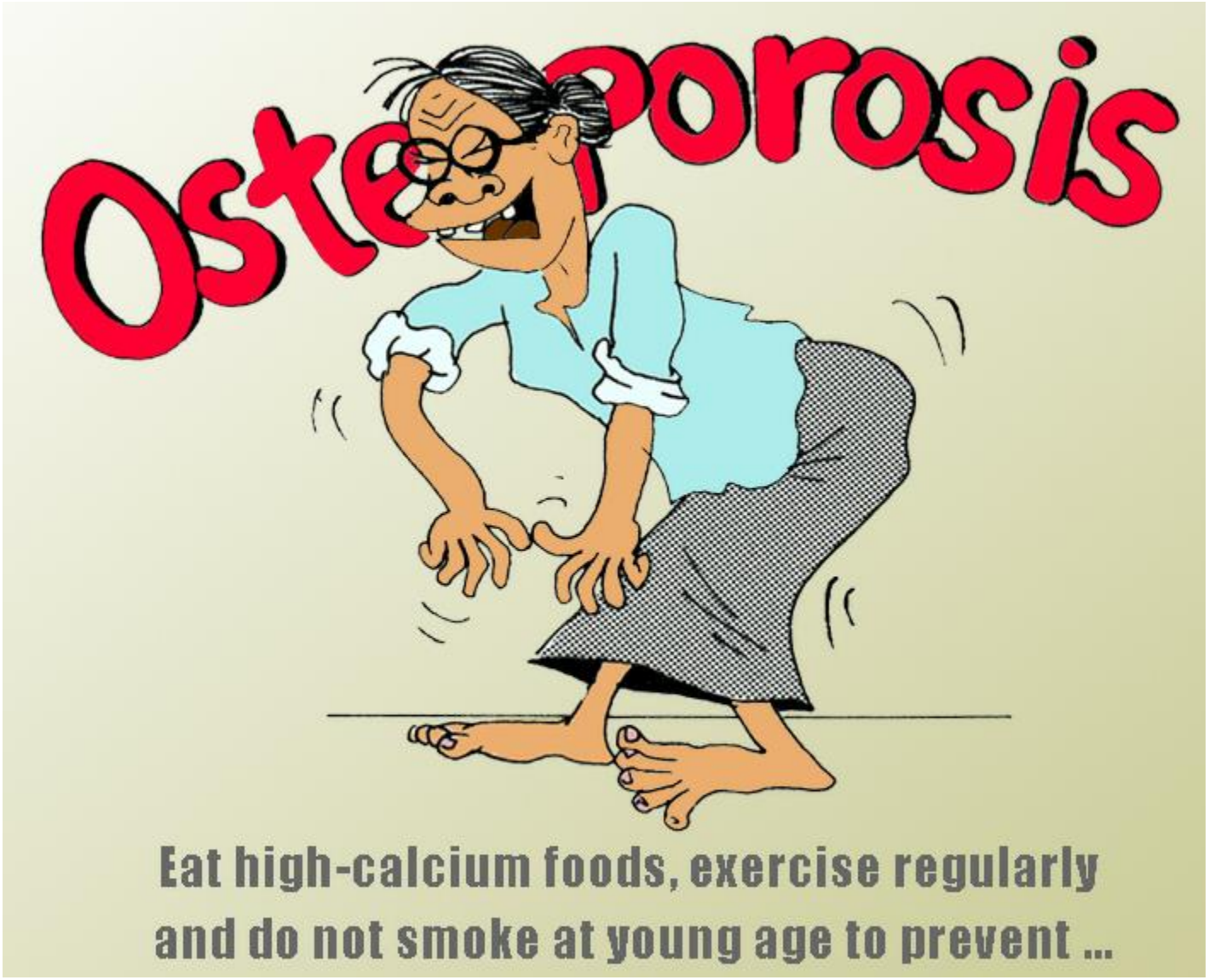


Osteoporosis in male

MH gozashti

Endocrinologist


Osteoporosis
Eat high-calcium foods, exercise regularly
and do not smoke at young age to prevent ...

