Diagnosis and management of osteoporosis in chronic kidney disease stages 4 to 5D

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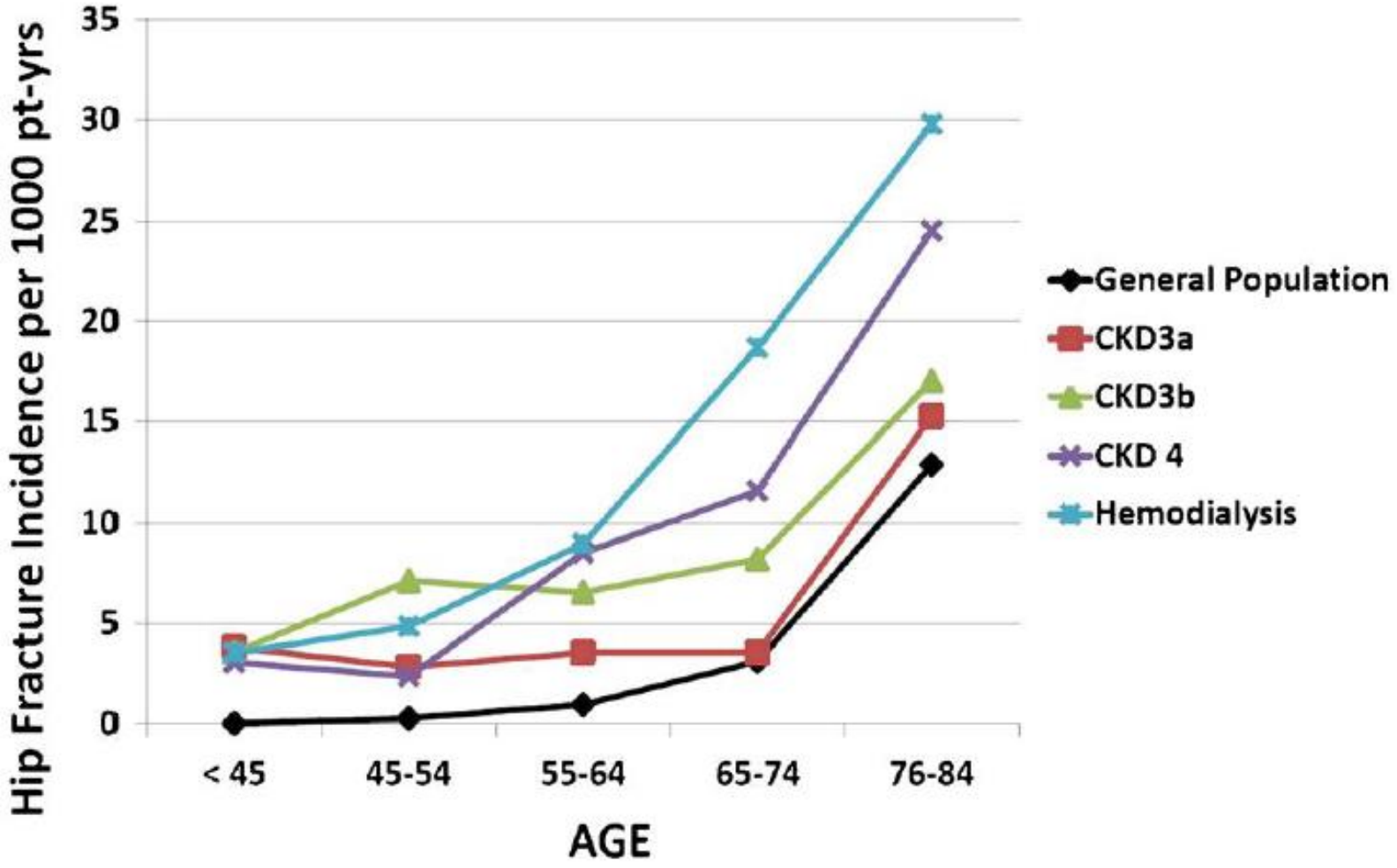
Disturbances in mineral and bone metabolism occur early in the course of CKD, to become almost universal in patients with advanced disease

CKD–mineral and bone disorder (CKD-MBD)

- Clinical syndrome that develops as a systemic disorder in CKD
- Manifested by abnormalities in bone and mineral metabolism and/or extra-skeletal calcifications
- Associates with fractures
- Cardiovascular morbidity and mortality



McNerny EMB, Nickolas TL. Curr Osteoporos Rep 2017;15:207–13.

