Accelerated Atherosclerotic Calcification and Mönckeberg’s Sclerosis: A Continuum of Advanced Vascular Pathology in Chronic Kidney Disease

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Autopsy studies have demonstrated the near universal presence of fatty streaks and fibroatheromas in the general population from which patients with chronic kidney disease (CKD) arise. The vast majority of patients with CKD have multiple conventional cardiovascular risk factors. Vascular atherosclerotic calcification develops in most patients as they transition from the general population to significant CKD as part of cholesterol crystallization within atherosclerotic lesions. Once present, however, atherosclerotic medial calcification can become prominent and has been previously identified as Mönckeberg’s sclerosis. A unifying concept supported by the preponderance of pathologic evidence contends that Mönckeberg’s sclerosis is a manifestation of accelerated atherosclerosis in patients with CKD. The term has also been used in rare cases to describe vascular calcinosis not related to CKD. This clarification is critical to advance the field in terms of pathologic diagnosis and treatment of CKD bone and mineral disorder. Factors that seem to promote the osteoblastic transformation of vascular smooth muscle cells and enhance deposition of calcium hydroxyapatite crystals include phosphorus activation of the Pit-1 receptor, bone morphogenic proteins 2 and 4, leptin, endogenous 1,25 dihydroxyvitamin D, vascular calcification activating factor, and measures of oxidative stress. These entities work to accelerate the atherosclerotic process in patients with CKD and may be future targets for diagnosis and treatment because randomized trials with hydroxymethylglutaryl-CoA reductase inhibitors have failed to attenuate the rate of progressive vascular calcification.


With the demographic changes in Western societies toward older, more obese, and proneness toward type 2 diabetes and hypertension, there is increasing interest in the effects of chronic kidney disease (CKD) on the cardiovascular system (1). The numbers of individuals in the United States who meet a definition of CKD on the basis of a reduced estimated GFR (eGFR) or evidence of kidney damage by imaging studies or biomarkers are expected to increase sharply during the next several decades. Because approximately half of all deaths in those with CKD are attributed to cardiovascular causes, there is rationale to explore CKD as a “cardiovascular risk state” and understand the pathobiologic evidence for changes in the vascular tree (2). There has been a recognition that CKD is associated with a bone and mineral disorder manifested by (1) laboratory abnormalities of calcium, phosphorus, parathyroid hormone, and vitamin D; (2) evidence of bone disease (renal osteodystrophy, fractures, or impaired linear growth); and (3) extraosseous calcification of soft tissues and the vasculature (3). This article takes a critical look at the vascular element of CKD-mineral bone disorder and proposes that vascular calcification represents an amplification of the atherosclerosis instead of the nonatherogenic process termed Mönckeberg’s sclerosis (4). We review the pathologic description of Mönckeberg’s sclerosis, review the medical literature, provide data supporting our hypothesis, and review the clinical studies to reduce vascular calcification.

Mönckeberg’s Sclerosis as a Pathologic Misconception

In 1903, Johann Georg Mönckeberg described medial calcification in arteries in predominately older individuals (4). Without details concerning renal function or diabetes, he described the pathologic findings of 130 patients (86 with light microscopy) as follows: 57 with no discernible disease, 43 with medial calcification, 18 with atherosclerosis and no medial calcification, and 12 with atherosclerosis and medial calcification. In the 55 patients who had any medial calcification, he described the stages: Stage 1, elastic yellow plaque; stage 2, atheroma present; and stage 3, ulcers and thrombus present. This observation was made without the aid of modern methods of evaluating human blood vessels for all of the principal components of atherosclerosis including lipid deposition, expression of adhesion molecules, inflammatory cell infiltrate, foam cells, activated vascular smooth muscle cells and pericytes, and extracellular matrix.
Thus, one could conclude that Mönckeberg’s original observations were simply describing various stages of atherosclerotic plaque. In 1912, Faber (5) published the idea that calcification in the coronary arteries was atherosclerotic in origin and not Mönckeberg’s sclerosis. In 1965, Eggen et al. (6) demonstrated that >95% of all coronary atherosclerotic lesions contained calcium in 1242 consecutive autopsies performed in predominately young (909 [73%] younger than 60 yr with <5% with significant luminal stenoses) in New Orleans, LA. Subsequently, the notion that Mönckeberg’s sclerosis occurs as a nonatheromatous lesion has been propagated in the literature by monocular studies focusing on the presence of medial calcification and thereby missing the core pathobiologic elements and natural history of atherosclerosis. A working definition of atherosclerosis put forward in a report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association, described atherosclerosis in stages. An initial (type I) lesion contains enough atherogenic lipoprotein to elicit an increase in macrophages and formation of scattered macrophage foam cells (7). As in subsequent lesion types, the changes are more marked in locations of arteries with adaptive intimal thickening. (Adaptive thickenings, which are present at constant locations in everyone from birth, do not obstruct the lumen and represent adaptations to local mechanical forces.) Type II lesions consist primarily of layers of macrophage foam cells and lipid-laden smooth muscle cells and include lesions grossly designated as fatty streaks. Type III is the intermediate stage between type II and type IV (atheroma, a lesion that is potentially symptomatic producing). In addition to the lipid-laden cells of type II, type III lesions contain scattered collections of extracellular lipid droplets and particles that disrupt the coherence of some intimal smooth muscle cells. This extracellular lipid is the immediate precursor of the larger, confluent, and more disruptive core of extracellular lipid that characterizes type IV lesions. Beginning around the fourth decade of life, lesions that usually have a lipid core may also contain thick layers of fibrous connective tissue (type V lesion) and/or fissure, hematoma, and thrombus (type VI lesion). Some type V lesions are largely calcified (type Vb), and some consist mainly of fibrous connective tissue and little or no accumulated lipid or calcium (type Vc) (7).

