به نام خداوند جان و خرد

Osteoporosis in CKD: A diagnosis & therapeutic challenge on the move

Dr. Shahrzad Shahidi

Professor of Nephrology

Isfahan University of Medical Sciences

Definitions

- **Osteoporosis** is defined as a hx of fragility fx &/or a T-score of -2.5 or lower on dual energy X-ray absorptiometry (DEXA).
- **Osteopenia or** Low bone mass is defined as a T-score between -1.0 & -2.5 on DEXA.

Falls are the **leading cause** of both fatal & nonfatal injuries in people aged ≥ **65**.

Definitions

- **Fragility fx** is one caused by a degree of trauma not expected to cause a fx; i.e., a fall from standing height or lower.
- Fragility fxs, such as vertebral compression fxs & distal forearm fxs, are common in the elderly but can occur at any age.
- Major osteoporotic fx is a fx of the hip, spine (clinical), wrist, or humerus.

Definitions

- **Osteoporosis** involves a loss of bone mass & changes in microarchitecture not associated with specific mineralization, cellularity or bone turnover defect.
- Although **OP & ABD** share some common clinical characteristics, their pathogenesis, histopathology & treatment are different.

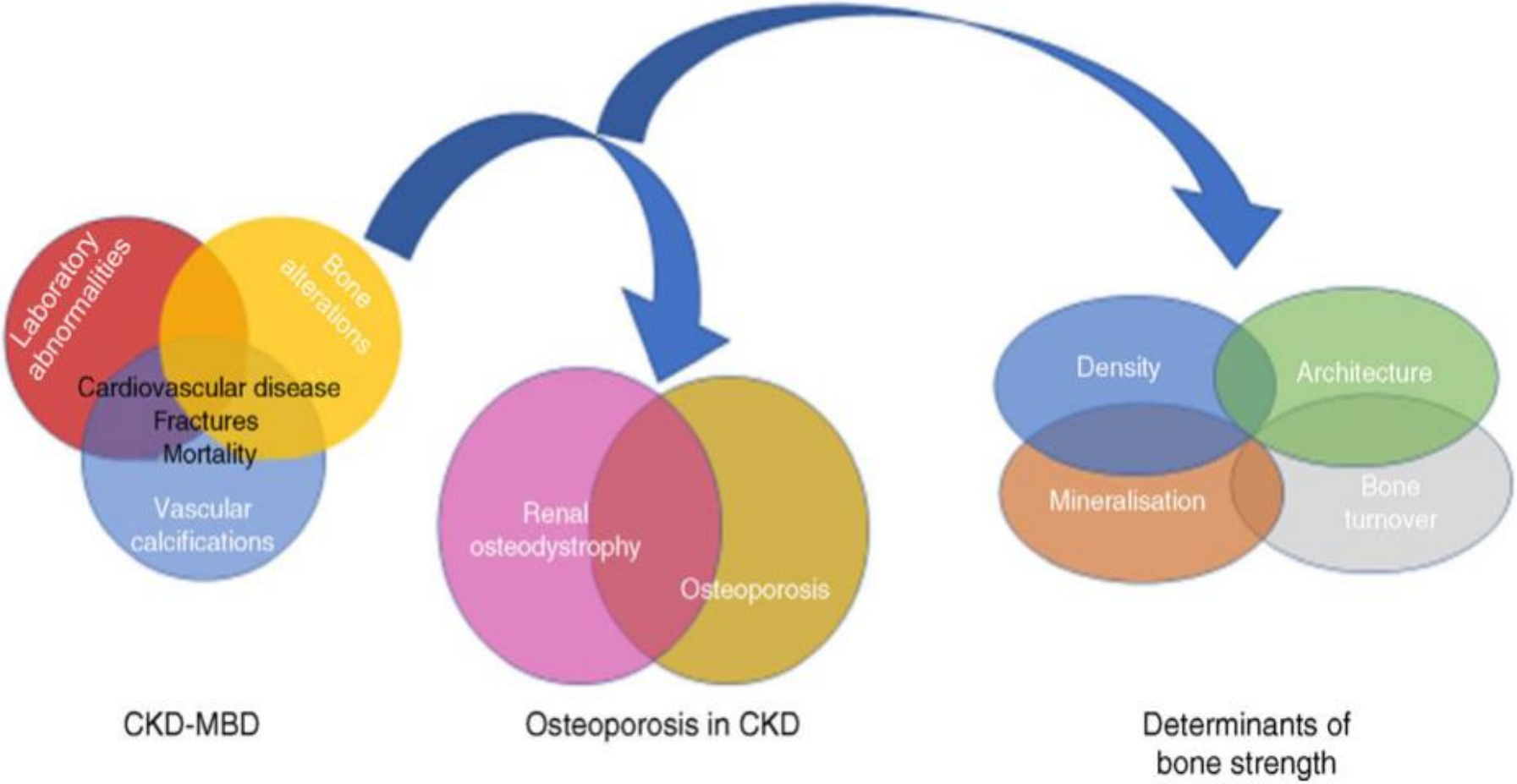
Definitions

- **Uremic OP** emphasizes the particularly complex relationship between BMD & the risk of Fx & mortality in CKD patients.

Epidemiology

- Fxs were more frequent in the group of dialysis patients vs. the general population in all countries, & **non-vertebral fxs** were always much more frequent than the vertebral fxs.
- All fxs occur at a younger age (**≠ 10 ys younger**) & are associated with a significant increase in morbidity & mortality i.e. the death/rehospitalisation rate is **4 ×** higher in patients on dialysis with fxs compared with patients with no fxs.

Relationship between CKD-MBD, ROD & OP



Nephrologia. 2018;38(5)

Diagnosis

Diagnosis

- **Peripheral DEXA & QUS bone densitometry**
  - Their results are more limited & not equivalent to DEXA. Abnormal results should be confirmed with central DEXA.
- **HR-pQCT**
  - Dose not provide information on bone turnover & mineralization that can be obtained from bone BX & it is expensive & not widely available.
