

# Osteoporosis

## Treatment of a Silently Developing Disease

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# What is osteoporosis?

- The word “osteoporosis” is often used synonymously with bone fragility
- The increased skeletal fragility, prototypic of the disorder, is the result of low bone mass, which is the quantity of bone contained within the vertebrae, hips or other bones, as well as disruption of the microarchitecture within a bone.
- There are multiple causes of osteoporosis in humans

# Multiple Causes of Osteoporosis

- Common and Well-Known Causes

- Age
- Menopause

- Alternative Causes

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- Endocrine Disorders

- Excess Steroids
- Hyperthyroidism
- Hypogonadism
- Hyperparathyroidism
- Diabetes Mellitus

- Kidney Disorders

- Hypercalciuria
- Renal Tubular Acidosis
- Chronic Renal Disease

- GI Disorders

- Celiac Disease
- Inflammatory Bowel Diseases
- Gastric Bypass Surgery
- Anorexia Nervosa
- Chronic Liver Diseases

- Hematological Diseases

- Multiple Myeloma
- Systemic Mastocytosis
- Beta Thalassemia Major

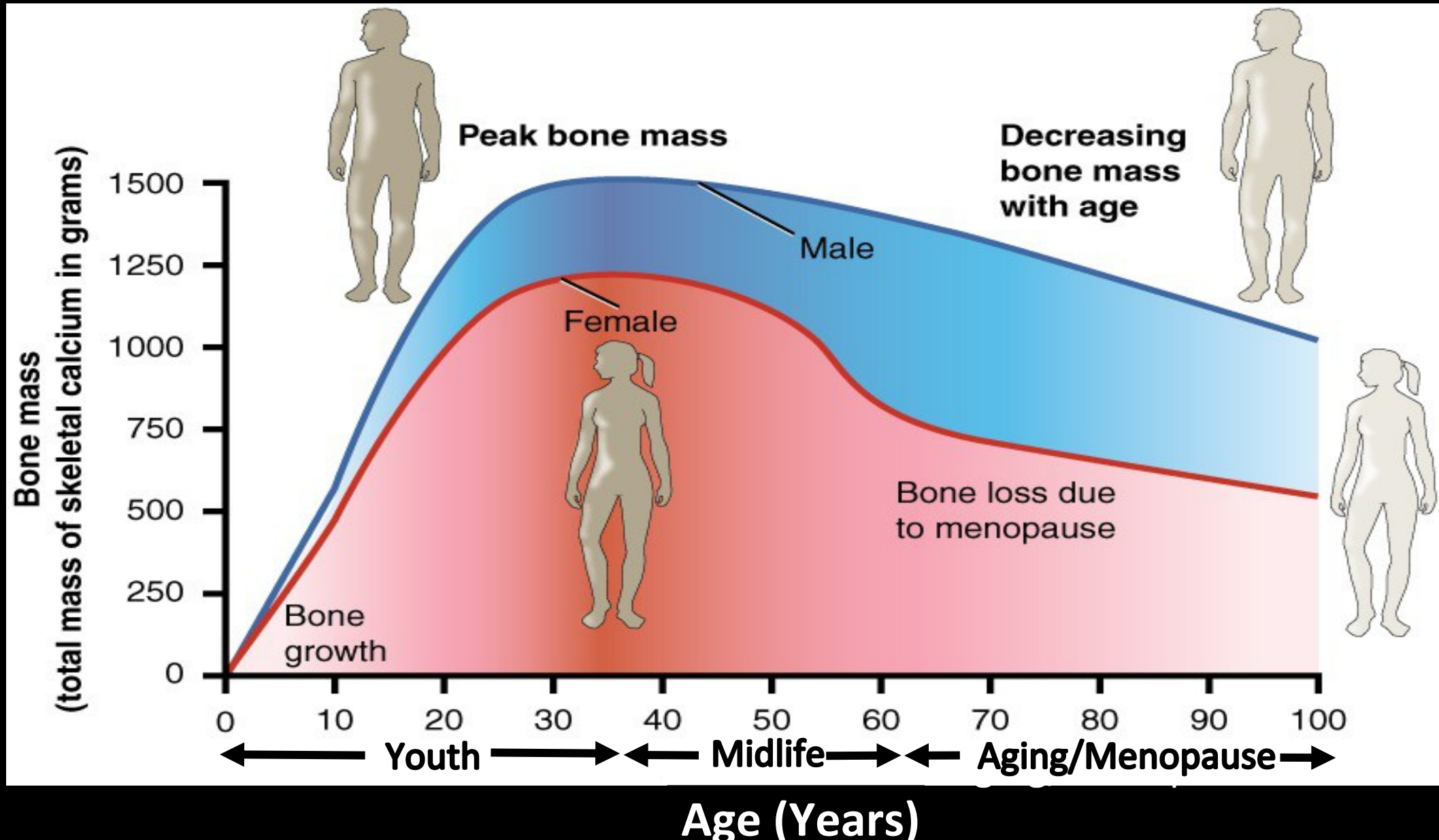
- Autoimmune Disorders

- Rheumatoid Arthritis
- Lupus
- Ankylosing Spondylitis
- Multiple Sclerosis

- Drugs

- Steroids
- Excess Thyroid Hormone
- Diuretics
- Anticonvulsants

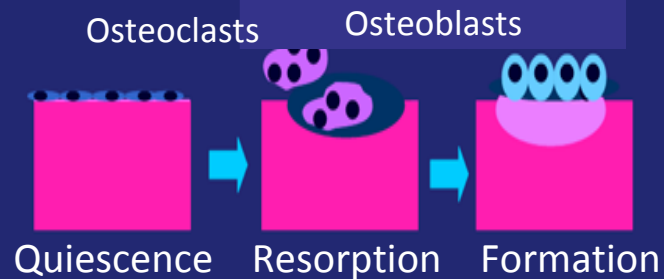
# The Role of Age and Menopause in the Genesis of Osteoporosis



