به نام خداوند جان و خرد

Osteoporosis Post transplant

Dr. Shahrzad Shahidi

Professor of Nephrology

Isfahan University of Medical Sciences

CASE

- 55-y.o. male, 9 months following successful KTx.
- Routine DEXA demonstrated a T-score of –2.6 at the femoral neck.
- He is on low-dose prednisone, tacrolimus, & MMF. In addition, he uses vit D supplements.
  - PTH: 140 pg/mL (15-65)
  - Ca: 8.8 mg/dL
  - Ph: 3.0 mg/dL

CASE

- **What would you do next?**

  A. Initiate bisphosphonate therapy

  B. Refer for subtotal parathyroidectomy

  C. Wait & see as appropriate

  D. Lower the dose of prednisone

Introduction

- The **major** bone diseases that affect KTRs are:
  - Osteoporosis
  - Osteonecrosis (AVN),

both of which cause significant long-term morbidity.

- Osteoporosis increases the risk of **fractures**.

Introduction

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

Introduction

- **iPTH** typically remains normal until the eGFR decreases to ≠ 45 mL/min/1.73 m^2
- **Calcitriol** level started to fall until eGFR was < 40 mL/min/1.73 m^2

Hsu CY. Int J Mol Sci.2020

Epidemiology

- **The risk of Fx in patients with organ transplants is very high (**particularly during the early phase after the surgery)**:**
  - **Almost 5 times & 20 times higher in male & female KTRs compared with age- & sex-matched control groups.**
  - **The risk is particularly high in perimenopausal women.**
  - **Fx seemed to occur frequently at an appendicular bone in KTRs**
- **The long-term risk of Fx based on a 15-y observational study was ~60%, which was almost 3 times higher than the expected risk.**

Kim SM. Medscape.2022

medicina

MDPI

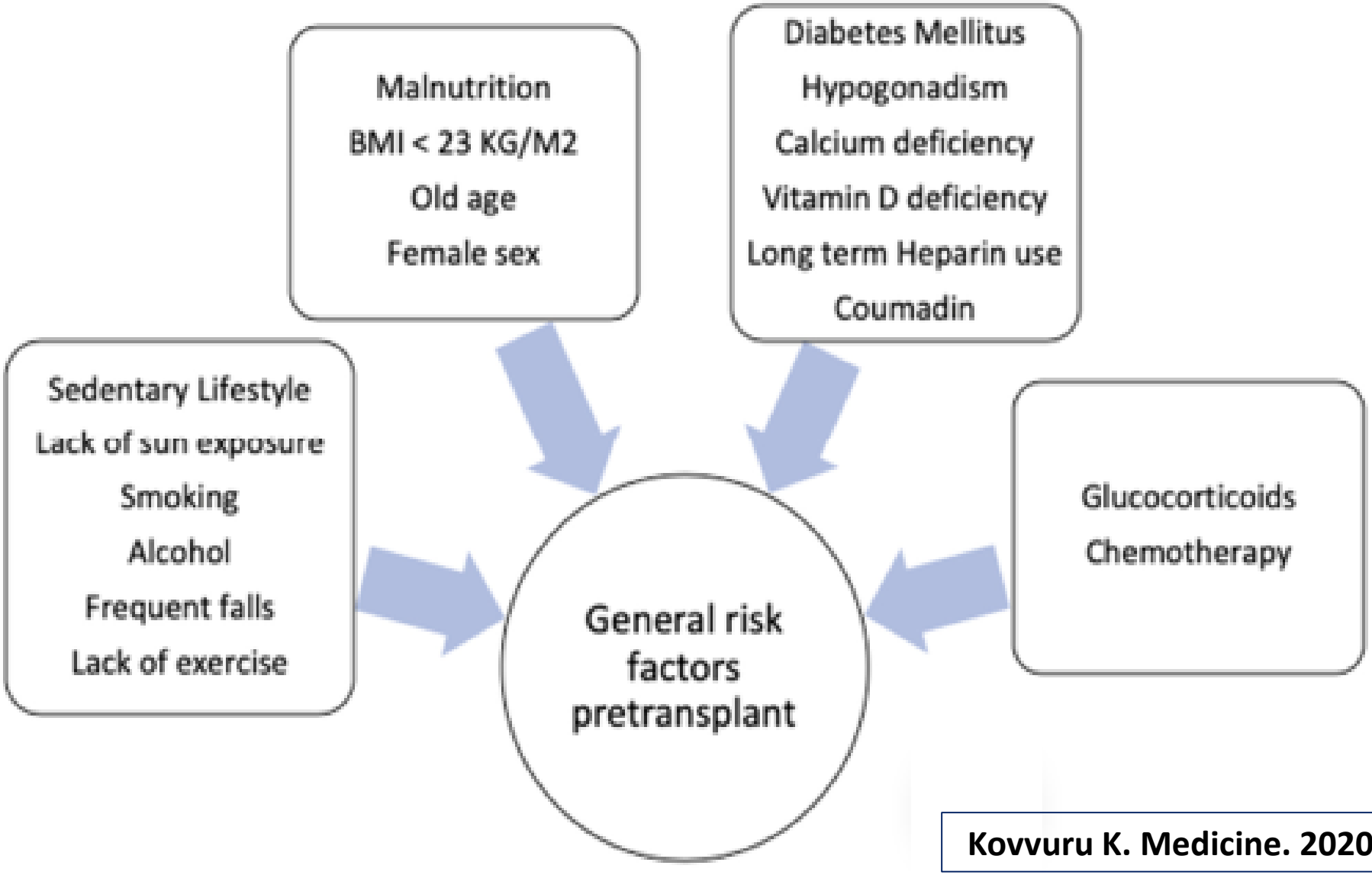
Review

Risk Factors and Management of Osteoporosis Post-Transplant

Karthik Kovvuru [1,*], Swetha Rani Kanduri [2], Pradeep Vaitla [2], Rachana Marathi [3], Shiva Gosi [4], Desiree F. Garcia Anton [2], Franco H. Cabeza Rivera [2] and Vishnu Garla [5]

