NEFROLOGIA 2017;xxx(xx):xxx–xxx

Sociedad Española de Nefrología

nefrología

Revista de la Sociedad Española de Nefrología

www.revistanefrologia.com

Review

Role of pyrophosphate in vascular calcification in chronic kidney disease

Daniel Azpiazu[a], *Sergio Gonzalo*[a], *Emilio González-Parra*[b], *Jesús Egido*[a,b], *Ricardo Villa-Bellosta*[a,*]

[a] *Fundación Instituto de Investigación Sanitaria, Fundación Jiménez Díaz, Madrid, Spain*
[b] *Servicio de Nefrología e Hipertensión, Fundación Jiménez Díaz, Universidad Autónoma, Madrid, Spain*

ARTICLE INFO

Article history:
Received 19 September 2016
Accepted 20 July 2017
Available online xxx

Keywords:
Vascular calcification
Pyrophosphate
Chronic kidney disease
Haemodialysis
Hydroxyapatite

ABSTRACT

Vascular calcification is a pathology characterized by the deposition of calcium-phosphate in cardiovascular structures, mainly in the form of hydroxyapatite crystals, resulting in ectopic calcification. It is correlated with increased risk of cardiovascular disease and myocardial infarction in diabetic patients and in those with chronic kidney disease (CKD). Vascular smooth muscle cells are sensitive to changes in inorganic phosphate (Pi) levels. They are able to adapt and modify some of their functions and promote changes which trigger calcification. Pi is regulated by parathyroid hormone and 1,25-dihydroxyvitamin D. Changes in the transport of Pi are the primary factor responsible for the regulation of Pi homeostasis and the calcification process.

Synthesis of calcification inhibitors is the main mechanism by which cells are able to prevent vascular calcification. Extracellular pyrophosphate (PPi) is a potent endogenous inhibitor of calcium-phosphate deposition both *in vivo* and *in vitro*. Patients with CKD show lower levels of PPi and increased activity of the enzyme alkaline phosphatase. Numerous enzymes implicated in the metabolism of PPi have been associated with vascular calcifications. PPi is synthesized from extracellular ATP by nucleotide pyrophosphatase/phosphodiesterase from extracellular ATP hydrolysis. PPi is hydrolyzed into Pi by

Abbreviations: ABCC6, ATP binding cassette subfamily C member 6; ADHR, autosomal dominant hypophosphatemic rickets; ALP, alkaline phosphatase; ANK, putative transporter progressive ankylosis; Cbfa-1, core-binding factor subunit alpha-1; CKD, chronic kidney disease; CPD, calcium-phosphate deposition; eNTPD1, ectonucleoside triphosphatediphosphohydrolase 1; eNTPD3, ectonucleoside triphosphatediphosphohydrolase 3; ENT1, equilibrative nucleoside transporter 1; FGF-7, fibroblast growth factor 7; FGF-23, fibroblast growth factor 23; GACI, generalized arterial calcification of infancy; IBGC, idiopathic basal ganglia calcification; MEPE, matrix extracellular phosphoglycoprotein; MMP2, matrix metallopeptidase 2; MMP9, matrix metallopeptidase 9; NaPi-IIa, sodium phosphate cotransporter type II member 1; NaPi-IIb, sodium phosphate cotransporter type II member 2; NaPi-IIc, sodium phosphate cotransporter type II member 3; NPP, pyrophosphatase/phosphodiesterase; NPP-1, pyrophosphatase/phosphodiesterase 1; NPP-3, pyrophosphatase/phosphodiesterase 3; OPN, osteopontin; PFA, phosphonoformic acid; Pi, inorganic phosphate; Pit-1, sodium phosphate cotransporter type III member 1; Pit-2, sodium phosphate cotransporter type III member 2; PPi, pyrophosphate; PTH, parathyroid hormone; PXE, pseudoxanthoma elasticum; SM22α, actin-binding protein smooth muscle 22α; sFRP-4, secreted frizzled-related protein 4; TIO, tumor-induced osteomalacia; TNAP, tissue-nonspecific alkaline phosphatase; VC, vascular calcification; VitD, 1,25-dihydroxyvitamin D; VSMCs, vascular smooth muscle cells; XLH, X-linked hypophosphatemia; 5NT, 5′-ectonucleotidase.

