“Dysmobility Syndrome”
The Future of Fracture Risk Reduction
Santa Fe Bone Symposium, August, 2014

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Disclosures

- Research support
  - Amgen
  - Eli Lilly
  - Merck
  - Opko

- Advisory boards
  - Amgen
  - Eli Lilly
  - Merck
  - Quest

Much of this is my opinion; Noted by orange text
Think, Don’t Just Accept Dogma/Status Quo

“Only doubt is certain and disbelief worth believing. Without this courage there can be no learning. Believe nothing.”

Anonymous
Why Do You Treat “Osteoporosis?”
We Need to Learn from History.....
~80% of Those Who Break Their Hip Receive **NO** Treatment to Reduce Future Fracture Risk (and it’s getting worse)

“**We are failing in our mission to deliver healthcare for those at high risk.**”

Prof John Kanis, M.D.
IOF President
Seville, Spain, April 2014

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

Our Job is to Optimize Musculoskeletal Health to Maintain Quality of Life and Prevent Falls/Fractures
Clinicians Have Historically Focused on the Bone

“Osteoporosis”

Focus on the Individual Patient’s Fracture Risk
Focusing **Solely** 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

5794 participants in the Rotterdam study; Mean follow-up 6.8 yrs FN BMD at baseline (Female data presented here)

Adapted from Schuit, Bone. 2004;34:195-202
Fracture Risk Calculators Are A Major Step in the Right Direction


www.shef.ac.uk/FRAX

Welcome to QFracture® website

QFracture is a new website which is used to estimate an individual’s risk of developing

- hip fracture or
- osteoporotic fracture (hip, vertebral, or distal radius fracture) over the next 10 years.

http://www.qfracture.org/
Remember That the FRAX Calculation Includes Only ~Half of All Fractures

“Major” Fractures Account For ~ Half of All Fractures

Amin, et. al., JBMR, 2013 DOI 10.1002/jbmr.2072
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."

Bolland MJ et al, JBMR 26:422-427, 2011
How Might Clinical Judgment Help Us Better Identify Those Who Will Fracture?

“THINK!”
G. Magnin, 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

Adapted from Cooper & Melton, Trends Endo Metab, 3:224-, 1992
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 Risk per 1000 person-years

Adapted from Hui, JCI 1988
But Also Recognize That There is Great Between-Individual Variability in Functional Status With Age

Chronologic Age ≠ Functional Age
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
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

It is Sarcopenia/Impaired Function That Predicts Hip Fracture?

Masud & Morris. 2001, Age & Ageing 30; Suppl 4:3-7
Geusens et. al., 2010, Therap Advances Musculoskel Dis 2:63-67
Impaired Physical Performance Does Increase 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
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.”

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

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
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.”


Fielding, et. al, J Am Med Dir Assoc 2011; 12: 249-256
Sarcopenia Becomes Common With Advancing Age

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+

Gielen, et. al., Calcif Tissue Int 2012: 91, 161-177

Delmonico, et. al., J Am Geriatr Soc. 2007 55:769-74

Laurentani, et. al., J Appl Physiol, 2003;95:1851-1860
Janssen, et. al., Am J Epidemiol, 2004;159:413-21
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

Jensen, J Parenter Enteral Nutr, 32;656-659, 2008
Perhaps The Diagnosis Should be “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; $\text{ALM/Ht}^2 < 5.45 \text{ kg/m}^2$
Osteoporosis; Femur T-score $\leq -2.5$

“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
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
Multiple Candidate Myokines Exist Including

- 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 periosteum at the muscle-bone interface

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
We Need to Consider Bone and Muscle Together to Optimally 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?
“To define sarcopenia, it is necessary to measure relative muscle mass, since absolute muscle mass is correlated strongly with height. ASM (kg/m$^2$) 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.”
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

- ALM/ht²
  - 51 year-old healthy competitive cyclist: 4.8 kg/m²
  - 86 year-old frail nursing home resident: 4.9 kg/m²
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

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
Even Bone Plus Muscle Isn’t The Whole Story
In Thinking About Fracture Risk, Need to Consider The Intersection of Aging, Sarcopenia and Obesity

Sources: CDC 2008 & US Census Bureau, 2011
“Sarcopenic Obesity” Inadequate Muscle Mass/Strength in the Presence of Elevated Body Fat

Studenski, ASBMR Annual Meeting, 2011

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

Fielding, et. al, J Am Med Dir Assoc 2011; 12: 249-256
Concept of “Sarcopenic Obesity”
Some Proposed Criteria for Sarcopenic Obesity

- Baumgartner: ASM/Ht$^2$ 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, 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
Global Longitudinal Study
60,393 women age ≥ 55
Followed for 2 years

“Our results demonstrate that obesity is not protective against fracture in postmenopausal women and is associated with increased risk of ankle and upper leg fractures.”

Should the Diagnosis be “Osteo-Sarcobesity?”

- Low Bone Mass
- Osteoporosis
- High Adipose Mass
- Obesity
- Low Muscle Mass
- Sarcopenia
Rather than Calling this Syndrome “Osteo-sarcobesity”….