Kovvuru K. Medicine. 2020

General risk factors for osteoporosis



Kovvuru K. Medicine. 2020

Major risk factors for OP in KTRs

1. Glucocorticoids
2. CNIs
3. Persistent hyperparathyroidism

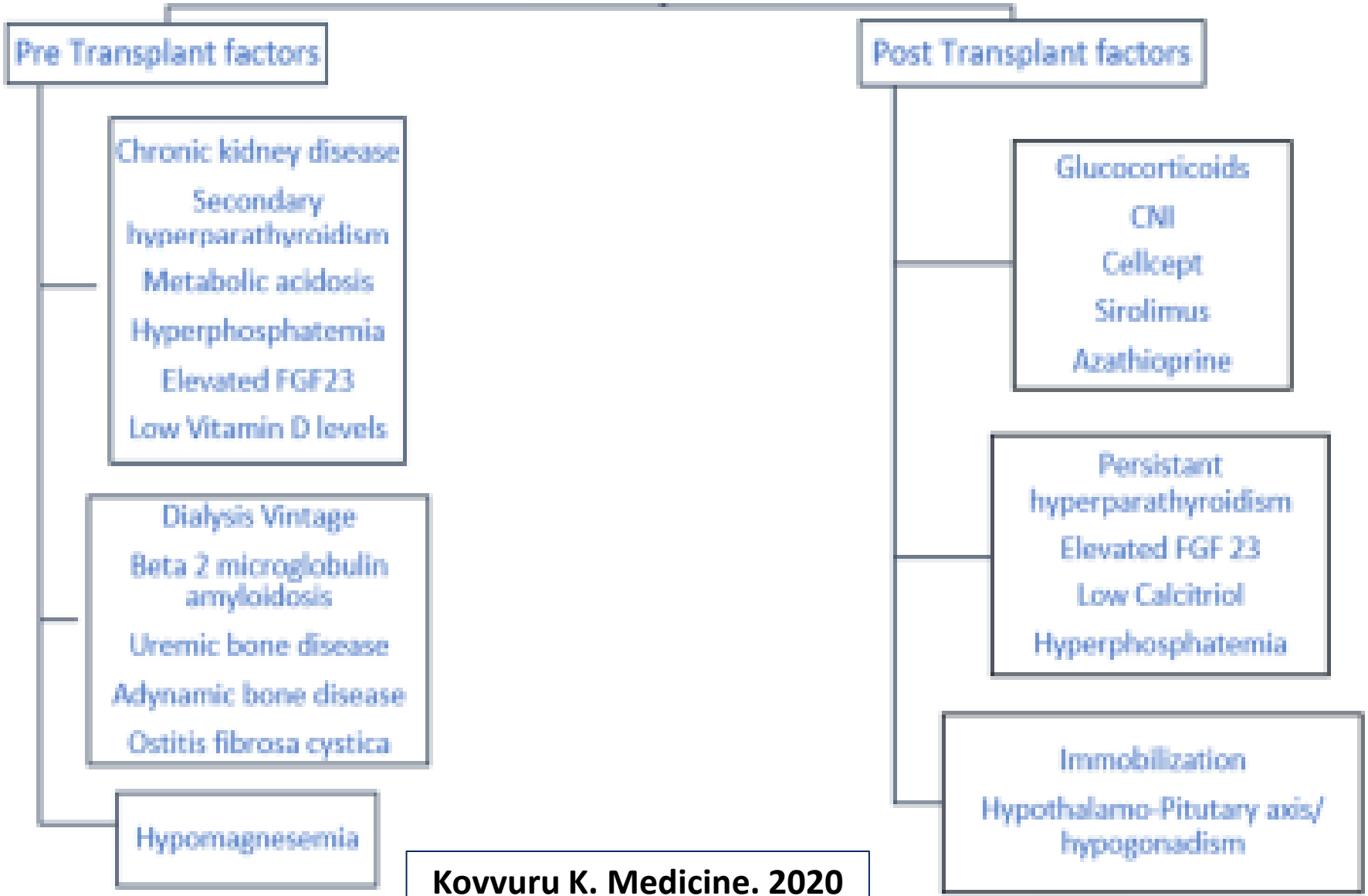
Hsu CY. Int J Mol Sci.2020

Major risk factors for OP in KTRs

- **Glucocorticoids** – Among transplant recipients, GC-induced suppression of bone formation is the **most important** risk factor for bone loss.
  - GCs are directly toxic to osteoblasts & lead to increased osteoclast activity.
  - Decreased Ca absorption in the gut
  - Reduced gonadal hormone production
  - Diminished insulin-like growth factor 1 production
  - Decreased sensitivity to PTH
  - Increased activity of RANKL
  - Increased osteoclastogenesis
- The **lower rates** of bone loss following KT documented in recent years may reflect the lower doses of GCs used to treat these patients.

