Osteoporosis in CKD (pathogenesis)

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Pathophysiology of bone disease in chronic kidney disease: from basics to renal osteodystrophy and osteoporosis

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The importance of the bone component of CKD-MBD

- The “old” cross-talk between kidney and bone (classically known as “renal osteodystrophies”)
- The cardiovascular system
- Independently related to cardiovascular disease and high mortality rates

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Bone cells

- The most important cells of bone tissue
  - Osteoblasts (OBs)
  - Osteoclasts (OCs)
  - Osteocytes
  - Bone-lining cells.

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Osteoblasts (OBs)

- OBs develop from pluripotential mesenchymal stem cells (MSCs).
- Bone morphogenic proteins (BMPs) and the Wnt signaling pathway are related to OB differentiation.
- The canonical Wnt signaling pathway induces transcription factors that favor OB differentiation
- the non-canonical Wnt pathway inhibits the differentiation of MSCs to other cell types

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The main function of OBs

- Bone matrix through the synthesis
- Secretion of type 1 collagen
- Non-collagenous proteins
- Releasing phosphate contained in their vesicles
  - Compose the main mineral of cortical bone (calcium hydroxyapatite crystals)

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Osteoclasts (OCs)

- Derive from precursor cells of the monocyte-macrophage lineage
- Differentiation and survival require the
  - Macrophage colony-stimulating factor (M-CSF)
  - Receptor activator of NF-κB ligand (RANKL)
- OB-synthesized osteoprotegerin (OPG) acts
  - High -affinity decoy receptor for RANKL
  - Inhibiting RANKL action on the OC-RANK receptor

The ratio between RANKL and OPG determines the degree of osteoclastic differentiation

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Osteoclasts (OCs) continue

- The main function of the OC is bone resorption
- Activated by
  - Binding to the bone matrix
  - Polarizing and forming podosomes and different membrane domains
- Each of these domains is extremely important for
  - Bone resorption
  - Collagen degradation
  - Return of calcium and phosphate to the bloodstream

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Osteocytes

- Osteocytes (mature OBs) represent 95% of all bone cells.
- Osteocytes influence OBs in two directions
  - Upregulating them through the production of messengers such as nitric oxide and prostaglandin E2
  - Downregulating them through the secretion of sclerostin
- Osteocytes the main source of FGF23
  - Suppressing phosphate reabsorption and calcitriol synthesis in the kidney

