Bone Loss After Bariatric Surgery: Causes, Consequences and Management

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Disclosures:

Amgen (Consultant, Advisory Board)
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Ultragenyx (Consultant)
Regeneron (DSMB)
Outline

• Causes of Abnormal Bone Metabolism in Obesity
• Skeletal Consequences of Bariatric Surgery: RYGB
• Mechanisms of Bone Loss
• Fracture Risk After Bariatric Surgery
• Management of Post-Operative Bone Loss
CAUSES OF ABNORMAL BONE METABOLISM IN OBESITY
Skeletal Metabolism in Obesity

• Common perception: protective of bone
• However, obese individuals are at increased fracture risk, particularly at peripheral sites

• Microarchitecture may be abnormal
  – Cortical bone may be preferentially affected

Factors Associated with Abnormal Bone in Obesity

- Increased marrow fat
- Visceral adiposity
  - May be associated with lower bone formation, worse structure and strength
- Increased intramuscular fat
  - May contribute to increased falls
- Diabetes
  - Despite higher BMD, fracture risk is increased
- Vitamin D deficiency and secondary hyperparathyroidism

Schellinger et al. 2004 AJR; Gilsanz et al. 2009 JCEM; Cohen et al. 2013 JCEM; Compston et al. 2013 JBMR; Vestergaard et al. 2007 Osteoporos Int
Sarcopenia and Frailty: other factors that contribute to fracture risk in Obesity
Background: Sarcopenia and Obesity both may contribute to fracture risk

Question: Does sarcopenia and obesity together contribute more to fracture risk than either alone?

Design: Sarcopenia (as per European Working Group); Obesity (30% body fat). 7.5 year follow up. MrOs (USA cohort; n=5,994; age > 65)

Referent: 4,357; Obese 1304 (21.9%); Sarcopenia 164 (2.8%); sarcopenia/obesity 128 (2.2%)
Results:

Sarcopenia alone or with obesity may increase risk for all clinical fractures in older men.

Conclusion

Sarcopenia alone or with obesity may increase risk for all clinical fractures in older men.
Background: U-shaped relationship between BMI and frailty is known.

Question: Does obesity contribute to frailty onset or progression?

Design: CaMos frailty index (n=7,753, av age 66); 5- and 10-year follow

Results: Baseline obesity (esp. marked obesity) associated with faster rate of frailty development
#1126: Kennedy et al. Baseline Obesity is Predictive of More Rapid Frailty Onset: a 10-year Analysis of the CaMOS Study, ASBMR, 2016

Reference Category = Normal BMI

Clinically significant change = 0.03
SKELETAL CONSEQUENCES OF BARIATRIC SURGERY
Limitations of Bone Studies in Bariatric Patients

- Small sample sizes
- High drop-out rates in studies > 1 year
- Heterogeneity
- Supplementation not standardized
  - Often not a formal part of protocol
  - Subjects in same cohort may use different regimen
  - Compliance not typically assessed

Stein and Silverberg 2014 *Lancet Diabetes Endocrinol*
Limitations of DXA in the bariatric population

- Artifact
  - Extreme obesity
  - Changes in fat mass
  - LS and hip affected by overlying pannus

- Extremely obese individuals may exceed the weight limits of many DXA machines

- DXA cannot distinguish between cortical and trabecular bone
  - May be differentially affected by surgery

Stein and Silverberg 2014 *Lancet Diabetes Endocrinol*
Bariatric Surgery

• **Gastric Banding**

• **Sleeve Gastrectomy**
  Mechanick. 2013 *Surg Obes Rel Dis*; Nogues. 2010 *Cirugia Espaniola*;

• **Roux-en-Y Gastric Bypass**
EFFECTS OF GASTRIC BYPASS ON BONE TURNOVER, AREAL/VOLUMETRIC BMD, AND SKELETAL MICROSTRUCTURE
Bone Turnover Markers Increase Progressively For At Least 18 Months

- Bone turnover increases as early as 3 months after RYGB
- Bone resorption markers increase by up to 200% over first 12-18 months
- Bone formation markers tend to increase to a lesser extent than bone resorption markers

Fleischer, Stein et al. 2008 JCEM; Coates et al. 2004 JCEM; Stein et al. 2013 JCEM; Yu et al. 2013 JBMR 2013; Bruno et al. 2010 JCEM 2010, Schafer et al, 2017, Shanbhogue et al, 2017; Bredella et al, 2018
Study of Bone Quality Changes After Bariatric Surgery

- 22 women, mean age 45 ± 10 years
- BMI 44 ± 5 kg/m²
- Followed for one year after surgery
- Mean weight loss 28±3 kg
- PTH rose 23%, Ca and 25OHD stable
- Increased bone resorption (CTX)

Stein et al. 2013 JCEM
Weight Loss After Surgery Associated with Bone Loss at Weight Bearing Sites

