Sarcopenia: The Future of Fracture Risk Reduction
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Why Do You Treat “Osteoporosis”?
Our Job is to Optimize Musculoskeletal Health to Maintain Quality of Life and Prevent Falls/Fractures

“Osteoporosis” Clinicians Have Historically Focused on the Bone
Focus on the Individual Patient’s Fracture Risk

Focusing Only on Bone Identifies Less than Half of Those Who Will Fracture
Only 44% of women (21% of men) who sustain non-vertebral fractures have “osteoporosis” by BMD

5784 participants in the Rotterdam study; Mean follow-up 6.8 yrs FN BMD at baseline
(Female data presented here)
Fracture Risk Calculators Are a Major Step in the Right Direction

- www.shef.ac.uk/FRAX
- http://www.qfracture.org/

Fracture Calculators Are Not Perfect

- 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

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

How Could Clinical Judgment Might Help Us Better Identify Those Who Will Fracture?

"THINK!"
G. Magrin, M.D.

Think “Beyond the bone”

Fracture Risk Increases Markedly After Age ~70 in Both Men and Women

- 60% of hip fractures in women occur after the age of 80
- Median age for hip fracture in women is ~ 83 years

But Bone Mass Does Not Have a Similar Dramatic Decline After Age 70

"Age" Powerfully Predicts Fracture

Adapted from Cooper & Melton, Trends Endo Metab, 3:224-, 1992
Hui, JCI 1988
There is great between-individual variability in functional decline with age. 

Chronologic age ≠ Functional age

Why do fractures increase with age?
- Multiple reasons:
  - Falls become common with advancing age
    - ~1/3 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
    - ~6% of US medical expenditures for older adults due to fall-related injury

Falls Risk Factors Predict Hip Fracture Independent of BMD
- These risk factors include:
  - History of falls
  - Direction of fall/Fall to the side
  - Self-reported health
  - Self-reported physical activity
  - Slower walking speed

Perhaps function predicts Hip Fracture….

Impaired physical performance increases hip fracture risk

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

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."

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


Geusens et al., 2010, Therap Advances Musculoskel Dis 2:63-67


Adapted from Cawthon, et al., J Bone Miner Res, 2006, 21:1037-1044
A Gross Oversimplification of Complex Processes...

Sarcopenia/Falls Is a Major Part of the Increase in Fracture Risk Currently Ascribed to “Age”

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.”


Muscle Strength Declines With Advancing Age

International Weightlifting Federation Records 2010 (69 kg class)

Age 65
Decline of 33% in Men
45% in Women

Age 80+
Decline of 55% in Men

www.mastersweightlifting.org

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.”


Sarcopenia Becomes Common With Advancing Age

Prevalence Depends on Definition, Study Population and Method Used

Sarcopenia Prevalence Summary

Prevalence depends on the definition, technique(s) used to measure muscle mass/strength and the reference population.

Prevalence may differ by gender and increases with age:

- <5% in women age 50-65; increasing to 30% age 80+
- Up to 50% in men age 80+

Galen, et al., Calcif Tissue Int 2012; 91, 161-177


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?

Is the Disease Fracture?
Is The Diagnosis “Sarco-osteoporosis”

Binkley and Buehring, J Clin Densitom, 12;413-416, 2009

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...”

Women with hip fracture often have sarcopenia and osteoporosis by DXA. 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

Is There Any Evidence That Sarco-osteoporosis Treatment Positively Affects Outcomes??

Sarco-osteoporosis Treatment 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.

Note: Usual care included inpatient orthogeriatric and allied health consultation followed by 6-12 weeks of standard inpatient/outpatient physical therapy.

ADL decline was less and fewer use of assistive devices


Interdependency of Bone and Muscle is Not a New Concept

The “mechanostat” model of bone regulation was described in 1960 by Dr. Frost in his “Utah Paradigm”

Holds that bone growth and loss is stimulated by local mechanical elastic deformation of bone due to muscle force.

