Osteosarcopenia: understanding bone, muscle & fat interactions

G Duque

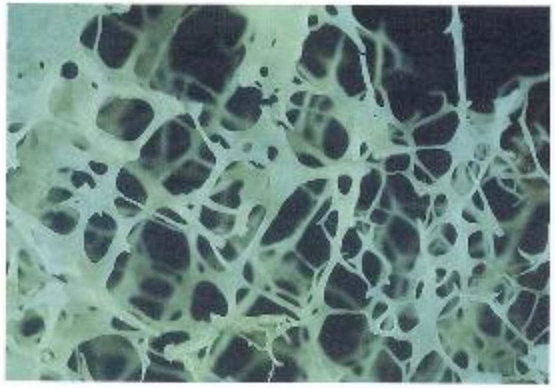
Joint IOF-ESCEO webinar

Osteosarcopenia: Understanding bone, muscle and fat interactions

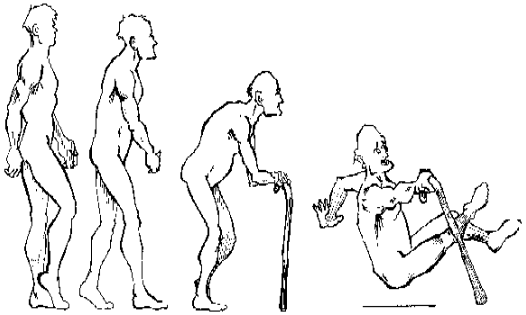
Professor Gustavo Duque, MD, PhD, FRACP, FGSA

Chair of Medicine & Director of the Australian Institute for Musculoskeletal Science (AIMSS)

Melbourne Medical School and Western Health



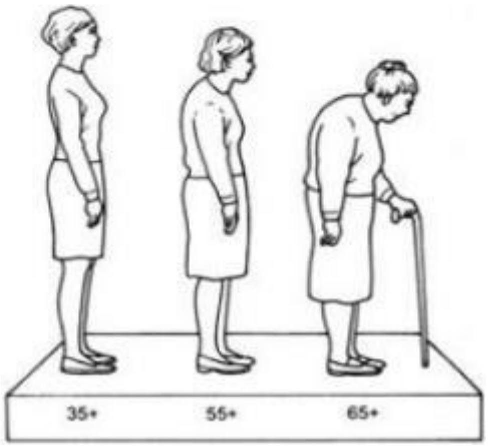
Osteopenia → Osteoporosis → Fractures



Rosenberg, I H, J Nutr 2007;127:9905-9915.