DIAGNOSIS AND MANAGEMENT

- **should the treatment and the target be the same as for female osteoporosis?**

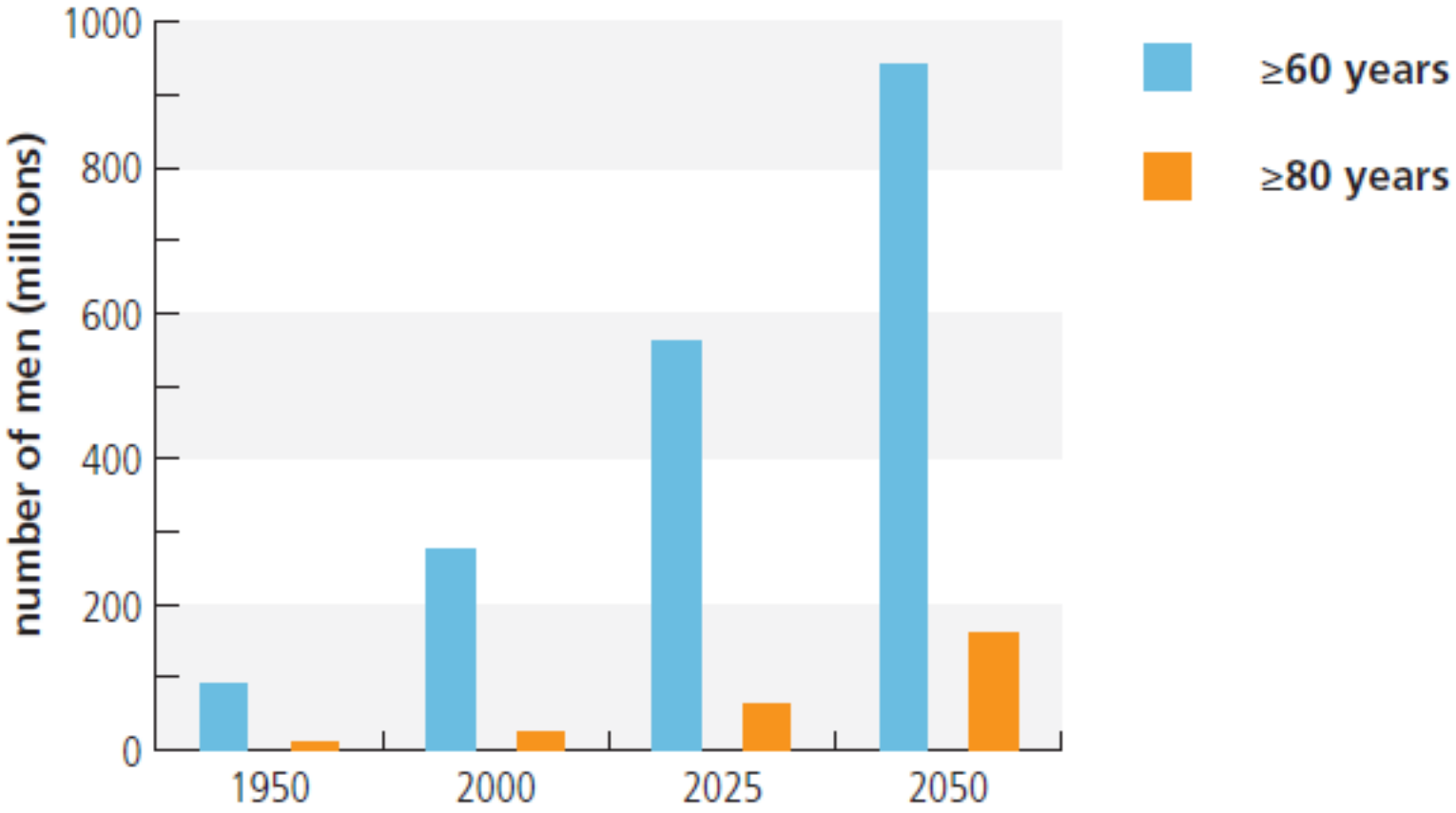
Epidemiology of male osteoporosis and fractures

- prevalence of osteoporosis in the US has been estimated in 3–6% in men >50 years and in 13–18% in women >50 years

- a study showed a comparable prevalence of osteoporosis for men aged 70 years or older and women aged 65 years



FIGURE 1 The ageing of the world's male population 1950–2050[1,2]



- In men, as in women, the incidence of fractures increases exponentially with age, although the increase **begins approximately 10 years later in men**

- In absolute numbers, the prevalence of vertebral or hip fracture in older men is approximately **one-third of that in women**,

