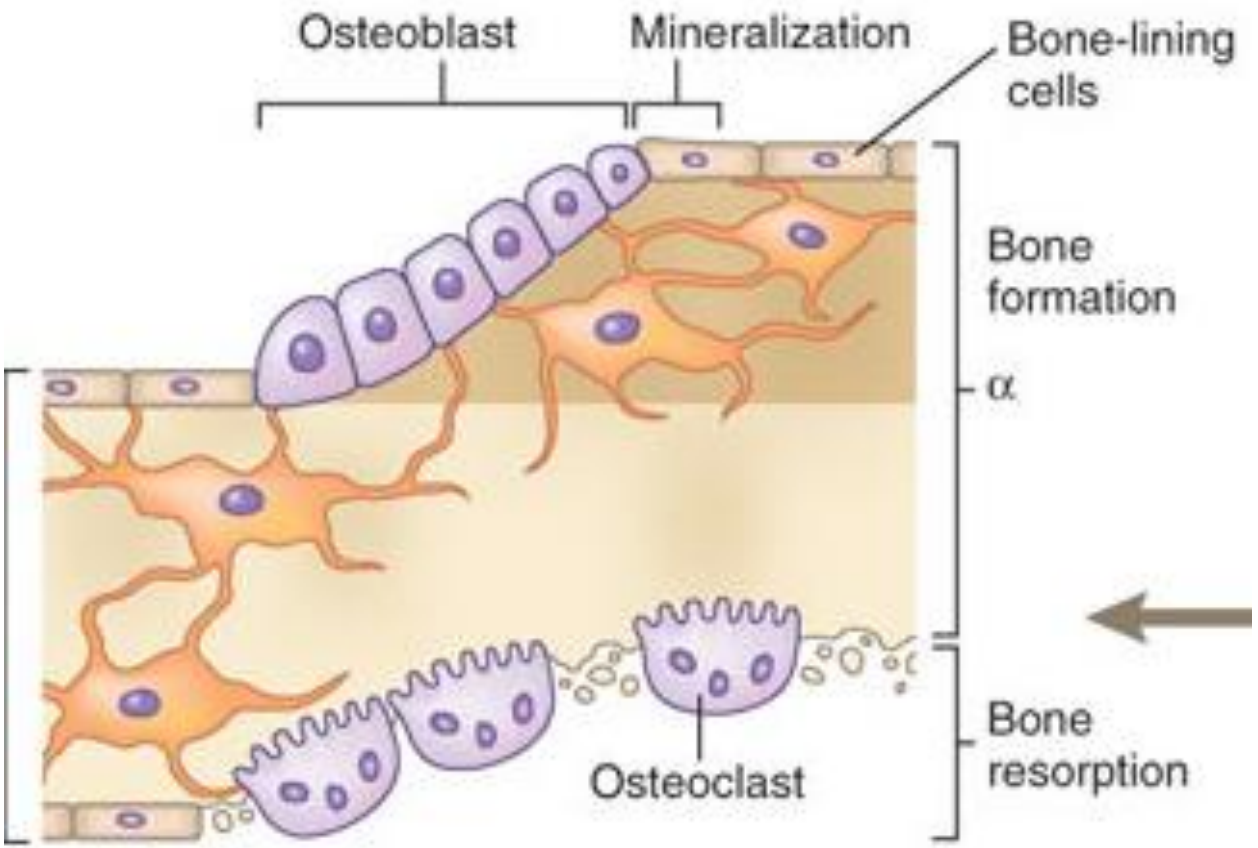
Pathophysiology of Postmenopausal & Glucocorticoid Induced Osteoporosis

