Diagnosis and Management of Osteoporosis

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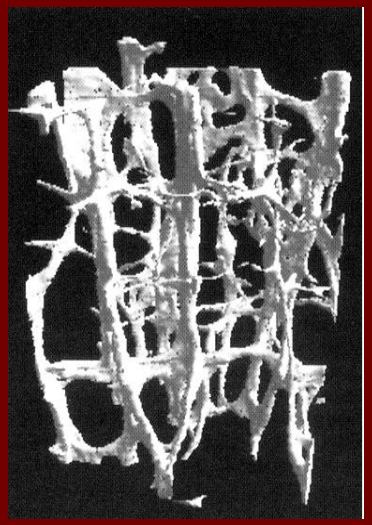
21 May 2015

Definition of Osteoporosis

- A skeletal disorder characterized by
  - **Compromised bone strength** predisposing to
  - An **increased risk of fracture**



- Bone strength reflects the integration of two main features:
  - **Bone density**
  - **Bone quality**

Overview

- Osteoporosis causes bones to become weak and brittle — so brittle that a fall or even mild stresses such as bending over or coughing can cause a fracture. Osteoporosis-related fractures most commonly occur in the hip, wrist or spine.

- Bone is living tissue that is constantly being broken down and replaced. Osteoporosis occurs when the creation of new bone doesn't keep up with the loss of old bone.

- Osteoporosis affects men and women of all races. But white and Asian women, especially older women who are past menopause, are at highest risk. Medications, healthy diet and weight-bearing exercise can help prevent bone loss or strengthen already weak bones.

Symptoms

- There typically are no symptoms in the early stages of bone loss. But once your bones have been weakened by osteoporosis, you might have signs and symptoms that include:
- Back pain, caused by a fractured or collapsed vertebra
- Loss of height over time
- A stooped posture
- A bone that breaks much more easily than expected

Causes

- Your bones are in a constant state of renewal — new bone is made and old bone is broken down. When you're young, your body makes new bone faster than it breaks down old bone and your bone mass increases. After the early 20s this process slows, and most people reach their peak bone mass by age 30. As people age, bone mass is lost faster than it's created.
- How likely you are to develop osteoporosis depends partly on how much bone mass you attained in your youth. Peak bone mass is partly inherited and varies also by ethnic group. The higher your peak bone mass, the more bone you have "in the bank" and the less likely you are to develop osteoporosis as you age.

Risk factorsUnchangeable risks

- **Your sex.** Women are much more likely to develop osteoporosis than are men.
- **Age.** The older you get, the greater your risk of osteoporosis.
- **Race.** You're at greatest risk of osteoporosis if you're white or of Asian descent.
- **Family history.** Having a parent or sibling with osteoporosis puts you at greater risk, especially if your mother or father fractured a hip.
- **Body frame size.** Men and women who have small body frames tend to have a higher risk because they might have less bone mass to draw from as they age.

Hormone levels

- **Sex hormones.** Lowered sex hormone levels tend to weaken bone. The fall in estrogen levels in women at menopause is one of the strongest risk factors for developing osteoporosis. Treatments for prostate cancer that reduce testosterone levels in men and treatments for breast cancer that reduce estrogen levels in women are likely to accelerate bone loss.
- **Thyroid problems.** Too much thyroid hormone can cause bone loss. This can occur if your thyroid is overactive or if you take too much thyroid hormone medication to treat an underactive thyroid.
- **Other glands.** Osteoporosis has also been associated with overactive parathyroid and adrenal glands.

Dietary factors

- **Low calcium intake.** A lifelong lack of calcium plays a role in the development of osteoporosis. Low calcium intake contributes to diminished bone density, early bone loss and an increased risk of fractures.

- **Eating disorders.** Severely restricting food intake and being underweight weakens bone in both men and women.

- **Gastrointestinal surgery.** Surgery to reduce the size of your stomach or to remove part of the intestine limits the amount of surface area available to absorb nutrients, including calcium. These surgeries include those to help you lose weight and for other gastrointestinal disorders.

Steroids and other medications

- Long-term use of oral or injected corticosteroid medications, such as prednisone and cortisone, interferes with the bone-rebuilding process. Osteoporosis has also been associated with medications used to combat or prevent:
- Seizures
- Gastric reflux
- Cancer
- Transplant rejection

Medical conditions

- The risk of osteoporosis is higher in people who have certain medical problems, including:
- Celiac disease
- Inflammatory bowel disease
- Kidney or liver disease
- Cancer
- Multiple myeloma
- Rheumatoid arthritis

Lifestyle choices

- Some bad habits can increase your risk of osteoporosis. Examples include:
- **Sedentary lifestyle.** People who spend a lot of time sitting have a higher risk of osteoporosis than do those who are more active. Any weight-bearing exercise and activities that promote balance and good posture are beneficial for your bones, but walking, running, jumping, dancing and weightlifting seem particularly helpful.
- **Excessive alcohol consumption.** Regular consumption of more than two alcoholic drinks a day increases the risk of osteoporosis.
- **Tobacco use.** The exact role tobacco plays in osteoporosis isn't clear, but it has been shown that tobacco use contributes to weak bones.

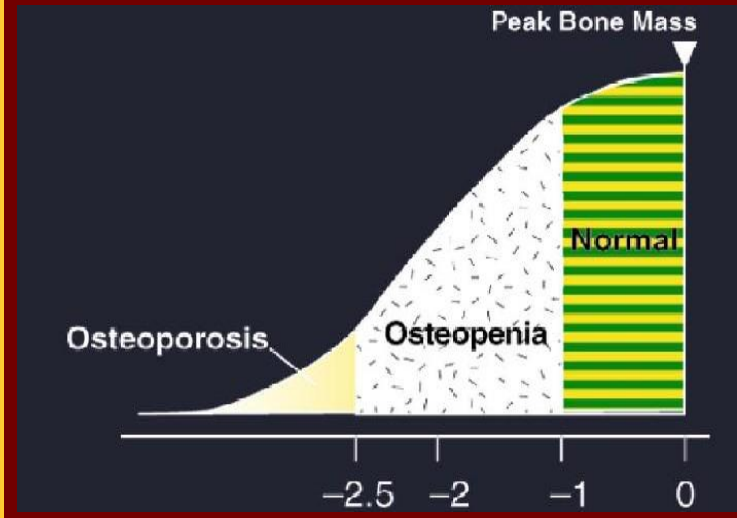
Complications

- Bone fractures, particularly in the spine or hip, are the most serious complications of osteoporosis. Hip fractures often are caused by a fall and can result in disability and even an increased risk of death within the first year after the injury.
- In some cases, spinal fractures can occur even if you haven't fallen. The bones that make up your spine (vertebrae) can weaken to the point of collapsing, which can result in back pain, lost height and a hunched forward posture.

WHO Criteria for Postmenopausal Osteoporosis

The T-score compares an individual's BMD with the mean value for young adults and expresses the difference as a standard deviation score

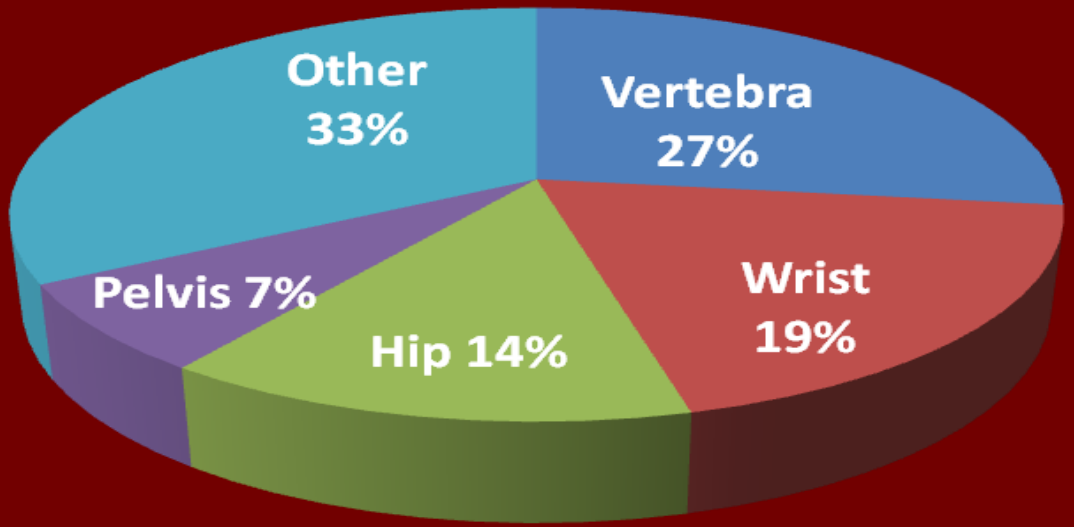
Category	T-score
Normal	-1.0 and above
Low bone mass (osteopenia)	-1.0 to -2.5
Osteoporosis	-2.5 and below