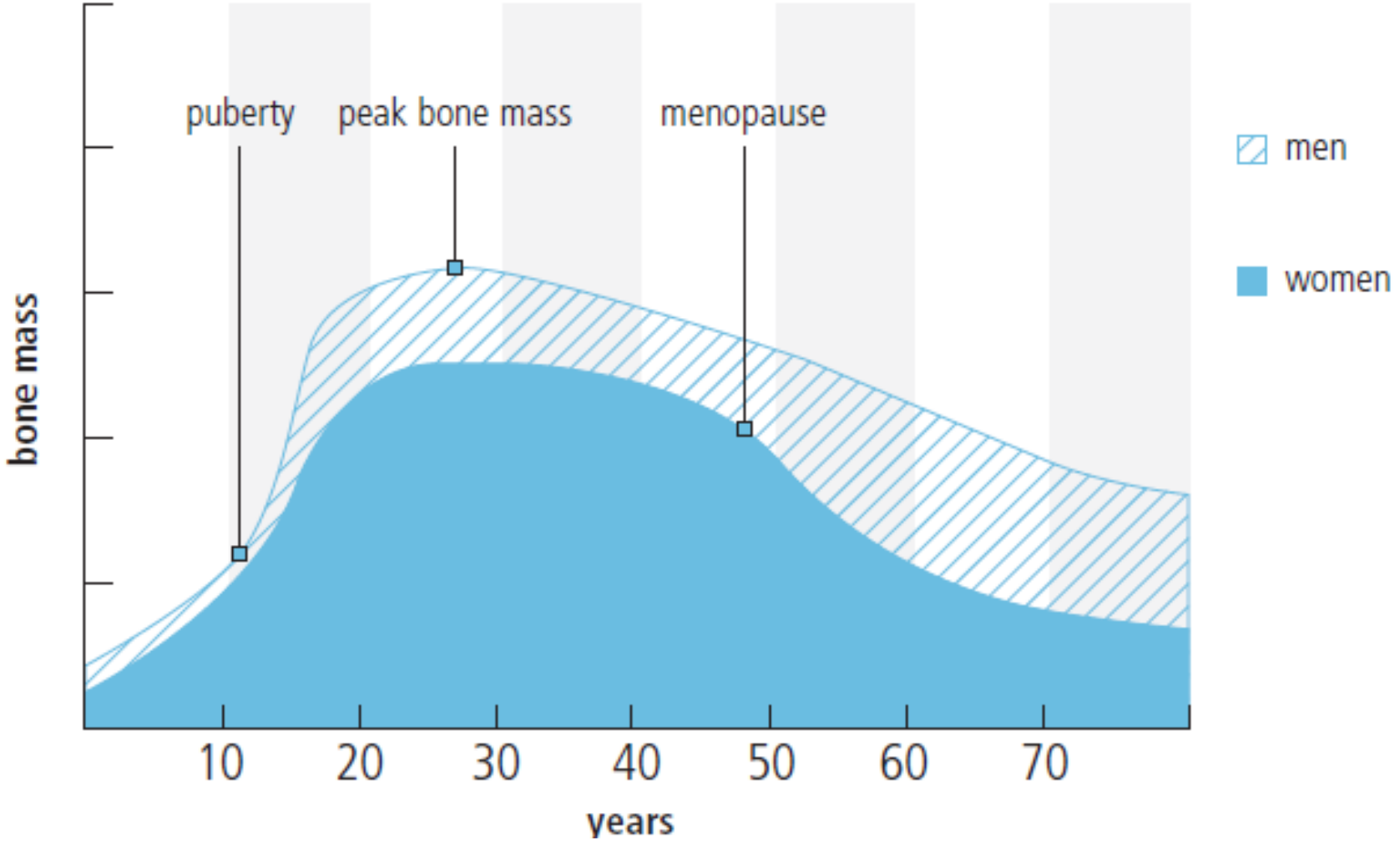
- but the mortality rate associated with hip fractures, as well as vertebral and other major fractures, **is higher in men than in women**

- **Compared with women, men are about two times more likely to die in the hospital after a hip fracture.**

ETIOLOGY OF MALE OSTEOPOROSIS

- Two main phases during life are fundamental for the development of osteoporosis:
- **achievement of peak bone mass**
- **bone turnover during aging.**

FIGURE 4 Bone mass throughout the life cycle[61]



- A 10% increase in peak BMD was predicted to delay the development of osteoporosis by 13 years.

