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Pathophysiological aspects of vascular calcification in chronic renal failure

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SUMMARY

The nephrology community has progressively recognized that vascular calcification in patients with chronic renal failure is a major problem in terms of morbidity and mortality. This type of soft tissue calcification is not only passive, as thought previously, but implies active processes as well. It results from disturbances of the normal balance between calcification inhibitors and promoters, acting both at the systemic and the local level, and from the phenotypic change of smooth muscle cells towards osteoblast-like calcifying cells in the vessel wall. The recognition of the main factors involved will allow in the future a more appropriate prophylactic and therapeutic approach of this clinically important complication of chronic renal failure.

Key words: ***Calcification. Chronic kidney disease. Vascular. Inhibitors. Vascular calcification.***

ASPECTOS FISIOPATOLÓGICOS DE LA CALCIFICACIÓN VASCULAR EN LA INSUFICIENCIA RENAL CRÓNICA

RESUMEN

La comunidad nefrológica ha aprendido progresivamente que las calcificaciones vasculares son un problema importante para la mortalidad y la morbilidad de los pacientes con insuficiencia renal crónica. Este tipo de calcificaciones de tejidos blandos no es solo pasiva como se ha pensado hasta ahora, sino que también están implicados en ella procesos activos. Es el resultado de la ruptura del balance entre inhibidores y promotores de la calcificación que actúan tanto a nivel sistémico como local y del cambio en el fenotipo de las células musculares lisas que se transforman en células parecidas a los osteoblastos con propiedades de calcificar. El conocer los principales factores implicados nos permitirá en el futuro tratar mejor y de forma profiláctica esta importante complicación de la insuficiencia renal crónica.

Palabras clave: ***Calcificación. Enfermedad renal crónica. Vascular. Inhibidores. Calcificación vascular.***

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INTRODUCTION

Patients with chronic kidney disease (CKD) may develop soft tissue calcification of various types and locations, including vascular calcification. The process starts long before reaching end-stage renal disease (ESRD)[1]. The propensity to calcify the vessel wall increases with CKD progression towards ESRD, where a «perfect storm of vascular calcification arises»[2]; the velocity of this increase is more marked in diabetic than in non-diabetic CKD patients[3]. In dialysis patients, the yearly progression of vessel wall calcification is dramatic[4,5]. Our understanding of the mechanisms involved in this process has greatly improved in recent years, as has our perception of the link between vascular calcification and cardiovascular morbidity and mortality in ESRD patients[6,7].

Before giving a brief update on present pathogenetic concepts it is important to mention the main patterns of arterial calcium deposits.

TYPES OF VASCULAR CALCIFICATION

There are different types of vascular calcification. In general, slowly progressive forms prevail which are characterized by either focal, patchy deposits of calcium and phosphate in atheromatous plaques («intima calcification»), or by diffuse deposits in the medial layer of the arterial tree («media calcification»). Frequently, the two forms are combined. Calciphylaxis, also called «calcific uraemic arteriolopathy», is a much more infrequent, rapidly progressive form of vascular calcification.

Atheromatous plaques of uraemic patients are more frequently and more intensively calcified than those of non-uraemic subjects[8]. The most marked difference compared with non-uraemic patients is not that of plaque size, but that of plaque composition.

Media calcification generally becomes visible on x-ray examination only after it has reached a certain degree of intensity. In advanced stages it often is associated with the occurrence of transformed smooth muscle cells in the media which exhibit the characteristics of osteoblast-like cells[9]. Media calcification is a manifestation of ageing, and in this perspective the uraemic state can be considered as a state of premature and accelerated ageing.

Of note, intima calcifications have a worse prognosis than media calcifications[10].

PATHOGENETIC MECHANISMS

General predisposing conditions

Changes of the vessel wall with ageing clearly represent the most important mechanism for vascular calcification. This is also true for patients with CKD, including those on renal replacement therapy. However, childhood and young adulthood do not protect against vascular calcium accumulation, as shown in one early post-mortem study in uremic children[11] and two more recent cross-sectional studies in young adults[5,12].

Diabetes has long been known to be another favouring condition. The association of diabetes with ESRD increases the risk of vascular calcification several-fold, compared with each morbid condition alone[13], and this appears to be independent of the calcium x phosphorus product[13,14].

Other well-known favouring conditions are male gender, white race, and dialysis vintage[6].

Of note, coronary artery calcification is inversely correlated with bone mass in dialysis patients[4], as in general population, probably due to excessive bone resorption of calcium and phosphate and their uptake by soft tissues, including blood vessels[15].

High plasma calcium and phosphorus

Abnormalities in mineral metabolism in general and disturbances in calcium and phosphorus metabolism in particular have traditionally been thought of as important determinants in patients with chronic renal failure. In this context, vascular calcification is seen as one component of a more generalized process of dystrophic, extra-skeletal calcification that affects a variety of soft-tissues, often in association with either hyperparathyroidism or hypoparathyroidism and with vitamin D overload[11,16,17]. However, many other systemic and local factors play important roles as well.

Disturbances of calcium and phosphate metabolism have long been shown to contribute to the pathogenesis of arterial calcification of either type. In recent years, it has become increasingly clear that elevations in plasma calcium, phosphorus and parathyroid hormone (PTH), either alone or combined, may be associated not only with soft tissue calcification, but also with the relative risk of cardiovascular and all-cause mortality[18-20]. Other systemic factors may also favour calcification such as leptin, oxidised LDL, corticosteroids, oestradiol, advanced glycation end products (AGE) and advanced oxidation protein products (AOPP) (fig. 1).