Hsu CY. Int J Mol Sci.2020

Pre & post-transplant risk factors associated with post KT osteoporosis



Kovvuru K. Medicine. 2020

Diagnosis

Evaluation of Bone Strength

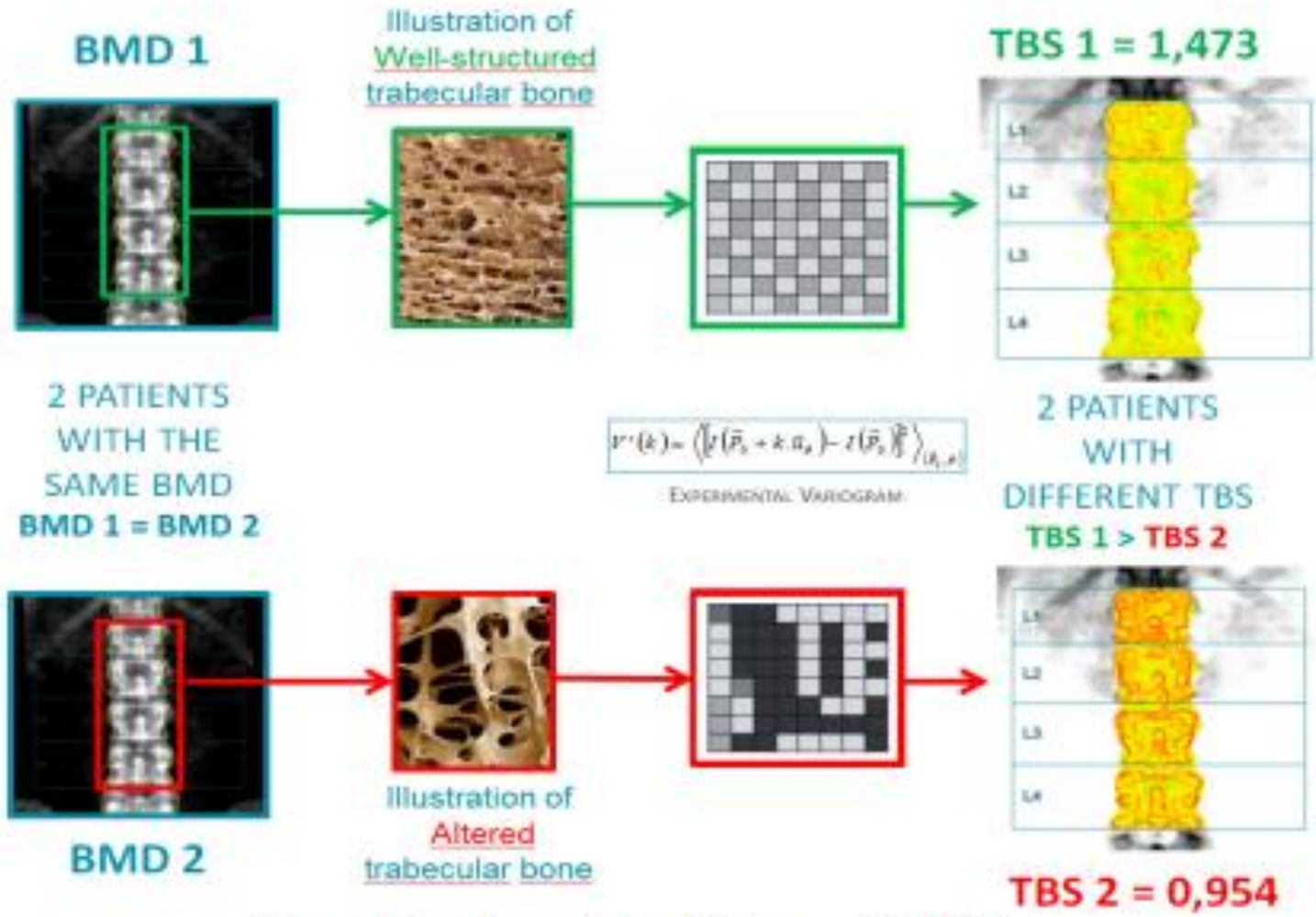
- DXA evaluates the bone **quantity** & not the bone quality.
- Non-invasive 3D imaging techniques that can detect microarchitecture & mineral density of both trabecular & cortical bones
  - Peripheral quantitative CT (pQCT)
  - High resolution pQCT (HRpQCT)
  - micromagnetic resonance imaging (microMRI)
- However, there are few data in evaluating these techniques in patients with CKD.

Hsu CY. Int J Mol Sci.2020

Trabecular bone score (TBS)

- TBS indirectly analyzes trabecular bone microarchitecture, may add further insight in Fx assessment.


