Where Are We At With Osteoporosis 2018?
WWHF June 2018

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Why Do We Treat “Osteoporosis?”

Fracture is What’s Important
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

Less than 1/10 patients with hip fracture being treated

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

DXA Obtained
Fell THE NEXT DAY
Right hip fracture
Discharged to NH at age 67!

- Most recent DXA April 2014 LS -2.4, FN -2.2
- Seen by FLS after humerus/patellar Fx
- Work up including DXA was initiated
A Different Approach to “Osteoporosis” is Needed

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

Albert Einstein
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

Binkley, et. al., J Bone Miner Res, 2017 32:1391-1394
The “Fragility Fracture” Concept Does Not Make Sense to Patients

Fragility Fracture, Osteoporosis-related Fracture, Low-trauma Fracture, etc May Be Part of the Problem

“…..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.”

Sale, et. al., Osteoporosis Int 2012, 23:2829-2834
Considering ALL fractures over age 50 as requiring evaluation avoids the argument that there’s nothing wrong with me:

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

“You may well be right; but let’s find out.”
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 Directly State: Fractures Reduce Quality of Life and Talk about Loss of Independence

Why should you be concerned?

The consequences of a fracture due to osteoporosis can be extremely serious:

- Chronic pain, immobility, and long-term disability – often leading to loss of independence and reduced quality of life.

20-24% DIE

Twenty to twenty-four per cent of people who have had a hip fracture will die in the first year following the fracture, and many other fracture types are also associated with an increased risk of death.

Hip fracture survivors often experience loss of function and independence, with 40% unable to walk independently and 60% requiring assistance a year later. In the year following a hip fracture, 33% are in a nursing home or totally dependent, placing a significant burden on family members who may have to become caregivers for their loved ones.

www.share.iofbonehealth.org/WOD/2012
Falling over isn’t part of the ageing process. Many falls are preventable, and we want to help you stay on your feet and living the life you want to live.

This booklet provides practical advice – whether you’re still working, newly retired, or happily enjoying a long retirement – there is something in here for everyone. As you will see, much of the advice is good, old-fashioned common sense, but for those of you who have spent a lifetime looking after others (and perhaps still do) this guide is a gentle reminder to look after yourself.

For even more information go to our website
www.livestronger.org.nz

or visit:
www.acc.co.nz
www.health.govt.nz
www.hqsc.govt.nz

www.acc.co.nz
Think About Muscle Function
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

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
We Do Not Require a Consensus Definition of Sarcopenia: 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
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

Heart Attack

Reduced QOL
Healthcare Cost
Death

Family History
Toxins, e.g., tobacco
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

You have osteoporosis and should take this medicine to reduce your risk.

I fell down! There's nothing wrong with me; he just wants to give me another bad drug.

Fractures can alter quality of life and independence; let's look at everything and see how to best reduce your future fracture risk.

Hmm, maybe there are things that should be done to keep me active and independent.
Existing and Future Fracture (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

Mithal, et. al., Ost Int, 2013; doi 10.1007/s00198-012-2236y
Calcium and Vitamin D Nutrition is in Chaos

Anyone That Tells You They Know the Right Answer is Kidding Themselves and You
Calcium Required for Bone
Vitamin D Required for Bone & Muscle
How Much is Needed?

- Meta-analyses will not resolve this issue (currently)
- Virtually all RCTs are flawed
- Don’t expect ongoing large RCTs to resolve this issue

Personal opinion
The “Bone” Field Largely Has, and Continues, to Ignore Heaney’s Guidance

Guidelines for optimizing design and analysis of clinical studies of nutrient effects

Robert P Heaney

Presented here is a system to standardize clinical studies of nutrient effects, using nutrient-specific physiological criteria. These guidelines are based mainly on analysis of the typical sigmoid curve of biological response to nutrients and are intended for design, interpretation, and pooling of studies of nutrient effects. Five rules have been articulated for individual studies of nutrients, and six for systematic reviews and/or meta-analyses.

