Clinica Chimica Acta xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Vascular calcification: from pathophysiology to biomarkers

Séverine Evrard [a], Pierre Delanaye [b], Said Kamel [c,d], Jean-Paul Cristol [e], Etienne Cavalier [a,*],
On behalf of the SFBC/SN joined working group on vascular calcifications
J. Arnaud [1], Ph. Zaoui [1], M.C. Carlier [2], M. Laville [2], D. Fouque [2], E. Cavalier [3], P. Delanaye [3], J.P. Cristol [4], A.S. Bargnoux [4], S. Kamel [5,6], Z. Massy [6,7], D. Prié [8], P. Urena-Torres [8], J.C. Souberbielle [8], A. Boutten [9,10], A. Guérin [11], T. Hannedouche [12], G. Jean [13], M.H. Lafage-Proust [14], G. London [15], L. Mercadal [16], L. Pieroni [17]

[1] CHU Grenoble
[2] CHU Lyon
[3] CHU Sart-Tilman Liège
[4] CHU Montpellier
[5] INSERM U1088
[6] CHU Amiens
[7] CHU Ambroise Paré
[8] Inserm/Université U 845
[9] APHP
[10] GH Paris Nord Val de Seine
[11] CH de Manhes
[12] CHU Strasbourg, Ph Brunet CHU Marseille
[13] Nephrocare Tassin-Charcot
[14] CHU St Etienne
[15] INSERM U970
[16] Pitié Salpétriere Paris
[17] CH Avignon

[a] Department of Clinical Chemistry, University of Liege, CHU Sart-Tilman, Liege, Belgium
[b] Department of Nephrology, Dialysis and Hypertension, University of Liege, CHU Sart-Tilman, Liege, Belgium
[c] Laboratoire de Biochimie, CHU Amiens, Amiens, France
[d] INSERM U1088, Université de Picardie Jules-Verne, Amiens, France
[e] Laboratoire de Biochimie, CHRU de Montpellier, Hôpital Lapeyronie, Montpellier, France

ARTICLE INFO

Article history:
Received 2 July 2014
Received in revised form 27 August 2014
Accepted 29 August 2014
Available online xxxx

Keywords:
Vascular calcification
Fibroblast growth factor-23
Fetuin-A
Matrix Gla protein
Bone morphogenetic protein-2
Osteoprotegerin

ABSTRACT

The link between vascular calcification (VC) and increased mortality is now well established. Over time, as clinical importance of this phenomenon has begun to be fully considered, scientists have highlighted more and more physiopathological mechanisms and signaling pathways that underlie VC. Several conditions such as diabetes, dyslipidemia and renal diseases are undoubtedly identified as predisposing factors. But even if the process is better understood, many questions still remain unanswered. This review briefly develops the various theories that attempt to explain mineralization genesis. Nonetheless, the main purpose of the article is to provide a profile of the various existing biomarkers of VC. Indeed, in the past years, a lot of inhibitors and promoters, which form a dense and interconnected network, were identified. Given importance to assess and control mineralization process, a focusing on accumulated knowledge of each marker seemed to be necessary. Therefore, we tried to define their respective role in the physiopathology and how they can contribute to calcification risk assessment. Among these, Klotho/fibroblast growth factor-23, fetuin-A, Matrix Gla protein, Bone morphogenetic protein-2, osteoprotegerin, osteopontin, osteonectin, osteocalcin, pyrophosphate and sclerostin are specifically discussed.

© 2014 Published by Elsevier B.V.

Abbreviations: 1,25 $(OH)_2$D, 1,25-dihydroxyvitamin D; ALP, alkaline phosphatase; AVK, vitamin K antagonists; BAX, BCL2-associated X protein; BMDM, bone marrow-derived macrophage; BMP-2, bone morphogenetic protein-2; CAC, coronary artery calcifications; CAD, coronary artery disease; CaSR, calcium-sensing receptor; Cfba1/Runx2, core-binding factor subunit 1 α / runt-related transcription factor 2; CKD, chronic kidney disease; cMGP, carboxylated MGP; CPP, calciprotein particles; dp-uc MGP, dephosphorylated uncarboxylated MGP; EPCs, endothelial progenitor cells; ePPi, extracellular PPi; Fet-A, fetuin-A; FGF-23, fibroblast growth factor-23; HD, hemodialysis; HIF-1α, hypoxia-inductible factor 1α; MGP, matrix gla protein; MVs, matrix vesicles; MVSC, multipotent vascular stem cells; ND, non dialysis; OC, osteocalcin; ON, osteonectin; OPG, osteoprotegerin; OPN, osteopontin.

* Corresponding author at: Department of clinical chemistry , University of Liège, CHU Sart-Tilman, Domaine du Sart-Tilman, B-4000 Liège, Belgium. Tel.: +32 4 366 88 22, +32 4 366 76 92; fax:+32 4 366 88 23.
E-mail address: etienne.cavalier@chu.ulg.ac.be (E. Cavalier).

http://dx.doi.org/10.1016/j.cca.2014.08.034
0009-8981/© 2014 Published by Elsevier B.V.

