Bone Loss After Bariatric Surgery: Causes, Consequences and Management

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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

Compston et al. 2011 *Am J Med*; Goulding et al. 2005 *JBMR*; Premaor et al. 2010 *JBMR.* Sornay Rendu 2013 *JBMR*; Sukumar et al 2011 *Osteoporos Int*

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

#1156: Harris, Strotmeyer, Boudreau, Brach, Kwoh, Lane, Orwoll, Schwartz, Cawthon, Cauley. The Risk of Fracture among Men with Sarcopenia and/or obesity or neither- ASBMR, 2017

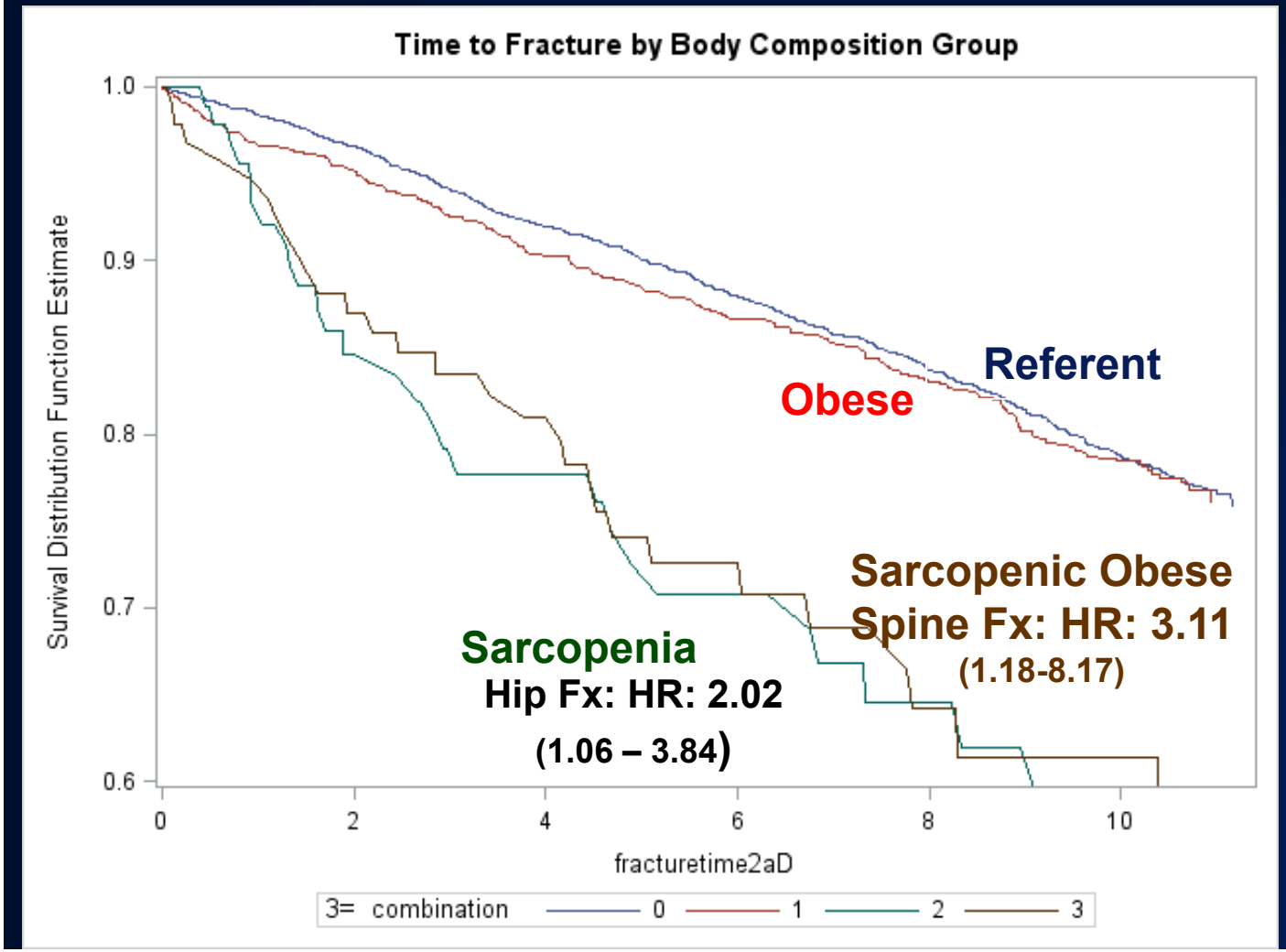
Background: Sarcopenia and Obesity both may contribute to fracture risk

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%)

#1156: Harris, Strotmeyer, Boudreau, Brach, Kwoh, Lane, Orwoll, Schwartz, Cawthon, Cauley. The Risk of Fracture among Men with Sarcopenia and/or obesity or neither, ASBMR, 2017

Results:



Conclusion

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

#1126: Kennedy et al. Baseline Obesity is Predictive of More Rapid Frailty Onset: a 10-year Analysis of the CaMOS Study, ASBMR, 2016

