Beyond the Break: Understanding Bone Health as Part of Overall Musculoskeletal Health

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CESHA

University Health Network

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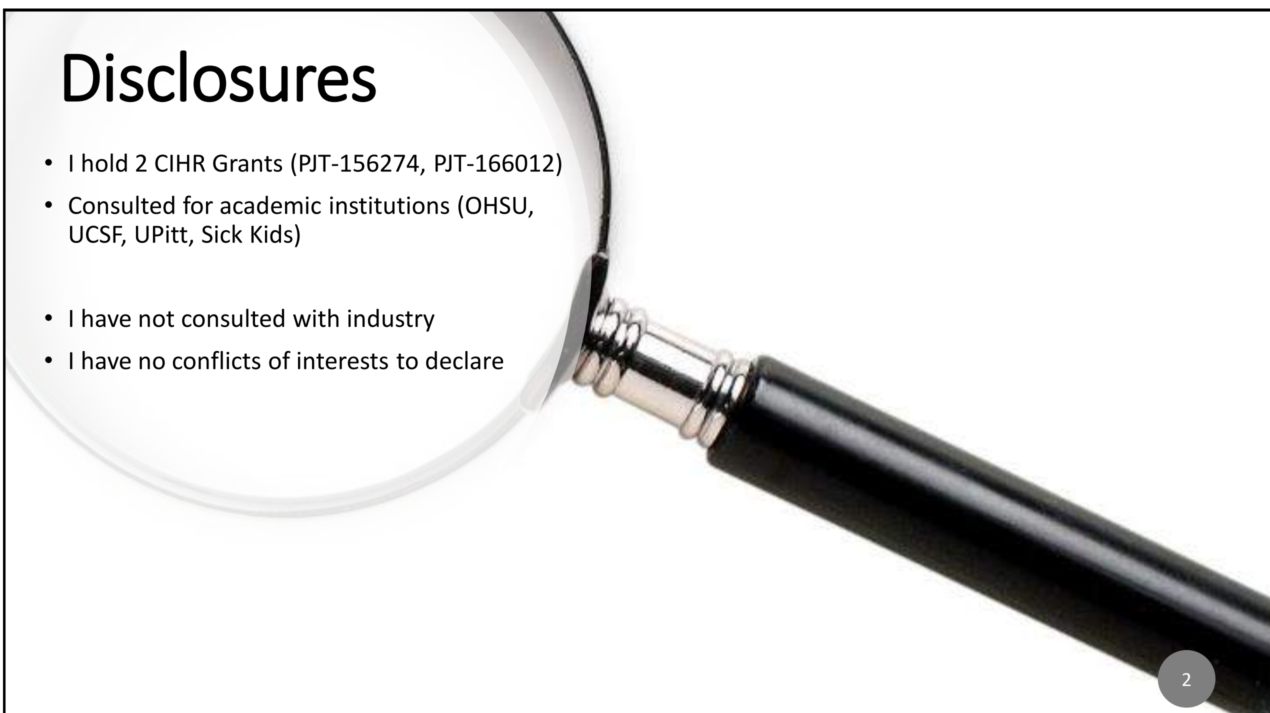

Disclosures

- I hold 2 CIHR Grants (PJT-156274, PJT-166012)
- Consulted for academic institutions (OHSU, UCSF, UPitt, Sick Kids)
- I have not consulted with industry
- I have no conflicts of interests to declare

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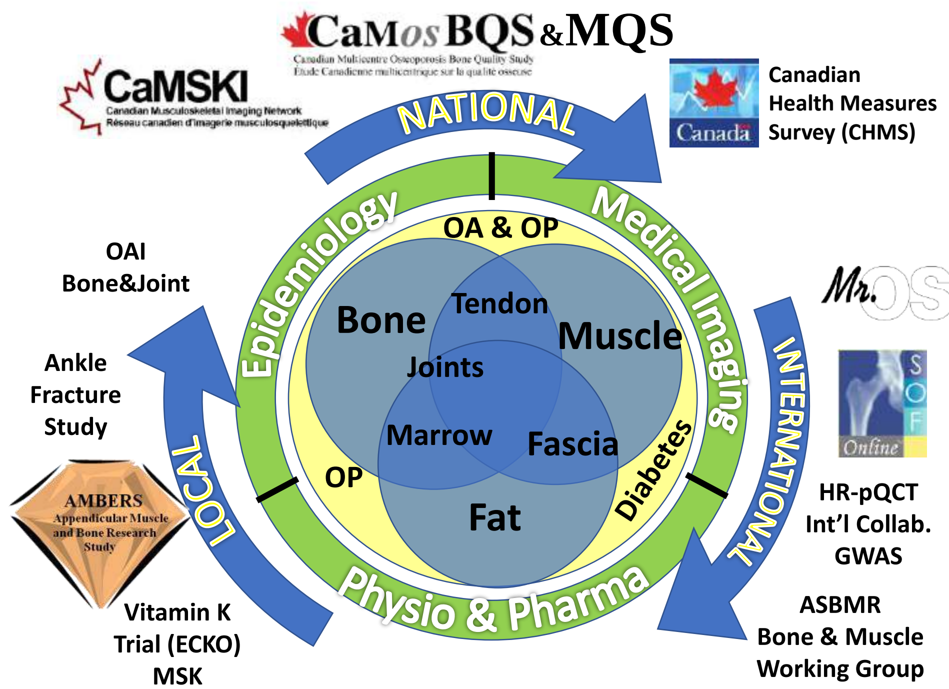

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Beyond the Break – Webinar Learning Objectives

1) Understand the origin and evolution of bone, muscle, fat, & cartilage
2) Appreciate the interactions between:
   a. Bones & muscles
   b. Fat in bones & muscles
   c. Bones & muscles surrounding joints

3) Summarize perspective on bone health as part of overall MSK health

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Origin and Evolution of bone, muscle, fat, & cartilage

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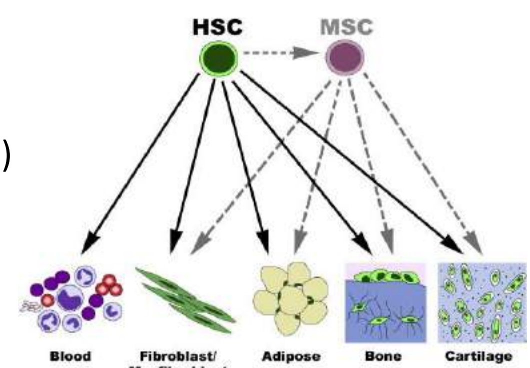
Bone, Muscle, Fat & Cartilage – the same stem cell with different lineage