Osteoporosis is a condition characterized by

- Low bone mass
- Qualitative bone deterioration
- Bone fragility and fracture susceptibility

A huge treatment gap exists between those at risk of fracture and those receiving treatment for the prevention of fragility fractures

This treatment gap may be even wider in patients with CKD stages 4–5D

Diagnosis of osteoporosis

- The operational definition of osteoporosis is based on an areal bone mineral density (BMD) assessed by DXA at the spine or hip < −2.5 SD from the BMD in young female adults (T-score)

The diagnosis of osteoporosis in CKD stages 4–5D is often considered one of exclusion

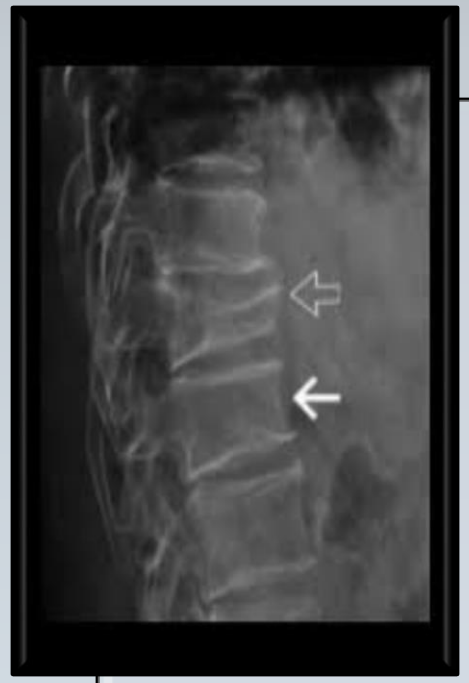
- Neither ROD nor CKD-MBD is the cause of low BMD or fragility fractures

We stand for an inclusive operational definition of osteoporosis according to the WHO, including patients with CKD 4–5D, in spite of the contributions of ROD/CKD-MBD to decrease bone strength in this population

Some doubts remain as to the consistency of the fracture risk prediction by DXA across stages of CKD and degree of PTH control

Clinical factor	CKD-MBD	Postmenopausal osteoporosis
PTH levels	Increased	Usually normal*
Alkaline phosphatase	Increased	Usually normal*
Bone mineral density	Weakly related to fracture risk	Predicts risk of fracture
Bone loss	Mostly in cortical bone	Trabecular and cortical bone
Bone formation rate	Either very low (in adynamic bone disease) or very high	Generally normal or slightly increased
Vascular calcification	Strongly associated	Weakly associated
Laboratory findings¶	Abnormal	Normal or mildly abnormal

Risk factors for fragility fractures



Clinical risk factors for osteoporosis in CKD patients comprise traditional risk factors

- Older age
- Female sex
- Low body mass index
- Fragility fracture history
- Glucocorticoid treatment
- CKD-specific risk factors such as long dialysis duration

BMD as assessed by DXA predicts fractures in patients with CKD stages 4–5D

However, DXA probably underestimates the actual fracture risk in patients with CKD 4– 5D

- It does not account for impaired bone quality

Bone fragility in CKD is a composite of primary osteoporosis and adverse skeletal effects of drugs, disturbances of calcium metabolism, and the uremic milieu itself

The association of bone turnover markers (BTMs) with fracture risk, overall, is inconsistent

JOURNAL ARTICLE EDITOR'S CHOICE

A higher serum alkaline phosphatase is associated with the incidence of hip fracture and mortality among patients receiving hemodialysis in Japan

Get access ›

Yukio Maruyama ✉, Masatomo Taniguchi, Junichiro J. Kazama, Keitaro Yokoyama, Tatsuo Hosoya, Takashi Yokoo, Takashi Shigematsu, Kunitoshi Iseki, Yoshiharu Tsubakihara