Osteoporosis Is a Serious Public Health Problem

Scope of the problem

- Affects 10.2 million Americans (80% women)
- 2 million fractures yearly
- **Direct cost $17 billion**
- The cost of care is expected to rise to $25.3 billion by 2025

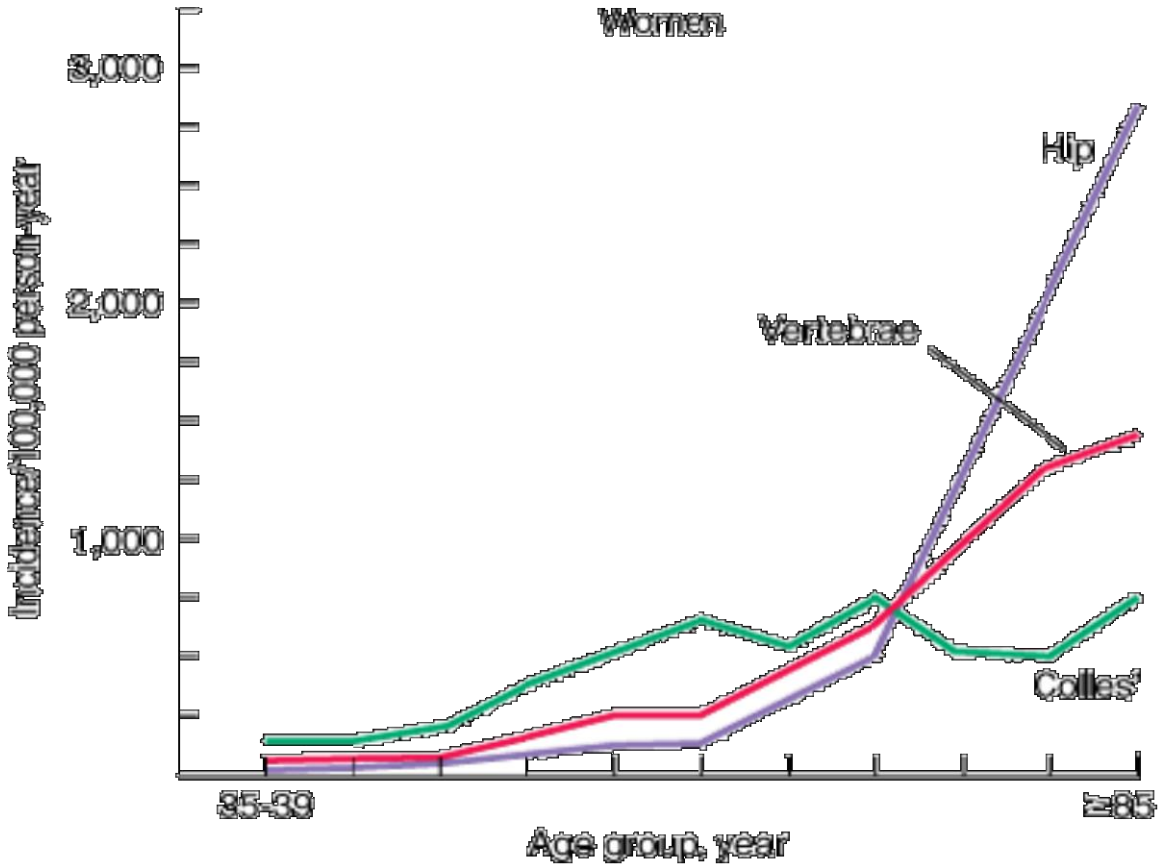


Distribution of Fractures

Prevalence of osteoporosis and osteopenia in the Iranians aged 50 years or older

- 22.2% and 59.9% in women , respectively
- 11.0% and 50.1% in men, respectively

Aghaei Meybodi HR, Khashayar P, Heshmat R, Rezaei Homami M, Nabipour I, Rajabian R, Omrani GH, Bahrami A,Larijani B. The prevalence of osteoporosis in an Iranian Population [Unpublished Data]



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Medical impact

- Hip fractures are associated with an 8 to 36 % excess mortality within 1 year
- Approximately 20% of hip fracture patients require long-term nursing home care
- 40 % fully regain their pre-fracture level of independence

- Office of the Surgeon General (US) (2004) Bone health and osteoporosis:a report of the Surgeon General. Office of the SurgeonGeneral (US), Rockville (MD). Available from: http://www.ncbi.nlm.nih.gov/books/NBK45513/. Accessed March 2014

Direct costs of hip fractures (USD)

- **TOTAL DIRECT COST (IN MILLION USD)**

2010	28
2020	51
2050	250

Aghaei Meybodi HR, Khashayar P, Heshmat R, Rezaei Homami M, Nabipour I, Rajabian R, Omrani GH, Bahrami A, Larijani B. The prevalence of osteoporosis in an Iranian Population [Unpublished Data]

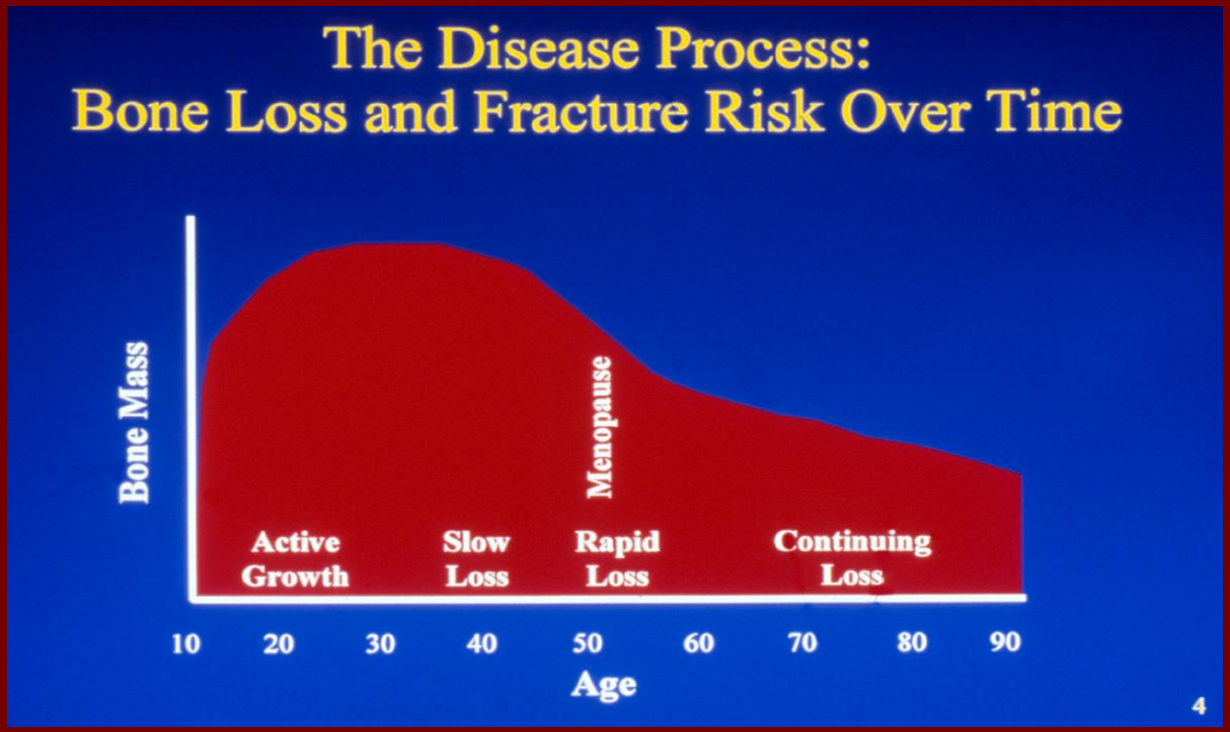
National Osteoporosis Foundation 2014 Guidelines

