Vascular–Bone Crosstalk in CKD-MBD

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Vascular–Bone Crosstalk in CKD-MBD
Introduction

- **Traditional view:** Vascular and skeletal systems were seen mainly as structural.
- **New perspective:** Both are active organs with endocrine and regulatory roles, influencing cardiovascular function, immunity, inflammation, energy balance, and mineral metabolism.
- **Bone–vascular connection:**
  - Bones are highly vascularized; microcirculation is critical for bone development and remodeling.
  - Pathological overlap includes vascular calcification and impaired bone metabolism, seen in aging, diabetes, osteoporosis, rare bone diseases, and especially CKD.
- **CKD impact:**
  - Cardiovascular disease is the most severe complication of CKD.
  - Disturbances in mineral and bone metabolism contribute to cardiovascular pathology, collectively termed **CKD-MBD**.
  - Despite research progress, effective treatments remain limited.

Epidemiology of Vascular Calcification in CKD

- VC = calcium-phosphate deposition in vessel walls & valves
- Common sites: coronary, aorta, iliac, femoral arteries
- Cardiovascular complications account for >50% of late-stage CKD deaths
- VC prevalence in HD patients ~8× higher than general population
- Coronary artery calcification = strong predictor of morbidity/mortality

Complex Paracrine Interplay between Bone-Vasculature Cells

- Bone and vessels develop together during embryogenesis via reciprocal regulation by osteokines and angiokines.
- In adults, bone vasculature regulates remodeling and fracture healing.

- Angiokines:
  - NO, prostaglandins, endothelin-1, RANKL/OPG, BMP2, Notch–Noggin, pleiotrophin.
- Osteokines:
  - VEGF-A, osteocalcin, SLIT3, PDGF-BB, MMPs.

- Balanced signaling ensures homeostasis; disrupted in CKD.

Complex Paracrine Interplay between Bone-Vasculature Cells

- **Vascular → Bone (Angiokines):**
  - **NO** → Osteoblast differentiation, mechanosensing
  - **Prostaglandins, Endothelin-1** → Osteoblast & progenitor proliferation
  - **RANKL / OPG** → Regulate osteoclast activity
  - **BMP2** → Bone formation (↑ in hypoxia/VEGF)
  - **Notch–Noggin, Pleiotrophin** → Osteoprogenitor recruitment/differentiation

- **Bone → Vascular (Osteokines):**
  - **VEGF-A** → Angiogenesis
  - **Osteocalcin** → Angiogenesis, NO signaling, systemic metabolic effects
  - **SLIT3** → Links bone formation & angiogenesis
  - **PDGF-BB (osteoclasts)** → Vessel growth, osteoblast recruitment
  - **MMPs** → ECM breakdown, angiogenesis

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Vasculature Changes in CKD

- **Systemic impact of CKD:**
  - Impairs cardiovascular system, bone, immune function, muscle strength, energy metabolism, fertility, and cognition.
  - Considered a **state of accelerated aging**.
- **CKD-MBD:**
  - Interrelated cardiovascular and skeletal pathology driven by reduced kidney function.
  - Initially explained by mineral imbalance and bone turnover abnormalities → vascular calcification.
- **Pro-calcifying factors:** uremic toxins, ROS, DNA damage, loss of inhibitors, CPPs, inflammation, circadian disruption.
- **Role of phosphate :** VSMC transdifferentiation into osteoblast-like cells via Pit1 transporter, expressing osteogenic markers (RUNX2, BMPs).
- **Mineral disturbances:** ↓α-Klotho, ↑FGF23 → later ↓Vit D, ↑PTH.

FGF23 & Klotho in CKD-MBD

- FGF23: bone-derived hormone, regulates phosphate & vitamin D
- Klotho: co-receptor for FGF23, mainly in kidney, parathyroid, vasculature
- High FGF23 / low Klotho → LV hypertrophy, arterial stiffness, increased VC
- Correlates with trabecular bone score and cardiovascular outcomes
  - FGF23 is negatively correlated with TBS
  - klotho is positively correlated with TBS.
  - FGF23 and klotho, in combination with TBS, show promise as early markers of trabecular bone impairment in CKD

Endothelial Dysfunction & Atherosclerosis in CKD

- Endothelium regulates vascular tone, permeability, inflammation, coagulation.
- **CKD injury:**
  - toxins, glycocalyx damage, hypertension, dyslipidemia, inflammation
- **Mechanisms:**
  - ↓NO, ↑oxidative stress, endothelial repair impairment
- **Atherosclerosis:**
  - endothelial injury → lipid deposition → foam cell formation → calcified plaque
- **Clinical note:**
  - atherosclerosis severe and frequent in CKD

Endothelial Dysfunction & Osteomimicry

- **Endothelial-to-mesenchymal transition (EndMT)**:
  - endothelial cells adopt mesenchymal/stem-like; differentiate into fibroblast or bone-like cells.
- Calcified CKD aortas show endothelial expression of bone genes.
- **Osteomimicry:** endothelium and VSMCs communicate via osteokines/angiokines, mimicking bone.
- **Research target:** identifying molecular signals for early therapeutic intervention.