March 15, 2016
Bone ECHO
Kate T Queen , MD

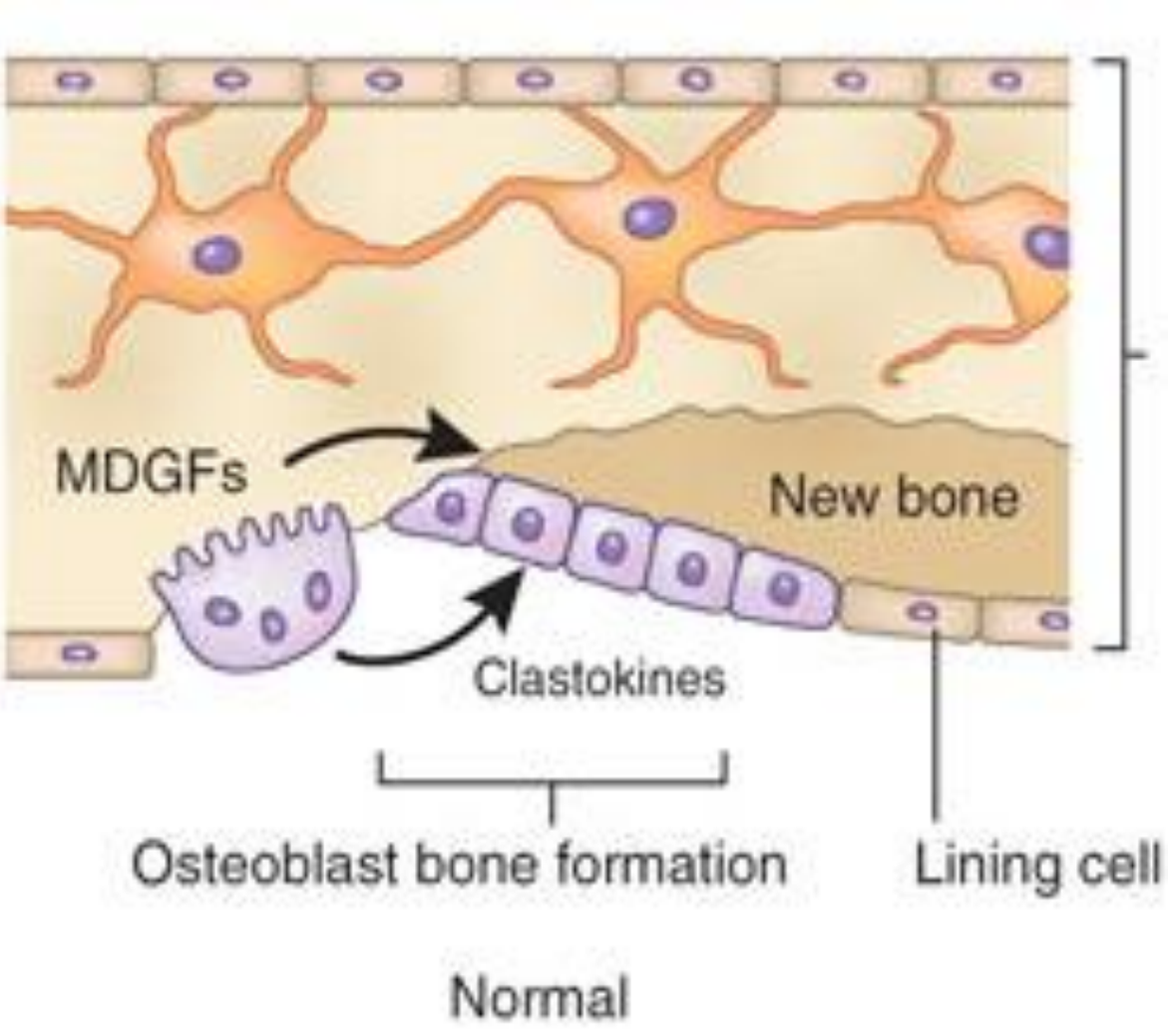
Review: normal bone formation

Bone Modeling



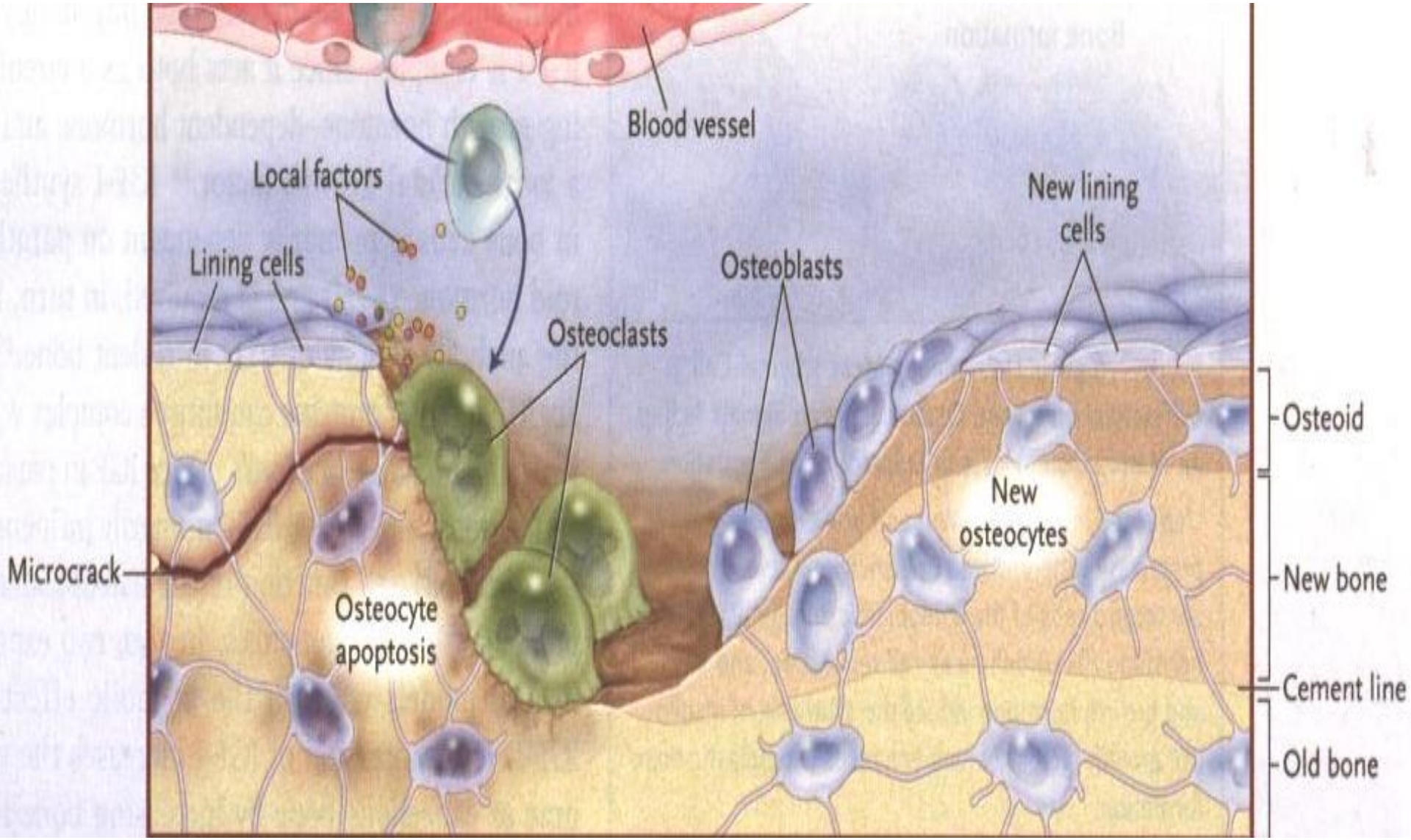
Normal shape modification

Remodeling


MDGFs
New bone
Clastokines
Osteoblast bone formation
Lining cell
Normal

Peak Bone Mass

- Maximum bone mass achieved in life
- Usually in the 3rd decade of life
- 60 -80% peak bone mass has genetic determinants (ethnicity, sex, body size)
- variability related to environmental factors (diet, exercise, habits, diseases, medications)
- Chronic diseases during childhood


Blood vessel
Local factors
Lining cells
Osteoclasts
Osteoblasts
New lining cells
Microcrack
Osteocyte apoptosis
New osteocytes
Osteoid
New bone
Cement line
Old bone

Cellular Components

10 % of bone volume

Osteoprogenitor cells

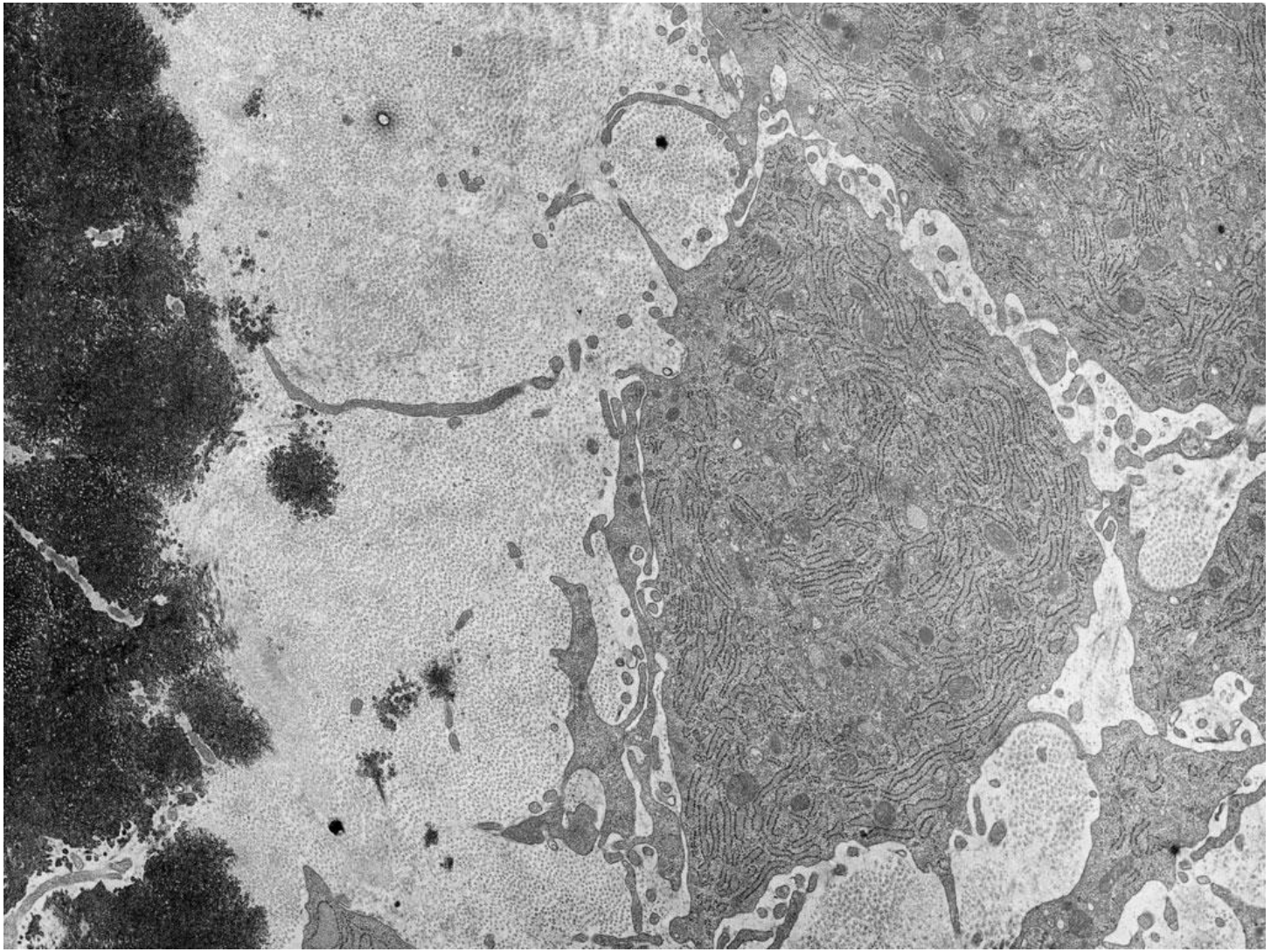
(mesenchymal stem cells)