* *Corresponding author.*
E-mail address: ricardo.villa@fjd.es (R. Villa-Bellosta).

https://doi.org/10.1016/j.nefro.2017.07.005

Please cite this article in press as: Azpiazu D, et al. Role of pyrophosphate in vascular calcification in chronic kidney disease. Nefrologia. 2017. https://doi.org/10.1016/j.nefro.2017.07.005

tissue-nonspecific alkaline phosphatase. ATP can be hydrolyzed to Pi via the ectonucleoside triphosphate diphosphohydrolase family. All these enzymes must be in balance, thereby preventing calcifications. However, diseases like CKD or diabetes induce alterations in their levels. Administration of PPi could open up new treatment options for these patients.

Papel del pirofosfato en la calcificación vascular en la enfermedad renal crónica

Palabras clave:
Calcificación vascular
Pirofosfato
Enfermedad renal crónica
Hemodiálisis
Hidroxiapatita

RESUMEN

La calcificación vascular es una enfermedad caracterizada por depósitos de fosfato de calcio, principalmente hidroxiapatita, en las estructuras cardiovasculares, dando como resultado calcificaciones ectópicas. Se ha relacionado con un mayor riesgo de padecer enfermedades cardiovasculares e infarto de miocardio en pacientes diabéticos y enfermos renales crónicos. Las células del musculo liso vasculares son sensibles a cambios en los niveles de fosforo inorgánico (Pi), adaptando y modificando su función y promoviendo cambios que desencadenan calcificaciones. El Pi es regulado por hormona paratiroidea y vitamina D. Cambios en el transporte de Pi son el primer factor responsable en la regulación de la homeostasis del Pi y el proceso de calcificación.

La síntesis de inhibidores de calcificación es el principal mecanismo por el que las células nos protegen frente a la calcificación vascular. El pirofosfato extracelular (PPi) es un potente inhibidor endógeno de los depósitos de fosfato-calcio, tanto *in vivo* como *in vitro*. Enfermos renales crónicos muestran bajos niveles de pirofosfato y una mayor actividad de la enzima fosfatasa alcalina. Diversas enzimas relacionadas con el metabolismo del PPi extracelular se han relacionado con calcificación vascular. El PPi se sintetiza a partir de ATP extracelular por la nucleótido pirofosfatasa/fosfodiesterasa a partir de la hidrólisis del ATP extracelular. El PPi es hidrolizado a Pi por la fosfatasa alcalina no específica de tejido. El ATP puede ser hidrolizado a Pi por la familia ectonucleósido trifosfato difosfohidrolasa. Todas estas enzimas deben estar en equilibrio, evitando así las calcificaciones; sin embargo, dolencias como la enfermedad renal crónica o la diabetes provocan alteraciones en sus niveles. La administración de pirofosfato puede abrir nuevas vías de tratamiento en estos pacientes.

Introduction

Vascular calcification (VC)[1–3] is a pathology characterized by the deposition of calcium-phosphate in cardiovascular structures, mainly in the form of hydroxyapatite crystals, resulting in vessel thickening and ectopic calcification. Vascular calcification originates in the aortic walls, where calcification takes place in the medial layer of the vessel (Monckeberg's medial sclerosis).[4] It is correlated with increased risk of cardiovascular disease and myocardial infarction[5] and is associated with aging and diseases like atherosclerosis, hypertension, and metabolic disorders, commonly appearing in diabetic patients and in those with chronic kidney disease (CKD).[6] Patients with CKD suffer several metabolic and enzymatic disturbances, which cause an increase in the level of serum inorganic phosphate (Pi) and glucose. High levels of phosphate have been associated with the expression of osteogenic genes, hydroxyapatite formation,[7] and overall appearance of vascular calcifications.

Vascular smooth muscle cells (VSMCs) are sensitive to Pi levels, being able to adapt and modify some of their functions. These changes in response to variation in Pi lead to processes that promote calcification. Some of these actions include extracellular matrix calcification, induction of apoptosis, vesicle release, and the expression of osteogenic and chondrogenic genes.[5] Many studies have indicated Pi as a major risk factor for cardiovascular diseases in CKD due to the following: 1) Pi is capable of upregulating the expression of osteogenic and chondrogenic genes like Runx2, osteopontin, and alkaline phosphatase (ALP), while downregulating genes that promote smooth muscle cell lineage such as SM22α[8,9]; 2) Pi may promote the activation of the proapoptotic pathway by reducing gene 6 and its receptor, which is implicated in the antiapoptotic pathway[10]; and 3) the matrix metalloproteinases MMP-2, MMP-9, and elastin-degrading enzymes can be upregulated by high levels of phosphate.[11,12]

In addition to the main role of Pi, the importance of calcium-phosphate deposition (CPD) in the vessels in the

Please cite this article in press as: Azpiazu D, et al. Role of pyrophosphate in vascular calcification in chronic kidney disease. Nefrologia. 2017. https://doi.org/10.1016/j.nefro.2017.07.005