Insights on Osteoscaropenia and Fracture Prevention in Older Adults

22nd Annual Santa Fe Bone Symposium
August 5, 2022

Neil Binkley, M.D.
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin, USA
Disclosures

• Research support
  ● Radius

• Consultant
  ● Amgen

- Some of this is my opinion
- Noted as such by orange text color
Objectives

• Recognize the need for a syndrome approach to reducing “osteoporosis-related” fractures

• Appreciate challenges in implementing the diagnosis of sarcopenia

• Summarize *rationale approaches* to non-pharmacologic osteoporosis therapy

• Encourage you to think about what “osteoporosis treatment” really means

“Think”
Why Do You Treat “Osteoporosis?”

Fracture is what’s important
But we are failing to prevent them
Failure to Recognize & Treat Osteoporosis (“Treatment Gap”) is a Worldwide Phenomenon

- Observational study in 8 European countries
- Women age 70+ seeing primary care provider
- Treatment gap = high risk not treated
- Those at high fracture risk defined as:
  - Prior fracture
  - T-score ≤ -2.5
  - Elevated FRAX risk

Treatment gap ranged from 53% (Ireland) to 91% (Germany)

“There is a large treatment gap in women aged ≥ 70 … in routine primary care across Europe. ..appears to be related to a low rate of osteoporosis diagnosis.”

McCloskey, et. al., Osteoporos Int, 2021, 32:251-259
Some Reports Are Even Worse

- 2,933 pts are 50+ who presented to ER with acute vertebral fracture
  - 2008-2014 Roanoke, VA
- Assessed DXA testing, Ca/D suppl, osteoporosis Rx & subsequent Fx

“…. Recognition and treatment of osteoporosis in patients at this institution remained dismal over time despite numerous calls to action on the topic in the orthopedic literature and elsewhere.”

Fig. 5. Treatment rate in previously untreated patients over time. The percentage of treatment naïve patients each year with an initial vertebral fracture who received a prescription for a medication approved by the FDA for osteoporosis. Data is only available for part of 2008 and 2014. FDA, food and drug administration.

Barton, et. al., The Spine Journal, 2018; doi.org/10.1016j.spinee.2018.08.004
Too Often, Osteoporosis Treatment Consists of Drug Decisions

Personal opinion

Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society* Clinical Practice Guideline

Eastell, et. al., J Clin Endocrinol Metab, 104: 1595–1622, 2019

A major “treatment gap” is only thinking about drug therapy
Fracture Prevention Is Not Just Prescribing a Bone Drug

Nonvertebral fracture risk reduction

- Alendronate: 27%\(^1\)
- Risedronate: 39%\(^2\)
- Zoledronate: 25%\(^3\)
- Denosumab: 20%\(^4\)
- Raloxifene: none\(^5\)

Note: NOT head to head studies

1. Black, et. al., JCEM, 2000; 85: 4118-4124
2. Harris, et. al, JAMA, 1999; 282:1344-1352
5. Ettinger, et. al, JAMA, 1999; 282:637-45

Adapted from Miller, et. al., JAMA. 2016; 316: 722-733
Bone Drugs Do Not Prevent Falls!
Importance of Falls Recently Emphasized

156 Patients with Periprosthetic Fx

- 89% due to falls
  - 8% spontaneous
- These are osteoporosis-related
  - Mean age 75 years
  - 74% female
  - Prior fracture in 46%
  - 45% had prior DXA; 29% CT for HU
    - Clinical osteoporosis in 66%

We are failing to prevent falls, fractures & periprosthetic fx

Whiting, et. al, To be presented at ASBMR 2022
"Failure is success in progress."

