update in pathogenesis of vascular calcification

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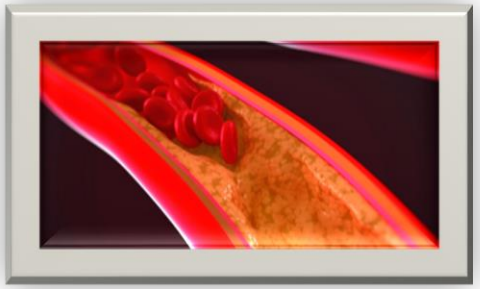
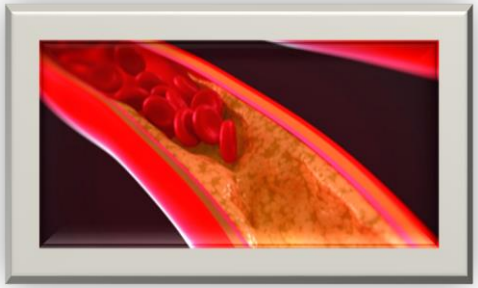


- ***Overview***
- ***Mechanism of vascular calcification***
- ***Factors involved in vascular calcification.***
- ***Calcification inhibitors***
- ***Therapeutic potentials***
- ***Conclusions***

Overview

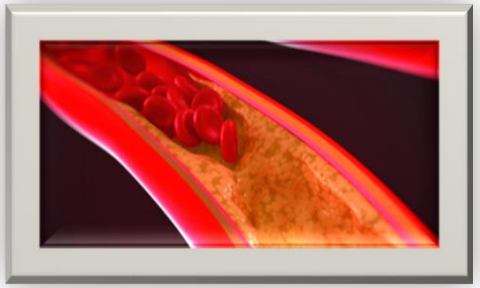


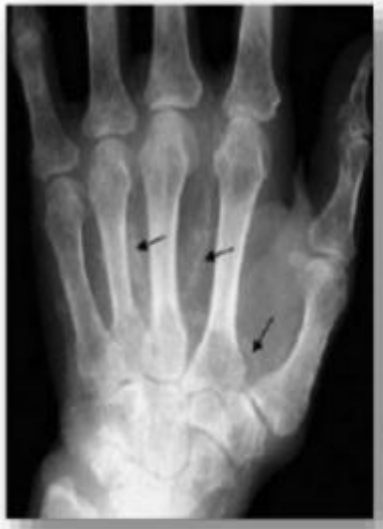
Cardiovascular disease is the most common cause of death in patients with CKD and

vascular calcification is one of the strongest predictors of cardiovascular risk.

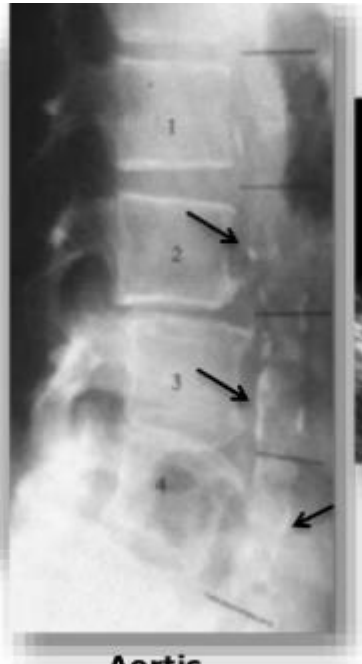
Vascular calcification is common in patients with CKD and ESRD,

in whom it correlates with both lower eGFR and CKD-MBD.

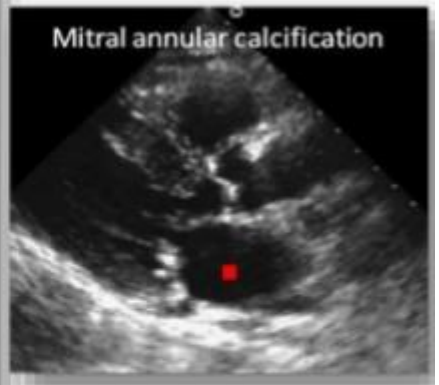




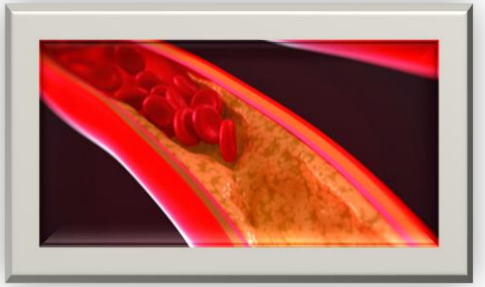
Digital Arteries Calcification



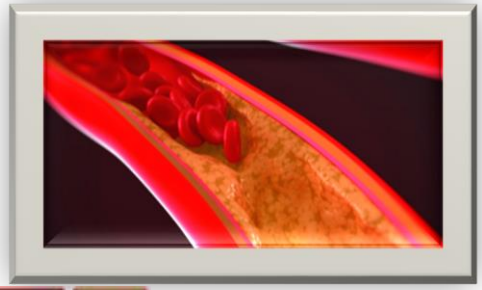
Aortic Calcifications



Overview



VC can be present at different layers of the arterial wall (intima, media, or both).



ARTERIOSCLEROSIS

Arterial Stiffness

Arterial Stenosis

ATHEROSCLEROSIS

adventitia

foam cells

VSMC

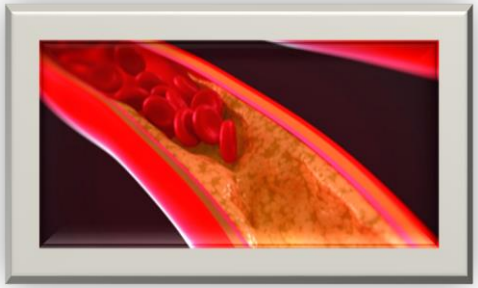
necrosis

intima

fibrous cap

calcification (concentric)

calcification (eccentric)



Arterial calcification

Intimal calcification

↓

Atherosclerosis

↓

Stenosis, occlusion

↓

Infarction, ischemia

Medial calcification

↓

Arteriosclerosis

↓

Stiffening

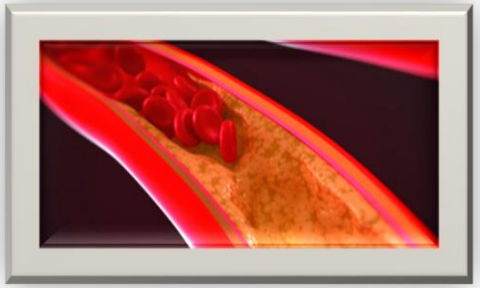
↓

↑Systolic and pulse pressures, early return of wave reflections

↓

Altered coronary perfusion, left-ventricular hypertrophy

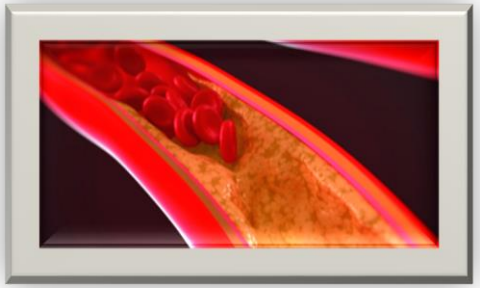
- **Overview**



- In contrast to the predominant intimal calcification observed in the absence of kidney disease,

- the pattern of vascular calcification in patients with advanced CKD includes both intimal and medial calcification.

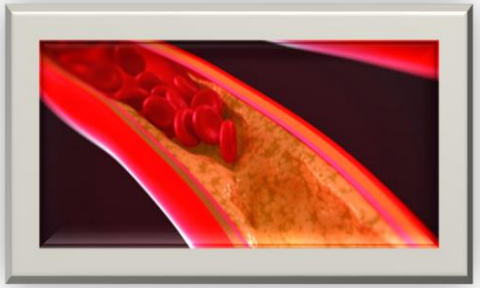
- Of note, the severity and progression of vascular calcification is generally much more marked in patients with CKD than in people of comparable age, gender, and ethnicity in the general population.