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

Siris, et. al, Osteoporos Int; 2012, 23:2093-2097
“We are hopeful that a similar approach will be evaluated in larger epidemiologic studies with multiple outcomes such as mobility disability, fractures, falls, and mortality to identify the combination of factors best able to predict adverse musculoskeletal outcomes in older adults.”

Binkley, et. al, Osteoporus Int, DOI 10.1007/s00198-013-2427-1
“Skeletal Muscle Function Deficit is proposed as a new terminology to embrace the evolving conceptualization of sarcopenia and other age-related muscle dysfunctions. It comprises a variety of contributory etiologies and has the potential to provide a framework for developing diagnostic categories useful in clinical practice and research.”

Data from 9 studies of community-dwelling older adults; n = 26,625
Used odds ratios for mobility impairment to develop cutpoints for
grip strength and lean mass

<table>
<thead>
<tr>
<th>Cutpoint</th>
<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td><strong>Weakness</strong></td>
<td></td>
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<tr>
<td>Recommended: Max grip strength (GS)</td>
<td>&lt; 26 kg</td>
<td>&lt;16 kg</td>
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<tr>
<td>Alternate: GS adjusted for BMI</td>
<td>&lt;1.0</td>
<td>&lt;0.56</td>
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<tr>
<td><strong>Appendicular lean body mass</strong></td>
<td></td>
<td></td>
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<tr>
<td>Recommended: ALM adjusted for BMI</td>
<td>&lt;0.789</td>
<td>&lt;0.512</td>
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<tr>
<td>Alternate: ALM</td>
<td>&lt;19.75 kg</td>
<td>&lt;15.02 kg</td>
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A Potential Approach to “Dysmobility Syndrome”

- Low ALM/ht²
  - < 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
- Dysmobility arbitrarily defined as a score ≥ 3

Fielding, et. al, J Am Med Dir Assoc 2011; 12: 249-256
This “FRAX-like” Approach Identifies Approximately The Right Proportion of Older Adults

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

Buehring, et. al, ASBMR Topical Meeting, July, 2012
Mass and Function Assessment Would Not be Difficult to Incorporate into Routine DXA Practice
A Clinical Diagnostic Approach for Dysmobility Syndrome is Feasible

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

- Diagnostic options (cutpoints need to be defined)
  - Normal, osteopenia/osteoporosis, sarcopenia, sarco-osteoporosis, dysmobility
  - Potentially with 10-year risk for falls, fracture & disability?
So Once We Have Diagnosed “Dysmobility Syndrome” (Or Whatever the Terminology Becomes)

What Are We Going to do About it???

Seems Likely That We Will Follow the Current “Osteoporosis” Paradigm
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/falls risk reduction**

- **Medications**
  Mithal, et. al., Ost Int, 2013; doi 10.1007/s00198-012-2236y
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  
  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
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
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)

**Activity - Tandem stand (Balance)**

**Instructions:**
- The heel of one foot is directly in front of the toe of the other
- Swap the foot that is in the front
- Use support from your hands as needed
- To be safe make sure that you have support readily available
- To make it more challenging use less support from your hands.

Idea for including Tandem Stand into your daily activities
- At the kitchen bench while waiting for the kettle to boil
- At the bathroom sink while cleaning your teeth
- While on the telephone

**Activity – One leg stand (Balance)**

**Instructions:**
- Stand on one leg
- The position of the other leg can be varied
- Support can be from hands, finger tips, trunk or the other foot
- Support can vary depending on what you are doing
- Use support as needed from:
  - Hands,
  - Tummy or hips
  - Knees.

Idea for including One Leg Stand into your daily activities
- While making your lunch
- While heating food in the microwave
- When you clean your teeth
- In the queue at the supermarket.

To be safe make sure that you have support readily available.
To make it more challenging use less support from your hands.

Potential Pharmacologic Approaches for Sarco-osteoporosis Include

- Anabolic steroids
- Selective androgen receptor agonists
- Myostatin antagonists
- Others
Is Testosterone the Way to Prevent Fractures?

- ADAM Questionnaire (Androgen Deficiency in the Aging Male)
  - Do you have a decrease in 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.”

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
Data Already Exists that 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

ADL decline was less and fewer use of assistive devices

“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.

Adapted from Singh, et. al, JAMDA, 13: 24-30, 2012
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/sarcopenic obesity and falls
Consensus definition of sarcopenia/dysmobility is evolving
   - Will include muscle function in addition to mass
DXA is the tool to bring dysmobility to the clinic
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.....
Sarcopenia/Dysmobility: What Can We Do Today?

Recognize the problem, reduce falls risk & optimize “osteoporosis” Rx

- **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
  - Reduce meds, home modifications, vitamin D, nutrition, PT, etc
- Use Garvan calculator to advise re: fracture risk

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

<table>
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<th>BMI: 34.3</th>
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<td>The ten year probability of fracture (%)</td>
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<tr>
<th>with BMD</th>
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<tr>
<td>Major osteoporotic</td>
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<td>Hip Fracture</td>
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<th>Any Osteoporotic / Fragility Fracture</th>
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<td><strong>24%</strong></td>
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<td>5 year risk</td>
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<th>Hip Fracture</th>
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<td><strong>11%</strong></td>
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<td>5 year risk</td>
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“The good physician treats the disease; the great physician treats the patient who has the disease.”

Sir William Osler
Thank You