Albert Einstein
Success in Progress

• Change the focus from osteoporosis to fracture
  ● Include all fractures in older adults
  ● Discuss the effect of fractures on QoL and independence

• Consider osteoporosis as just one part of a syndrome leading to fracture
  ● Need to address more than just the bones

Binkley, et. al., J Bone Miner Res, 2017 32:1391-1394
Not News, But Worthy of Emphasis
We need to think about fracture risk, not just T-score osteoporosis

5794 participants in the Rotterdam study;
Mean follow-up 6.8 years
FN BMD at baseline

~55% of women
(female data shown here)
~80% of men
who sustain non-vertebral fractures have a T-score better than -2.5

Adapted from Schuit, Bone. 2004;34:195-202
We Should Learn From Others and Consider the Heart Attack Analogy

Treatment is Directed at Various Conditions to Reduce Risk For a Potentially Catastrophic Outcome

Metabolic Syndrome

- Hyperlipidemia
- Hypertension
- Diabetes
- Obesity

Heart Attack

- Advancing age
- Family History
- Toxins, e.g., tobacco
- Reduced QOL
- Healthcare Cost
- Death
The Same Approach Makes Sense for Musculoskeletal Health, i.e., “Bone Attack”
Treatment Should be Directed at Various Conditions to Reduce Risk For a Potentially Catastrophic Outcome

Treating just the bones without thinking about other things that cause fractures is comparable to treating hyperlipidemia and ignoring diabetes and hypertension in patients with metabolic syndrome.
Dysmobility Syndrome May be Too Complex: Osteosarcopenia is Increasingly Recognized

Osteosarcopenia: epidemiology, diagnosis, and treatment—facts and numbers

Ben Kirk\(^1,2\) \(\circ\), Jesse Zanker\(^1,2\) \(\circ\) & Gustavo Duque\(^1,2\) \(\circ\)

Osteosarcopenia

Dr James Paintin,
Academic FY2 Doctor, MRC Life Course Epidemiology Unit, University of Southampton,
Southampton SO16 6YD

Bone-Muscle Mutual Interactions

Nuria Lara-Castillo\(^1\) • Mark L. Johnson\(^1\)

Myokines, osteokines and adipokines involved in this crosstalk include IL-6, IL-7, IL-15, PGE2, TGF\(\beta\), irisin, IGF-1, BDNF, myostatin, FGF2, osteocalcin, sclerostin, leptin, resistin, adiponectin...
“Osteosarcopenia should be considered a geriatric giant of the XXI century due to its high prevalence in older persons and the vast personal burden of sufferers. To understand and effectively diagnose and treat osteosarcopenia, we still require a clear definition of sarcopenia, innovative biomarkers and diagnostic methods, and interventions with dual effect on bone and muscle.”

Osteoporosis Pathogenesis is Multifactorial

- Hormonal declines
  - GH/IGF-1, testosterone, estrogen
- Increased inflammation
  - IL-6, TNF-alpha, etc, etc.
- Malnutrition
  - Protein, vitamin D
- Sedentariness/Diseases leading to decreased use
- Toxin exposure
- Neuronal loss
- Reduced bone “quality” expressed ultimately as reduced function
  - Changes in structure, fat and connective tissue

Are osteoporosis and sarcopenia the same process?
With the disease being fracture?

Jensen, J Parenter Enteral Nutr, 32;656-659, 2008
Sarcopenia: the Age-related Gradual Loss of Muscle mass, Strength and Function

Sarc for flesh (muscle), penia for deficiency

Term coined in 1989; more recently defined as: "The age-associated loss of skeletal muscle mass and function… a complex syndrome associated with muscle mass loss alone or in conjunction with increased fat mass."

Fielding, et. al, J Am Med Dir Assoc 2011; 12: 249-256
Recent Consensus Definition of Sarcopenia

European Working Group on Sarcopenia in Older People (EWGSOP)

Criteria:
1. Low muscle strength
2. Low muscle quantity or quality
3. Low physical performance

• *Probable sarcopenia* is identified by low strength
• *Diagnosis is confirmed* by also documenting low muscle quantity
• *Severe sarcopenia* if all three criteria met

Sarcopenia formally recognized as a muscle disease with ICD-10 Diagnosis Code (M62.84) in 2016

Cruz-Jentoft, et al., Age and Ageing 2019; 48: 16–31
“The lack of a consensus definition of sarcopenia… has limited the ability of clinicians to diagnose and treat… and hindered the development of therapies.”