- Osteoblasts
- Bone lining cells
- Osteocytes

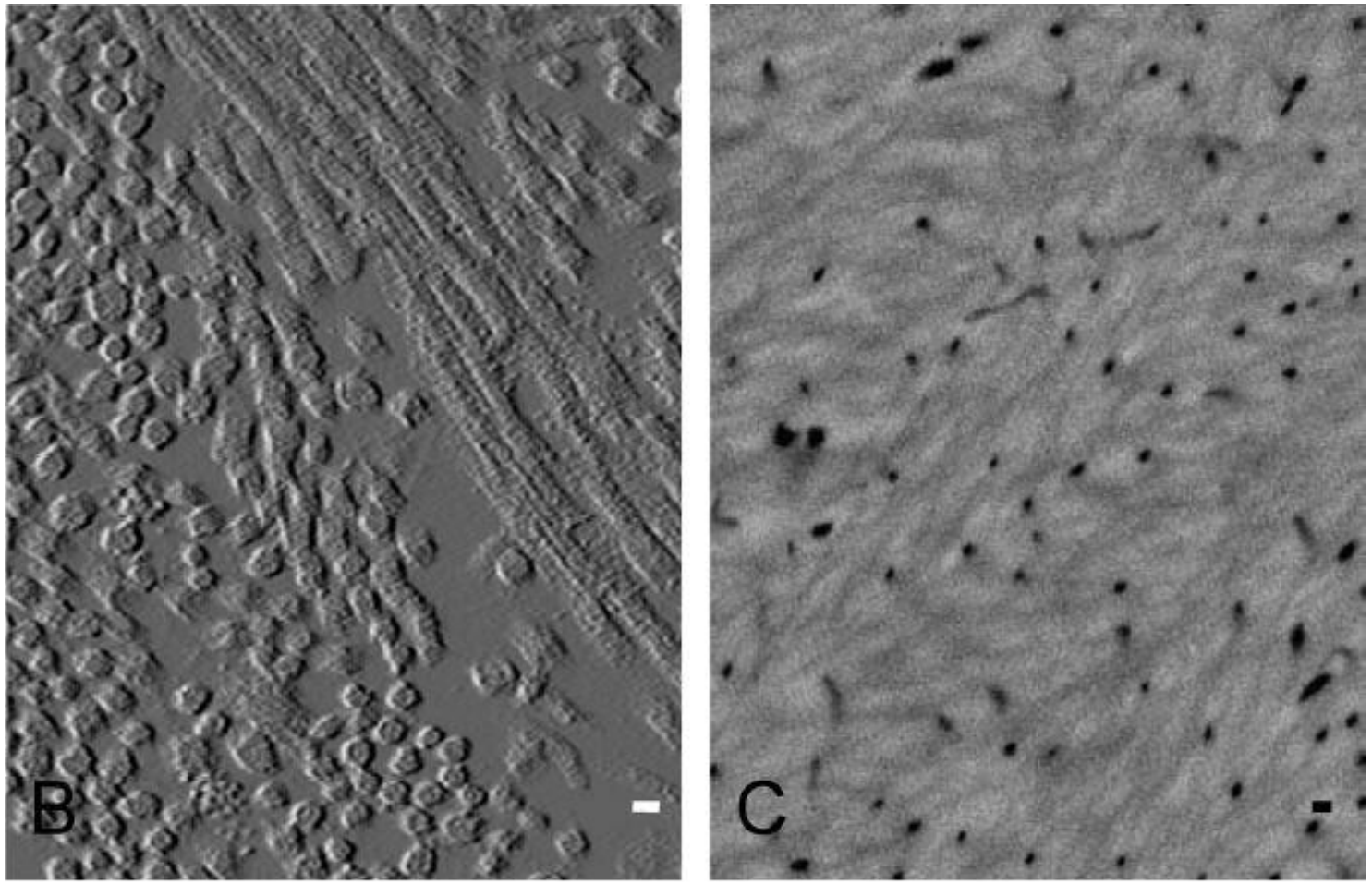
Hematopoetic stem cells

- Osteoclasts

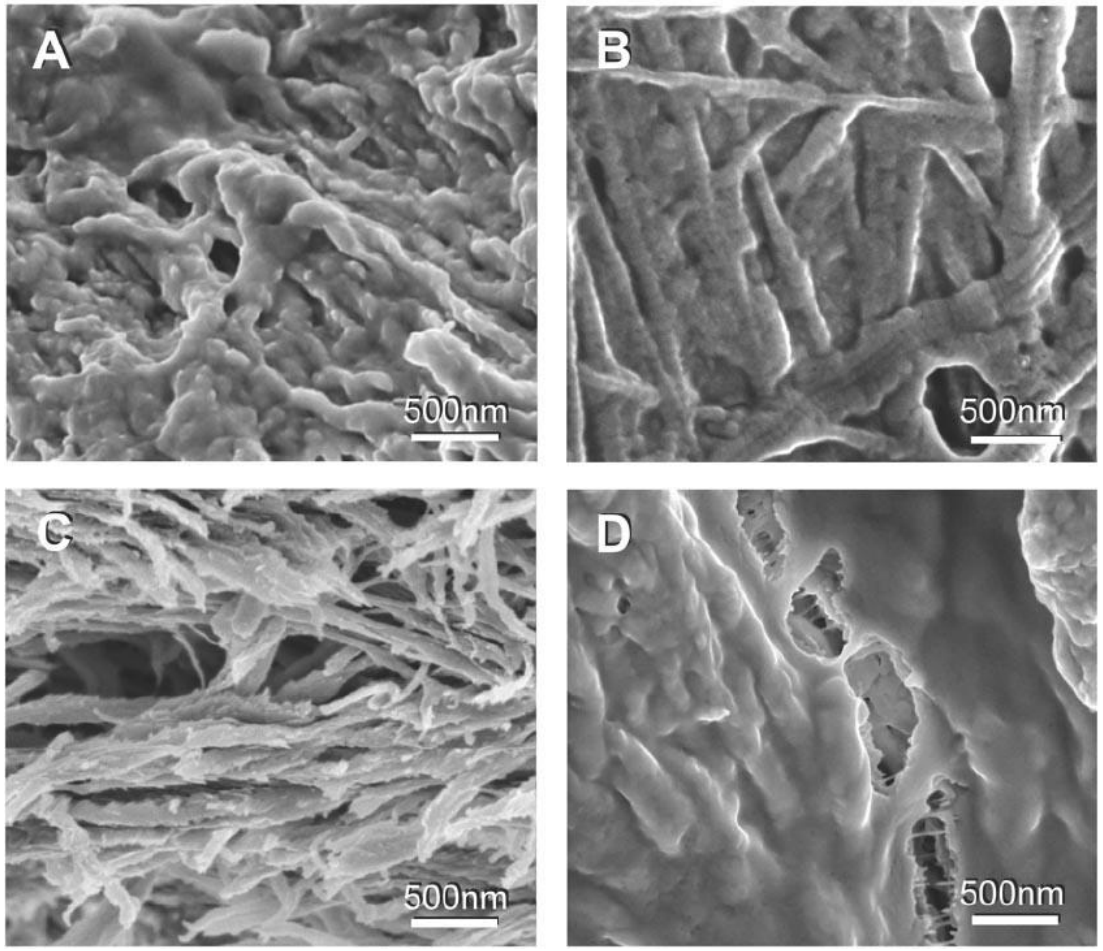
Osteoblasts

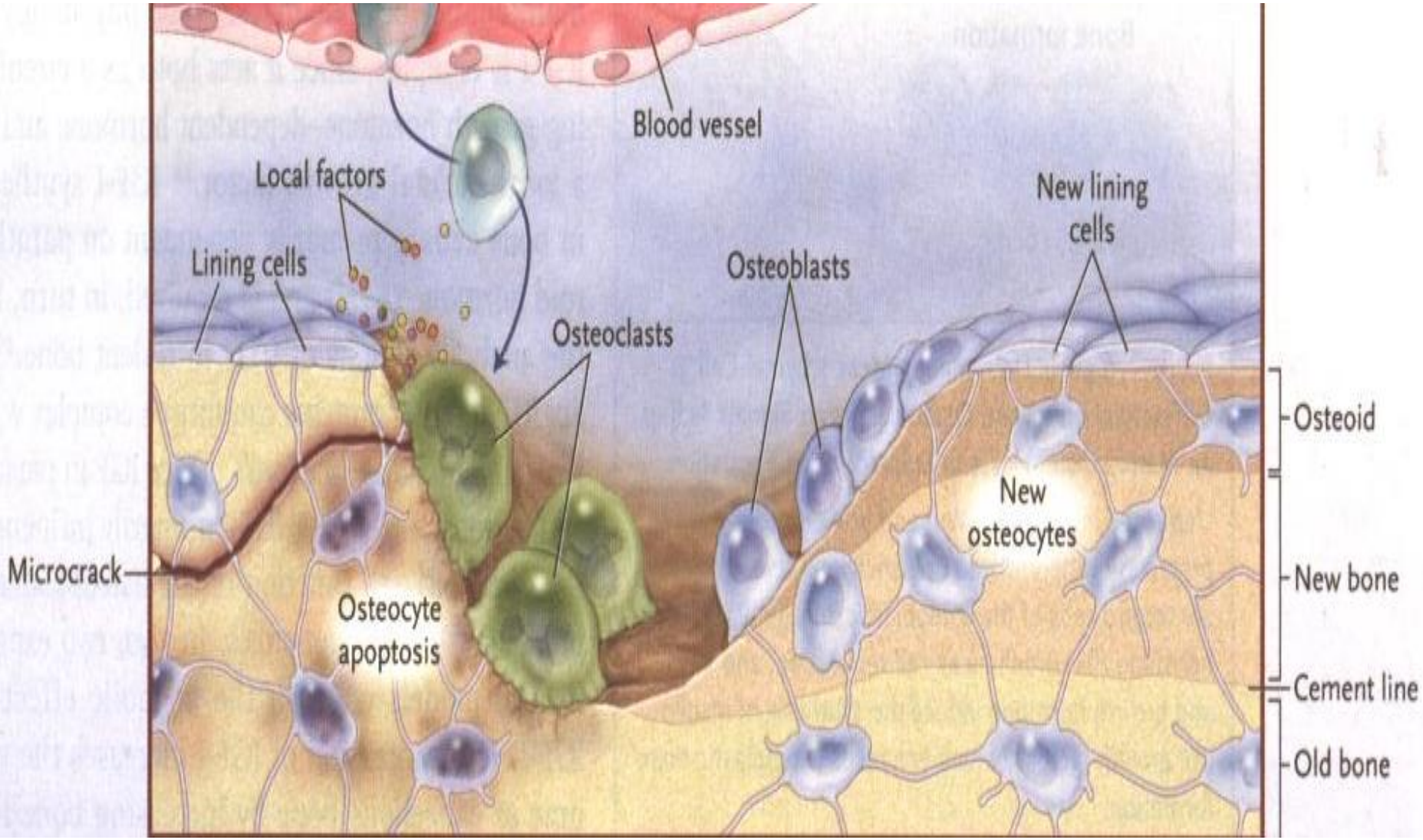


Extracelluar Components