Major clinical recommendations

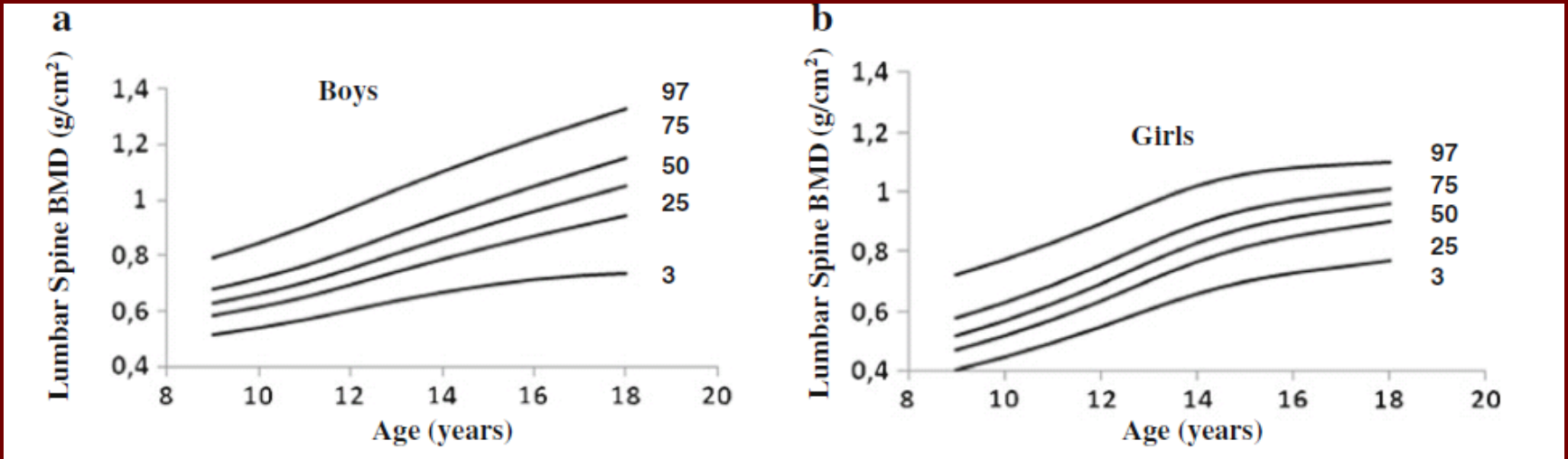
- Universal (risk, diet, vitamin D, exercise, smoking, monitoring)
- Diagnosis (BMD, vertebral imaging, causes of secondary osteoporosis)
- Monitoring (BMD)
- Treatment (initiation criteria, options, duration)

Basic pathophysiology

- Bone mass in older adults equals the peak bone mass achieved by age 18–25 minus the amount of bone subsequently lost.



Normative data and percentile curves of bone mineral density



Jeddi M, Roosta MJ, **Dabbaghmanesh** MH, Omrani GR, Ayatollahi SM, Bagheri Z, Showraki AR, Bakhshayeshkaram M.Normative data and percentile curves of bone mineral density in healthy Iranian children aged 9-18 years.Arch Osteoporos. 2013;8(1-2):114

- Peak bone mass is determined largely by genetic factors, with contributions from nutrition, endocrine status, physical activity, body composition and health during growth.

- Ashouri E, Meimandi EM, Saki F, **Dabbaghmanesh** MH, Omrani GR, Bakhshayeshkaram M.The impact of LRP5 polymorphism (rs556442) on calcium homeostasis, bone mineral density, and body composition in Iranian children.J Bone Miner Metab.2014 Dec 17. [Epub ahead of print]
- Jeddi M, **Dabbaghmanesh** MH, RanjbarOmrani G, Ayatollahi SM, Bagheri Z, Bakhshayeshkaram.Body composition reference percentiles of healthy Iranian children and adolescents in southern Iran. M.Arch Iran Med. 2014 Oct;17(10):661-9.

Calcium Nutrition

- Peak bone mass may be impaired by inadequate calcium intake during growth among other nutritional factors (calories, protein, and other minerals), thereby leading to increased risk of osteoporosis later in life.

Vitamin D status in the studied population

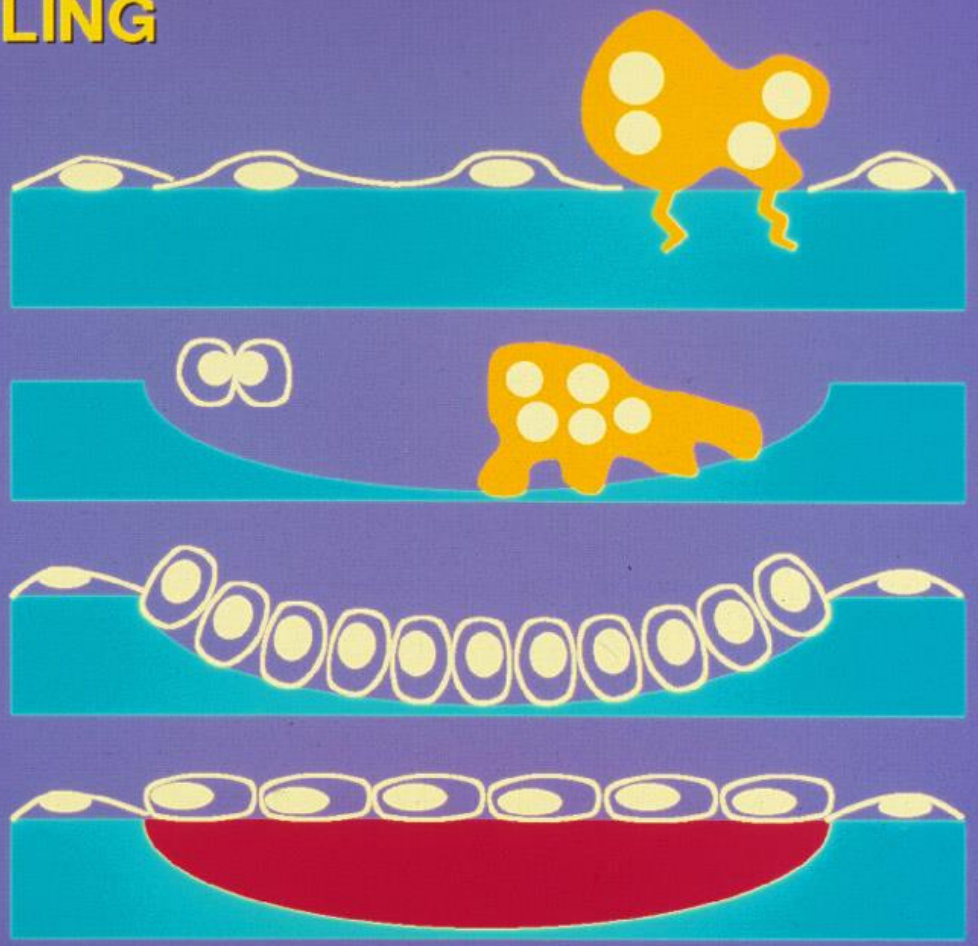
Vitamin D status	Boys		Girls		Total	
	n	%	n	%	n	%
Normal (>30 ng/ml)	12	5%	7	3%	19	4%
Vitamin D Insufficiency (20-30 ng/ml)	40	17%	30	13%	70	15%
Vitamin D deficiency (10-20 ng/ml)	164	68%	161	68 %	325	68%
Severe vitamin D deficiency (<10 ng/ml)	25	10%	38	16%	63	13%
Total	241	100%	236	100%	477	100%