- **Central DEXA**
  - Gold standard
- **Bone Bx**
  - Rarely used due to logistical difficulties involved.

KDIGO 2017 Update for CKD-MBD

- 3.2.1: In patients with CKD G3a to G5D with evidence of CKD–MBD &/or risk factors for op, we suggest **BMD** testing to assess fx risk if results will impact treatment decisions. (Grade 2B)

Diagnosis

- BMD measured as T-score (number of SD from BMD of women aged 20–29) exponentially increases the risk of fx.
- In the absence of BMD measurement, this could be indicated by the presence of a major risk factor (other than age) or 2 minor risk factors, or, according to different guidelines, 2 major or 1 major + 2 minor.
- Other risk factors important for nephrologists would be:
  - **The use of loop diuretics, chronic use of heparin or anticoagulants, PPIs, antihistamines, SSRIs, estrogen & testosterone blockers, antiepileptics, aromatase inhibitors, etc.**

FX risk factors

- **Major (RR ≥ 2)**

1. BMD ≤ -2.5
2. Previous Fx
3. Age ≥ 65
4. BMI ≤ 20
5. Hx of hip fx in a first- degree relative
6. HPTH
7. Untreated premature ovarian failure
8. Falls in the previous year (≥ 2)
9. Eating disorder
10. Chronic malnutrition or malabsorption syndromes

FX risk factors

- **Minor**
  1. Female gender
  2. Early menopause (40-45 y)
  3. Current smoker
  4. Consumption of ≥ 3 u alcohol/day
  5. Type 1 DM
  6. RA
  7. Hyperthyroidism

FRAX® Fracture Risk Assessment Tool

Home | Calculation Tool | Paper Charts | FAQ | References | English

- Asia
- Europe
- Middle East & Africa
- North America
- Latin America
- Oceania

- Abu Dhabi
- **Iran**
- Jordan
- Kuwait
- Lebanon
- Morocco
- Palestine
- Syria
- Tunisia

Welcome to FRA

The FRAX® tool has been d
individual patient models that i
bone mineral density (BMD) at

Dr. John A Kanis
Professor Emeritus,
University of
Sheffield

The FRAX® models have
population-based cohorts fron
Australia. In their most soph
computer-driven and is availa
paper versions, based on th
available, and can be downloa

The FRAX® algorithms give th
output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture).