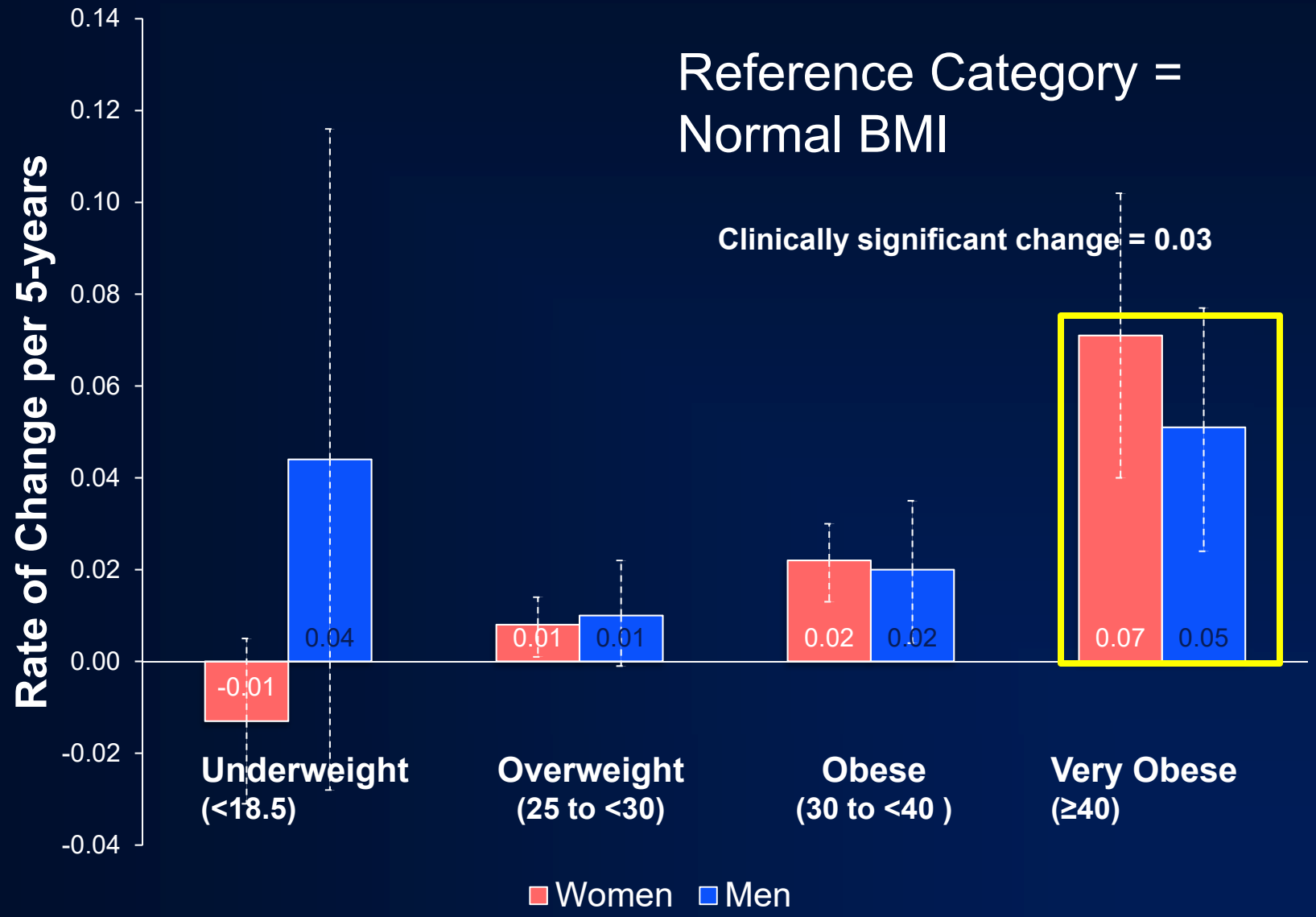
Background: U-shaped relationship between BMI and frailty is known.

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



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

Giusti et al. *International journal of obesity* 2005; Pugnale et al. *Int J of obesity* 2003
Guney et al. *Obes Surg* 2003; von Mach et al. *Metabolism: clinical and experimental* 2004

- Sleeve Gastrectomy

Mechanick. 2013 *Surg Obes Rel Dis*; Nogues. 2010 *Cirugia Espaniola*;
Ruiz-Tovar. 2013 *Obes Surg*; Pluskiewicz. 2012 *Obes Surg.*

- **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

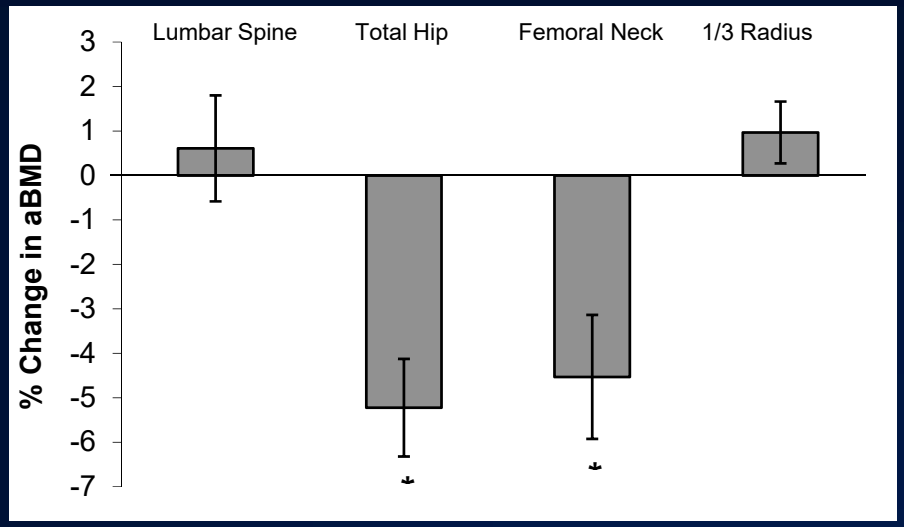
Study of Bone Quality Changes After Bariatric Surgery