* Vitamin D status was not dependent on sex (P=0.145)

Saki F, Dabbaghmanesh M.H, Omrani G.R, Bakhshayeshkaram M.Vitamin D Deficiency and Its Associated Risk Factors in Children and Adolescents in Southern Iran., Public Health Nutrition Journal, Cambridge University. 2015,accepted for publication

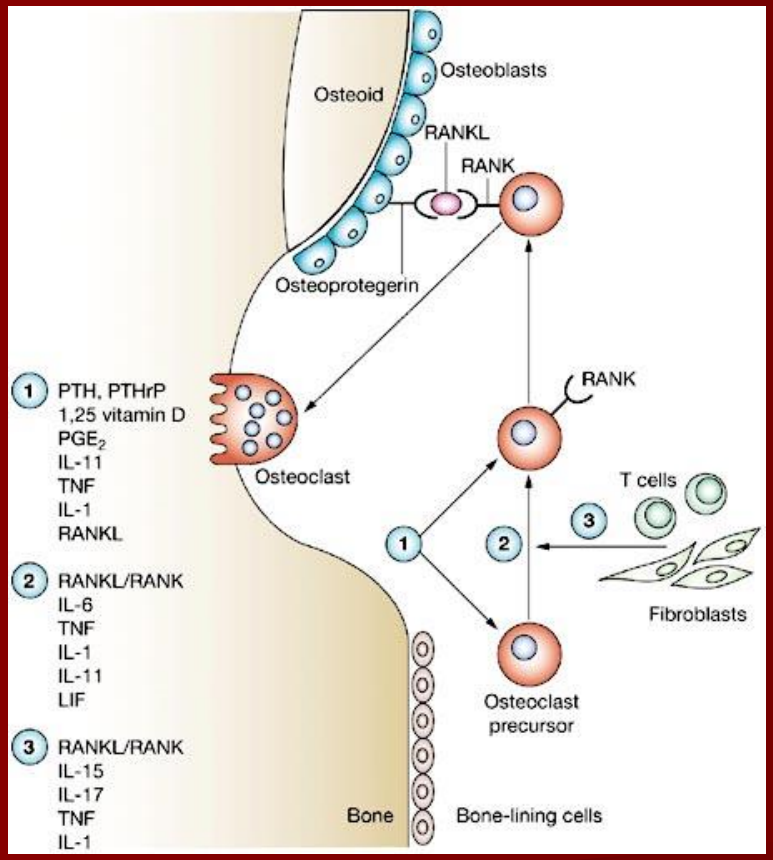
NORMAL REMODELING

1. Osteoclast Recruitment and Activation
2. Resorption and Osteoblast Recruitment
3. Osteoblastic Bone Formation
4. Completed Remodeling Cycle



- After age 30–45, however, the resorption and formation processes become imbalanced, and resorption exceeds formation.
- This imbalance may begin at different ages and varies at different skeletal sites; it becomes exaggerated in women after menopause.

Mechanisms of bone remodeling

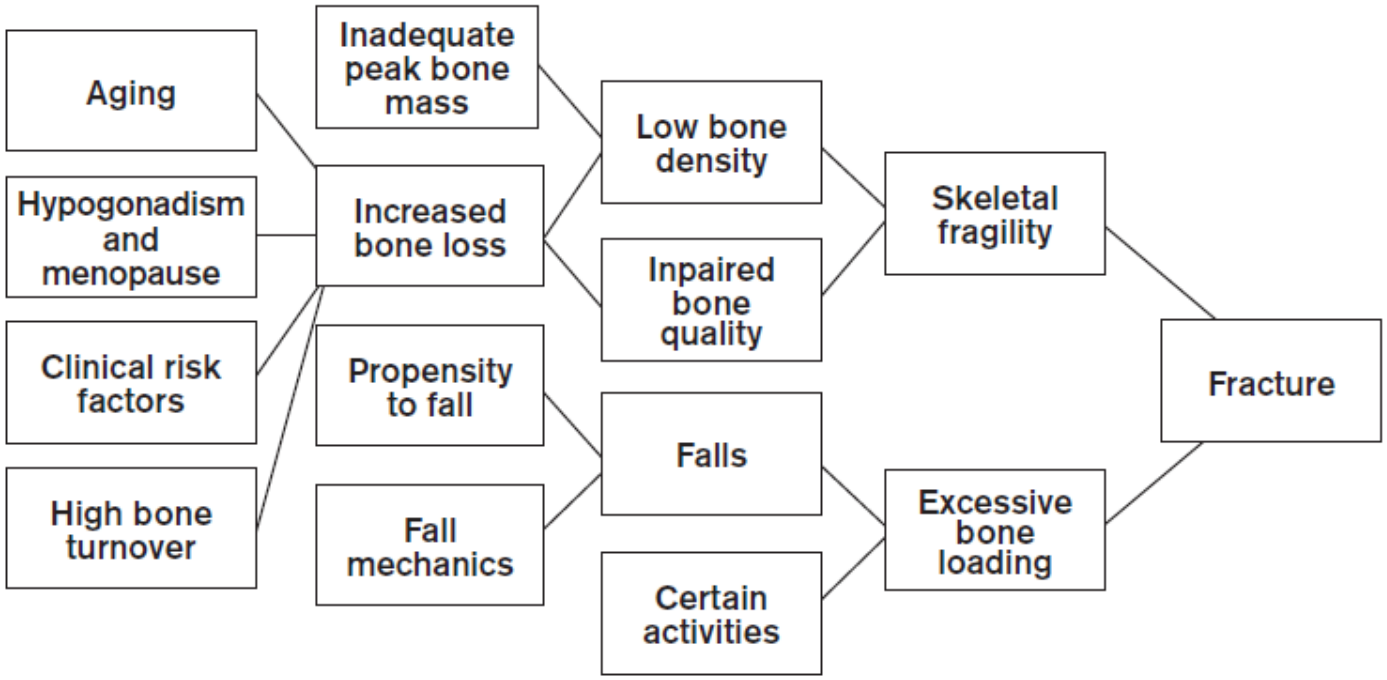


Lane NE (2006) Therapy Insight: osteoporosis and osteonecrosis in systemic lupus erythematosus
Nat Clin Pract Rheumatol **2:** 562–569 doi:10.1038/ncprheum0298

nature CLINICAL PRACTICE RHEUMATOLOGY

Pathogenesis for osteoporotic fracture

FIGURE 2. Pathogenesis of Osteoporosis-Related Fractures



From: Cooper C and Melton LJ[7], with modification.

