MANAGEMENT OF OSTEOPOROSIS IN PATIENTS WITH CKD : A DIAGNOSTIC AND TREATMENT CHALLENGE

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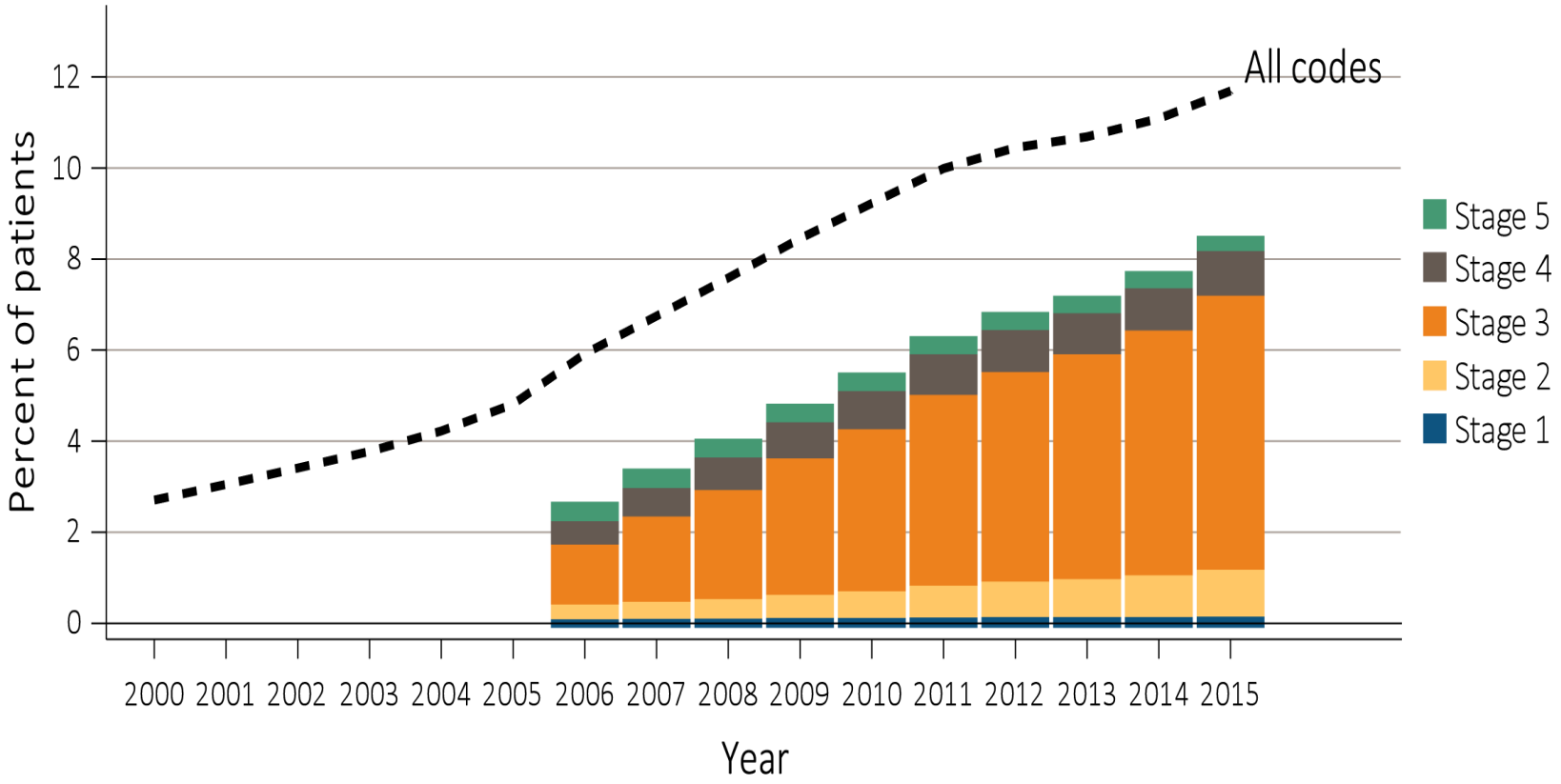
SPED Semiannual Meeting

Outline

- Background
- Epidemiology of skeletal fractures in CKD
- Assessment of Fracture Risk in CKD-MBD
- Management
- Summary- Key Concepts

The Medicare population with CKD is growing; more are identified earlier



Reference: USRDS Annual Data Report (NIDDK, 2017)

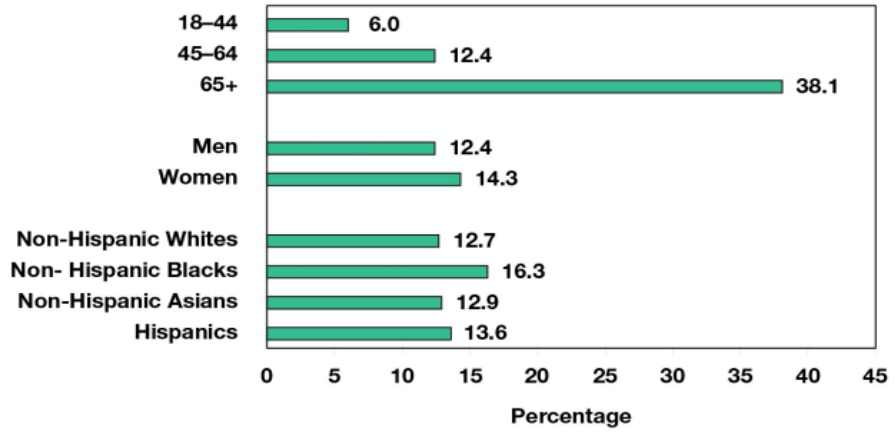
CKD by Age, Sex, and Race/Ethnicity

CKD by Age, Sex, and Race/Ethnicity

According to current estimates:*

- CKD is more common in people aged 65 years or older (38%) than in people aged 45–64 years (12%) or 18–44 years (6%).
- CKD is slightly more common in women (14%) than men (12%).
- CKD is more common in non-Hispanic Black adults (16%) than in non-Hispanic White adults (13%) or non-Hispanic Asian adults (13%).
- About 14% of Hispanic adults have CKD.

Percentage of US Adults Aged 18 Years or Older With CKD*



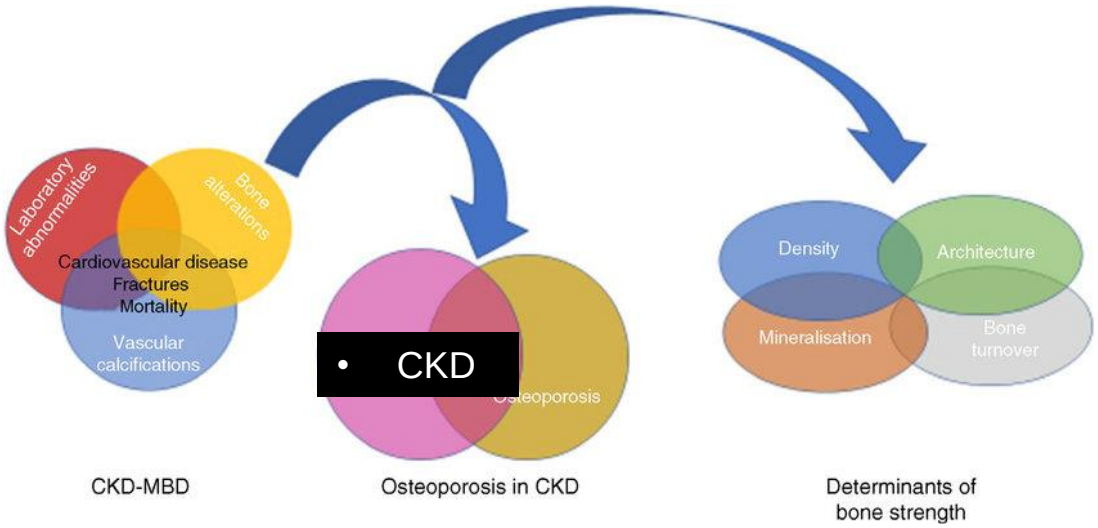
View Larger

Stage	GFR. (ml/min/1.73 m
1	90
2	60-89
3	30-59
4	15-29
5	<15

CDC

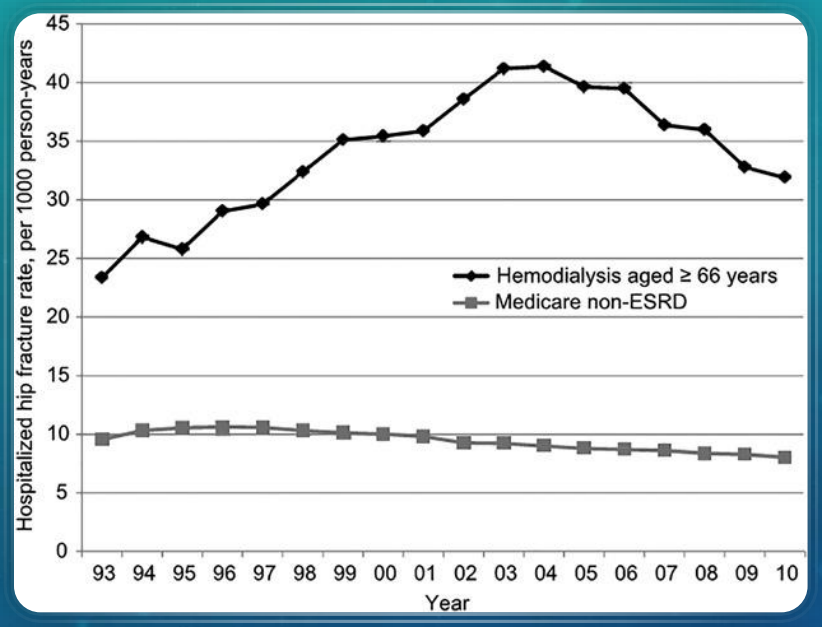
CKD-MBD and Bone disease

Clinical syndrome which is manifested by either one or a combination of:	CKD-MBD associated with
• Abnl. of ca, Phospate, PTH, Vit D metab • Abnl of bone turnover, mineralization, vol or strength • Vascular or soft tissue calcification	• fractures and • CV morbidity and mortalitymet