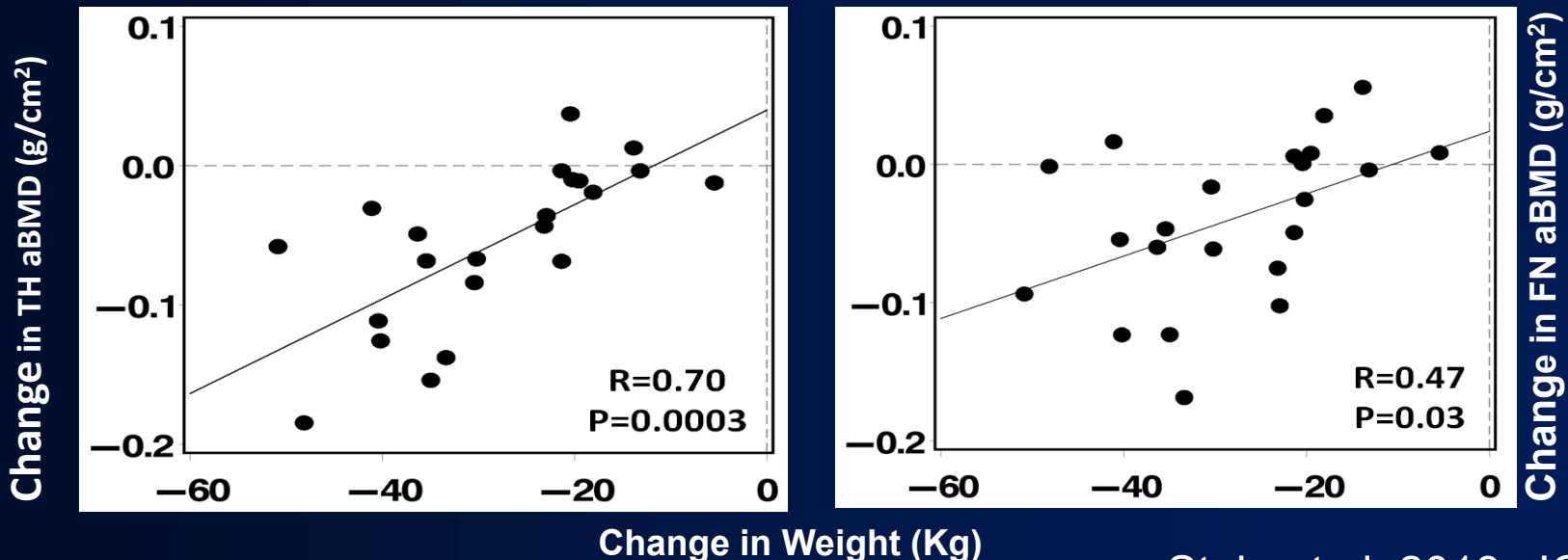
- 22 women, mean age 45 ± 10 years
- BMI 44 ± 5 kg/m^2
- Followed for one year after surgery

- 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

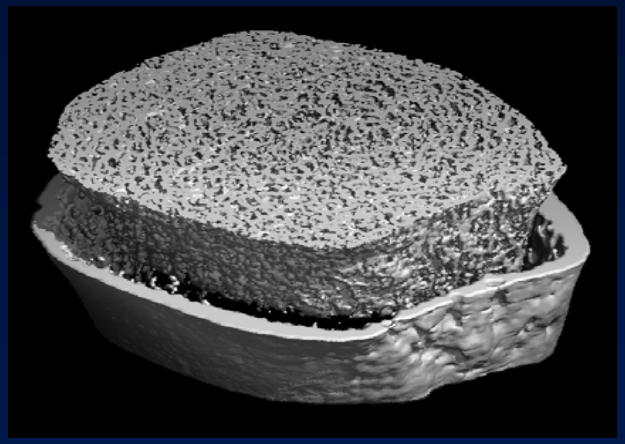




Stein et al. 2013. JCEM

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; Sornay-Rendu. JBMR. 2009; Stein. JBMR. 2010; Melton OI 2010; Vilayphiou. Bone. 2010; Liu. JBMR 2010