Clarification

https://www.sheffield.ac.uk/FRAX/tool.aspx?country=68

FRAX Desktop Application

Click here to view the applications available

Web Version 4.1

View Release Notes

Links

www.iofbonehealth.org

www.nof.org

www.jpof.or.jp

www.esceo.org

FRAX available as iPhone App

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: Iran Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: Date of Birth: Y: M: D:
2. Sex — Male / Female
3. Weight (kg)
4. Height (cm)
5. Previous Fracture — No / Yes
6. Parent Fractured Hip — No / Yes
7. Current Smoking — No / Yes
8. Glucocorticoids — No / Yes
9. Rheumatoid arthritis — No / Yes
10. Secondary osteoporosis — No / Yes
11. Alcohol 3 or more units/day — No / Yes
12. Femoral neck BMD (g/cm^2)

Select BMD

Clear Calculate

Weight Conversion

Pounds → kg

Convert

Height Conversion

Inches → cm

Convert

00061629

Individuals with fracture risk assessed since 1st June 2011

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: Iran Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 55 Date of Birth: Y: 1964 M: 7 D: 23
2. Sex — Male / Female
3. Weight (kg): 69.5
4. Height (cm): 160
5. Previous Fracture — No / Yes
6. Parent Fractured Hip — No / Yes
7. Current Smoking — No / Yes
8. Glucocorticoids — No / Yes
9. Rheumatoid arthritis — No / Yes
10. Secondary osteoporosis — No / Yes
11. Alcohol 3 or more units/day — No / Yes
12. Femoral neck BMD (g/cm^2)

T-Score: -3.2

Clear Calculate

BMI: 27.1

The ten year probability of fracture (%)

with BMD

Major osteoporotic	15
Hip Fracture	7.6

If you have a TBS value, click here: Adjust with TBS

Weight Conversion

Pounds → kg Convert

Height Conversion

Inches → cm Convert

00061627

Individuals with fracture risk assessed since 1st June 2011

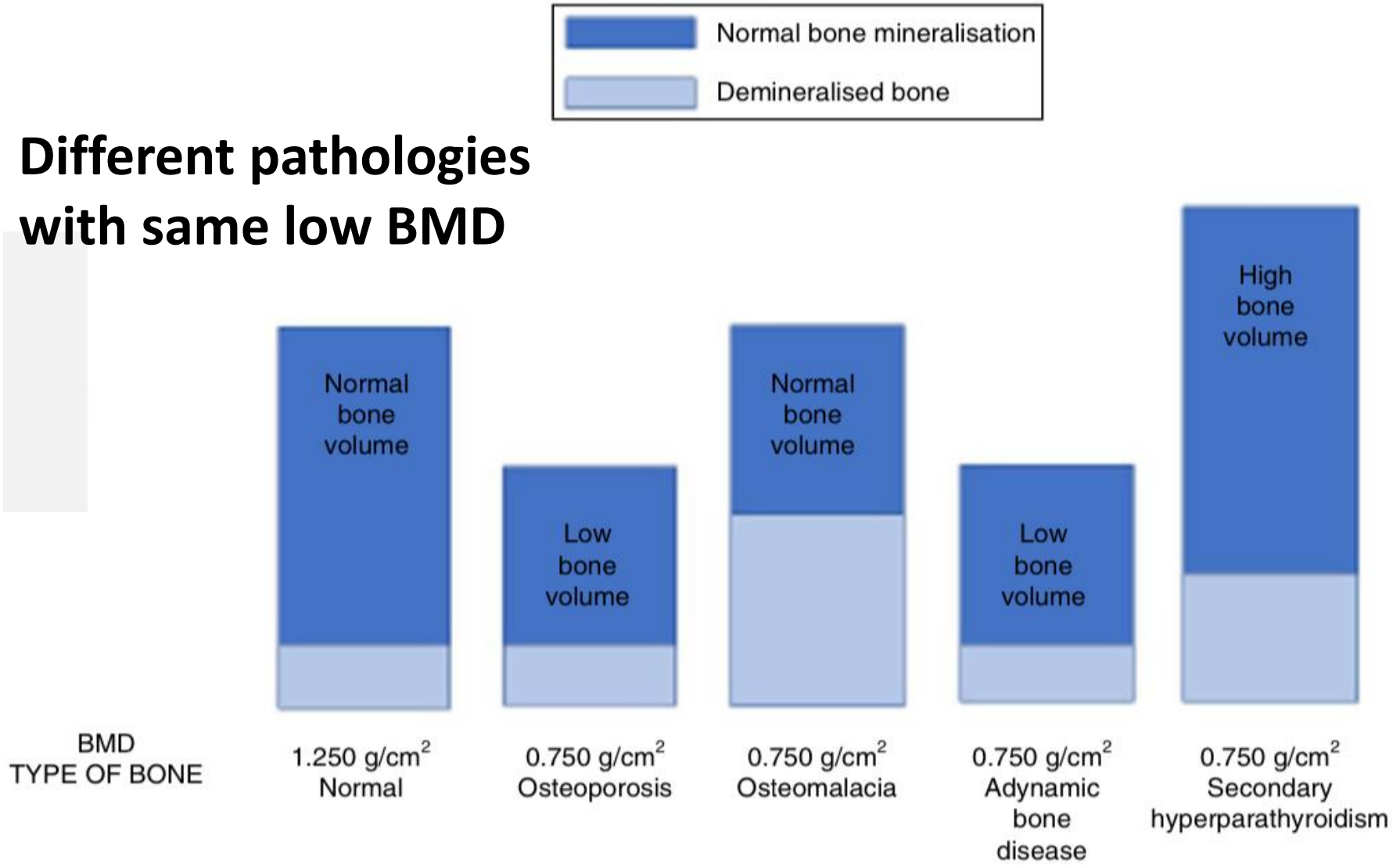
Nephrologia. 2018;38(5)