We performed a MEDLINE search for articles published from 1957 to 2008 with the term “Mönckeberg’s sclerosis” in the title to identify publications clearly calling out this purported pathologic entity. There were 15 citations, five of which were written in languages other than English. Of the remaining 10 articles written in English, five were case reports and five presented data from series of patients. The case reports concerned notable medial calcification in a variety of peripheral arterial vessels (Table 1) (8–12). Almost all cases met clinical definitions of calciphylaxis characterized by calcification of the tunica media, small vessel mural calcification with or without endovascular fibrosis, extravascular calcification, and vascular thrombosis, leading to tissue ischemia (including skin ischemia and necrosis). Even though Mönckeberg seemed to have no intention of describing calciphylaxis, the term Mönckeberg’s sclerosis clearly was used to describe this phenomenon. In no case were complete efforts made to evaluate for elements of atherosclerosis including risk factors; known atherosclerotic disease; or histologic evaluation for lipids, inflammation, adhesion molecules, cytokines, or other known elements of the atherosclerotic process. Thus, one interpretation is that Mönckeberg’s sclerosis is a manifestation of calciphylaxis or calcinosis superimposed on systemic atherosclerosis, the unique feature being skin necrosis, soft tissue calcification, and limb ischemia warranting amputation.

The five case series of Mönckeberg’s sclerosis are summarized in Table 2 (13–17). All of these case series concerned samples of primary peripheral arteries from amputation or other surgical procedures and proceeded with a variety of

### Table 1. Case reports of purported Mönckeberg’s sclerosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age</th>
<th>CKD Status</th>
<th>Diabetes</th>
<th>Artery</th>
<th>Calciphylaxis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amillo (8)</td>
<td>1977</td>
<td>64</td>
<td>NR</td>
<td>NR</td>
<td>Hand</td>
<td>Yes</td>
<td>Toe-to-hand transfer after amputation</td>
</tr>
<tr>
<td>Top (9)</td>
<td>2002</td>
<td>20</td>
<td>No</td>
<td>No</td>
<td>Peripheral arteries (temporal, femoral)</td>
<td>No</td>
<td>Unusual presentation of medial calcification in a young patient without diabetes Artery rupture during surgery</td>
</tr>
<tr>
<td>Shabat (10)</td>
<td>2004</td>
<td>73</td>
<td>NR</td>
<td>NA</td>
<td>Popliteal</td>
<td>No</td>
<td>Artery rupture during surgery</td>
</tr>
<tr>
<td>Couri (11)</td>
<td>2005</td>
<td>63</td>
<td>Normal</td>
<td>No (impaired fasting glucose present)</td>
<td>Aorta, iliac, femoral</td>
<td>No</td>
<td>Massive soft tissue calcification of larynx/pharynx</td>
</tr>
<tr>
<td>Sorensen (12)</td>
<td>2007</td>
<td>65</td>
<td>ESRD</td>
<td>Yes</td>
<td>Penile</td>
<td>Yes</td>
<td>All limbs amputated/penis amputated, hyper PTH</td>
</tr>
</tbody>
</table>

*CKD, chronic kidney disease; NR, not reported; PTH, parathyroid hormone.*
descriptions of the specimens from a total of 102 patients. As noted, not a single article reported eGFR or other measures of renal function. None of the articles revealed enough information to determine whether calciphylaxis was present; however, most suggested that these were cases of chronic stable patients. The report by Goebel and Füssl (13) attempted to identify medial calcification by plain x-ray patterns of calcification in the legs without histologic confirmation. In the article by Shanahan et al. (14), calcification was found in the intima and media in eight (38%) of 21 and media alone in 14 (67%) of 21 cases. In cross-sections of the artery wall, where calcification solely occurred in the media, adjacent deposits of lipid material and atheroma were located in the thickened intimal layer (Figure 1). Thus, this can now be easily interpreted as atherosclerosis. In a report from Schoppet et al. (16), a comparison of clinical and histologic characteristics of patients with atherosclerosis and Mönckeberg’s sclerosis found no distinguishing features, including clinical parameters or anatomic locations of histologic findings. The results of histomorphologic methods used (von Kossa staining, in situ ligand immunohistochemistry, and in situ hybridization) were consistent for both atherosclerosis and Mönckeberg’s sclerosis. Calcific processes included expression of osteoprotegerin, receptor activator of NF-κB ligand, TNF-related apoptosis-inducing ligand protein, and mRNA expression patterns were similar for atherosclerosis and Mönckeberg’s sclerosis patterns; in particular,