# The Mechanisms Underlying the Bone Loss Due to Age and Menopause

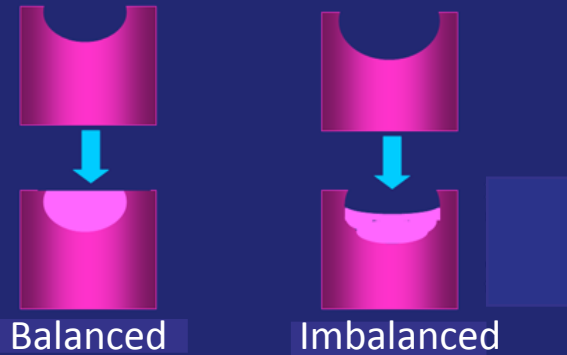
## Normal Skeletal Physiology

### Continuous Bone Remodeling

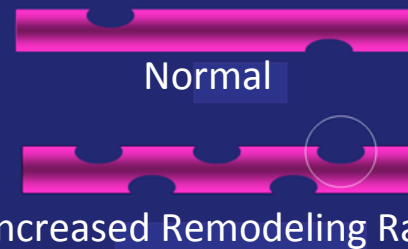


## Mechanisms of Bone Loss

### Remodeling Imbalance



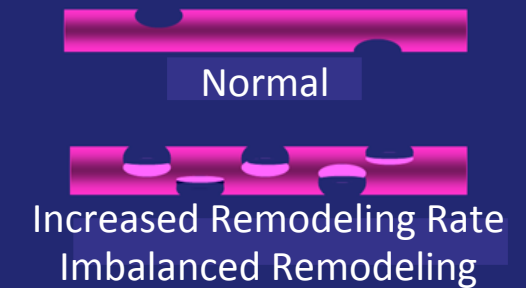
### Increased Remodeling Rate



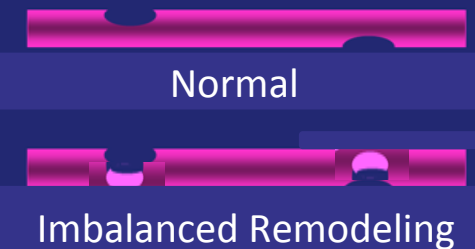