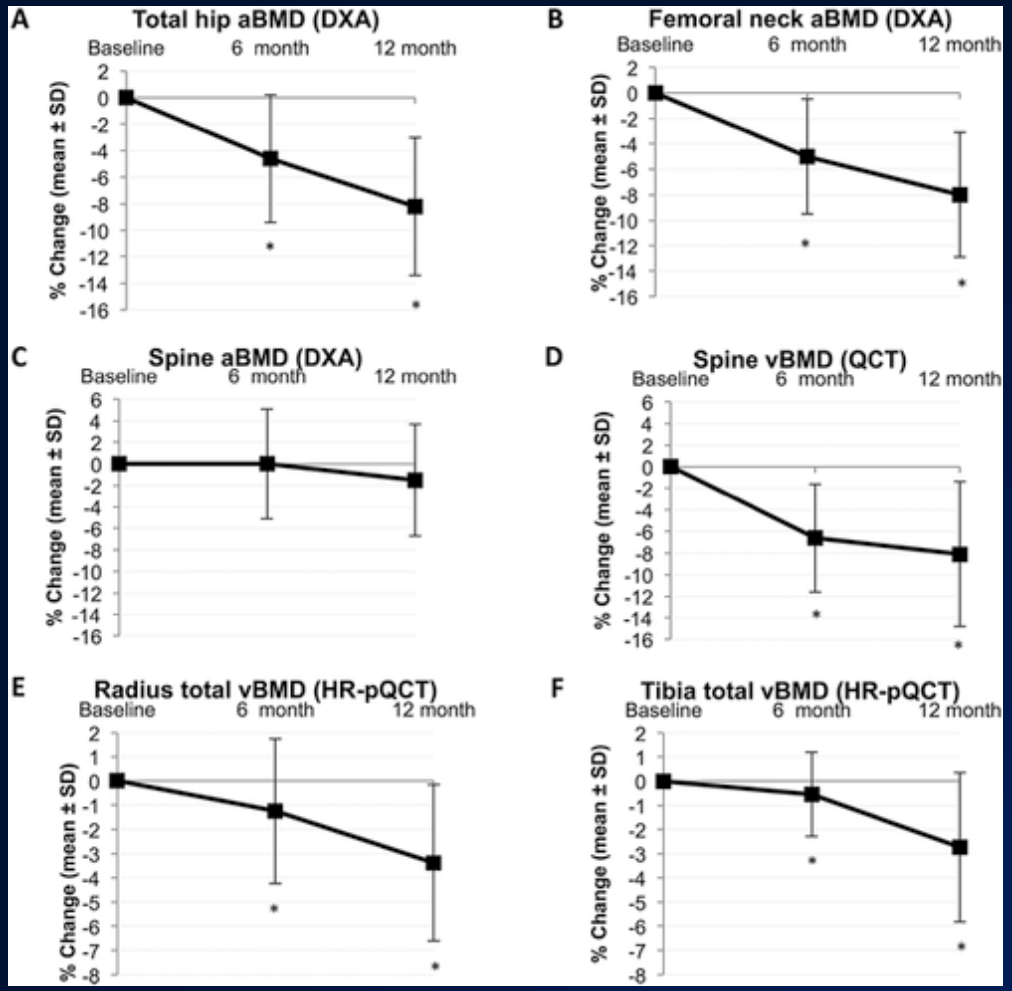
Effects of RYGB on BMD and Skeletal Microstructure. Schafer et al, J Bone Min Res, 2017

- 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

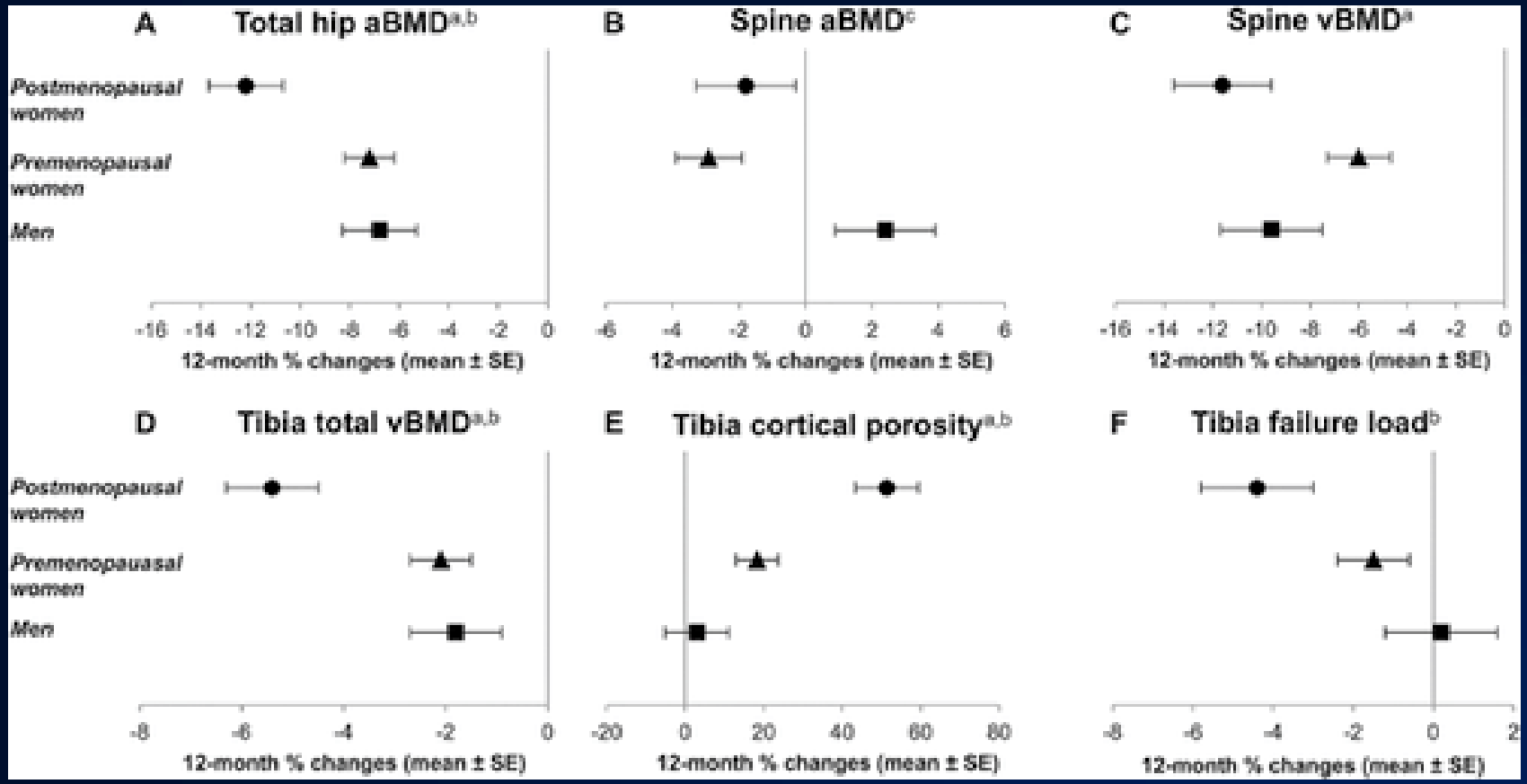
- General Results after 12 months:
  - Anthropomorphic:
    - Weight: -37 kg
    - Total body fat: -27 kg
    - Lean mass: -9 kg
    - Visceral adipose: -108 cm^2
  - Laboratory:
    - 25(OH) D: 42 to 37 ng/mL
    - Uca: 184 to 131 mg
    - PTH: 42 to 48 pg/mL
    - CTX: +278%; P1NP: +111% (baseline values normal)

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



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



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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?