More muscle, more strain, more bone
Less muscle, less strain, less bone

Frost H.M., The Utah Paradigm of Skeletal Physiology Vols 1 and 2, ISMNI, 1960
Frost, HM, J Bone Miner Metab, 2000; 18:305-316

Muscle Talks to Bone

Candidate Myokines Include

- IGF-1, FGF-2, IL-6, IGFBP-5, Osteonectin, TGF-B1, matrix metalloproteinase, leukemia inhibitory factor, FGF-21, Wnt3a, myostatin, others…..
- Receptors for IGF-1 and FGF-2 are localized to the peristeam at the muscle-bone interface
- Some of these myokines likely are bone anabolic
Molecules should exist that increase muscle mass AND (by secretion of osteogenic myokines) also improve bone strength


Bone (Osteocytes) Talks to Muscle

- The prime sensors of mechanical strain
  - Strain might also be sensed by osteoblasts, adult muscle cells and even perivascular cells
- Produce sclerostin, DKK1, frizzled protein, osteocalcin, etc
- Osteocyte dendrites may directly connect to muscle and the vascular system

ASBMR Topical Meeting, July 2012

We Need to Consider Bone and Muscle Together to Optimaly Prevent Fracture, But Sarcopenia is Not Being Diagnosed Clinically Today

A proposition of the European Consensus was:
“There is no increased awareness by clinicians, therefore no effect on clinical care.”
J. Bauer, FNIH Consensus Meeting, May 2012

How Might We Diagnose Sarcopenia Today?

Mass-based Diagnostic Approaches Are Not Perfect For Bone
(Not Everyone With Osteopenia Has Lost Bone and/or Is At High Fracture Risk)
The Same is True for Muscle:
Cannot Simply Diagnose Sarcopenia Based on Low Mass

Example of Why Muscle Mass Should Not Be The Sole Diagnostic Criterion for Sarcopenia
Appendicular lean mass/ht² cutpoint < 5.45 kg/m²

<table>
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<tr>
<th>ALM/ht²</th>
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<td>4.8 kg/m²</td>
<td>4.9 kg/m²</td>
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51 year-old healthy competitive cyclist
86 year-old frail nursing home resident

The Decline in Muscle Strength is Much Greater than the Decline in Muscle Mass
Data from the Baltimore Longitudinal Study
(Knee extensor strength and lean mass by DXA)

Muscle “Quality” Declines With Age:
Need to Measure Mass + Function

To define sarcopenia, it is necessary to measure relative muscle mass, since absolute muscle mass is correlated strongly with height. ASM (kg/m²) was calculated as an index of relative skeletal muscle mass, and it is directly analogous to the use of the body mass index for grading relative adiposity.”


Criteria for the diagnosis of sarcopenia

Diagnosis is based on documentation of criterion 1 plus (criterion 2 or criterion 3)

1. Low muscle mass
2. Low muscle strength
3. Low physical performance

“Sarcopenic Obesity” Inadequate Muscle Mass/Strength in the Presence of Elevated Body Fat

Persons with Reduced Body Mass Out of Proportion With Their Adipose Mass

Some Proposed Criteria for Sarcopenic Obesity

- Baumgartner-ASM/Ht² less than 2 SD below mean young reference and body fat greater than 28% in men and 40% in women
- Davison (from NHANES)-upper 2 quintiles of body fat and lower three quintiles of muscle mass
- This is a “work in progress”
- There has been a recent proliferation of studies evaluating diagnostic cutpoints to define, and effect of sarcopenic obesity

Obesity Effects on BMD and Fx Are Complex

- Osteoblasts and adipocytes both arise from mesenchymal stem cells
- Obesity is associated with chronic inflammation
  - Higher TNF alpha, IL-6, CRP, etc.
- Adipokines are produced by adipose tissue
  - Leptin is increased in obesity and stimulates inflammatory responses
  - Adiponectin, an anti-inflammatory cytokine, is lower in obese than non-obese
- Obesity affects sex steroids
- Fat adversely affects muscle function
Obesity Increases Fracture Risk

MOS, 5995 men age 65+
(only 6 underweight, i.e., < 18.5 kg/m²)
Hazard ratios adjusted for age, race, hip BMD, Hx of fx and walk pace

"Obesity is common among older men, and when BMD is held constant, it is associated with an increased risk of fracture."

"The combination of hip fracture and obesity, both of which adversely affect physical function, may be particularly likely to lead to disability or institutionalization."


Should the Diagnosis be “Osteo-Sarcobesity”?

Should we Diagnose “Dysmobility Syndrome” (Along the Lines of Metabolic Syndrome) and Base This Diagnosis On Risk of Adverse Outcomes???

What’s in a name? What constitutes the clinical diagnosis of osteoporosis?
E. A. Siris, S. Boonen, P. J. Mitchell, J. Blaakena, S. Sliwers

"...if the clinical diagnosis is limited to a T-score diagnosis, a great many patients at risk for fractures will have their risk go unrecognized."

"Shouldn’t an older individual determined to be at high risk... be diagnosed as having osteoporosis?"