TBS
bone structure
QUALITY
BMD
bone density
QUANTITY



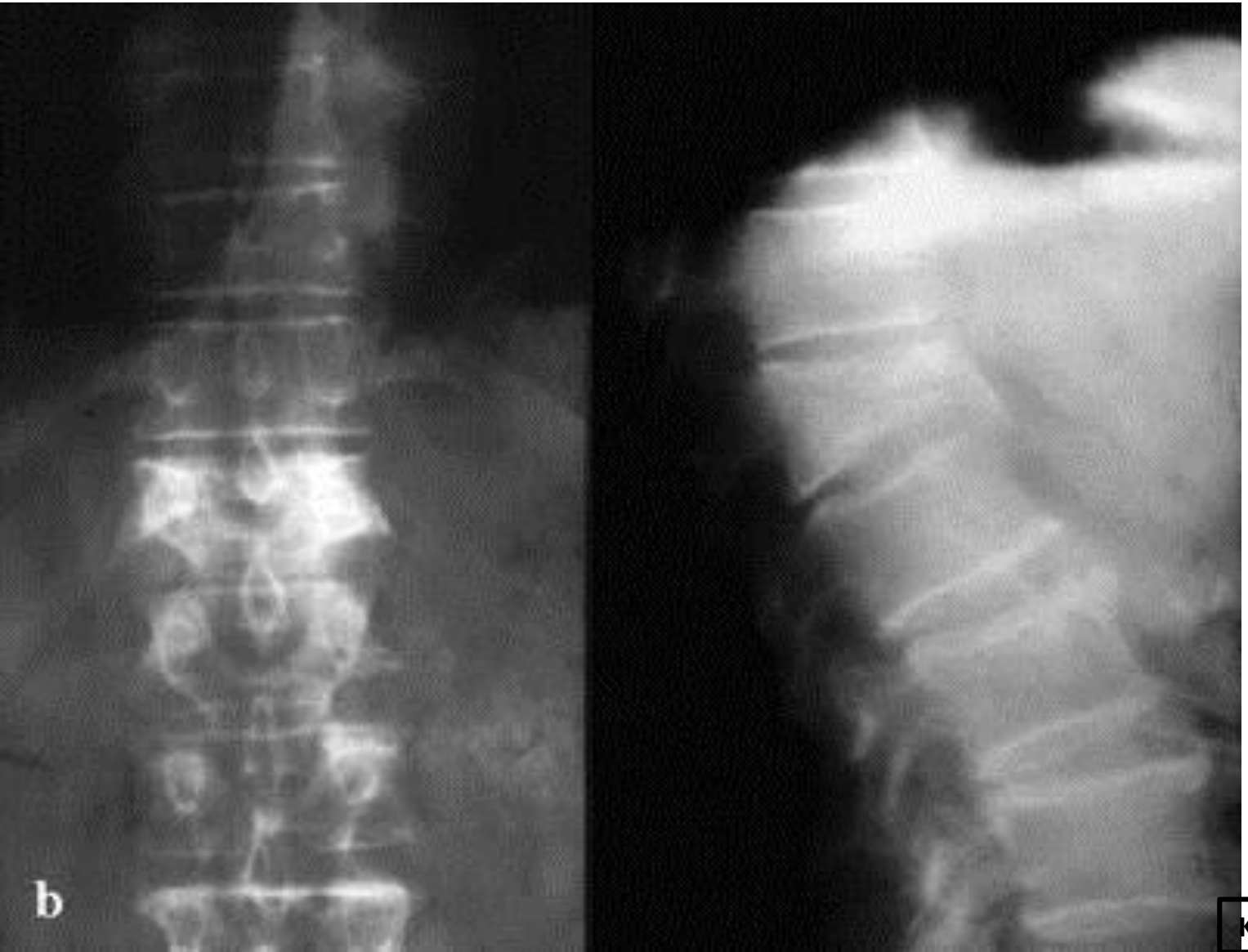
2 patients with different TBS

= different therapy decisions

TBS

- TBS' maximum impact is observed in patients with **osteopenic/normal BMD** values who display low TBS scores & consequently have a higher combined risk of Fx or in patients whose Fx risk is close to the intervention threshold.
- TBS helps doctors identify patients at risk of Fx due to **secondary OP** caused by such as OA, DM, Endocrine diseases, GCs, CKD, Breast Cancer patients treated with Aromatase Inhibitors, etc.

Anteroposterior & lateral radiographs of an L1 osteoporotic wedge compression Fx



Kim SM. Medscape.2022

KDIGO 2017 Update for CKD-MBD

- 5.1: In patients in the immediate post–KTx period, we recommend measuring serum **Ca & ph** at least **weekly**, until stable (1B).
- 5.2: In patients after the immediate post–KTx period, it is reasonable to base the frequency of monitoring serum Ca, Ph, & PTH on the presence & magnitude of abnormalities, & the rate of progression of CKD (Not Graded).

KDIGO 2017 Update for CKD-MBD

CKD Stage	Ca & Ph	PTH
G1T- G3bT	6–12 ms	**once,** with subsequent intervals depending on baseline level & CKD progression
G4T	3-6 ms	6-12 ms
G5T	1-3 ms	3-6 ms

KDIGO 2017 Update for CKD-MBD

- In CKD patients receiving treatments for CKD-MBD, or in whom biochemical abnormalities are identified, it is reasonable to **increase the frequency** of measurements to monitor for efficacy & side effects (Not Graded).
- It is reasonable to manage these abnormalities as for patients with CKD G3a–G5 (Not Graded).

KDIGO 2017 Update for CKD-MBD

- 5.5: In patients with **CKD G1T–G5T** with risk factors for osteoporosis, we suggest that **BMD** testing be used to assess Fx risk if results will alter therapy (2C).

BMD

- DEXA scans are recommended at the time of Tx & 1 & 2 years following Tx.
- Parenteral bisphosphonate should be considered when the BMD *T*-score is less than or equal to –2 SD.

Kim SM. Medscape.2022

Management

Prevention of osteoporosis

- Encourage lifestyle changes
- Maintain the lowest possible GC dose
- Treat with Calcium & vit D3
  - Ca intake of **1000 mg/day**, preferably from food
  - Target serum 25 OH vit D level of **>30 ng/mL**
- Treat persistent hyperparathyroidism

LIFESTYLE MEASURES

- Including:
  1. Adequate Ca & vit D intake
  2. Exercise
  3. Cessation of smoking
  4. Avoiding excessive alcohol intake
  5. Fall prevention

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

Tricco AC. 2017. JAMA

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.