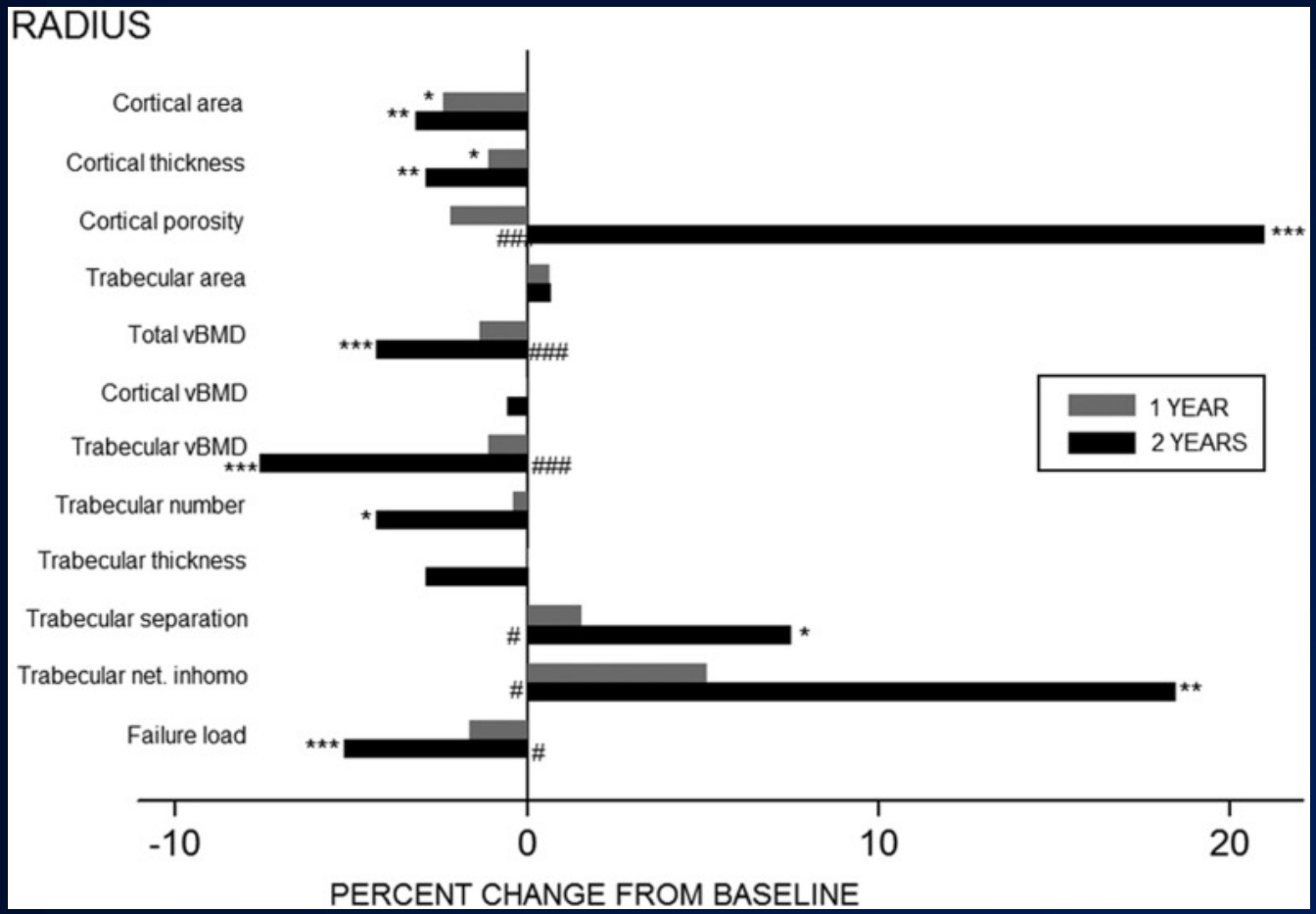
Bone structural changes after RYGB: a 2-year longitudinal study. Shanbhogue et al., E J Endocrinol, 2017