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
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<th>CKD Status</th>
<th>Diabetes</th>
<th>Artery</th>
<th>Calciphylaxis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goebel</td>
<td>1983</td>
<td>60</td>
<td>67</td>
<td>NR</td>
<td>32%</td>
<td>Pedal</td>
<td>No</td>
<td>Postbilateral lumbar sympathectomy for neuropathy promoted medial arterial calcification as detected on X-ray.</td>
</tr>
<tr>
<td>Shanahan</td>
<td>1999</td>
<td>21</td>
<td>62</td>
<td>NR</td>
<td>43%</td>
<td>Tibial, popliteal, peroneal, tibial</td>
<td>No</td>
<td>Specimens from leg amputation. Medial calcification seen in all patients with diabetes and one without diabetes. Calcification in the media occurred in the absence of lipid and macrophages. Lipid deposition adjacent to dense medial calcification.</td>
</tr>
<tr>
<td>Castillo</td>
<td>1999</td>
<td>131</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Temporal artery biopsy</td>
<td>No</td>
<td>Atherosclerosis (63%), giant cell arteritis (13%), 6% had calcific sclerosis confined to the tunica media, which was associated with mild tissue disorganization surrounding the calcific plaque and disruption of the internal elastic lamina.</td>
</tr>
<tr>
<td>Schoppet</td>
<td>2004</td>
<td>12</td>
<td>75</td>
<td>3/10 chronic renal failure</td>
<td>50%</td>
<td>Carotid, Femoral</td>
<td>No</td>
<td>Calciﬁcation in neointimal layer in atherosclerosis (50%), medial calcification in Mönckeberg’s sclerosis (50%). Osteoprotegerin localized to calcified areas in media and neointimal layer.</td>
</tr>
<tr>
<td>Micheletti</td>
<td>2008</td>
<td>14</td>
<td>74</td>
<td>NR</td>
<td>42%</td>
<td>Dorsalis pedis, posterior tibialis, radial, thyroid, pedal, knee, breast, uterus, temporal</td>
<td>No</td>
<td>All specimens diagnosed as “Mönckeberg medial calcification” demonstrated calcification of both internal elastic lamina and media, inconsistent with the medical literature.</td>
</tr>
</tbody>
</table>

Table 2. Published case series of purported Mönckeberg’s sclerosis

![Table 2](https://example.com/table2.png)
osteoprogerin and TNF-related apoptosis-inducing ligand were predominantly adjacent to areas of calcification and apoptosis around the circumference of vessels. Finally, Michelleti et al. (17) reviewed the histology slides of 12 patients who were determined to have Mönckeberg’s sclerosis on first review. All of the specimens showed disruption of internal elastic lamina as in atherosclerotic disease; however, there was little evidence of inflammation. Reduplication and breaks of the internal elastic lamina were frequent findings associated with laminal and medial calcification. In some cases, there was intimal fibrosis associated with the lesions consistent with fibroatheroma. There was no assessment or reporting of lipid material or associated with the lesions consistent with fibroatheroma. There was no assessment or reporting of lipid material or associated with the lesions consistent with fibroatheroma.

Figure 1. Histologic section demonstrating purported Mönckeberg’s sclerosis with medial calcification; however, inspection of the intimal space shows a large lipid deposit characteristic of atherosclerosis. The correct interpretation is that this is medial calcification in the setting of atherosclerosis, not Mönckeberg’s sclerosis. Adapted from reference (14).

Accelerated Atherosclerotic Calcification in Chronic Kidney Disease

Atherosclerotic calcification begins as early as the second decade of life, just after fatty streak formation (7). Coronary artery lesions of young adults have revealed small aggregates of crystalline calcium within the lipid core of a plaque (7). Calcium phosphate \( \text{Ca}_3(\text{PO}_4)_2 \times \text{Ca(OH)}_2 \), which contains 40% calcium by weight, precipitates in diseased coronary arteries by a mechanism similar to that found in osteogenesis and bone remodeling (18). Hydroxyapatite, the predominant crystalline form in calcium deposits, is secreted primarily in vesicles that pinch off from arterial wall cells (vascular smooth muscle cells and pericytes), analogous to the way matrix vesicles pinch off from chondrocytes in developing bone (19,20). One of the principal stimuli for this component of atherosclerosis seems to be activation of the Pit-1 receptor by phosphorus (21). Thus, increasing serum phosphorus levels, through the normal range in the general population, those with symptomatic atherosclerosis, and all stages of CKD has been linked to higher rates of cardiovascular events and death (22–26) Coronary artery calcification (CAC) is an excellent radiographic proxy of atherosclerosis and seems to occur exclusively in atherosclerotic arteries and is absent in the normal vessel wall (27,28). Measurement of atherosclerotic CAC by electron-beam computed tomography (EBCT) with magnetic resonance imaging correlation has demonstrated that the calcified component can be several millimeters thick, implying calcification across the full thickness of the artery wall because it cannot distinguish between intimal and medial layers (29).

