Dysmobility Syndrome: The Future of Fracture Risk Reduction?
NAMS, Oct 14, 2017
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Why Do You Treat “Osteoporosis?”
Fracture is What’s Important and We Are Failing to Prevent Them.....

Disclosures
Research support
Novartis
Viking
Consultant
Amgen
Radius

• Some of this talk is my opinion
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United HealthCare data:
Proportion of patients in each quarter (2004-2013) who received a BP or other osteoporosis med after hip fx
- n = 22,000+
- Average age 72
- 68% female

Kim, et. al., J Bone Min Res. 2016. DOI: 10.1002/jbmr.2832

Less than 1 in 10 patients with hip fracture are being treated
“To draw an analogy from another field, in 2016 it is virtually inconceivable that a patient discharged from the hospital following a myocardial infarction would not be prescribed a full armamentarium of drugs for secondary cardiovascular prevention (eg, a statin, antihypertensive, and others). Yet what is inconceivable for a patient following a myocardial infarction is the norm in the vast majority of patients discharged from hospital after a hip fracture.”

Failure Personified
67 year old female; seen by FLS December 2016
COPD with intermittent prednisone bursts
Dietary calcium low at ~300 mg/day
Received ALN for a few months 2013
History of falls which resulted in:
– Left distal tibial fracture age 63
– Left hip fracture at age 64
– Left distal radius fracture age 65
– Humerus and patella fracture age 65
Most recent DXA April 2014 LS -2.4, FN -2.2
Seen by FLS after humerus/patellar Fx
Work up including DXA initiated

“Insanity: doing the same thing over and over again and expecting different results.”
Albert Einstein

A Different Approach to “Osteoporosis” is Needed

A Potential Approach to Improve the Osteoporosis Care Crisis

Change the focus from osteoporosis to fracture
Include ALL fractures in older adults
Acknowledge that fractures affect QOL and independence
Consider osteoporosis as just one part of a syndrome leading to fracture
Need to address all components of the syndrome, not just the bones
“…..we have demonstrated that there appeared to be nothing “fragile” about a fragility fracture based on patients’ communication of their fracture.”

“….. in other words, the term fragility or low trauma,…..does not resonate with patients.”

Get Rid of the “Fragility Fracture” Concept
Fragility Fracture, Osteoporosis-related Fracture, Low-trauma Fracture, etc May Be Part of the Problem

“…..even fractures occurring with intermediate or high trauma are predictive of recurrent fractures. As a result, we suggest that all fractures in older adults should be similarly evaluated for behaviors, risk factors and risk of recurrence that may benefit from interventions.

Binkley, et. al., Submitted for publication

Getting Rid of the “Fragility Fracture” Concept
Fragility Fracture, Osteoporosis-related Fracture, Low-trauma Fracture, etc May Be Part of the Problem

Considering ALL fractures over age 50 as being in need of evaluation avoids the argument that:

“Anyone would have fractured if they fell like I did!”

“You may well be right; but let’s find out and try to make sure it doesn’t happen again.”

Fractures = Need for Evaluation
(Bone Attacks = Disease, Just Like Heart Attacks = 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.”
We Need to State that Fractures Reduce Quantity and Quality of Life

A Potential Approach to Improve the Osteoporosis Care Crisis

- Change the focus from osteoporosis to fracture
- Include ALL fractures in older adults
- Acknowledge that fractures affect QOL and independence
- Consider osteoporosis as just one part of a syndrome leading to fracture
- Need to address all components of the syndrome, not just the bones

Need to Consider Osteoporosis as Part of a Syndrome Leading to Fracture; We Have Called this “Dysmobility” (Difficulty Walking) but the Name is Unimportant

- Rather than focusing on a single component, i.e., osteoporosis, sarcopenia, or obesity, an opportunity exists to combine clinical factors thereby allowing improved identification of older adults at risk... Such a combination could be termed dysmobility syndrome.”

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

Adapted from Schuit, Bone. 2004;34:195-202
Despite the Fact That Approximately 1/6 Fragility Fractures Occur in People With NORMAL BMD….

Our Guidelines Call this “Osteoporosis”

“The diagnosis of osteoporosis is established by measurement of BMD or by the occurrence of adulthood hip or vertebral fracture in the absence of major trauma (such as a motor vehicle accident or multiple story fall).”