Diagnosis

- BMD alone dose not distinguish between its underlying causes (HPTH, ABD &/or senile OP, etc.).
- In patients with CKD (especially mild-moderate), risk factors for fx should be assessed & quantified if possible (i.e. with **FRAX**) in a similar way to the general population.

Nephrologia. 2018;38(5)

Different pathologies with same low BMD



Nephrologia. 2018;38(5)

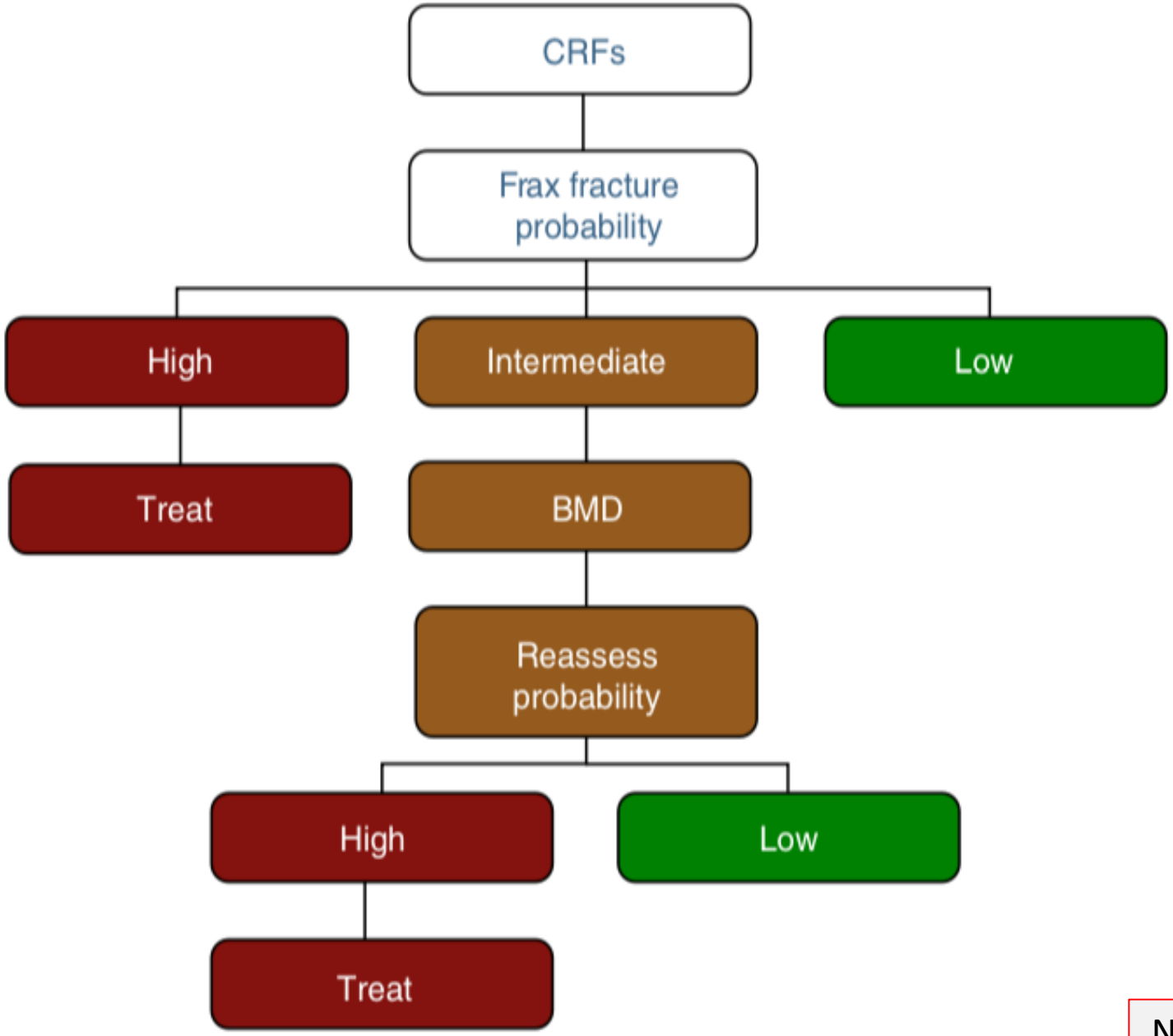
KDIGO 2017 Update for CKD-MBD

- 3.2.2: In patients with CKD G3a to G5D, it is reasonable to perform a bone biopsy if knowledge of the type of ROD will impact treatment decisions. (Not graded) due to limited clinical experience with performance of bone biopsy & evaluation of the results, as well as growing evidence that antiresorptive therapies are effective in patients with CKD stage G3a to G4, **bone biopsy is no longer a prerequisite for initiation of these therapies**.

Diagnosis

- As fxs occur at a younger age 2011 Spanish guidelines suggested that:
  - BMD should be performed in **women > 50** ys of age & **men > 65** ys of age with CKD (unlike the usual indication in women >65 ys of age & men >70 ys of age).

Nephrologia. 2018;38(5)



Nephrologia. 2018;38(5)