Kidney disease, particularly nephrotic syndrome, has been associated with the very early development of atherosclerosis in case reports of infants and young children (30,31). The preponderance of the medical literature supports the concept that patients with CKD have accelerated atherosclerosis in part because of greater numbers of atherosclerotic risk factors and a variety of pathobiologic processes that accelerate many facets, including ingress of cholesterol into the vessel wall, expression of adhesion molecules, recruitment of inflammatory cells, oxidation and modification of LDL cholesterol, activation and migration of vascular smooth muscle cells, transformation of vascular smooth muscle cells into osteoblast-like cells, secretion of calcium pyrophosphate crystals, fibrosis, and both inward and outward remodeling (21,32). It is widely recognized that atherosclerotic disease is the leading cause of death in patients with CKD (33). In studies in which an attempt to define what role, if any, Mönckeberg’s sclerosis plays as a unique process in patients with CKD, authors have concluded that Mönckeberg’s sclerosis and atherosclerosis are indistinguishable (34). After reviewing inferior gastric artery specimens from 41 patients with ESRD, all of whom had one or more atherosclerotic risk factors and 10 with known atherosclerotic disease in coronary
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Specimens with CKD Studied</th>
<th>Method of Establishing Arterial Media Calcification</th>
<th>Age</th>
<th>CKD Status</th>
<th>Atherosclerotic and Cardiovascular Risk Factors</th>
<th>Findings</th>
<th>Stains Used</th>
</tr>
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<tbody>
<tr>
<td>Nayir et al. (52)</td>
<td>2001</td>
<td>12</td>
<td>Internal iliac artery obtained during transplantation</td>
<td>14.6</td>
<td>HD</td>
<td>Hypertension</td>
<td>Five of 12 arteries had medial mucoid ground substance; two of 12 arteries had atherosclerotic plaques. No mention of medial calcification/plaques.</td>
<td>H&amp;E, trichrome (collagen), van Gieson (elastic fibers). No staining for lipid or inflammation.</td>
</tr>
<tr>
<td>Sakata et al. (53)</td>
<td>2003</td>
<td>7 (10 controls)</td>
<td>Nonatherosclerotic areas of aorta from patients without diabetes studied at autopsy</td>
<td>65.5</td>
<td>HD</td>
<td>No clinical data mentioned (except nondiabetic)</td>
<td>Medial calcification was more prominent in patients with ESRD than in control subjects.</td>
<td>H&amp;E, fuchsin (elastin), trichrome (collagen), von Kossa (calcium), antibodies against pentosidine (glycoxidation product). No staining for lipid.</td>
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<td>Gross et al. (54)</td>
<td>2007</td>
<td>23 (23 control subjects)</td>
<td>Autopsy study of coronary arteries</td>
<td>65.5</td>
<td>3 PD/10 HD/10 CKD</td>
<td>Hypertension (23), smoking (1), MI (5), peripheral arterial disease (4), stroke (2). Diabetes excluded.</td>
<td>Calcified plaques occupied significantly higher percentage of the media area in renal (16.6%) versus nonrenal patients (3.8%).</td>
<td>H&amp;E, von Kossa, von Gieson, immunohistochemistry. No staining for lipid.</td>
</tr>
<tr>
<td>Chowdhury et al. (55)</td>
<td>2004</td>
<td>41 specimens from patients with CKD (149 without CKD)</td>
<td>Radial artery harvested for coronary artery bypass surgery</td>
<td>54.1</td>
<td>CKD (creatinine &gt;2.5 mg/dl)</td>
<td>All patients had CAD and underwent CABG. Age &gt;50 yr (8.6%), smoking (9.8%), obesity (5%), diabetes (9.5%), hyperlipidemia (9%), peripheral arterial disease (13.5%), family history of CAD (5.1%).</td>
<td>11 (26.8%) of 41 specimens had medial calcification.</td>
<td>H&amp;E. No staining for lipid or inflammation.</td>
</tr>
<tr>
<td>Schwarz et al. (56)</td>
<td>2000</td>
<td>27 (27 control subjects)</td>
<td>Autopsy study of coronary arteries</td>
<td>69.5</td>
<td>21 HD/6 CKD</td>
<td>Hypertension (12), diabetes (8), MI (4), peripheral arterial disease (5)</td>
<td>More calcified plaques in patients with ESRD. No media calcification was reported. Media thickness was higher in renal patients.</td>
<td>H&amp;E, von Kossa, von Gieson, antibodies used for immunohistochemical staining. No staining for lipid.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>No. of Specimens with CKD Studied</td>
<td>Method of Establishing Arterial Media Calcification</td>
<td>Age</td>
<td>CKD Status</td>
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<td>Findings</td>
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<tr>
<td>Clyne et al.</td>
<td>1986</td>
<td>94</td>
<td>Autopsy study of coronary arteries</td>
<td>59</td>
<td>35 HD/10 PD/49 ESRD but not on dialysis</td>
<td>Autopsy-proven congestive heart failure (35), acute fatal MI (12), nonfatal MI (17), pericarditis (7).</td>
<td>36 patients had no or minimal arteriosclerosis, 57 patients had moderate to severe arteriosclerosis (&gt;50% obliteration)</td>
<td>Media calcification not studied.</td>
</tr>
<tr>
<td>Lindner et al. (58)</td>
<td>1974</td>
<td>21</td>
<td>Autopsy study of the coronary and cerebral blood vessels</td>
<td>37</td>
<td>21 HD</td>
<td>Fatal coronary artery disease (8), heart failure (3), stroke (3).</td>
<td>Autopsy-proven &gt;50% occlusion in major coronary or cerebral vessels (cardiovascular related deaths) in 14 of 21 patients.</td>
<td>Media calcification not studied.</td>
</tr>
<tr>
<td>Lewin et al.</td>
<td>1971</td>
<td>1</td>
<td>Autopsy study of coronary arteries</td>
<td>22</td>
<td>1 HD (initially on PD)</td>
<td>Hypertension</td>
<td>Small coronary arteries and arterioles had calcification of the internal elastic lamina, media, and intimal proliferation leading to narrowing or occlusion of the lumen.</td>
<td>H&amp;E, von Kossa. No staining for lipid or inflammation.</td>
</tr>
<tr>
<td>Lachman et al. (60)</td>
<td>1977</td>
<td>1</td>
<td>Autopsy study of the coronary, mesenteric, renal, celiac, splenic, and iliac arteries</td>
<td>41</td>
<td>1 PD</td>
<td>Hypertension, congestive heart failure</td>