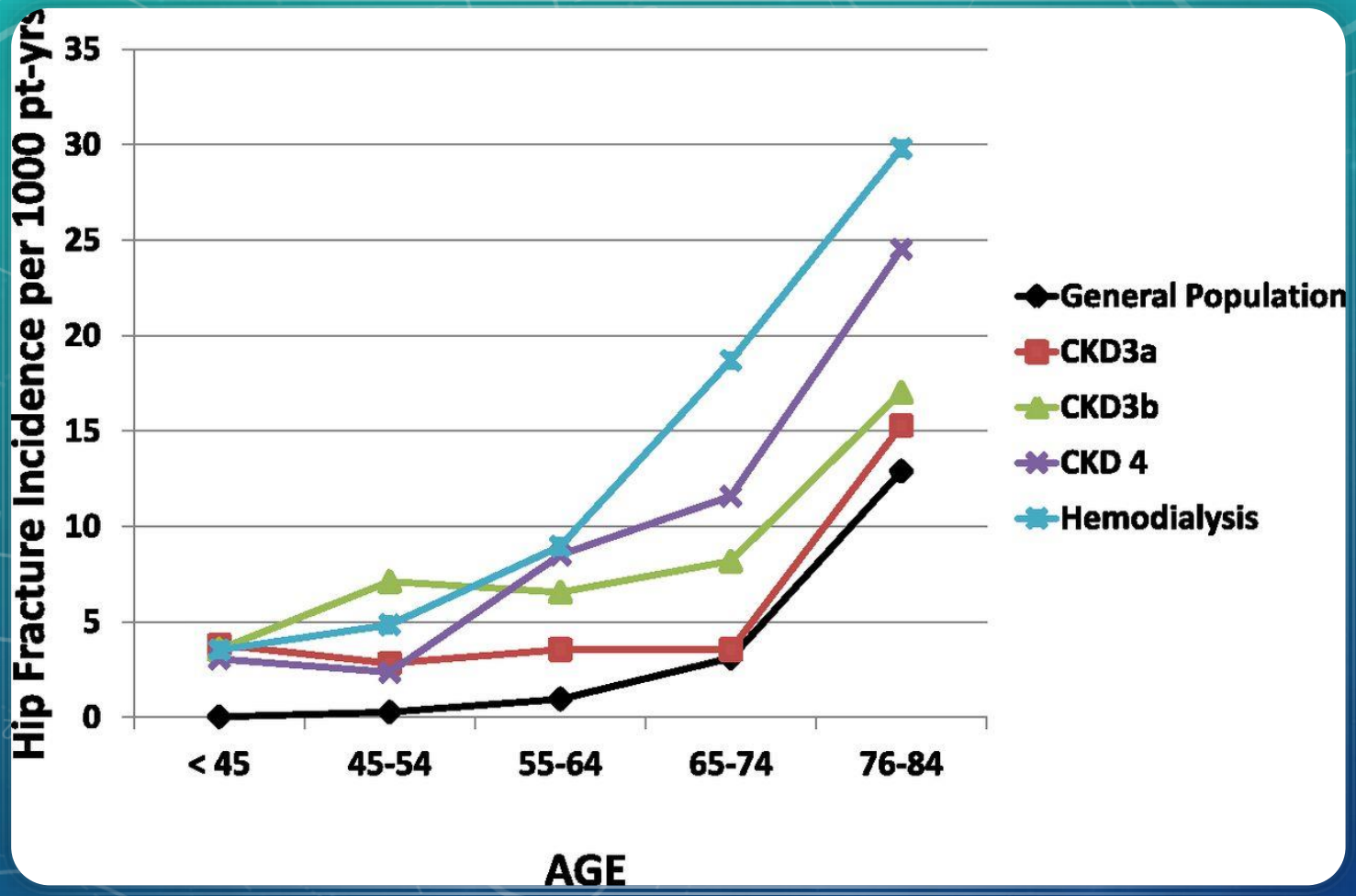
JBMR 2016;31:1803

FRACTURE EPIDEMIOLOGY IN CKD AND ESRD



- Fractures are very common in CKD and the prevalence progresses as renal function deteriorates
- Risk of skeletal fractures is up to 5x higher in pts with eGFR < 15 ml/min vs those with eGFR > 60 ml/min
- 4-fold higher incidence of fractures in pts. with HD.; as well as a 3.7x increased risk of death even after adjusting for age, gender, and ethnicity
- Fractures in CKD patients occur at an age 10-15 yrs.younger than in non-CKD pts.

Endocr conn2020;9:R93
JBMR 2018;6:302



Age Standardized rate of Hip fracture by Kidney Disease Category

JBMR : 31: 10: 1803-1809

General and CKD- Specific Risk Factors for Bone Loss and Fractures

General

- Non- modifiable
  - Age, sex, ethnicity, past hx of freacture, low BMI
- Modifiable
  - Smoking, alcohol
  - Medications
  - Diabetes mellitus
  - Sarcopenia
  - Chronic inflammatory disorders

CKD specific Factors

- HPT disordered mineral metabolism
- low vitamin D
- Chronic inflammation
- Metabolic acidosis
- Medications : steroids, Aluminum phosphate binders,Ppi etc
- Dietary restrictions
- FGF23
- Dkk1 inhibition of Wnt/b catenin
- Sclerostin

- Higher prevalence of General Risk Factors

JBMR 2018;2:309-22

Assessment of Fracture Risk

BMD as assessed by DXA

- Several recent longitudinal studies in pts across the spectrum of CKD and ESKD have demonstrated that low BMD at the hipand forearm do predict incident fractures

- VFA
- BTMs
- HR-pQCT
  - not currently practical beacause of cost and limited availability
- TBS is a parameter of bone quality related to bone microarchitecture and fx risk
  - TBS was developed to assess trabecular microarchitectureby using software analysis that measures grayscale homogeneneity from lumbar DXA images
  - Shown to predict fractures independently of clinical Rfs and areal BMD by DXA
  - Predicted higher fracture risk in pts with GFR < 60 ml/min
  - Additional confirmatory studies needed in pts. With CKD

Ndt 2021;36:42
JBMR 2018;2:309

FRAX PREDICTS FRACTURE IN CKD

- Ost Intl 2018

% fxs over 5 yrs	GFR >=60	GFR 30-60	GFR <30 ml/min
Observed MOF	7.5	9.0	10
Predicted MOF w BMD	5.0	7.0	6.4
Predicted MOF w/out BMD	5.7	7.9	7.0

ADJUSTED ASSOCIATION OF T-SCORES AT DIFFERENT SITES WITH INCIDENT FRACTURES IN CKD PATIENTS : REGINA STUDY

Assoc of T-score with incident fracture	OR of fracture /1 SD lower
TH T-score	1.47
FN. T-score	1.44
LS. T-score	1.22
Radius. T-score	1.04

•Can J Kidney Health and Disease Vol6:1-10,2019

ASSOCIATION OF FN BMD (PER SD DECREASE) WITH RISK OF FRACTURE

	HR (95% Confidence Interval)			
	overall	No CKD	CKD	P value for CKD BMD interaction
Unadjusted	2.42	2.45	2.32	0.72
Adjusted for age, race, sex and BMI	2.26	2.14	2.69	0.70
+ PTH ,vit D status	2.30	2.15	2.74	0.68

•Clin J Am Soc Nephrol 7:1130,2012

KDIGO 2017 Guidelines BMD

New 3.2.1: In patients with CKD G3a-G5D with evidence of CKD-MBD and/or risk factors for osteoporosis, we suggest bone mineral density (BMD) testing to assess fracture risk if results will impact treatment decisions *(2B).*

Old 3.2.2: In patients with CKD G3a–G5D with evidence of CKD-MBD, we suggest that BMD testing NOT be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (*2B*).