National Osteoporosis Foundation

Approach to the diagnosis and management of osteoporosis

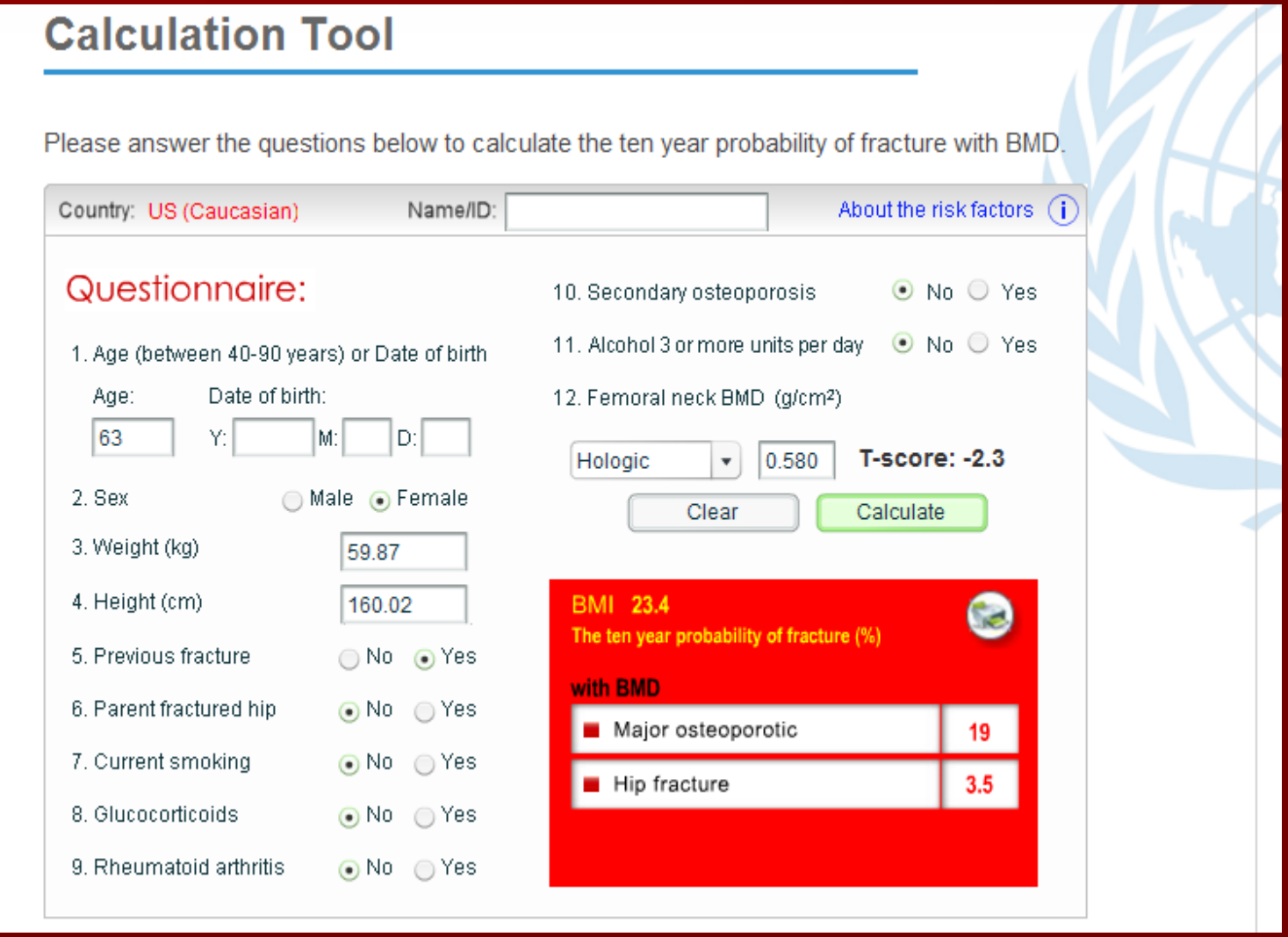
CLINICAL ASSESSMENT AND TESTING

- History taking
- to identify the factors that increase the risk for low bone mineral density, falls and resultant fractures.

Risk Factors for Osteoporosis Fracture

- Personal history of fracture as an adult
- Early menopause (<45 years) or bilateral ovariectomy
- History of fracture in first-degree relative
- Prolonged premenstrual amenorrhea (>1 year)
- Female sex
- Low calcium intake
- Advanced age
- Alcoholism
- Caucasian race
- Impaired eyesight despite adequate correction
- Dementia
- Recurrent falls
- Inadequate physical activity
- Current cigarette smoking
- Poor health/frailty
- Low body weight [<58 kg (127 lb)]

Several of these risk factors have been included in the WHO 10-year fracture risk model



Physical examination

- The appropriate physical examination maneuvers serve two purposes:

1. To assess risk factors for future fragility fractures
2. To screen for possible undiagnosed vertebral fractures.

Most pertinent points

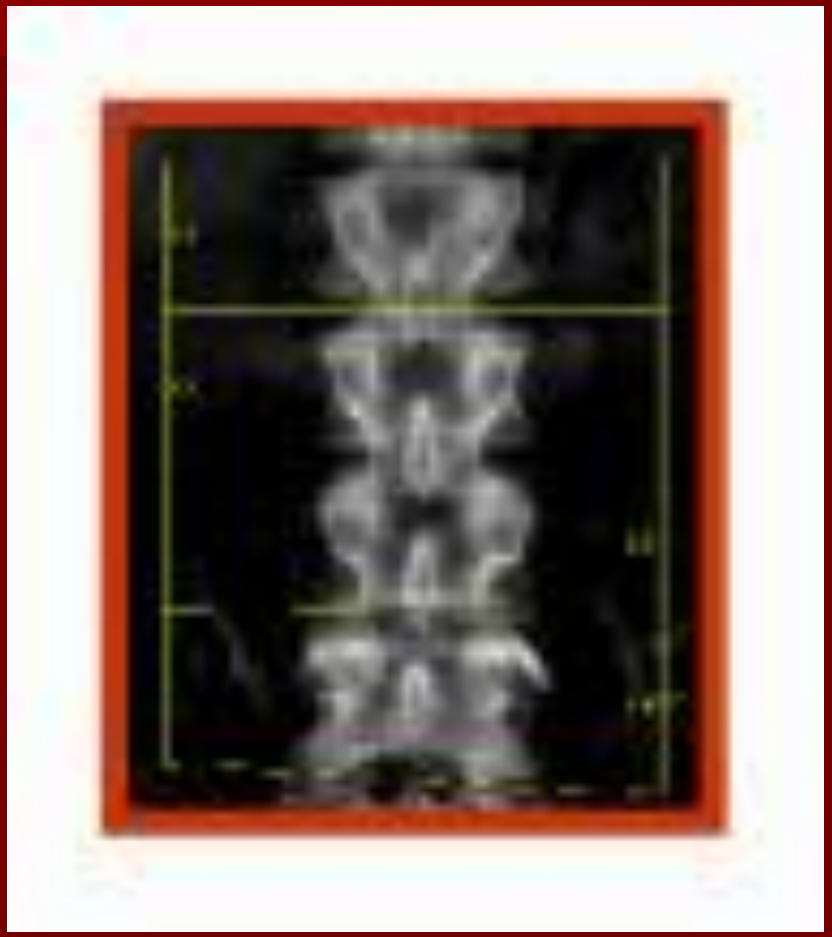
- Get-up-and-go test
- Screening for vertebral fractures
  - Occiput-to-wall distance of > 5 cm)

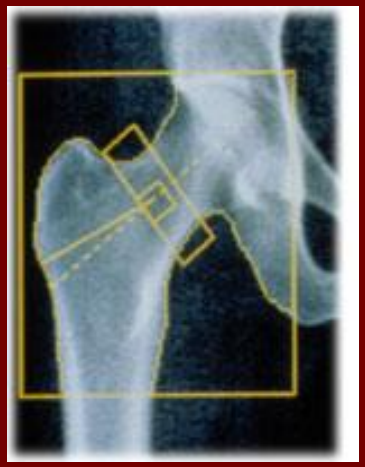
Diagnosis

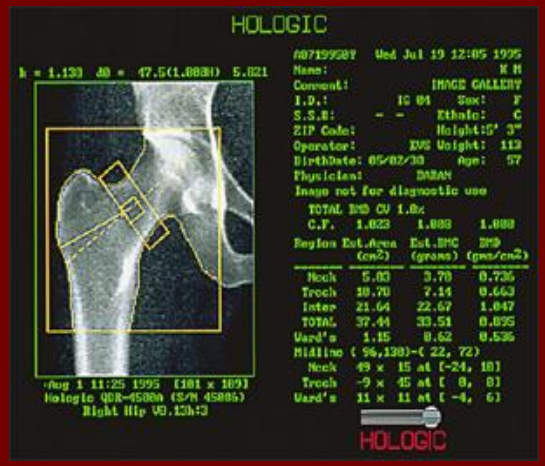
- The diagnosis of osteoporosis is established by :