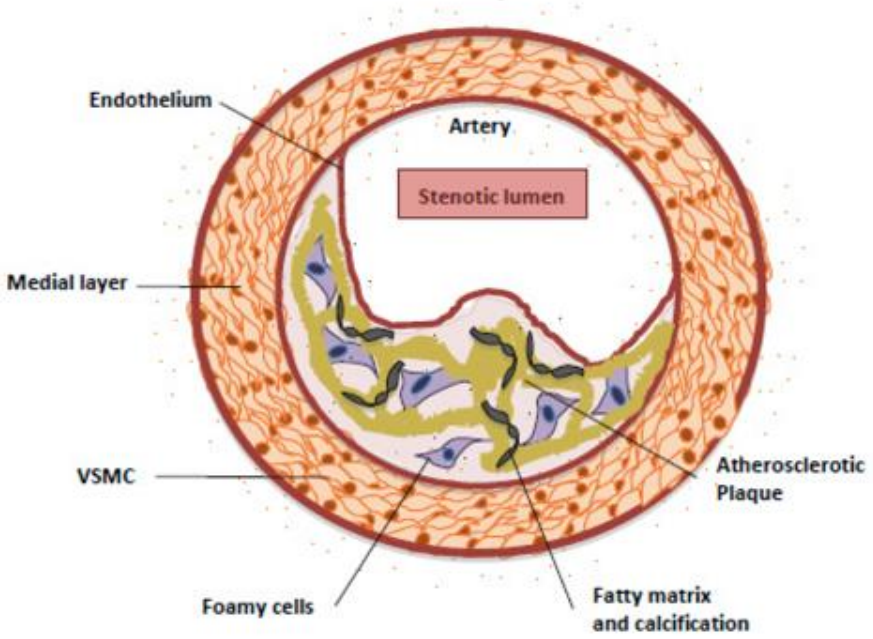
Vascular Medial Calcification

- Diffuse medial layer calcification → loss of elasticity, increased cardiac load.
- Leads to LV hypertrophy and heart failure in CKD.

- **Cellular mechanism:**
  - VSMC dedifferentiation into osteogenic phenotype expressing RUNX2, BMP2, osterix.
  - Wnt pathway activation; contributions from pericytes, adventitial fibroblasts.

- Key insight:
  - VSMC-derived osteogenic activity drives cardiovascular calcification.