Tricco AC. 2017. JAMA

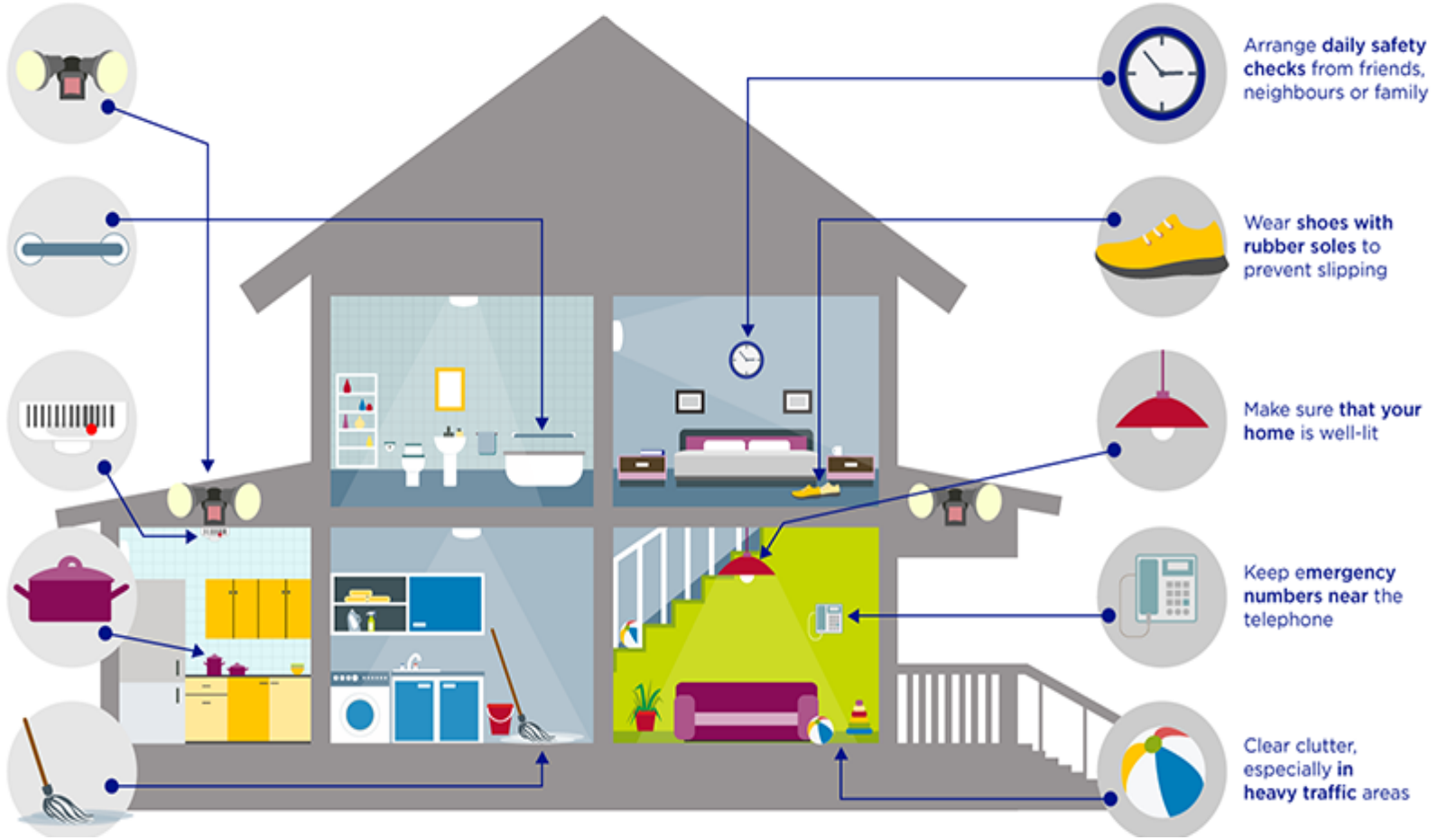
What type of fall-prevention programs may be effective for reducing injurious falls in older people?

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.

Tricco AC. 2017. JAMA

Western Cape Government

Safety at home for the elderly



Grab rails

KDIGO 2017 Update for CKD-MBD

- 5.3: In patients with **CKD G1T–G5T**, we suggest that 25(OH)D levels might be measured, & repeated testing determined by baseline values & interventions (2C).
- 5.4: In patients with CKD G1T–G5T, we suggest that **vit D** deficiency & insufficiency be corrected using treatment strategies recommended for the **general population** (2C).

nutrients

MDPI

IF: 6.706

Review

Vitamin D and Calcium Supplementation and Urolithiasis: A Controversial and Multifaceted Relationship

Piergiorgio Messa [1,*], Giuseppe Castellano [1,2], Simone Vettoretti [1], Carlo Maria Alfieri [1,2], Domenico Giannese [3], Vincenzo Panichi [3] and Adamasco Cupisti [3]

1 Nephrology, Dialysis and Renal Transplantation, Fondazione IRCCS Ca' Granda Ospedale Policlinico Milan, 20122 Milan, Italy
2 Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy
3 Department of Clinical and Experimental Medicine, University of Pisa, 56126 Pisa, Italy
* Correspondence: piergiorgio.messa@gmail.com

Abstract: Patients with urolithiasis, and particularly those with hypercalciuria, frequently have a marked reduction of bone mineral content up to the levels of osteoporosis, with a significant

Messa P. nutrients. 2023.31 March

Vit D &/or Ca Supplementation in the General Population

- Most of the clinical trials **did not show** any significant association between vit D & Ca supplementation & the risk of developing the urinary stone disease.