NOF Clinician’s Guide: 2014

Does This Man Have Osteoporosis?

History of fall with scalp laceration 2 months prior
Severe knee OA, unable to arise from chair without using his arms
Slipped in his garage with left hip fracture at age 66; BMI = 34.9

We Need to Think About More Than Just the Bones and Focus on Fracture

FN 1.190 g/cm²; T-score = +0.9
TF 1.241 g/cm²; T-score = +1.0

History of fall with scalp laceration 2 months prior
Severe knee OA, unable to arise from chair without using his arms
Slipped in his garage with left hip fracture at age 66; BMI = 34.9

L1-L4 1.989 g/cm²; T-score = +6.4
L1-L4 2.189 g/cm²; T-score = +1.9

Fracture Risk Calculators, e.g. FRAX, Are An Important Step in the Right Direction

• 1422 healthy post-menopausal women
• Followed ~ 10 years
• Fracture risk estimated using Garvan and FRAX calculators with BMD measurement
• Quintiles by risk calculations, n ~ 245

While an Improvement, Fracture Calculators are An Imperfect Estimate of Risk

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

www.shef.ac.uk/FRAX
It is clear that low bone density, i.e., osteoporosis is only part of the clinical constellation that contributes to what is currently called "Osteoporosis-Related" fracture. Think "Beyond the Bone."

We know that "Age" powerfully predicts fracture risk per 1000 person-years.

<table>
<thead>
<tr>
<th>BMD (grams/cm²)</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.00</td>
<td>45</td>
</tr>
<tr>
<td>0.50-1.00</td>
<td>55</td>
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<tr>
<td>0.25-0.50</td>
<td>65</td>
</tr>
<tr>
<td>0.60-0.99</td>
<td>75</td>
</tr>
</tbody>
</table>

Adapted from Hui, JCI 1988; 81:1804-1809

Chronologic age is a poor predictor of functional status.

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

There must be a better way to estimate a patient's fracture risk than simply using age...
These risk factors include:
- History of falls
- Self-reported health
- Self-reported physical activity
- Slower walking speed

**Indicators of Impaired Function**

**Falls Risk Factors Predict Hip Fracture Independent of BMD**

Masud & Morris. 2001, Age & Ageing 30; Suppl 4: 3-7

Geusens et al., 2010, Therap Adv. Musculoskel Dis 2: 83-87

**Falls Risk Is What Actually Predicts Fracture**

**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.”


**Women With Hip Fracture Often Have Sarcopenia and Osteoporosis by DXA**

313 white women with low-trauma hip fracture
Sarcopenia; ALM/Ht² < 5.45 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...”

Adapted from Di Monaco, et al, Arch Gerontol Geriatr, 52; 71-71, 2011
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?”

Dysmobility, i.e. Impaired Walking:
This Also Allows Consideration of Other Things that Might Cause Difficulty in Walking or Increase Falls Risk, e.g., Balance, Neuropathy, etc, etc.

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

Advancing age
Family History
Toxins, e.g., tobacco

Heart Attack
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 Osteoporosis Without Considering Other Parts of the Syndrome Causing Fractures is Comparable to Treating Hyperlipidemia and Ignoring Hypertension and Diabetes in Patients With Metabolic Syndrome

With This Approach, Bone Drugs Become Only Part of the Solution
Is There Any Evidence That Dysmobility Syndrome is Linked to Adverse Health Outcomes?

Adapted from Looker A, Osteoporos Int 2015; 26:93-102

NHANES 1999-2002 data (n = 2975) assessed relationship between dysmobility and mortality in adults age 50+

“Dysmobility was associated with increased mortality risk”
“Additional work is needed to evaluate relationship with other outcomes”

Dysmobility Syndrome Predicts Fractures Independent of FRAX Score

5,826 men in the MrOS cohort followed for a mean of 6.2 years ~7% had dysmobility defined as ≥ 3 of:
- Low BMD
- High fat mass
- Slow gait speed
- Low grip strength
- History of fall within past year
- Low ALM/ht²

Dysmobility syndrome is an independent predictor of fracture, even when adjusted for FRAX score

Buehring, et. al, presented at ASBMR 2016

Dysmobility Syndrome: An Important Concept but CLEARLY A WORK IN PROGRESS

What factors to include requires further study:
- Arthritis?
- Multiple Fractures?
- Multiple and/or injurious falls
- Diabetes?
- Neuropathy?
- Balance
- Etc, etc