Nephrology Dialysis Transplantation, Volume 29, Issue 8, August 2014, Pages 1532–1538,

JOURNAL ARTICLE

Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients—a single-center cohort study Get access ›

Soichiro Iimori, Yoshihiro Mori, Wataru Akita, Tamaki Kuyama, Shigeru Takada, Tomoki Asai, Michio Kuwahara, Sei Sasaki, Yusuke Tsukamoto

Nephrology Dialysis Transplantation, Volume 27, Issue 1, January 2012, Pages 345–351,

Bone-specific ALP (BALP) outperformed DXA in fracture risk prediction

In clinical practice, the marker that has the most value in discriminating bone turnover in CKD is BSAP

PTH levels shows relationship with fracture risk in CKD stage 5D with both very high and low levels conferring an increased fracture risk

Assessment of fracture risk

In patients with CKD stages 4–5D, DXA may be considered in postmenopausal women, or men > 50 years of age

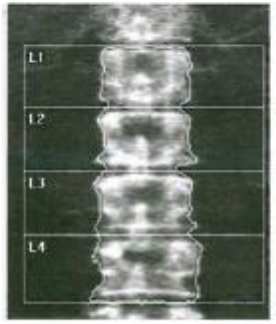
- Routine DXA testing (screening) in all CKD 4–5D patients is not supported by current evidence

The hip and the lumbar spine are the primary skeletal sites to evaluate BMD by DXA

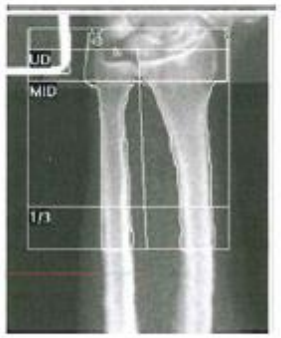
- The forearm may be included in the DXA evaluation skeletal site panel

Trabecular bone score and alternative imaging techniques need further clinical evaluation prior to clinical implementation

Sources of Bias



- Aortic calcification
- Scoliosis
- Hypertrophic degenerative disease
- Compression fractures
- Calcium, barium, or lanthanum within the gastrointestinal tract
- Renal lithiasis
- Focal sclerotic bone lesions