ESRD CKD STAGE 4-5D

Controlling the excessive fracture burden in pts. with CKD stages 4-5D remains an impressive challenge

The reasons are 2-fold

the pathophysiology of bone fragility is complex and multifaceted comprising a mixture of age-related, drug – induced,and CKD-related bone abnormalities

current armamentarium of osteoporosis medications has not been developed or, or adequately studied, in pts with CKD G4-G5D

NDT 2021;36:42-59

Bone Changes Associated with Hormonal and Metabolic Changes of ESRD

- **Decreased Bone Density**

Alterations in bone microarchitecture

- Cortical porosity
- Cortical thinning and trabeculation
- Trabecular thinning and dropout
- Disruption in balance and orientation of newly formed and mature bone

Decreased bone quality

- Mineralization (OM)
- **Abnormal remodeling**
  - Adynamic bone disease
  - Low turnover
  - High turnover
- Microdamage accumulation
  - Reduced resistance to impact
- AGEP cross-linking

JBMR 2018;2:309

Strategies to Evaluate Bone Fragility In CKD

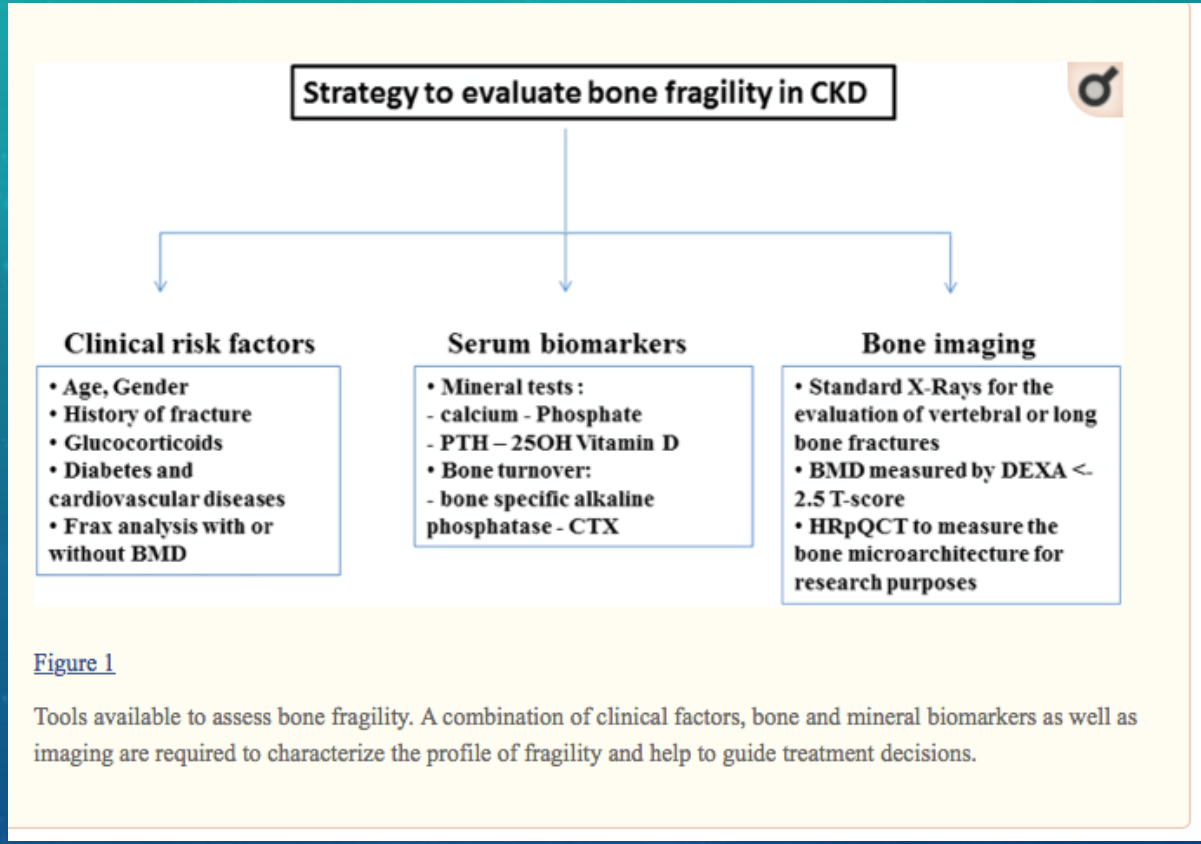


Figure 1

Tools available to assess bone fragility. A combination of clinical factors, bone and mineral biomarkers as well as imaging are required to characterize the profile of fragility and help to guide treatment decisions.

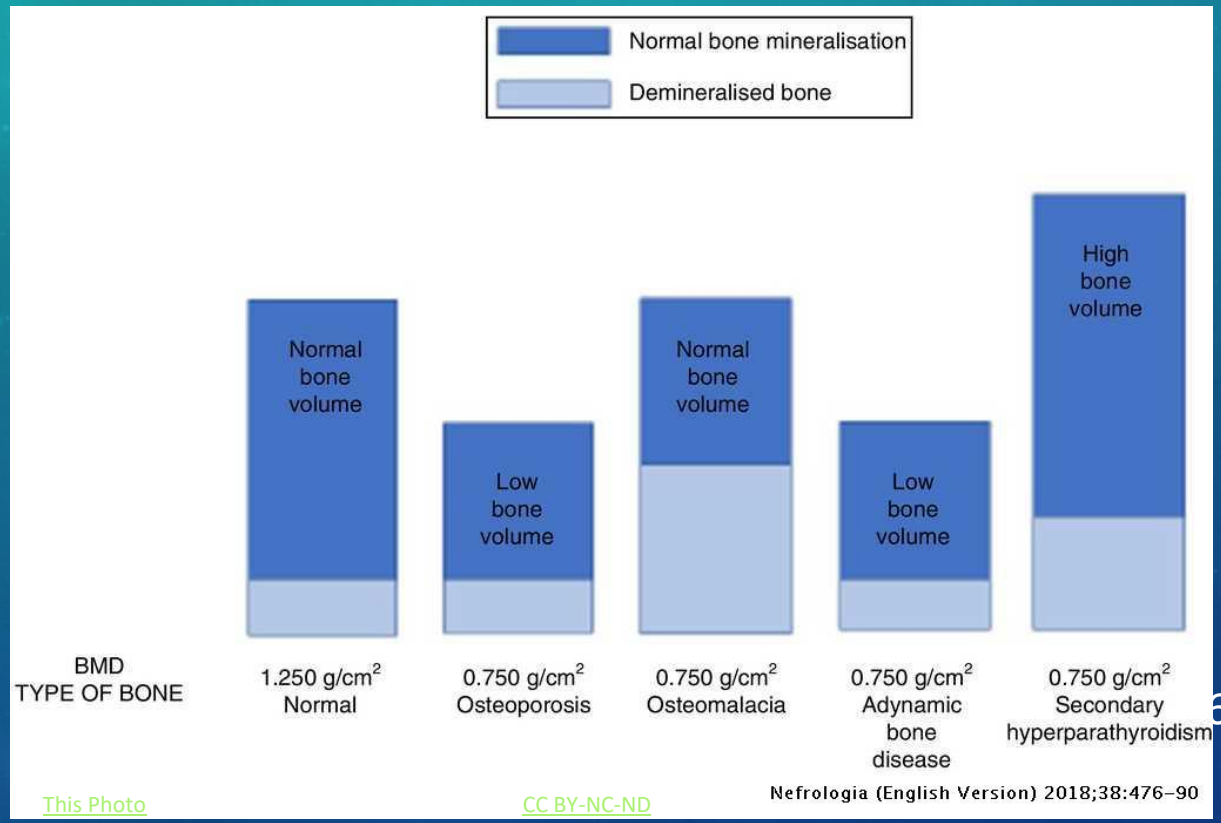
Endocrine connections R93-101,2020

BMD, Risk of Fracture, and CKD

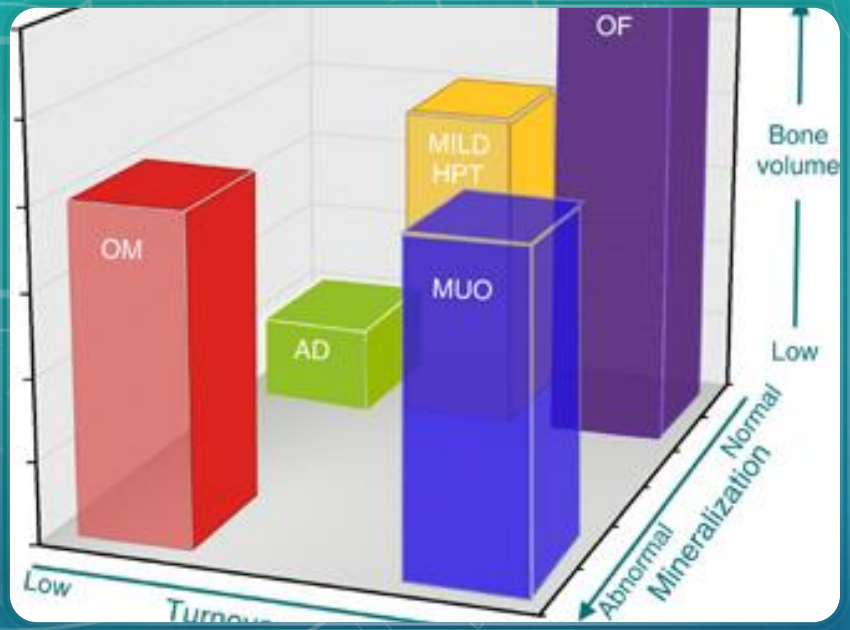
- 5 prospective cohort studies evaluating DXA and incidence of fractures in adults with CKD stages 3a-5D have confirmed the good predictive capacity. of BMD in patients with CKD
- Recent meta-analysis and systematic review of 13 studies in pts. with CKD (pre-dialysis and dialysis) showed that BMD was significantly lower in patients with fractures
- Altogether, low BMD is a risk factor for fracture but this might not be sufficient to initiate a bone-specific treatment as in non-CKD patients because of mineralization defects
- Important to consider that different forms of ROD can show a similar decrease in BMD in CKD pts.
- Patients with high turnover or low turnover ROD can show the same BMD as a classic “senile” OP profile