<td>Coronary arteries had marked atherosclerosis with luminal narrowing &gt;75% by intimal atherosclerotic plaques and medial calcific deposits. Medial calcification alone (no intimal deposits) was seen in mesenteric, renal, celiac, splenic, and iliac arteries. No inflammatory cells in the blood vessels examined.</td>
<td>H&amp;E, Movat (elastic fibers) and lipid stain. No staining for inflammation.</td>
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<tr>
<td>Ibels et al. (61)</td>
<td>1979</td>
<td>18 (18 control subjects)</td>
<td>Renal and internal iliac artery samples obtained during transplantation</td>
<td>28</td>
<td>18 HD</td>
<td>Hypertension (13), smoking (9), peripheral vascular disease (1), family history of MI (1). None had diabetes</td>
<td>Uremic patients had greater prevalence of intimal thickening and calcification of internal elastic lamella and media than control subjects. Lipid deposits were seen in one renal artery (intimal thickening) and one iliac artery (plaque).</td>
<td>H&amp;E, von Kossa (phosphates), alizarin red S (calcium, magnesium), van Gieson (elastic tissue), lipid (oil red )</td>
</tr>
<tr>
<td>Qiao et al. (62)</td>
<td>2005</td>
<td>1</td>
<td>Autopsy study of coronary arteries</td>
<td>6</td>
<td>PD</td>
<td>Hypertension</td>
<td>Diffuse medial calcification in medium and large coronary arteries. Mild intimal proliferation and no evidence of atherosclerotic plaque.</td>
<td>H&amp;E. No staining for lipid or inflammation.</td>
</tr>
<tr>
<td>Moe et al. (34)</td>
<td>2002</td>
<td>39</td>
<td>Proximal inferior epigastric artery undergoing renal transplantation</td>
<td>45</td>
<td>25 HD, 14 PD, 2 not on dialysis</td>
<td>Hypertension, diabetes, stroke, mild nonobstructive coronary artery disease, nonischemic cardiomyopathy with heart transplant. Diabetes (14), history of CAD (8), peripheral vascular disease (2), hypertension (37), smoking (12), hyperlipidemia (10).</td>
<td>Medial calcification was mild/moderate in five vessels and severe in seven. No macrophages or cellular infiltrates in medial calcification.</td>
<td>Mac Neal and alizarin red S (calcium), immunohistochemical staining.</td>
</tr>
<tr>
<td>Rostand et al. (63)</td>
<td>1979</td>
<td>33</td>
<td>Autopsy study of coronary arteries</td>
<td>43</td>
<td>HD</td>
<td>Hypertension, hypertriglyceridemia, ischemic heart disease (26%)</td>
<td>70% stenosis of coronary arteries in seven of 33 patients who had autopsy. Medial calcification not studied.</td>
<td>Not described</td>
</tr>
<tr>
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<tr>
<td>Ansari et al. (64)</td>
<td>1993</td>
<td>106</td>
<td>Autopsy study of the coronary arteries and aorta</td>
<td>53</td>
<td>HD</td>
<td>Smoking (45%), hypertension (94%), family history of cardiovascular disease (57%), diabetes (26%)</td>
<td>MI present in 27 patients (12 acute). Coronary atherosclerosis present in 91 patients (45 had &gt;70% stenosis, 18 had 50 to 70% stenosis, 28 had &lt;50% stenosis). Medial calcification not studied.</td>
<td>Not described</td>
</tr>
<tr>
<td>Curry et al. (65)</td>
<td>1977</td>
<td>20</td>
<td>Autopsy study of coronary arteries</td>
<td>24</td>
<td>CKD</td>
<td>Nephrotic syndrome, diabetes (4), hypertension (19)</td>
<td>Significantly more coronary atherosclerosis in patients with nephrotic syndrome (8 with &gt;75% stenosis, 3 with 50 to 75% stenosis and 9 with &lt;50% stenosis).</td>
<td>Movat stain. No staining for lipid or inflammation.</td>
</tr>
<tr>
<td>Kallen et al. (30)</td>
<td>1977</td>
<td>1</td>
<td>Autopsy study of coronary arteries</td>
<td>5</td>
<td>CKD</td>
<td>Idiopathic nephrotic syndrome, hyperlipidemia</td>
<td>Partial to complete obstruction of coronary arteries. Atherosclerotic plaques with intimal proliferation. Medial calcification not studied.</td>
<td>Not described</td>
</tr>
<tr>
<td>Ibels et al. (66)</td>
<td>1974</td>
<td>9</td>
<td>Autopsy study of coronary arteries</td>
<td>–</td>
<td>Renal transplant</td>
<td>History of ischemic heart disease (five of nine), hypertension (15), stroke (3), peripheral vascular disease (11), hypertension (18), diabetes (6), smoking (5)</td>
<td>Coronary thrombosis. Medial calcification not studied.</td>
<td>Not described</td>
</tr>
<tr>
<td>Ori et al. (67)</td>
<td>2005</td>
<td>20 (52 control subjects)</td>
<td>Mesenteric artery operative specimen (15), angiography (3)</td>
<td>70.8</td>
<td>19 HD/1 PD</td>
<td>Ischemic heart disease (15), stroke (3), peripheral vascular disease (11), hypertension (18), diabetes (6), smoking (5)</td>
<td>Two of 11 mesenteric artery specimens had medial calcifications.</td>
<td>H&amp;E, von Kossa. No staining for lipid or inflammation.</td>
</tr>
</tbody>
</table>
Table 3. (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of Specimens with CKD Studied</th>
<th>Method of Establishing Arterial Media Calcification</th>
<th>Age</th>
<th>CKD Status</th>
<th>Atherosclerotic and Cardiovascular Risk Factors</th>
<th>Findings</th>
<th>Stains Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shanahan et al.</td>
<td>1999</td>
<td>30</td>
<td>Peripheral arteries after leg amputation</td>
<td>48 to 93</td>
<td>Nine with diabetes, 21 without diabetes, ?CKD</td>
<td>Leg amputation patients: Suspected to have CKD, peripheral vascular occlusive disease, diabetes (nine of 30)</td>
<td>Extensive medial calcification in all patients with diabetes and one of 21 without diabetes. Medial calcification occurred in the absence of macrophages and lipid.</td>
<td>H&amp;E, oil red O (lipid), von Kossa, immunohistochemistry</td>
</tr>
<tr>
<td>Antikainen et al. (68)</td>
<td>1994</td>
<td>10</td>
<td>Autopsy study of renal arteries</td>
<td>12.6 HD</td>
<td>HD</td>
<td>Congenital nephrotic syndrome of the Finnish type</td>
<td>Various degrees of intimal thickening seen in nine of 10 specimens. Short breaks in internal elastic lamina observed. Lipid staining in intimal layer in seven specimens. Medial calcification not studied.</td>
<td>H&amp;E, Sudan black and oil red O (lipid), immunohistochemistry</td>
</tr>
</tbody>
</table>