- Mesenchymal stem cells differentiate into bone, muscle, cartilage and fat (connective)
- Evidence of mutually exclusive cell line commitment[1]
- Preferential commitment to fat lineage → loss in bone, muscle etc [2,3]
- No surface markers – determined by phenotype, function



(1: Quan Kang et al, 2009, 2: Rosen et al, 2009, 3: Rozman et al, 1989)

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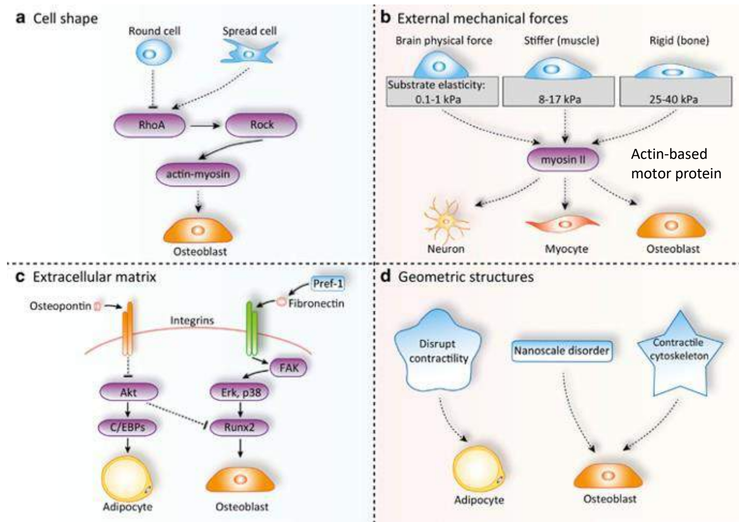
Determinants of MSC differentiation

- Differentiation driven by:

1. **transcription factors**
   (Runx2 Osterix(bone) vs. PPARg CEBP(fat))
2. **microRNA**
   (miR-455-3p (cartilage), miR-320 (bone))
3. **oxygen level**
   (hypoxia (cartilage))
4. **physical environment**
   (stiffer ECM (muscle), rigid (bone))



(Chen et al 2016, Cell Death & Differentiation)

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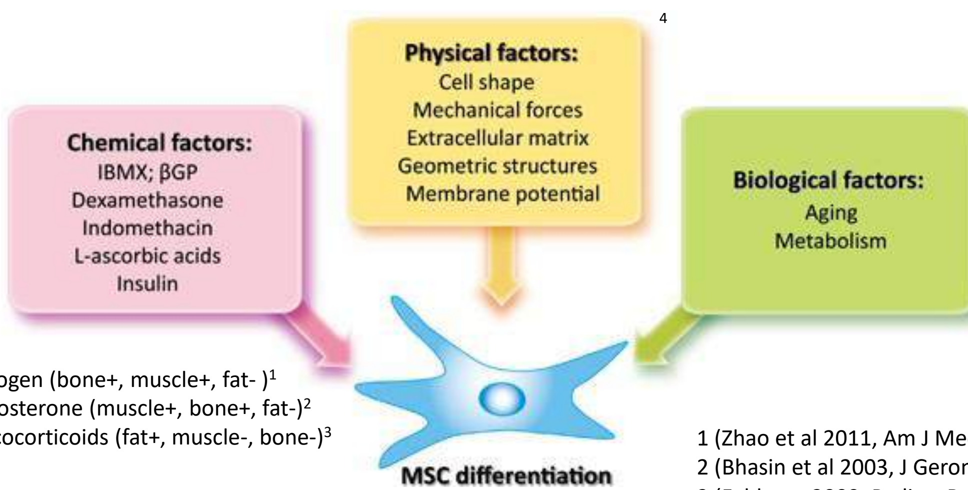
Other non-cellular factors affecting MSC differentiation



Estrogen (bone+, muscle+, fat-)[1]
Testosterone (muscle+, bone+, fat-)[2]
Glucocorticoids (fat+, muscle-, bone-)[3]

1 (Zhao et al 2011, Am J Med Sci)
2 (Bhasin et al 2003, J Gerontol)
3 (Feldman 2009, Pediatr Res)
4 (Chen et al 2016, Cell Death & Differentiation)

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Estrogen and Bone

- key regulator of bone metabolism[1]
- deficiency → osteoporosis
- Menopause → declines BMD
  - 9.1% @ FN & 10.6% @ LS[1]
- [estrogen] associated with fractures[2]
  - <5 pg/mL associated with a 2.5-fold increased hip & vert fx

1.Greendale GA et al. Bone mineral density loss in relation to the final menstrual period in a multiethnic cohort: results from the Study of Women's Health Across the Nation (SWAN). *J Bone Miner Res.* 2012; 27(1):111-8.

2. Cummings SR et al. Endogenous hormones and the risk of hip and vertebral fractures among older women. *NEJM*. 1998;339(11):733-8.

Estrogen and Muscle, Joints, Pain

- Estrogen may attenuate age-related decline in lean muscle mass[3,4]
- impact joints tissues, including articular cartilage
- Associated with chronic pain in muscles and joints[5]

3. Chesterton LS, Barlas P, Foster NE, Baxter GD, Wright CC. Gender differences in pressure pain threshold in healthy humans. *Pain*. 2003;101(3):259-66.

4. Fillingim RB. Sex, gender, and pain: women and men really are different. *Current Review of Pain*. 2000;4(1):24-30.

5. de Kruijf M, Stolk L, Zillikens MC, de Rijke YB, Bierma-Zeinstra SM, Hofman A, Huygen FJ, Uitterlinden AG, van Meurs JB. Lower sex hormone levels are associated with more chronic musculoskeletal pain in community-dwelling elderly women. *Pain*. 2016;157(7):1425-31.