↑ RankL → ↑ Osteoclast Number/Activity

## Pathogenesis of Osteoporosis

### Pathogenesis of Menopausal Bone Loss

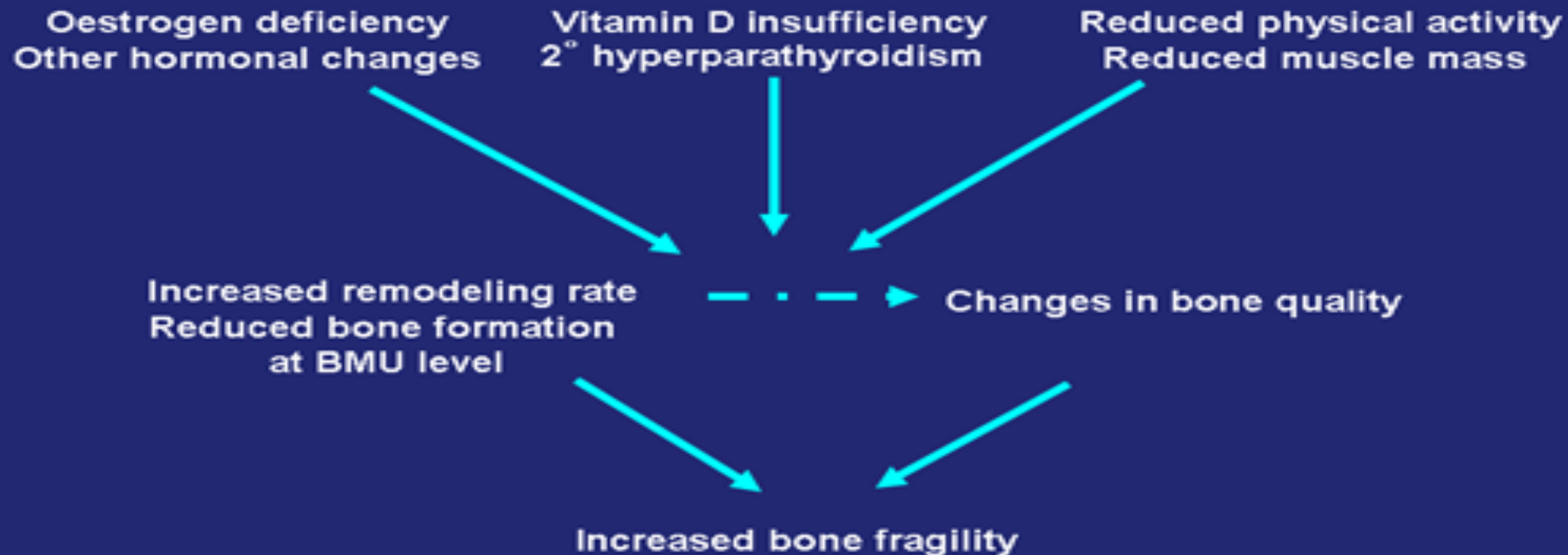


### Pathogenesis of Age Dependent Bone Loss

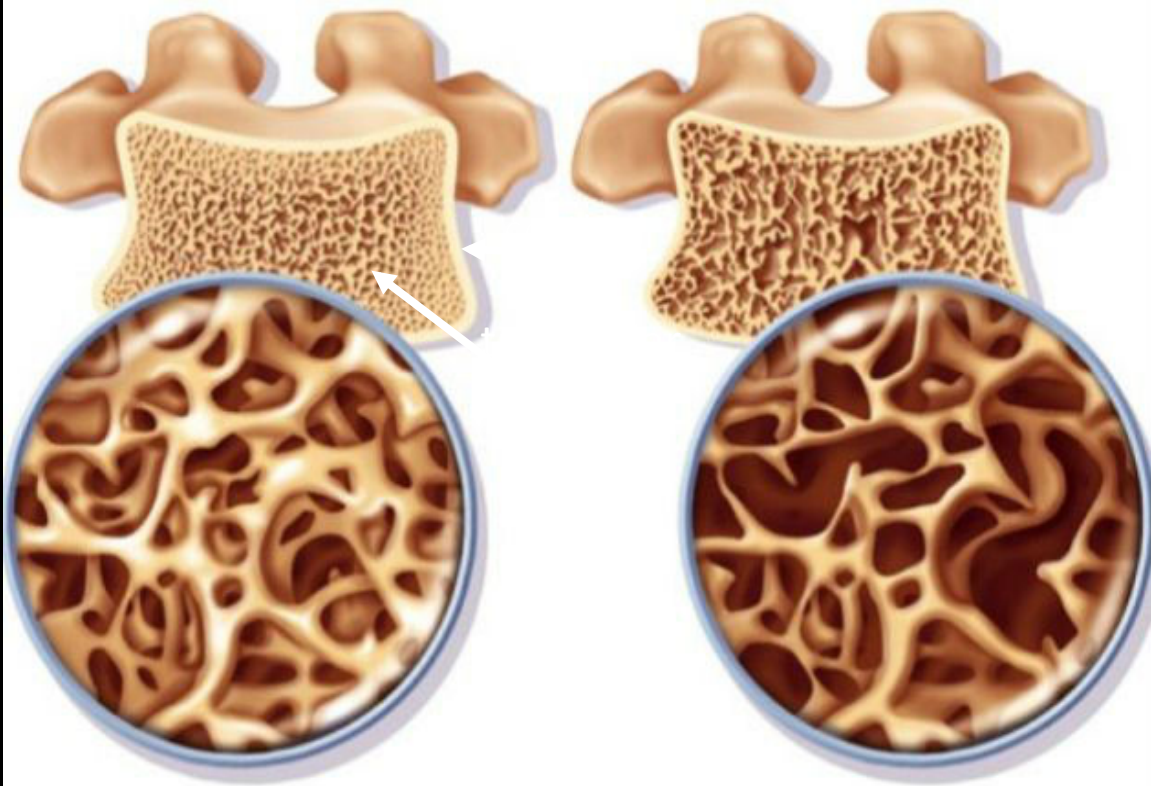


# Pathogenesis of Osteoporosis

## Genes and the environment



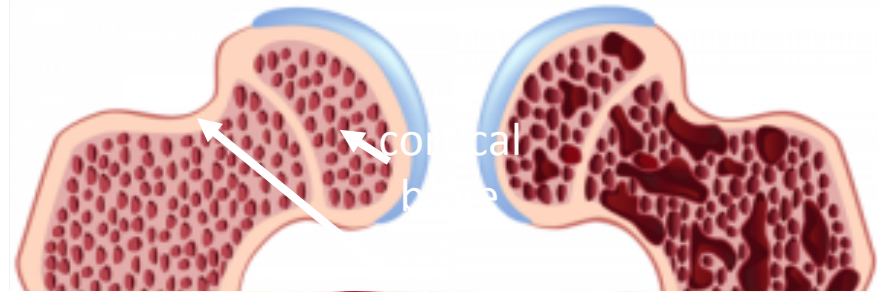
## Vertebrae



Normal

Osteoporosis