Collagen – Type 1



Extracelluar Components
Inorganic Matrix

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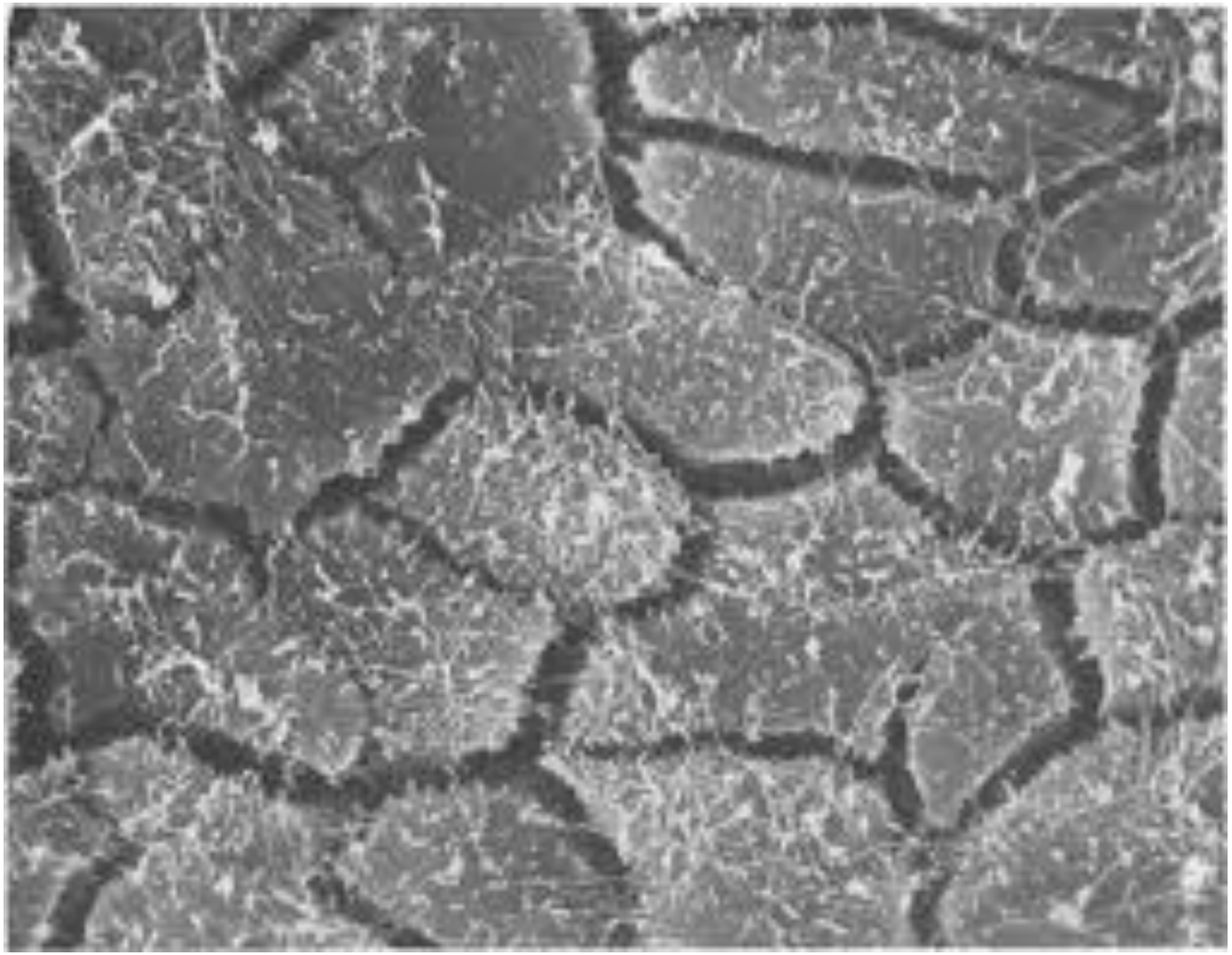
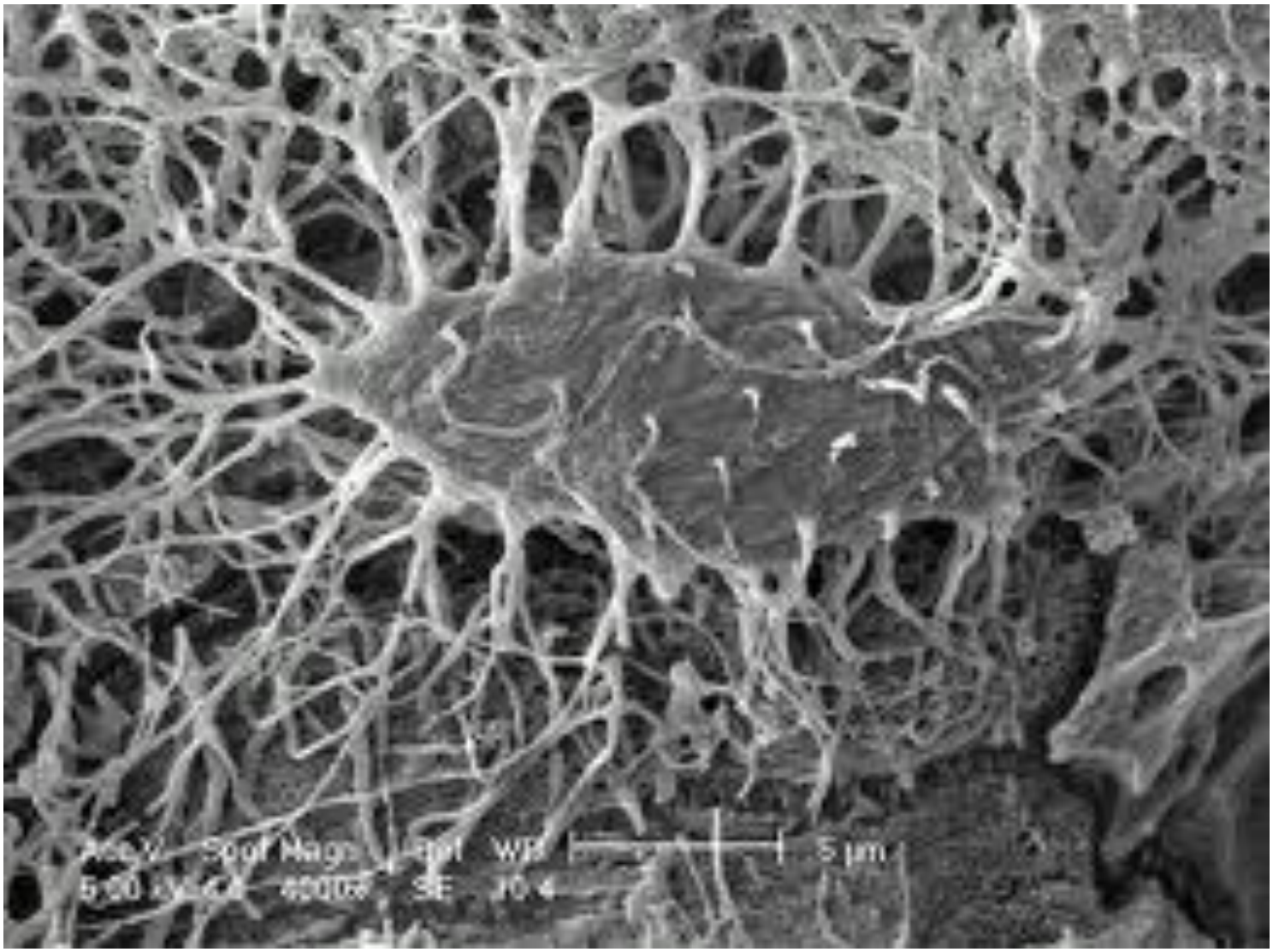
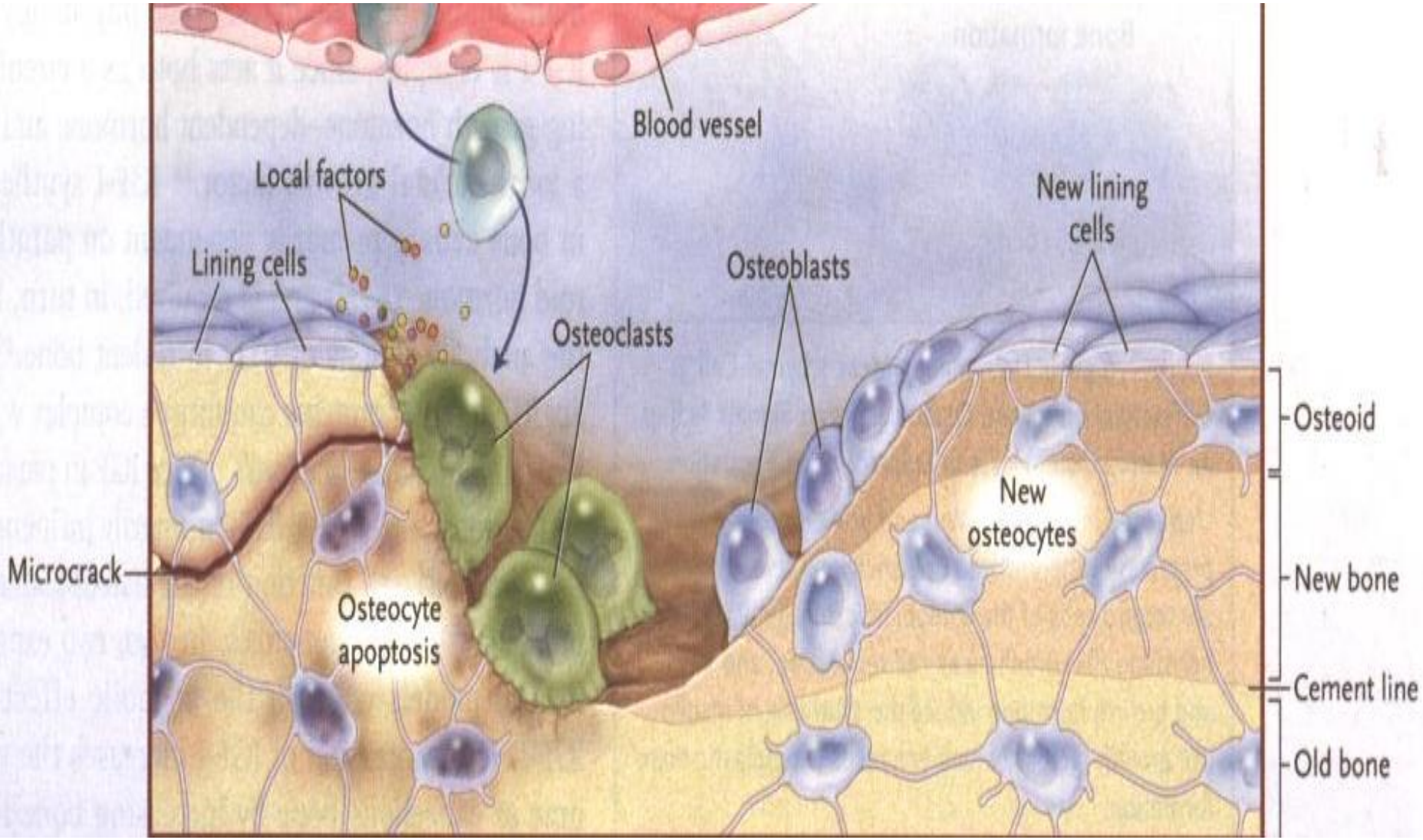
Bone Lining Cells