Interactions: Bone & Muscle

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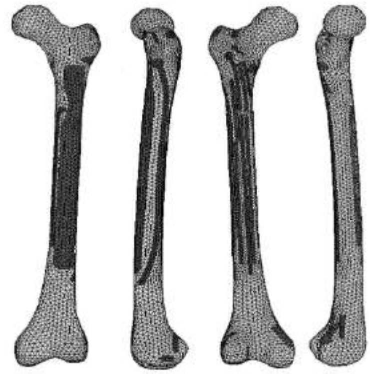
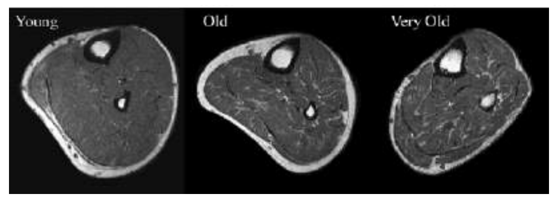
Bone-muscle interaction

- Muscle contraction – largest voluntary load on bone (Ferretti et al, 1998, 2000; Kohrt et al, 2009)
- Electrical activity of muscle modulates bone metabolism (Nagasaka et al, 2006; Park et al, 2004; Rittweger et al, 2006)
- Bone models & remodels in response to mechanical stimuli – mechanostat (Frost, 1998; Cointry et al, 2004)



(Polgar et al, 2003)



(MacNeil et al, 2009)

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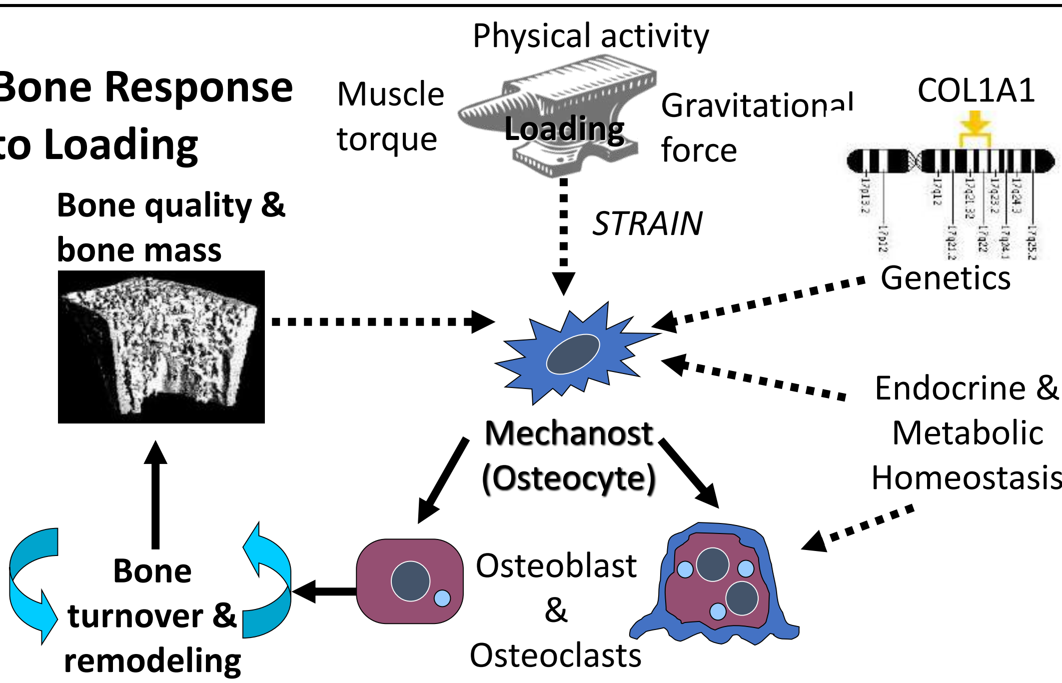
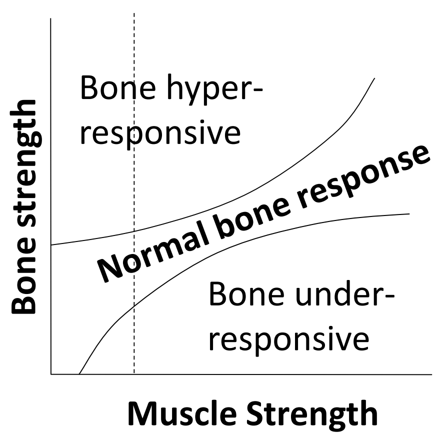
Bone Response to Loading



(Adapted from Ferretti, Cointry et al, 2004)

Bone-muscle (B-M) indices

- Positive relationships between muscle & bone mass/strength (Frost, 1997, 1998)



- Proposed bone:muscle ratios as indicators of bone response to muscle (Ferretti et al, 1998, 2000, 2001)

Bone strength, size or mass responds to…

B-M Index = **Bone parameter** / **Muscle parameter**

…differences in muscle strength, size and mass

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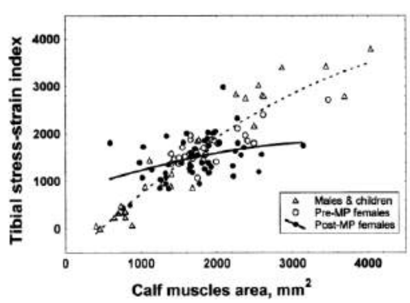
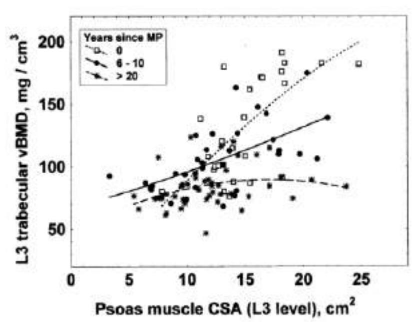
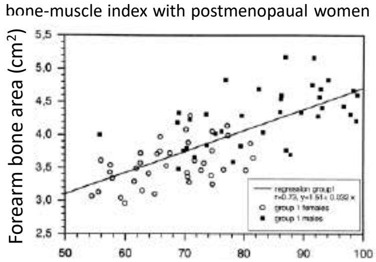
Sex & Menopause Effects on Bone-Muscle Relationships



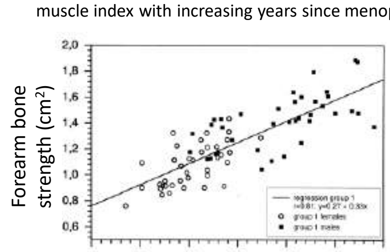
Ferretti et al, 2003; Scheissl et al, 1996 – declining bone-muscle index with postmenopaual women



Ferretti et al, 2003; Ferretti et al, 1996 – declining bone-muscle index with increasing years since menopause



(Rittweger et al, 2000)



(Rittweger et al, 2000)

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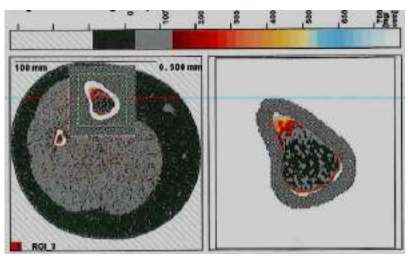
MrOS: Lower B-M indices → increased fx risk

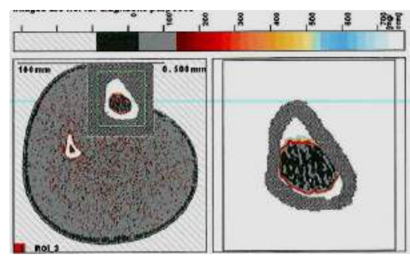
- All men   Mean age: 77.2 ± 5.1 years   Mean BMI: 28.0 ± 4.0 kg/m^2 5 Years   N= 1163 (79 fx)