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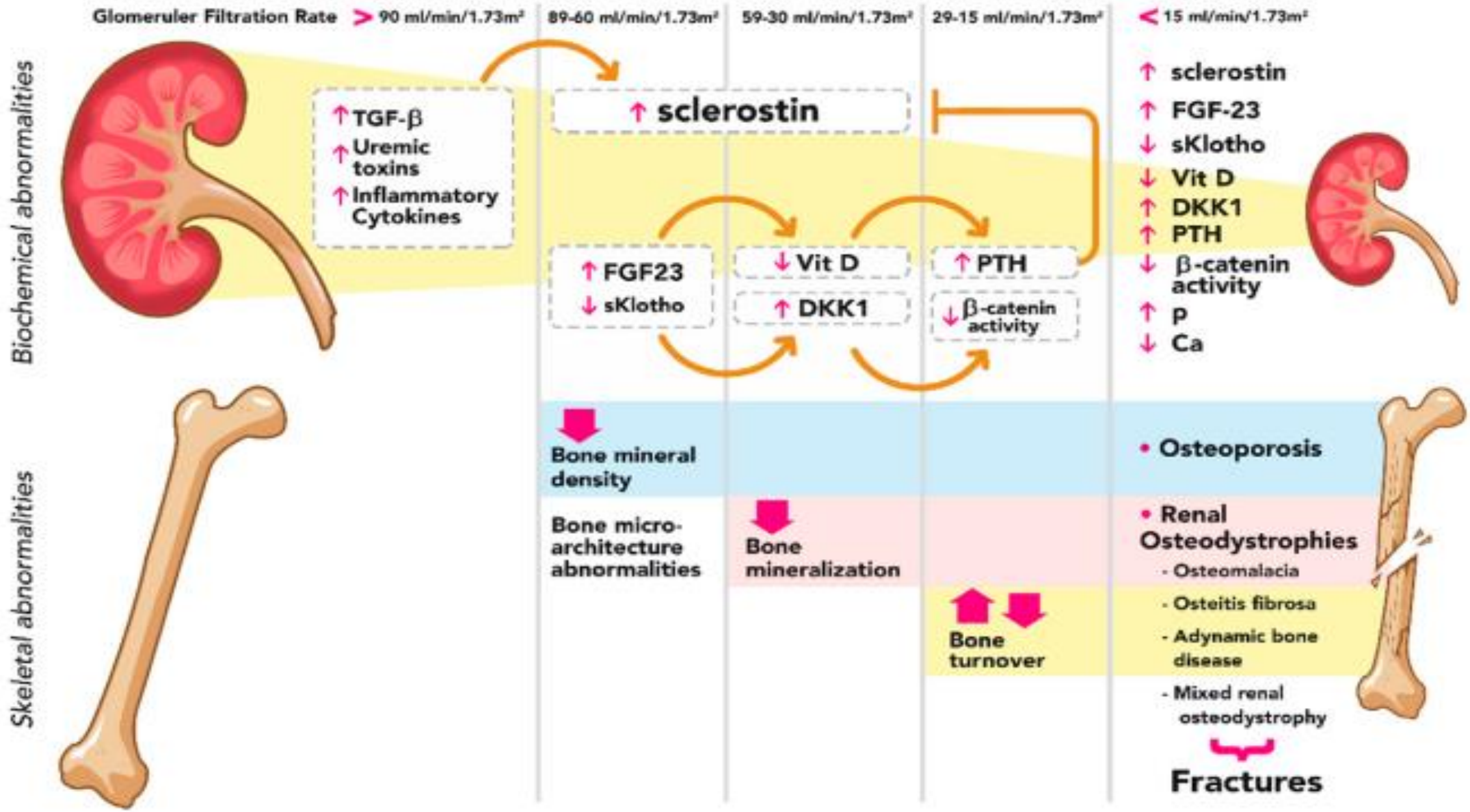

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Review

Osteoporosis in Patients with Chronic Kidney Diseases: A Systemic Review

Chia-Yu Hsu [1,2,†], Li-Ru Chen [3,4,†] and Kuo-Hu Chen [5,6,*]

- This review was modeled based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

- Chronic kidney disease (CKD) is associated with the development of mineral bone disorder (MBD), osteoporosis, and fragility fractures.

Int. J. Mol. Sci. **2020**, *21*, 6846; doi:10.3390/ijms21186846

Osteoporosis

- WHO defines osteoporosis as a T score ≤ -2.5.
- CKD is an independent risk factor of osteoporosis
- The prevalence of osteoporosis was 31.8% among CKD G3–5 patients
- National Health and Nutrition Examination Survey (NHANES III)
  - Osteoporosis was twice as common in those with eGFR < 60 mL/min than those with eGFR > 60 mL/min

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The Longitudinal Aging Study Amsterdam (LASA)

- Amsterdam (LASA) survey
  - Increase incident fracture risk
  - Greater fracture risk after adjusting age, race, and BMD
  - Incidence of hip fracture in hemodialysis (HD) group was higher than that in peritoneal dialysis (PD) or KT groups
- The consequence of fractures increased the mortality rate in CKD patients with non-dialysis and with dialysis
- Thus, the goal
  - Prevention CKD-induced MBD
  - Treating subsequent osteoporosis

Hall ET AL . *J. Am. Geriatr. Soc.* **2018**, *66*, 532–538.