- NIA funded the Sarcopenia Definitions and Outcomes Consortium in 2016
- Develop evidence based cutpoints to identify persons at risk for adverse outcomes
- Developed position statements based upon data from epidemiologic studies, clinical trials and special populations
- 13 approved positions published in 2020

- Muscle weakness, as defined by **low grip strength**, should be included in the definition of sarcopenia
  - Sex-specific cutpoint may vary by age, race, disease and other factors
- **Usual gait speed** should be included in the definition of sarcopenia
- Lean mass by DXA should not be included in the definition of sarcopenia

“The SDOC position statements… offer a rational basis for an evidence based definition of sarcopenia.”

I Find it Surprising that Gait Speed is as an Essential Part of the Diagnosis

- Slow gait speed can be due to:
  - Sarcopenia
  - Osteoarthritis
  - Cardiac disease
  - Respiratory disease
  - Neurologic disease
  - Obesity
  - Etc
- Medications to address low muscle mass/function seem likely to fail in clinical trials that include gait speed as part of primary outcome
Not All, but Some Studies Find Gait Speed Unrelated to Three Measures of “Muscle” Mass

Gait speed is associated with mortality\(^1\) because it indicates that “something” is wrong. It seems unlikely to be altered by a drug that increases muscle mass/function and thus unwise to be part of the definition of sarcopenia and a primary endpoint of clinical trials.

Personal opinion

\(^1\)Studenski, et. al., JAMA, 2011; 305: 50-58
Increased Muscle Mass *Has to Translate to Improved Strength/Performance*

If it doesn’t, why do professional athletes look like this?

Lack of an easy study primary outcome that also can be used clinically (e.g., BMD) has inhibited drug development.
Why Can’t we Just Use DXA-measured Appendicular Lean Mass?

ALM is NOT muscle; it is primarily WATER

“Ugly giant bags of mostly water.”
Star Trek TNG; Home Soil; season 1

IAEA Human Health Series, #15, 2010; pp 21
Extracellular Water is Preserved With Age While Intracellular Water Declines

Used bio-impedance spectroscopy to measure lower leg
- Total water
- Intracellular water (ICW) and
- Extracellular water (ECW)

“The expansion of ECW relative to ICW… masked actual muscle cell atrophy with aging.”

It is Possible to Improve DXA: Combine With BIS and Measure Legs

“Creation of a variable (ALM/E/Ic) …. could well be an improved approach to predict functional status. DXA-measured ALM should be corrected for fluid distribution.”

Kuchnia, et. al, Arch Osteoporos, 2018; 13: 97

“Corrected leg lean mass [LLM/(E/I)L] is a powerful and clinically relevant method that accounts for muscle quality.”

Unclear why

Rush, et al, JBMR Plus, V5, August 2021, e10527
You All Know About Opportunistic CT for Bone; Could CT Be Used to Assess Muscle?

Outpatient cohort; 9223 adults mean age 57 with CT followed for median of 8.8 years; 686 major and 219 hip fractures

Muscle HU and bone HU are comparably related to MOF

CT not ideal due to cost and radiation exposure

Deuterated Creatine Dilution Looks Promising as a Measure of Muscle Mass

- ~98% of total body creatine in skeletal muscle
  - Creatine turned over via conversion to creatinine
- Oral dose of deuterated creatine ($D_3$-creatine) is 100% bioavailable and transported to skeletal muscle
- Urinary enrichment reaches steady state at ~2 days and remains stable for 2
- Requires only oral dosing and a single spot fasted urine

Highly correlated ($r = .87$) with MRI whole body muscle

Evans, et. al., J Cachexia Sarcopenia Muscle, 2019; 10: 14-21
Muscle Mass by D₃-creatine Dilution Related to Performance and Falls

- 1382 men in MrOS
- Mean age 84.2 yrs
- SPPB and self reported falls

Muscle mass by D3-creatine correlated with function

Lowest quartile OR for serious injurious falls 2.49

Only 14 articles in PubMed since 2018
Unclear why so few

Even If/When a Diagnostic Approach And Primary Endpoint is Agreed Upon, A Drug is Still Needed

New Osteoporosis Drug Wins F.D.A. Approval
By Warren E. Leary
Oct. 3, 1995

See the article in its original context from October 3, 1995, Section C, Page 7 | Buy Reprints

New York Times subscribers* enjoy full access to TimesMachine—view over 150 years of New York Times journalism, as it originally appeared.