Osteocytes

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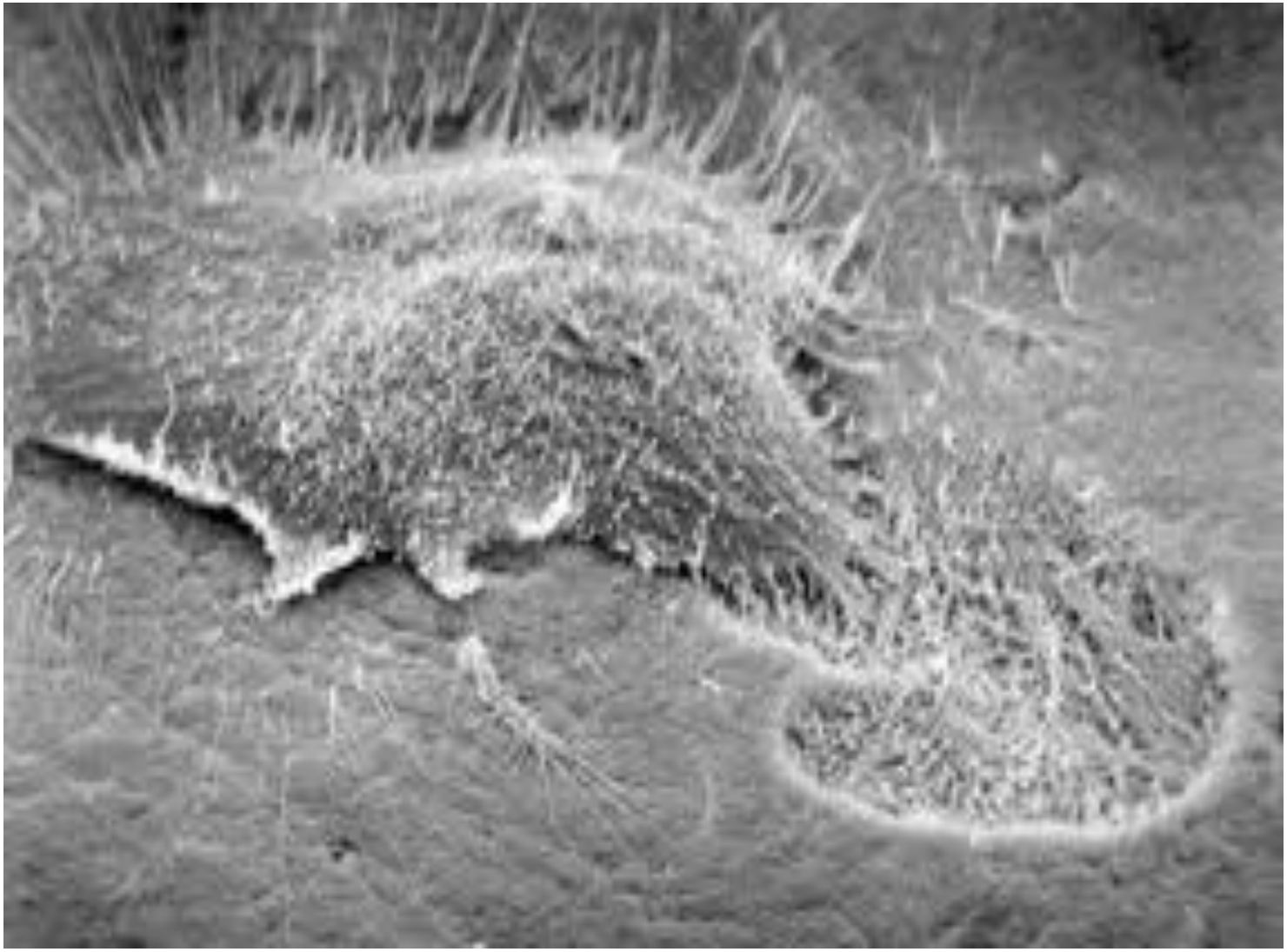
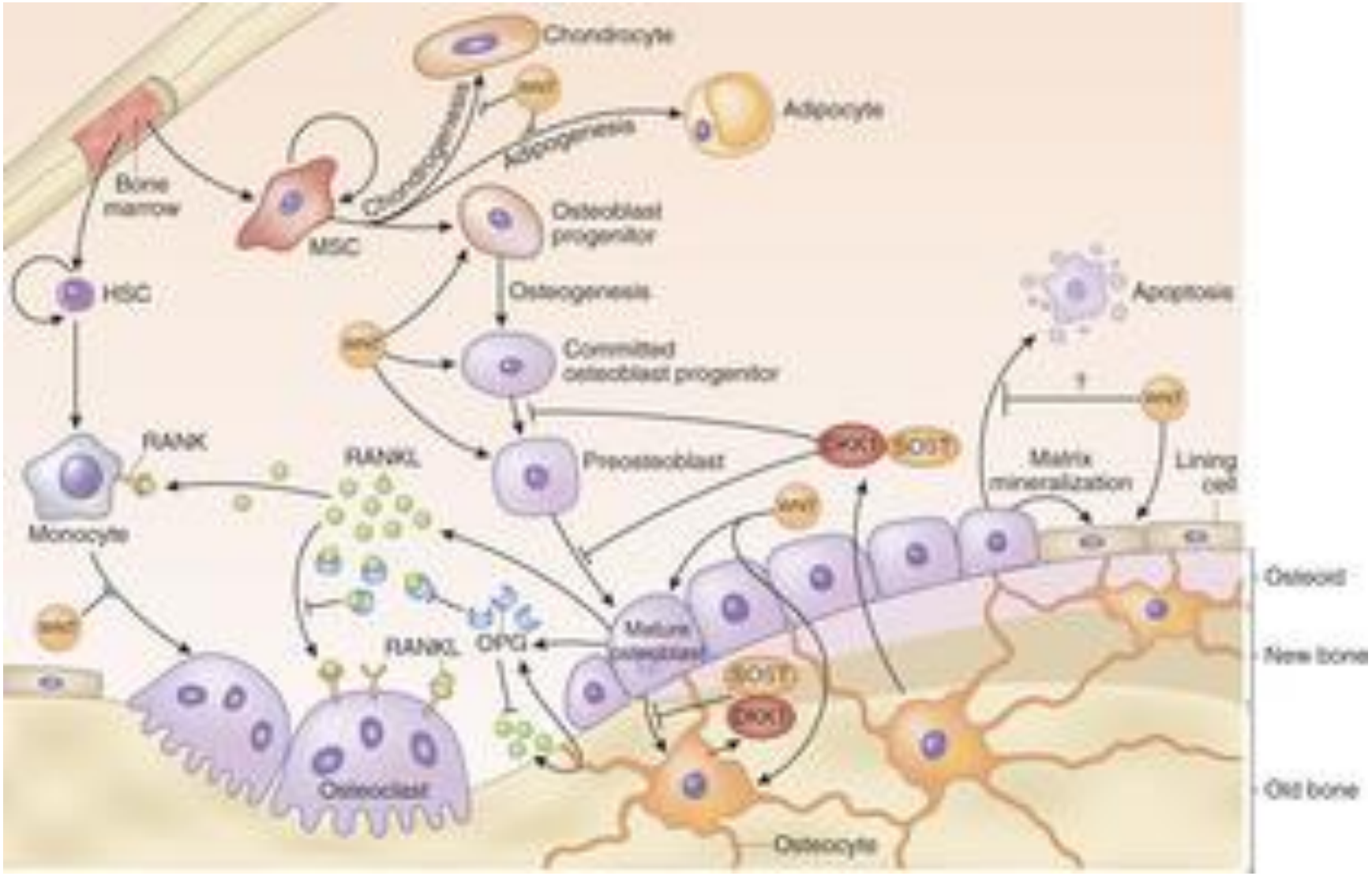
Osteoclast