Characteristics of CKD-MBD

- CKD-MBD describes abnormalities
  - Mineral metabolism
  - Skeletal health
  - Soft tissue calcifications

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Disorders of Calcium Balance

- Hypocalcemia is common in CKD patients.
- Total serum calcium concentration decreases due to
  - Phosphate retention
  - Decreased 1,25(OH)2D (calcitriol) concentration
  - Resistance to the calcemic actions of PTH on bone
- Calcium -sensing receptor (CaSR) on parathyroid glands
  - Contributes to increased PTH secretion and abnormal bone remodeling

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Calcium balance

- Serum calcium alone cannot serve as a proxy measurement of the whole-body calcium balance.

- Whole -body calcium retention
  - Deficit total calcium inputs subtract total body loses

- A positive balance may increase vascular calcification and cardiovascular events

- A negative balance may increase the risk of osteoporosis and fracture

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Disorder of Phosphorus Metabolism

- Phosphate retention begins early in CKD
  - Hypocalcemia
  - Decreasing calcitriol synthesis
  - Increasing PTH gene expression

- Secondary hyperparathyroidism (SPTH)
- Serum phosphate levels
- Renal proximal tubular phosphate resorption
  - PTH and fibroblast-growth-factor (FGF)-23
- Serum phosphate typically remain normal until eGFR < 20 mL/min/1.73 m2

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Disorder of Parathyroid Hormone Metabolism

- The prevalence of SPTH increases as CKD progress
  - PTH included phosphate retention
  - Decreased free ionized calcium level
  - Decreased calcitriol level
  - Increased FGF-23 level
  - Reduced expression of vitamin D receptors (VDRs)
  - Calcium -sensing receptors (CaSRs)
  - FGF receptors
  - Kloth in the parathyroid glands.

Serum intact PTH (iPTH) typically remains normal until the eGFR decreases to approximately 45 mL/min/1.73 m2

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Disorder of Vitamin D Metabolism

- A serum 25(OH)D (calcidiol) level < 30 nmol/L indicates vitamin D deficiency
- Vitamin D deficiency is associated with cardiovascular events
- Calcitriol level started to fall until eGFR was <40 mL/min/1.73 m2

- The primary cause why calcitriol level declines is the increase in FGF-23 concentration, rather than the loss of functioning renal tissue

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Factors affecting bone strength in CKD-MBD

Factor	Main Effect	Category
↓ Kloth	↑ FGF-23 level [13]	Humoral
↑ FGF-23 [1]	↑ phosphate excretion [14] ↓ calcitriol synthesis [14,15]	Humoral
↑ Sclerostin	↓ bone formation [14,16] ↑ osteoclastogenesis [17]	Humoral
↑ dickkopf1	↓ bone formation [16,18]	Humoral
↑ phosphate	↑ SPTH [3] [19] ↓ calcitriol synthesis [20]	Mineral
↑ uremic toxins [2]	↓ PTH receptor [21] ↑ skeletal resistance to PTH [21]	Uremia
↓ 1,25$(OH)_2$ D	↑ PTH secretion [20,22] ↓ calcium [23]	Humoral
↓ calcium	↑ SPTH [23] ↑ abnormal bone remodeling [23]	Mineral
↑Skeletal resistance to PTH	↑ SPTH [24]	Humoral

TMV system

- Kidney Disease: Improving Global Outcomes (KDIGO) group recommends three parameters
  - Bone turnover
  - Mineralization
  - Volume
- Bone biopsy is the gold standard for the diagnosis and classification of bone diseases in CKD

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TMV Characteristics of Renal Osteodystrophy

- Bone turnover
  - Rate of skeletal remodeling, or the ratio between bone formation, and bone resorption
- Mineralization
  - How well bone collagen becomes calcified during the formation phase of skeletal remodeling
- Volume
  - The amount of bone per unit volume of tissue
- Bone strengths is determined by bone quantity, and bone quality
  - Bone quality refers to the structure and material parameters that enables bone to bear load and resist fracture