- **Osteoporosis has been described as a ‘paediatric disease with geriatric consequences’**

- **Childhood and adolescence** may represent the optimal window of opportunity in which exercise can improve bone strength and protect against osteoporosis and associated fragility fractures in old age, assuming the gains achieved are maintained in later life.

- **Calcium intake** approximately 40% of adult peak bone mass is acquired during the two years around puberty
- Accordingly, ensuring adequate dietary calcium intake during this period of growth is essential.

- **Protein intake** proteins are building blocks and help to maintain strong bones, conversely low protein intake is associated with impaired skeletal growth thereby influencing peak bone mass.

- Important influences on peak bone mass for young males include:
- **hormones (especially the growth hormone axis and sex steroids,**
- **exercise and body weight,**
- **calcium intake,**
- **vitamin D level,**
- **protein intake**
- **genetic predisposition**.

- factors that can adversely affect peak bone mass in young males include:
- **smoking,**
- **alcohol consumption,**
- **certain childhood diseases,**
- **medications such as glucocorticoids or anti-epileptic drugs.**
-

- The **skeleton renews every 10 years** through a process called bone remodeling by which the old bone is replaced by the new one.

- Ageing in men is associated with increased rates of bone turnover, leading to imbalance of bone resorption relative to formation.

- This imbalance leads to **decreases in BMD of about 1% per year,** which can begin soon after peak bone mass, at about the age of 40 years.

- Age-related BMD loss is gender different, affecting lesser men than women because men do **not undergo a strong reduction in sex hormone** levels as observed during menopause.

- Consequently, the increased rates for both **vertebral and hip fractures in men are delayed by about 10 years with respect to women**

- The **trabecular BMD loss seems to begin in the third decade of life in both sexes**, independently from gonadal function.

- The lifetime loss of the trabecular bone at spine has been calculated in 55% in women and 45% in **men and it is greatly accelerated in women at menopause .**

- Since men do not experience this rapid decline in sex hormones, the loss of trabecular bone loss is attenuated.

- On the contrary, **the cortical bone is substantially maintained in both sexes until around the sixth decade.**

- Male osteoporosis is typically classified into **primary and secondary** forms .

- Types of primary male osteoporosis include:
- **the age-related osteoporosis (>60 years)**
- **the idiopathic forms observed in young and middle-aged men.**

- up to **40% of postmenopausal women and 60% of men have factors contributing** to osteoporosis when evaluated for underlying causes of the disease

- Based also on clinical experience, **about two thirds of men have factors contributing to** osteoporosis,

Table 1 Etiology and risk factors of male osteoporosis.

Primary osteoporosis (30–35%)
Idiopathic in young and middle-aged men
Age related (>60 years)
Secondary osteoporosis (65–70%)
Endocrine diseases
Hypogonadism
Cushing syndrome
Acromegaly
Hyperparathyroidism
Hyperthyroidism
Diabetes mellitus
Delayed puberty
Growth hormone deficiency
Estrogen deficiency
Vitamin D deficiency
Lifestyle
Alcohol intake
Sedentary lifestyle
Smoking
Undernutrition
Inadequate calcium intake

Medications
- Glucocorticoids
- Androgen deprivation therapy (ADT)
- Antiepileptics
- Immunosuppressants
- Chemotherapeutics
- Treatments for HIV

Other diseases
- Malabsorption syndromes (coeliac disease, inflammatory bowel diseases, bariatric surgery)
- Low BMI (BMI <20)
- Rheumatoid arthritis and ankylosing spondylosis
- Chronic liver or kidney disease
- HIV infection
- Chronic obstructive pulmonary disease
- Neoplastic diseases
- Idiopathic hypercalciuria
- Multiple myeloma
- Mastocytosis
- Osteogenesis imperfecta
- Neuromuscular diseases
- Ehlers-Danlos syndrome

Table 4. Risk factors to assess in order to prevent fragility fractures in men, according to the Endocrine Society [86]. The FRAX assessment tool is also recommended.