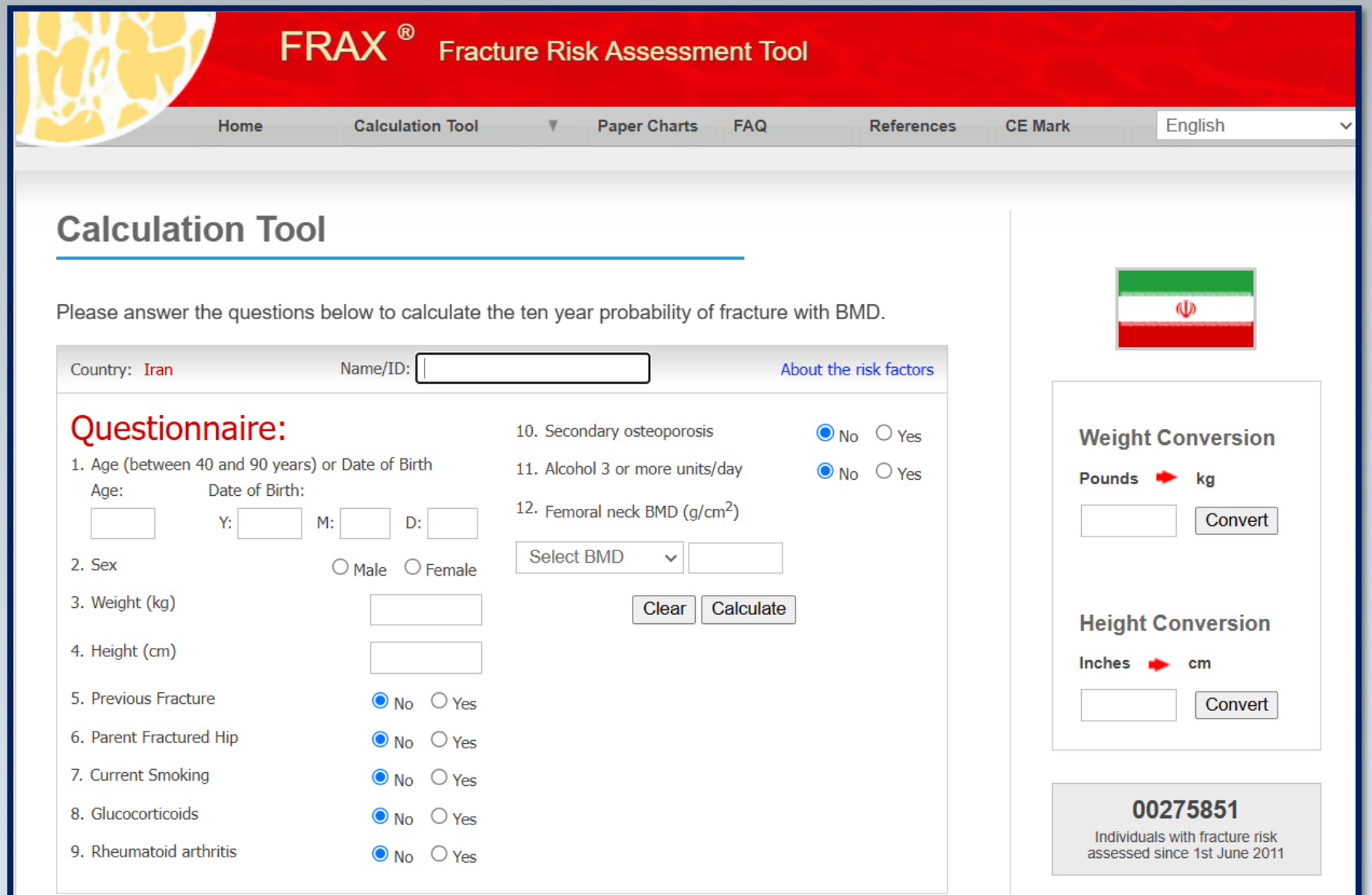


- AV fistula

Vertebral fracture assessment (VFA), and/or lateral spine imaging, is recommended

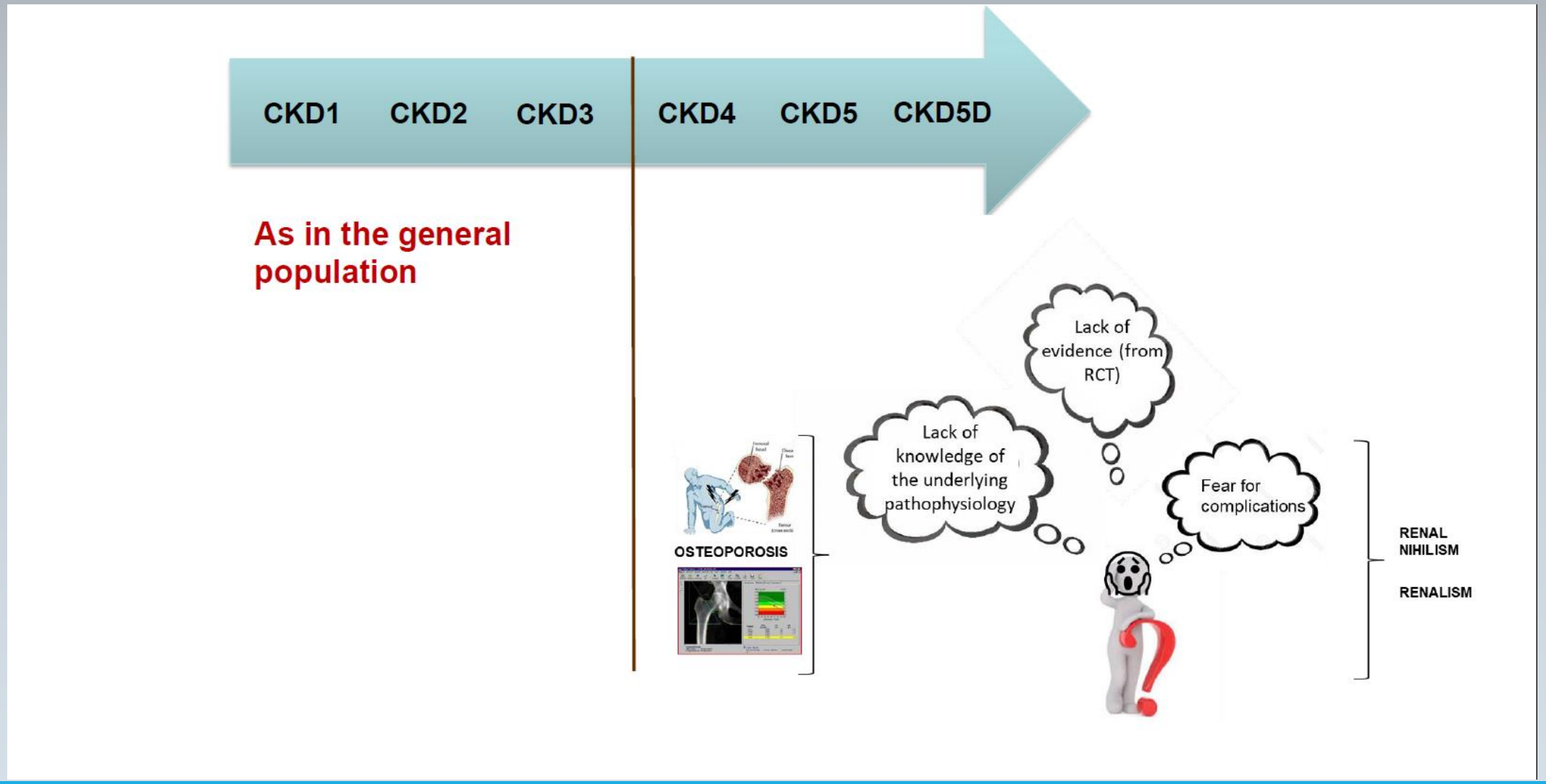
- All patients undergoing DXA evaluation
- Patients with a history of ≥ 4 cm height loss
- Kyphosis
- Recent or current long-term oral glucocorticoid therapy