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Bone Turnover in CKD

- The high bone turnover
  - Osteitis fibrosa cystica and mixed uremic osteodystrophy
- The low in patients
  - Adynamic bone disease and osteomalacia
- Evaluation of Bone Turnover
  - Very high PTH levels (≥585 pg/mL {osteitis fibrosa }
  - Very low PTH levels (<100 pg/mL) { adynamic bone disease}
- PTH of >323 pg/mL high from non-high bone turnover
- PTH < 103.8 pg/mL low from non-low turnover
- KDIGO suggests using PTH trends instead of absolute targets

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Evaluation of Bone Strength

- Dual-energy X-ray absorptiometry (DXA)
  - Bone quantity
  - bone quality.

- Non -invasive 3D imaging techniques that can detect microarchitecture and mineral density

  - Peripheral quantitative computed tomography (pQCT)
  - High resolution pQCT (HRpQCT)
  - Micromagnetic resonance imaging (microMRI)

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Review

Systemic Activation of Activin A Signaling Causes Chronic Kidney Disease-Mineral Bone Disorder

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Bone vital functions

- Bone is a dynamic tissue
  - Bone remodeling
- Regulated by mature osteoclasts and osteoblasts controlled
  - Cytokines
  - Chemokines
  - Hormones
  - Biochemical stimuli
- Osteoclasts remove the damaged bone
- Osteoblasts replace the resorbed matrix and mineralize it

Skeletal fragility

- Osteoporosis
- Imbalance in bone remodeling
  - Favoring osteoclast activity
- Significant cause of morbidity and mortality world wide

What is Activin A?

- Activin A is a homodimer
  - βA-βA subunits that belongs
    - TGF-β superfamily of cytokines
- Activin A was initially discovered related to its capacity to induce the release of follicle-stimulating hormone

  - High affinity to activin receptor type llA (ActRllA)
  - Less affinity to activin receptor type llB (ActRIIB)

Known as the activin receptor-like kinase 4 (ALK4)

What is function of Activin A in CKD mouse models ?

- High -turnover osteopenia caused by increased osteoclast numbers and activated osteoclastic bone resorption compared to that of control mice
- Treatment with RAP-011, a ligand trap of ActRIIA
  - An antiresorptive effect in CKD mouse models
- Activin A seems to be a positive regulator for osteoclastic development and bone resorption in vivo

Int. J. Mol. Sci. **2018**, *19*, 2490; doi:10.3390/ijms19092490

Activin A other vital biological processes in development and homeostasis

- Regulation of embryogenesis
- Development of the reproductive system
- Maintenance of pluripotent stem cells
- Regulation of immune response
- Wound healing
- Development of limbs
- Craniofacial development