## Femora (Hips)

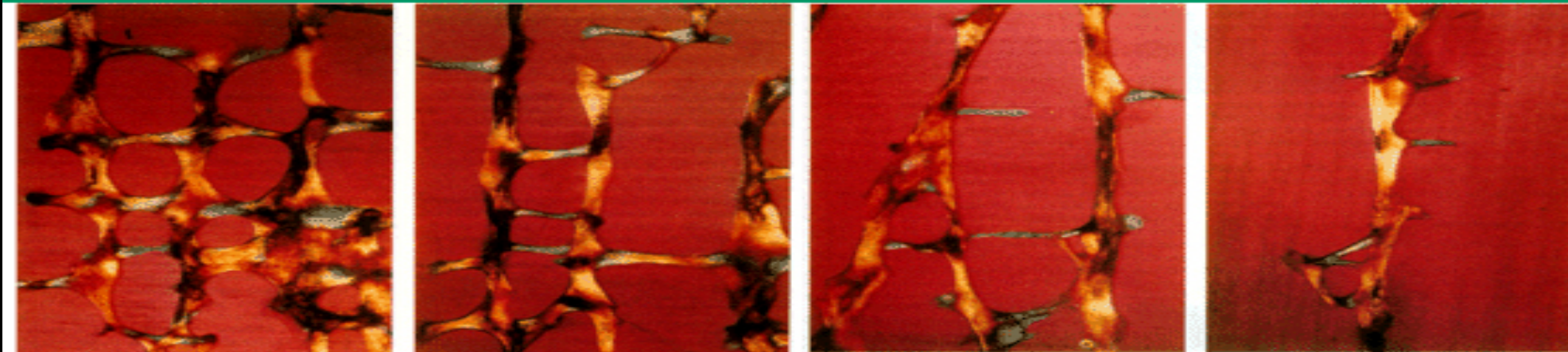


Normal

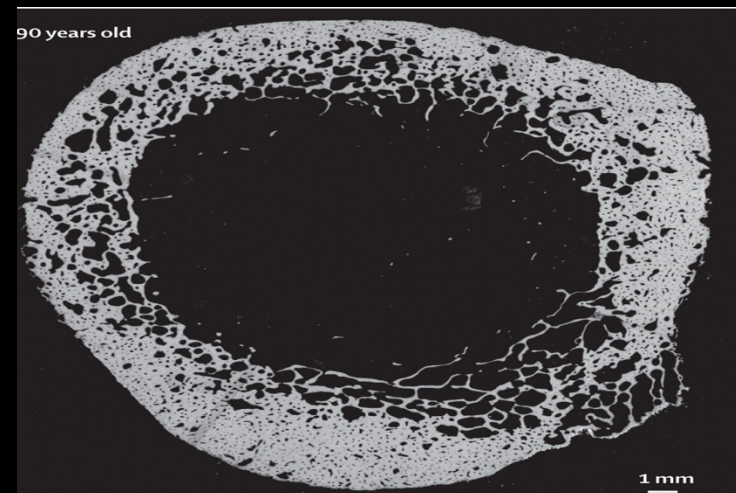
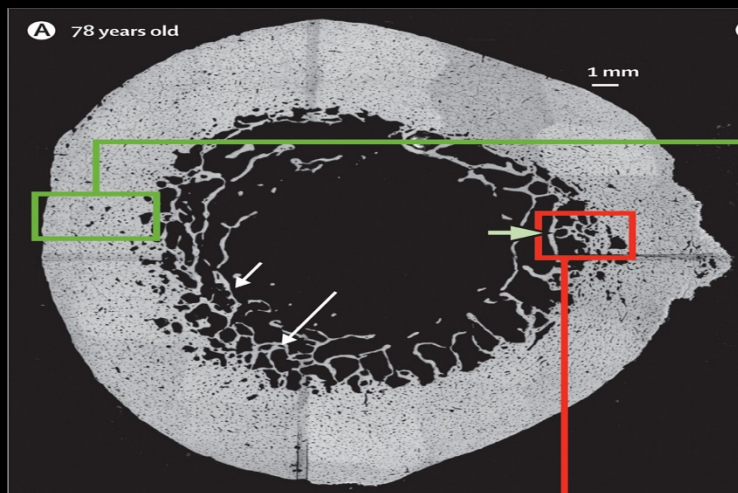
Osteoporosis



# Microstructural Changes in Osteoporotic Bone



Unbalanced remodeling upon trabeculae cause them to thin, perforate and disappear



Unbalanced intracortical remodeling upon canal surfaces enlarge and coalesce the canals and fragment the cortex