- 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



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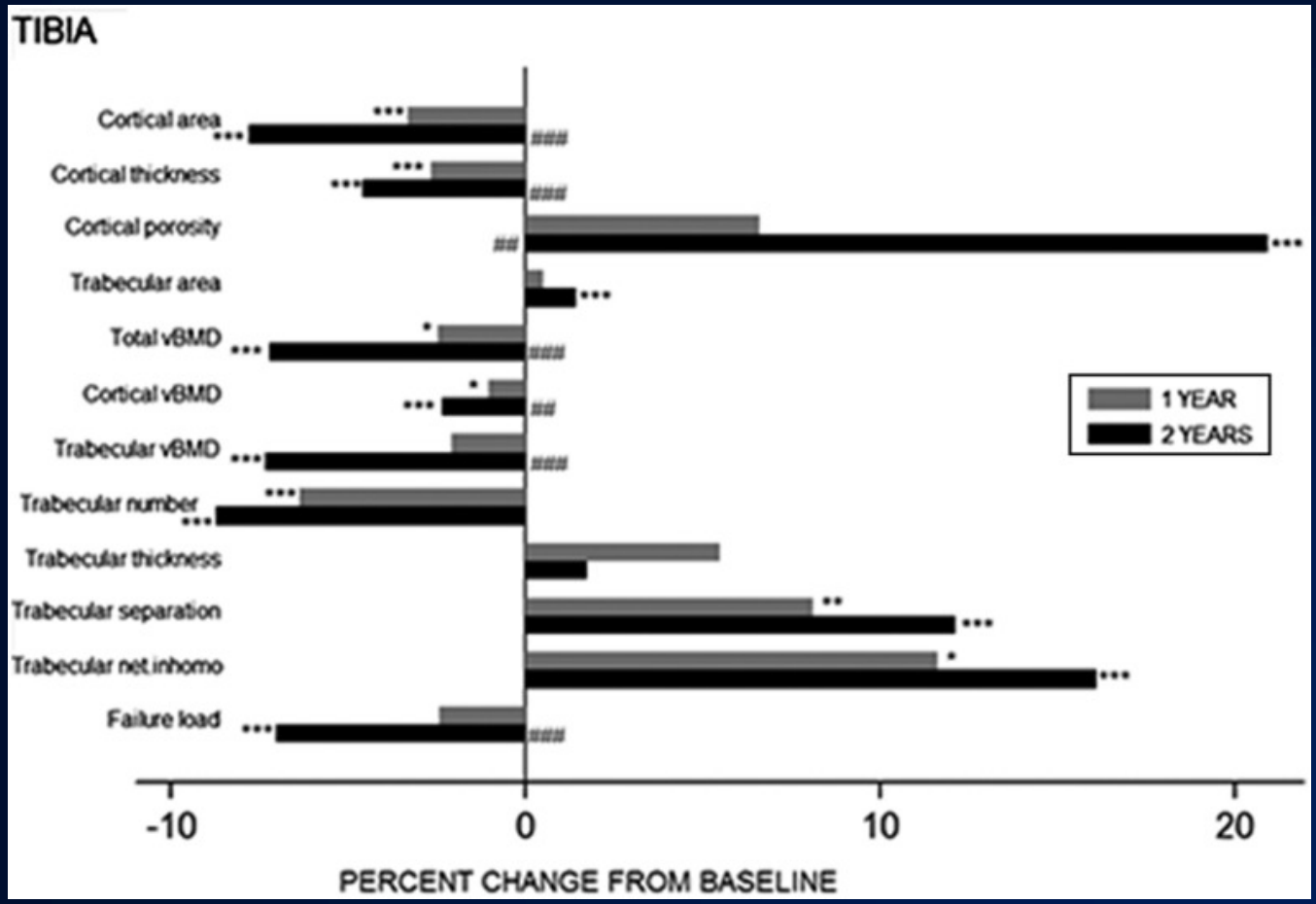

Bone structural changes after RYGB: a 2-year longitudinal study. Shanbhogue et al., E J Endocrinol, 2017

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 microarchitural deterioration

#1125: Greenblatt, Linderman, Rourke, Bouxsein, Finkelstein, Yu. Longitudinal 5-year Changes in Bone Density and Microarchitecture After Roux-En-Y Gastric Bypass (RYGB), ASBMR, 2017

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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INDEX	0-2 yrs	2-5 yrs
DXA	↓ at all sites	↓ hip, 1/3 rad
CT- LS	↓	↓ ↓
HRpQCT- Radius	↓ Ctth/Tbn/ ↑ Tbsep	↓ Ctth/Tbn/ ↑ Tbsep

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

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- Nutritional/malabsorptive (vitamin D, calcium, other nutrients)
- Biomechanical: skeletal unloading (initial effect?)
- Hormonal: secondary hyperparathyroidism (PTH levels do not changes 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

