Updates on the Mechanisms and the Care of Cardiovascular Calcification in Chronic Kidney Disease

Lucie Hénaut, PhD,[*] Jean-Marc Chillon, PhD, PharmD,[*,†] Saïd Kamel, PhD, PharmD,[*,‡] and Ziad A. Massy, PhD, MD[§,‖]

Summary: In chronic kidney disease (CKD), the progressive decrease in renal function leads to disturbances of mineral metabolism that generally cause secondary hyperparathyroidism. The increase in serum parathyroid hormone is associated with reduced serum calcium and calcitriol levels and/or increased serum fibroblast growth factor-23 and phosphate levels. The resulting CKD-associated disorder of mineral and bone metabolism is associated with various other metabolic dysregulations such as acidosis, malnutrition, inflammation, and accumulation of uremic toxins. It favors the occurrence of vascular calcification, which results from an imbalance between numerous inhibitors and promoters of soft-tissue mineralization. This review provides an overview of the most recent state of knowledge concerning the mechanisms that lead to the development of vascular calcification in the CKD setting. It further proposes directions for potential new therapeutic targets.
Semin Nephrol 38:233-250
Keywords: Chronic kidney disease, vascular calcification, promoters, inhibitors, treatments

Vascular calcification is a degenerative process characterized by the accumulation of calcium and phosphate salts within the arterial wall. It is observed in nearly all arterial beds and can develop in the media, the intima, or both. Calcification of the intimal layer usually occurs as a consequence of atherosclerosis and may be responsible for coronary ischemic events. Conversely, medial calcification is nonocclusive and preferentially develops along elastic fibers. As a consequence, medial calcification increases vessel stiffness, arterial pulse-wave velocity, systolic blood pressure, and pulse pressure, favoring the development of cardiac failure, left ventricular hypertrophy, and diastolic dysfunction. Vascular calcification is a complex process that involves not only the precipitation of minerals (ie, mineral step) but also is a tightly regulated, cell-mediated process, similar to bone formation (ie, cellular step). Despite significant recent growth of knowledge about vascular calcification, the order of appearance and time course of these two steps and of the initiating pathogenic events is still subject to debate. It is extremely difficult, if not impossible, to assess this in patients with chronic kidney disease (CKD).[1] Of interest, a recent time course study in uremic rats showed that an increase in tissue nonspecific alkaline phosphatase (TNAP) and Wnt inhibitor Dkk1 expression in the aorta preceded initial calcium deposition, and that this increase was preceded only by increases in circulating fibroblast growth factor (FGF)23 and activin A.[2] The presence of vascular calcification in the general population is predicted by traditional Framingham risk factors such as age, sex, family history, hypertension, tobacco use, diabetes, and dyslipidemia. In patients with CKD, vascular calcification is more prevalent and more severe than in the general population. Although CKD patients generally have a high prevalence of the traditional risk factors, vascular calcification in this population also is associated with several nontraditional risk factors. They include the CKD-associated disorder of bone and mineral metabolism (CKD-MBD), inflammation, oxidative stress, and the accumulation of uremic toxins, and predispose to earlier and accelerated vascular calcification as well as an excess cardiovascular morbidity and mortality.

The present review has two goals. First, we offer an overview of the current knowledge concerning a

[*]*Laboratory MP3CV, Centre Universitaire de Recherche en Santé, Amiens, France.*
[†]*Direction de la Recherche Clinique et de l'Innovation, Amiens University Hospital, Amiens, France.*
[‡]*Laboratory of Biochemistry, Amiens University Hospital, Amiens, France.*
[§]*Division of Nephrology, Ambroise Paré University Hospital, Assistance publique – Hôpitaux de Paris, Boulogne-Billancourt/Paris, France.*
[‖]*Inserm U1018, Team 5, Centre de recherche en Epidémiologie et Santé des Populations, Université de Versailles Saint-Quentin-en-Yvelines, Paris-Saclay University, Villejuif, France.*

Financial support: Supported by the Recherche hospitalo-Universitaire project Search Treatment and improve Outcome of Patients with Aortic Stenosis (L.H.).

Conflict of interest statement: Z. A. Massy has received grants for CKD REIN and other research projects from Amgen, Baxter, Fresenius Medical Care, GlaxoSmithKline, Merck Sharp and Dohme-Chibret, Sanofi-Genzyme, Lilly, Otsuka, and the French government, as well as fees and grants to charities from Amgen, Bayer, and Sanofi-Genzyme. These sources of funding are not necessarily related to the content of the present article.