FRAX® predicts fracture probability in all CKD stages



10 years Probability of major osteoporotic fracture > 20% or hip > 3%

Management


CKD1
CKD2
CKD3
CKD4
CKD5
CKD5D
As in the general population
OSTEOPOROSIS
Lack of evidence (from RCT)
Lack of knowledge of the underlying pathophysiology
Fear for complications
RENAL NIHILISM
RENALISM

Intervention thresholds for pharmacological intervention

CKD patients > 50 years of age with a prior fragility fracture (major osteoporotic fracture [MOF]) may be considered for treatment without the need for further BMD assessment

In the absence of a MOF, a DXA T-score threshold < −2.5 SD at the lumbar spine or hip is recommended

- Recognizing a higher threshold of −2.0 or −1.5 may be more appropriate

FRAX® country-specific intervention thresholds are appropriate in CKD patients

Non-pharmacological intervention

Since patients with CKD are at risk of negative calcium balance and low vitamin D stores, it is advocated to assess daily calcium intake and circulating 25(OH)D levels

- Supplementation of calcium (preferentially through diet) should be considered
  - Calcium intake below 800 mg/day
  - Vit D levels below 30 ng/dL
  - Total exogenous elemental calcium input should not exceed 1200 mg per day to avoid accelerated vascular calcification

Regular weight-bearing exercise should be advised

CKD patients have an increased falls risk

Foods and drinks with calcium

Food	Calcium in milligrams
Milk (skim, 2%, or whole; 8 oz [240 mL])	300
Yogurt (6 oz [168 g])	250
Orange juice (with calcium; 8 oz [240 mL])	300
Tofu with calcium (0.5 cup [113 g])	435
Cheese (1 oz [28 g])	195 to 335 (hard cheese = higher calcium)
Cottage cheese (0.5 cup [113 g])	130
Ice cream or frozen yogurt (0.5 cup [113 g])	100
Fortified non-dairy milks (soy, oat, almond; 8 oz [240 mL])	300 to 450
Beans (0.5 cup cooked [113 g])	60 to 80
Dark, leafy green vegetables (0.5 cup cooked [113 g])	50 to 135
Almonds (24 whole)	70
Orange (1 medium)	60