Chondrocyte
Wnt
Adipocyte
Chondrogenesis
Adipogenesis
Bone marrow
MSC
Osteoblast progenitor
HSC
Osteogenesis
Apoptosis
Committed osteoblast progenitor
Wnt
?
Wnt
RANK
RANKL
Preosteoblast
PKA
SOST
Matrix mineralization
Lining cell
Monocyte
Wnt
Wnt
Osteoid
RANKL
OPG
Mature osteoblast
New bone
SOST
PKA
Old bone
Osteoclast
Osteocyte

Postmenopausal Osteoporosis

Postmenopausal Bone Loss

Cellular / molecular level

Estrogen promotes:

- mesenchymal stem cell differentiation to osteoblast lineage
- Preosteoblast to osteoblast differentiation
- Limits osteocyte and osteoblast apoptosis
- Estrogen increases:

  - Osteoblast production of growth factors (IGF1,TGF beta) and procollagen synthesis

Postmenopausal Bone Loss

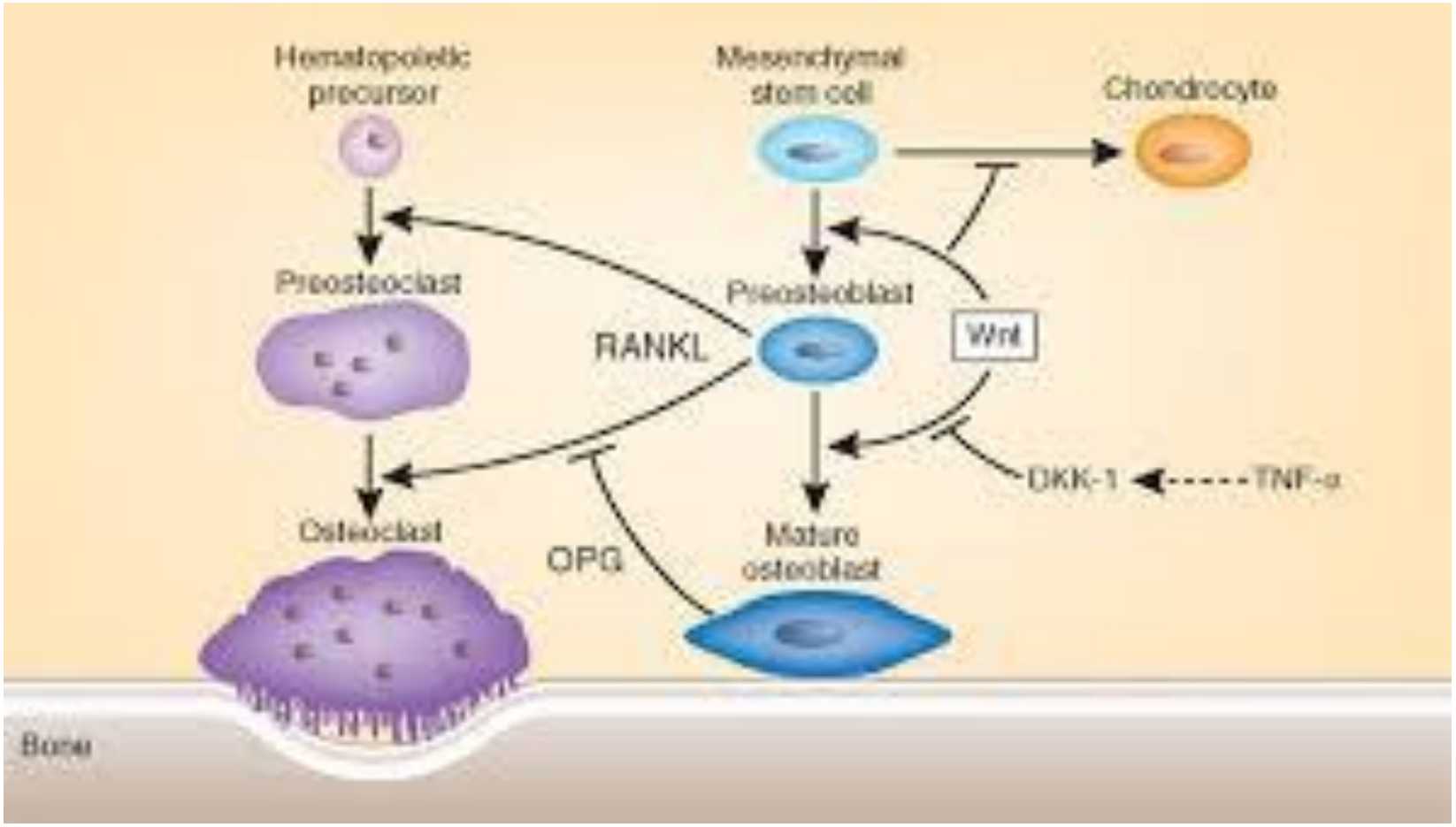
Cellular / molecular level

Estrogen promotes:

- Reduces serum and bone marrow levels of Sclerostin (potent inhbitor of Wnt signaling)
- Estrogens effects on osteoclasts:

  - Reduces production of RANKL (central molecule in osteoclast development)

  - Increases production of OPG (soluble RANKL decoy receptor)


Hematopoietic precursor
Mesenchymal stem cell
Chondrocyte
Preosteoclast
Preosteoblast
RANKL
Wnt
DKK-1
TNF-α
Osteoclast
OPG
Mature osteoblast
Bone

Postmenopausal Bone Loss

- Prior to menopause
  bone formation = resorption rates

- Declining estrogen levels
  - increase BMU activation frequency
  - extension of resorption phase

- Bone resorption increases by 90%
  Bone formation by 45%

Postmenopausal Bone Loss

With accelerated bone loss:

- Efflux of calcium into extracelluar fluid

- Compensatory mechanisms – limit hypercalcemia:
  * Increased renal calcium clearance
  * Decreased intestinal calcium absorption
  * Partial suppression of PTH secretion

Postmenopausal Bone Loss

Declining estrogen:

increased RANKL and decreases OPG – increased osteoclast development / activity

- cytokines produced by osteoblasts, now rise including IL1, IL6, TNF alpha, MCSF(macrophage colony stimulating factor) all of which play a role in mediating bone resorption
- Loss impact on promoting apoptosis of osteoclast lineage cells and of mature osteoclasts

Summary

Estrogen deficiency

- Increased renal calcium clearance
- Decreased intestinal calcium absorption
- Partial suppression of PTH secretion

- **Increases osteoclast recruitment, differentiation , and survival**
- Osteoblast activity and differentiation declines. Increase in premature apoptosis
- T cell generated cytokines increase that promote bone resorption (IL1, IL6, TNF alpha)

Glucocorticoid Induced Osteoporosis

Glucocorticoid Induced Osteoporosis

- 2nd most common kind of osteoporosis
- Most common iatrogenic form of the disease
- Fractures may occur in 30-50% of patients on chronic glucocorticoid therapy
- Often asymptomatic prevalent vertebral fractures
- Increase risk of future vertebral fractures independent of BMD