Intimal calcification

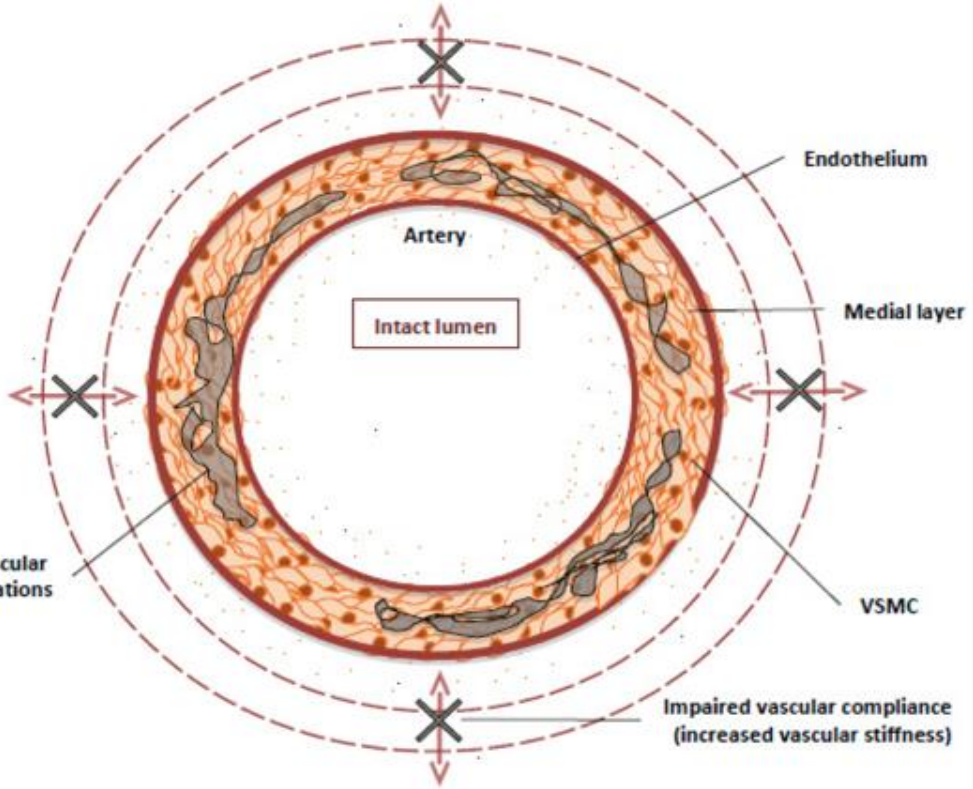


Plaque rupture

Vessel occlusion

Ischemia

Medial calcification



Arterial stiffness

Pulse pressure

LVH

New Concept in CKD-MBD Pathology

- **Classical:** systemic effects via toxins, inflammation, hormones disturbances affecting erythropoiesis, blood pressure, mineral metabolism, and bone turnover .

- **New:** CKD reactivates developmental pathways (Wnt, TGF-β, Activin A).
  - Wnt inhibitors disrupt bone formation.
  - Activin A promotes fibrosis, inhibits osteogenesis.

- **Clinical implication:** Kidney-derived factors (Wnt ligands/inhibitors, activin A) contribute to CKD-MBD by dysregulating bone and vascular homeostasis beyond traditional mineral and toxin pathways.

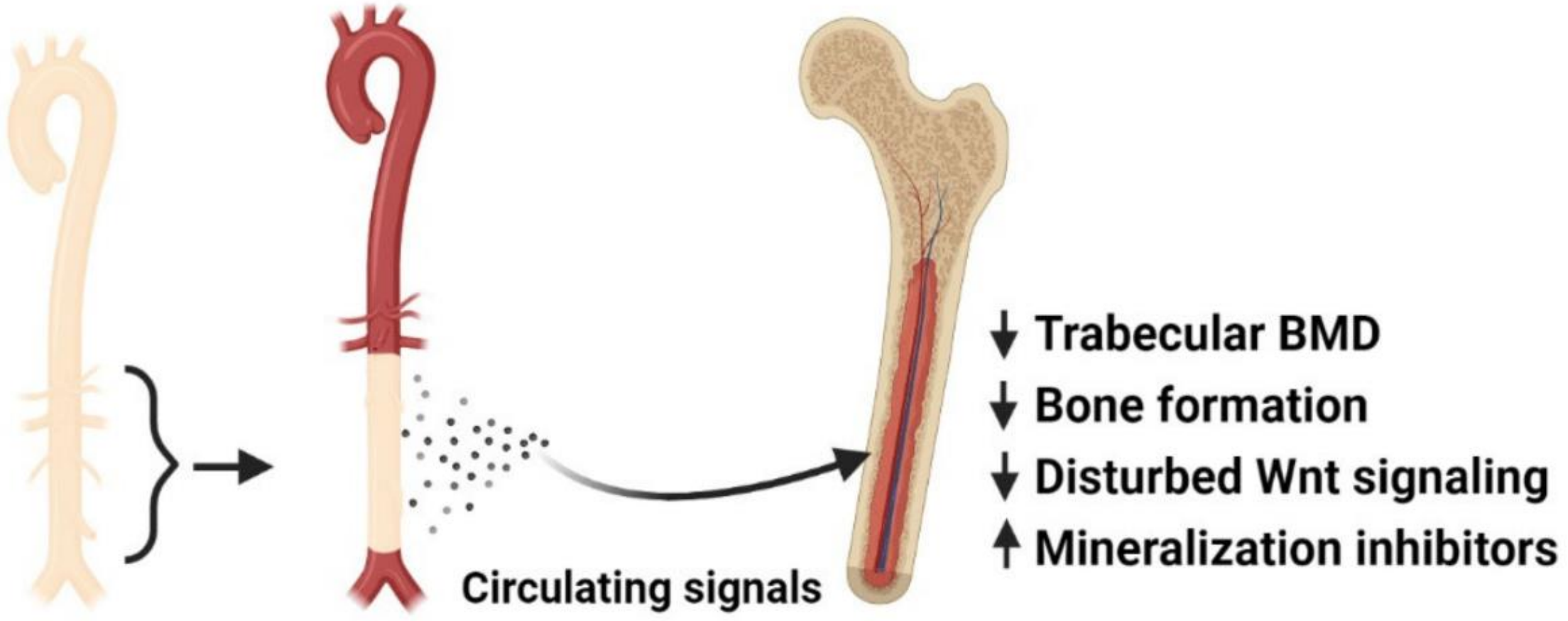
New Vascular Factors in CKD

- Injured kidneys secrete Activin A and Wnt inhibitors (sclerostin) causing systemic vascular effects independent of GFR reduction.
- Vascular calcification persists despite renal recovery; fibrosis and EMT remain dynamic.
- **Experimental interventions:**
  - BMP7 therapy reduces phosphate and aortic calcium but not established calcification.