Please cite this article as: Evrard S, et al, Vascular calcification: from pathophysiology to biomarkers, Clin Chim Acta (2014), http://dx.doi.org/10.1016/j.cca.2014.08.034

UNCORRECTED PROOF

ARTICLE IN PRESS

Contents

1. Introduction

Occurrence of vascular calcification (VC) is not new. Arterial calcification has been discovered in the "Iceman" who lived 5000 years ago [1] and scientists had already paid attention to this phenomenon – and to its relation with renal disease – in the 19th Century[2]. VC increases with age and is notably dysregulated in diabetes, dyslipidemia, renal disease and hypertension [3]. Bone formation involves hydroxyapatite [Ca10(PO4)6(OH)2] crystals, whose development begins in matrix vesicles (MVs) that bud from osteoblasts. Vascular smooth muscle cells (VSMCs) that have undergone osteoblast differentiation are also able to release similar vesicles with shared protein content [4]. Such differentiation is restrained or inhibited under normal conditions and there is a balance with osteoclast differentiation experienced by monocytes and macrophages within the vascular wall. Moreover, the reaction which allows crystal growth is thermodynamically unfavorable and is inhibited by pyrophosphate [3]. In some situations, physiological balance is broken and VC is able to progress.

For a long time, VC has been considered as an ageing fatality. Despite the fact we cannot completely deny the link with ageing, VC is no longer regarded as a passive process. Today, it is considered as an actively regulated and complex process that remains not completely understood. We know that many dynamic changes can trigger or promote VC and a lot of theories emerged during the last two decades. We will describe hereafter some of the physiopathological mechanisms. It is important to underline that these different mechanisms are not mutually exclusive [5].

2. Overview of vascular calcification : from genetics to osteoblastic differentiation

2.1. Genetic predisposition

As shown in Fig. 1, genetic predisposition certainly plays an important role in the genesis of this phenomenon. According to Rutsch et al., 2011 [6], 40–50% of cases of coronary calcification can be attributed to genetics. Genome-wide association studies have identified several loci linked to coronary arterial calcification, like 6p21.3, 6p24, 10q21.3 and 9p21 [3,7–9]. Interestingly, some of these regions also appear to be related to coronary atherosclerosis [7] and the 6p24 locus is also linked to myocardial infarction [10]. An implication of several single polymorphisms located at 9p21 locus near the cyclin genes has been suggested in the genesis of pathology [9]. These genes encode cyclins that may be broadly linked to cellular senescence and inflammation but the accurate causative DNA sequences remains debated [3].

Genes ENPP1 and NT5E are respectively implicated in infancy and idiopathic VC. The first one encodes a protein which transforms ATP to adenosine and pyrophosphate (PPi, inhibitor of calcification) whereas the second one converts AMP into adenosine and inorganic phosphate (Pi, accelerator of mineralization). The VC phenotype caused by mutations in these genes underlines the role of PPi and Pi in pathogenesis [3]. Mutations in ABCC6, a gene encoding a nucleoside-sensitive transporter, have also been linked to hereditary calcification. Alternative action of ABCC6 may include deficient hepatic production of inhibitory factor of matrix Gla protein (MGP), an important inhibitor of calcification [3,11].

2.2. Osteoblastic differentiation

One major mechanism in the development of VCs is similar to that of bone formation. First, vascular smooth muscle cells (VSMCs) undergo osteogenic differentiation into phenotypically distinct osteoblast-like cells [5,12]. In the case of renal failure, phosphate plays a key role in this mechanism [13,14]. In vitro, high extracellular phosphate concentrations induce a rise in intracellular phosphate concentration which is actively mediated by Pit-1, a sodium dependent phosphate co-transporter [14,15]. This increasing phosphate concentration in the VSMC induces a phenotypic switch of VSMCs into osteoblast-like cells [5,14,16]. The protein Cfba1/Runx2 (core-binding factor subunit 1α/runt-related transcription factor 2) is a specific and indispensable transcriptional regulator for this osteoblastic differentiation. Its expression is also enhanced with high extracellular phosphate [14,16,17]. These "new" cells will express alkaline phosphatase (ALP), secrete, under the control of Cfba-1, bone-associated proteins (such as osteopontin [18], collagen type 1, osteoprotegerin, bone morphogenic protein-2 and osteocalcin [14,19]) and release mineralization-competent MVs in the extracellular matrix [13,14,20]. VSMCs release MVs under normal physiological conditions and these MVs are protected from mineralization by the presence of calcification inhibitors. Under pathological conditions, a combination of factors makes the MVs "mineralization competent" [21]. Moreover, an increase of intracellular phosphate level mediated by Na/Pi transporter is thought to induce VSMC apoptosis

UNCORRECTED PROOF

Please cite this article as: Evrard S, et al, Vascular calcification: from pathophysiology to biomarkers, Clin Chim Acta (2014), http://dx.doi.org/10.1016/j.cca.2014.08.034

Download English Version:

https://daneshyari.com/en/article/8311383

Download Persian Version:

https://daneshyari.com/article/8311383

Daneshyari.com