Pharmacological intervention

Prior to initiating anti-osteoporosis drugs

- CKD-MBD therapy should be optimized and metabolic disturbances known to harm bone, such as metabolic acidosis, should be well controlled

guideline summary www.kidney-international.org

Executive summary of the 2017 KDIGO Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters

CrossMark

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Markus Ketteler[1], Geoffrey A. Block[2], Pieter Evenepoel[3], Masafumi Fukagawa[4], Charles A. Herzog[5], Linda McCann[6], Sharon M. Moe[7,8], Rukshana Shroff[9], Marcello A. Tonelli[10], Nigel D. Toussaint[11], Marc G. Vervloet[12] and Mary B. Leonard[13]

Antiresorptive agents (bisphosphonates and denosumab) are first-line therapy in patients with postmenopausal and primary male osteoporosis

These drugs have similar efficacy, improving BMD and reducing fracture rates, in subjects with CKD up to stage 4

Data in advanced CKD is scarce, limited by small sample sizes, and yielded inconsistent findings

JOURNAL ARTICLE

Effects of Denosumab and Alendronate on Bone Health and Vascular Function in Hemodialysis Patients: A Randomized, Controlled Trial

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Ken Iseri, Makoto Watanabe, Hisako Yoshikawa, Hisao Mitsui, Teruhiko Endo, Yuichiro Yamamoto, Masayuki Iyoda, Kakei Ryu, Taro Inaba, Takanori Shibata

Journal of Bone and Mineral Research, Volume 34, Issue 6, 1 June 2019, Pages 1014–1024,
https://doi.org/10.1002/jbmr.3676

Published: 28 January 2019 **Article history** ▾

Beware for severe hypocalcemia when using denosumab

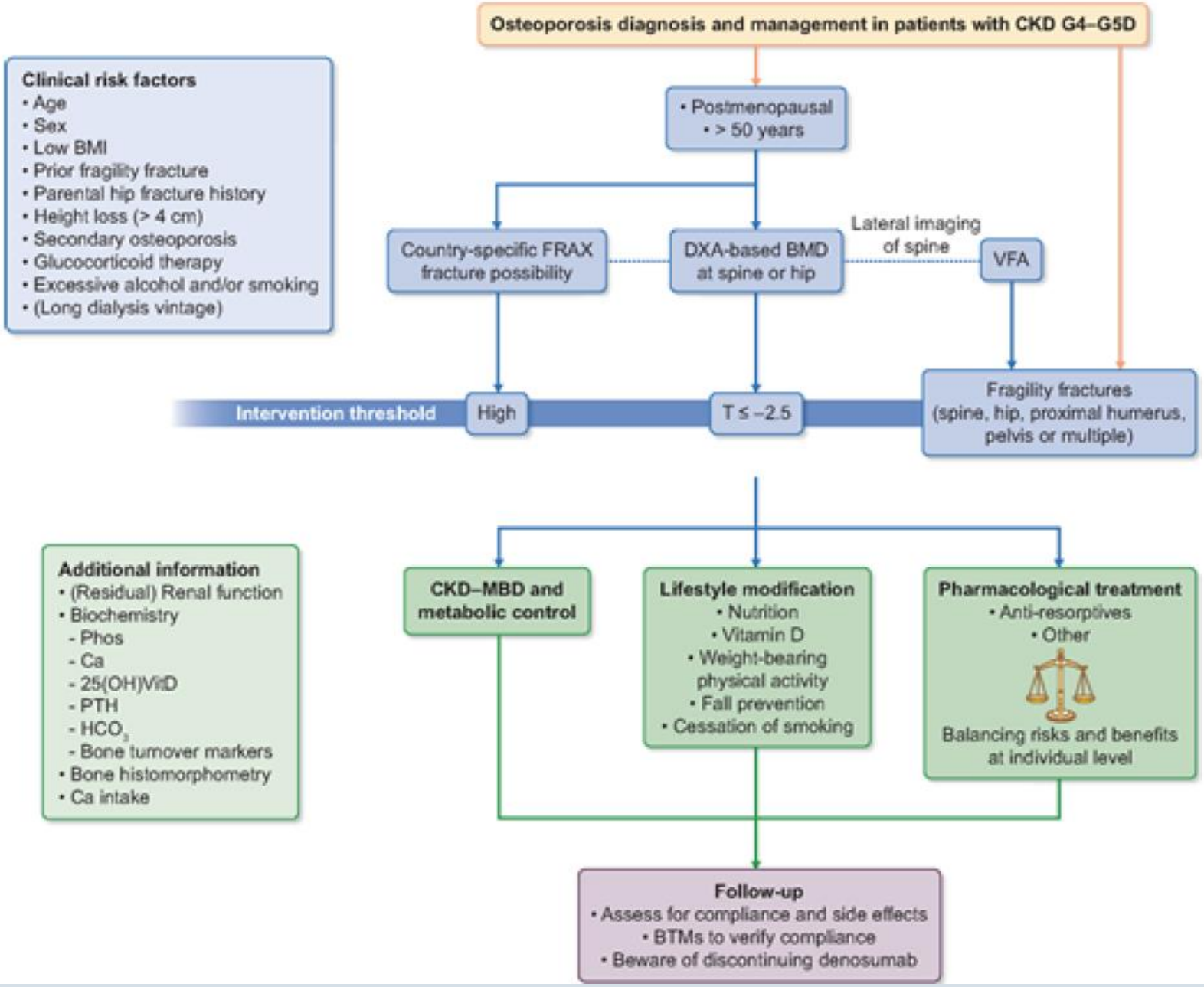
Denosumab and alendronate treatment improved LSBMD, reduced BTM, and appeared to be safe in hemodialysis patients with osteoporosis