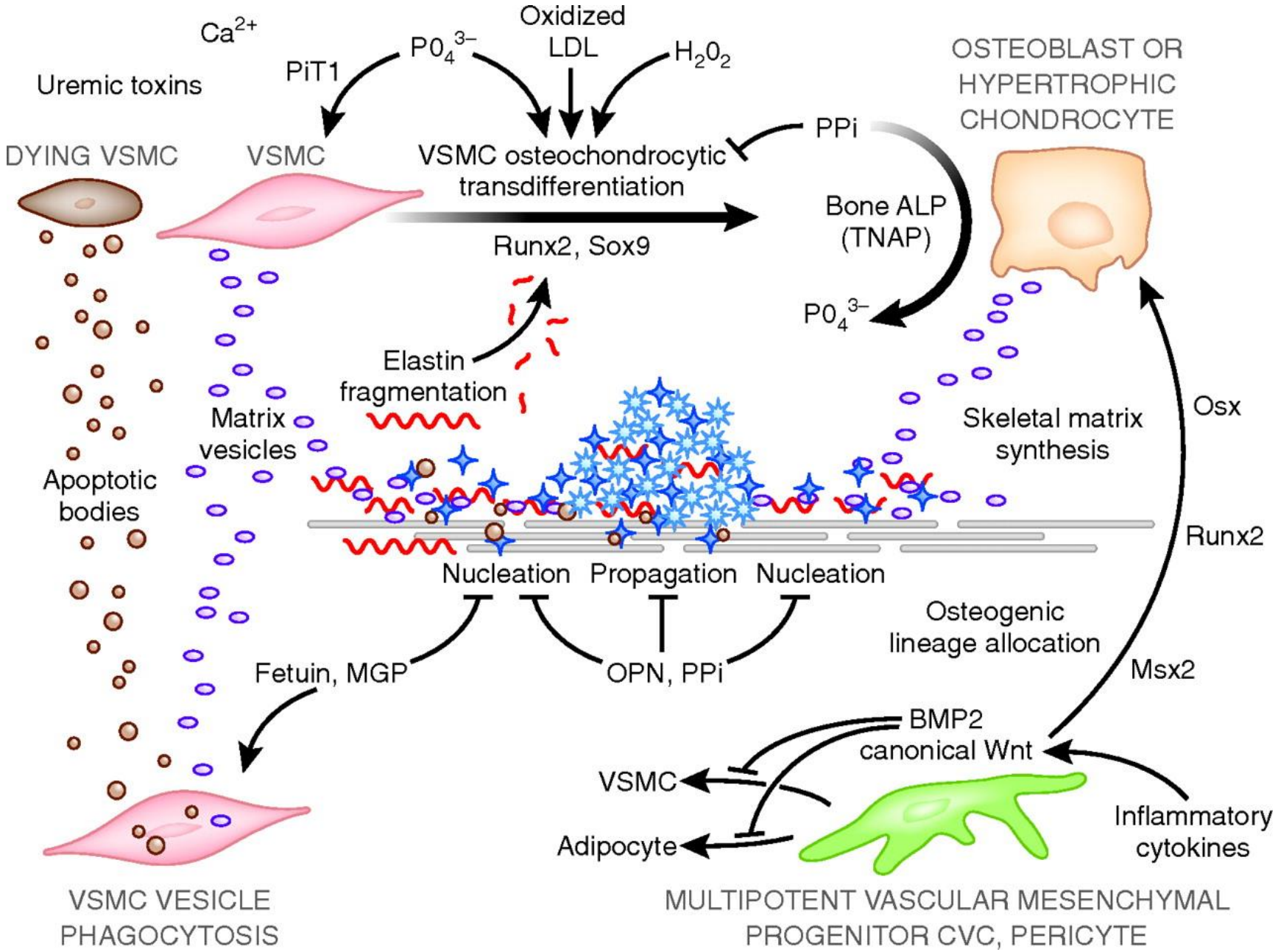
Microcalcification or spotty calcification present in atheromatous plaques, though very difficult to detect using regular radiological techniques, may negatively impact plaque stability.

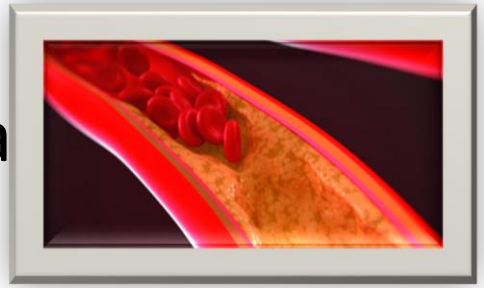
This clearly is a very different process compared to the large longitudinal confluent regions of arterial wall calcification typically seen in stage 5 CKD.

Calcification of the tunica media



Arterial medial calcification is not just the result of the simple passive process of calcium deposition but an active process in response to pathological conditions, including Aging, inflammation, diabetes, CKD, and phenotypic switch of resident cells.


Ca^{2+}
Uremic toxins
PiT1
$P0_4^{3-}$
Oxidized LDL
H_20_2
OSTEOBLAST OR HYPERTROPHIC CHONDROCYTE
PPi
DYING VSMC
VSMC
VSMC osteochondrocytic transdifferentiation
Bone ALP (TNAP)
Runx2, Sox9
$P0_4^{3-}$
Elastin fragmentation
Matrix vesicles
Apoptotic bodies
Skeletal matrix synthesis
Osx
Runx2
Nucleation
Propagation
Nucleation
Osteogenic lineage allocation
Msx2
Fetuin, MGP
OPN, PPi
BMP2
canonical Wnt
VSMC
Adipocyte
Inflammatory cytokines
VSMC VESICLE PHAGOCYTOSIS
MULTIPOTENT VASCULAR MESENCHYMAL PROGENITOR CVC, PERICYTE



- Several risk factors may induce accelera vascular aging ;

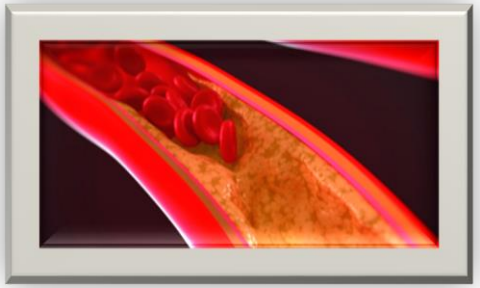
"classic";

calendar age, gender, CKD and dialysis vintage, inflammatory status, disorders of calcium phosphate, and diabetes, and

"non-classic";

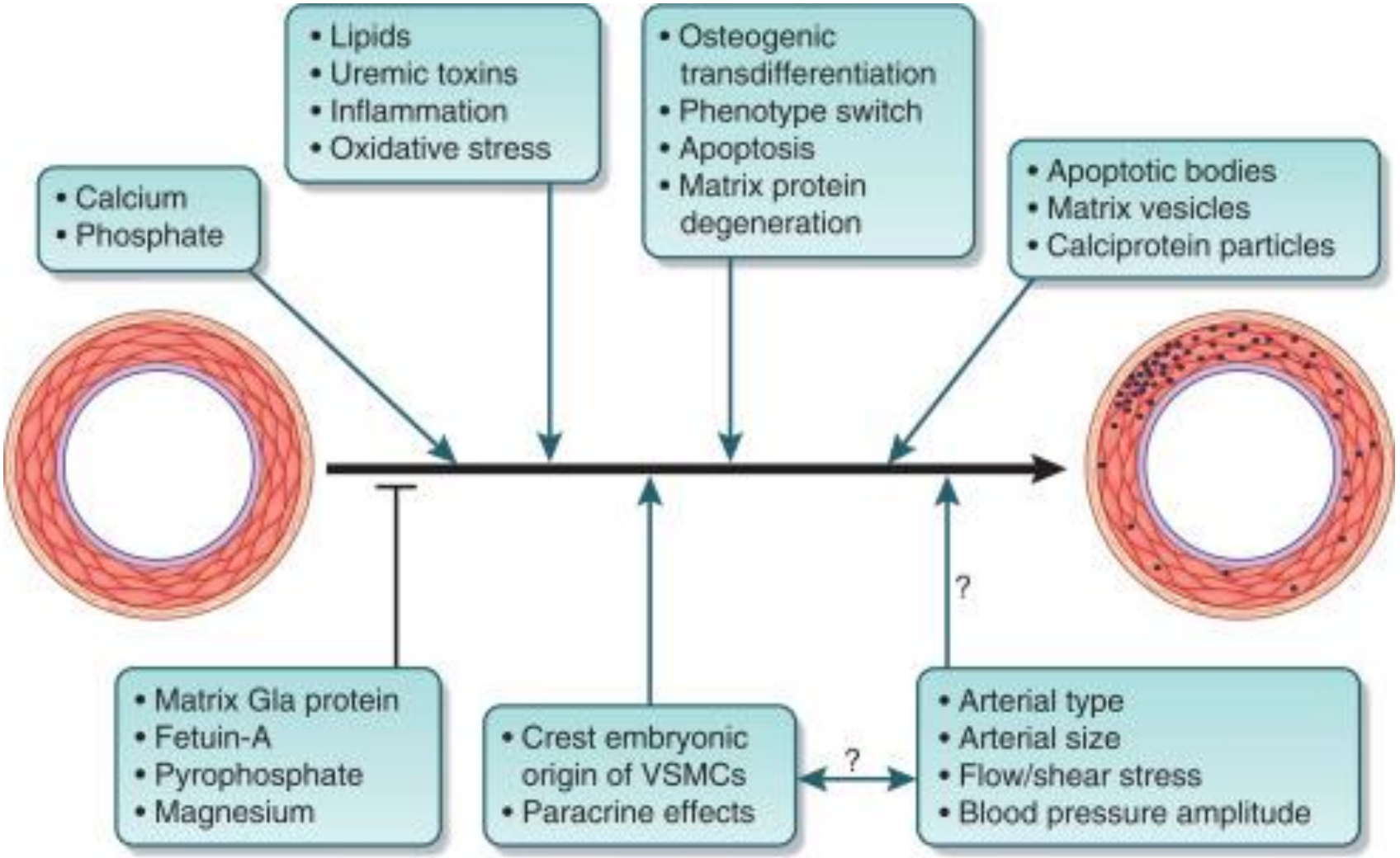
as abnormal levels of bone-related proteins:

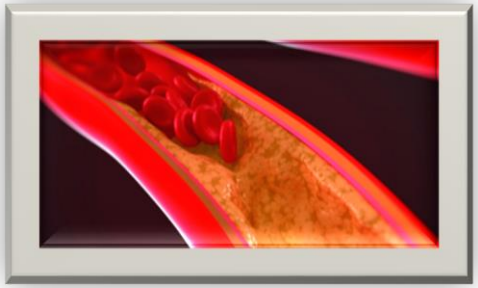
fetuin-A , MGP , pyrophosphate, osteoprotegerin, and BMP-2.