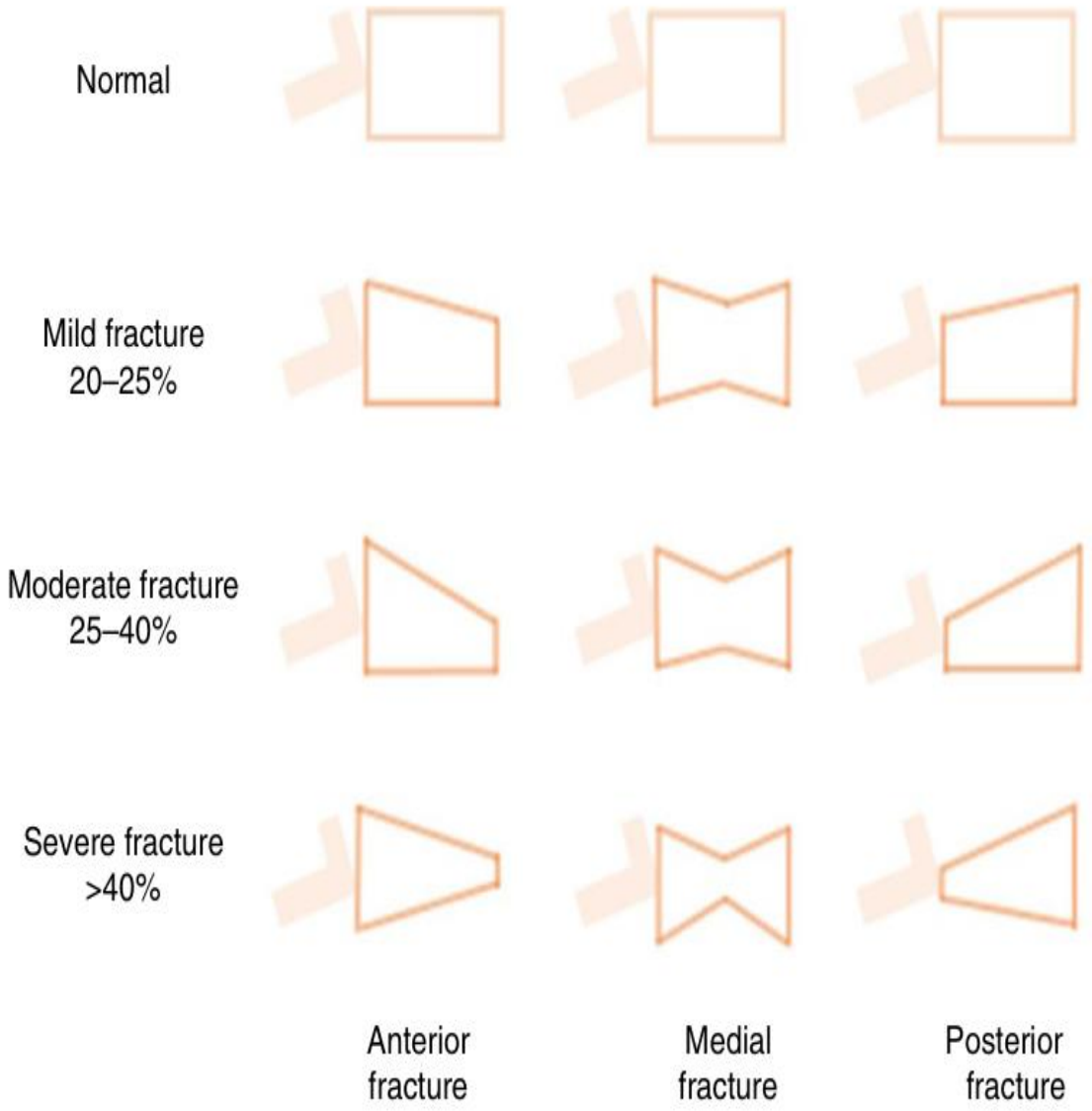


Fig. 5 – Schematic representation of Genant's semi-quantitative approach to the visual measurement of vertebral deformities. Normal = 0; mild = 1; moderate = 2; severe = 3; doubtful = 0.5. Vertebral fractures are often diagnosed fortuitously (morphometric fracture), although diagnosis can also be made on the basis of symptoms. It is based on more than 20% loss

Management

JAMA | Original Investigation

Comparisons of Interventions for Preventing Falls in Older Adults
A Systematic Review and Meta-analysis

Andrea C. Tricco, PhD; Sonia M. Thomas, MSc; Areti Angeliki Veroniki, PhD; Jemila S. Hamid, PhD; Elise Cogo, ND; Lisa Strifler, MSc; Paul A. Khan, PhD; Reid Robson, MSc; Kathryn M. Sibley, PhD; Heather MacDonald, MSc; John J. Riva, DC; Kednapa Thavorn, PhD; Charlotte Wilson, MSc; Jayna Holroyd-Leduc, MD; Gillian D. Kerr, MD; Fabio Feldman, PhD; Sumit R. Majumdar, MD; Susan B. Jaglal, PhD; Wing Hui, MSc; Sharon E. Straus, MD, MSc

IMPORTANCE Falls result in substantial burden for patients and health care systems, and given the aging of the population worldwide, the incidence of falls continues to rise.

OBJECTIVE To assess the potential effectiveness of interventions for preventing falls.

DATA SOURCES MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Ageline databases from inception until April 2017. Reference lists of included studies were scanned.

Editorial page 1659

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 1706

What type of fall-prevention programs may be effective for reducing injurious falls in older people?

- In a network met-analysis including 54 studies & 41 596 participants:
  - Exercise (OR, 0.51)
  - Combined exercise, vision assessment & treatment, & environmental assessment & modification (OR, 0.30)
  - Combined exercise, & vision assessment & treatment (OR, 0.17)
  - Combined clinic-level quality-improvement strategies, multifactorial assessment and treatment, Ca & vit D supplementation (OR, 0.12)

  were significantly associated with reductions in injurious falls.
- Combinations of interventions likely to be more effective than usual care for preventing injurious falls.

What type of fall-prevention programs may be effective for reducing injurious falls in older people?

1. Be physically active.
2. Check your vision.
3. Wear proper shoes or slippers.
4. Check your medications—especially sleeping pills.
5. Be safe in the bathroom.
6. Get the right equipment.
7. Avoid too much alcohol.
8. Eliminate household hazards.
9. Consider vit D.
10. Talk to your health care team about your risk.