SUBSCRIBE

*Does not include Crossword-only or Cooking-only subscribers.

ASSAMMENT OF FRACTURE RISK AND ITS APPLICATION TO SCREENING FOR POSTMENOPAUSAL OSTEOPOROSIS
Report of a WHO Study Group

My bias is that osteoporosis advanced because there was a diagnosis (DXA T-score) and a drug (alendronate). No widely available quantifiable test for muscle and there is no drug therapy…
Objectives of SPRINTT

- Provide operationalization of physical frailty & sarcopenia
  - Mobility disability; inability to walk 400 meters in 15 minutes
- Identify a target population of older adults
- Evaluate effectiveness of a multicomponent intervention
  - Nutritional counseling and exercise aerobic, strength, flexibility and balance
- 1519 community dwelling men and women age 70+
- SPPB 3-9; able to walk 400 meters

Incident mobility disability at 36 months in those with SPPB of 3-7 (n = 1205)

No effect if SPPB 8-9

"Such an intervention may be proposed as a strategy to preserve mobility in older people at risk of disability."

Bernabel, et. al., BMJ, 2022; 377:3068788
Is SPPB (Short Physical Performance Battery) The Best Inclusion Criterion?

SPPB of 3-7 being proposed for at least 1 current medication study

Maximum 12 possible points

- **Gait speed** (Timed 4 meter walk)
  - 0 = unable; 1 if > 8.7 sec; 2 6.2-8.7 sec; 3 if 4.8 to 6.2; 4 if < 4.8 sec

- **Chair stand** (Time to rise from a chair 5x without using arms)
  - 0 = unable w/in 60 sec; 1 = > 16.7 sec; 2 = 13.7-16.7; 3 = 11.2-13.7; 4 = < 11.2

- **Tandem stance**
  - Side by side, then semi-tandem, then tandem stance for 10 sec

Use of a Low (i.e., Bad) SPPB is Targeting a Severely Affected Population

- Planned clinical trial; inclusion SPPB 3-7
- A prior study by our group
- Inclusion criteria: age 70 years+, residing in community or retirement facilities, able to stand without assistance, no clinically significant acute disease and able to sign IC

48M/48F; mean age 80.8 years, mean BMI 25.6 kg/m²
7% SPPB < 7; none below 6

I worry that this is comparable to requiring multiple vertebral fractures as the inclusion criterion in pivotal osteoporosis medication trials

Will improvement in ability to walk 400 meters within 15 minutes in a severely limited patient population impress patients, clinicians, regulators or 3rd party payers?

Data from Buehring, et. al., J Am Geriatr Soc, 2013; 61: 418-22
Suggestions for design of RCTs for sarcopenia/frailty

- Primary outcome: Mobility disability
  - Inability to walk 400 m within 15 minutes
- Clinically relevant change muscle strength and/or function
  - Short physical performance battery (SPPB), gait speed, grip strength
- Body composition, e.g., ALM
- Falls
- Use of health and social care services

Cesari, et. al., J Frailty Aging, 2022; 11: 135-142
Many Medications Being Considered

"Several promising agents are in the pipeline and currently being explored...

