Sarcopenia ("Dysmobility Syndrome")
The Future of Fracture Risk Reduction?

Northern California Institute for Bone Health
Update on Osteoporosis and Skeletal Health, May 20, 2016

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On Our Watch, We Have Failed to Prevent Fractures

~80% of Those Who Break Their Hip Receive NO Treatment to Reduce Future Fracture Risk (and it’s getting worse)


Why Do You Treat “Osteoporosis?”

Fracture is What’s Important
We Need to Convey the Message That Fractures Indicate Disease (Just Like Heart Attacks Indicate Disease)

“I had a heart attack climbing stairs. I have high cholesterol and blockages in the arteries to my heart.”

“I broke my ______ falling down the stairs. It was an accident; anyone would have fractured if they fell like I did.”

Focusing Only on Bone Identifies Less than Half of Women Who Will Fracture

Only 44% of women (and 21% of men) who sustain non-vertebral fractures have “osteoporosis” by BMD

Focusing Only on Bone Identifies Less than Half of Women Who Will Fracture

Remember that Fracture Calculators are An Imperfect Estimate of Risk

“FRAX® assessment does not tell you who to treat which remains a matter of clinical judgement.”

How Might We Improve Clinical Judgment To Help Us Better Identify Those Who Will Fracture?

“THINK!”

G. Magnin, M.D.

Think “Beyond the bone”
But Bone Mass Does Not Have A Similar Dramatic Decline After Age 70

The Increase in Fracture Risk Must Include Something Else in Addition to BMD


We Know That “Age” Powerfully Predicts Fracture

Adapted from Hui, JC1188;811804-BMD

Chronologic Age is a Poor Predictor of Functional Status

There must be a better way to estimate a patient's fracture risk than simply using age....

Why Do Fractures Increase With Age?

Multiple reasons....
- Falls become common with advancing age
  - ~1/3rd of adults age 65 and >40% over age 75 fall each year
- Many osteoporosis-related fractures due to falls
  - Over 90% of hip fractures due to falls

Guideline for falls prevention; AGS/BGS, JAGS 49:664-672, 2001

Does Age Truly Affect Fracture Risk?

- Dubbo osteoporosis study; 3851 men and women age 60+
- All fractures x-ray confirmed
- Measured BMD, body sway and quad strength

"Subjects with fracture have significantly higher body sway and lower muscle strength than subjects without fracture and, more importantly, that age alone has NO influence on the probability of fracture."


Falls Risk Factors Predict Hip Fracture Independent of BMD

- These risk factors include
  - History of falls
  - Self reported health
  - Self reported physical activity
  - Slower walking speed

Surrogates of sarcopenia

Sarcopenia/Impaired Function Is What Actually Predicts Fracture

Masud & Morris. 2009. Age & Ageing 38;Suppl 43:7
Impaired Physical Performance Increases Hip Fracture Risk

Evaluated the association of physical performance and hip fracture risk in MrOS: 5995 men age 65+

“Poor physical function is independently associated with an increased risk of hip fracture in older men.”

Adapted from Cawthon, et al., J Bone Miner Res, 2008, 23:1037-1044

Sarcopenia: the Age-related Gradual Loss of Muscle mass, Strength and Function

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.”


There is No Single Consensus Definition of Sarcopenia at this Time

All current definitions include a measure of lean mass and measure(s) of physical function

<table>
<thead>
<tr>
<th>European Working Group</th>
<th>International Working Group</th>
<th>Foundation of the NIH</th>
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<tbody>
<tr>
<td>ALM/BMI</td>
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<tr>
<td>M: 7.26 kg/m²</td>
<td>M: ≤ 7.23 kg/m²</td>
<td>M: ≤ 0.769 F: ≤ 0.512</td>
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<tr>
<td>F: 5.45 kg/m²</td>
<td>F: ≤ 5.67 kg/m²</td>
<td>F: ≤ 0.312</td>
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<td>Gait Speed: ≤ 0.8 m/s</td>
<td>Gait Speed: ≤ 1.0 m/s</td>
<td>Grip Strength: M: ≤ 30 kg F: ≤ 20 kg</td>
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Cruz-Jentoft, Age Aging, 2010, 39:412-423

Fielding, JAMDA, 2011, 12:249-256


Consequences of Sarcopenia Include:

- Impaired ability to perform activities of daily living/functional impairment
- Falls
- Fractures
- Reduced quality of life
- Healthcare costs
- Death

“Impaired muscle strength is highly predictive of incident disability and all-cause mortality in the elderly.”


Women with Hip Fracture Often Have Sarcopenia and Osteoporosis by DXA

313 white women with low-trauma hip fracture
- Sarcopenia: ALM/BMI < 4.54 kg/m²
- Osteoporosis, Femur T-score ≤ -2.5

“We show... A significant association between sarcopenia and osteoporosis in a large sample of hip-fracture women. Data supports... preventive strategies and treatment options for sarcopenia and osteoporosis targeting both bone and muscle...”