KDIGO 2017 Update for CKD-MBD

- 4.2.2: In adult patients with CKD **G3a to G5** not on dialysis, we suggest that calcitriol & vit D analogues **not be routinely** used. (Grade 2C) It is reasonable to reserve the use of calcitriol & vit D analogues for patients with CKD G4 to G5 with severe & progressive HPTH. (Not graded)

KDIGO 2017 Update for CKD-MBD

- 4.2.4: In patients with CKD **G5D** requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vit D analogues, or a combination of calcimimetics with calcitriol or vit D analogues. (Grade 2B)

KDIGO 2017 Update for CKD-MBD

- 4.3.1: In patients with CKD **G1–G2** with op &/or high risk of fx, as identified by WHO criteria, we recommend management as for the general population (1A).
- 4.3.2: In patients with CKD **G3a–G3b** with PTH in the normal range & op &/or high risk of fx, as identified by WHO criteria, we suggest treatment as for the general population (2B).

KDIGO 2017 Update for CKD-MBD

- 4.3.3: In patients with CKD **G3a to G5D** with biochemical abnormalities of CKD–MBD & low BMD &/or fragility fxs, we suggest that treatment choices take into account the magnitude & reversibility of the biochemical abnormalities & the progression of CKD, with consideration of a bone biopsy. (Grade 2D)

KDIGO 2017 Update for CKD-MBD

- **Bisphosphonate** & **Denosumab** are the **most** widely used antiresorptive agents for osteoporosis.
- The amount of bisphosphonate retained in the skeleton is likely a function of:
  - **The baseline remodeling space**
  - **The chronic rate of bone turnover**
  - **The GFR.**

KDIGO 2017 Update for CKD-MBD

- Approximately 50% of the absorbed dose of oral bisphosphonates & of the administrated dose of IV bisphosphonates is excreted by the kidney.
- Oral bisphosphonates have **never** been shown to have renal toxicity, while IV bisphosphonates, especially Zolindronic acid, may acutely reduce GFR via a tubular lesions that mimics **ATN**.

TABLE 101-6 Inhibition of Metaphyseal Bone Resorption in Vivo by Bisphosphonates

Chemical Modification	Examples	Anti-resorptive Potency
First generation: short alkyl or halide side chain	Etidronate	1
	Clodronate	10
Second generation: NH_2-terminal group	Tiludronate*	10
	Pamidronate	100
	Alendronate	100-1000
Third generation: cyclic side chain	Risedronate	1000-10,000
	Ibandronate	1000-10,000
	Zoledronate	10,0000

Endocrinolo Metab Clin North Am. 1998;27.

Bisphosphonates

- They have a high affinity for bone mineral,& therefore, they are typically retained in the skeleton for **several years**.
- Over the past decade, data suggest that these agents are safe in patients with an eGFR of 15-59 ml/min/1.73m^2.

Clin J Am Soc Neph. 2018;13(6): 962-060

Denosumab

- Is a monoclonal antibody that is directed against RANK ligand & inhibits osteoclast proliferation & development.
- 60 mg/6 ms SQ.
- Is effective at reducing the fx risk & the efficacy is not influenced by the kidney function.
- This agent is liable to cause **hypocalcemia** in patients with an impaired renal function.

Inter Med. 2017;56

Denosumab

- Hypocalcemia induced by denosumab should be avoided by practicing appropriate precaution & preemptively administering **active vit D** to eligible CKD patients before starting denosumab.
- The serum Ca levels usually reach their nadir around **7 days** after administration, with a less-extensive Ca decrease with the second denosumab administration.

Inter Med. 2017;56

Teriparatide (rhPTH)

- 20 µg/day SQ for 18-24 ms.
- 20 µg/week in dialysis patients.
- Potential for serum **Ca elevation**.

Inter Med. 2017;56

Abaloparatide

- Is an analog of **PTHrp.**
- Is more purely anabolic with approximately **50%** lower risk of hypercalcemia.