The importance of combining pharmaceutical and exercise interventions should not be overlooked."
Integrating Sarcopenia and Falls into FRAX Would be an Ideal Way to Facilitate Clinical Implementation

**Questionnaire:**

1. Age (between 40 and 90 years) or Date of Birth
   - Age: 60
   - Date of Birth: Y: _, M: _, D: 
2. Sex
   - Male
3. Weight (kg)
   - 96
4. Height (cm)
   - 184
5. Previous Fracture
   - No
6. Parent Fractured Hip
   - No
7. Current Smoking
   - No
8. Glucocorticoids
   - No
9. Rheumatoid arthritis
   - No
10. Secondary osteoporosis
    - Yes
11. Alcohol 3 or more units/day
    - Yes
12. Femoral neck BMD (g/cm²)
    - GE-Lunar: 0.753 T-score: -2.1

**Falls**
- Any fall: 75%
- Injurious fall: 28%

**Sarcopenia**

**Diabetes**

**Symptomatic Osteoarthritis**
A FRAX Update is Coming

• 64 cohorts; mostly population based
  • > 2.1 million participants, 20+ million person years, >194,000 fractures

• FRAXplus™; web based adjunct that will adjust fracture probability including:
  • Site/recency of prior fracture, L-spine BMD, glucocorticoid dose, TBS, DM, falls history

• Facilitate identification of those at highest risk for fracture

Vandenput, et. al, IOF oral presentation, March 2022
Johansson, et. al., IOF oral presentation, March 2022
The field is struggling with a diagnostic test and medications are not close to the clinic.

Unclear when FRAXplus will be available.

What can we do clinically now?
Emphasize Non-pharmacologic Fracture Risk Reduction Approaches

• Falls risk reduction
  • Exercise, physical therapy, balance training

• Nutrition
  • Despite obesity epidemic undernutrition common in older adults
    - ~40% of hip fracture patients have energy/protein malnutrition
  • Inadequate protein intake reduces muscle synthesis
    - ~40% of older adults not meeting current RDA of 0.8 g/kg daily
    - Protein intake of 1.2-1.5 g/kg daily is likely optimal
  • Optimize calcium intake and vitamin D status

• Prescribe bone drugs when fracture risk is high

Mithal, et. al., Ost Int, 2013; doi 10.1007/s00198-012-2236y
Clinically, Ask About Falls

• How many times have you fallen in the past year?
  • Did any of these falls cause injury?
• Would you please stand up for me?

If history of falls, particularly injurious falls and/or cannot arise without use of arms:

Likely has sarcopenia and is at increased risk for falls and fracture
A Clinical Common Sense Falls Approach

1. Ask About Falls

- “When was the last time that you fell down?”
- “Tell me about it”
  - Circumstances, prodrome, environmental factors, time
  - Can risk taking behaviors be addressed?
- “How many times have you fallen in the last year?”
- “Did any of these falls cause injury?”

Based on AGS/BGS 2010 Guideline: Prevention of Falls in Older Persons available at americangeriatrics.org
A Clinical Common Sense Falls Approach

2. Reduce or Eliminate Medications

- Neuroleptics, antipsychotics, antidepressants
- Incontinence medications (strong anticholinergics)
- Sleepers; including OTC
- Antihistamines, 1st and 2nd generation
- Any medication with: “drowsiness, dizziness, dry mouth, ataxia, confusion….” as adverse effects
- Ask about ETOH; alone or interacting with meds

Based on AGS/BGS 2010 Guideline: Prevention of Falls in Older Persons available at americangeriatrics.org
A Clinical Common Sense Falls Approach

3. Consider Physical Therapy Evaluation

- For “gait abnormality, falls, balance and strengthening assessment and treatment”
- Assess need for assistive device and if so teaching

Based on AGS/BGS 2010 Guideline: Prevention of Falls in Older Persons available at americangeriatrics.org
Exercise is Routinely Recommended

- Improves muscle strength
- Preferably resistance training
  - This works; strength gains of 30% to >100% rapidly
- Injuries not common but do occur; may require supervision
- Recent review concluded “…resistance and endurance exercises prevent development of sarcopenia.”

Papadoupoulou, et. al., Nutrients 2021, 13; 4499. doi.org/10.3390/nu13124499

- But, we don’t exercise….
  - Only 32% of 23,153 adults age 35-65 years exercise for ≥ 3.5 hours per week  Ford, et. al., Arch Intern Med, 169;1355-1362, 2009
  - ~12% of people age 65-74 and 10% of those ≥ 75 perform strength training exercise two or more days/week  MMWR, 53;25-28, 2004
“What is the best exercise to prevent falls?”

