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REVIEW

The lipid theory in the pathogenesis of calcific aortic stenosis

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Abstract *Aims:* Biologically active phenomena, triggered by atherogenesis and inflammation, lead to aortic valve (AV) calcification. Lipids play an important role in activating the cell signaling leading to AV bone deposition. This review, based on evidence from animal and human studies, mainly focused on the involvement of lipids and atherogenic phenomena in the pathogenesis of calcific aortic stenosis (AS).
Data synthesis: The role of elevated low density lipoproteins for the risk of both vascular atherosclerosis and AS has been elucidated. Lipid disorders act synergistically with other risk factors to increase prevalence of calcific AS. Atherosclerosis is also involved in the pathogenesis of bone demineralization, a typical hallmark of aging, which is associated with ectopic calcification at vascular and valvular levels. Animal studies have recently contributed to demonstrate that lipids play an important role in AS pathogenesis through the activation of molecular cell signalings, such as Wnt/Lrp5 and RANK/RANKL/Osteprotegerin, which induce the transition of valvular myofibroblasts toward an osteogenic phenotype with consequent valvular bone deposition. Although all these evidence strongly support the lipid theory in AS pathogenesis, lipids lowering therapies failed to demonstrate in controlled trials a significant efficacy to slow AS progression. Encouraging results from animal studies indicate that physical activity may counteract the biological processes inducing AV degeneration.
Conclusions: This review indicates a robust interplay between lipids, inflammation, and calcific AS. This new pathophysiological scenario of such an emerging valvular disease paves the way to the next challenge of cardiovascular research: “prevent and care aortic valve stenosis”.

Background

Calcific aortic stenosis (AS) is the most prevalent form of valvular heart disease in the Western world. Aortic valve (AV) sclerosis is observed in 75% of people aged more than 85 years, with severe AS reaching a 3% prevalence in the population over 75 years [1]. New insights in the pathogenesis of AS have accumulated in recent years. In fact, AS was previously thought to be the result of a passive,

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degenerative disorder of aging, related to mechanical stress. Recent in vitro and in vivo studies have instead demonstrated that atherogenesis and inflammation trigger biologically active and progressive phenomena leading to valve calcification and bone deposition [2,3]. At this regard, it has been found that lipids play an important initiating role in activating cell signaling leading to valvular calcification, and oxidized low-density lipoproteins (ox-LDLs) have been identified in calcified valves [4]. The hypothesis that lipids play a role in the development of calcific AS is further supported by the observation of diffused atherosclerotic lesions in the aortic leaflets, as well as in coronary arteries, of patients with familial hypercholesterolemia and no other traditional atherosclerotic risk factors [5]. A causative role of elevated LDLs in the risk of both vascular atherosclerosis and AS has been supported by the Cardiovascular Health Study [6] whereas an association between other studies early, pre-stenotic lesions of AV and increase (up to 50%) rate of coronary events was also reported, thus supporting a mechanistic relationship between atherosclerosis and valvular and vascular lesions [7,8]. Calcific AS is also significantly associated with increased prevalence of metabolic syndrome (MS) which is characterized by a cluster of cardiovascular risk factors including atherogenic dyslipidemia [9]. Finally, dyslipidemia also seems to be the link between bone loss and cardiovascular calcification as indicated by the observation that patients with lower bone density and osteoporosis have more severe atherosclerosis [10–12].

The aims of the present review were: i) to summarize evidence on the involvement of lipids and atherogenic phenomena in the pathogenesis of calcific AS gained from animal and human studies; ii) to identify relationships between AV disease and other pathologic conditions that recognize lipid metabolic disorders as common pathogenetic mechanisms; iii) to explore the putative molecular and cellular mechanisms leading to AV calcification and evaluate potential links with other biological phenomena that characterize vascular atherosclerosis and altered bone turnover; iv) to review the current controversies regarding the efficaciousness of lipid lowering therapies to slow AS progression; v) to report the results of experimental studies testing the efficacy of physical training in AS primary prevention.

Role of lipids in the pathogenesis of aortic stenosis: experimental and clinical evidence

Experimental studies in mice have demonstrated that increased cholesterol levels after an high cholesterol diet enhance oxidative state in the AV endothelium associated with increased levels of Ox-LDL and abundant inflammatory cell infiltrates, containing mast cells, macrophage and T lymphocytes [13]. Accordingly, himmunoistochemical studies of human stenotic AV described the presence of oxidized LDLs, T-cells and macrophages in the subendothelial layer of the fibrosa and close to calcium accumulation [4,14]. These histological evidence raised the hypothesis that the combination of extracellular oxidized lipids and matrix vesicles released from aortic valve myofibroblasts might represent nuclei for subsequent calcium deposition and calcium nodules formation. In vitro studies, showing that oxidized LDLs strongly promote mineralization when assessed in isolated AV interstitial cells [15], further supported the role of lipids oxidation as a crucial step in the pathogenesis of AV calcification. It has also been demonstrated that the small dense LDLs, that have greater ability to infiltrate tissues and are prone to the oxidation process, were the only lipid fraction associated with the accumulation of ox-LDL in the AV are the small, dense LDL that [16]. In this vein, the high proportion of small, dense LDLs in patients with MS [9] might explain the faster progression rate of AS in this group of patients [9]. The clinical association between LDLs and AS has been recently evaluated in 6942 patients of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium [17]. In this study, genetic elevation in LDL-C, but not in HDL-C or triglycerides, was associated with increased prevalence of AV calcium and incident AS at a follow-up of 15 years. Yet, the role of HDL in AS remains controversial, since, due to their antiatherogenic and anti-inflammatory properties, a protective role in AS pathogenesis and progression would be expected. In this regard, an high total cholesterol/HDL ratio and low serum HDL-cholesterol levels have been found to be associated with a rapid rate of AS progression [18]. Furthermore, the amount of valvular HDL is reduced in human stenotic AV [19]. Besides to the recognized effect on LDL-oxidation reduction, increased expression of adhesion molecules, increased nitric oxide production, and inhibition of apoptosis represent additional potential protective mechanisms of HDL on AV degeneration [20,21]. Yet, other evidence suggest that HDL might promote AS. In fact, in explanted stenotic human AV, apolipoprotein A1 of HDL has been found close to calcific nodules and contributes to the production of amyloid proteins which promote the transition of isolated valvular interstitial cells (VICs) toward an osteoblast phenotype [22]. Studies conducted on hypercholesterolemic rabbits showed that infusion of apoA-I mimetic could favorably affect AS progression in terms of valve area and leaflets thickness [23]. It has been hypothesized that HDLs might be retained and modified in AV, thus promoting lipid retention and contributing to trigger mineralization by being transformed into amyloid substance.

AS and altered bone turnover: the role of lipids

It has been shown that mature lamellar bone formation occurring in calcified human AV presents similarities to osteoblastogenesis during skeletal bone formation [3]. Histological and immunohistochemical studies have demonstrated that stenotic AV expresses osteopontin, bone sialoprotein, osteocalcin, alkaline phosphatase, and the osteoblast-specific transcription factor core-binding factor alpha 1 (Cbfa1) [3]. Skeletal bone osteogenesis involves the differentiation of mesenchymal cells into preosteoblasts and osteoblasts with consequent synthesis