The prevalence and progression of VC increases rapidly once patients are on dialysis and

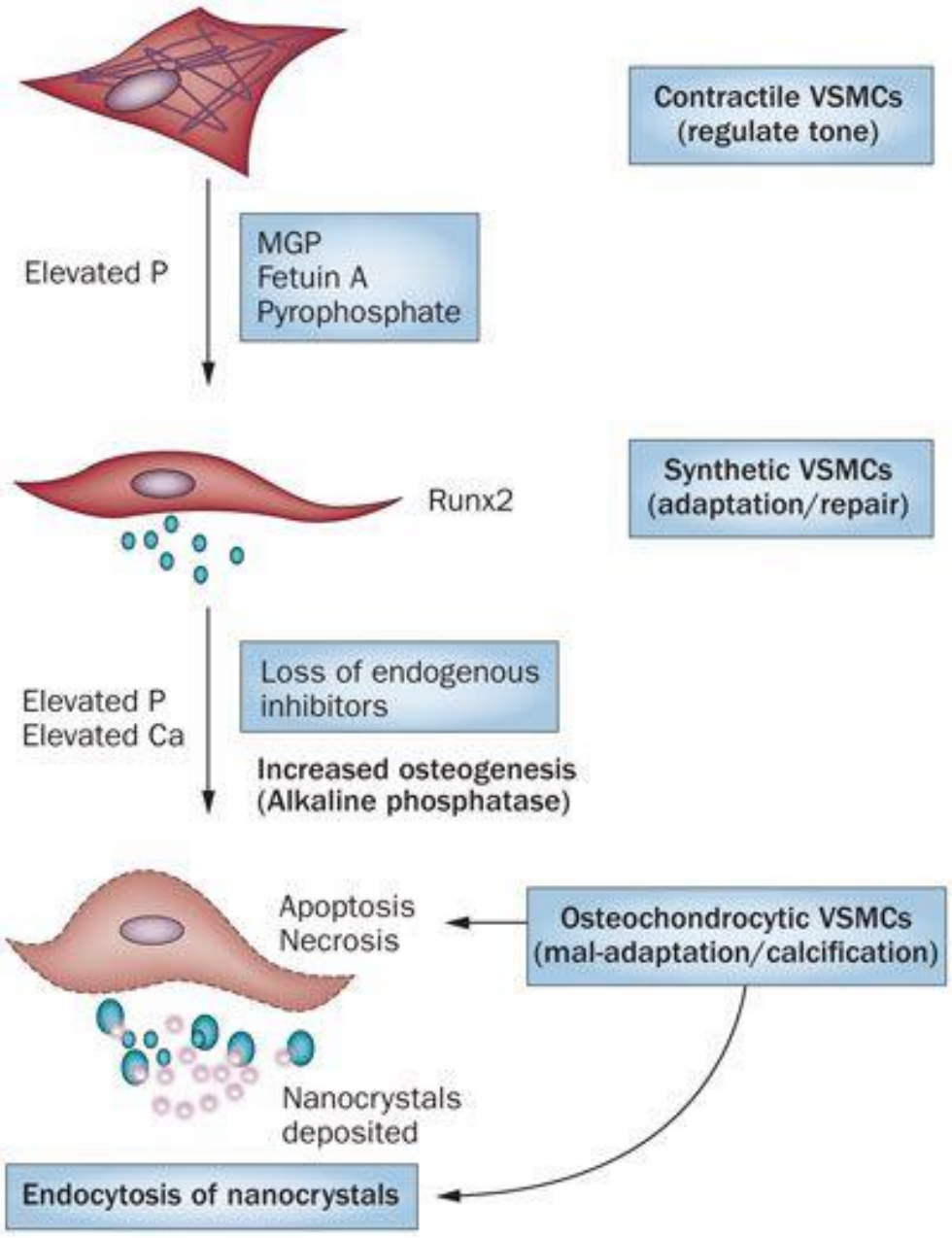
the phenotype of vessels of younger dialysis patients is comparable with that of octogenarians without CKD.

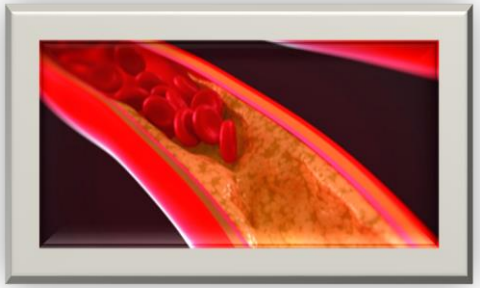

• Lipids
• Uremic toxins
• Inflammation
• Oxidative stress
• Osteogenic transdifferentiation
• Phenotype switch
• Apoptosis
• Matrix protein degeneration
• Calcium
• Phosphate
• Apoptotic bodies
• Matrix vesicles
• Calciprotein particles
?
• Matrix Gla protein
• Fetuin-A
• Pyrophosphate
• Magnesium
• Crest embryonic origin of VSMCs
• Paracrine effects
?
• Arterial type
• Arterial size
• Flow/shear stress
• Blood pressure amplitude



The pathogenesis of especially P-induced VC indeed that high P concentration in growth media causes VC through **specific activation of the core-binding factor alpha-1, an osteoblast-specific gene, that regulates the expression of several bone morphogenic proteins.**

- Clearly, all these data indicate that VC is an active pathobiological process.


Contractile VSMCs
(regulate tone)
Elevated P
MGP
Fetuin A
Pyrophosphate
Runx2
Synthetic VSMCs
(adaptation/repair)
Elevated P
Elevated Ca
Loss of endogenous
inhibitors
Increased osteogenesis
(Alkaline phosphatase)
Apoptosis
Necrosis
Osteochondrocytic VSMCs
(mal-adaptation/calcification)
Nanocrystals
deposited
Endocytosis of nanocrystals



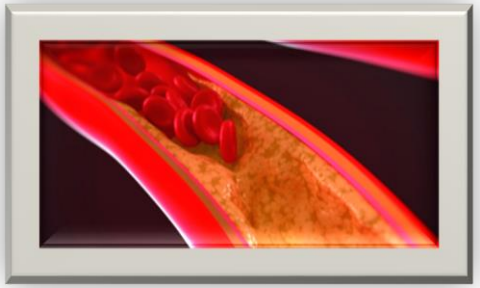
- the mechanism behind how phosphorus results in apoptosis is uncertain, but may be due to interruptions in normal mitochondrial energy metabolisms of VSMC is a key regulator of VSMC calcification .