Withdrawal of denosumab therapy is associated with a 30% increase in vertebral fractures in postmenopausal women

Denosumab must either be administered continuously or followed by another antiresorptive therapy

Acknowledging that low bone turnover is highly prevalent among patients with CKD stages 4 – 5D, anabolic agents could be considered promising

- Efficacy data are very poor (PTH-analogs)
- Data is Non-existing (romosozumab)


Osteoporosis diagnosis and management in patients with CKD G4–G5D
Clinical risk factors
• Age
• Sex
• Low BMI
• Prior fragility fracture
• Parental hip fracture history
• Height loss (> 4 cm)
• Secondary osteoporosis
• Glucocorticoid therapy
• Excessive alcohol and/or smoking
• (Long dialysis vintage)
• Postmenopausal
• > 50 years
Country-specific FRAX fracture possibility
DXA-based BMD at spine or hip
Lateral imaging of spine
VFA
Intervention threshold
High
T ≤ –2.5
Fragility fractures (spine, hip, proximal humerus, pelvis or multiple)
Additional information
• (Residual) Renal function
• Biochemistry
- Phos
- Ca
- 25(OH)VitD
- PTH
- HCO3
- Bone turnover markers
• Bone histomorphometry
• Ca intake
CKD–MBD and metabolic control
Lifestyle modification
• Nutrition
• Vitamin D
• Weight-bearing physical activity
• Fall prevention
• Cessation of smoking
Pharmacological treatment
• Anti-resorptives
• Other
Balancing risks and benefits at individual level
Follow-up
• Assess for compliance and side effects
• BTMs to verify compliance
• Beware of discontinuing denosumab

Monitoring

Early monitoring of BTMs informs on the therapeutic response

- Non-kidney-retained bone turnover markers (BALP,trimeric P1NP, TRAP5b) are preferentially used in the setting of CKD, especially in patients with non-stable kidney function

The measurement of BTMs after withdrawal of osteoporosis therapy is potentially useful to evaluate offset of effect:

- An increase more than the LSC reflects loss of treatment effect and identifies patients that are likely to experience a decrease in BMD
- A major caveat is that BTMs are grossly elevated 2 days after a fracture and remain elevated for at least 12months

Repeat BMD informs on the long-term treatment effect

The time interval to when a treatment effect can be detected may vary depending on treatment modality and underlying type of ROD

Monitoring BMD in postmenopausal women during the first 3 years after starting treatment with a potent bisphosphonate was unnecessary and could be misleading