“The best exercise program is one that you will actually do.”

Personal opinion
Recommend Balance Training: Tai Chi Works

“Tai Chi is strongly recommended as an appropriate and safe exercise for older adults for general health and fall prevention.”

Osteoporosis Society of Hong Kong Guidelines

- A low impact exercise that requires high neuromuscular coordination
- Short term training improved trunk flexibility, leg muscle strength, muscle endurance, balance and coordination
- Reduces risk of multiple falls

Huang, et. al., BMJ Open 2017;7:e013661

Meta-analysis
- 18 trials
- 3894 participants
- Reduced number of fallers and rate of falls
Is Vitamin D Important in Muscle Function or Falls?

The field is in chaos; I don't believe that anyone knows the right answer.

“...higher monthly doses of vitamin D had no benefit on lower extremity function and were associated with increased risk of falls.”

“The use of vitamin D supplement, especially vitamin D$_3$ could reduce incidence of fall. Only vitamin D with calcium supplement showed benefit in fracture reduction.”


“The USPSTF found adequate evidence that vitamin D supplementation has no benefit in preventing falls in older adults. The USPSTF recommends against vitamin D supplementation to prevent falls in community-dwelling adults.”

“...higher monthly doses of vitamin D had no benefit on lower extremity function and were associated with increased risk of falls.”

Bischoff-Ferrari, et. al, JAMA Intern Med, 2016;176: 175-183
Clinical Trials and Subsequent Meta-Analyses Need to Focus on Biology Not Just Trial Methodology

“*The question of how much vitamin D is* Meta-analyses of flawed RCTs *yield flawed conclusions methodology rather than on biology*”

Heaney, RP, NEJM, 2012, 367, 77-78
Nutrition RCTs Are Flawed by Failure to Consider Basal Vitamin D Status

• “...If the basal status is deficient, then an increase in intake will usually produce a measurable benefit.

• If the nutritional status is replete, an increase in intake will usually produce a null effect,

• and if the nutritional status is high, an increase in intake might be expected to increase risk of toxicity.”

“This point is so obvious from simple inspection of the curve that one should have thought it would go without saying.”

Heaney RP, Nutr Reviews 2013, 72:48-54
“Vitamin D₃ supplementation did not result in a significantly lower risk of fractures than placebo among generally healthy midlife and older adults who were not selected for vitamin D deficiency, low bone mass, or osteoporosis.”


Note: Mean 25(OH)D at baseline = 30.7 ng/mL

“...no subgroups defined according to baseline 25(OH)D level, even below 20 ng/mL, benefited from supplements. Thus, there is no justification for measuring 25(OH)D in the general population or treating to a target serum level.

.....those receiving treatments for osteoporosis that might cause hypocalcemia may benefit from vitamin D supplementation; the need for measuring serum 25(OH)D levels in these groups remains uncertain.

The fact that vitamin D had no effect on fractures should put to rest any notion of an important benefit of vitamin D alone to prevent fractures in the larger population. .. providers should stop screening for 25(OH)D levels or recommending vitamin D supplements, and people should stop taking vitamin D supplements to prevent major diseases or extend life.”

Cummings and Rosen, N Engl J Med, 2022; 387:368-370
"No subgroups benefitted…"
Could we expect fewer fractures in those with low 25(OH)D?

Unlikely to demonstrate fracture reduction in a study of ~400 people.