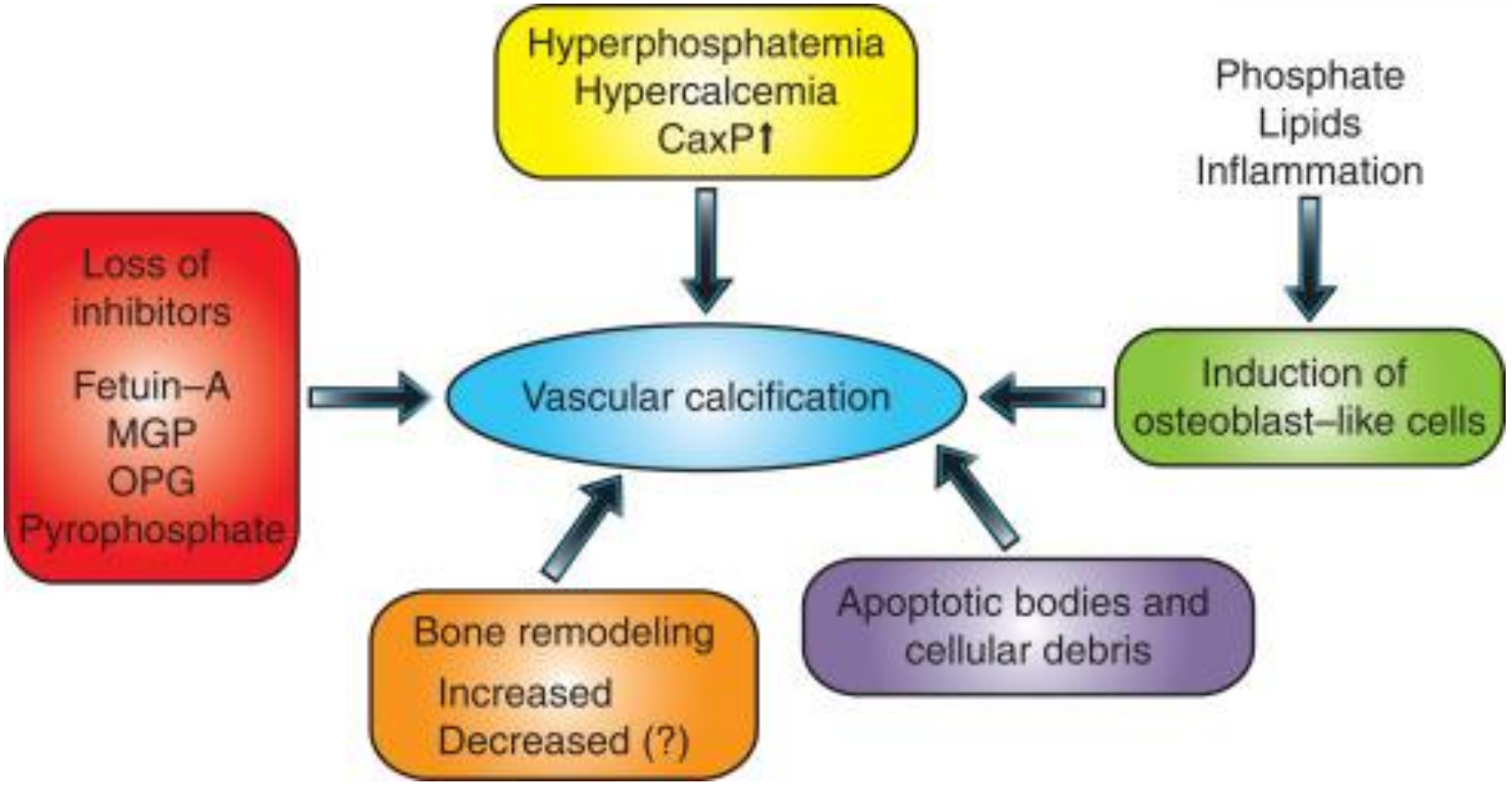
Apoptosis in VSMC occurs before the onset of calcification .

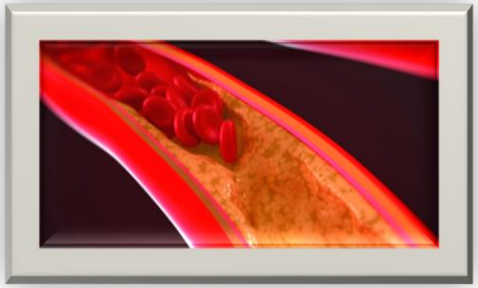
- Matrix vesicles, produced by budding from chondrocytes and osteoblasts, appear to play a role in apoptosis induced vascular calcification .

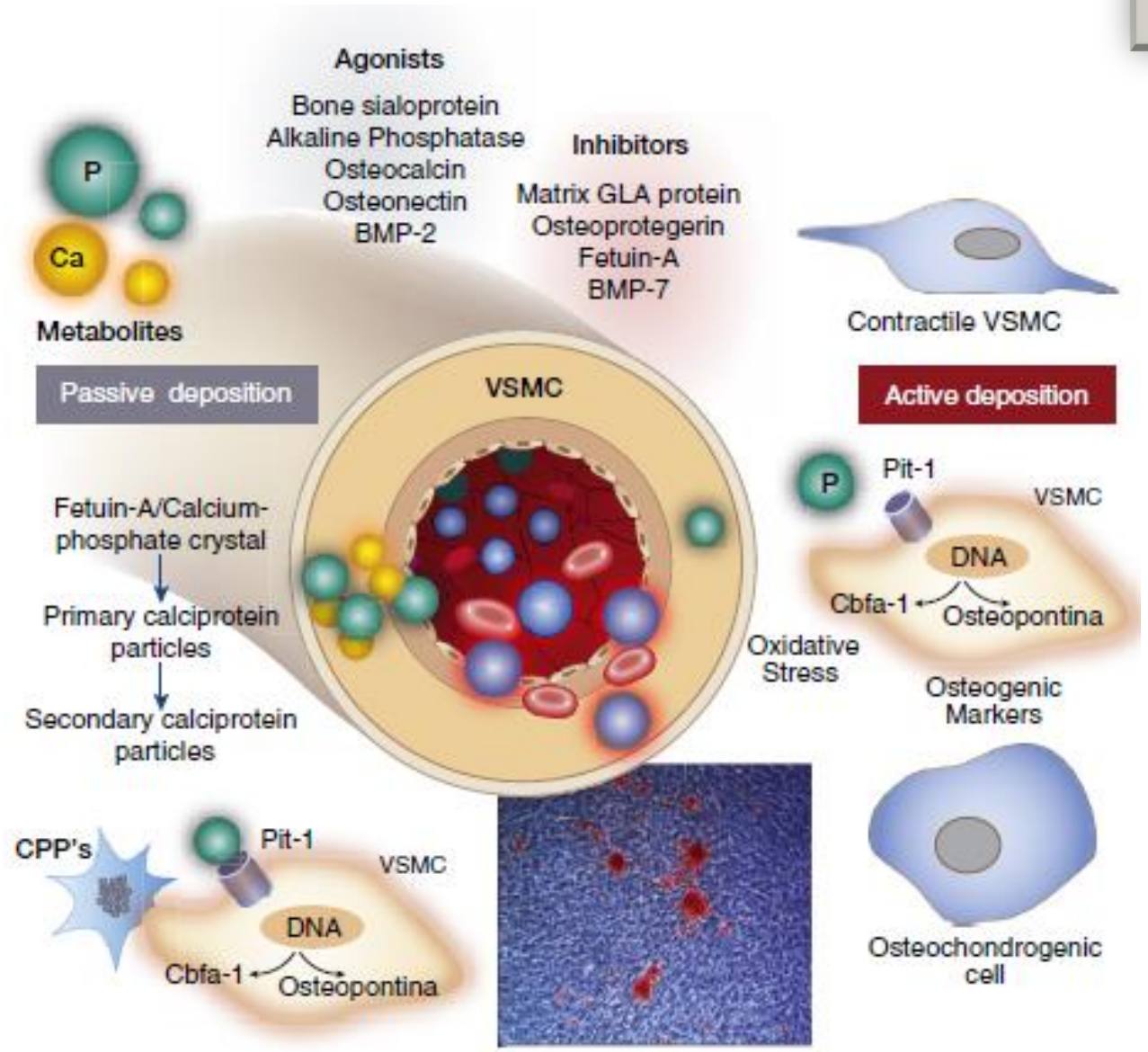
- The matrix vesicles originated from VSMC may be fragments of apoptotic cells.

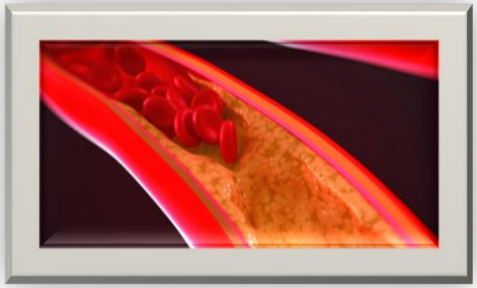
- These matrix vesicles/apoptotic bodies possess the capacity to concentrate and crystallize calcium as they have all of the essential proteins for calcification .




Hyperphosphatemia
Hypercalcemia
CaxP↑
Phosphate
Lipids
Inflammation
Loss of inhibitors
Fetuin–A
MGP
OPG
Pyrophosphate
Vascular calcification
Induction of osteoblast–like cells
Bone remodeling
Increased
Decreased (?)
Apoptotic bodies and cellular debris




Agonists
Bone sialoprotein
Alkaline Phosphatase
Osteocalcin
Osteonectin
BMP-2
Inhibitors
Matrix GLA protein
Osteoprotegerin
Fetuin-A
BMP-7
P
Ca
Metabolites
Contractile VSMC
Passive deposition
VSMC
Active deposition
Fetuin-A/Calcium-phosphate crystal
Primary calciprotein particles
Secondary calciprotein particles
P
Pit-1
VSMC
DNA
Cbfa-1
Osteopontina
Oxidative Stress
Osteogenic Markers
CPP's
Pit-1
VSMC
DNA
Cbfa-1
Osteopontina
Osteochondrogenic cell



fetuin-A;