*aCAD, coronary artery disease; CABG, coronary artery bypass graft; H&E, hematoxylin and eosin; HD, hemodialysis; MI, myocardial infarction; PD, peritoneal dialysis.*
or peripheral arteries, Moe et al. (34) demonstrated predominately medial calcification (with visually thickened intima on reproduced slides) but did not stain for lipid or inflammatory components of atherosclerosis (35). In the discussion, the authors stated, “Despite past thoughts that medial calcification and atherosclerotic/plaque calcification are mechanistically distinct, thus far, there is no evidence to support this hypothesis.” This statement does not imply that there cannot be unique mechanisms in ESRD that amplify the atherosclerotic calcification process, because the work by Moe et al. demonstrated considerable involvement of a variety of osteogenic factors. Accordingly, it is prudent to abandon the term Mönckeberg’s sclerosis and use the American Heart Association Committee on Vascular Lesions of the Council on Arteriosclerosis classification (7). In this classification, what has been termed Mönckeberg’s sclerosis can be classified as American Heart Association stage Va and VII lesions (Figure 2) (7). These lesions tend to be lipid depleted, have little or no inflammation, and have dense calcification of the media as well as other layers in the vessel wall depending on the degree of atherosclerotic involvement. Recent studies identified components of the calcification process, including a novel gene for vascular calcification associated factor, which was shown to be important in pericyte osteogenic differentiation, extending from the subintimal space to the adventitia (36); therefore, the location of calcification in the vessel wall is inherent to the pathology of atherosclerosis and cannot be used to distinguish atherosclerosis from nonatherosclerotic disease. Finally, new techniques to evaluate the structure and presence of cholesterol crystals (Figure 3) have identified the calcification process to be closely linked to cholesterol crystallization (Figure 4). Cholesterol seems to be the initial trigger for the nidus of calcification to form. In atherosclerotic rabbits, the development of atheromatous plaque is a prerequisite for calcification (37,38). In bench-top studies, addition of cholesterol to the calcium phosphate crystals formed shapes similar to those seen in human plaques (39). These are typically ball-shaped concretions similar to those that we have observed (Figure 3). By using scanning electron microscopy and energy-dispersive spectroscopy, we have demonstrated a coexistence of cholesterol crystals and calcium crystals. There are differences in the two types of crystal shapes, with cholesterol crystals being elongated with regular repeating patterns and calcium phosphate crystals having distortions and less regular forms especially when mixed with cholesterol crystals. By x-ray energy-dispersive spectroscopy, the presence of calcium can be readily identified (Figure 4). Although these findings do not causally link cholesterol crystallization with calcification, they strongly suggest that the processes occur in very close proximity within the vessel wall. Accepting that vascular calcification is a fundamental component of the atherosclerotic process, a next reasonable question would be, “Can this process be attenuated or reversed?”