Parameter	HR	95% CI	C stat	p-value
Bone strength/muscle area	**1.42**	**(1.09, 1.84)**	**0.6051**	**0.009**[a]
Bone mass/muscle mass	**1.74**	**(1.36, 2.24)**	**0.6461**	**< 0.001**[a]
LS BMD	**1.51**	**(1.15, 1.99)**	**0.6257**	**0.003**
TH BMD	**2.09**	**(1.62, 2.69)**	**0.6776**	**<0.001**

- a = adjusted for grip strength, walking speed & aBMD



59 year old male with fx



59 year old male without fx

(Wong et al 2014, J Musculoskel Neur Int)

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Discriminative Power for Fx

- Most bone-muscle indices had poor sensitivity and specificity for identifying those with fractures

Parameter	AUC	Sensitivity	Specificity	p-value
Bone strength/muscle area	**0.579**	**56.06%**	**53.56%**	**0.009**
Bone mass/muscle mass	**0.621**	**58.96%**	**58.12%**	**<0.001**
LS BMD	**0.643**	**60.45%**	**59.53%**	**<0.001**
TH BMD	**0.672**	**61.94%**	**61.46%**	**<0.001**

- DXA – difficult to tease out true lean tissue mass
- Analyses done in general area but not specific muscle group inserting into bone

(Wong et al 2014, J Musculoskel Neur Int)

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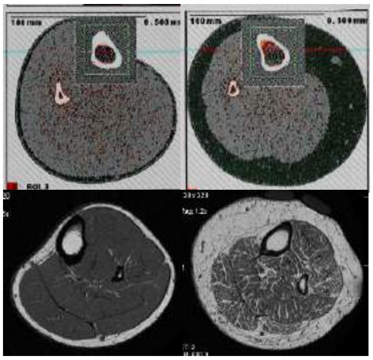
Muscle Properties & Odds for Fragility Fractures

CaMos Canadian Multicentre Osteoporosis Study / Étude Canadienne multicentrique sur l'ostéoporose

■All women Mean age: 72.2 ± 7.7 years Mean BMI: 27.7 ± 5.4 kg/m^2 4 Years N= 525 (46 fx)



Muscle fat volume accounts for 54% of variance in muscle density (MD)

Variable	OR (Unadj)	Expressed per SD	OR (Adj)	Expressed per SD
MD	**1.57 (1.19,2.08)**	**-3.77**	**1.68 (1.20, 2.34)**	**-3.76**
MM	1.13 (0.88, 1.45)	-66.37	1.31 (0.98, 1.75)	-66.76
MCSA	0.98 (0.76, 1.26)	-954.4	1.15 (0.85, 1.55)	-966.0
pQCT Muscle density + bone at the 66% site				
MD + $vBMD_i$	**1.56 (1.18, 2.06)**	**-3.72**	**1.67 (1.20, 2.32)**	**-3.71**
pQCT Muscle density + bone at the 4% site				
MD + $vBMD_i$	**1.63 (1.22, 2.17)**	**-3.72**	**1.64 (1.17, 2.29)**	**-3.71**

Lower muscle and bone density associated with fractures independently of one another

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Bone*Muscle Interactions' Associations with Fractures

Bone*Muscle @ 66% site	N(Fx)	Interaction P-value
Density	449(37)	**0.002**
Area	449(37)	0.363
Content	449(37)	0.120

Conditional Effects	**HR (95% CI)**
Cortical vBMD @ **1st (lowest) quartile of MD**	0.59(0.34,1.02)
Cortical vBMD @ **2nd quartile of MD**	1.09(0.75,1.58)
Cortical vBMD @ **3rd quartile of MD**	**2.01(1.30,3.12)**
Cortical vBMD @ **4th (highest) quartile of MD**	**3.74(1.90,7.35)**

- Normal muscle but abnormal bone was associated with a higher risk for fragility fractures
- Effect largely at the cortex
  - effect blunted for integral vBMD, and
  - not significant for trabecular vBMD

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Weaker Muscles can → Frailty

Frailty Phenotype (*Fried et al.)*

- Rules-based & physiological

Defined by ≥ 3 criteria:

- decreased grip strength
- slow walking speed
- decreased physical activity
- weight loss
- self-reported exhaustion

Result is ordinal or binary

Fried, J Gerontol A Biol Sci Med Sci 2001.

Cumulative Deficits "Frailty Index" (*Rockwood et al.) framework*

- Holistic: diseases, cognition, mood, psychosocial items
- 30-70 cumulative deficits
- calibrated to specific criteria
- Continuous scale – values from 0 to 1

Rockwood, Journal of Gerontology: Medical Sciences, 2007.

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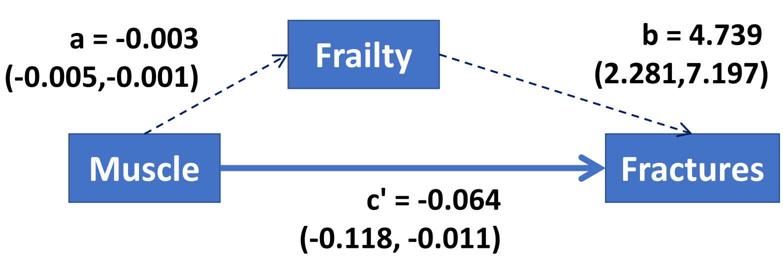
Frailty Mediates the Muscle-Fracture Relationship

- 26/525 (5.0%) women were frail (CFI>0.25)

	NOT FRAIL			FRAIL (CFI >0.25)			
Variable	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**P value**
MD (mg/cm^3)	499	**71.86**	3.39	26	**69.44**	4.62	**0.004**
MCSA (mm^2)	499	**5981**	938	26	**5573**	780	**0.009**
MM (mg)	499	**429.50**	68.11	26	**386.20**	56.53	**0.001**



Muscle may play a role in fracturing bones in 2 ways:

1) weaker forces acting on bone makes bone fragile
2) poorer muscles make individuals frail and due to lack of energy, they fall and break bones

Direct effect:
c' = **-0.064 (-0.118,-0.011)**

Indirect effect:
-0.003 x 4.739 = **-0.015(-0.033,-0.004) (23.4%)**

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Interactions: Fat in Bone & Muscle