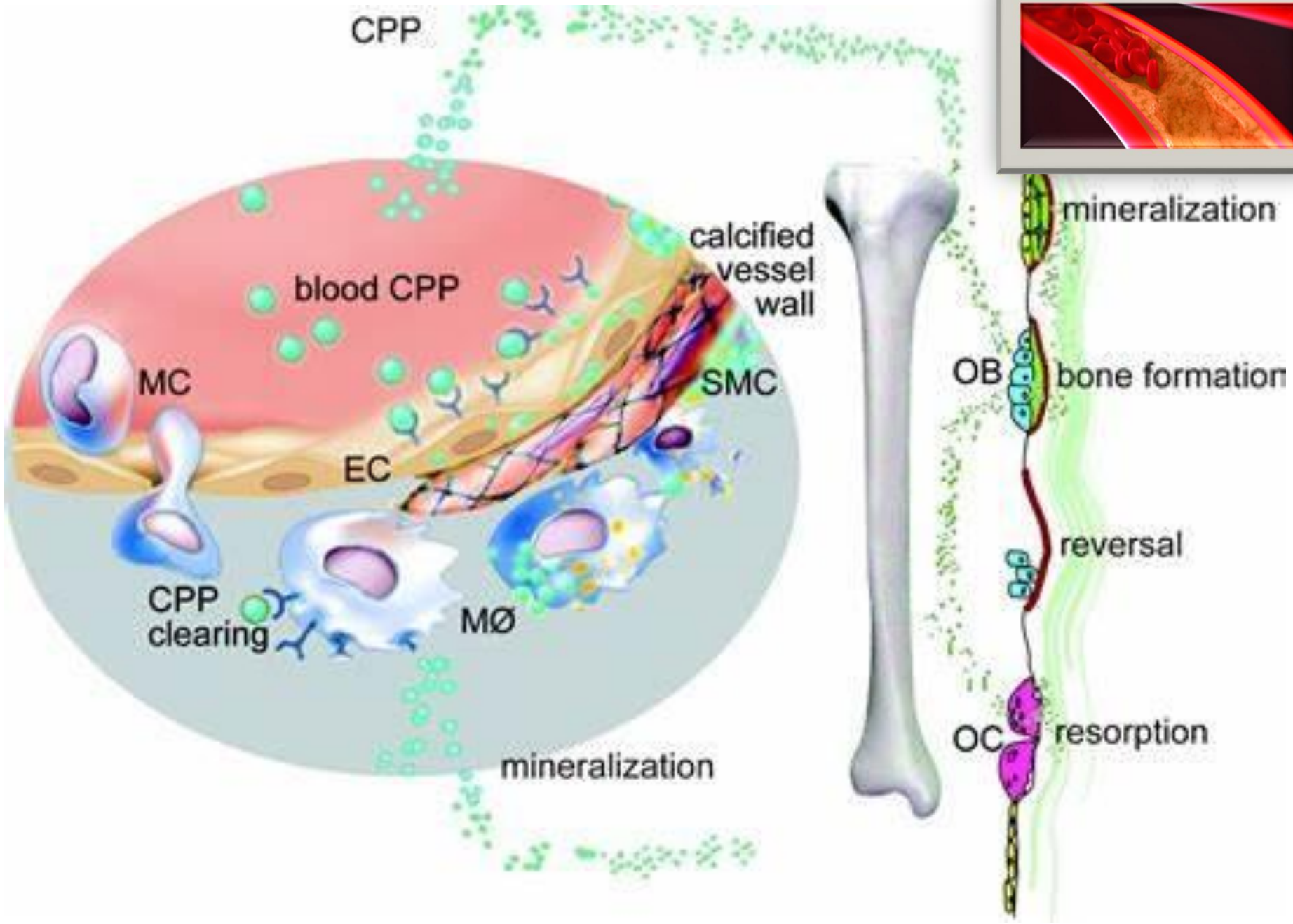
a hepatocyte-derived glycoprotein,

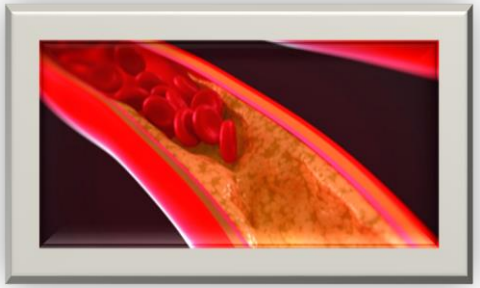
Fetuin-A is an extracellular calcium-regulatory protein acting as a strong inhibitor of Ca-P deposition.

Fetuin-A is one of the most abundant proteins in bone, accounting for 25% of noncollagenous proteins,

primary CPP

secondary CPPs,


CPP
blood CPP
calcified vessel wall
MC
SMC
EC
CPP clearing
MØ
mineralization
mineralization
OB
bone formation
reversal
OC
resorption



fetuin-A has antiapoptotic activity in VSMC.

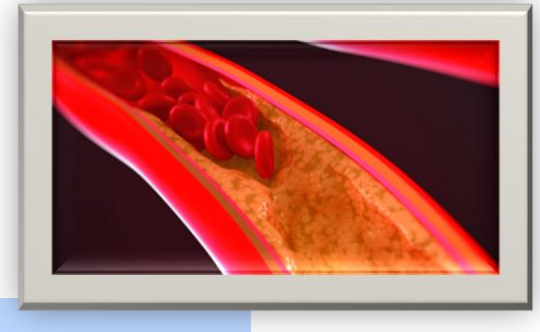
Fetuin-A is responsible for mineral accumulation in bone from plasma.

Specifically,fetuin-A binds calcium phosphate and calcium carbonate with high affinity.

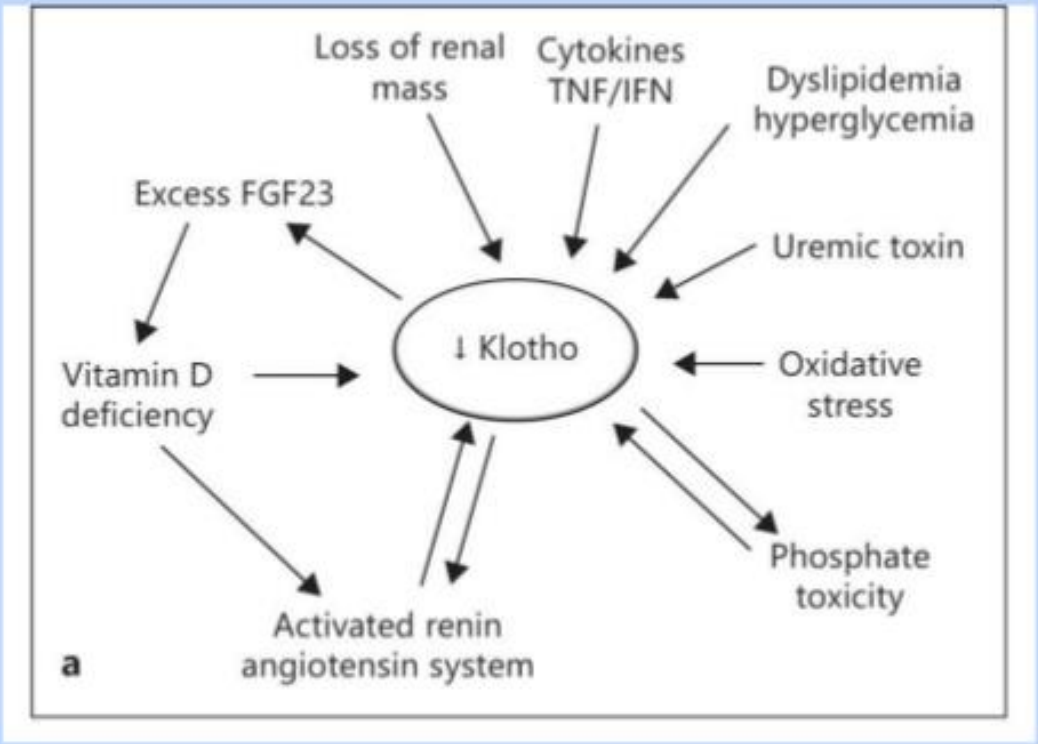
In CKD fetuin-A declines.

Hemodialysis patients with lower serum fetuin-A levels have a major risk of cardiovascular (CV) and all-cause mortality.