Heaney RP, Nutr Reviews 2013, 72:48-54
Virtually All Studies Fail to Recognize that Nutrients are Not the Same as Drugs

Meta-analyses of flawed studies yield flawed conclusions
Most Studies Fail to Recognize That We Are Not All The Same

Meta-analyses of flawed studies yield flawed conclusions
COMMON SENSE
Paleolithic Calcium Intake = ~1,000 mg/day
The IOM recommends 1,000 mg of calcium daily age 19-50, 1200 mg for Age 51+

Frassetto, et. al., Eur J Clin Nutr 2009: 63; 947-955
Do Calcium Supplements Cause Vascular Disease?

The NOF and ASPC expert panel says NO

“The NOF and ASPC adopt the position that there is moderate-quality evidence (B level) that calcium with or without vitamin D intake from food or supplements has no relationship (beneficial or harmful) with the risk for cardiovascular and cerebrovascular disease, mortality, or all-cause mortality in generally healthy adults at this time. …calcium intake from food and supplements that does not exceed the tolerable upper level of intake (2000 to 2500 mg/d) should be considered safe from a cardiovascular standpoint.”

Calcium Summary: June 2018

- Aim for 1,000-1,200 mg/day
  - Ideally through diet (+ supplements if needed)
  - Close to the “Paleo” diet
  - One “serving” is ~250 mg
  - It is possible to get too much of anything; the jury is still out regarding vascular events

- There is no “best” calcium supplement
  - Don’t spend $$$$ 
  - If supplements are needed they should be taken with a meal

Personal opinion
Vitamin D Likely Important for Bone & Muscle

- Common sense; target the level of highly sun exposed people


Mean 25(OH)D
46 ng/mL
Be Aware That “30 ng/mL” is NOT 30 ng/mL

VDSP recommends that 25(OH)D assays perform with a CV <10%

If your lab is meeting this target, an individual patient 25(OH)D result of 30 ng/mL is actually 24-36 ng/mL

What to Do? Aim a Little High

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

<table>
<thead>
<tr>
<th>Measured</th>
<th>“True” Value</th>
<th>Maintain</th>
<th>Maximum</th>
</tr>
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<tr>
<td>25(OH)D</td>
<td>20 ng/mL</td>
<td>~15 to ~ 25 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>
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</tbody>
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Recognize that the reported value may be low: with this approach, the maximum is likely to be ~40 to ~50 ng/mL, below that attainable by UV exposure.
Vitamin D Summary: June 2018

- The field remains chaotic (and passionate)....
- Vitamin D inadequacy (however defined) is common
- Vitamin D is cheap and virtually side effect free
  - Can’t pick a single dose to assure whatever you believe to be vitamin D adequacy
  - Daily dosing makes physiologic sense
- Ancestral human 25(OH)D mean is ~ 40 ng/mL
- Our current “25(OH)D” measurements are imperfect
  - Assay improvements are needed; progress being made
- RCTs with better study designs need to be conducted;
  - This is not happening yet; expect chaos to continue
Older Adults Need More Protein

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

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

Mithal, et. al., Osteoporos Int, 24, 1555-1566, 2013
Other Nutrients Possibly Important in Bone/Muscle Health (nobody knows…)

- Magnesium: maybe but no guidance
- Strontium: heavier than calcium; deposits in bone thus increasing BMD. Toxicity? (avoid)
- Vitamin K: doesn’t help
- Acid diets: controversial
- Caffeine/soft drinks: replace milk
- Phytoestrogens: ~20; likely natural SERMS, differential effects and unknown dose
When Are “Bone Drugs” Indicated?