Messa P. nutrients. 2023.31 March

Definition of UL risk & suggested actions where there is a strong indication for prescribing vit D &/or Ca supplem.

	Low risk
Characteristics of patients	- No current or past personal history of UL - No familial history of UL - No bariatric surgery
actions	advice to abundant fluid intake to obtain urine volume output > 2 lither per day normalize the total consumption of calcium with the diet (800-1000 mg/day)

Messa P. nutrients. 2023.31 March

Definition of UL risk & suggested actions where there is a strong indication for prescribing vit D &/or Ca supplem.

	Low risk	Medium risk
Characteristics of patients	- No current or past personal history of UL - No familial history of UL - No bariatric surgery	- No current or past personal history of UL - **Familial history of UL or Previous bariatric surgery**
actions	advice to abundant fluid intake to obtain urine volume output > 2 lither per day normalize the total consumption of calcium with the diet (800-1000 mg/day)	Low risk indications + Avoid calcium supplementation After 3 months from the start of therapy and every 12 months thereafter: control serum calcium and 25.OH-D levels (avoid overcoming 40 ng/mL) In patients with bariatric surgery, add 1-2 g of citrate K/Mg salts

Messa P. nutrients. 2023.31 March

Definition of UL risk & suggested actions where there is a strong indication for prescribing vit D &/or Ca supplem.

	Low risk	Medium risk	High risk
Characteristics of patients	- No current or past personal history of UL - No familial history of UL - No bariatric surgery	- No current or past personal history of UL - **Familial history of UL or Previous bariatric surgery**	- **current or past personal history of UL** - **HC stone formers** - **Evaluate the risk of UL recurrence**
actions	advice to abundant fluid intake to obtain urine volume output > 2 lither per day normalize the total consumption of calcium with the diet (800-1000 mg/day)	Low risk indications + Avoid calcium supplementation After 3 months from the start of therapy and every 12 months thereafter: control serum calcium and 25.OH-D levels (avoid overcoming 40 ng/mL) In patients with bariatric surgery, add 1-2 g of citrate K/Mg salts	low risk indications + Avoid calcium supplementation After 3 months from the start of therapy and every 12 months thereafter: control serum calcium, urinary calcium excretion, and 25.OH-D levels (avoid overcoming 40 ng/mL) 1-2 g of citrate K/Mg salts Consider, if possible, the use of thiazide diuretics

Messa P. nutrients. 2023.31 March

KDIGO 2017 Update for CKD-MBD

- 5.6: In patients in the first 12 ms after KT with an eGFR > approximately 30 ml/min/1.73 m^2 & low BMD, we suggest that treatment with vit D, calcitriol/alfacalcidol, &/or antiresorptive agents be considered (2D).