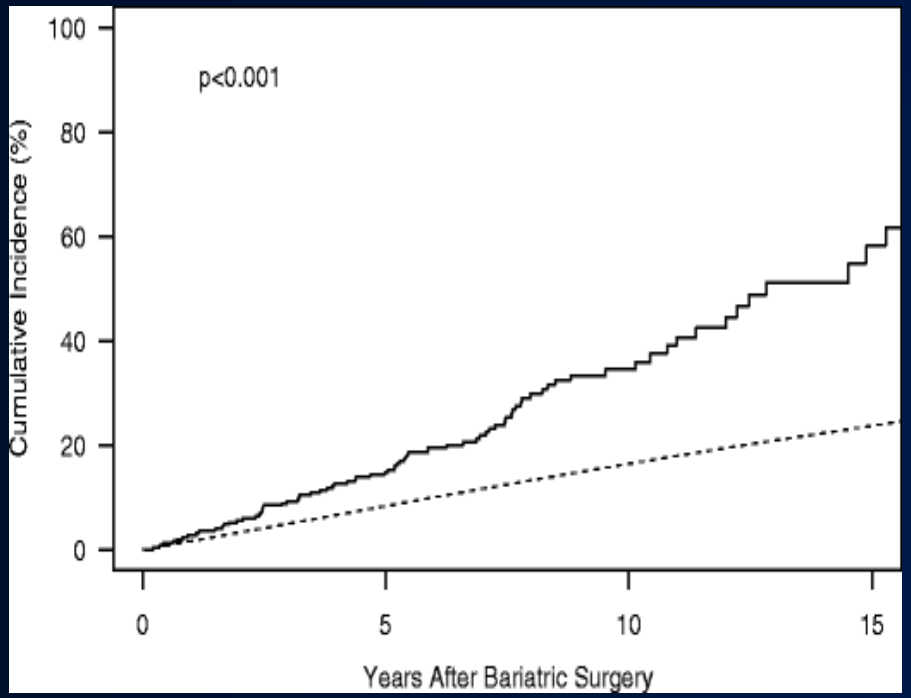
Fracture Risk After Bariatric Surgery

- 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

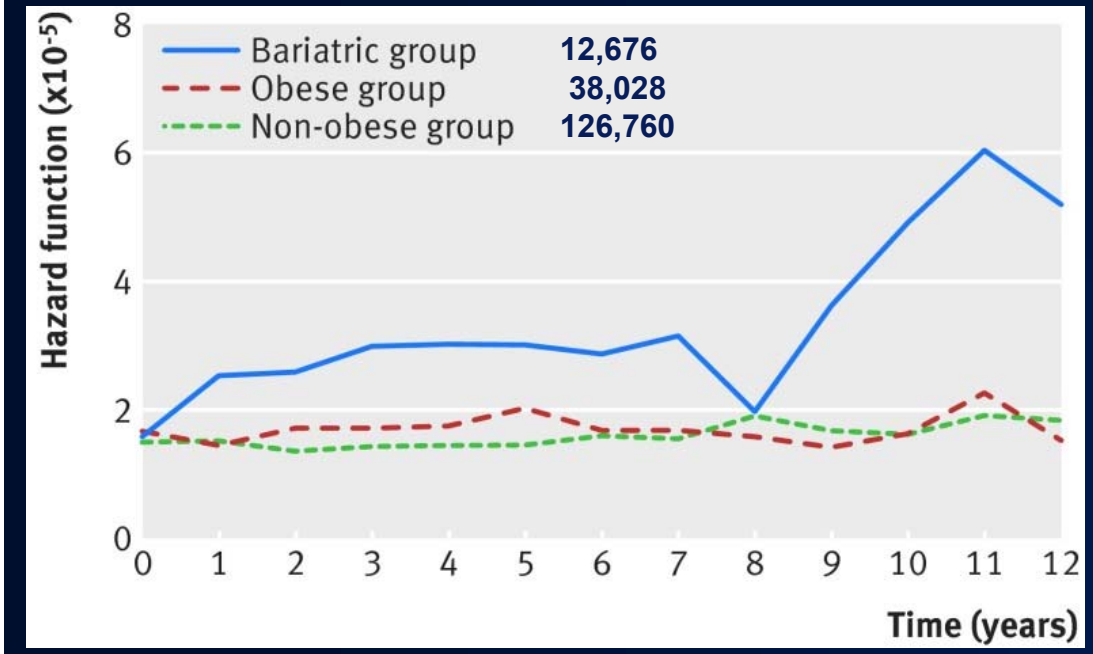


- Increased risk of all fracture and fragility fracture
- Risk greatest for appendicular fractures
  - >50% foot, leg or hand
- Vitamin D deficiency and lower pre-op activity were predictors of fracture

Nakamura et al. 2013. *Osteoporos Int*

Fracture risk following bariatric surgery

Rousseau et al. BMJ 2016



4 years after surgery:

4.1% vs

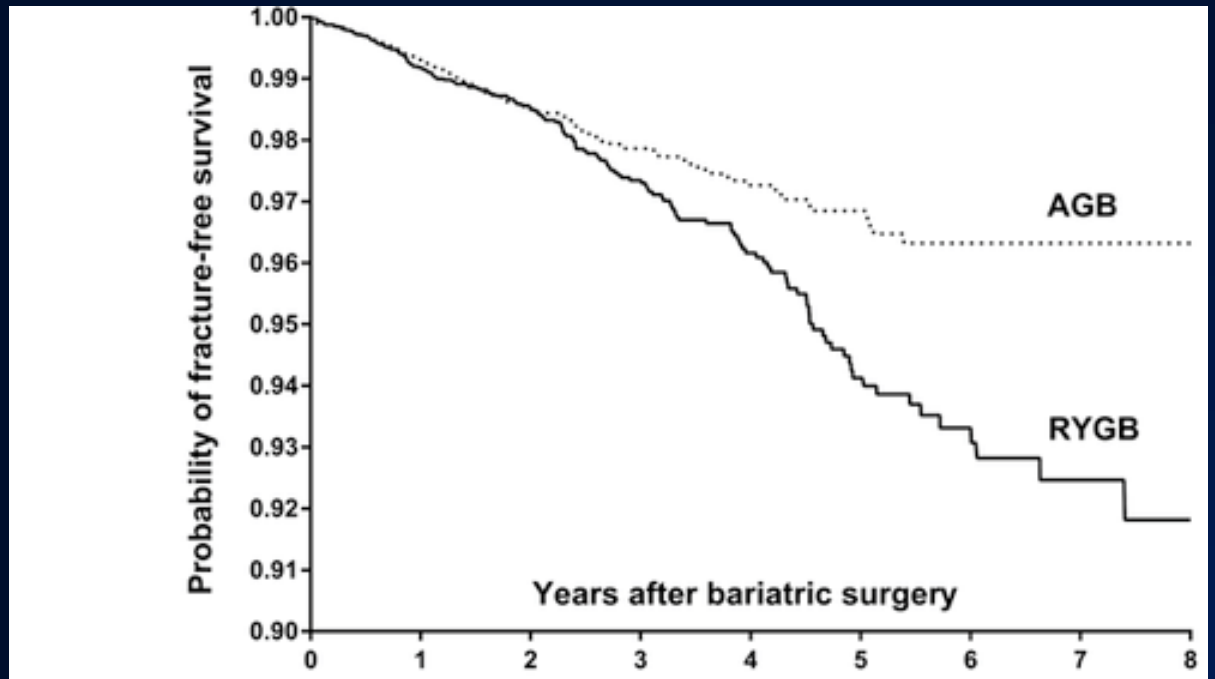
2.7% obese vs

2.4% non-obese

Rousseau et al. The pattern of fracture risk changes from an obesity to an osteoporotic pattern. BMJ, 2017