1. Measurement of BMD
2. The occurrence of adulthood hip or vertebral fracture in the absence of major trauma

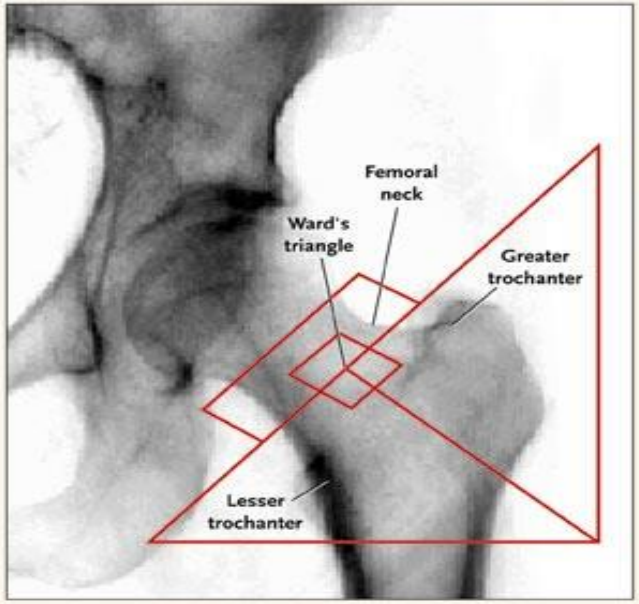
DEXA

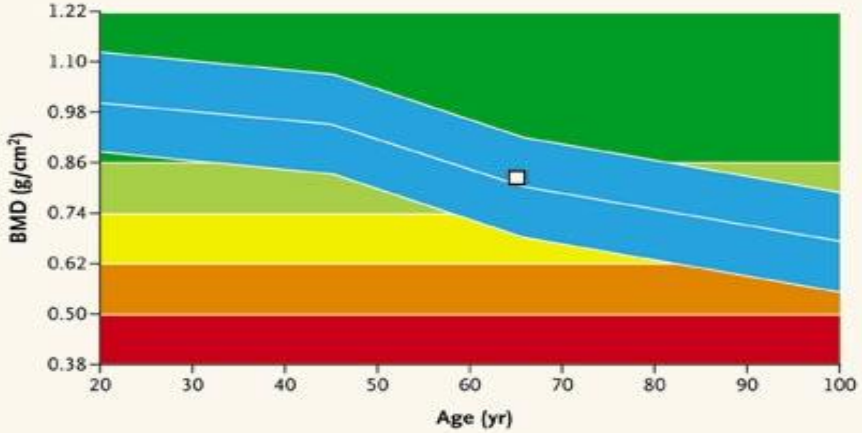





HOLOGIC
Name:
Comment: IMAGE GALLERY
Operator:
Physician:
Image not for diagnostic use
TOTAL BMD CV 1.0%
Region Est.Area (cm2) Est.BMC (grams) BMD (gms/cm2)
Neck 5.03 3.78 0.736
Troch 10.70 7.14 0.663
Inter 21.64 22.67 1.047
TOTAL 37.44 33.51 0.895
Ward's 1.15 0.62 0.536
Midline (96,130)-(22, 72)
Neck 69 x 15 at [-24, 10]
Troch -9 x 45 at [0, 0]
Ward's 11 x 11 at [-4, 6]
HOLOGIC

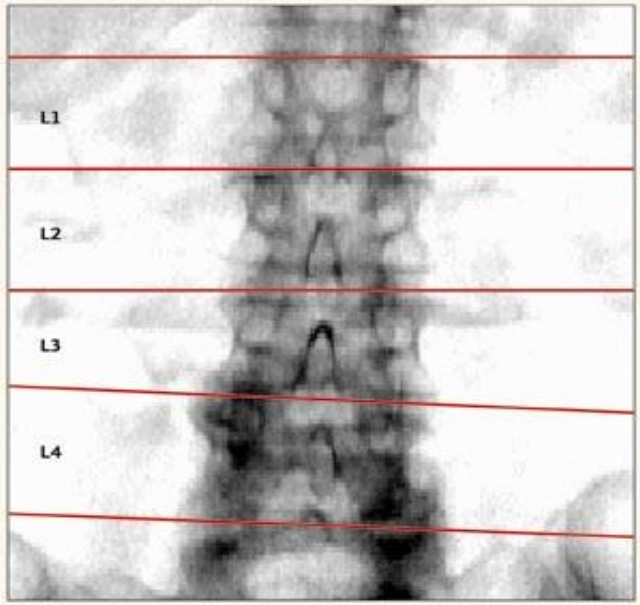
A

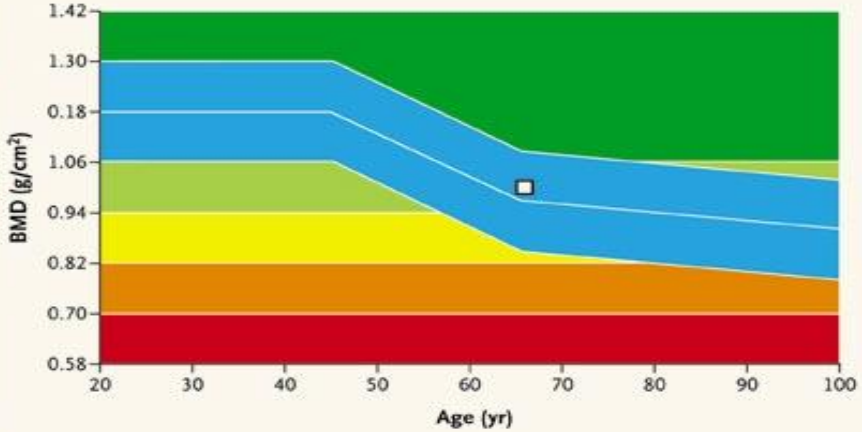




Region	BMD (g/cm2)	Young adult (%)	Young adult (T)	Age-matched (%)	Age-matched (Z)
Neck	0.829	85	−1.3	101	+0.1
Ward's triangle	0.670	74	−1.8	101	+0.1
Trochanter	0.769	97	−0.2	107	+0.5
Total	0.941	94	−0.5	106	+0.4

B





Region	BMD (g/cm2)	Young adult (%)	Young adult (T)	Age-matched (%)	Age-matched (Z)
L1	0.772	68	−3.0	84	−1.3
L2	0.975	81	−1.9	98	−0.2
L3	1.039	87	−1.3	104	+0.4
L4	1.203	100	0.0	121	+1.7
L2–L4	1.086	91	−0.9	109	+0.8

- BMD measured by DXA at the one-third (33 %) radius site can be used for diagnosing osteoporosis when the hip and lumbar spine cannot be measured or are unusable or uninterruptable.

Who Should Have a Bone Density Test?

Women age 65 and older Men age 70 and older
Postmenopausal women and men ages 50–69 with clinical risk factors
Adults who have a fracture after age 50
Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids) associated with low bone mass or bone loss

NOF: National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. www.nof.org. Accessed August 2014.

Vertebral Imaging

Consider vertebral imaging tests for the following individuals:***
• All women age 70 and older and all men age 80 and older if BMD T-score at the spine, total hip or femoral neck is ≤ -1.0.
• Women age 65 to 69 and men age 70 to 79 if BMD T-score at the spine, total hip or femoral neck is ≤ -1.5
• Postmenopausal women and men age 50 and older with specific risk factors: ▪ Low trauma fracture during adulthood (age 50) ▪ Historical height loss of 1.5 inches or more (4 cm)* ▪ Prospective height loss of 0.8 inches or more (2 cm)** ▪ Recent or ongoing long term glucocorticoid treatment

* Current height compared to peak height during young adulthood
** Cumulative height loss measured during interval medical assessment
*** If bone density testing is not available, vertebral imaging may be considered based on age alone

National Osteoporosis Foundation

Biochemical markers

- Biochemical markers of bone turnover can aid in risk assessment and serve as an additional monitoring tool when treatment is initiated.