In my opinion, VITAL decisively proves that vitamin D is a vitamin, not a bone active drug. The facture data in the small group with low 25(OH)D does not seem decisive for patients with osteoporosis or prior fracture.
## Table. Summary of USPSTF Rationale

<table>
<thead>
<tr>
<th>Rationale</th>
<th>Assessment</th>
</tr>
</thead>
</table>
| Detection                                      | • Vitamin D requirements may vary by individual, and there is no one 25(OH)D level that defines deficiency for all individuals.  
• Total 25(OH)D levels are currently considered the best marker of vitamin D status; however, levels are difficult to measure accurately.  
• Evidence suggests that results vary by testing method and between laboratories using the same testing methods.                                                                                     |
| Benefits of early detection and intervention and treatment | • No direct evidence on the benefits of screening for vitamin D deficiency.  
• Adequate evidence that treatment of asymptomatic vitamin D deficiency has no benefit on mortality, risk for fractures in persons selected solely on the basis of low vitamin D levels (as opposed to clinical risks such as low bone density), or incidence of type 2 diabetes mellitus.  
• Inadequate evidence on the benefit of treatment of asymptomatic vitamin D deficiency on other outcomes, including falls, cancer, cardiovascular events, depression, infection, or physical functioning.  
• Despite adequate evidence to conclude no benefit for a few health outcomes, evidence on the benefits of treatment of asymptomatic vitamin D deficiency in adults for other health outcomes remains inadequate.  
The overall evidence on the benefits of treatment of asymptomatic vitamin D deficiency in adults is inadequate.                                                                 |
| Harms of early detection and intervention and treatment | • No direct evidence on the harms of screening for vitamin D deficiency.  
• Adequate evidence that the harms of treatment of vitamin D deficiency are small to none.                                                                                                                                 |
| USPSTF assessment                              | The overall evidence on the benefits of screening for vitamin D deficiency is lacking. Therefore, the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults cannot be determined.                                                                 |

IF We Are Going to Measure 25(OH)D and Recommend Supplements; What is the Target?

No consensus regarding optimal 25(OH)D concentration

How Can This Be?

Red = severe deficiency; Orange = mild deficiency; Green = Sufficiency, does not benefit from additional supplementation

From Sempos & Binkley, Public Health Nutr, 2020; 23: 1153-1164
We May Not Know Subjects Vitamin D Status at Study Start (Often vitamin D replete and generally have not used standardized 25(OH) measurements)

We Don’t Know Subjects Vitamin D Status at Study End (Different 25(OH)D increase between people)

Huge Bolus Dosing Not the Same as Daily Supplementation

The “Evidence” is Flawed

Clinically; Apply Common Sense

Personal opinion
Common Sense; Target the 25(OH)D Level of Highly Sun-exposed People

Mean 25(OH)D 36 ng/mL using standardized assay)
Binkley, et. al, Presented at ASBMR 2017; manuscript in preparation

Mean 25(OH)D 46 ng/mL
Recognize that Assay Variability Exists:
Aim a Little High

To Maintain Serum 25(OH)D of $\geq 20$ ng/mL or $\geq 30$ ng/mL

<table>
<thead>
<tr>
<th>Measured</th>
<th>“True” Value</th>
<th>Maintain</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH)D</td>
<td>20 ng/mL</td>
<td>~17 to ~ 23 ng/mL</td>
<td>~30 ng/mL</td>
</tr>
<tr>
<td>25(OH)D</td>
<td>30 ng/mL</td>
<td>~24 to ~36 ng/mL</td>
<td>~40 ng/mL</td>
</tr>
</tbody>
</table>

With this approach, the maximum is likely to be ~40 to ~50 ng/mL, below that attainable by UV exposure.
Older Adults Have Higher Protein Needs

Many reasons for this

Deutz, et al., Clin Nutr, 33, 929-936, 2014
Expert Group Recommendations

- For health older people, the diet should provide at least **1.0 to 1.2 g protein/kg body weight/day**
  - Not clear whether best spread across meals or as a large “pulse”
  - Not clear that specific amino acids, e.g., leucine, are best

- For older people who are malnourished or at risk of malnutrition (acute or chronic illness) diet should provide 1.2-1.5 g/kg/day with even higher intake if severe illness

  Deutz, et. al., Clin Nutr, 33, 929-936, 2014

- A protein intake of **1.0-1.2 g/kg of body weight per day** is probably optimal for older adults

