Arterial Intima and Media Calcification: Distinct Entities with Different Pathogenesis or All the Same?

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Medical students have been taught since more than 100 yr that there are at least two types of pathologic calcium phosphate deposition in the arterial wall, namely, intima calcification and media calcification. The medical community has become used to making this distinction since the initial description, in the year 1903, by the German pathologist Johann Georg Mönckeberg, at Strasbourg University Medical School, of arterial media calcification, a disease entity called after him "Mönckeberg's mediasclerosis" or "Mönckeberg's mediacalcinosis" (1). Since then, this type of calcification has been considered to be different from that of the intima. In the latter, calcium phosphate crystals are located within the cholesterol-rich lesions characteristic of atherosclerosis.

Did Mönckeberg get it wrong? This challenging hypothesis has recently been formulated by McCullough (Divisions of Cardiology, Nephrology, Nutrition, and Preventive Medicine, William Beaumont Hospital, Royal Oak, MI; personal communication, October 3, 2007) at a meeting of experts in the bone and mineral disorder associated with chronic kidney disease, to the surprise of the other members of the workgroup. Clearly, modern tissue staining techniques and cellular and molecular tools developed for the analysis of normal vessel wall structure and its changes in various disease states were not available to pathologists at the start of the 20th century. Moreover, it is not easy to get rid of established definitions and classifications, let alone dogmas, all of the more when they are more than 100 yr old. Let us not forget that to break dogmas an open-minded spirit is an important prerequisite as well. We all have in mind long-lived dogmas in medicine, which eventually proved to be either partially incorrect or totally erroneous. Koch's postulates, namely, the four criteria designed to establish a causal relationship between a causative microbe and a disease, can serve as an example for changing dogmas (2). It is admitted at present that fulfillment of all four postulates is no longer required to demonstrate causality. The discovery of *Helicobacter pylori* by the Australian researchers Marshall and Warren is another instructive example for a fallen dogma (3). When Marshall first suggested in the early 1980s that stomach ulcers were caused by this infectious agent, he was nearly laughed off the stage at an international infectious disease conference. The dogma then was that peptic ulcers were of endogenous, often stress-related origin and that no bacteria could survive in the hostile gastric acid environment. Marshall and Warren won the 2005 Nobel Prize in Medicine for their discovery made 25 yr earlier. A further instructive example, more in the field of interest of the present debate, is the discovery by Ed Brown and the late Steven C. Hebert in 1993 of the existence of a calcium-sensing receptor and the demonstration that extracellular calcium can bind to and activate this receptor (4). The prevailing theory then was that there were no receptors that could sense extracellular cations to induce transcellular signaling pathways.

Not all definitions and classifications, however, whether at the height of a dogma or not, become necessarily outdated at some point in time. Many of them have never been put into question. Let us cite as an example hormone, vitamin, or nutrient deficiency states, which lead to long-defined disease entities, such as diabetes, hypothyroidism, scorbut, rickets/osteomalacia, or anemia, respectively. The same is true for the strong association of some monogenic diseases with single gene modifications or deletions. Yet we know that the phenotypic expression of the same gene defect may vary between and even within families, sometimes to a surprising degree.

Challenges of established theories often are refreshing. They may stimulate further research into apparently settled issues and lead to new discoveries. However, they also may eventually turn out to be misleading and inappropriate.

How about arterial calcification in chronic kidney disease? In recent years, we have progressively abandoned the concept of an entirely passive process in association with an elevated calcium $\times$ phosphorus product in the extracellular fluid compartment in favor of that of an actively regulated process, with numerous actors and counteractors on and behind the scene, including a possible cross-talk between the bone and the vessel (5–8). Calcification can occur in all types of arteries, both the large ones of the elastic type and the smaller ones of the muscular type. The location and degree of vascular calcification very much depend on the underlying disease. In patients with advanced stages of chronic kidney disease, both large and small arteries calcify frequently. Typical plain x-ray aspects either show a patchy distribution thought to be characteristic of in-

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tima calcification in association with atherosclerosis or in a pipeline-like distribution attributed to media calcification (9,10). However, in many patients with end-stage kidney disease, if not the majority of them, the two processes develop in parallel.

When having a closer look at the numerous branches of the large vascular tree, we realize that its ramifications have not all been created equal. Although all of them may calcify, only some of them develop atherosclerosis, including the coronary arteries, the aorta, and the arteries of the abdomen and lower extremities. In contrast, others appear relatively or entirely resistant to the atheromatous process, such as the arteries of the upper extremities. Patterns of atherosclerosis susceptibility are strongly influenced by intrinsic differences in the cells composing the vascular system at different locations (11). Smooth muscle cell lineage diversity appears to be an important determinant of the unique properties of artery wall cells found at different anatomic sites (12). Of interest for the present discussion, the weak propensity of the brachial, radial, and ulnar arteries toward atherosclerosis does not go in parallel with the sometimes extensive calcifications observed at these vascular locations.

Media calcification can be induced experimentally in animals who are fairly resistant to atherosclerosis, such as various wild-type strains of rats and mice, by creating chronic renal failure and feeding pharmacologic amounts of vitamin D or its derivatives. Thus, it appears that media calcification can occur in the absence of intima calcification and atherosclerosis, at least in the experimental animal. Whether this is also true for the human condition is the object of the present debate. Of note, media calcium deposition is not a homogeneous condition either. Thus, hydroxyapatite is the predominant mineral in diabetic arterial medial calcification, but in vitamin D toxicity, it is whitlockite (13).

Finally, the clinical relevance of intima calcification is thought to be different from that of media calcification. Whereas intima calcification appears to contribute to plaque vulnerability, possibly in a biphasic manner, media calcification contributes to vascular stiffness, which, in turn, increases pulse-wave velocity to decrease diastolic blood pressure and increase systolic blood pressure (14). From a prognostic point of view, the distinction between intima and media calcification appears to be useful as well. London *et al*. have shown, using arterial ultrasonography, that maintenance hemodialysis patients with predominant intima calcification have a higher relative risk of mortality than those with predominant media calcification, whose relative risk in turn is much greater than in those with no calcification (10). The problem in patients, however, is that a clear-cut distinction between intima and media calcification is impossible with presently available noninvasive imaging techniques. Only light microscopy analysis of vessel samples collected during surgery or postmortem allows that distinction under the condition that appropriate staining methods are used. The problem becomes even worse when considering the fact that most adult patients with chronic kidney disease suffer from both intima and media calcification.

These are the main reasons for the present debate. Let us see now the arguments provided for and against the established distinction between media and intima calcification, and let us hope that the reader will have a better understanding of this issue after having carefully weighed the pros and the cons put forward by the two experts.

Disclosures

None.

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