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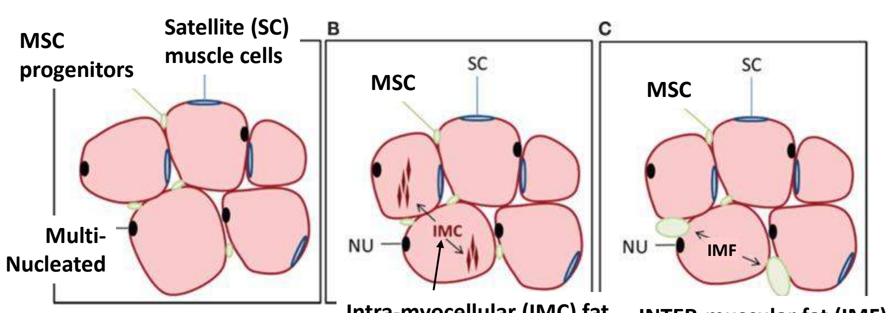
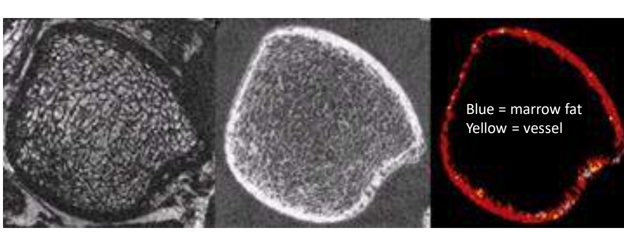
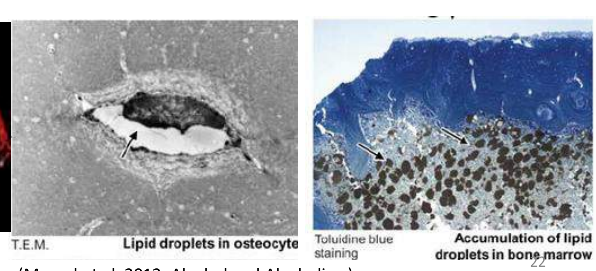
Fat accumulates within muscle and bone



(Hamrick et al 2016, Front Endocrinol)



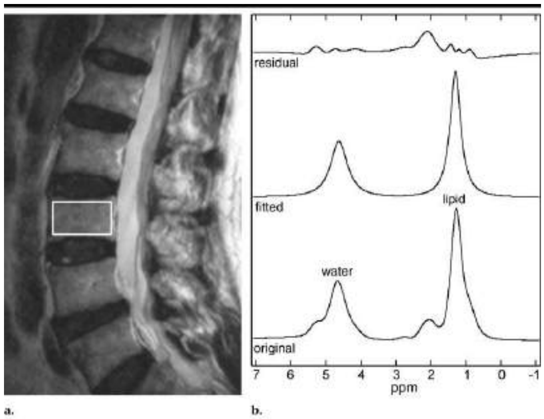
(Goldstein et al 2010, Ann Biomed Eng)



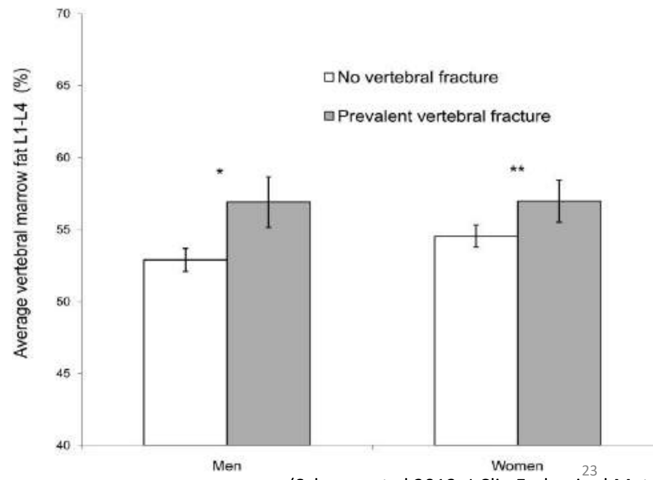
(Maurel et al, 2012, Alcohol and Alcoholism)

Vertebral marrow fat associated with weaker bones

Effect of marrow fat on Spine QCT	Men (N = 118)		Women (N = 139)	
	% Diff	(95% CI)	% Diff	(95% CI)
Trabecular vBMD	**−6.14**	**−11.90 to 0.00**	**−10.49**	**−17.21 to −3.23**
Total vBMD	−1.00	−4.09 to 2.19	**−4.83**	**−7.93 to −1.63**
Axial strength	−6.99	−15.90 to 2.86	**−15.57**	**−23.06 to −7.35**
CSA	−0.30	−2.79 to 2.26	−0.23	−2.36 to 1.95



(Griffith et al, 2005, Radiology)



(Schwarz et al 2013, J Clin Endocrinol Metab)

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The Appendicular Muscle and Bone Extension Research Study (AMBERS) (N=312) – CIHR Funded

AMBERS Appendicular Muscle and Bone Research Study

	No Osteoporosis (N=269)				Osteoporosis (N=54)				
Variables	Mean/N	SD/%	Min	Max	Mean/N	SD/%	Min	Max	**p-Value**
Age (years)	75.26	6.06	63	89	76.48	5.58	67	86	0.173
BMI (kg/m²)	30.08	5.61	17.93	48.24	26.34	5.9	16.41	53.8	**<0.001**
66% FA (mm²)	812.64	386.88	223.43	2553.11	886.7	881.69	329.33	6320.94	0.354
66% pFA (%)	13.16	5.31	4.97	34.67	14.68	7.22	6.74	42.62	*0.094*
66% MD (mg/cm³)	67.43	5.94	46.44	76.1	67.59	4.37	52.86	74.04	0.853
66% MwD (mg/cm³)	21.61	10.78	0.00	57.50	16.99	8.01	2.40	40.90	**0.004**

(Wong et al, 2020 J Bone Miner Res)