Address reprint requests to Z. A. Massy, MD, PhD, Division of Nephrology, Ambroise Paré University Hospital, 9 Ave Charles de Gaulle, F-92104 Boulogne Billancourt Cedex, France. E-mail: ziad.massy@aphp.fr

0270-9295/ - see front matter

https://doi.org/10.1016/j.semnephrol.2018.02.004

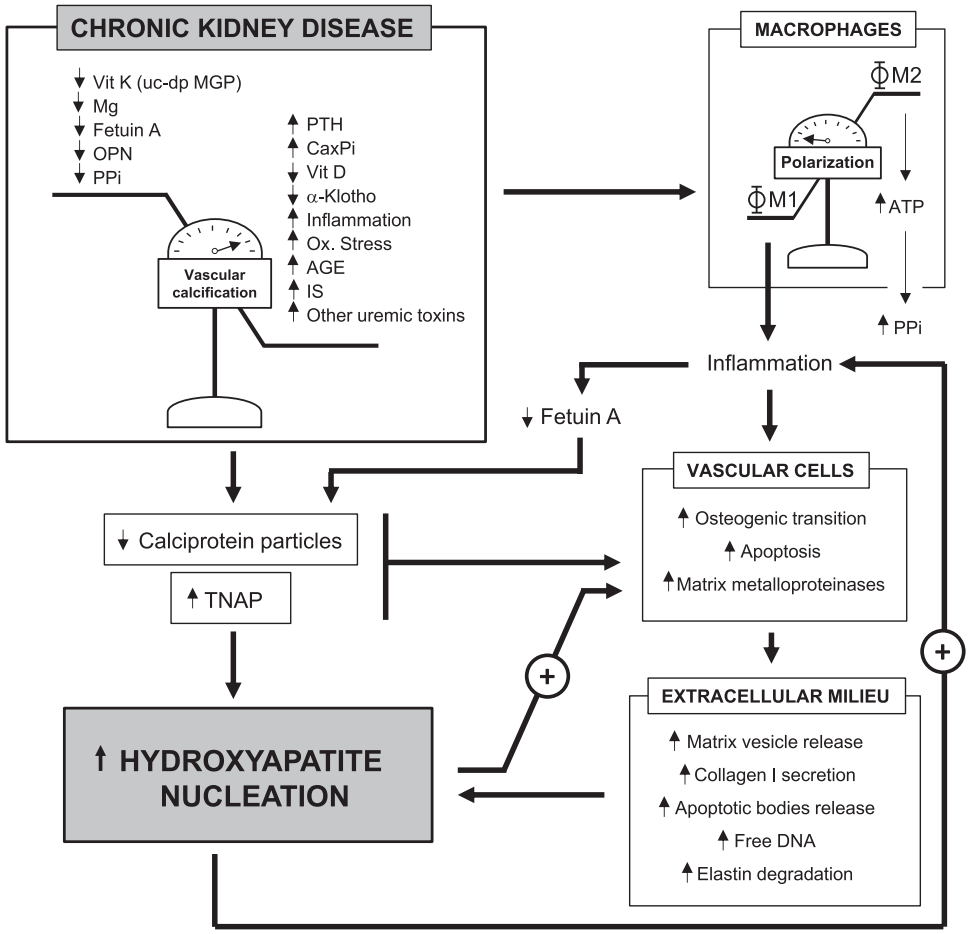

Figure 1. Development of vascular calcification in CKD: a schematic view. CaxPi, calcium phosphate product; IS, indoxyl-sulfate; OPN, osteopontin; Ox. Stress, oxidative stress; PPi, pyrophosphate; uc-dp MGP, uncarboxylated-dephosphorylated matrix gla protein; Vit D, vitamin D; Vit K, vitamin K.

variety of mechanisms by which vascular calcification develops in the CKD setting. The main focus is on recently identified mechanisms. Because the implications of parathyroid hormone (PTH) and vitamin D have been discussed in numerous previous reviews, these important factors will not be addressed here in any detail. Second, we present an in-depth examination of potential new therapeutic targets, based on novel pathogenic insights.

UREMIC SYNDROME AND VASCULAR CALCIFICATION

Under physiological conditions, blood vessels are protected from supersaturated concentrations of serum calcium (Ca) and phosphate (P) by a number of active inhibitors. Among them, pyrophosphate, matrix Gla protein (MGP), and fetuin-A have been shown to prevent the transformation of soluble, amorphous calcium phosphate (Ca/P) complexes into harmful, stable hydroxyapatite crystals. In the CKD population, a decrease in levels of active inhibitors and a simultaneous increase in levels of active inducers of calcification are responsible for the extremely high prevalence of intimal and medial vascular calcification[3–5] (Fig. 1). Disturbances of mineral metabolism are key inducers of vascular calcification in these patients. Particularly, increased Ca and P levels are associated with vascular calcification in patients with CKD and may directly promote vascular calcification.[6–9] In addition, chronic low-grade inflammation, malnutrition, and the gradual accumulation of uremic retention solutes, such as advanced-glycation end products (AGEs) or indoxyl sulfate, promote various types of vascular damage that impact vascular calcification.

Disturbances of Calcium and Phosphate Metabolism

Although hyperphosphatemia is considered the main risk factor for the development of vascular calcification in CKD patients,[9] evidence also implicates a pivotal role for increased serum Ca levels[10] and increased Ca × P product.[11,12] It is noteworthy that vascular calcification in CKD generally develops before measurable