Factors likely need to have different weights rather than simply being scored equally
Dysmobility syndrome (as crudely defined) predicts mortality and falls

Additional studies need to examine whether it predicts other health outcomes, e.g., falls and fractures
Integrating Dysmobility Risk into FRAX is an Ideal Way to Facilitate Clinical Implementation

**Questionnaire:**

1. Age (between 40 and 80 years) or date of Birth
2. Sex: Male | Female
3. Weight (kg)
4. Height (cm)
5. Previous Fracture
6. Parent Fractured Hip: Yes | No
7. Current Smoking: Yes | No
8. Glucocorticoids: Yes | No
9. Rheumatoid arthritis: Yes | No
10. Secondary osteoporosis: Yes | No
11. Alcohol 3 or more units/day: Yes | No
12. Femoral neck BMD (g/cm²)

**FRAX Output:**

- T-score: 2.1
- Prob. of fracture (0-100):
  - Major osteoporotic:
  - Vertebral:
  - Non-vertebral:

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

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 dysmobility and is at increased risk for falls and fracture

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

In Summary:
THE HEALTH CONSEQUENCE OF IMPORTANCE 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
  - ~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

Protein is Important for Bone and Muscle Health

Recommendations European Society for Clinical Nutrition & Metabolism

- Current recommended protein intake 0.7-0.8 g/kg body weight/day
- Older adults likely need more
  - ~10% of older adults and ~35% of institutionalized do not meet the current recommended intakes
  - Imbalance between protein supply and demand can lead to skeletal muscle loss

Protein Intake Recommendations: European Society for Clinical Nutrition and Metabolism

Many reasons for higher protein needs

- Anabolic resistance
- Disease-related protein catabolism
- Low postprandial amino acid availability
- Decreased muscle perfusion
- Sarcopenia

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

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

Doherty, J Applied Physiol, 95;1717-1727, 2003

US Adults Spend ~60% of Total Leisure
Time Doing One Activity

http://www.agingstats.gov/agingstatsdotnet/Main_Site/Data/2012_Documents/Docs/EntireChartbook.pdf
#page=140

Need Cultural Change Towards Exercise

Potential Pharmacologic Approaches
for Dysmobility Syndrome Include

Anabolic steroids
Selective androgen receptor agonists
Myostatin antagonists
Others

Muscle Medications Might Ideally be Used After
Illnesses/Events to Get Back to Baseline
We Don’t Have Muscle Medications Today, But We Do Have “Bone” Drugs

They Work, But Are Not Being Used

Bone Active Medications 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

The Risk of AFF (and ONJ) Increases With Treatment Duration and the Benefit is Unclear: I Stop Rx After 3-5 Years

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

Many patients “know” that osteoporosis drugs are “bad;” thus need to quantify risk of fracture vs. AEs. Consider the Garvan calculator (gives five year risk) especially if prior fractures or sarcopenia/falls

Calculators Help Put Actual Numbers to Fracture Risk: Consider the Garvan Calculator

67 yo female; multiple falls, multiple fractures & a T-score of -2.5

https://www.sheffield.ac.uk/FRAX/tool.jsp
Comprehensive Care (Dysmobility Syndrome 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."

Adapted from Singh, et. al, JAMDA, 13: 24-30, 2012

Dysmobility Syndrome
What To Do Today?

Recognize fracture (not just osteoporosis) as the problem
May be fatal
May lead to inability to live independently
Can be prevented (or at least have the risk for another fracture reduced)
Reflects a syndrome, not just "osteoporosis"
ALL fractures after age 50 require consideration of evaluation
- It’s not just “I fell”

Fracture is the Outcome of Importance
Due to a Syndrome of Osteoporosis, Sarcopenia, Obesity, Diabetes and Other Factors
We Need to Focus Not Just on Bone, But On the Patient

Dysmobility Syndrome
What To Do Today?

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 may increase risk

Optimize calories, calcium, vitamin D and protein status
- 2,000 IU daily is a reasonable place to start
- Measure 25(OH)D in those with falls/fractures
- Consider nutritionist evaluation

Use existing "osteoporosis" medications to treat the bones

Personal opinion
“The good physician treats the disease; the great physician treats the patient who has the disease.”

Sir William Osler