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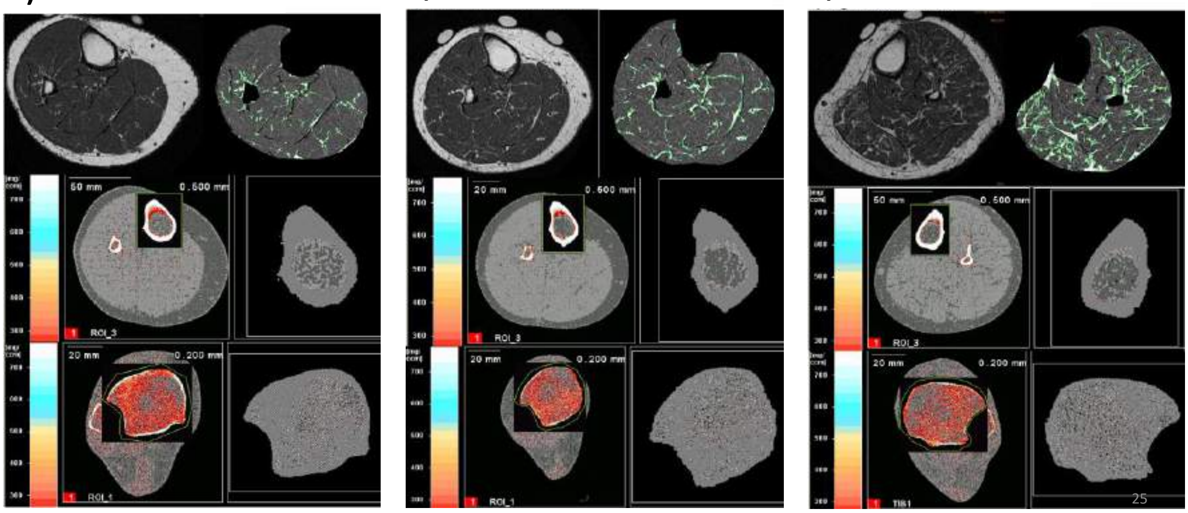
Fat infiltration in bone & muscle are related

Higher fracture risk associated with more muscle fat and more bone marrow fat

A) LOW fracture risk **B) MODERATE fracture risk** **C) HIGH fracture risk**



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Fat infiltration in bone & muscle are related

Higher fat content in bone marrow & calf muscle <u>better related in those with osteoporosis</u>

	Per 10 mg/cm^3	Fully Adjusted		
Muscle fat	**Marrow Fat**	**B**	**SE**	**P-value**
FA (mm^2)	MwD (thres) 66%	-84.08	27.56	**0.002** [a]
pFA (%)	MwD (thres) 66%	-0.90	0.30	**0.003**
MD (mg/cm^3)	MwD (thres) 66%	0.68	0.25	**0.007**

	Per 10 mg/cm^3	No Osteoporosis (N=246)			Osteoporosis (N=51)			
Muscle fat	**Marrow fat**	**B**	**LowerCI**	**UpperCI**	**B**	**LowerCI**	**UpperCI**	**Int P***
FA (mm^2)	MwD (thres) 66%	-29.10	-66.94	8.74	**-591.33**	**-1004.70**	**-177.96**	**<0.001** [a]
pFA (%)	MwD (thres) 66%	-0.36	-0.90	0.17	**-3.90**	**-7.41**	**-0.39**	**0.048**
MD (mg/cm^3)	MwD (thres) 66%	0.40	-0.13	0.94	0.92	-0.45	2.29	0.775

(Wong et al, 2020 J Bone Miner Res)

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Interactions: Bone & Muscle in Joints

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Joint Diseases - Osteoarthritis (OA)

- Increased incidence of OA in the **knee joint** (Buckwalter et al. 2007)
- By 2040, 24% of Canadians will have arthritis, **with up to 60% being women over 65**

- Affects **cartilage, knee angle** but **subchondral bone** and **bone marrow** also impacted
- Traditionally associated with obesity & post-trauma
  - Treated with weight management & pain management

Image from Sofat et al. 2011

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Distribution of Non-Overweight in Knee OA Patients

Osteoarthritis Initiative (OAI): men and women with KL ≥ 2 (N=1086) (Wong et al, 2018 abstract)
- **18.4%** **< BMI of 25 kg/m^2**
  - 37.2% between 25 and 30 kg/m^2, 44.4% >= 30 kg/m^2

Ulm Osteoarthritis Study (N=809 candidates for TKA & THA) (Sturmer et al, 2000)
- **14.1%** **< BMI of 25 kg/m^2**
  - 45.0% between 25 and 30 kg/m^2, 40.9% >= 30 kg/m^2

Swedish cohort (N=825 JSW <= 3mm) (Holmberg et al, 2005)
- **19.0%** **< BMI of 25 kg/m^2**
  - 50.0% between 25 and 30 kg/m^2, 30.5% >= 30 kg/m^2

Catalonia Spain (N=83,469, primary care doctor record of knee OA diagnosis) (Reyes et al, 2016)
- **10.5%** **< BMI of 25 kg/m^2**
  - 37.6% between 25 and 30 kg/m^2, 51.8% >= 30 kg/m^2

COPCORD, Northern China (N=983, doctor dx w/ radiographic confirmation) (Zhang et al, 2013)
- **47.2%** **< BMI of 24 kg/m^2**
  - 35.3% between 24 and 28 kg/m^2, 14.4% >= 28 kg/m^2

Singapore Chinese Health Study (N=1649 TKR for severe knee OA) (Leung et al, 2015)
- **35.7%** **< BMI of 24 kg/m^2**
  - 34.5% between 24 an 27 kg/m^2, 29.8% >= 27kg/m^2

Arthritis Clinics in Phillipines (N=533 w/ radiographic evidence) (Racaza et al, 2012)
- **18.2%** **< BMI of 23 kg/m^2**
  - 33% between 23 and 25 kg/m^2 48.8% above 25 kg/m^2

Mean distribution
of non-overweight knee OA :
24.95%
(range 10.5-47.2%)

COPCORD, Southern China (N=244, symptomatic & radiographic knee OA) (Zeng et al, 2006)
- **36.48%** **< BMI of 24 kg/m^2,**
- 46.31% between 24 and 28 kg/m^2
- 17.21% >= BMI of 28 kg/m^2

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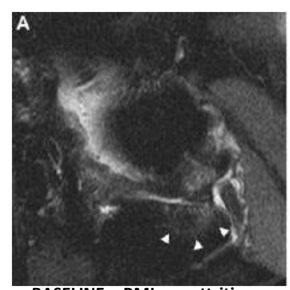
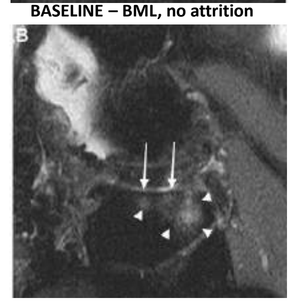
Recognized bone abnormalities in Knee OA

Bone Marrow Lesions (BMLs) in Knee OA

- **BML =** Acute or recurrent damage within subchondral bone leading to inflammation (Sharkey et al. 2012)
- BMLs associated with weight bearing pain **(RR: 2.0, p<0.001)** (Lo et al. 2009)
- Larger BMLs associated with subchondral attrition (flattening) (**OR:18.8(15.9,22.4)**) (MOST Study, Roemer et al. 2010)
- Weaker bone from OP may increase risk of subchondral bone damage → **BML** formation



BASELINE – BML, no attrition



30 Mo Follow-up – BML & attrition

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Is there any basis for bone metabolism / osteoporosis to influence osteoarthritis?