**Microstructural deterioration produces bone fragility out of proportion to the bone loss producing it**



# The Impact of Age-Dependent and Postmenopausal Osteoporosis

- In the USA, approximately 54 million people >50 years of age have an increased risk of fracture
- From 2005 to 2015 to 2025 the total number of age related fragility fractures per year in the United States has increased, or will increase, from 2.1 to 2.51 to 3.04 million, or overall 45%, solely on the basis of growth in the elderly population at risk
- Using current criteria, the prevalence of osteoporosis in men over 50 years of age is 16%, while that for women is 30%; however, the prevalence increases in men to 46.3% and in women to 77.1% amongst those greater than 80 years of age
- Collectively, these data clearly indicate that the diagnosis of osteoporosis at a relatively early age is of paramount importance, as is treatment designed to manage existent disease and prevent progression of the disease with age.
- Nevertheless, treatment of osteoporosis over the last several years is at a perigee, crashing because of possible therapeutic complications to only 20% of patients requiring treatment.

# Will You Develop Osteoporosis?

- A woman of 50 years of age has a 50% chance of having a vertebral compression fracture in her lifetime, while a man of similar age has a 20-25% chance of sustaining a vertebral compression fracture in his lifetime
  - Women with pre-existing vertebral fractures have an approximate 7X greater risk for subsequent vertebral fractures
  - Yet only 16% of women who suffer a fragility fracture receive treatment during the ensuing 6 months
- A woman of 50 years of age has a 20-25% chance of sustaining a hip fracture during her lifetime, while a man of similar age has a 10-15% chance of suffering a hip fracture during his lifetime.
  - While the rate of hip fracture increases with age, the increment in women and men is particularly striking after age 70 years.
  - Indeed, most hip fractures occur between the ages of 80-90 years
  - Occurrence of a vertebral fracture increases the risk of a hip fracture by 77%

# The Diagnosis of Osteoporosis

- Osteoporosis is characterized by low bone mass, microarchitectural disruption, and increased skeletal fragility
- A clinical diagnosis of osteoporosis may be made by the presence of a fragility fracture, particularly at the spine, hip, wrist, humerus, rib, and/or pelvis
- In the absence of a fragility fracture, bone mineral density (BMD) assessment by dual energy absorptiometry (DXA) is the standard test to diagnose osteoporosis

# Bone Mineral Density Measurements

The National Osteoporosis Foundation recommends measurement of bone density if:

You are a woman age 65 years or older

You are a man age 70 years or older

You break a bone after age 50 years

You are a woman of menopausal age with risk factors

You are a postmenopausal woman under age 65 years with risk factors

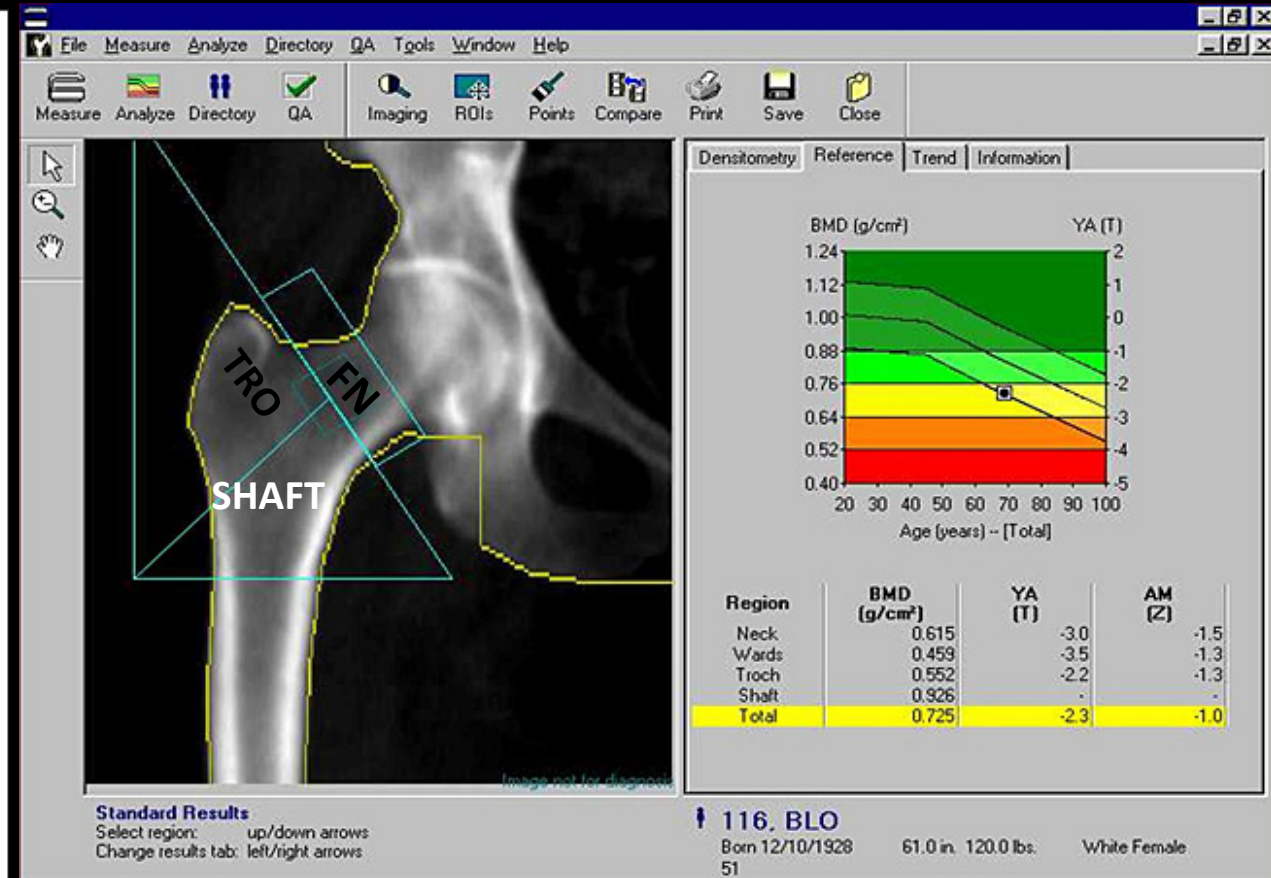
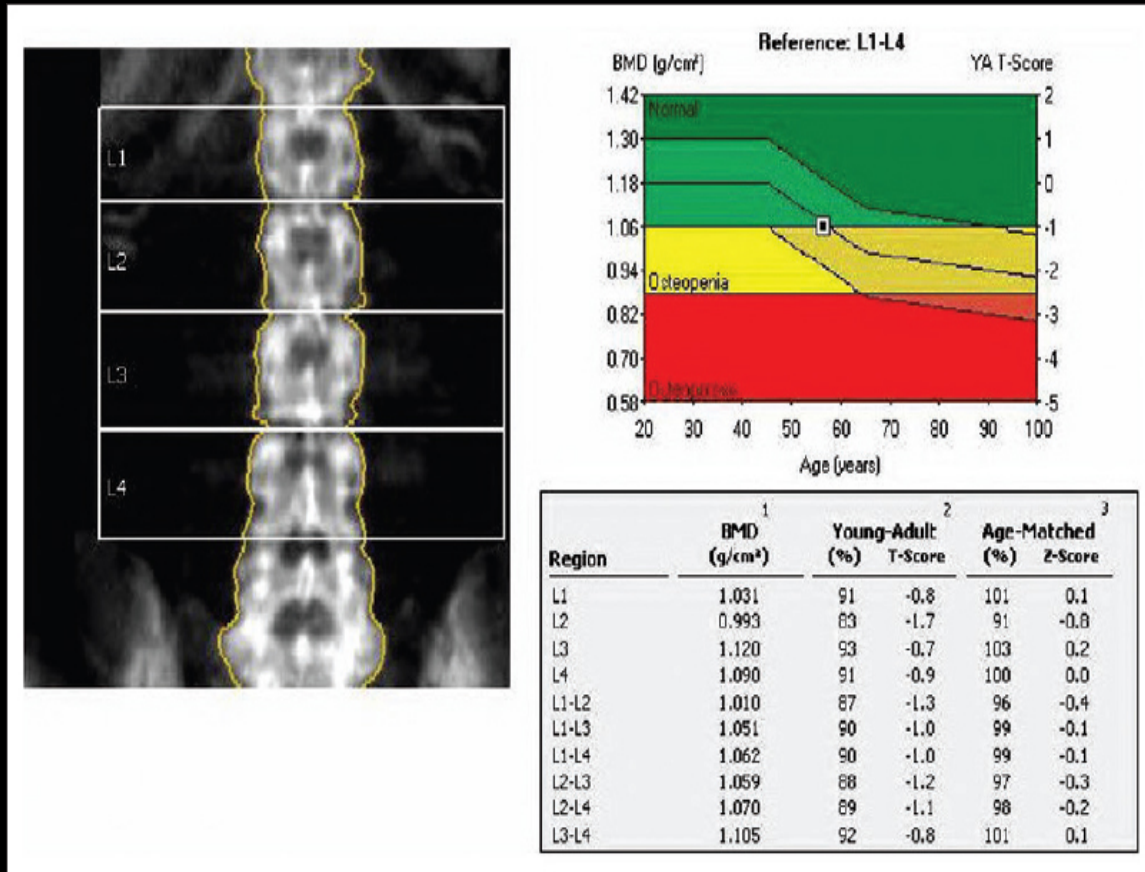
You are a man age 50-69 years with risk factors

**RISK FACTORS** Increased risk of falling    History of hip fracture in a parent    Small, thin body frame    Previous broken bone as an adult    Cigarette smoking    Inactive lifestyle    Ingesting insufficient calcium and/or vitamin D