In conclusion, we believe that it is time for our field to revisit the criteria for making a clinical diagnosis of osteoporosis.


A Potential Approach to “Dysmobility Syndrome”

- Low ALM/h² < 7.26 kg/m² (M)/< 5.45 kg/m² (F)
- Obesity
  - Total body % fat > 40% (M)/>30% (F)
- BMD T-score ≤ -2.5 (WHO)
- Low grip strength < 30 kg (M)/< 20 kg (F)
- Slow gait speed (< 1.0 meter/sec)
- History of ≥ 1 fall in last 12 months
- Sarcopenia arbitrarily defined as a score ≥ 3


This “FRAX-like” Approach Identifies Approximately The Right Proportion of Older Adults

In this small cohort; a simple “FRAX-like” to define sarcopenia found 36% to have prior fragility fracture and 50% to have fallen within the last year; ROUGHLY the correct prevalence of fractures and falls....

Existing and Future Dysmobility Syndrome Treatments

- **Nutrition**
  - Under-nutrition is common
  - Inadequate protein intake reduces muscle synthesis
    - ~40% do not meet the current RDA of 0.8 g/kg daily
    - Protein intake of 1.2-1.5 g/kg daily is likely optimal
  - Vitamin D
- **Exercise/physical therapy**
- **Medications**

Exercise Works!

Even in elderly nursing home residents, 10 weeks of progressive resistance exercise training

- Increased walking speed
- Increased stair climbing ability
- Increased spontaneous activity
- Decrease in depressive symptoms

Physical Exercise

- 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

- Watching TV is THE Leisure Activity of Older Adults

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<th>Percent of leisure time</th>
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<tr>
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<tr>
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A Clinical Diagnostic Approach for Dysmobility Syndrome is Feasible

- **Gait speed**
- **Grip strength**
- **DXA: spine, hip and total body**
  - **BMD**
  - Appendicular lean mass/height
  - Percent body fat (or other fat measurement, e.g., fat/lean)

- Diagnostic options (cutpoints need to be defined)
  - Normal, osteopenia/osteoporosis, sarcopenia, sarco-osteoporosis, sarcobesity, osteo-sarcobesity
  - Potentially with 10-year risk for falls, fracture & disability?

Watching TV is THE Leisure Activity of Older Adults

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Table 295: Average number of hours and percentage of total leisure time that people age 55 and over spent doing selected leisure activities on an average day, by age group. 2010

Ford, et. al., J Appl Physiol, 96;1717-1727, 2003

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

Morley, J Nutr Health Aging, 12;452-496, 2008


http://www.agingstats.gov/agingstatsdotnet/Main_Site/Data2012/TV_Documents/Docs/EntireChartbook.pdf#page=142
Potential Pharmacologic Approaches for Sarco-osteoporosis Include
- Anabolic steroids
- Selective androgen receptor agonists
- Myostatin antagonists
- Others

Myostatin Antagonists??
Myostatin is a Negative Regulator of Skeletal Muscle Growth
- Myostatin: A secreted growth factor
- (member of the TGF beta family)
- Inhibits muscle differentiation & growth
- Produced primarily in skeletal muscle cells
- Acts on muscle by binding to the activin type II receptor

Dysmobility Summary
- Muscle, bone and fat are interlinked
  - The decline in muscle and bone mass and quality observed with aging likely reflects shared mechanisms
- Likely that much of the “age” effect on fractures is due to sarcopenia/falls
- Consensus definition of sarcopenia is evolving
  - Will include muscle function in addition to mass
- DXA is the tool to bring dysmobility to the clinic
  - “Devil in the details” issues remain; notably how to incorporate obesity
- Dysmobility Syndrome: The Future of Fracture Reduction?
  - Exercise
  - PT
  - Nutrition
  - Reduce meds
  - Improve vision
  - Bone meds
  - Home modifications
  - Vitamin D
  - Muscle meds?

Is This “Osteoporosis” Revisited??
- A problem has been recognized; clinical application is needed
- Who decides?
  - There is no biological threshold to define sarcopenia or sarcopenic obesity
  - Osteoporosis?? “At the WHO working group meeting, someone stood up and drew a line.” S. Cummings
- How to best define “disease”
  - Seems logical that it be based on risk of adverse outcomes, e.g., falls and fractures
  - Diagnosis based on risk (“FRAX-like”)?
  - “Needs to be intuitive to primary care.” J. Kanis
- Logical that this be WHO.....

Treat the Person, Not Just Their Bones
“The good physician treats the disease; the great physician treats the patient who has the disease.”
Sir William Osler