Stein et al. 2013. JCEM
High Resolution Peripheral Quantitative Computed Tomography (HR-pQCT)

- Non-invasive technology, voxel size 61-82 µm
- Allows for *in vivo* assessment at distal radius and tibia of
  - Bone size
  - Volumetric bone density
  - Microarchitecture
    - Cortical thickness
    - Trabecular Number, Thickness, Separation
- Allow estimation of bone strength
- Discriminate fracture status
- Can help elucidate the structural basis for fragility

Boutroy. JBMR. 2008; Somay-Rendu. JBMR. 2009; Stein. JBMR. 2010; Melton CI 2010; Vilayphiou. Bone. 2010; Liu. JBMR 2010
Effects of RYGB on BMD and Skeletal Microstructure. Schafer et al, J Bone Min Res, 2017

- Design: 48 obese adults: BMI 44 +/- 7
  - 27 premenopausal; 11 postmenopausal; 10 men
- Time points: baseline, 6 and 12 months
- Measurements: DXA, QCT, HRpQCT, biochemistries
- Indices:
  - areal and volumetric BMD, bone strength; cortical porosity
  - 25-OH D, PTH, urinary calcium, bone turnover markers
Effects of RYGB on BMD and Skeletal Microstructure. Schafer et al, J Bone Min Res, 2017

- General Results after 12 months:
  - Anthropomorphic:
    - Weight: -37 kg
    - Total body fat: -27 kg
    - Lean mass: -9 kg
    - Visceral adipose: -108 cm²
  - Laboratory:
    - 25(OH) D: 42 to 37 ng/mL
    - Uca: 184 to 131 mg
    - PTH: 42 to 48 pg/mL
    - CTX: +278%; P1NP: +111% (baseline values normal)
Effects of Gastric Bypass Surgery on Bone Mass and Microarchitecture Occur Early and Particularly Impact Postmenopausal Women, First published: 05 February 2018, DOI: (10.1002/jbmr.3371)

Effects of RYGB on BMD and Skeletal Microstructure.
Schafer et al, J Bone Min Res, 2017

![Graphs showing changes in bone mass and microarchitecture after gastric bypass surgery.](image-url)
Effects of Gastric Bypass Surgery on Bone Mass and Microarchitecture Occur Early and Particularly Impact Postmenopausal Women, First published: 05 February 2018, DOI: (10.1002/jbmr.3371)
Effects of RYGB on BMD and Skeletal Microstructure. Schafer et al, J Bone Min Res, 2017

Summary: Changes more evident in postmenopausal women
- Areal and volumetric BMD decline
- Estimated strength declines
- Cortical porosity increases

Conclusion:
- Fracture risk might be increased
- Is early intervention warranted?
Bone structural changes after RYGB: a 2-year longitudinal study. Shanbhogue et al., E J Endocrinol, 2017

- Design: 25 obese adults: BMI 42 (38-47)
  - 15 postmenopausal women; 10 men
- Time points: baseline, 12 and 24 months
- Measurements: DXA, HRpQCT, biochemistries
- Indices:
  - Areal and Volumetric BMD, bone strength; cortical porosity
  - 25-OH D, PTH, bone turnover markers
Bone structural changes after RYGB: a 2-year longitudinal study. Shanbhogue et al., E J Endocrinol, 2017

- General Results after 24 months:
  - Anthropomorphic:
    - Weight: -31 kg by yr 1; no further loss in yr 2
    - Total body fat: -21 kg by yr 1; no further loss in yr 2
    - Lean mass: -9 kg by yr 1; no further loss in yr 2
  - Laboratory:
    - 25(OH) D: 13.6 to 37 ng/mL
    - PTH: 5.1 pmol/l to 4.8 pmol/l
    - CTX: +40%; P1NP: +113% (baseline values normal)
  - DXA:
    - Lumbar Spine: --3.5% at Yr 1: -5.3% at Yr 2
    - Total Hip: -8.2% at Yr 1: -10.5% at Yr 2
Bone structural changes after RYGB: a 2-year longitudinal study. Shanbhogue et al., E J Endocrinol, 2017
Bone structural changes after RYGB: a 2-year longitudinal study. Shanbhogue et al., E J Endocrinol, 2017
Summary:

- Areal and volumetric BMD decline
- Estimated strength declines progressively over the 2 years, despite no further loss in weight
- Cortical porosity increases more markedly in year 2 than in year 1

Conclusion:

- Microstructure continues to deteriorate even after weight loss has stabilized
- Other pathogenetic factors besides weight loss are responsible to microarchitectural deterioration
Background: By DXA, bone loss occurs within 2 yrs of RYGB surgery

Question: What are the longer term consequences of RYBG after 2 years when weight loss has been stabilized?