	Obesity + Bariatric Surgery vs non-obese controls		Obesity: no bariatric surgery vs non obese controls	
	Before	After	Baseline	later
Upper Ext Fx	↓	↑	↓	↓
Central	↔	↑	↔	↔
Lower Ext Fx	↑	↓	↑	↑

Risk After Bariatric Surgery: Roux-en-Y vs Gastric banding. Yu et al. J Bone Min Res, 2017



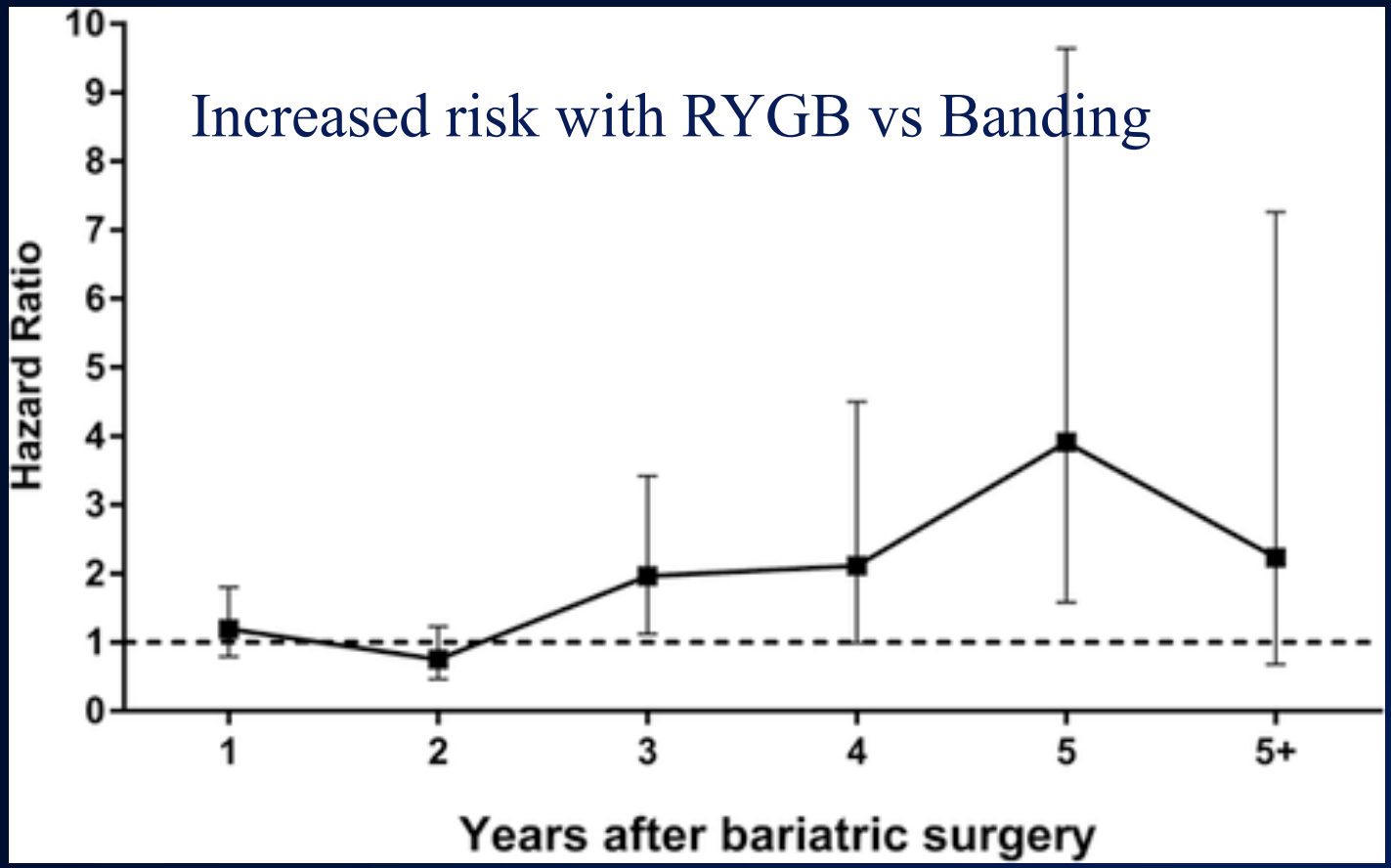
Number at risk	RYGB	7516	6217	4229	2764	1735	1032	578	306	143
	AGB	7516	6217	4359	2937	1834	1122	621	307	73
Events	RYGB	--	50	27	35	20	22	5	3	1
	AGB	--	42	37	19	10	6	4	0	0

Source:
Claims data base
2005-2015

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

Fracture Risk After Bariatric Surgery: Roux-en-Y Gastric Bypass Versus Adjustable Gastric Banding, Volume: 32, Issue: 6, Pages: 1229-1236, First published: 02 March 2017, DOI: (10.1002/jbmr.3101)

Risk After Bariatric Surgery: Roux-en-Y vs Gastric banding. Yu et al. J Bone Min Res, 2017



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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

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- 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