International Journal of
Molecular Sciences

MDPI

IF: 6.208

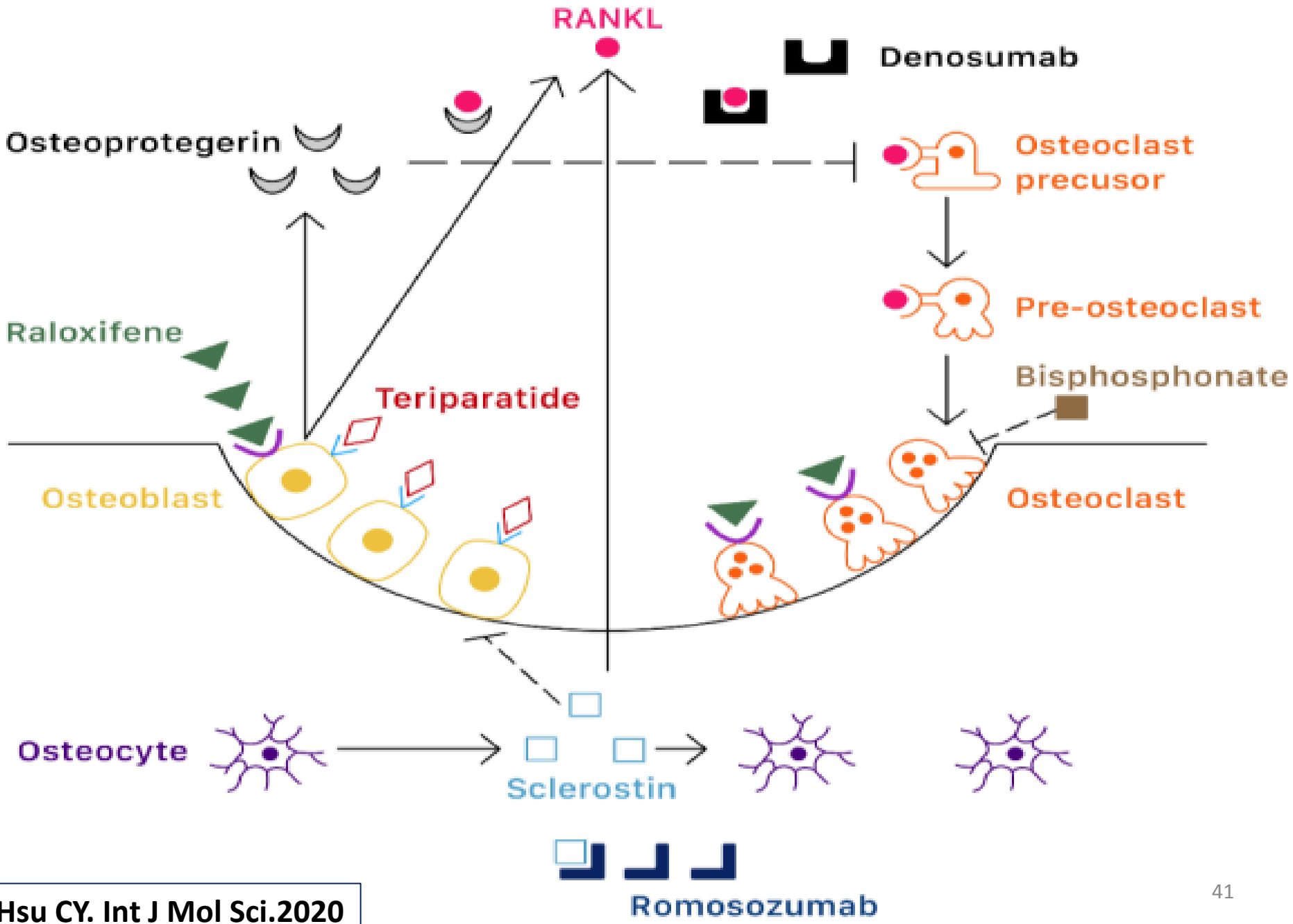
Review

Osteoporosis in Patients with Chronic Kidney Diseases: A Systemic Review

Chia-Yu Hsu [1,2,†], Li-Ru Chen [3,4,†] and Kuo-Hu Chen [5,6,*]

1 Department of Rehabilitation Medicine, Ten-Chan General Hospital, Zhongli, Taoyuan 320, Taiwan; f927kimo@gmail.com
2 Department of Biomedical Engineering, Chung Yuan Christian University, Taoyuan 320, Taiwan
3 Department of Physical Medicine and Rehabilitation, Mackay Memorial Hospital, Taipei 104, Taiwan; gracealex168@gmail.com

Hsu CY. Int J Mol Sci.2020



Hsu CY. Int J Mol Sci.2020

KDIGO 2017 Update for CKD-MBD

- 5.6(con):We suggest that treatment choices be influenced by the presence of CKD-MBD, as indicated by abnormal levels of **Ca, Ph, PTH, Alp, & 25(OH)D** (2C).
- It is reasonable to consider a **bone biopsy** to guide treatment (Not Graded).
- There are **insufficient data** to guide treatment after the first 12 ms.

KDIGO 2017 Update for CKD-MBD

- 5.7: In patients with CKD **G4T–G5T** with known low BMD, we suggest management as for patients with **CKD G4–G5** not on dialysis (2C).

KDIGO 2017 Update for CKD-MBD

- **Cinacalcet** is **not** approved for the treatment of hyperparathyroidism in KTRs; however, it is clinically used, especially in patients with significant hypercalcemia.
- While efficiently correcting hypercalcemia, cinacalcet so far has **failed** to show a beneficial impact on bone mineralization in the transplant population.

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 & 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**.

Inhibition of Metaphysial Bone Resorption In vivo by Bisphosphonate

Chemical Modification	Examples	Anti-resorptive potency
First generation: short alkyl	Etidronate Clodronate	1 10
Second generation: NH2-terminal group	Tiludronate Pamidronate Alendronate	10 100 100-1000
Third generation: cyclic side chain	Risedronate Ibandronate Zolendronate	1000-10000 1000-10000 100000

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

Bisphosphonates

- Should not be used **routinely** in patients with an eGFR < 30 ml/min & should only be considered in such patients by clinicians with expertise in MBD & after excluding ROD.