### Attenuation of Vascular Calcification and LDL Cholesterol Reduction

Two nonrandomized studies using statins (hepatic hydroxymethyl glutaryl-CoA reductase inhibitors) demonstrated attenuation of progression in CAC associated with LDL cholesterol reduction (40,41). The annualized relative change of the CAC score in 32 of 66 patients who achieved an LDL cholesterol level <100 mg/dl with cerivastatin 0.3 mg/d orally decreased from 27 to −3.4% (P < 0.0001) on serial EBCT examinations (40). Callister et al. (31) reported on 149 patients with coronary artery disease (CAD) and demonstrated in those for whom the achieved LDL cholesterol was <120 mg/dl that there was regression of CAC by EBCT 12 to 15 mo apart. There was a correlation (r = 0.50) between the reduction in LDL cholesterol and the change in CAC by EBCT with regression in CAC beginning to occur on the line of best fit at an approx-
imate LDL cholesterol level <100 mg/dl. Some patients in these studies had arrest or reversal in the calcification process; however, the determinants beyond LDL cholesterol reduction of this reversal process are not completely understood.

Five randomized, prospective, comparative trials of statins in the general population did not exclude patients on the basis of eGFR, attempting to show attenuation or reversal of CAC by EBCT (42–46). All of these trials, which totaled 2273 patients, failed to demonstrate that LDL cholesterol reduction can modify the rate of progression of CAC, which is, on average, approximately 25% per year; however, in the larger studies with sufficient follow-up time, as expected, there has been a reduction in cardiovascular events associated with LDL cholesterol reduction with statins. In addition, the Coronary Artery Calcification Treatment with Zocor (CATZ) study testing simvastatin 80 mg/d versus placebo for 12 mo in 80 patients failed to demonstrate a difference in the progression of abdominal aortic calcification measured by CT (46). Finally, the Investigators Scottish Aortic Stenosis and Lipid Lowering Therapy, Impact on Regression (SALTIRE) trial tested atorvastatin 80 mg/d versus placebo for 12 mo in 80 patients failed to demonstrate a difference in the progression of abdominal aortic calcification measured by CT (46). The subgroup analyses based on renal function have not been reported from these trials, but, taken on average, it seems that LDL cholesterol reduction does not influence the rate of atherosclerotic calcification; however, despite the advancement of calcification, it seems that LDL cholesterol reduction, as expected, reduces rate of myocardial infarction and cardiovascular death. The most plausible explanation for this finding is that statins create plaque stabilization at the level of the endothelium and perhaps change the characteristics of the lipid pool and necrotic core; however, once initiated, the vascular calcification process is not influenced by either LDL-C cholesterol lowering or potential pleiotropic effects of statins. Thus, monitoring the progression of CAC is not a valid approach for detecting a change in the risk for atherosclerotic events.