- **NOF**
  - T-score ≤ -2.5
  - Prior spine or hip fracture
  - Osteopenia with 10 year fracture risk > 20%

- **FDA-approved medications**
  - Bisphosphonates
  - Denosumab
  - Calcitonin
  - Raloxifene
  - Teriparatide
  - Abaloparatide
Many Experts are Not Treating Treat T-score Osteoporosis and Treating Based on Fracture Risk
(Osteoporosis Canada approach)

> 20% risk; Rx
< 10% risk; Don’t’ Rx
10-20%; obtain T/L radiographs or VFA and think about treating

UW now reporting FRAX for all with T-score ≤ -1.1

http://www.osteoporosis.ca/health-care-professionals/guidelines/
2016 Updated AACE Treatment Guidelines

Prior fragility fractures or indicators of higher fracture risk**

- Alternate therapy: 
  - Evaluate for causes of secondary osteoporosis
  - Correct calcium/vitamin D deficiency and address causes of secondary osteoporosis
  - During the holiday, another agent such as teriparatide or raloxifene could be used.

Camacho, et. al., Endocr Pract. 2016;22(Suppl 4)
We Need to Balance Long-Term Benefits vs. Long Term Risks

Benefits
Decreased fractures
Decreased mortality
Maintained Independence & QOL
↓ Healthcare costs

Risks
GI
Acute phase reaction
ONJ
Atypical femur fractures
Nephrotoxicity
Eye problems
Musculoskeletal pain
Esophageal cancer?
Atrial fib?

“I find myself more in fear of the side effects of the recommended medications than I do of my cancer--silly perhaps but nonetheless an issue for me. I don't want my cancer to recur but also don't want my spine to collapse.”
Calculators Help Put Actual Numbers to Fracture Risk (Consider using Garvan; esp if falls/fractures)

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

http://www.garvan.org.au
Short-term Bone Drug Rx Cuts Fracture Risk ~ in Half

There is Virtually No Doubt that This Benefit Outweighs Risks for the First 3-5 Years of Treatment

After Fracture or at High Risk Treat for 3-5 years

Should We Be Treating Longer?
The Pathophysiology of ONJ and AFF Remain Debated and are Certainly Multifactorial. But the Risk Increases With Duration of Therapy.

As AFF and ONJ occur with two classes of anti-resorbers (bisphosphonates and denosumab) it seems to me that “oversuppression” of bone remodeling is involved.
The Oral Surgeons State that Medication Related Osteonecrosis of the Jaw (MRONJ) Increases A LOT After 4 Years of Rx

Name change due to cases with denosumab and antiangiogenic Rx

- “For patients receiving oral BP therapy to manage osteoporosis, the prevalence of ONJ increases over time, from nearly 0% at baseline to 0.21% after at least 4 years of BP exposure.”
  
  “Median duration of BP exposure for patients with ONJ and ONJ-like features was 4.4 years.”

AFF Incidence Increases With Duration of Bisphosphonate Exposure (US Data)

- 1.8 million Kaiser Permanente enrollees ≥ 45 years of age
- Potential AFF identified by ICD-9 diagnosis and CPT procedure codes
  - All radiographs reviewed
- 142 femur fractures met ASBMR criteria for AFF
  - 128 (90%) had previous BP exposure
  - 14 (10%) no prior BP exposure
  - Age adjusted incidence rose with increasing duration of BP exposure

~ 1.1 per 1000 pt-yrs after 10 years

Adapted from Dell RM, J Bone Miner Res, 2012;27:2544-50
I’m not treating ANYONE that does not meet one of these three criteria.

Thus, this is a de facto 10-year Rx recommendation.

“For treatment up to 10 years with oral bisphosphonates and 6 years with intravenous bisphosphonates, estimates of benefits and risks are based on much weaker data.”

Adler, et. al., J Bone Miner Res, 2016; 31:16-35
“The risk of atypical femoral fracture, but not osteonecrosis of the jaw, clearly increases with BP therapy duration, but such rare events are outweighed by vertebral fracture risk reduction in high-risk patients.”