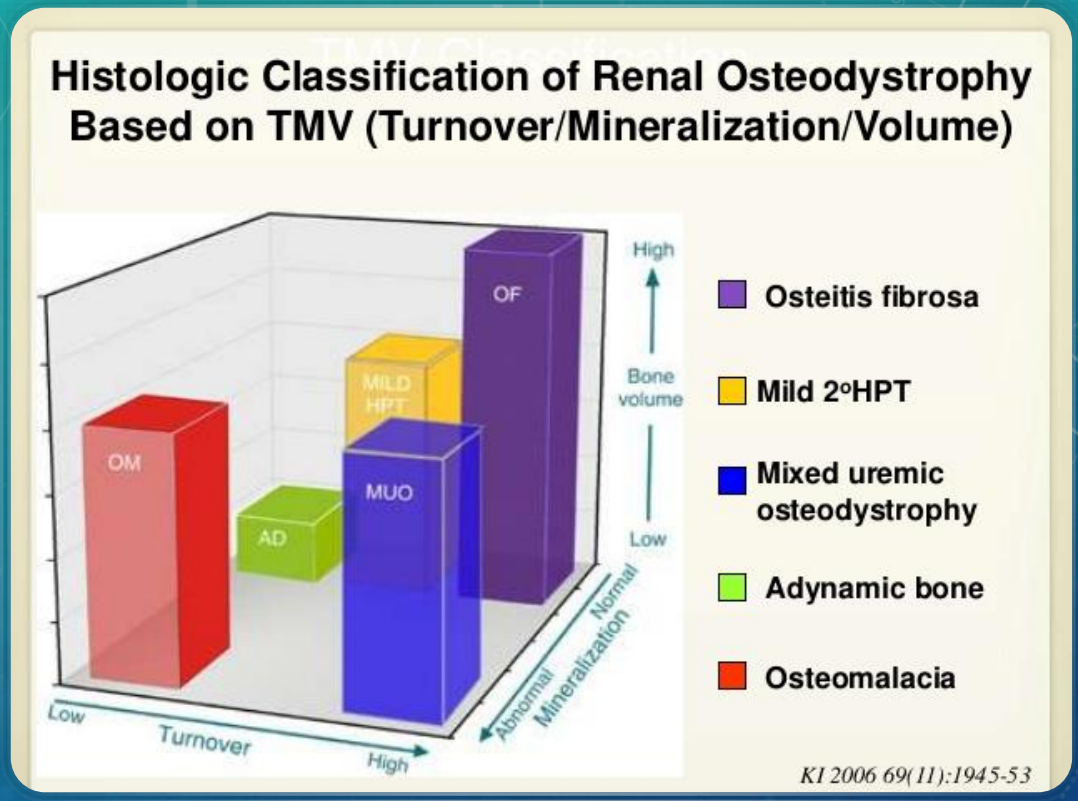
Nefrologia
2018;38:476

Bone Disease in ESRD
Different Pathologies can Show the Same low BMD



Nefrologia 2018;38:476





BONE DISEASE IN ESRD : TMV CLASSIFICATION

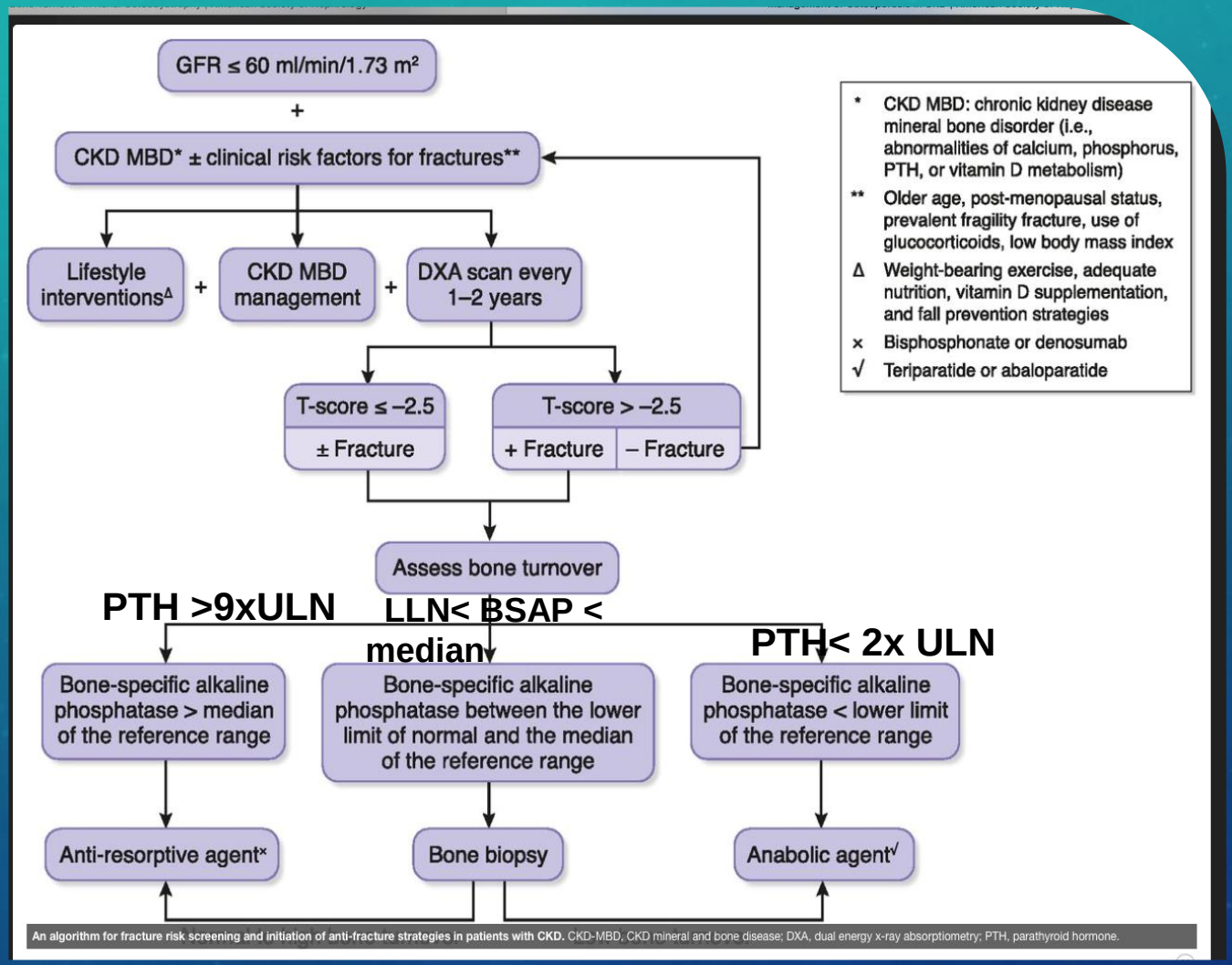
KI 2006; 69:1945

Biochemical Markers of Bone Turnover and Risk of Fracture

- In the absence of bone biobsy, intact PTH and BSAP are the best (although suboptimal) surrogate biomarkers for CKD histology studies
- BTMs are useful when they are at the extremes of their ranges
- At those extremes they can help distinguish between low and non-low turnover and high and non-high turnover bone disease
- Sensitivity and specificity of PTH levels in pts on dialysis is greater in the low range (associated with ABD) ie PTH < than 2x LLN or in the very high range (9xULN) where it is associated with 2ndary HPT
- Both low and high levels of PTH associated with a decrease in BMD and a high incidence of fractures

Curr osteoporos Rep 2018;16:712

Proposed Algorithm: KDIGO Guideline for Patients with CKD G3a-G5



GUIDELINE 3.2.3 AND 3.2.4

3.2.3: In patients with CKD G3a–G5D, we suggest that measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover *(2B).*

3.2.4: In patients with CKD G3a–G5D, we suggest not routinely measuring bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal propeptide) and breakdown (such as type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline) *(2C).*

TESTING FOR CKD-MBD

New 3.2.2: In patients with CKD G3a–G5D, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions *(Not Graded).*

Old 3.2.1: In patients with CKD G3a–G5D, it is reasonable to perform a bone biopsy in various settings including, but not limited to: unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and prior to therapy with bisphosphonates in patients with CKD-MBD (*Not Graded*).

Treatment of ROD and Preventing Fractures in CKD

- Ultimate goal of treating osteoporosis is to prevent fracture
- Until the release of the 2017 KDIGO guidelines , BMD testing in CKD3-5D was not routinely recommended
- There are no antifracture treatments specifically developed for pts. with CKD-MBD
- However, since emerging data and anecdotal experience with existing agents suggests that they are safe….
- CKD-MBD as a cause of fracture (2ndary HPT,ABD) or low BMD must be excluded prior to consideration of pharmacologic therapy

MANAGEMENT

- Before initiating an antiresorptive or anabolic agent to treat CKD-associated osteoporosis, we stress the importance of managing CKD-MBD through control of
  - hyperphosphatemia,
  - vit D deficiency and
  - Hyperparathyroidism

- Nonpharmacologic strategies :
  - Lifestyle intervention
  - Calcium and vit D supplementation
  - Smoking cessation
  - Weight-bearing exercises
  - Fall prevention
  - improved nutrition
  - Moderating alcohol intake

Clin J am soc nephrol2018;13:962

ANABOLIC AGENTS

- Teriparatide
  - Similar BMD and fracture efficacy in subjects with GFR 50-79 ml/min when compared to non-CKD patients
  - Post hoc analysis of the FPT , teriparatide had improvement in BMD and safety in pts. with GFR as low as 30 ml/min
  - However, sample size was limited and only enabled exam of fx efficacy in subjects with GFR < 80 ml/min or > 80 ml/min
  - In all clinical trials pts with elevated bl PTH were excuded ; thus no clinical trial data examining pts with evidence of CKD MBD
  - Hypercalcemia , hyperuricemia > common
  - Improved LS BMD in adynamic bone disease
  - ABD associated with elevated serum sclerostin
  - PTH inhibits sclerostin binding to osteoclasts