Global bone Abnormalities in Knee OA population

- Bone resorption markers **31-87%** higher in OA vs controls BUT no different from OP group (p<0.01) (Chingford study, Bettica et al. 2002)
- Women with OA more likely to fracture limbs (**OR 2.49(1.77, 3.48)**) compared to controls with normal or osteopenic bone density (Chan et al. 2014)
- Men with vert disc space narrowing & osteophytosis at increased risk of vert fractures (**HR: 1.84-2.52**) (Pariente et al. 2017)

Type I collagen telopeptides	
	N-terminal
Control	37.0 (25.5, 60.4)
Prog OA	53.9 (39.6, 79.1)†
Non-Prog OA	40.1 (28.1, 56.5)§
Osteoporosis	59.8 (44.1, 80.4)†
	C-terminal
Control	126.5 (77.5, 205.8)
Prog OA	214.0 (145.2, 285.4)‡
Non-Prog OA	180.6 (96.1, 246.7)¶
Osteoporosis	236.5 (178.9, 293.2)†

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Recognized muscle abnormalities in knee OA

Muscle Association with Osteoarthritis

- Radiographic knee OA was associated with baseline sarcopenia in women **(RR: 1.91(1.71, 3.11))** (Misra et al. 2018)
- Leg lean mass was lower in knee OA **(19.2 ± 2.7%)** compared to controls (**21.0 ± 2.9%**) (p<0.001) (Toda et al. 2000)
- Baseline knee extensor strength in **women** associated with knee OA **(OR:1.72(1.16, 2.56))** (Culvenor et al. 2016)
- Higher knee adduction moment associated with greater cartilage loss (**20.5% variance explained**) (Maly et al, 2015)
- No studies examining periarticular muscle specifically

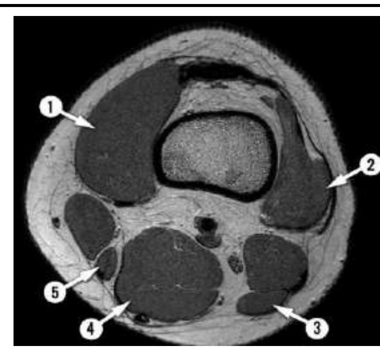

Image from www.radiopaedia.org

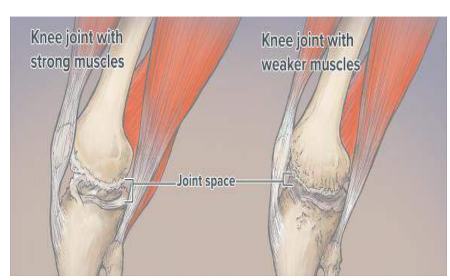

Image from www.arthritis-health.com 32

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Osteoarthritis (OA) Initiative (N=1086)

- 15.2% of patients with knee OA have osteoporosis
  - **18.4% BMI of <25 kg/m²**
  - 37.2% between 25 and 30 kg/m²
  - 44.4% >= 30 kg/m²

Var	OP (214)	No OP (845)	P-value
Age	67.2± 8.4	64.2± 8.9	**<0.001**
BMI	29.1± 4.9	30.5± 4.9	**<0.001**
PASE	128± 77	154± 84	**<0.001**
Serum Vit D	27.74 ±10.42	25.60 ±9.78	0.237
FN BMD T-score (167)	0.21± 1.15	0.49± 1.10	0.180

Compartment	No Osteoporosis (N=237)	Osteoporosis (N=52)	P-Value*
Medial aBMD	1.135 g/cm²	1.042 g/cm²	**<0.001**
Lateral aBMD	1.023 g/cm²	0.925 mg/cm²	**<0.001**
Medial Tb.Sp	1.637 mm	2.245 mm	**<0.001**
# of BMLs	1.23 # total	0.96 # total	**0.043**
Edema in BMLs	2.66%	1.99%	**0.040**

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In the OP Group – Cartilage was not associated with pain (but neither was bone*)

General Linear Model with OP Group Interaction – Followed by Pick-a-Point Probing

Cartilage measures	No Osteoporosis (N=852)	Osteoporosis (N=165)	Interaction P-value
Expressed per 1 mm lower	KOOS Symptoms (lower scores greater symptoms)		
Medial wb ThC (mm)	**-2.4(-1.4,-3.5)**	0.7(-2.0,3.5)	**0.027**
Lateral wb ThC (mm)	**-2.3(-1.4,-3.3)**	1.7(-1.2,4.6)	**0.008**
Medial mean ThC (mm)	**-4.0(-0.3,-7.7)**	6.5(-3.0,16.1)	**0.038**
Lateral mean ThC (mm)	**-7.4(-4.8,-9.9)**	2.5(-5.4,10.3)	**0.011**
Affected wb ThC (mm)	**-4.1(-3.1,-5.1)**	0.2(-2.7,3.0)	**0.003**
Affected mean ThC (mm)	**-9.5(-6.2,-12.8)**	3.0(-6.5,12.5)	**0.009**
	WOMAC Stiffness (Higher scores greater symptoms)		
Medial wb ThC (mm)	**0.2(0.1,0.3)**	0.0(-0.3, 0.2)	0.093
Lateral wb ThC (mm)	**0.2(0.1,0.3)**	-0.2(-0.5,0.1)	**0.022**
Medial mean ThC (mm)	**0.6(0.2,0.9)**	-0.8(-1.8,0.2)	**0.021**
Lateral mean ThC (mm)	**0.5(0.3,0.8)**	-0.5(-1.3,0.4)	**0.035**
Affected wb ThC (mm)	**0.3(0.2,0.4)**	0.0(-0.3,0.3)	0.054
Affected mean ThC (mm)	**0.8(0.5,1.1)**	-0.4(-1.4,0.6)	**0.047**

* Subchondral DXA and MRI was only examined in 289 with only 52 OP cases

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The Appendicular Muscle and Bone Extension Research Study (AMBERS) (N=312) – CIHR Funded

- 48 month prospective cohort study
- imaging bones and muscles (peripheral CT, DXA)
- captured knee surgeries, radiographic ascertainment
- Knee OA diagnosis validated against primary care data