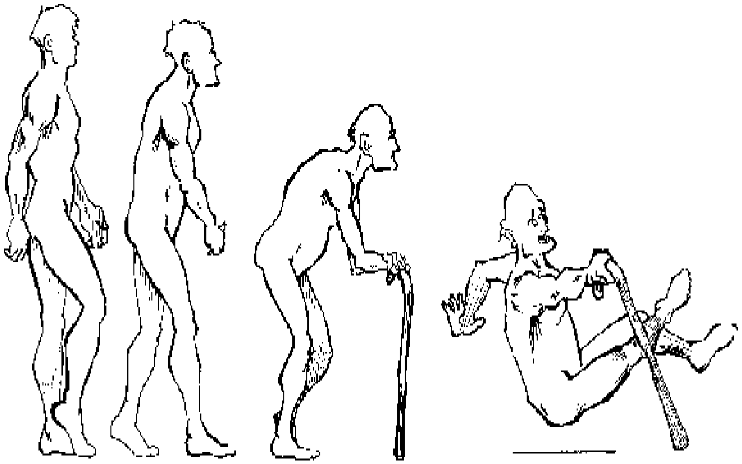
Sarcopenia → Falls

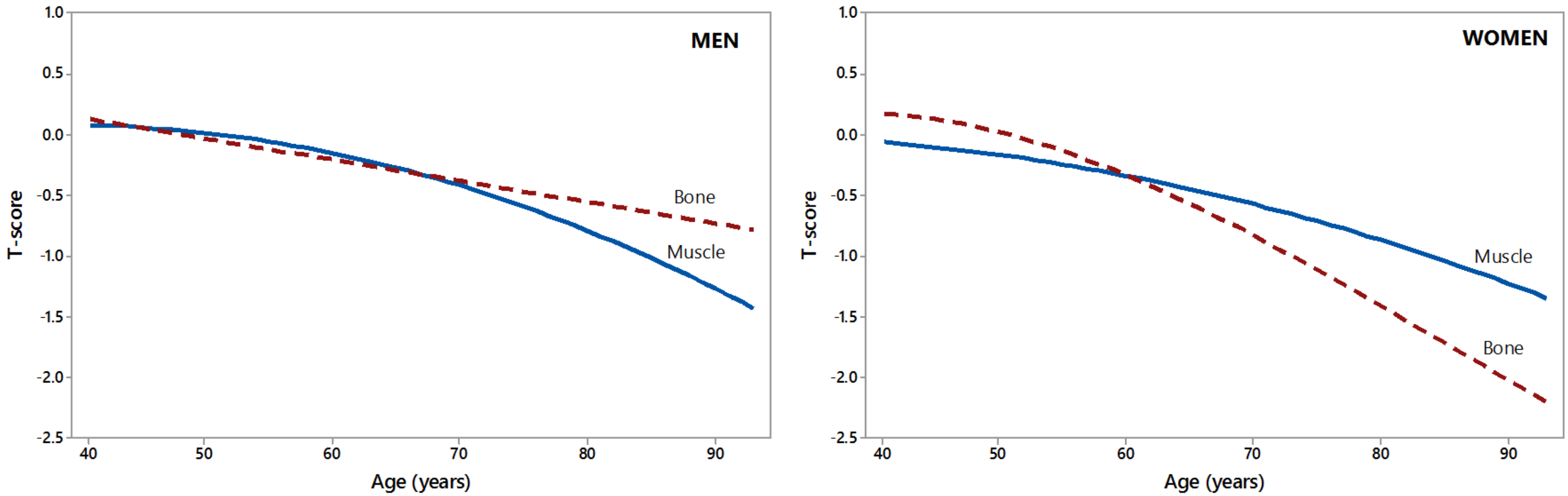
aimss Australian Institute for Musculoskeletal Science