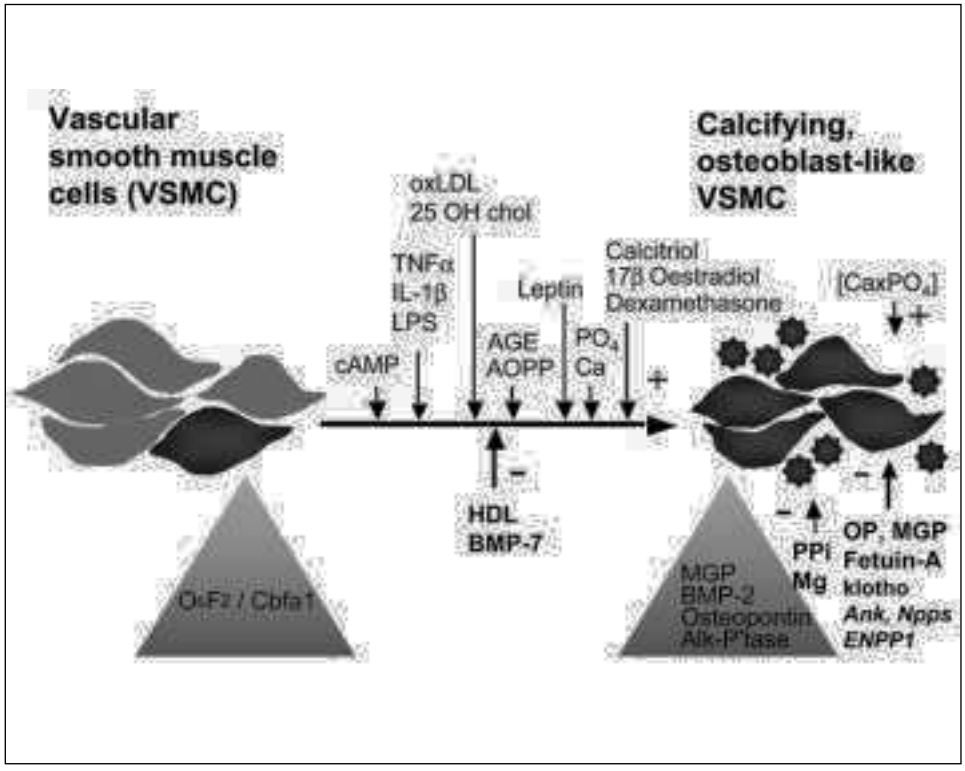

Fig. 1.—Transformation of vascular smooth muscle cells (VSMC) to the phenotype of osteoblast-like, calcifying cells in response to the action of numerous local and systemic factors (reproduced from Drueke and Rostand, NDT 2002; 17: 1365-8). *AGE, advanced glycation end-products. Ank, ankylosis protein (transporting Ppi to extracellular milieu). AOPP, advanced oxidation protein products. BMP-2, bone morphogenetic protein-2. ENPP1, ecto-nucleotide pyrophosphatase/phosphodiesterase 1. HDL, high-density lipoprotein. Klotho, klotho protein (regulator of ageing). MGP, matrix-gla protein. Npps, nucleotide pyrophosphatase (responsible for ectopic ossification). oxLDL, oxidised low-density lipoprotein. PPi, inorganic pyrophosphate. OP, osteopontin. O_5F_2/Cbfa1, osteoblast-inducing transcription factor.*

From a pathophysiological point of view, the frequently observed elevation of the plasma calcium × phosphorus ion (Ca × P) product was initially thought to be one of the main mechanisms involved in arterial media calcification of CKD patients, in addition to age and diabetes. However, since not all ESRD patients with comparable age, Ca × P products and nephropathy types develop progressive vascular calcification, the deposition of calcium and phosphate in soft tissues has long been regarded as the result of a more complex interaction between a variety of systemic and local factors.

Local mechanisms

Many local factors are involved in the regulation of the calcification process, by either inhibiting or stimulating vascular calcification and the associated phenotypic transformation of local vascular smooth muscle cells towards osteoblast-like calcifying cells[21] (see fig. 1). The latter is associated with an up-regulation of the key osteoblast regulatory factor Cbfa1 in vitro and also with its up-regulation in dialysis patients in vivo. Moreover, the emergence of these calcifying cells goes along with the de novo expression of several bone-associated proteins[22].

A variety of factors inhibit the phenotypic change and/or apatite crystal formation by the osteoblast-like cells at the local level (fig. 1). They include inorganic compounds such as pyrophosphate and magnesium and organic compounds such as proteins and lipoproteins. Gla-containing proteins such as Matrix gla protein (Mgp) exert an important inhibitory role at the site of the arterial wall[23]. Numerous paracrine and endocrine vascular factors control calcium deposition as well, including BMG-2, BMP-7, Wnts, PTHrp, osteopontin, osteoprotegerin and fetuin-A[22,24,25]. Oxidative stress enhances the differentiation of vascular smooth muscle cells into osteoblast-like cells whereas it reduces differentiation markers in bone osteoblastic cells and marrow stromal cells[26]. Finally, several genetically transmitted diseases are favouring conditions as well via the generation of abnormal gene products including klotho, Ank, Npps and ENPP1.

Of particular interest to the nephrology community are recent studies showing that phosphate and calcium are capable of stimulating directly, both independently and synergistically, extracellular matrix mineralization by vascular smooth muscle cells *in vitro*[27-29].

CONCLUSION

Vascular calcification in CKD patients, like in general population, is both a passive and an active process. It is generally the result of disturbances of the complex and subtle balance between inhibitors and promoters, acting both at the systemic and the local level. For the clinical nephrologist it is important to identify the main factors involved in each CKD patient, so the most appropriate prophylactic and therapeutic measures can be taken.

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