Osteoporosis Pathogenesis is Multifactorial

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


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Perhaps the Diagnosis Should be “Sarco-osteoporosis”

Interdependency of Bone and Muscle is Not a New Concept

Even Bone + Muscle Isn’t the Whole Story

Sarcopenic Obesity: The combination of low muscle mass and function (sarcopenia) and high fat mass (obesity) that adversely affects health and independence

Too Little Bone, Too Little Muscle and Too Much Fat is Bad...

Should the Diagnosis be “Osteo-Sarcobesity?”
Combining Clinical Information for Risk Calculation and Diagnostic Classification Criteria is NOT a New Idea

Consider the Heart Attack Analogy
Treatment is Directed at Various Conditions to Reduce Risk For a Potentially Catastrophic Outcome

The Same Approach Makes Sense for Musculoskeletal Health
Treatment Should be Directed at Various Conditions to Reduce Risk For a Potentially Catastrophic Outcome

A Potential Score-Based Approach to Diagnose Poor Musculoskeletal Health / Dysmobility Syndrome
- Risk factors were arbitrarily selected:
  - Low Appendicular lean mass / height$^2$
  - High percent body fat
  - Osteoporosis based on BMD T-score ≤ -2.5
  - Low grip strength
  - Slow gait speed
  - History of ≥ 1 fall in last 12 months
- 1 point per risk factor for a total possible score of 6
- Dysmobility syndrome was defined by a score of ≥ 3

Is There Any Evidence That Dysmobility Syndrome is Linked to Adverse Health Outcomes?

- National Health and Nutrition Examination Survey (NHANES) 1999-2002 Dataset
- NHANES data was linked to National Death Index
- Dysmobility defined as 3 or more of high body fat, osteoporosis, low muscle mass, low muscle strength, slow gait or falling risk
- Adapted the originally proposed risk factors
  - Knee strength was used instead of grip strength
  - Balance problems instead of history of falls
Dysmobility Syndrome: An Important Concept but Clearly a Work in Progress

- Which factors to include requires further study:
  - Arthritis?
  - Multiple Fractures?
  - Multiple and/or injurious falls
  - Diabetes?
  - Neuropathy?
  - Others??
- Factors likely need to have different weights rather than simply being scored equally
- Dysmobility syndrome predicts falls and mortality
  - Additional studies need to examine whether it predicts other health outcomes, e.g., falls and fractures

Diabetes Almost Certainly Should be Included as a Risk Factor

Manitoba, CA clinical data
3518 M/W age 50+ with, and 36085 without DM at Time of BMD testing
Mean f/u 5.4 years
Fx ascertained by ICD code

“FRAX underestimated observed major osteoporotic and hip fracture risk in diabetics. We conclude that diabetes confers an increased risk of fracture that is independent of FRAX derived with BMD.”


Osteoarthritis Perhaps Should Also Be Included as a Risk Factor

- 2412 women and 1452 men; age >45 years
- Dubbo Osteoporosis Epidemiology Study (DOES)
- Median follow-up 7.5 years
- OA by self-report
- Fx incidence from X-ray reports

“Women with OA have an increased risk of fragility fracture”


Integrating Dysmobility Risk into FRAX is an Ideal Way to Facilitate Clinical Implementation

Questionnaire:
- Age (between 45 and 75 years)
- Gender
- Height (cm)
- Weight (kg)
- Previous fracture
- Patient reported fracture
- Current smoking
- Hypertension
- Cardiovascular disease
- Diabetes
- Fracture risk was significantly higher in women with OA; Mainly observed in osteopenia

Development of Such a Calculator Will Take Time: Can We “Diagnose” Dysmobility in Clinic Today?

We Should Not Require a Consensus Definition: We Can Ask our Patients

◆ 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/dysmobility and is at increased risk for falls and fracture

A Recent Patient Who (I Think) Has Dysmobility Syndrome….

66 yo white male; recent L hip fracture with a fall in his garage
Wt 248#, Ht 5’ 11” (BMI = 34.6), severe knee OA and unable to arise from chair without use of his arms; Labs ALL normal

In Summary:
THE DISEASE IS FRACTURE
Osteoporosis, Sarcopenia, Obesity, DM and “Other” Conditions are Part of the Fracture Risk Syndrome

How Can We Take This to Clinical Care?