  Mithal, et. al., Osteoporos Int, 24, 1555-1566, 2013
A Need Exists for an Older-Adult Friendly Protein Calculator Plus Easy to Follow Guidance Regarding How to Get Enough

\[ \sim 85 \text{ kg} \times 1.2 \text{ g/kg} = \sim 100 \text{ grams} \]

- 3 eggs \sim 18 \text{ g}; toast \sim 3 \text{ g}
- Ham/cheese sandwich \sim 20 \text{ g}
- 1 8 oz glass milk \sim 8 \text{ g}
- 4 oz chicken \sim 30 \text{ g}
- 1 cup cottage cheese \sim 25 \text{ g}

USDA Dietary Guideline (2020) - 10-30% energy: 73 - 219 grams (291 - 874 kcal)

WHO/FAO (2007) - 0.83 g/kg body weight: 72 grams (286 kcal)
Clinically, Think About When to Intervene….

Dogma States Bone & Muscle Decline With Age

Thus, intervening any time would be fine…
Dogma is Likely Incorrect

Acute illness causes step-wise bone/muscle loss
Bone/Muscle Loss Occurs With Hospitalization
Increases fracture risk

- Risedronate phase 3 trial annualized bone loss in the placebo group ~ twice as great if SAE of hospitalization\(^1\)
- 214 hospitalized older adults (mean age 78); 45% had acute reduction in ADL function and 15% fell within 1 month of hospitalization\(^2,3\)
- Chart review of 3075 older adults age 70-79 years mean f/u 6.6 years\(^4\)
  - 66% hospitalized; 26% 3 or more times

\(^1\)Heaney, et. al., Osteoporos Int, 2006; 17:212-216
\(^2\)Mahoney, et. al, J Am Geriatr Soc, 1994; 42:269-274
\(^3\)Mahoney, et al., Arch Intern Med, 2000; 160:2788-2795
\(^4\)Gardner, et. al., Arch Intern Med, 2008; 168:1671-1677
Illness/Hospitalization is the Time to Intervene

Personal opinion

When muscle and bone active medications become available they should be used after illness/hospitalization
From a Health Systems Standpoint: Consider Orthogeriatric Care

Orthogeriatric care is a medical-surgical multidisciplinary care model that brings health professionals from trauma, orthopedics and geriatric medicine together to treat the fracture and frailty issues affecting people with fractures (generally hip)

- Intuitively logical
- Various models exist
  - Ortho admission/geriatrics consult
  - Geriatrics admission/ortho consult
  - Integrated care model
“There is moderate quality evidence that orthogeriatrics reduces length of stay, in-hospital mortality, 1-year mortality, and delirium of hip fracture patients and may reduce complications and cost, while the effect on functional outcome is inconsistent.

There is currently insufficient evidence to recommend one or the other type of orthogeriatric care model.”

Heghe, et. al., Calcif Tissue Int, 2022; 110:162–184
Success in Progress

What does the bone/muscle field need?

• An accurate and widely available measure of muscle mass
  • D₃ creatine, BIS, DXA/BIS, CT
• An improved target for RCTs
  • Muscle mass, function, falls, BMD/fractures?
• Medication(s) that improves both muscle and bone mass
  • ? (they have to be out there….)
• Education of clinicians and patients with implementation
  • This should not be a difficult as bone medications; patients will feel better/note improved function
Bone/Muscle and Fracture Risk
What to do clinically today

- Reduce falls
  - Ask “How many times have you fallen in the past year?”
  - Observe gait, ask to stand up without use of arms
  - Implement falls risk reduction strategies including Tai Chi & PT consult
- Reduce medications
- Optimize calories, calcium, vitamin D and protein status
  - 1,000-1,200 mg calcium daily
  - 2,000 IU vitamin D daily is reasonable
  - Measure 25(OH)D in those with falls/fractures
- Use existing osteoporosis medications to treat the bones when fracture risk is high
- Implement orthogeriatrics model if feasible
- Watch for improved muscle measurement(s) and, hopefully medications active on bone and muscle

Personal opinion
Thank You