Abaloparatide

  - No data in CKD

- Romosozumab
  - No data in CKD
  - Potential concern for use based on MI/CVA risk and gigher CV risk in CKD

MANAGEMENT

- 4.3.1In patients with CKD G1-G2 with osteoporosis and/or high risk of fracture as identified by WHO criteria, we recommend management as for the general population
- 4.3.2 In patients with CKD G3a-G3b **with PTH in the nl. range** and OP and/or high fracture risk ,as identified by WHO criteria ,we suggest Rx as the general population
- 4.3.3 In pts. With CKD G3a- G5d. **With biochemical abnl.of CKD-BMD** and low BMD and/or fragility fractures , we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnl. and the progression of CKD,

MANAGEMENT

- Decision about specific anti-osteoporotic Rx. in CKD pts. should take several factors into account.the indication of these agents in CKD 4-5 is OFF label
- Recent systematic review, updating evidence on the efficacy and safety of common OP medications (BP,RLX, denosumab, teriparatide) concluded that effects on BMD, fracture risk, and safety are not clearly established among CKD pts.
- **That being said, the absence of evidence doesn’t equate to evidence of an absence of effect**
- Specific treatment should be initiated, particularly in pts. with a low trauma fracture in which OM and ABD have been r/o
- Decision should be based by consensus of both the specialist and educated patient
- Antiresorptive Rx can be considered in pts with high bone turnover disease

Ann Intern Med 2017;166:649
Ndt 2021; 36:42

Treatment of Bone with Bisphosphonates, other Osteoporosis Medications

Antiresorptive agents Bisphosphonates

- There are no primary safety and efficacy data on the use of antiresorptives in pts with CKD-MBD
- Retrospective analysis of the FIT data and pooled data from 9 risedronate studies revealed that 7-10.% had renal impairment (GFR <30-45); 37-45% had moderate impairment (eGFR >= 30-59)
- FIT creat >1.27 & PTH .>85 pg/ml were excluded; inadequate data on fracture prevention in those with > severe CKD
- Therefore, there are inadequate data with regard to fracture prevention in those with > severe CKD –MBD
- CKD 3-5D with evidence of MBD further evaluation of the ROD type is needed pre RX
- Recent post hoc analysis of 3 Japanese RCTs compared risedronate to placebo analyzed according to GFR
    - BMD and inhibition of BTM didn't differ in GFR subgroups

JBMR Plus 2018;2:309-322

DENOSUMAB

- Monoclonal antibody vs RANKL
- Not cleared by the kidney; therefore no restriction of its use in pts. with eGFR < 35 ml/min
- However, pts with CKD, GFR < 30ml/min, are at higher risk for hypocalcemia)
- post hoc analysis of FREEDOM trial (GFR cutoff used < 30 ml/min for exclusion)
  - Denosumab was effective in reducing fracture risk among women with GFR >=30 ml/min
  - Treatment effect was compared across CKD stages
  - Similar treatment efficacy (BMD and fracture reduction) and safety profile in women with GFR >= 30 ml/min(post hoc analysis)
  - Inadequate data with regard to fracture prevention efficacy in those with > severe kidney disease resulting in 2ndary HPT and in late stage renal disease
- Rapid OFF effects and potential risk for BMD loss and V Fxs as in non-CKD pts likely

JBMR Plus 2018;2:309-322

Clinical Case #1

- 70 y/o female with hx of HTN and CKD referred for consideration of OP Rx
- Hx of Colles fracture at age 60 .No other history of fracture
- No significant ht loss or morphometric VFx
- Hip fx in mother at age 75
- Labs ca 9.2,P 3,8,PTH 92 creat 1.6, 25 OHD 19 ng/ml e GFR 30 ml/min
- BMD T-score: spine -1.3, FN -2.3, prox 1/3 radius -2.6
- FRAX hip 4.8%,MOF 26%

CALCITRIOL AND VITAMIN D

New 4.2.1: In patients with CKD G3a–G5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency *(2C).* **New 4.2.2**: In adult patients with CKD G3a–G5 not on dialysis, we suggest calcitriol and vitamin D analogs not be routinely used *(2C).* It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD G4–G5 with severe and progressive hyperparathyroidism *(Not Graded).*

BP therapy in Stage 4 CKD : informed opinion

- Consideration of reduced dose alendronate (35 mg weekl;y or 70 mg q 2 wks)
  - Likely adjusts for reduced renal excretion
  - Antifracture efficacy is based on lower dose in registration trials (5 mg /d for 2 yrs and 10 mg/d for 1 yr)
  - Treatment dose risedronate based on available data
  - Hold Tx below GFR 20ml/min (evidence free-zone)
  - Lack of evidence that BP po cause renal harm
  - Attention to 25 OHD and PTH status

Conclusions

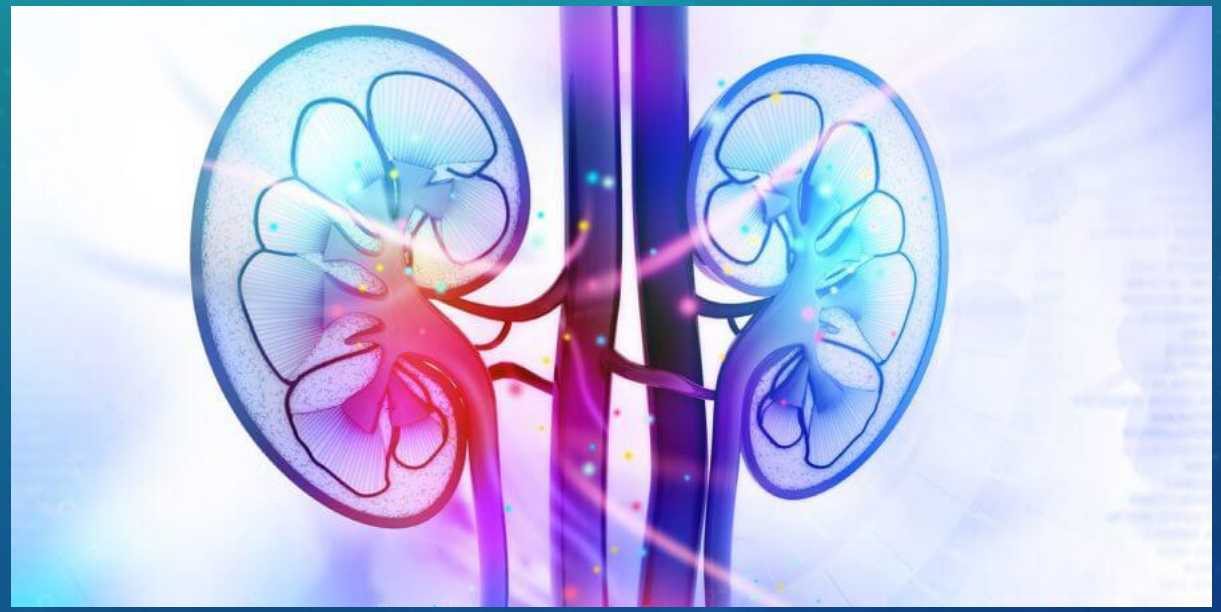
In view of complexities, multidisciplinary approach recommended

Patients with CKD have a higher risk of fractures than general population. Non-vertebral fractures are > common

Loss of BMD determines not only a high risk of fracture but also a significant increase in associated morbidity and mortality

2017 KDIGO suggests using BMD to assess the risk of fracture in pts. with CKD 3a-5D with evidence of CKD-MBD and/orOP risk factors , if the result can impact therapeutic decisions

Pharmacologic agents that are directed at the CKD population is of paramount importance



Choice of Drugs

- GFR >= 30 ml/min
  - If there is no evidence of CKD-MBD pharmacologic options for the treatment of osteoporosis don't differ from pts. w/out CKD
  - Efficacy is similar in these pts group as evidenced by clinical trials and
  - cohort groups which included subsets of pts. who had similar degrees of renal impairment

- GFR <30ml/min High risk or fracturing pts. With G_4: ,G_5 , or G_5D : **Few Data**
  - Post hoc analysis of trials in women with OP and G4 CKD showed efficacy
  - Some would agree to use of BP but modifying dosing interval : risedronate every other week and not > than 3 yrs
  - Denosumab Limited clinical experience in CKD :
    - In CKD 5D associated with clinically signicant hypocalcemia

Management of Osteoporosis in CKD

No Fragility Fracture

- GFR < 30 ml/min,low BMD (G4-G5)
  - KDIGO suggests no treatment with OP therapy
  - If + CKD MBD : management and monitoring of 2ndary HPT and mineral metabolism is necessary
- GFR < 30 ml/min
  - DXA alone shouldn't be used for FX risk assessment
  - Few data that show BMD predicts fracture in pts. With G4 or G5 CKD

Hx of Fragility Fracture

- GFR < 30ml/min (G4-G5)
  - Only patients with no evidence of RO on biochemical testing or bone biobsy are candidate
  - Challenging clinical issue is how to manage the high-risk or fracturing patient with G4-G5D
- Without evidence of CKD-MBD
  - Choices: bisphosphonates, raloxifene, denosumab

Without Evidence Of CKD-MBD

- GFR 15-30 ml/mi (G4) Few Data
  - Without evidence of RO on biochemical testing or bone biobsy and+ fragility fracture KDIGO suggests pharmacologic Rx when it is clear that the risk of mortality from a recurrent fx ie hip is high
  - Controversial
  - If BPs are administered dosing interval and duration should be modified

Sensitivity and Specificity by DXA or QCT in Detecting Histologically determined Low Blood Vol.