Clin J Am Soc Neph. 2018;13(6): 962-060

Selective Estrogen Receptor Modulators

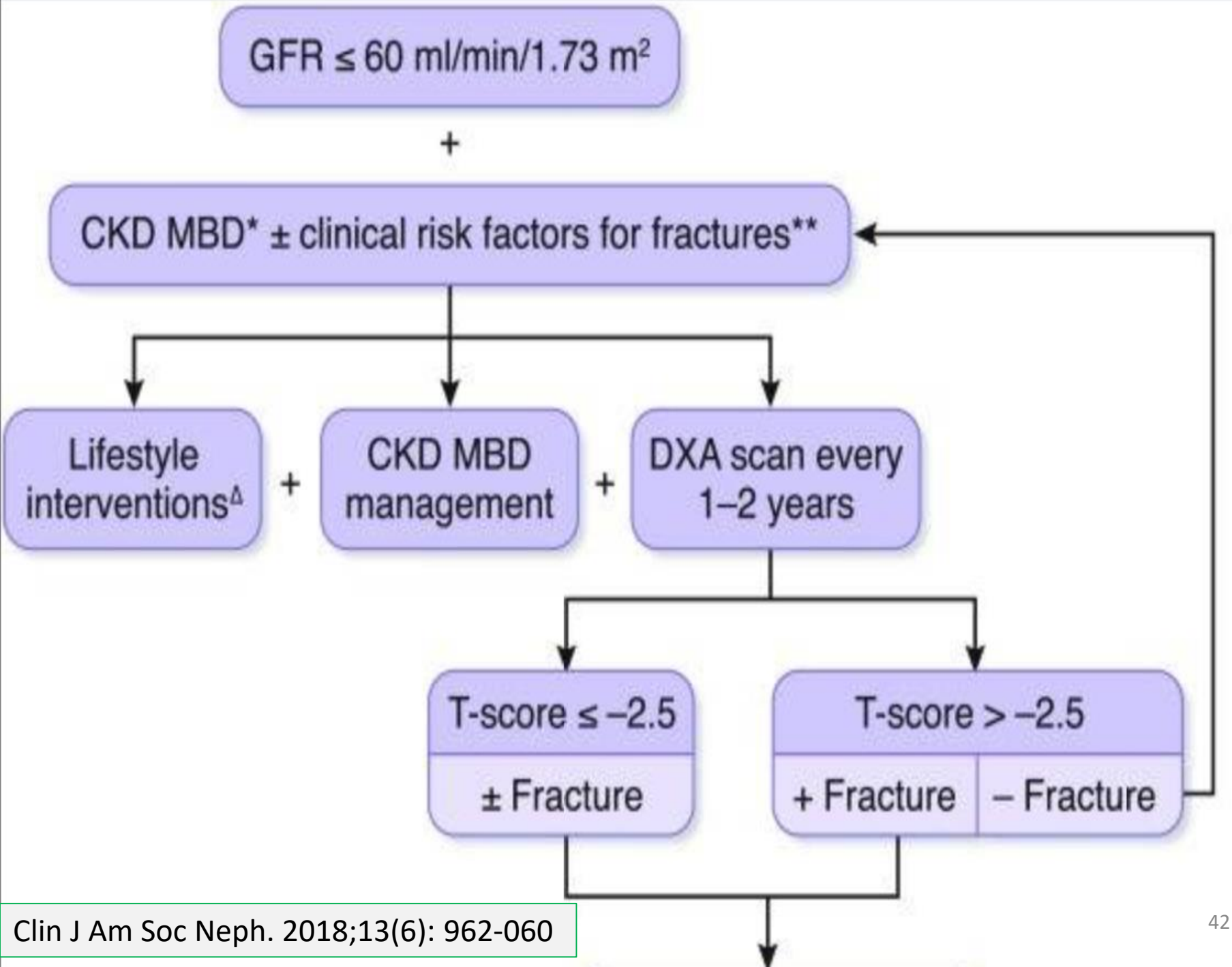
- Raloxifen 60 mg/day
- Estrogen agonist on bone & antagonist effects on breast & uterus

Inter Med. 2017;56

Selective Estrogen Receptor Modulators

- SERMs must be administered with caution, since prolongation of the plasma elimination half-life has been reported in patients with CKD.
- SERMS are contraindicated in the patients who have or once had **venous thrombosis** as CKD patients, especially nephrotic patients who may suffer from coexisting venous thrombosis.

Inter Med. 2017;56



Clin J Am Soc Neph. 2018;13(6): 962-060

Clin J Am Soc Neph. 2018;13(6): 962-060