Risk factors for Fragility Fractures in Men (*Endocrine Society*)
History of fracture after age 50
Delayed puberty
Hypogonadism
Hyperparathyroidism
Hyperthyroidism
Chronic obstructive pulmonary disease
Drugs such as glucocorticoids or GnRH agonists
Alcohol abuse
Smoking

Screening guidelines for male osteoporosis

- **there is no universally accepted policy** for screening of male population to identify individuals with osteoporosis or those at high risk of fracture



- osteoporosis may be defined simply by the occurrence of a **low-trauma fracture,** by **a BMD of 2.5 or more s.d**. below the normal young mean as suggested by WHO, or by calculation of fracture risk

- Assessment of risk factors for osteoporosis and Dual energy X-ray Absorptiometry (DXA) are recommended **in men >65–70 years** from some endocrine and osteoporosis scientific societies
- (International Society for Clinical Densitometry)



- The American College of Physician suggests performing DXA in **men >65 years only** when risk factors are documented to increase the risk for osteoporosis and/or are candidates for drug therapy

- For younger men (<50 years), only the Canadian Osteoporosis Society (52) made recommendations for DXA screening,
- highlighting the most frequent conditions that are associated with accelerated bone loss and/or fracture, such as **prolonged use of glucocorticoids, hypogonadism (including ADT) and malabsorption syndrome.**

- The International Society for Clinical Densitometry (www. iscd.org/official-positions/2019-iscd-official-positions-adult/, accessed 20 Dec 2019) makes no age limitations for DXA **screening in men with risk factors for low BMD, being recommended in all men <70 years.**

- **Interestingly, the United States Preventive Services Task Force does not recommend osteoporosis screening in men justified by insufficient evidence.**

- osteoporosis screening for men with hypogonadism from the European Academy of Andrology :

- recommended in all cases when testosterone **levels are <300 ng/dL** (10.4 nmol/L),
- when patients are candidate to ADT
- when history of hypogonadism is documented, especially if occurred during puberty or early adult life.

Table 6. Most recent guidelines on indications for screening of osteoporosis in men.

Society	Year	DXA	X-rays
Canadian Osteoporosis Society [94]	2010	(1) Men ≥ 65 years (2) Men 50–64 years with risk factors (3) Men < 50 years with fragility fracture, prolonged use of glucocorticoids, use of other high-risk medications (i.e. aromatase inhibitors or androgen deprivation therapy), hypogonadism, malabsorption syndrome, primary hyperparathyroidism, other disorders strongly associated with rapid bone loss and/or fracture.	
Endocrine Society [86]	2012	(1) Men ≥ 70 (2) Men 50–69 yrs old with risk factors (history of fracture after age 50; diseases/conditions such as delayed puberty, hypogonadism, hyperparathyroidism, hyperthyroidism, or chronic obstructive pulmonary disease; drugs such as glucocorticoids or GnRH agonists; life choices such as alcohol abuse or smoking; or other causes of secondary osteoporosis)	

NOF [17]	2014	(1) Men age 70 and older, regardless of clinical risk factors. (2) Men age 50 to 69 with clinical risk factors for fracture. (3) Adults who have a fracture at or after age 50. (4) Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids in a daily dose ≥5 mg prednisone or equivalent for ≥3 months) associated with low bone mass or bone loss.	Vertebral X-rays: (1) All men aged 80 and older if BMD Tscore at the spine, total hip, or femoral neck is ≤−1.0 (2) Men aged 70 to 79 if BMD T-score at the spine, total hip, or femoral neck is ≤−1.5 (3) Men aged 50 and older with specific risk factors: ▪ Low-trauma fracture during adulthood (age 50 and older), ▪ Historical height loss of 1.5 in. or more (4 cm), ▪ Prospective height loss of 0.8 in. or more (2 cm), ▪ recent or ongoing long-term glucocorticoid treatment

- we suggest that osteoporosis should be considered in **all men when risk factors for low BMD and fractures are present**, independently from age.

- Age *per se* is sufficient for screening after the age of 65–70 years.

- Of particular note, **BMD does not always** correlate with fracture risk and a fraction of fractures happen in men with normal BMD or BMD in the range of osteopenia, especially in some population such as
- **men with HIV, diabetes or endocrine-related forms,**
- **because the fracture risk in these patients is related more to bone quality than bone mass**