- **Vasculature → bone signaling hypothesis:** Calcified arteries upregulate circulating factors (sclerostin, SFRP4, activin A) that may inhibit bone Wnt signaling and impair bone formation, suggesting direct pathological crosstalk between calcified vessels and bone tissue.

Calcified Vasculature Affects Bone Metabolism

- CKD calcified vessels secrete bone-regulatory factors.
- **Experimental model:** CKD aorta transplantation ↓ bone density and mineralization genes.
  - ↑Sost (sclerostin), ↓Wnt signaling in bone.
- **Ex vivo findings:**
  - Calcified aorta secretes sclerostin, Dkk1, Activin A → confirmed vascular-to-bone signaling.
- Vascular–bone crosstalk explains concurrent vascular calcification and low bone mass.
- **Therapeutic paradox:** anti-sclerostin may improve BMD but risk VC


Circulating signals
Trabecular BMD
Bone formation
Disturbed Wnt signaling
Mineralization inhibitors

Calcification Paradox

- **Calcification paradox:** bone demineralization with vascular calcification in CKD.
- **Mechanism:** vascular calcification produces **pro-osteogenic and anti-mineralization proteins** (osteopontin, ANKH):
  - OPN: dual role, inhibits crystal growth, but chronic overexpression may promote VC
  - Central to bone–vascular axis and calcification paradox
- **Negative feedback loop:** reducing calcium/phosphate incorporation in bone promotes vascular deposition.
- Defects exceed vitamin D abnormalities; involve systemic vascular–bone signaling.

Disturbances in Wnt Pathway in Renal Osteodystrophy

- **Renal osteodystrophy:** Bone disorders range from low to high turnover and mineralization defects (TMV classification).
- **Wnt pathway disturbances:**
  - Vascular calcification increases bone sclerostin → Wnt inhibition → ↓bone formation.
  - Early CKD: sclerostin elevation precedes FGF23 rise suggesting early initiation of bone dysfunction linked to vascular changes.
  - Neutralizing Dkk1/sclerostin improves bone and prevents calcification in models.
  - Later CKD: PTH resistance → high turnover bone disease , ↓sclerostin.

RANKL–OPG Pathway

- RANKL promotes osteoclast differentiation and bone resorption
- OPG acts as a decoy receptor, preventing VC and bone loss
- RANKL–OPG imbalance contributes to CKD-MBD pathology

RUNX2: Master transcriptional Regulator

- A master transcriptional regulator of osteoblast differentiation and bone formation
- A hallmark of osteogenic transdifferentiation in vascular calcification
- Activated by BMP-2, ERK/MAPK, PI3K/AKT, oxidative stress
- Marker of active VC, potential therapeutic target

Calciprotein Particles (CPPs) & Serum Calcification Propensity

- **Calciprotein Particles (CPPs)** are **colloidal complexes** composed of **calcium-phosphate crystals** stabilized by **serum proteins** (mainly **fetuin-A**, albumin, and other acidic proteins).

- They act as a **natural buffering and detoxifying system** to prevent **precipitation of calcium and phosphate** when serum levels rise.
- Two types:
  - CPP1: soluble, physiologic; CPP2: crystalline, pathogenic

- T50 = time for CPP1→CPP2; lower T50 → higher VC risk

- CPPs induce VSMC osteogenic differentiation, EC stress, macrophage inflammation

Therapeutic Strategies Targeting Bone–Vascular Axis

- Sclerostin/WNT modulation: balance bone vs. VC
- RANKL/OPG modulation: denosumab or OPG enhancement
- CPP stabilization: phosphate binders, calcimimetics, CPP adsorption
- Integrated approaches needed for dual bone & vascular protection

Conclusion

- CKD-MBD: complex disorder affecting bone & vasculature
- VSMC osteogenic transdifferentiation is central to VC
- Bone–vascular axis understanding is key for integrative therapy
- Future therapies should target molecular drivers (RUNX2, BMP-2, CPPs)

Thank You