Method: 21 subjects followed for 5 yrs with DXA, Lumbar CT, and HRpQCT

Results: Wgt loss (33 kg) stable after 2 years; 25-OH D and serum calcium stable and unchanged from baseline
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<th>0-2 yrs</th>
<th>2-5 yrs</th>
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<td>DXA</td>
<td>↓ at all sites</td>
<td>↓ hip, 1/3 rad</td>
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<td>CT- LS</td>
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<td>HRpQCT- Radius</td>
<td>↓ Ctth/Tbn/↑ Tbsep</td>
<td>↓ Ctth/Tbn/↑ Tbsep</td>
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Conclusion: After RYGB, when wgt loss has been stabilized, continued densitometric and microarchitectural deterioration of bone occurs.
After RYGB……

- **BMD (areal and volumetric)**
  - **Hip:** consistent declines in areal BMD with greatest in year 1: ran. Losses range from 8-11% in year 1
  - **Spine:** changes, if present, are more modest
  - **Radius:** - most studies report no change

- **Microstructure**
  - Progressive and pervasive deterioration in cortical and trabecular compartments continue after weight loss has stabilized
  - Bone strength compromised by FEA

Coates 2004; Nielson 2012; Fleischer 2008; Vilarassa 2011; Stein 2013; Carrasco 2009; Pereira 2007; Sinha 2011; Schafer 2017, Shanbhogue 2017
MECHANISMS OF BONE LOSS AFTER BARIATRIC SURGERY
MECHANISMS OF BONE LOSS AFTER BARIATRIC SURGERY

- Nutritional/malabsorptive (vitamin D, calcium, other nutrients)
- Biomechanical: skeletal unloading (initial effect?)
- Hormonal: secondary hyperparathyroidism (PTH levels do not change substantially); estrogen loss due to loss of adipose tissue; changes in adipocyte and gut cytokines (leptin, adiponectin, PYY)
- Sarcopenia (loss of lean body mass)
- High bone turnover
FRACTURE RISK AFTER BARIATRIC SURGERY
Fracture Risk After Bariatric Surgery

- Retrospective cohort study using UK General Practice Research Database
- 2079 bariatric patients and 10,442 matched controls
  - Age, sex, BMI
- Majority of subjects had gastric banding
- Patients followed to time of first fracture, mean 2.2 years
- No increased risk of fracture
  - Any, osteoporotic, non-osteoporotic
- Trend toward increased fracture
  - 3-5 yrs post-op
  - Subjects with the most weight loss

Laimohamed A. et al. 2012 *BMJ*
Fracture Risk After Bariatric Surgery

- Historical cohort study, median follow up 8 years
- Compared 258 bariatric subjects (90% RYGB) with expected fracture incidence in community based population

- Increased risk of all fracture and fragility fracture
- Risk greatest for appendicular fractures - >50% foot, leg or hand
- Vitamin D deficiency and lower pre-op activity were predictors of fracture

Nakamura et al. 2013. *Osteoporos Int*
Fracture risk following bariatric surgery
Rousseau et al. BMJ 2016

4 years after surgery: 4.1% vs 2.7% obese vs 2.4% non-obese
Rousseau et al. The pattern of fracture risk changes from an obesity to an osteoporotic pattern. BMJ, 2017

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<thead>
<tr>
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<th>Obesity + Bariatric Surgery vs non-obese controls</th>
<th>Obesity: no bariatric surgery vs non obese controls</th>
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<tr>
<td><strong>Before</strong></td>
<td>Before</td>
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<td><strong>After</strong></td>
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Source: Claims data base 2005-2015

Time dependent increase in non-vertebral fractures with RYBG vs AGB

Increased risk with RYGB vs Banding
MANAGEMENT OF SKELETAL HEALTH AFTER GASTRIC BYPASS SURGERY
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- Strive for nutritional adequacy (calcium, vitamin D, etc)
- Appropriate exercise regimen
- Bone mineral density at regular intervals
MANAGEMENT OF SKELETAL HEALTH AFTER BYPASS SURGERY

- Strive for nutritional adequacy (calcium, vitamin D, etc)
- Appropriate Exercise Regimen
- Bone mineral density at regular intervals
- **Measure 25-OH D levels at regular intervals and adjust vitamin D supplementation to keep levels > 30 ng/mL**

- Specific use of a therapeutic for the skeleton should be based upon standard indications (i.e., fracture, BMD, FRAX) but oral bisphosphonates should probably be avoided.
Conclusions

- Abnormal bone metabolism is a feature of obesity and gastric bypass surgery.

- In each case, the factors are multifactorial.

- Loss of bone mass and skeletal deterioration after gastric bypass surgery cannot be explained by weight loss alone.

- Fracture risk is increased after bariatric surgery.

- Management guidelines are focused on adequate nutrition and prevention of further bone loss.
Thank You