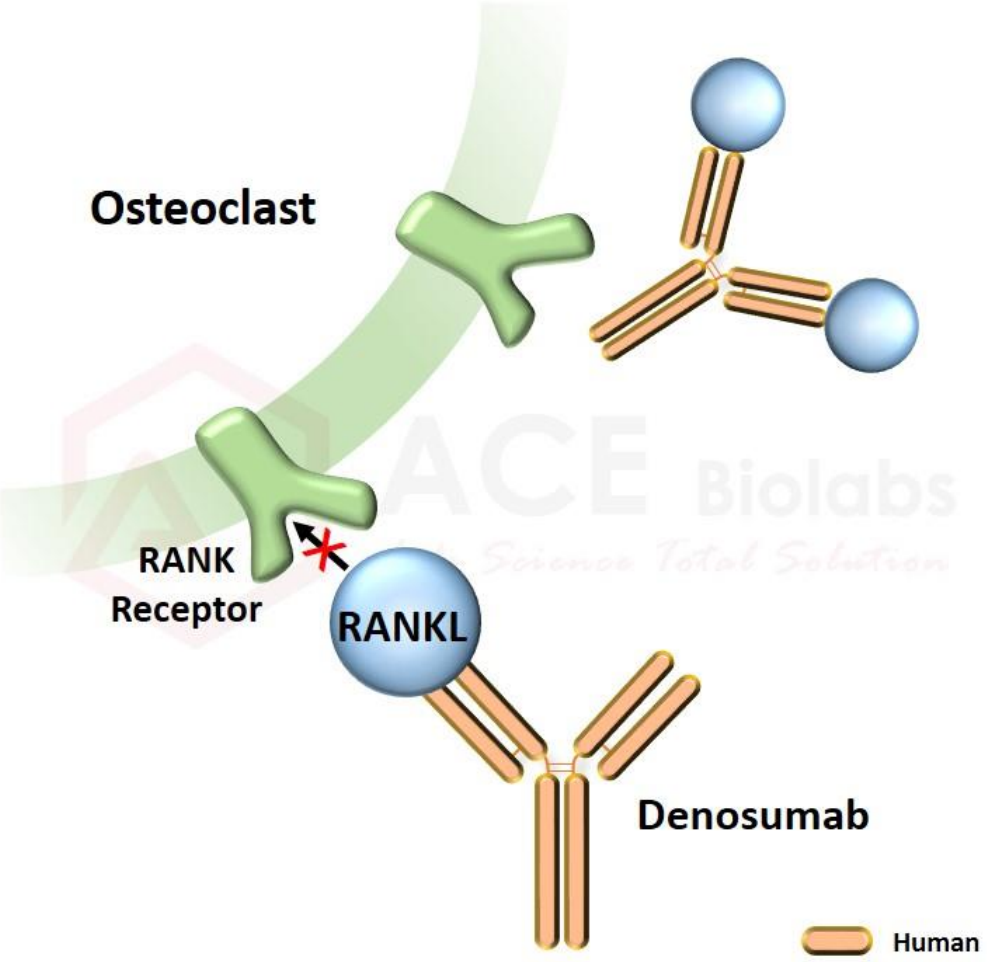
Bisphosphonates

- If an antiresorptive agent such as a bisphosphonate is used, significant increases in **spine BMD** may be observed within **1 year**.
- An increase in **femoral neck BMD** may not be seen until after an average of **4-5 years** & probably longer with weaker antiresorptive agents.

Kim SM. Medscape.2022

Denosumab

- Is a monoclonal antibody that is directed against RANK ligand & inhibits osteoclast proliferation & development.
- 60 mg/6 ms SQ.



Inter Med. 2017;56

Denosumab

- 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

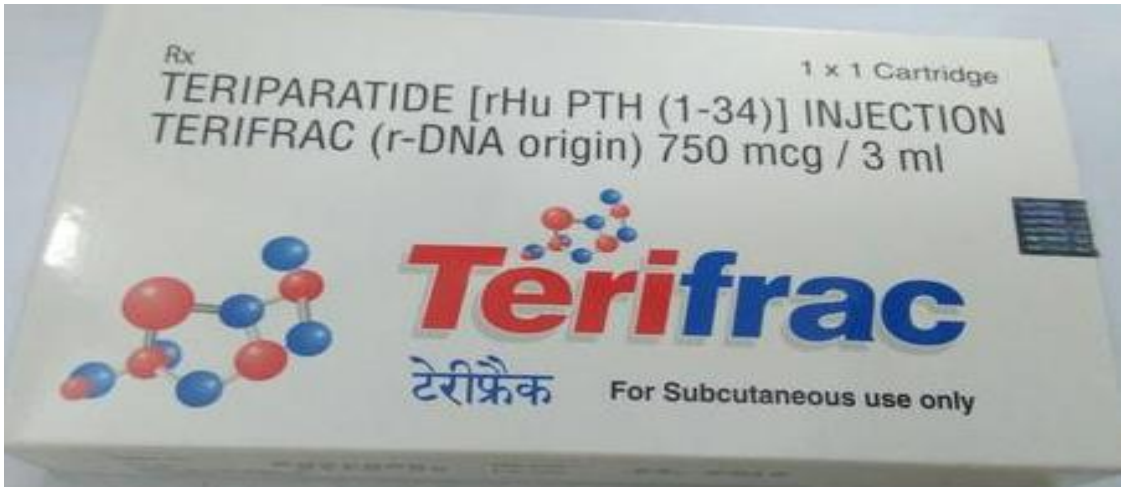
- Hypocalcemia induced by denosumab should be avoided by practicing appropriate precaution & preemptively administering **active vit D** to eligible CKD patients before starting denosumab.
- The serum Ca levels usually reach their nadir around **7 days** after administration, with a less-extensive Ca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

with the second denosumab administration.

Inter Med. 2017;56

Teriparatide (rhPTH)

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



Inter Med. 2017;56

Teriparatide (rhPTH)

- Some authors **use** teriparatide in patients who:
  - Develop fragility Fxs while receiving bisphosphonates or denosumab as preventive therapy
  - As first-line therapy in patients who are at high risk for fractures if bone turnover is demonstrated to be low by bone turnover markers or bone biopsy.
- After **stopping** teriparatide, antiresorptive therapy may be considered if the patient's bone turnover is expected to rebound.

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

FDA Recommendations for Use of Bisphosphonates in CKD

Bisphosphonate	Acceptable to use in
Alendronate	GFR ≥ 35 mL/min/1.73 m^2
Ibandronate, risedronate, teriparatide	GFR > 30 mL/min/1.73 m^2
Abaloparatide	Any GFR (but has not been studied in ESRD[1])
Denosumab	Any GFR • Studied in women with postmenopausal osteoporosis and normal PTH levels[2] • Risk for hypocalcemia when used by patients with advanced CKD[2]
Romosozumab	N/A (has not been studied in patients with CKD)

CASE

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- Routine DEXA demonstrated a T-score of –2.6 at the femoral neck.
- He is on low-dose prednisone, tacrolimus, & MMF. In addition, he uses vit D supplements.
  - PTH: 140 pg/mL (15-65)
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CASE

- **What would you do next?**

A. Initiate bisphosphonate therapy

B. Refer for subtotal parathyroidectomy

C. Wait & see as appropriate

D. Lower the dose of prednisone

CASE

- **What would you do next?**

A. Initiate bisphosphonate therapy

B. Refer for subtotal parathyroidectomy

C. Wait & see as appropriate

D. Lower the dose of prednisone

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