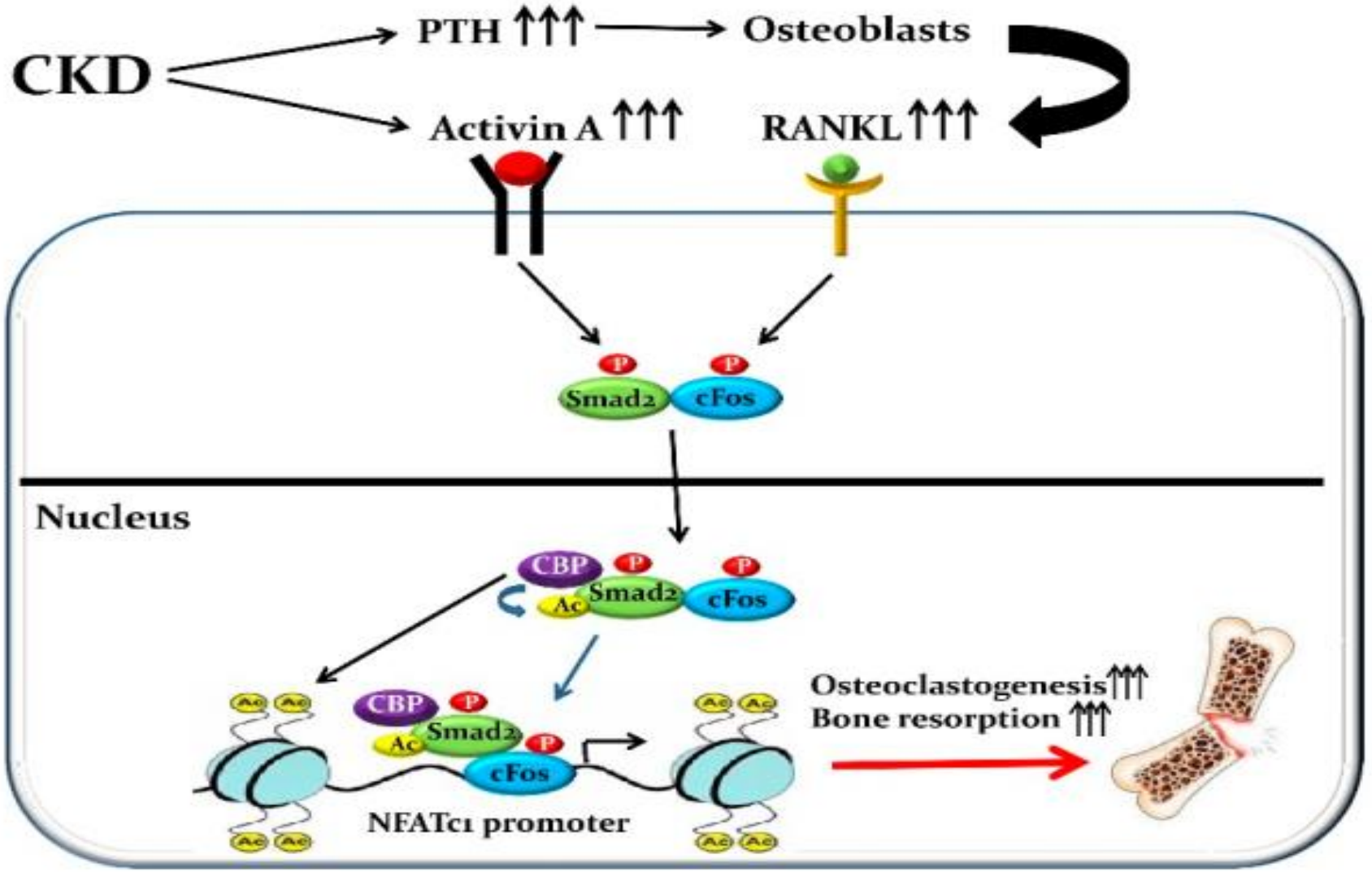
Int. J. Mol. Sci. **2018**, *19*, 2490; doi:10.3390/ijms19092490

Activin a Biology in Osteoclastogenesis

- In the skeleton, activin A is secreted by osteoblasts and osteoclasts
- Have fundamental roles in both embryonic skeletal development and postnatal bone homeostasis

Int. J. Mol. Sci. **2018**, *19*, 2490; doi:10.3390/ijms19092490

Activation of activin A signaling stimulates RANKL-induced osteoclast development and function in CKD



Int. J. Mol. Sci. **2018**, *19*, 2490; doi:10.3390/ijms19092490

Activin a Biology in Osteoblast Development and Function

- Smad-dependent TGF-β signaling stimulates proliferation, chemotaxis and early differentiation of osteoblasts from mesenchymal stem cells to immature osteoblasts.

- it suppresses osteoblast maturation, mineralization and transition into osteocyte
- Inhibitory effects on TGF-β for mature osteoblasts and bone mineralization has been well-established.
- The roles of activin A for osteoblast differentiation and function

Int. J. Mol. Sci. **2018**, *19*, 2490; doi:10.3390/ijms19092490

از تمامی دوستان خواهشمندم

اصلا خسته نباشید