Site and method	Sensitivity %	Specificity %
FN DXA	83	78
FN QCT	58	78
TH DXA	72	78
TH QCT	64	89
Spine DXA	47	78
Spine QCT	53	78
DXA any site	89	78
QCT any site	72	78

Clin. Nephrol vol 85:77-83,2016

CLINICAL CASE #2

- 72 y./o caucasian female with ESRD on HD
- Prior T7-8 compression fxs; L2 compression Fx 3 months ago
- Rt FN fracture with ground level fall 6 mos. Ago
- No fam hx of hip fx
- Rx : calcium, ergocalciferol (50,000IU/mo), doxecalciferol,
- Labs Bun32/creat 4.7, ca/Ph 9.2/4.2,PTH 550 pg/ml, 25 OHD 35 ng/ml,BSAP increased
- DXA T-score spine +0.2, FN -1.1,TH -0.8, 1/3 radius -2.3

Candidates for Pharmacologic Treatment

- Assess general lifestyle measures
  - FRAX
  - Calcium and Vitamin D
  - Fall prevention
  - Sarcopenia
- Assess Fracture RiskBMD
  - Prior fragility fracture
  - Presence or absence of CKD-MBD : must be excluded as a cause of fracture or of low BMD prior to consideration of pharmacologic RX
- GFR >= 30 ml/min and neg CKD-MBD
  - Treat as for patients without cKD

GFR 15-30 ml/min and with Evidence of cKD-MBD

- Antiresorptive drugs should NOT be administered
- No evidence for the effectivenes of any antiresorptive RX to reduce fracture risk in this patient population
- Principal goal in this group to prevent or manage RO

Am J Med 2009;122:522
Bone 2011;49:77

Assessment of PTH

New 4.2.1: In patients with CKD G3a–G5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency *(2C).*

Old 4.2.1: In patients with CKD G3a–G5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency (*2C*).

It is reasonable to correct these abnormalities with any or all of the following: reducing dietary phosphate intake and administering phosphate binders, calcium supplements, and/or native vitamin D (*Not Graded*).

EFFICACY

- Few data evaluating fracture prevention efficacy and long -term adverse effects of pharmacologic therapy in pts. with dec. renal function
- In all OP pharmacologic clinical trials,pts with inc. baseline PTH levels were excluded
- Therefore, no clinical trials examining efficacy of pharmacotherapy in pts. With evidence of CKD-MBD

Proposed Algorithm for Treatment Decision in Patients with CKD and Fracture

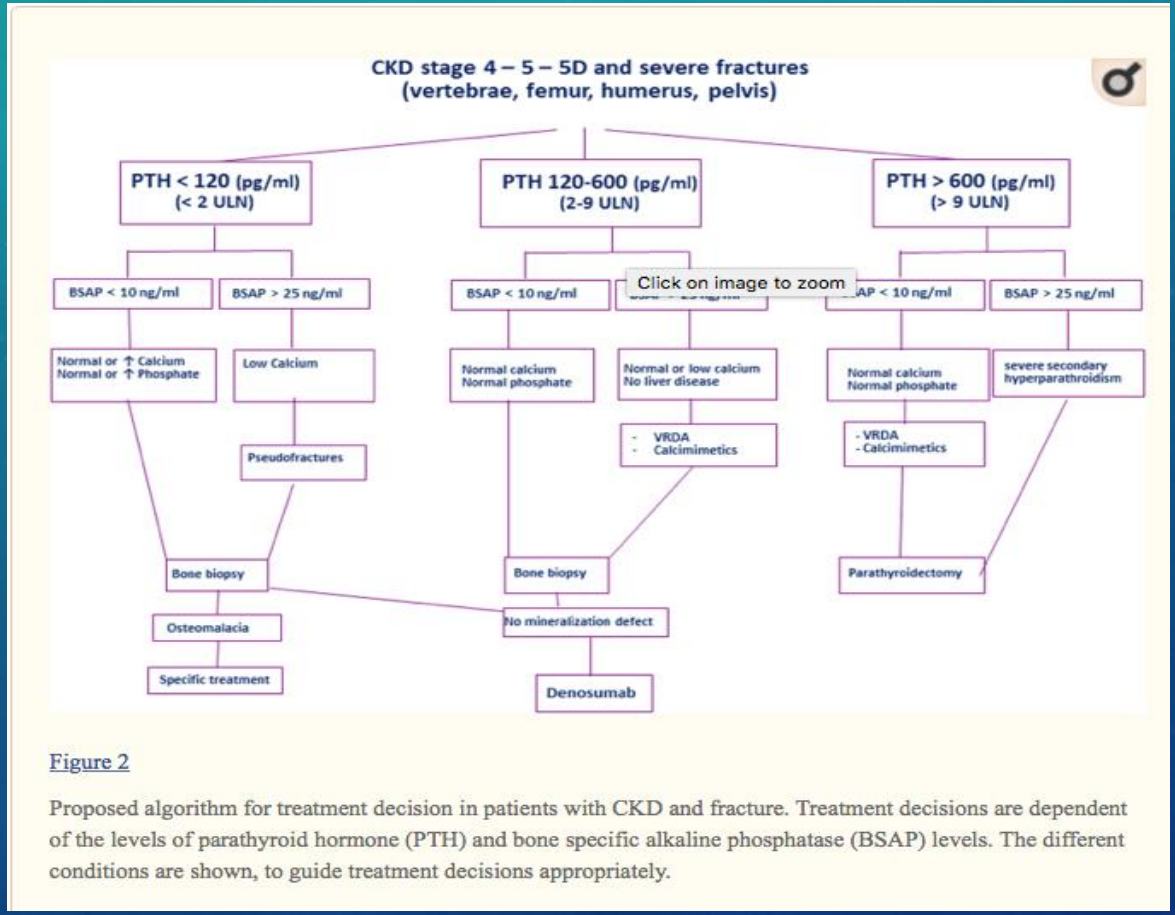


Figure 2

Proposed algorithm for treatment decision in patients with CKD and fracture. Treatment decisions are dependent of the levels of parathyroid hormone (PTH) and bone specific alkaline phosphatase (BSAP) levels. The different conditions are shown, to guide treatment decisions appropriately.

Testing for CKD-MBD

New 3.2.2: In patients with CKD G3a–G5D, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions *(Not Graded).*

Old 3.2.1: In patients with CKD G3a–G5D, it is reasonable to perform a bone biopsy in various settings including, but not limited to: unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and prior to therapy with bisphosphonates in patients with CKD-MBD (*Not Graded*).

KDIGO Definition of Renal Osteodystrophy

- An Alteration of bone morphology in pts. With CKD
- It is one measure of skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry assessed in bone biobsy

Bone Density and Fracture Risk Assessment tool

- Clinical relevance of FRAX in CKD remains unclear
- Different studies suggest that > research is needed to determine the usefulness of FRAX in CKD and ESRD.
- More specifically,some of the clinical factors included in current FRAX algorithms may not be relevant in these pts.and CKD-specific. fracture assessment tools need to be developed
- Predictors of fracture specific to kidney disease, for example, BSAP or PTH should be included

Curr Osteoporos Rep.2015;13:166

Management of Patients with CKD
Hx of fragility fractures

- GFR </= 15 ml/min
  - **No evidence of RO on bone biobsy ,no CKD-MBD**
  - KDIGO suggests pharmacologic therapy only when it is clear that risk of mortality from a recurrent fracture is high if untreated
  - Have a higher incidence of CKD-MB. Therefore, preferable to assess for RO with bone biobsy prior to considerin antiresorptive therapy.
  - However, if bone biobsy is not feasible AND :
    - BSAP is elevated and PTH level is > 350 pg/ml adynamic bone disease is unlikely
  - Rx ? If Bx shows no RO
  - Oral BPs risedronate 35 mg every other week
    - Risedronate 2.5 mg/d was as effective to decrease vertebral or hip fracture in 2 clinical trials

HISTOMORPHOMETRIC FINDINGS IN DIFFERENT METABOLIC BONE DISEASE

	turnover	**mineralozation**	**Bone vol**
OM	low	abnl	Low to nl
Adynamic bone disease	low	Nl/abnl	Low to nl
PTH b one disease	high	nl	L,NL,H
Mixed uremic osteodystrophy	Nl to high	abnl	Low to nl
osteoporosis	L,Nl,H	nl	Low