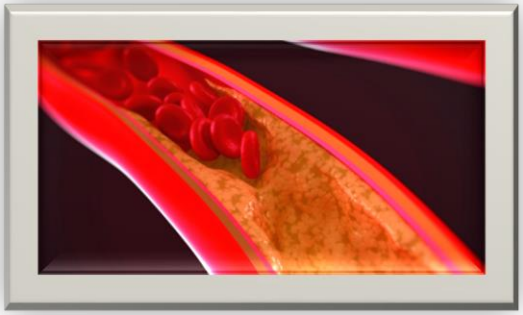
- Klotho deficiency
- FGF23

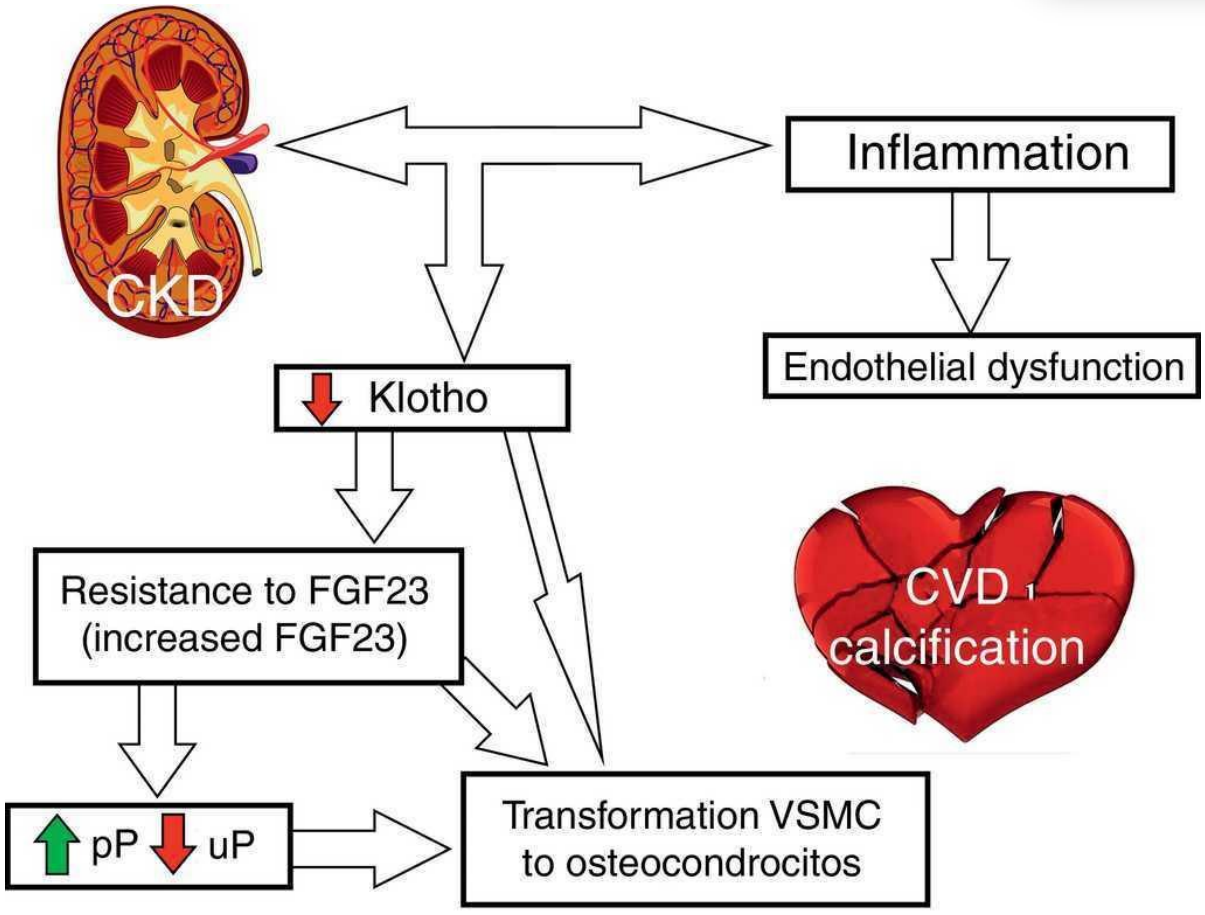


Klotho Deficiency in CKD

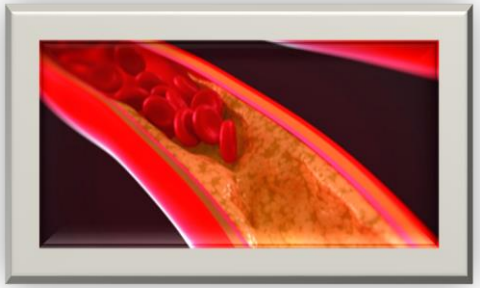


Hu MC et al. Contrib Nephrol. 2013;180:47-63.





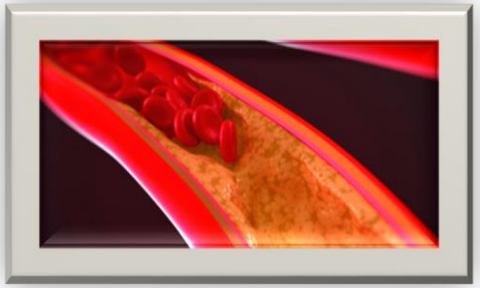
Nefrologia (English Version). 2016;36:368–75

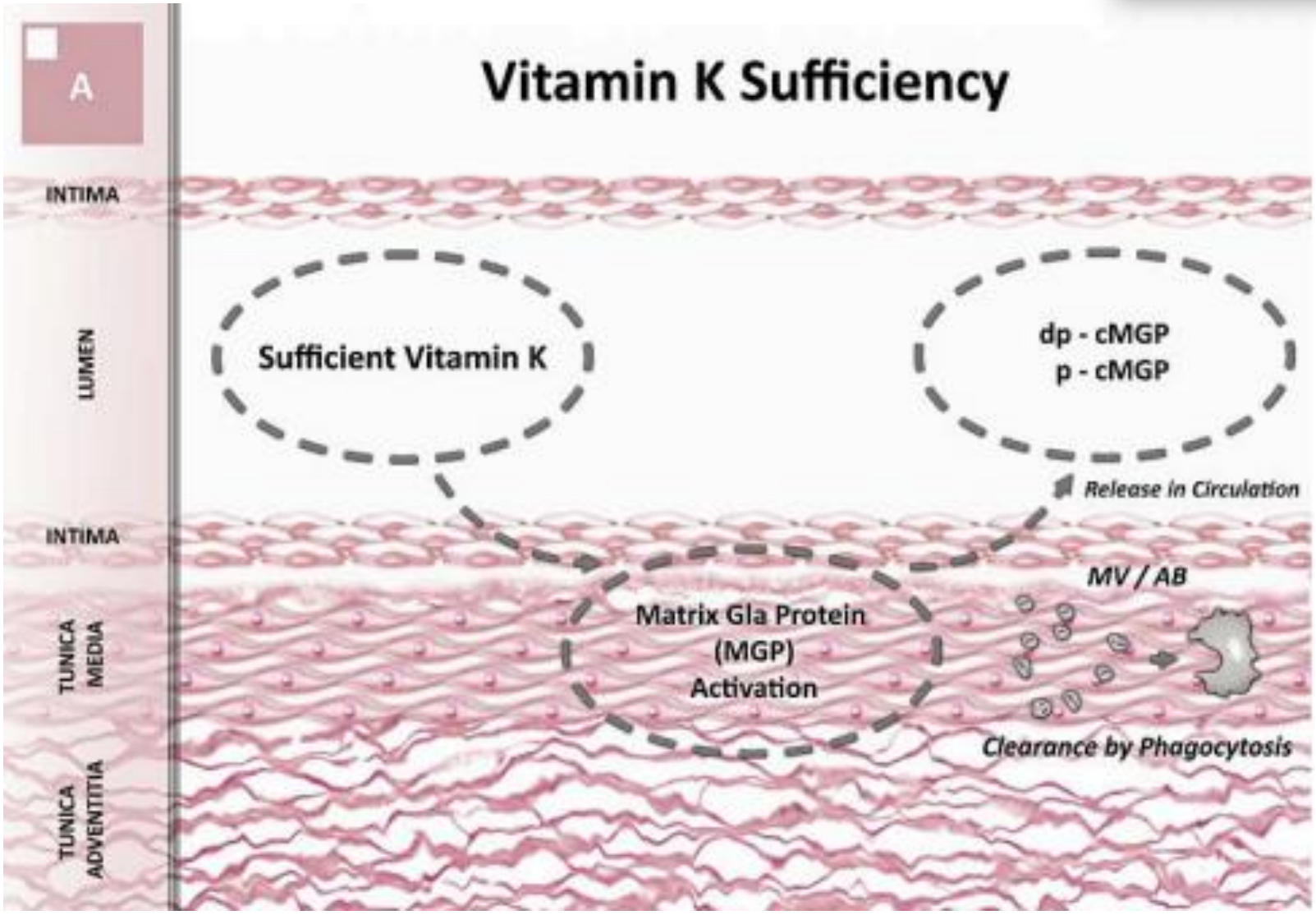


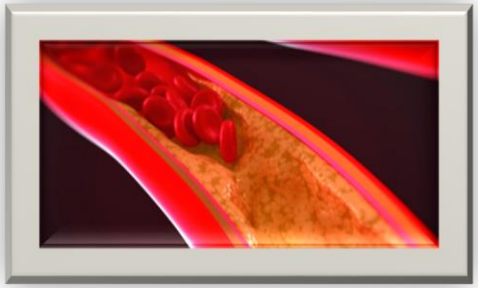
Extracellular MGP;