Univariate General Linear Models

	Knee OA (N=80)				No Knee OA (N=232)				
Variables	**Mean/#**	**SD/%**	**Min**	**Max**	**Mean/#**	**SD/%**	**Min**	**Max**	**p Value**
Age (years)	76	5.8	64	89	75.4	6.1	63	86	0.186
Height (cm)	156.68	6.68	144	174	155.4	6.32	141	172	0.285
Weight (kg)	78.89	13.73	57	115	67.94	13.86	35	108	**0.015**
TUG (s)	10.73	2.69	6.68	18.78	10.36	3.35	6.12	38.53	0.055
BMD T-score	-1.54	1.03	-3.6	0.9	-1.71	1.03	-5.7	3.2	0.824
Antires Use	53	37.9%			54	29.5%			0.114
GC Use	11	7.9%			10	5.5%			0.387
Fragility Fx	11	7.9%			13	7.1%			0.798

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Knee OA & OP BONE Differences in Postmenopausal Women –AMBERS (N=312)

General Linear Model – Accounting for covariates: age, BMI, use of OP medication, GC use, kidney/liver disease/diabetes

Tibial bone vars	**KOA+OP vs. Neither**			**KOA+OP vs. OP**			**KOA+OP vs KOA**		
	B	**Lower CL**	**Upper CL**	**B**	**Lower CL**	**Upper CL**	**B**	**Lower CL**	**Upper CL**
Trabecular separation (mm)	**0.101**	**0.029**	**0.173**	-0.003	-0.108	0.101	**0.139**	**0.077**	**0.201**
Bone volume (fraction)	**-0.081**	**-0.141**	**-0.021**	-0.001	-0.059	0.056	**-0.113**	**-0.176**	**-0.050**
Cortical BMD (mg/cm^3)	**-57.43**	**-101.18**	**-13.68**	-19.75	-53.26	13.76	**-56.86**	**-108.25**	**-5.47**
Trabecular BMD (mg/cm^3)	**-16.56**	**-31.89**	**-1.23**	-1.35	-11.44	8.74	**-21.16**	**-39.34**	**-2.98**

Bone properties in those with both Knee OA and OP are no different from those with just OP alone

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Postmenopausal Knee Imaging of Intramedullary Pressure (PoKIMP Study) – CIHR Funded

- Cross-sectional study, target N=125 – convenience sampling
- Postmenopausal women 50-85 years old, BMI < 25 kg/m^2
- Variable degrees of knee pain
- No joint replacements and no RA
- No contraindications to MRI, no kidney disease (for Gd injection)

- Anteroposterior knee radiographs
- Peripheral CT of knee (subchondral bone & periarticular muscle)
- MRI: PD-weighted, water-excitation, fat-water separated Dixon, perfusion MRI (DCE-MRI)
- Functional measures, 3 pain measures (painDETECT, ICOAP, KOOS)

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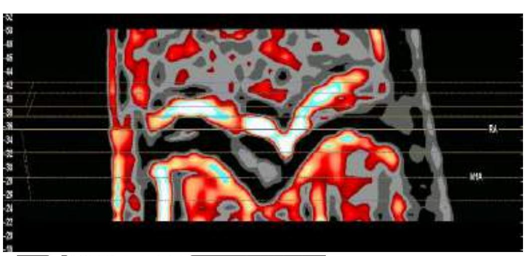
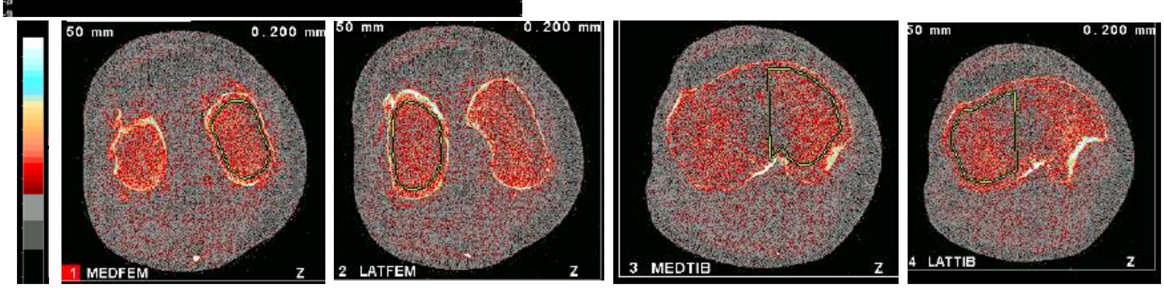
Analysis of subchondral bone from peripheral CT



- Reference lines placed at each compartment
- ROI defined by contouring and reducing by 20% in area
- ROI centered in articulating region



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Difference in subchondral bone properties between groups

N=50	Healthy		Knee OA		
Subchondral Tib/Fem	Mean	SD	Mean	SD	p-value
Tissue Mineral Density	351.9	40.07	304.2	52.39	**<0.001**
Bone Mineral Density	307.7	50.81	252.1	65.41	**<0.001**

- Variances can be assumed to be equal (p value: 0.11)

Univariate analysis due to low sample size at present

Difference in periarticular muscle between groups

N=50	Healthy		Knee OA		
Periarticular measures	Mean	SD	Mean	SD	p-value
Fat area	744.7	289.5	638.1	199.7	**0.012**
Fat content	12.42	3.63	10.98	2.80	**0.010**
Total area	3767	713	3545	481	**0.033**
Total density	69.91	5.61	75.58	9.52	**<0.001**

- Variances are not equal (p value < 0.05)

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Synthesis of Tissue Interactions

- Bone-Muscle-Joints interact in varying degrees
- Loss of integrity of one could affect the other
  - And may be complemented by invasion of fat
- Common denominator:
  - Its origin: mesenchymal stem cells – driven by differentiation
  - External factors: hormones, drugs, environment, exercise
- Effects may not be restricted to one (central) site

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Perspective

- We should pay attention to not only bone, but also muscle loss and fat accumulation
- Abnormalities in bone, muscle and fat are not restricted to hip & spine
  - they could also affect the joints
- Common culprits should not be ignored:
  - estrogen loss, androgen loss / deprivation, glucocorticoid use
- How might we approach these related insults comprehensively?
- Should we integrate the way we study / treat MSK conditions?

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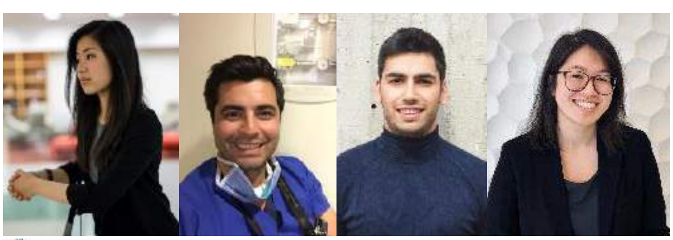
Acknowledgements



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