# Bone Density Measurements

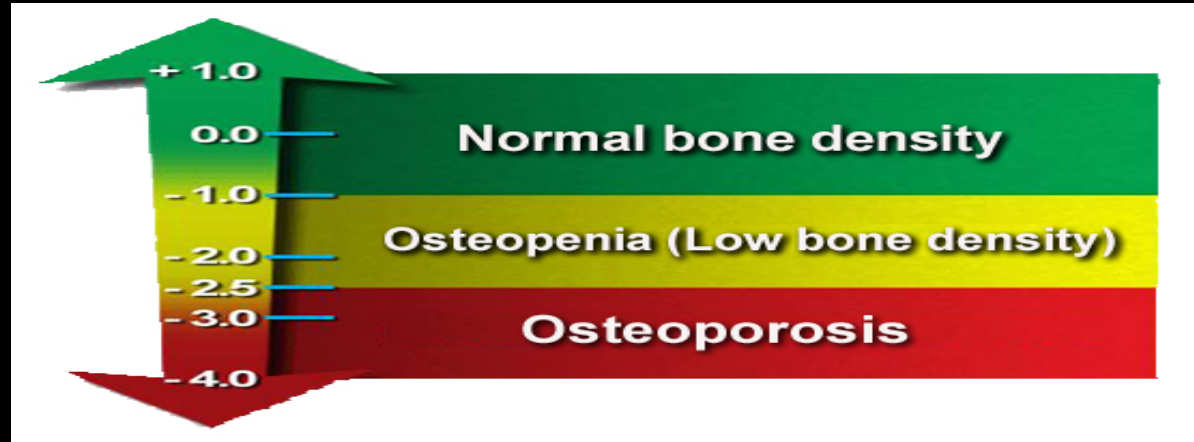
## Lumbar Vertebrae 1-4

## HIP





# Interpretation of Bone Mineral Density Measurements



- A clinical **diagnosis of osteoporosis** may be made when the T-score is  $\geq 2.5$  standard deviations below the mean in a young adult population at any site measured by dual energy BMD
- Low bone density or **osteopenia** is present when the T-score score is 1-2.5 standard deviations below that in a young adult population at any measured site

# Consequences of Decreased Bone Mineral Density

- Approximately 30-50% of women and 15-20% of men suffer the fractures associated with osteoporosis (diagnosed by BMD)
- However, women and men with osteopenia are not free of fracture risk
- Indeed, most women and men sustaining fragility fractures have osteopenia and many have so-called “normal” bone density
- This apparent cognitive dissonance results from the inability of BMD measurements to identify whether the decreased bone density is associated with microstructural bone deterioration that severely predisposes to fragility fractures
- Unfortunately, the necessary high resolution imaging methods necessary to identify such microarchitectural changes are not yet widely available.

# Osteopenia: Determining Risk for Fracture

- A reasonably large percentage of women and men with osteopenia who are at risk for fracture can be identified by applying a Fracture Risk Assessment Tool (FRAX), which weights the impact of various clinical factors and bone density measurements to “determine” the probability of osteoporotic fractures
- Postmenopausal women and men  $\geq 50$  years of age with osteopenia should be considered having osteoporosis if, using the FRAX tool, the 10 year probability of a major osteoporotic fracture is  $\geq 20$  percent and/or that for a hip fracture is  $\geq 3$  percent

What are the “Effective Treatments” for Postmenopausal and Age-Dependent Osteoporosis?

Anti-Resorptive Therapy; Anabolic Therapy

What Therapy is “Effective” for the Varied Presentation of this Disease

Mild vs Severe Bone Loss; Recurrent Fractures; Side Effects of the Multiple Treatment Regimens; Obligatory Multiple Drug Therapy

# Varied Presentation of Patient >50 Years of Age

- Normal Bone Density without a Fragility Fracture
- Normal Bone Density with a Fragility Fracture **DX: Osteoporosis : Treat**
- Mild to Moderate Decrease in Bone Density (1-2.5 SD Decrease) without a Fragility Fracture : PRAX Non-Diagnostic : No Treatment : Follow Serially
- Mild to Moderate Decrease in Bone Density (1-2.5 SD Decrease) without a Fragility Fracture : PRAX Diagnostic **DX: Osteoporosis : Treat**
- Mild to Moderate Decrease in Bone Density (1-2.5 SD Decrease) with a Fragility Fracture **DX: Osteoporosis : Treat**
- Moderate+ Decrease in Bone Density (>2.5 SD Decrease) with or without Fragility Fracture : **DX Osteoporosis : Treat**
- Severe Decrease in Bone Density (>>2.5 SD Decrease with Single or Multiple Fragility Fractures) : **DX Osteoporosis : Treat**



# Treatment Options

- Although calcium and vitamin D are ancillary treatment options for osteoporosis, they are limited to providing adequate bone mineral and active vitamin D, to do away with the effects of vitamin D insufficiency/deficiency and to provide adequate mineral for bone formation
- These agents do not influence the enhanced bone resorption and remodeling imbalance that lead to the osteoporosis due to aging and menopause