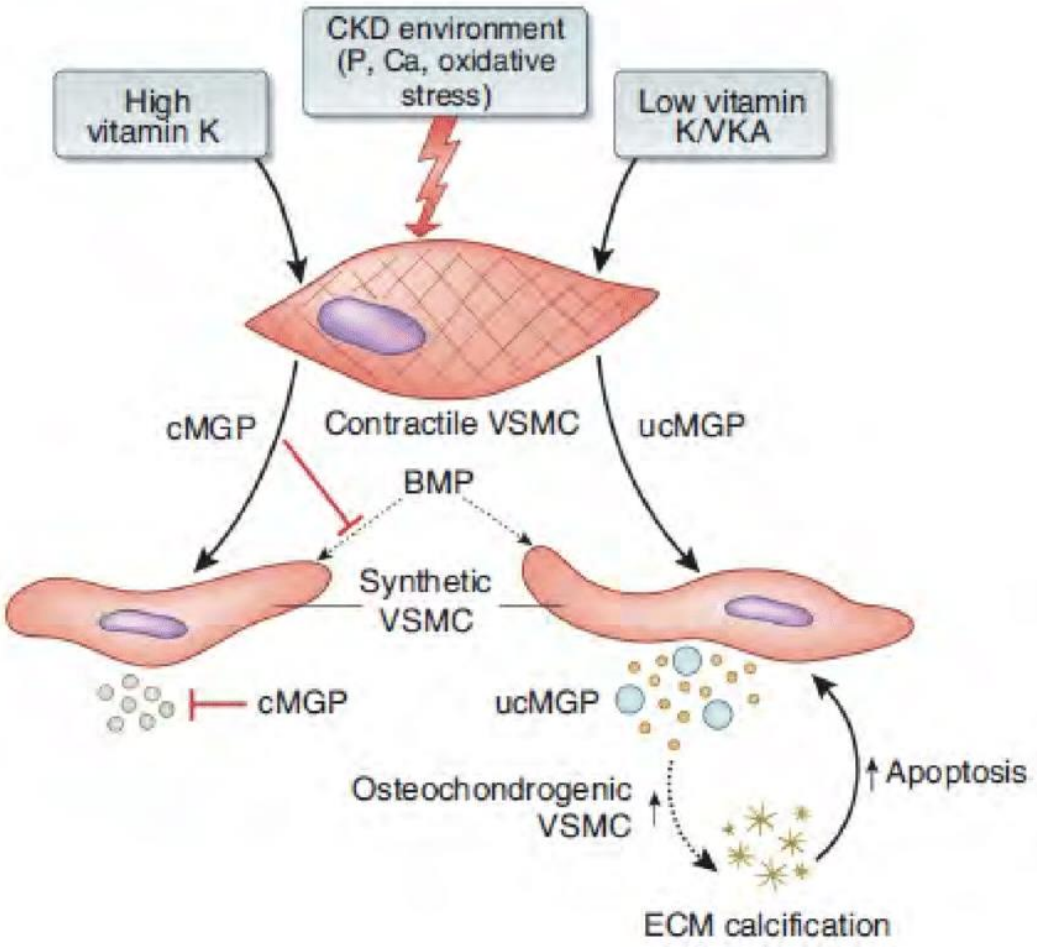
matrix-carboxyglutamic acid protein (Matrix-Gla protein, MGP)

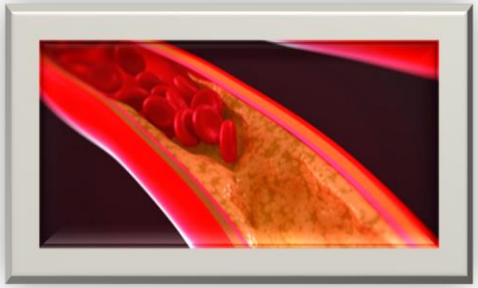
•




A
Vitamin K Sufficiency
INTIMA
LUMEN
INTIMA
TUNICA MEDIA
TUNICA ADVENTITIA
Sufficient Vitamin K
dp - cMGP
p - cMGP
Release in Circulation
MV / AB
Matrix Gla Protein
(MGP)
Activation
Clearance by Phagocytosis




CKD environment (P, Ca, oxidative stress)
High vitamin K
Low vitamin K/VKA
cMGP
Contractile VSMC
ucMGP
BMP
Synthetic VSMC
cMGP
ucMGP
Apoptosis
Osteochondrogenic VSMC
ECM calcification

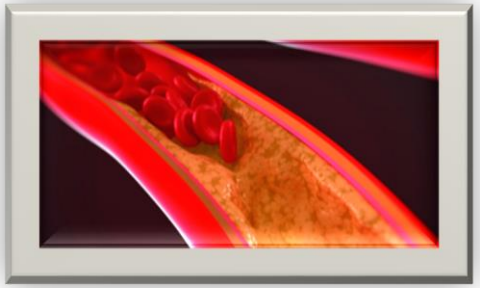


The second prominent feature in the medial layer of CKD patients is local inflammation.

*Importantly, it is **possible that the previously mentioned cellular changes** are induced by inflammation,*

while the opposite may occur as well:

inflammation induced by micro-calcification.



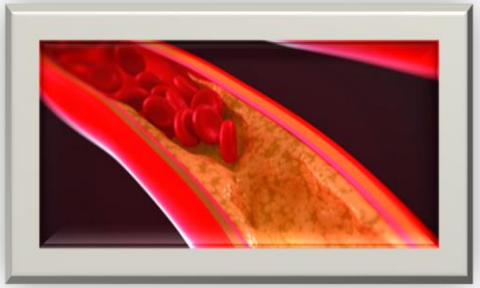
Calcification of the tunica intima

Calcification in association with atherosclerosis is not a new phenomenon.

There is mounting evidence pointing to a different process than the sequence of events occurring in the medial layer, as described above, driving calcification in atherosclerotic plaques.

- More so than in the medial layer, calcification in the intima appears to be a secondary phenomenon of inflammation but still dependent on infiltrating cells into the early atheromatous lesion.

- Infiltrating cells are mostly VSMC and macrophages.



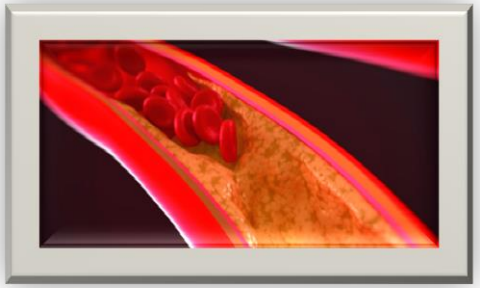
VSMC-derived BMP2 enhances plaque calcification,exacerbated by factors derived from infiltrating macrophages.

Moreover, these macrophages downregulate MGP, thereby reducing defense against crystallization.

Microcalcification in turn may attract macrophages.

Interestingly, osteochondrogenesis appears to be a ***secondary phenomenon of primary inflammatory processes*** in the plaque or its surroundings.

In this respect, ***atherosclerotic plaque calcification fundamentally differs from primary media calcification, in which transdifferentiation of local VSMC appears to be a more proximal event.***



Once established, atherosclerosis and calcification alter local mechanical shear stress.

Recent preclinical studies suggest that mechanical sensing influences arterial wall shear stress on the inflammatory signaling pathway.

In fact, both high and low wall shear stress may impact apoptosis signal regulation, e NOS , inhibitor of NFK B kinase, VCAM 1, and other pathways that play a fundamental role in the pathogenesis of VC.

Thus, biomechanical forces (i.e., wall shear stress) play *an important role* in the natural history of coronary atherosclerosis

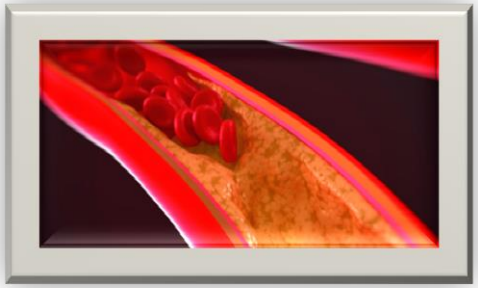
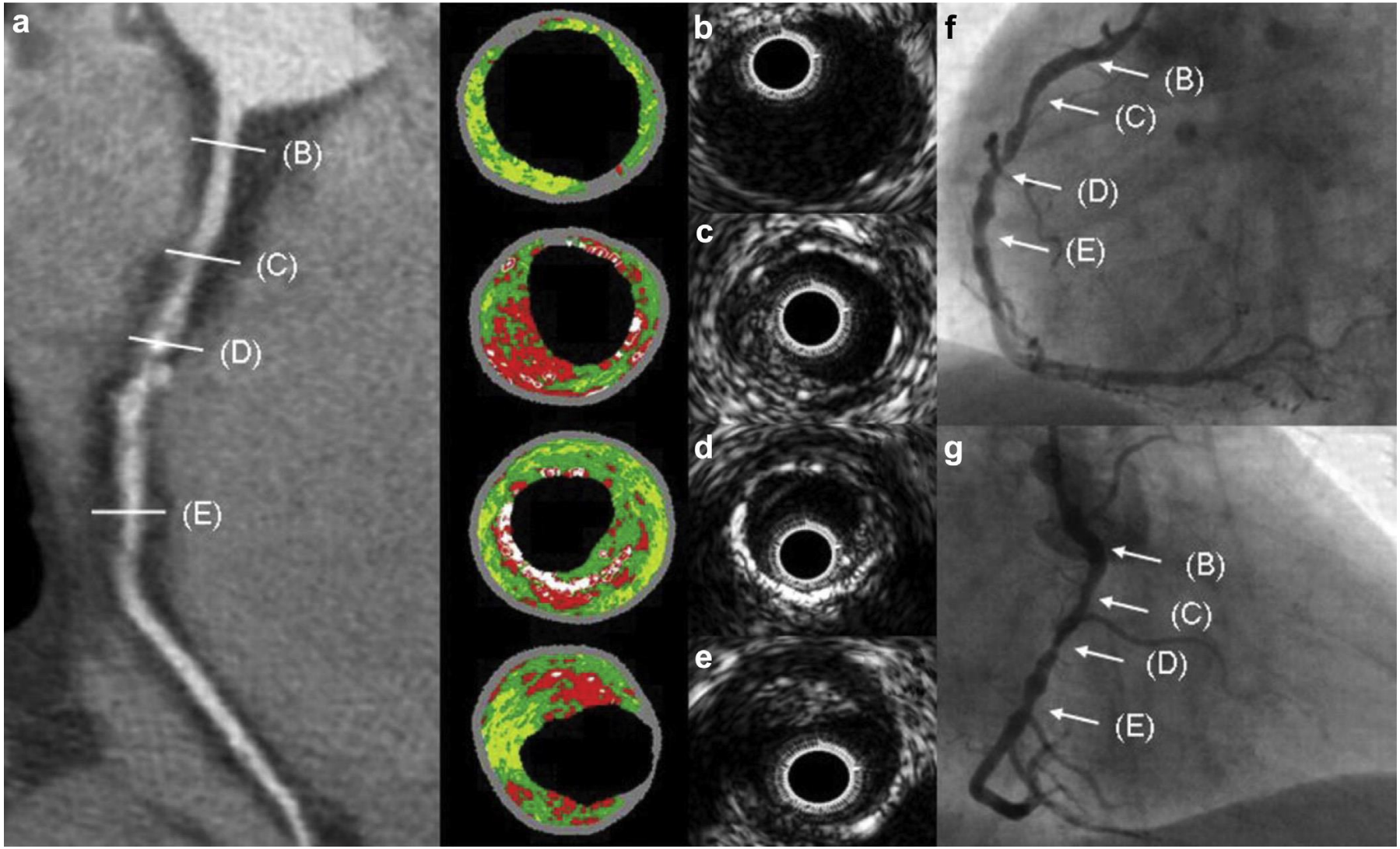