Acta rheumat 2018;43:201

Bone Changes Associated with Hormonal,metabolic End Stage Kidney Disease

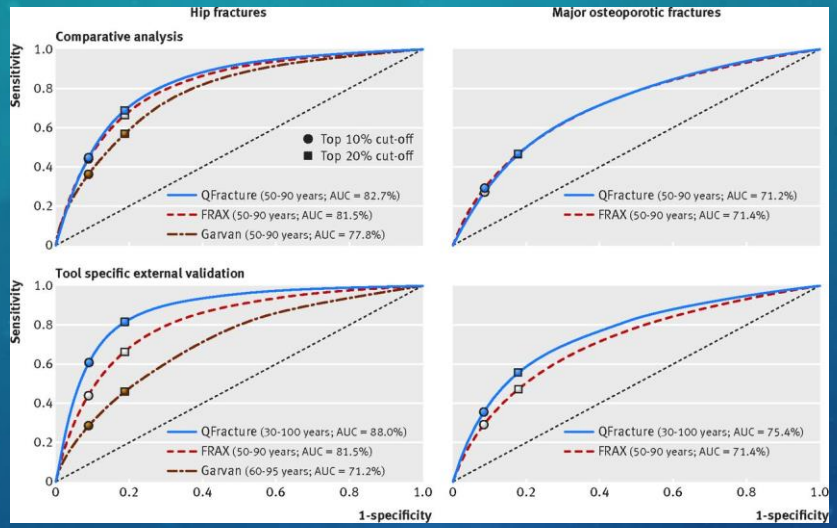
Decreased Bone Density

- Alterations in bone microarchitecture
  - Cortical porosity cortical thinning
  - Trabecular thinning and dropout
  - Disruption in balance and orientation of newly formed and mature bone

Decreased Bone Quality

- Osteomalacia
- Abnormal remodeling
  - Adynamic bone disease
  - Low turnover
  - High turnover
- Microdamage accumulation
  - Reduced resistance to impact
- Advanced glycation end products cross-linking

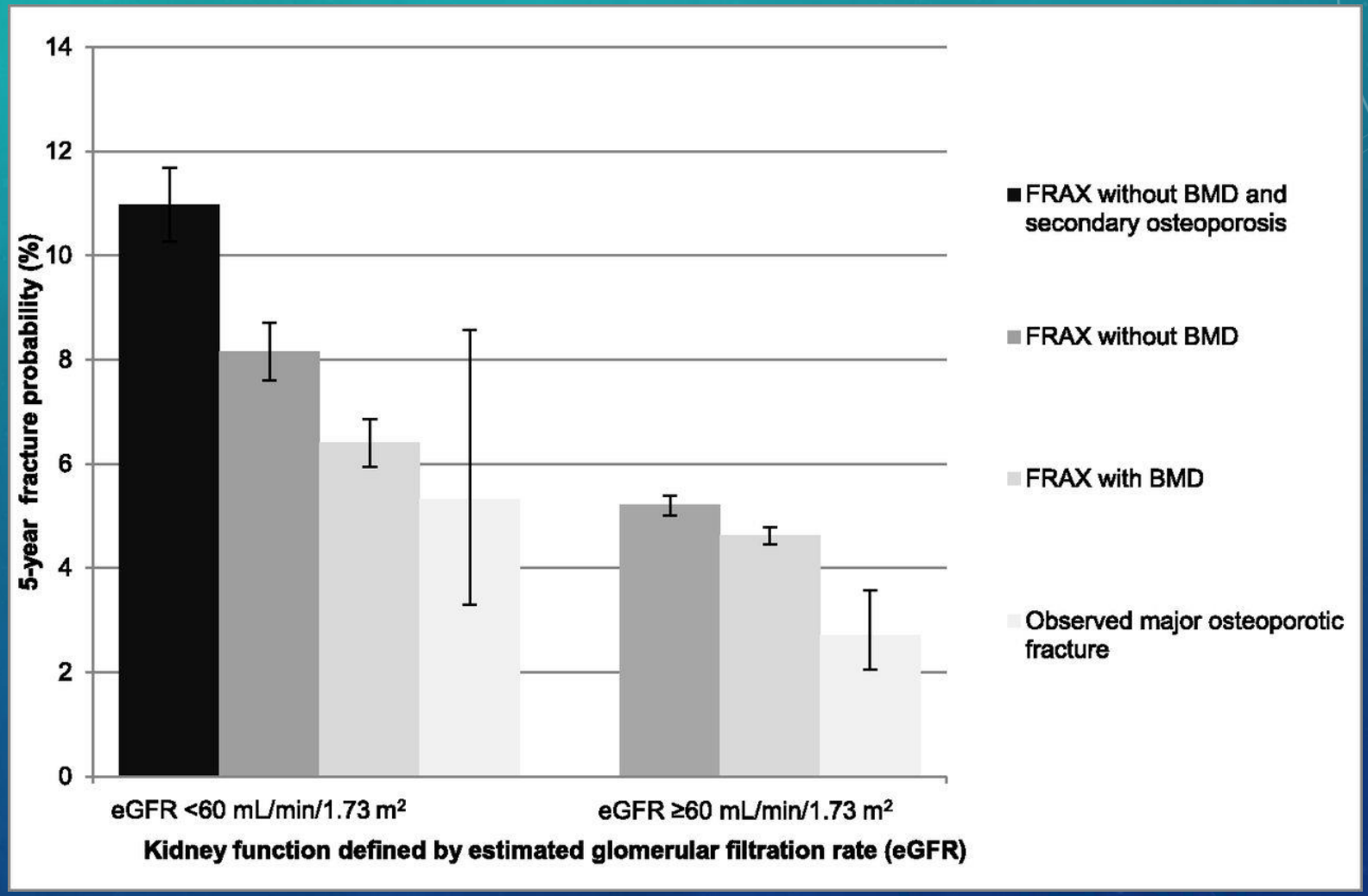
JBMR 2018 vol2 ;p 309



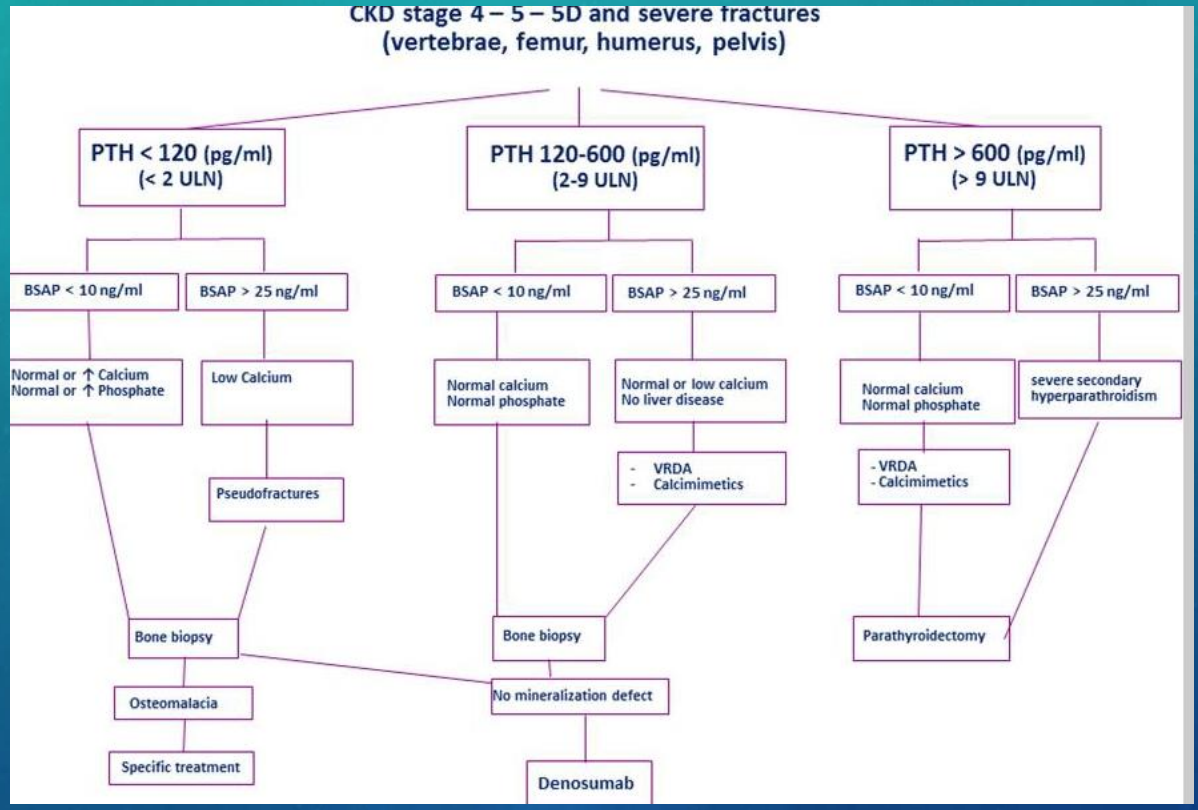
Choice of Drug

- GFR >= 30 ml/min
  - If there is no evidence of CKD-MBD, pharmacologic options for the treatment of osteoporosis don't differ from pts. w/out CKD
  - Efficacy is similar in these pts group as evidenced by clinical trials and
  - cohort groups which included subsets of pts. who had similar degrees of renal impairment
- GFR <30ml/min High risk or fracturing pts. With G_4: ,G_5 , or G_5D : Few Data
  - Post hoc analysis of trials in women with OP and G4 CKD showed efficacy
  - Some would agree to use of BP ,other won't, but modifying dosing interval : risedronate every other week and not > than 3 yrs
  - Denosumab Limited clinical experience in CKD :
    - In CKD 5D associated with clinically signicant hypocalcemia

Mean predicted 5-year fracture risk from the Canadian FRAX tool (with and without BMD) and observed 5-year major osteoporotic fracture risk (Kaplan–Meier) according to eGFR.