Glucocorticoid Induced Osteoporosis

- Reduction in BMD biphasic:
  - 6-12 % loss in the 1st year followed by
  - Slower annual loss of about 3%

- Risk of fracture escalates as much as 75% in 1st 3 months before significant decline in BMD

- Pts steroids various disorders pred 10mg/day > 90 days – 7 fold increase in hip fractures and 17 fold increase in vertebral fractures

  (Steinbuch, et al 2004 OI 15:323-328)

Glucocorticoid Induced Osteoporosis

- GIOP diffuse. Effects cortical and trabecular bone. Predilection for fractures in sites of predominately trabecular (cancellous)

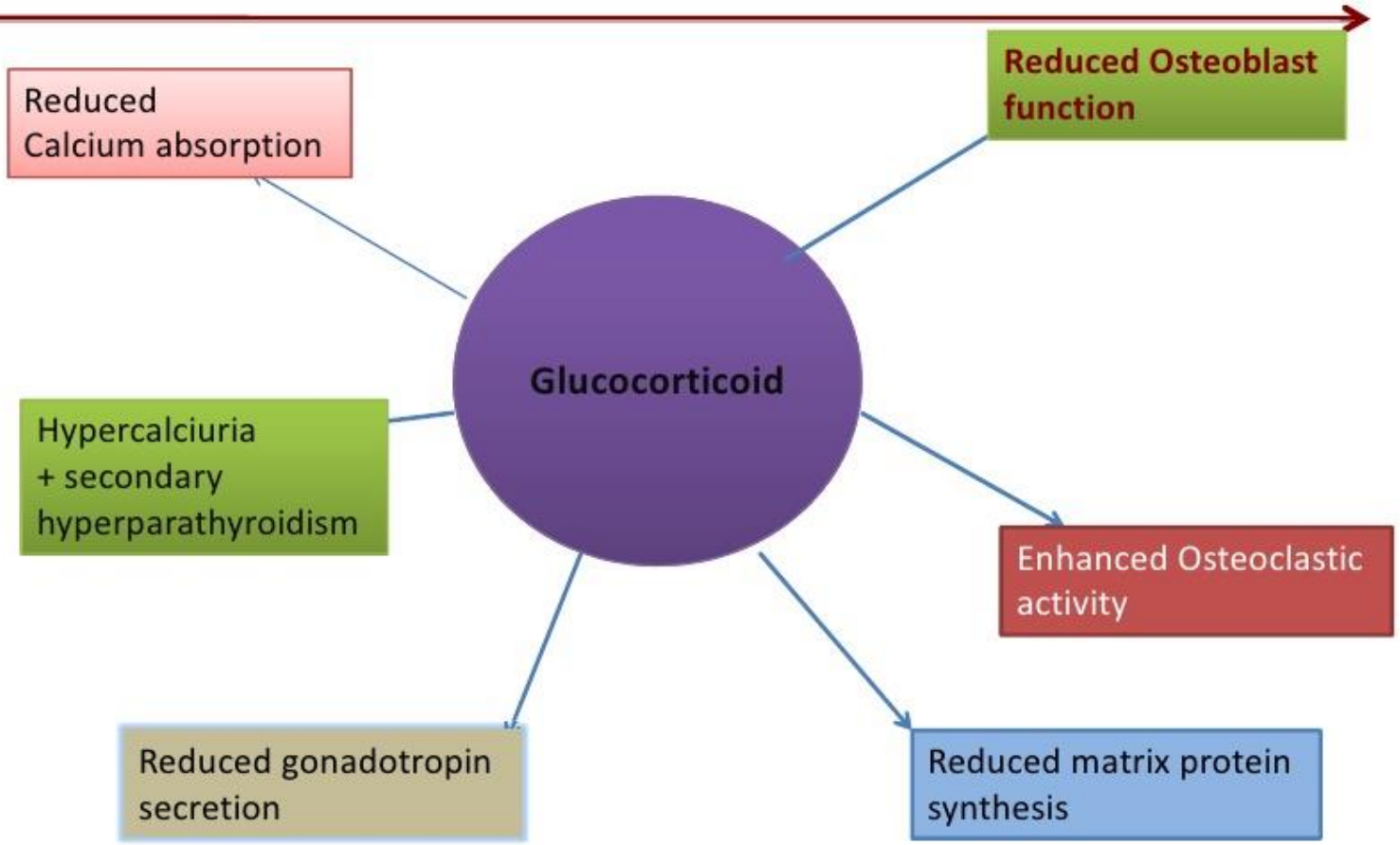
Architectural changes

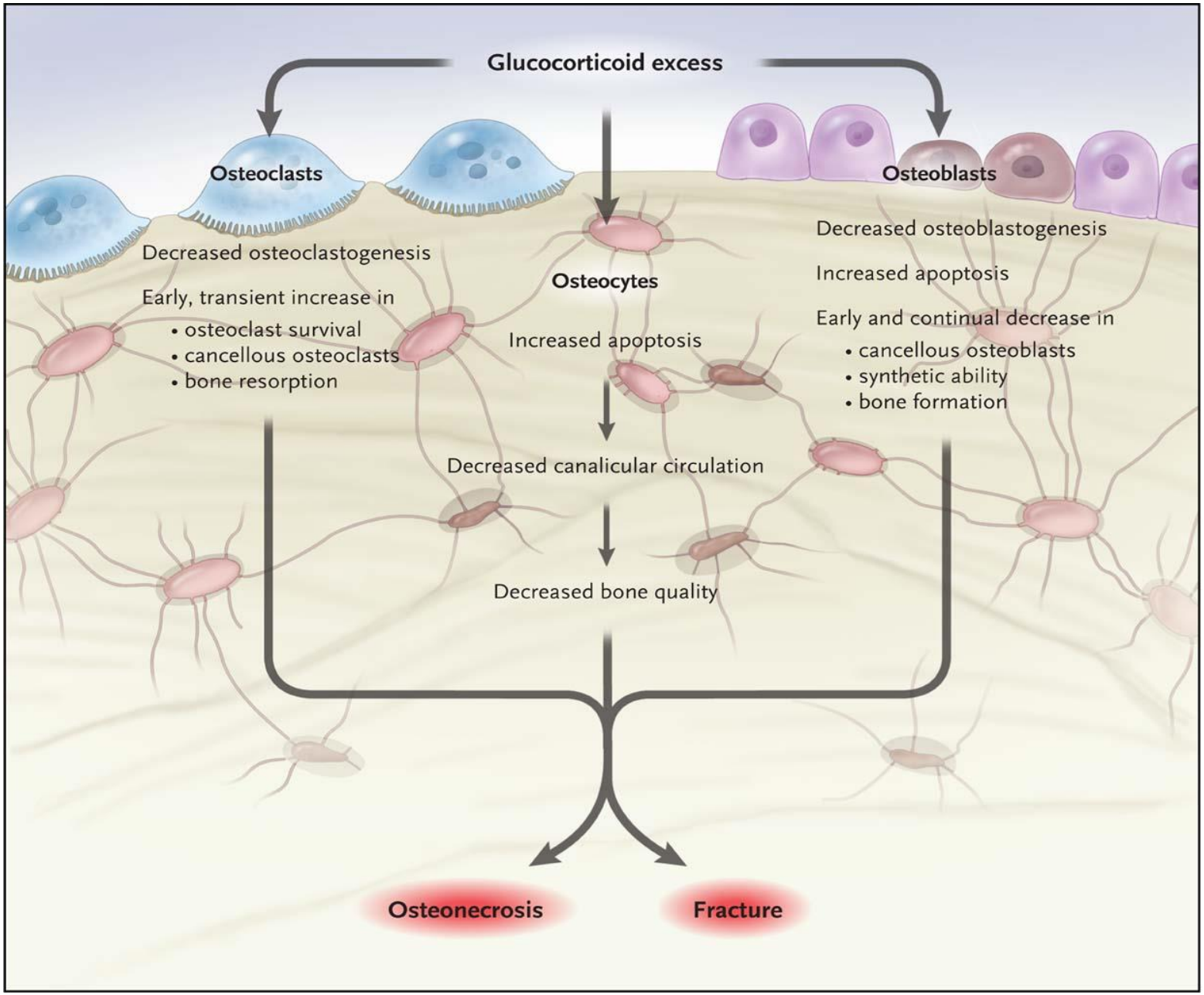
- Loss of trabecular connectivity
- Impact of loss of horizontal trabeculae