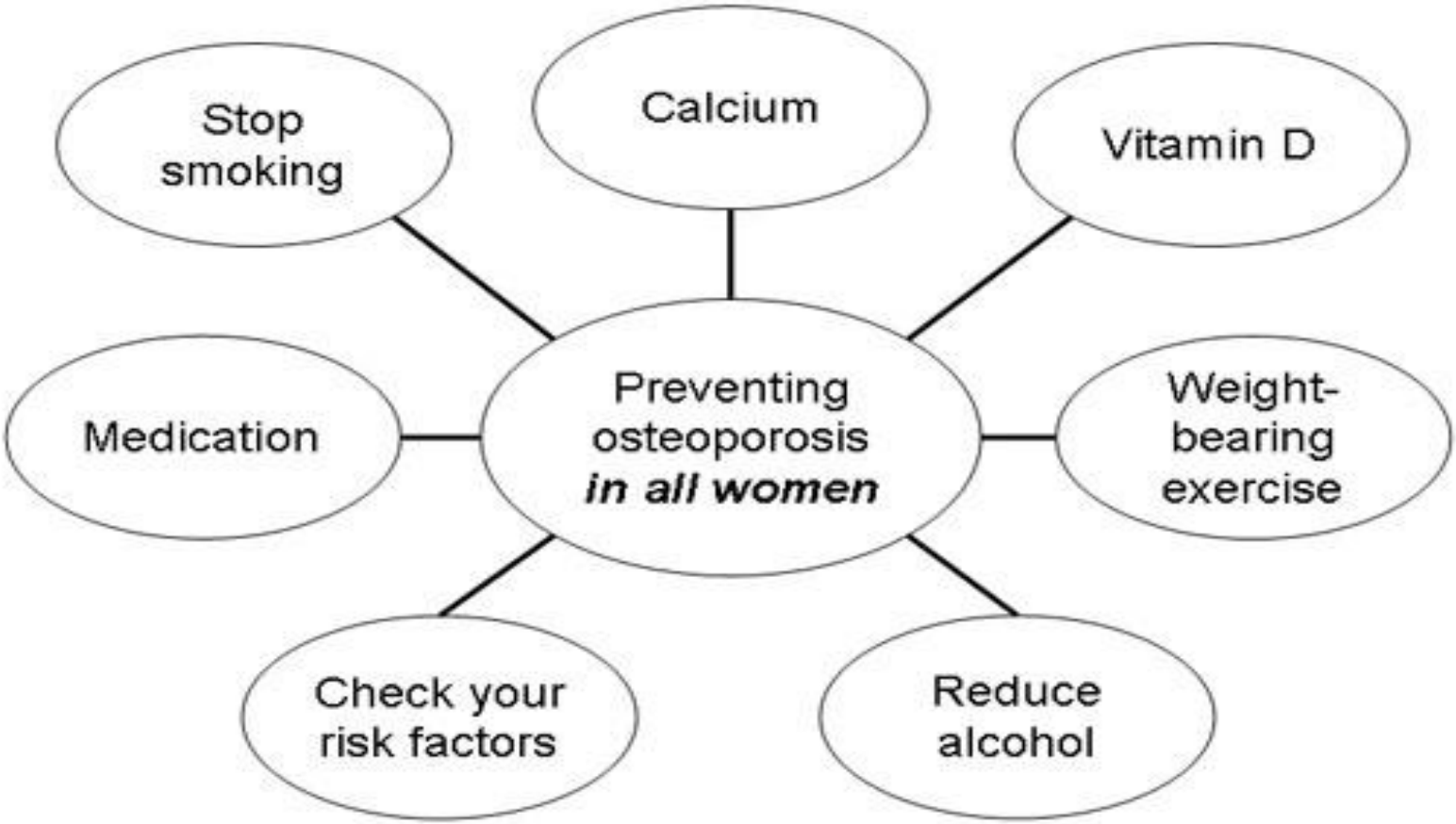
Table 5. Laboratory tests suggested by the National Osteoporosis Foundation [17].

Laboratory Tests for Diagnosis of Secondary Osteoporosis in Men	
Blood or serum	▪ Complete blood count (CBC) ▪ Chemistry levels (calcium, renal function, phosphorus, and magnesium) ▪ Liver function tests ▪ Thyroid-stimulating hormone (TSH) +/− free T4 ▪ 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


Don't let your bones age faster than you.
STOP
OSTEOPOROSIS
NOW
For healthy bone consult your doctor

Therapeutic approach to male osteoporosis and target of treatment

- pharmacological therapy in men is recommended for men with:
- **hip and/or vertebral fragility fracture,**
- **men with a T-score (spine, hip) lower than –2.5 s.d.,**
- **and men with T-score between −1 and −2.5 (spine, hip) and fracture risk over 20% or hip fracture risk in 10 years ≥3% according to FRAX.**