Kyla L. Naylor et al. CJASN 2015;10:646-653


CKD stage 4 – 5 – 5D and severe fractures
(vertebrae, femur, humerus, pelvis)
PTH < 120 (pg/ml)
(< 2 ULN)
PTH 120-600 (pg/ml)
(2-9 ULN)
PTH > 600 (pg/ml)
(> 9 ULN)
BSAP < 10 ng/ml
BSAP > 25 ng/ml
BSAP < 10 ng/ml
BSAP > 25 ng/ml
BSAP < 10 ng/ml
BSAP > 25 ng/ml
Normal or ↑ Calcium
Normal or ↑ Phosphate
Low Calcium
Normal calcium
Normal phosphate
Normal or low calcium
No liver disease
Normal calcium
Normal phosphate
severe secondary
hyperparathroidism
- VRDA
- Calcimimetics
- VRDA
- Calcimimetics
Pseudofractures
Bone biopsy
Bone biopsy
Parathyroidectomy
Osteomalacia
No mineralization defect
Specific treatment
Denosumab

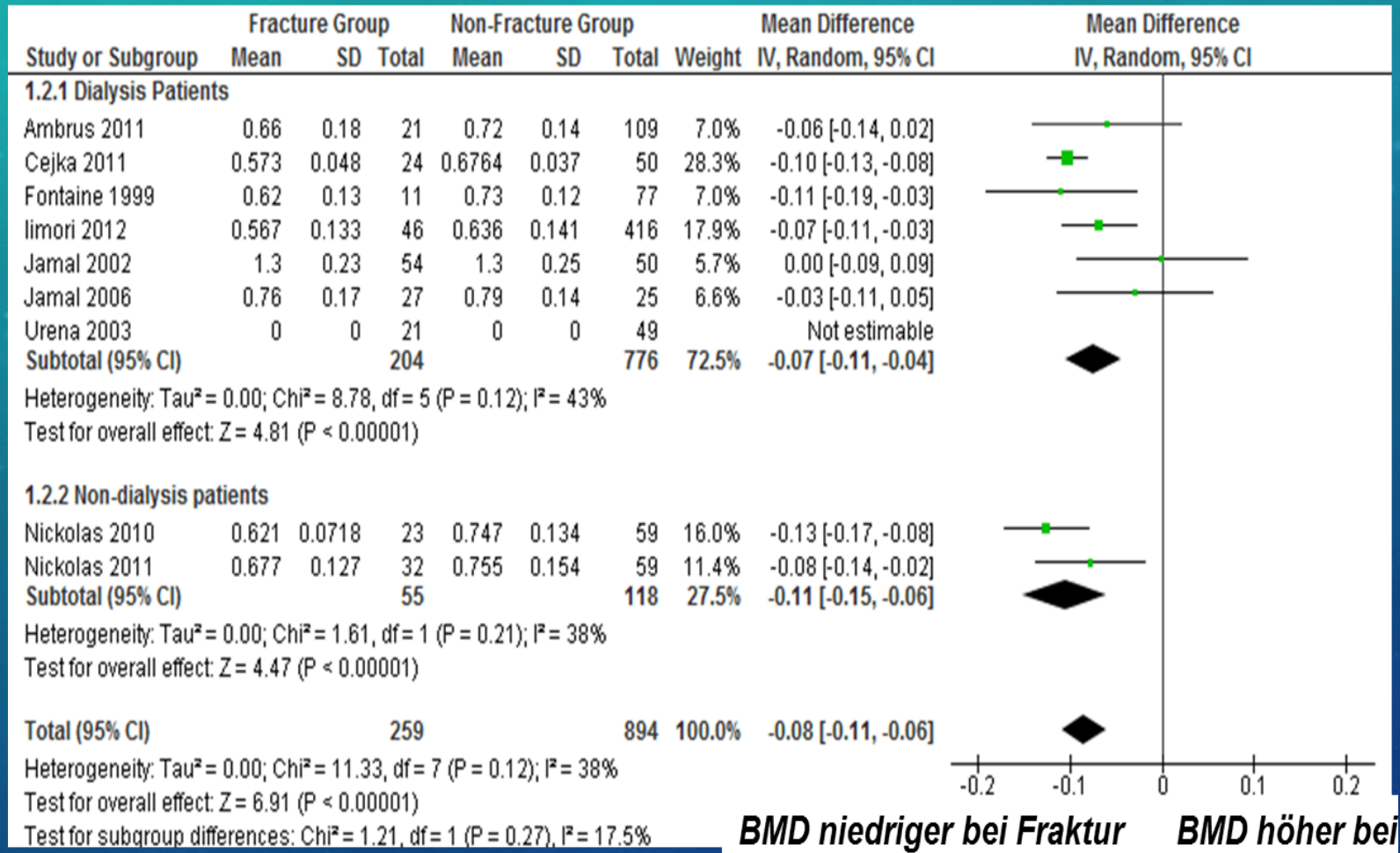
BMD and Fracture Risk in Older individuals with CKD

HR (95% Confidence Interval)				
	overall	No CKD	CKD	P value for CKD OP interaction
unadjusted	2.85 (2.23,3.64)	2.97 (2.24,3.93)	2.53 (1.55,4.13)	0.56
Adjusted for age, raace, sex,and BMI	1.77 (1.35,2.32)	1.64 (1.20,2.25))	2.10 (1.24,3.59)	0.74
+ parathyroid status and Vit.D status	1.76 (1.34,2.32)	1.63 (1.18,2.23)	2.10 (1.23,3.59)	0.75

Clin J Am Soc Nepro 2012
Vol 7:1130

META-ANALYSIS

DEXA-determined femoral BMD



Study or Subgroup	Fracture Group Mean	SD	Total	Non-Fracture Group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 Dialysis Patients								
Ambrus 2011	0.66	0.18	21	0.72	0.14	109	7.0%	-0.06 [-0.14, 0.02]
Cejka 2011	0.573	0.048	24	0.6764	0.037	50	28.3%	-0.10 [-0.13, -0.08]
Fontaine 1999	0.62	0.13	11	0.73	0.12	77	7.0%	-0.11 [-0.19, -0.03]
Iimori 2012	0.567	0.133	46	0.636	0.141	416	17.9%	-0.07 [-0.11, -0.03]
Jamal 2002	1.3	0.23	54	1.3	0.25	50	5.7%	0.00 [-0.09, 0.09]
Jamal 2006	0.76	0.17	27	0.79	0.14	25	6.6%	-0.03 [-0.11, 0.05]
Urena 2003	0	0	21	0	0	49		Not estimable
Subtotal (95% CI)			**204**			**776**	**72.5%**	**-0.07 [-0.11, -0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 8.78, df = 5 (P = 0.12); I² = 43%								
Test for overall effect: Z = 4.81 (P < 0.00001)								
1.2.2 Non-dialysis patients								
Nickolas 2010	0.621	0.0718	23	0.747	0.134	59	16.0%	-0.13 [-0.17, -0.08]
Nickolas 2011	0.677	0.127	32	0.755	0.154	59	11.4%	-0.08 [-0.14, -0.02]
Subtotal (95% CI)			**55**			**118**	**27.5%**	**-0.11 [-0.15, -0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 1 (P = 0.21); I² = 38%								
Test for overall effect: Z = 4.47 (P < 0.00001)								
Total (95% CI)			**259**			**894**	**100.0%**	**-0.08 [-0.11, -0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 11.33, df = 7 (P = 0.12); I² = 38%								
Test for overall effect: Z = 6.91 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.21, df = 1 (P = 0.27), I² = 17.5%								

BMD **low**
in case of fracture

BMD **high**
in case of fracture

RATIONALE FOR UPDATE

- Multiple new prospective studies have documented that lower dual-energy X-ray absorptiometry (DXA) BMD predicts incident fractures in patients with CKD G3a–G5D.
- The order of these first two recommendations was changed, since a DXA BMD result might impact the decision to do a bone biopsy.

Strategy to evaluate Bone Fragility in CKD

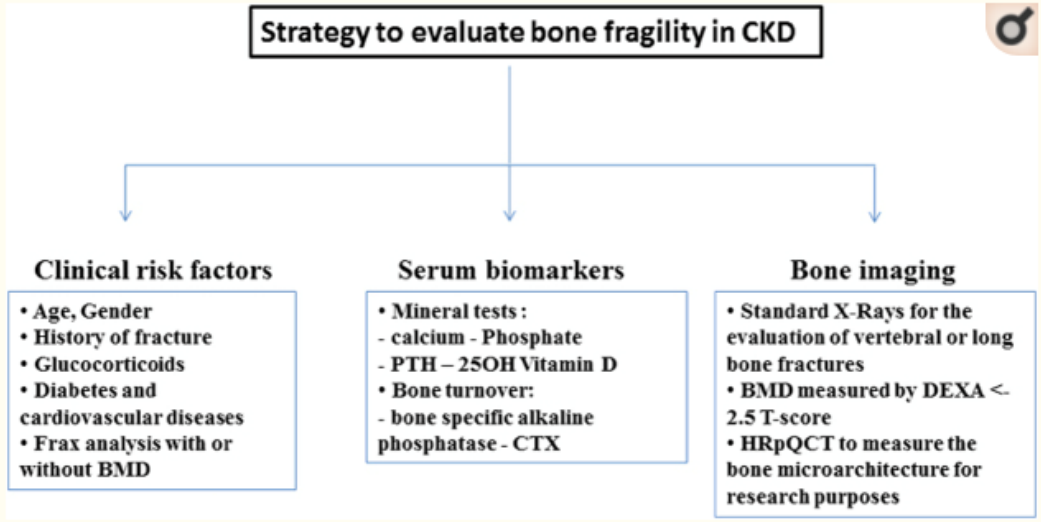


Figure 1

Tools available to assess bone fragility. A combination of clinical factors, bone and mineral biomarkers as well as imaging are required to characterize the profile of fragility and help to guide treatment decisions.