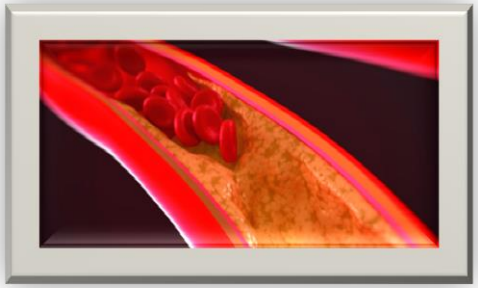
Table 1 | Properties of atherosclerotic plaques at high risk of rupture

Large and necrotic lipid core
Spotty calcification
Neovascularization
Macrophage and other cellular infiltration
Thin fibrous cap

Example of discordant findings using different imaging techniques in a patient with unstable angina.

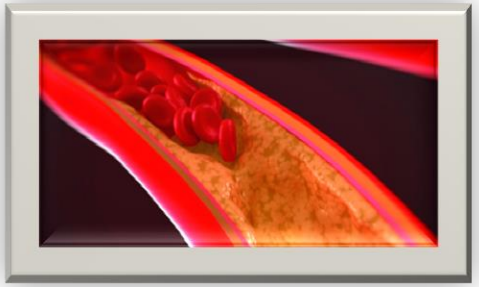
(a) On the left a multiplanar reconstruction of ***multisliced CT*** demonstrates noncalcified and mixed plaques.
The middle panels show both grayscale **intravascular ultrasound** images and the **corresponding colored virtual histology** intravascular ultrasound images. (b) On location, a small amount of plaque in the proximal right coronary artery is seen, not visible on multisliced CT. Thin cap fibroatheroma with a large amount of necrotic core is detected in (c) proximally and (e) distally located noncalcified plaques of the right coronary artery. (d) A corresponding cross-section of a mixed plaque in the midright coronary artery shows plaque with calcium on virtual histology intravascular ultrasound. (f,g) Multiple obstructive stenoses in the right coronary artery were confirmed on invasive coronary **angiography**, but the severity of anatomical stenosis does not correspond to the quantity of necrotic core, for instance visible on location c. Virtual histology intravascular ultrasound plaque components: dark green, fibrotic tissue; light green, fibro-fatty tissue; red, necrotic core; white, dense calcium.



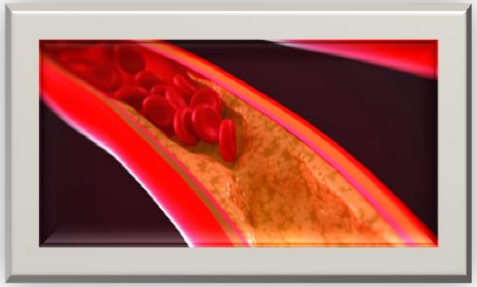


Conclusion;

In CKD patients, many different factors are involved in the pathogenesis of VC, which is usually much more pronounced than in people without CKD.



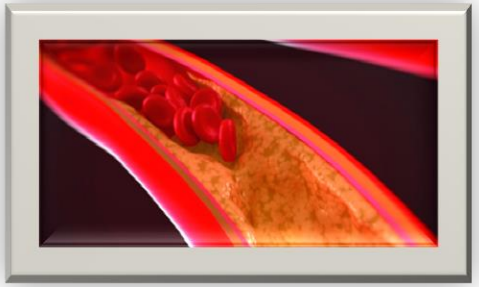
Is it possible to reverse VC in CKD?



Given the undisputed role of some components of mineral balance, the focus has been on these components.

As higher serum concentrations of P are associated with more extensive CAC in CKD patients, Overall, however, clinical studies with various P binder therapies have been rather disappointing in terms of clinical outcomes and found only relatively small differences in the progression of vascular calcification.

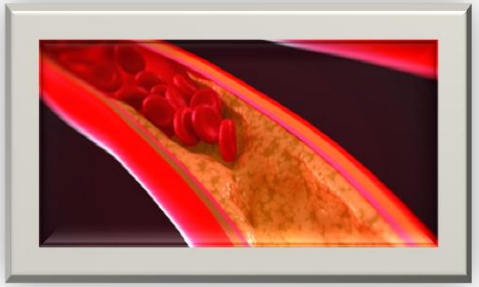
In ESRD, the avoidance or limited use of calcium-containing P binders is advocated in part based on a more rapid progression of CAC.



Vitamin D associated with VC in hemodialysis patients (**U-shaped relationship).**

Vitamin D retains a likely mixture of **procalcific effects**, such as a direct effect on VSMC, promoting VC by raising P and calcium, over-suppression of PTH leading to adynamic bone disease and low bone turnover.

On the contrary, vitamin D may also have **anti-inflammatory and immunomodulatory** effects across the CV system, **inhibit the production of renin and myocyte proliferation**, and prevent or alleviate overt hyperparathyroidism.

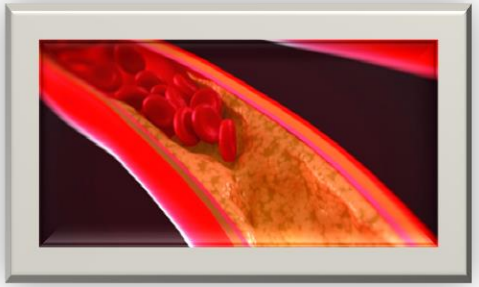


Recently, the effects of **calcimimetics** have gained interest.

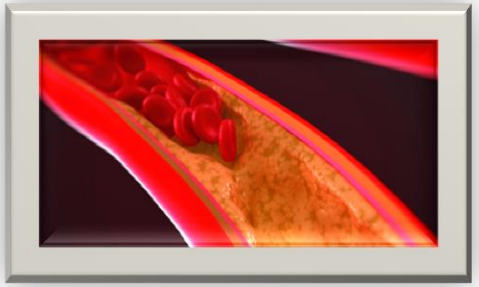
However, **none of these interventions**, although possibly affecting the rate of progression, actually induced **absolute regression** of VC.

- The potential role of sodium thiosulfate, a treatment associated with calciphylaxis, as a chelating agent for clinical arterial calcification deserves additional exploration.

- A final promising development is the supplementation of vitamin K, because its deficiency limits the bioactivity of MGP as a calcification inhibitor.



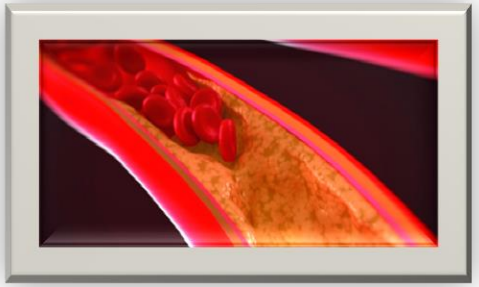
- Intuitively, ***kidney transplantation*** could be considered the best option to regress VC, but observational studies following mainly CAC are **generally disappointing** in this regard



In terms of treatment, several key questions remain.

Although without doubt the amount of calcification is associated with overall atherosclerotic volume, more intense calcifications do not predict future plaque rupture and subsequent arterial occlusion by thrombosis. .

Despite the consistent epidemiological association between the amount and progression of VC, no study has convincingly demonstrated that interventions that modulate the course of VC change patient outcome.



However, given the complex and diverse nature of processes leading to VC,….

Interventions that target several pathological interacting processes …could be a useful approach for future research.


Thank You