Table 1 – Pathophysiology of corticosteroid-related bone loss

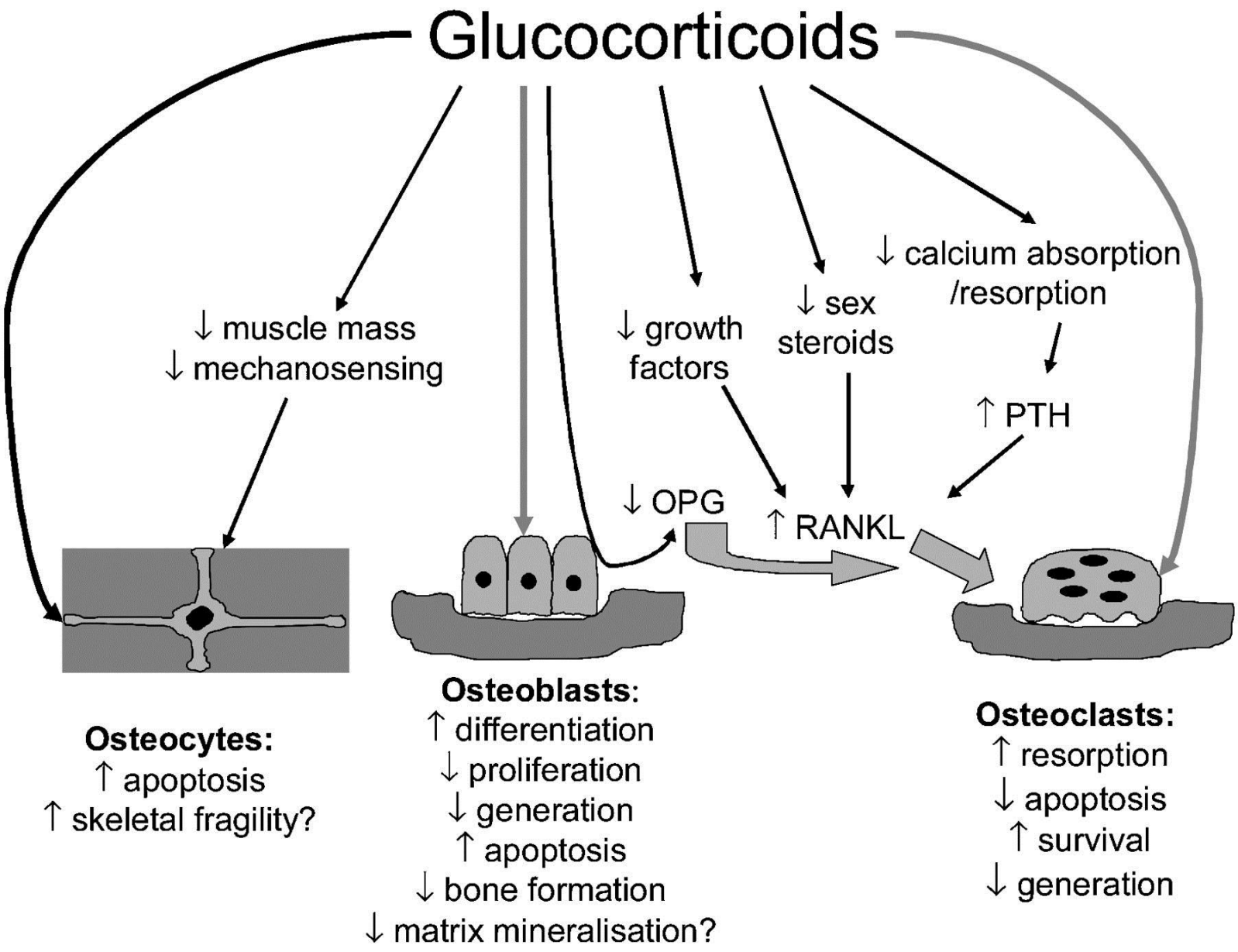
Effects of corticosteroid use	Result
Inhibition of vitamin D–mediated calcium absorption, hypercalciuria	Secondary hyperparathyroidism
Inhibition of gonadotrophin secretion, decreased gonadal hormone secretion	Hypogonadism
Bone cell aging and death	Early aging and death of osteocytes and osteoblasts, impaired formation and function
Bone cell longevity and function	Osteoclastic longevity, bone destruction
Changes in bone quality: trabecular thinning and perforations	Microarchitectural destruction, loss of strength, increased fracture risk

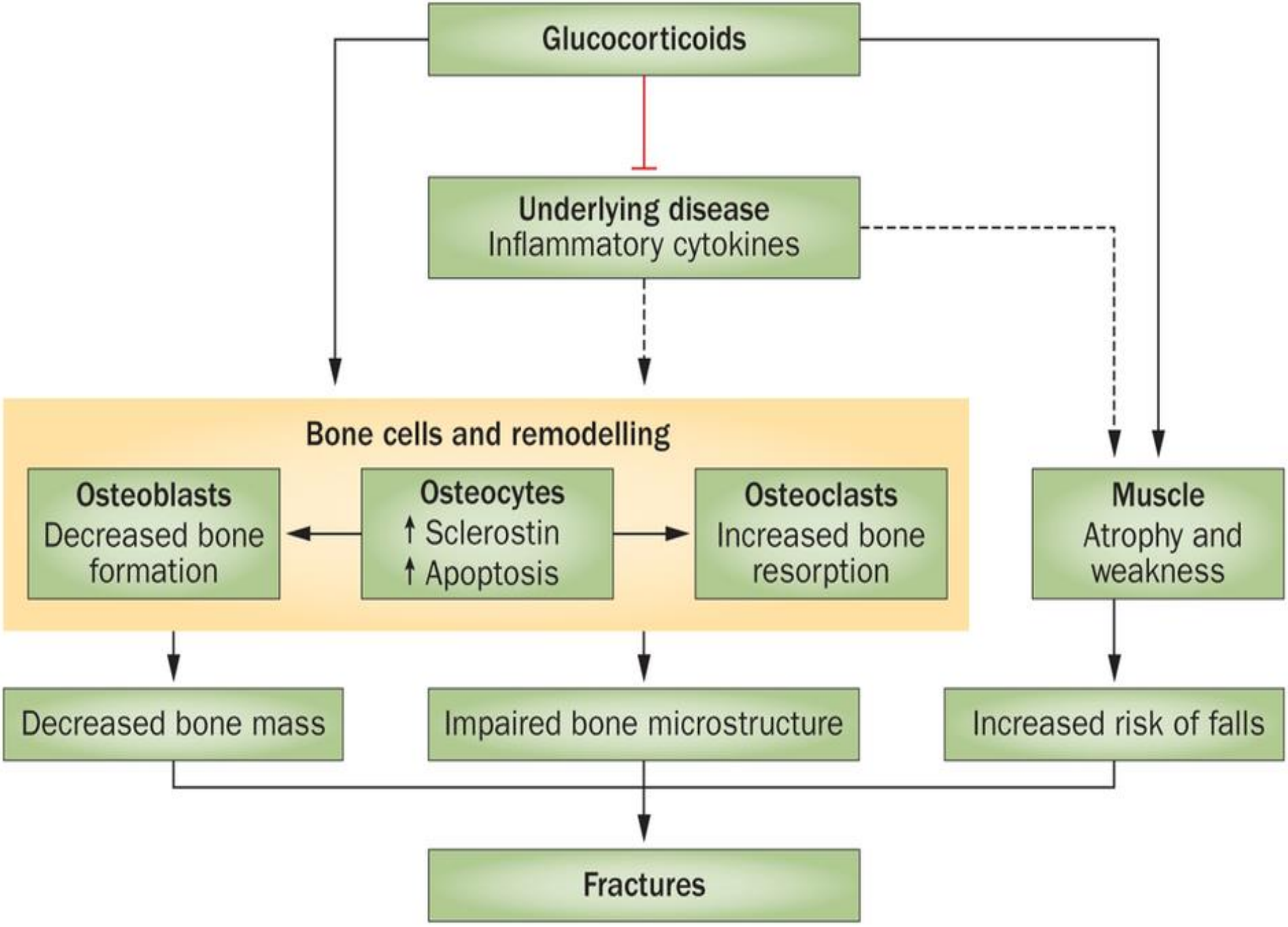
Glucocorticoid induced Osteoporosis





Weinstein, RS NEJM 2011:365:62-70


Glucocorticoids
↓ muscle mass
↓ mechanosensing
↓ growth factors
↓ sex steroids
↓ calcium absorption /resorption
↑ PTH
↓ OPG
↑ RANKL
Osteocytes:
↑ apoptosis
↑ skeletal fragility?
Osteoblasts:
↑ differentiation
↓ proliferation
↓ generation
↑ apoptosis
↓ bone formation
↓ matrix mineralisation?
Osteoclasts:
↑ resorption
↓ apoptosis
↑ survival
↓ generation


Glucocorticoids
Underlying disease
Inflammatory cytokines
Bone cells and remodelling
Osteoblasts
Decreased bone formation
Osteocytes
↑ Sclerostin
↑ Apoptosis
Osteoclasts
Increased bone resorption
Muscle
Atrophy and weakness
Decreased bone mass
Impaired bone microstructure
Increased risk of falls
Fractures

Summary

- Reduced calcium absorption
- Hypercalcuria
- Decrease in gonadotropins
- Osteoclasts increased longevity - early
- **Osteoblasts / Osteocytes**
  - **- Reduced formation/function**
  - **- Early aging /death**