pathways are involved in the development of diabetes and atherosclerosis. The major pathways are intriguing and are challenging to alter. However, behavioral changes or pharmacological interventions can modify many of them.

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