Seems Likely That We Will Follow the Current “Osteoporosis” Paradigm

Existing and Future Dysmobility Syndrome Treatments Look Like What We are Currently Calling Osteoporosis Treatment

◆ Nutrition
  ◆ Under-nutrition is common
  ◆ ~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
  ◆ Calcium and Vitamin D
  ◆ Exercise/physical therapy/falls risk reduction
  ◆ Medications

Why is There So Much Controversy and Confusion About Bone/Muscle Nutrition?
Most Studies Fail to Recognize that Nutrients are Not the Same as Drugs

Calcium Required for Bone
Vitamin D Required for Bone & Muscle
- Calcium ~1200 mg/day (diet + supplements)
- Vitamin D: USPSTF and AGS recommend vitamin D to reduce falls risk
  - Daily intake = "enough"

If You Are Going to Supplement and Not Measure 25(OH)D, Need to Give a High Dose to Assure Achieving a Level > 30 ng/mL

In this study of 91 postmenopausal women receiving 2,500 IU daily, 40% did not attain a 25(OH)D of >35 ng/mL

We Need More Protein To Preserve Muscle Mass and Function
Expect new dietary intake recommendations sometime in the not too distant future
1.2 grams/kg = ~54 grams/100 pounds
190 lb = ~100 grams...
(I need to eat a chicken breast, 3 large eggs, a can of tuna and a glass of milk)

Exercise Works
- Improves muscle strength
- Preferably resistance training
  - This works; strength gains of 30% to >100% rapidly
- Injuries not common but do occur
- May require supervision (PT)

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, 168:1351-1359, 2008)
- ~12% of people age 65-74 and 10% of those ≥ 75 perform strength training exercise two or more days/week
US Adults Spend ~60% of Total Leisure Time Doing One Activity


Need Cultural Change Towards Exercise

Mark Twain Had It Wrong.....

"Whenever I get the urge to exercise, I lie down until the feeling passes away."

DO SOMETHING.....

LIFE: Lifestyle-integrated Functional Exercise Program (Examples)

Potential Pharmacologic Approaches for Dysmobility Syndrome Include

- Anabolic steroids
- Selective androgen receptor agonists
- Myostatin antagonists
- Others

Is Testosterone the Way to Prevent Bone Attacks?

- ADAM Questionnaire (Androgen Deficiency in the Aging Male)
  - Do you have a lack of libido?
  - Do you have a lack of energy?
  - Do you have a decrease in strength and/or endurance?
  - Are you falling asleep after dinner?
  - Are you grumpy?

"Additional large-scale research is needed to provide the data necessary to determine the safety and efficacy of hormone replacement with age and to elucidate what its influence is on functional performance, enhanced health span and longevity."


This is NOT Why I Think Sarcopenia Medications are Needed
This is Why I Think Muscle Medications are Needed

Muscle Medications Might Ideally be Used After Illnesses/Events to Get Back to Baseline

Current Osteoporosis Medications

- Estrogen
- Raloxifene (Evista)
- Calcitonin (Miacalcin)
- Bisphosphonates
  - Alendronate (Fosamax)
  - Risedronate (Actonel)
  - Ibandronate (Boniva)
  - Zoledronate (Reclast)
- Teriparatide (Forteo)
- Denosumab (Prolia)

These medications work; they cut fracture risk approximately in half

Bisphosphonates Are Extremely Well Studied and Documented to Reliably Reduce Fracture Risk by ~50%

In People at High Risk for Fracture, Especially Those Who Have Recently Sustained a Fragility Fracture, BPs (or other osteoporosis medications) Should be Prescribed for 3-5 years

People are concerned about drug risks but not fracture risk; We need to convey drug and disease risk

Comprehensive Treatment After Hip Fracture Reduces Mortality and NH Readmission

124 patients with hip fracture 12 mo of high-intensity weight lifting exercise and targeted treatment of balance, osteoporosis, nutrition, vitamin D/calcium, depression, cognition, vision, home safety, polypharmacy and social support vs. usual care

The intervention reduced mortality, nursing home admissions and ADL dependency compared with usual care.

Sarcopenia/Dysmobility What Can We Do Today?

- Recognize the problem; dysmobility with falls and fractures:
  - May be fatal
  - May lead to inability to live independently
  - Can be prevented (or at least have the risk for another reduced)
- Reflects disease of bones/muscles (and other systems): it’s not just “getting old”
  - Having falls/fractures indicates increased risk for another
- Requires evaluation: it’s not just “I fell”
Use "osteoporosis" medications to treat the bones
Consider the Garvan calculator to advise re: fracture risk in patients with sarcopenia/falls
Many patients “know” that osteoporosis drugs are “bad”

68 yo White woman, wt 200#, ht 64”, T-score -2.0, wrist Fx, 3 falls last year

Many patients “know” that osteoporosis drugs are “bad”

Reduce falls
- Ask “How many times have you fallen in the past year?”
- Observe gait, ask to stand up without use of arms
- “The usual” falls risk reduction strategies including a PT consult
- Recognize that obesity increase risk

Food is a good thing, but excess is not
Nutritional supplements improve outcomes after hip fracture

Optimize vitamin D status
- 2,000 IU daily is a reasonable place to start
- Measure 25(OH)D in those with falls/fractures

Use existing “osteoporosis” medications to treat the bones

It is My Opinion That “Age-Related Fracture” is the Disease and That This Results from a Syndrome of Osteoporosis, Sarcopenia, Obesity and Diabetes Plus Other “Stuff”
We Need to Focus Not Just on Bone, But On the Patient

“The good physician treats the disease; the great physician treats the patient who has the disease.”
Sir William Osler

Thank You