2014 Universal Recommendations

Counsel on the risk of fractures
Eat a diet rich in fruits and vegetables (supplemented if necessary) to a total calcium intake of •1000 mg per day for men 50-70 •1200 mg per day for women ≥ 51 •1200 mg per day for men ≥ 71
Vitamin D intake should be 800-1000 IU per day (age ≥50), supplemented if necessary
Regular weight-bearing and muscle-strengthening exercise
Fall prevention evaluation and training
Cessation of tobacco use and avoidance of excessive alcohol intake

Adequate intake of calcium and vitamin D

- Controlled clinical trials have demonstrated that the combination of supplemental calcium and vitamin D can reduce the risk of fracture.

Table 9 Estimating daily dietary calcium intake

Step 1: Estimate calcium intake from calcium-rich foods[a]			
Product	# of servings/day	Estimated calcium/serving, in mg	Calcium in mg
Milk (8 oz.)	_____	×300	= _____
Yogurt (6 oz.)	_____	×300	= _____
Cheese (1 oz. or 1 cubic in.)	_____	×200	= _____
Fortified foods or juices	_____	×80 to 1,000[b]	= _____
			Subtotal = _____
Step 2: Add 250 mg for nondairy sources to subtotal above			+250
			Total calcium, in mg = _____

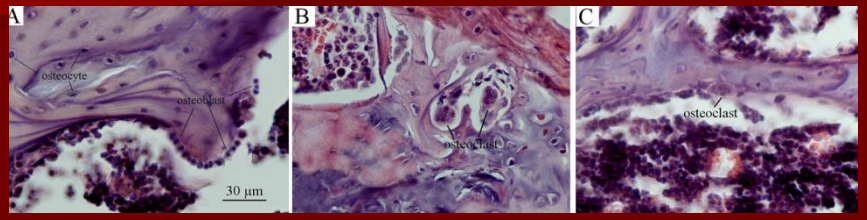
- Intakes in excess of 1200 to 1500 mg/day may increase the risk of developing kidney stones, cardiovascular disease, and stroke.
- Increasing dietary calcium is the first-line approach, but calcium supplements should be used when an adequate dietary intake cannot be achieved.

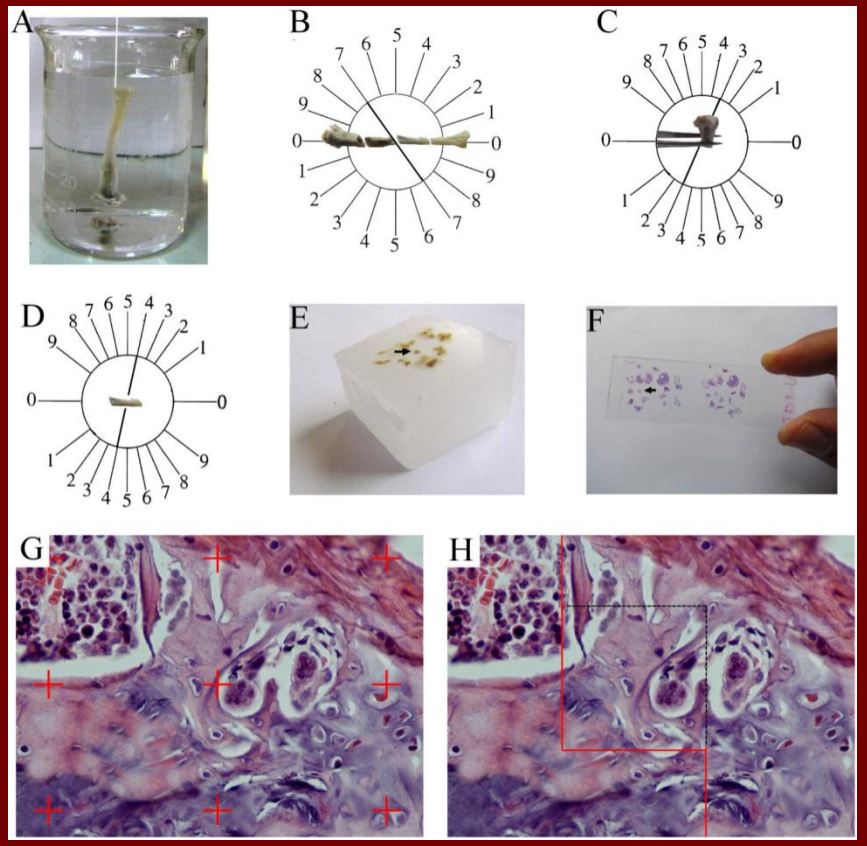
- Prentice RL, Pettinger MB, Jackson RD et al (2013) Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study.Osteoporos Int 24(2):567–580


Bone-building Foods

Osteoporosis International

Stereological study of the effect of black olive hydroalcoholic extract on osteoporosis in vertebra and tibia in ovariectomized rats





Dabbaghmanesh M.H et al, accepted 2015

Vitamin D

- Serum 25(OH)D levels should be measured in patients at risk of deficiency.
- Vitamin D supplements should be recommended in amounts sufficient to bring the serum 25(OH)D level to approximately 30 ng/ml (75 nmol/L)

Whom to Treat: NOF Guidelines 2014

Women ≥ 65 and men ≥ 70
(younger with risk factors)

DXA

T-score ≤ -2.5 in the lumbar spine, total hip, or femoral neck
or
Hip or spine fracture (clinical or radiographic)

YES

for TREATMENT

T-score between -1.0 and -2.5

FRAX 10-y fracture risk

YES

≥ 3% for hip fracture
or
≥ 20% for major osteoporotic fractures

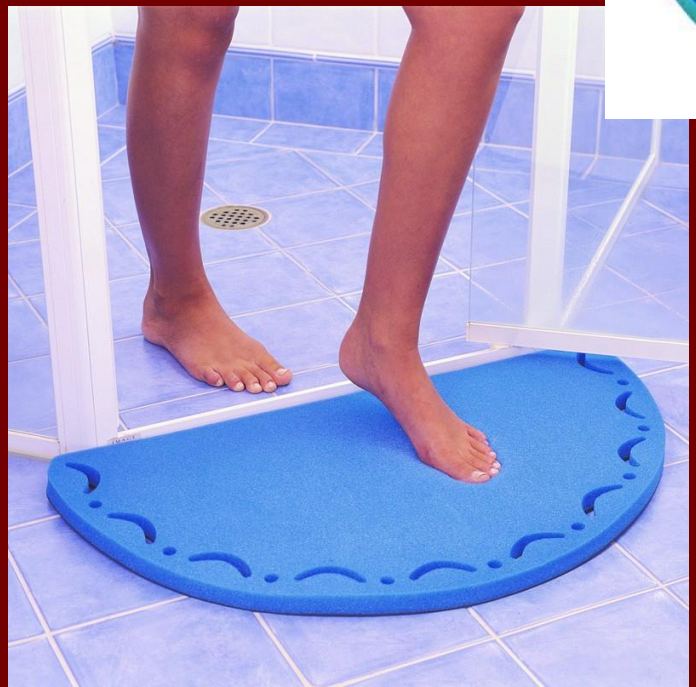
nof.org/hcp/resources/913. Accessed August 2014.

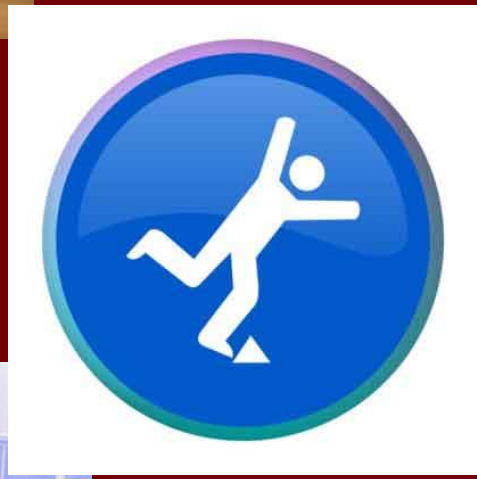
Secondary cause

- Metabolic bone diseases other than osteoporosis,such as hyperparathyroidism or osteomalacia, may be associated with low BMD.