Stop smoking
Calcium
Vitamin D
Medication
Preventing osteoporosis *in all women*
Weight-bearing exercise
Check your risk factors
Reduce alcohol

Non-pharmacological approach

- Maintaining a healthy lifestyle is essential also during adulthood, **with adequate sun exposition, normal body weight, avoiding excessive alcohol intake and smoking.**

- Physical activity and targeted exercises could improve muscular mass, strength and resistance and therefore reduce falls risk



- Although there is **no strong evidence that physical activity might prevent fractures**, observational studies found that the physical activity-related BMD increase is approximately 2% in older men and that it helps maintaining muscle mass and strength

Supplement and replacement therapy

- there are few published studies on calcium and **vitamin D supplementation in men**, and they are often controversial.

- based on evidence derived from studies in postmenopausal osteoporotic women, the same therapeutic approach is commonly applied in men.

- A daily calcium intake of 1000 mg for men under 70 years and 1200 mg for men over 70 years is generally suggested, and calcium **supplementation should be prescribed only if dietary intake is inadequate**

- Vitamin D supplementation is often necessary, as hypovitaminosis D is common in the elderly mainly **as a result of reduced sunlight exposure and a decreased functional capacity of the skin.**

- **Dietetic supplementation** of vitamin D is not able to restore normal levels of 25-hydroxy vitamin D,

- therefore, aside with adequate sun exposure, guidelines suggest supplementation in an individualized dose, based on serum 25-hydroxy vitamin D levels, starting from 800 UI/day



- the choice to supplement with the inactivated form of **vitamin D (cholecalciferol)** or with the 25-hydroxylated form **(calcifediol)** should consider also the pathogenesis of hypovitaminosis

- men with hypogonadism could better benefit from treatment with **calcifediol**
- because the testis participates with the liver in the 25 hydroxylation of cholecalciferol and this approach allows for rapid restoring of 25-hydroxy vitamin D levels , as **for men with liver dysfunction**

- obese men might also benefit from supplementation with **calcifediol** because cholecalciferol is more sequestrated in the adipose tissue than calcifediol

- guidelines on vitamin D supplementation generally **suggest treatment with cholecalciferol or simply do not differentiate** between cholecalciferol and calcifediol,

- Although it is necessary to restore vitamin D levels and maintain an optimal calcium homeostasis, the efficacy of calcium and vitamin D supplementation **alone in reducing fracture risk is controversial, but it could indeed improve BMD**

Antiosteoporotic drugs

- the data from clinical trials are incredibly few for male osteoporosis

- Bisphosphonates are suggested for men with osteoporosis and increased fracture risk, including those with secondary osteoporosis, such as hypogonadism

- A possible limitation of daily or weekly oral therapy in male osteoporosis (as for alendronate and risedronate) **could be the poor adherence**.

- Compliance could be improved with longer half-life drugs, for example, zoledronate i.v. once/year.

- The duration of bisphosphonate treatment is not well determined.

- since the occurrence of rare cases of osteonecrosis of the jaw and atypical femoral fractures, **a 'therapeutic holiday' from oral bisphosphonate** after 5 years of administration and after 3 years for i.v. bisphosphonates



- reassessment at 2 to 3 years for patients not at high fracture risk and without fractures antecedent to treatment

- The data on denosumab in male osteoporosis are even more limited
- No data are available for non-vertebral fractures.
- Denosumab finds best indication to treat bone loss in patients with **primary osteoporosis, those receiving ADT for prostate cancer and hypogonadal men**



- Unlike bisphosphonates, **the beneficial effects of denosumab on bone is rapidly reversible**, since an increase in osteoclastogenesis occurs early after withdrawal.

- Therefore, it has **not yet been established how long the patients should** be treated with denosumab, or whether and when it should be discontinued

- Generally, denosumab is mostly discontinued when patients have reached **a target T-score outside the osteoporosis zone**

- **Bisphosphonates are suggested** after stopping denosumab to reduce the increased risk of rebound-associated fractures



- Teriparatide is **the only anabolic agent** approved for male osteoporosis and reported in randomized controlled studies.

- In women, it increases both lumbar and femoral BMD and reduces fracture risk.