Adler, et. al., J Bone Miner Res, 2016; 31:16-35

Is This Really True?
Numbers for Risk of Fracture vs. Risk of AFF/ONJ with Long-term Rx from ASBMR Task Force

Per 100,000 patients Rx; Yr 9-10

- **NO** data that hip or wrist fractures are prevented
- 1470 vert fx prevented
- 113 AFF caused
  - (assuming; incorrectly) that **ALL** AFF are caused by BP
- 26 cases of ONJ caused
- 1470/139 = 10.6 spine fractures prevented per AFF/ONJ case caused

Adapted from Adler, et. al., J Bone Miner Res, 2016; 31:16-35
My Take on Long-term Treatment

- The data for both benefit and risk are very weak
  - i.e., “evidence based” is not based on evidence
- Not at all clear that long-term turnover suppression and BMD stability/increases are good (and might be bad)
- Long-term Rx likely prevents some vertebral fractures
- No evidence that we are preventing hip or non-vertebral fractures with bisphosphonates (sample sizes likely too small)
- We are causing some AFF
- We are causing some ONJ
- How much ONJ and AFF is unclear, BUT an ~10 vertebral fractures prevented to one substantial adverse event caused does not sound favorable to me

Personal opinion
I Recommend BP Holidays All the Time

- If “doing well,” stable or increasing BMD and no fractures; BP holiday after 3-5 years (almost always)
  - What to do with denosumab is unclear
- If “treatment failure;” teriparatide or abaloparatide
- Monitor holiday with turnover markers and BMD every other year (no data)
  - BMD decline or turnover marker increase, the holiday is over

NOTE: This is a conservative approach not shared by all in the field
Do Not Take Holidays with Denosumab
Discontinuation leads to rapid bone loss

- One year observational follow up after up to 8 years of dmab in phase 2 study
- 8 of 82 (9.8%) experienced at least 1 fracture
- 4 had multiple vertebral fractures

“...if denosumab treatment is discontinued for any reason, it seems very prudent that therapy with another anti-remodeling agent, such as a long-acting BP, be continued...”

A Multiple Vertebral Fracture Syndrome Has Been Reported Following DMAb Discontinuation

- 9 women with 50 rebound-associated vertebral fractures after dmab discontinuation
  - All VF were spontaneous; mean # 5.5
  - VF occurred rapidly after last dmab injection (9-16 months)
  - The fracture risk was low for most of these women
- Studies needed to define Rx regimens after dmab discontinuation
When individuals on antiresorptives are switched to teriparatide, hip BMD declines for at least 12 mo
  - More pronounced with dmab

“The common practice of switching to teriparatide only after patients have an inadequate response to ARs (fracture or inadequate BMD effect) is not the optimal utilization of anabolic treatment.”

“When possible, we suggest anabolic therapy first, followed by potent antiresorptive therapy.”
Summary: Fracture Syndrome ("Osteoporosis")
What To Do Today?

- Recognize fracture as the problem:
  - May be fatal
  - Threatens INDEPENDENCE
  - 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”

Personal opinion
Fracture Syndrome ("Osteoporosis")
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

- Use existing "osteoporosis" medications to treat the bones starting with anabolic agents in those at high risk
  - Use antiresorbers for 3-5 years

Personal opinion
Summary: An Approach to Reduce Fracture Risk

- Recognize fracture as the problem
  - Affects QOL and INDEPENDENCE
- All fractures after age 50 need evaluation including basic laboratory & BMD measurement
  - Calcium, creatinine, alk phos, 25(OH)D, CBC
  - Need to personally review the DXA scan image
- Think about falls
  - Home safety, vision, if weakness or balance issues PT eval
- Calcium intake of 1000-1200 mg daily, vitamin D of at least 1,000 IU; consider protein in older adults
- Treat with bone meds for 3-5 years if fracture risk high
  - Recent fracture, falls, FRAX MOF ≥ 20%

Personal opinion
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
Thank You