**Phosphate Binders and Attenuation of Vascular Calcification**

Previous studies showed that vascular calcification is markedly enhanced in ESRD and associated with cardiovascular and all-cause mortality. In patients with ESRD, the amplified CAD found by EBCT has been associated with advanced age; duration of dialysis; phosphorus levels; and the conventional cardiovascular risk factors including diabetes, elevated LDL cholesterol, depressed HDL cholesterol, and elevated triglycerides (47).

In the Treat to Goal trial by Chertow et al. (48), 200 dialysis-dependent patients were randomly assigned to sevelamer (a gastrointestinal phosphate binder and bile acid sequestrant) versus calcium carbonate/calcium acetate (gastrointestinal phosphate binder alone) and had EBCT scans done at baseline and at 52 wk. Investigators were not blinded to the measures of CaPO4 balance and were allowed to adjust phosphate binders and dialysate calcium and use vitamin D/vitamin D analogues. The final LDL cholesterol levels in the sevelamer and the calcium groups were 65 and 103 mg/dl, respectively (P < 0.0001). This is consistent with the known bile acid sequestrant properties of sevelamer. In that trial, there was attenuation of progression of CAC with sevelamer with no differences in calcium, phosphorus, or parathyroid hormone, suggesting the change in CAC was more related to LDL cholesterol reduction with sevelamer or excess of calcium ingestion in the calcium binder arm.

The second study to examine this question, Renagel In New Dialysis patients (RIND), randomly assigned a smaller group of 127 incident patients who were new to dialysis to either sevelamer hydrochloride or calcium-based binder, predominately calcium carbonate, and found that the annual rates of progression of CAC were 13.4 and 25.3%, respectively (P = 0.06) (49). Again there was an LDL cholesterol reduction from 72 to 60 mg/dl with sevelamer compared with an increase in LDL cholesterol from 72 to 81 mg/dl with calcium carbonate. At a median of 44 mo, the difference in unadjusted mortality rates for patients who were assigned to calcium-containing binders (10.6/100 patient-years; 95% confidence interval [CI] 6.3 to 14.9) compared with 5.3/100 patient-years (95% CI 2.2 to 8.5) for

![Figure 4](image.jpg)
those who were assigned to sevelamer; this difference was of borderline significance ($P = 0.05$ with overlapping CI). The most recent trial, Calcium Acetate Renal Evaluation-2 (CARE-2), randomly assigned 203 patients with ESRD to calcium acetate plus atorvastatin or sevelamer plus atorvastatin and measured the progression of CAC at 6 and 12 mo by EBCT (50). In the calcium acetate group, 97% received atorvastatin with an average daily dosage of 33 mg. In comparison, 79% of sevelamer-treated patients received atorvastatin at an average daily dosage of 28 mg ($P = 0.016$). The LDL cholesterol levels were reduced in both treatment groups with mean serum LDL cholesterol levels decreasing from 112 to 69 mg/dl in the calcium acetate group and 108 to 62 mg/dl in the sevelamer group ($P = 0.03$), and despite treatment with the statin and phosphate binder, there was no differential attenuation in the annual progression of CAC, which were 35% in the calcium acetate group and 39% in the sevelamer group. Thus, from these trials, there are no convincing data that either the type of phosphate binder or the use of statins can attenuate the rate of CAC progression in ESRD.

This comparative concept was extended to the Dialysis Clinical Outcomes Revisited (DCOR) trial, which recruited more than 2100 patients and compared the difference in mortality and morbidity outcomes for patients who received sevelamer hydrochloride and those who used calcium-based phosphate binders, again predominately over-the-counter calcium carbonate. Despite the LDL cholesterol reduction with sevelamer, there was no reduction in mortality between the treatment groups ($9\%$ relative risk reduction with sevelamer, $P = 0.30$) (51). Thus, stabilization of the progression of CAC with sevelamer, if it occurs in ESRD, does not translate to reductions in mortality.

Conclusions

Mönckeberg’s sclerosis has been a pathologic misconception for more than 100 yr. The published histologic and clinical data suggest that Mönckeberg’s sclerosis describes advanced calcific atherosclerosis as the common and important pathobiology that is present in patients with CKD. In rare cases of demineralizing disorders, unrelated to CKD, Mönckeberg’s sclerosis has been used to describe a fulminant vascular calcinosis syndrome. Attempts to modify the rate of measurable accumulation of calcium in atherosclerotic lesions with statins have failed; however, drugs that modify components of CKD-MBD including hyperphosphatemia hold promise and are worthy of future trials but need to focus on reductions in cardiovascular events because CAC may not be a reliable surrogate for response to treatment.

Disclosures

None.

References

15. Castillo BV Jr, Torczynski E, Edward DP: Mönckeberg’s...