Consider the following diagnostic studies for secondary causes of osteoporosis
Blood or serum
Complete blood count (CBC)
Chemistry levels (calcium, renal function, phosphorus, and magnesium)
Liver function tests
Thyroid-stimulating hormone (TSH) +/− free T_4
25(OH)D
Parathyroid hormone (PTH)
Total testosterone and gonadotropin in younger men
Bone turnover markers
Consider in selected patients
Serum protein electrophoresis (SPEP), serum immunofixation, serum-free light chains
Tissue transglutaminase antibodies (IgA and IgG)
Iron and ferritin levels
Homocysteine
Prolactin
Tryptase
Urine
24-h urinary calcium
Consider in selected patients
Protein electrophoresis (UPEP)
Urinary free cortisol level
Urinary histamine


CAUTION
WET
FLOOR



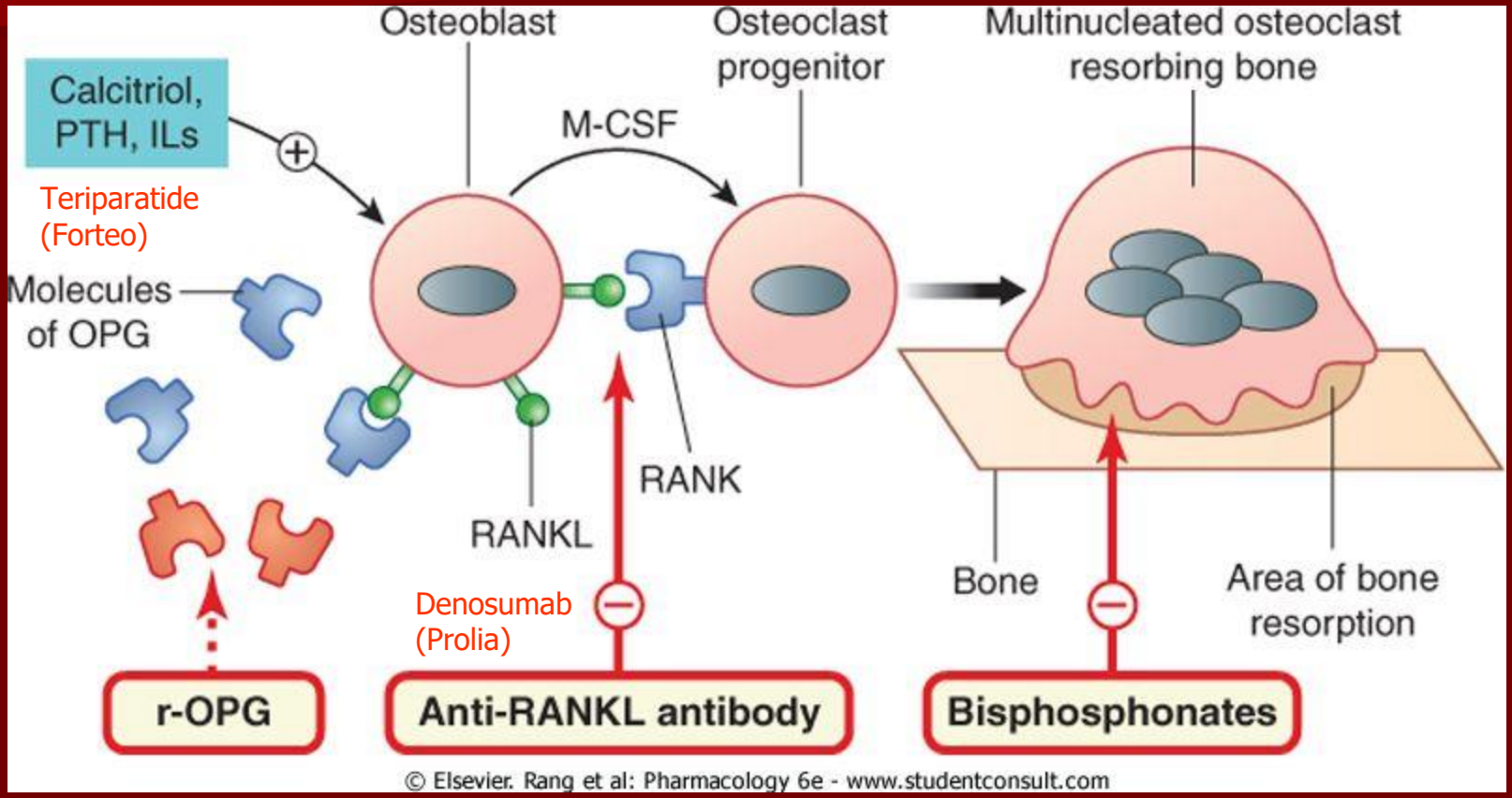



Quit Smoking

Pharmacologic Options

- Antiresorptives
  - Estrogens/HRT
  - Selective-estrogen receptor modulators (SERMS)
  - Bisphosphonates
  - Calcitonin
- Anabolic
  - PTH

Treatment


Osteoblast
Osteoclast progenitor
Multinucleated osteoclast resorbing bone
Calcitriol, PTH, ILs
M-CSF
Teriparatide (Forteo)
Molecules of OPG
RANK
RANKL
Denosumab (Prolia)
Bone
Area of bone resorption
r-OPG
Anti-RANKL antibody
Bisphosphonates
© Elsevier. Rang et al: Pharmacology 6e - www.studentconsult.com

FDA-approved Medications

Osteoporosis→	Post-menopausal		Glucocorticoid-induced		Male
Drug	**Prevent**	**Treat**	**Prevent**	**Treat**	
Estrogen	✓				
Calcitonin* (Miacalcin®, Fortical®)		✓			
Raloxifene (Evista®)	✓	✓			
Ibandronate (Boniva®)	✓	✓			
Alendronate (Fosamax®)	✓	✓		✓	✓
Risedronate (Actonel®)	✓	✓	✓	✓	✓
Risedronate (Atelvia®)		✓			
Zoledronate (Reclast®)	✓	✓	✓	✓	✓
Denosumab (Prolia™)		✓			✓
Teriparatide (Forteo®)		✓		✓	✓

Diab DL, Watts NB. *Endocrinol Metab Clin North Am*. 2013;42(2):305-317.

Evidence for Fracture Reduction

Drug	Vertebral Fracture	Nonvertebral Fracture	Hip Fracture
Calcitonin	✓		
Raloxifene	✓		
Ibandronate	✓		
Alendronate	✓	✓	✓
Risedronate	✓	✓	✓
Zoledronic acid	✓	✓	✓
Denosumab	✓	✓	✓
Teriparatide	✓	✓	

Diab DL, Watts NB. *Endocrinol Metab Clin North Am*. 2013;42(2):305-317

Conjugated estrogens/bazedoxifene

- Conjugated estrogens/bazedoxifene is approved by the FDA for women who suffer from moderate-to-severehot flashes (vasomotor symptoms) associated with menopause
- To prevent osteoporosis after menopause

Sequential and combination therapy

- For more severe osteoporosis, sequential treatment with anabolic therapy followed by an antiresorptive agent is generally preferred to concomitant combination therapy.

Monitoring

- Monitor treatment with DXA every 2 years
  - Do not "over-interpret" change
  - Be happy when BMD is stable OR increasing
- Changes in the BMD of less than 3–6 % at the hip and 2–4 % at the spine from test to test may be due to the precision error of the testing itself.
- Why do some patients lose BMD on treatment?
  - Adherence
  - Drug pharmacokinetics
  - Underlying disorders that need to be addressed

Duration of treatment

- Bisphosphonates may allow residual effects even after treatment discontinuation
- It is reasonable to discontinue bisphosphonates after the initial treatment period 3 to 5 years in people who appear to be at modest risk of fracture.
- Those who appear to be at high risk for fracture, continued treatment with a bisphosphonate or an alternative therapy should be considered.

- Black DM, Bauer DC, Schwartz AV, Cummings SR, Rosen CJ(2012) Continuing bisphosphonate treatment for osteoporosis—forwhom and for how long? N Engl J Med 366(22):2051–2053