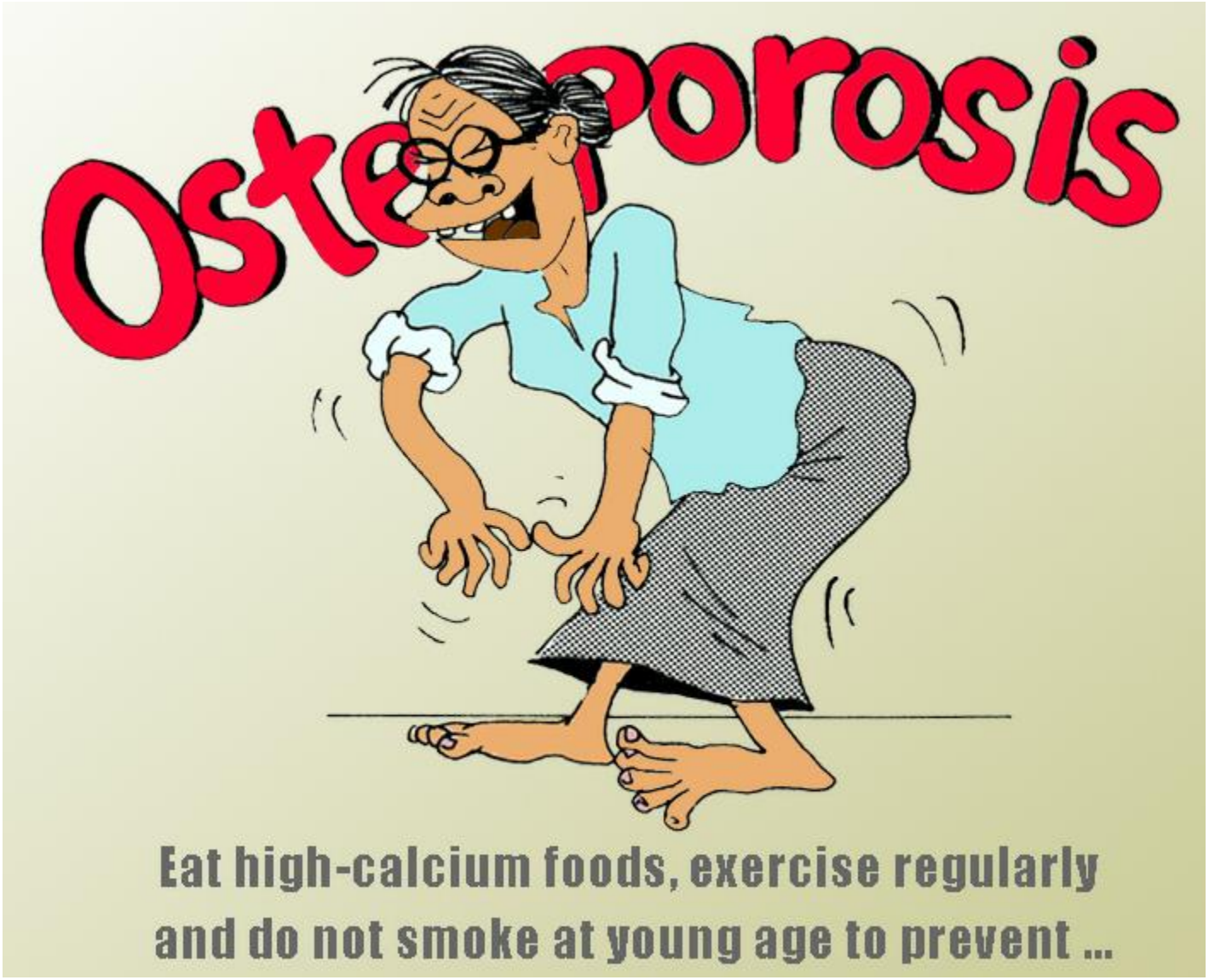
- Furthermore, it seems to be more effective than **bisphosphonates in glucocorticoid-induced** osteoporosis.

- It is administered s.c. at a daily dose of 20 μg, for **a maximum period of 24 months**, because its safety and efficacy have not been evaluated over 2 years.

- Teriparatide is generally well tolerated.

- calcium and vitamin D supplementation is always **recommended before starting antiosteoporotic** treatment when there is a deficiency condition, and it should be maintained during treatment.

- Furthermore, men receiving chronic therapy with **high dosage glucocorticoids and men receiving ADT for prostatic cancer are also candidates to antiosteoporotic drugs.**


Osteoporosis
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and do not smoke at young age to prevent ...


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