# Treatment Options

- Normal Bone Density with a Fragility Fracture **DX: Osteoporosis : Treat**
- Mild to Moderate Decrease in Bone Density (1-2.5 SD Decrease) without a Fragility Fracture : PRAX Diagnostic **DX: Osteoporosis : Treat**
- Mild to Moderate Decrease in Bone Density (1-2.5 SD Decrease) with a Fragility Fracture **DX: Osteoporosis : Treat**

## Principle of Therapy

**Manage the Current Status and Limit Progression of the Bone Loss**

**Drug Class : Antiresorptive Agent**

# Anti-Resorptive Therapy

- Bisphosphonates (e.g. alendronate [Fosamax]; risedronate [Actonel]; and zoledronate [Zometa]) are currently the first line treatment and most common anti-resorptive therapy used
  - Depend on inhibition of an enzyme required for osteoclast mediated bone resorption
  - The result is slowing of the remodeling process and a reduction of fracture risk compared to that in untreated subjects, in whom rapid remodeling continues
  - However, microstructural deterioration is not eliminated, which likely explains why the fracture risk reduction is modest at best (~50% at the vertebrae, but only ~20-30% at non-vertebral fractures that comprise 80% of all fractures in the community)
  - In any case, cessation of therapy after 3-5 years does not eliminate the effects of treatment for a variable period of time
  - Of course, in large studies there are some differences in the efficacy of the various bisphosphonates tested
    - Risedronate suppresses bone remodeling and possibly fracture risk reduction more quickly
    - **Zoledronate appears more effective following cessation of therapy**
  - GI side effects and atypical femoral fractures are among the side effects to this drug therapy

# Anti-Resorptive Therapy

- Denosumab (Prolia) is an alternative drug therapy to suppress bone resorption and is an antibody for RANK-ligand, a major regulator of osteoclast development and function
  - Administered (60 mg) subcutaneously every 6 months, the treatment produces almost complete suppression of bone remodeling and after 3 years results in a 68% reduction in vertebral fractures, 40% reduction in hip fracture, and 20% reduction in non-vertebral fractures.
  - The more complete suppression of resorption accounts for the greater increases in BMD achieved in postmenopausal women treated with denosumab compared to bisphosphonates
  - Whether these BMD difference translated to differences in fracture risk reduction between the two groups is not known
  - Controlled trials have been conducted for only 3 years
  - Despite these positive outcomes, cessation of denosumab treatment creates a rebound increase in bone remodeling and increased fracture risk, necessitating commencement of bisphosphonate therapy at sometime around the time denosumab treatment is discontinued

# Anti-Resorptive Therapy

- Selective Estrogen Receptor Modulators (SERM), such as Raloxifene, reduce the rate of bone remodeling by only 20-30%, thereby producing only a modest and transitory increase in BMD
- Most importantly, SERM treatment accounts for only a very modest vertebral fracture risk reduction and no non-vertebral fracture risk reduction



# Treatment Options

- Moderate+ Decrease in Bone Density ( $>2.5$  SD Decrease) with or without Fragility Fracture : **DX Osteoporosis : Treat**
- Severe Decrease in Bone Density ( $>>2.5$  SD Decrease with Single or Multiple Fragility Fractures) : **DX Osteoporosis : Treat**

## **Principle of Therapy**

**Increase bone density and maintain the increase long term**

**Drug Class : Anabolic Agent (followed by Antiresorptive Agent for Maintenance)**

# Anabolic Therapy for Osteoporosis

- Teriparatide (Forteo) and Abaloparatide (Tymlos) increase bone formation and thereby bone volume and strength, resulting in a decrease in fracture risk.
  - Indicated in those patients with a high risk for fracture, defined as a history of fragility fracture, multiple risk factors for fracture, a profound decrease in bone density, and/or failure of, or intolerance to, other available drug treatment for osteoporosis
  - Use is limited because of the unknown relevance to humans of rodent osteosarcoma induction by these drugs; treatment is limited to 18-24 months during a lifetime.
  - These drugs uniquely increase trabecular bone thickness and improve trabecular microarchitecture
  - Further information necessary
    - While Teriparatide consistently reduces vertebral fracture incidence, no data are available regarding hip fractures and evidence for non-vertebral fracture reduction is inconsistent
    - Data regarding Abaloparatide effects on hip fracture are likewise absent but there is a decrease in non-vertebral fractures
  - Treatment with these agents requires follow-up with a bisphosphonate for at least 3 years

# Summary

- Osteoporosis begins as a silent disease
- Osteoporosis becomes a complex disease, both pathologically and clinically
- The presentation of active disease is very variable, but therapy is essential to prevent progression of the disease from that evident at presentation
- There are multiple treatment options for osteoporosis, none of which cures the disease, and each of which seems appropriate under variable circumstances, despite possible complications
- Careful consideration must be applied to ascertaining the diagnosis of osteoporosis, choosing the correct treatment strategy, and providing careful and thorough follow-up.

# THE FUTURE

-/-SHNURRING-3



↑ *Slit3*



CD31<sup>hi</sup>EMCN<sup>hi</sup> Endothelium



↑ ↑ Bone Density

Questions?