Fractures

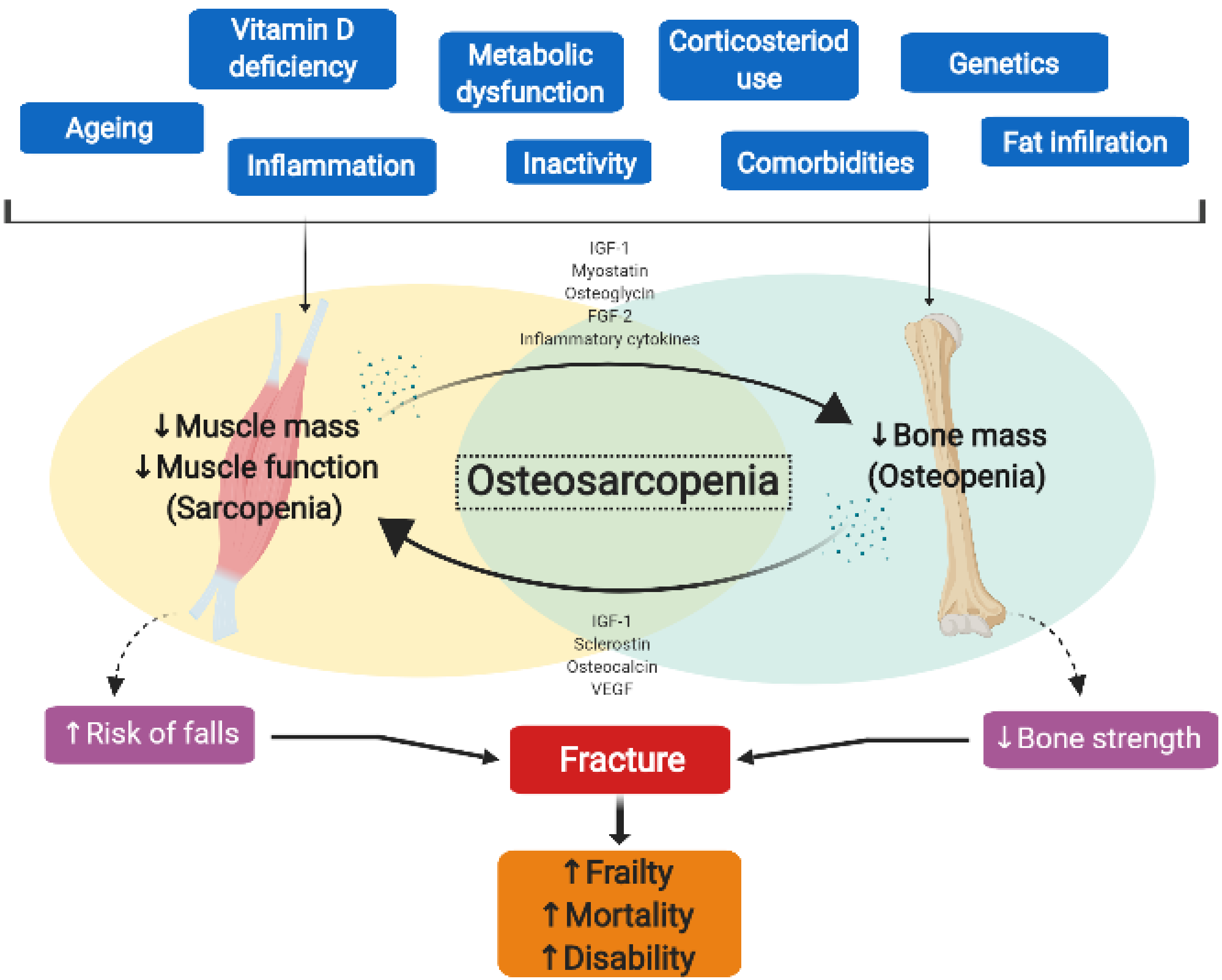
Falls





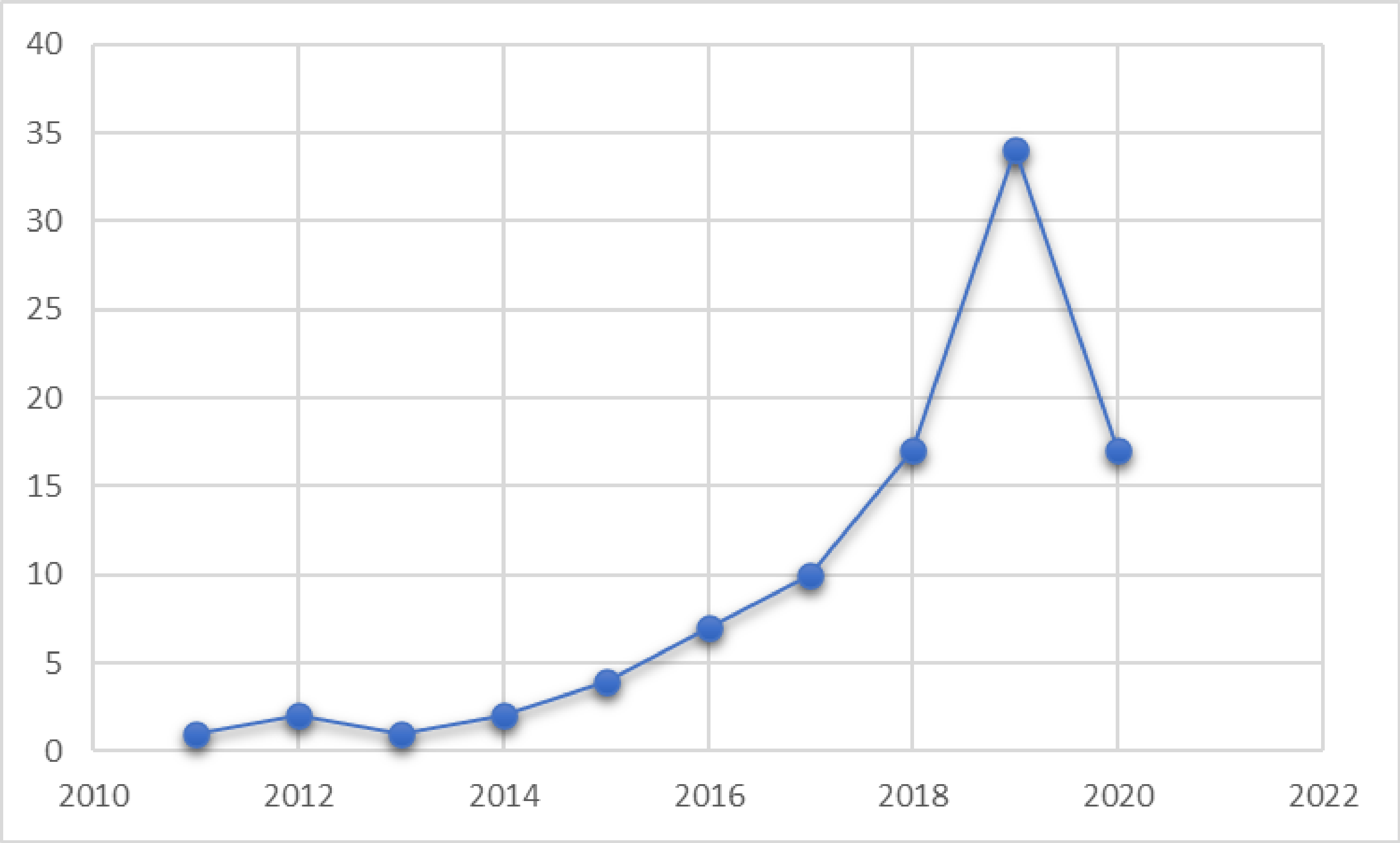
Pasco et al. In: Osteosarcopenia: Bone, Muscle and Fat Interactions. Ed: G. Duque

Osteosarcopenia



Kirk et al, Aging Med. 2019

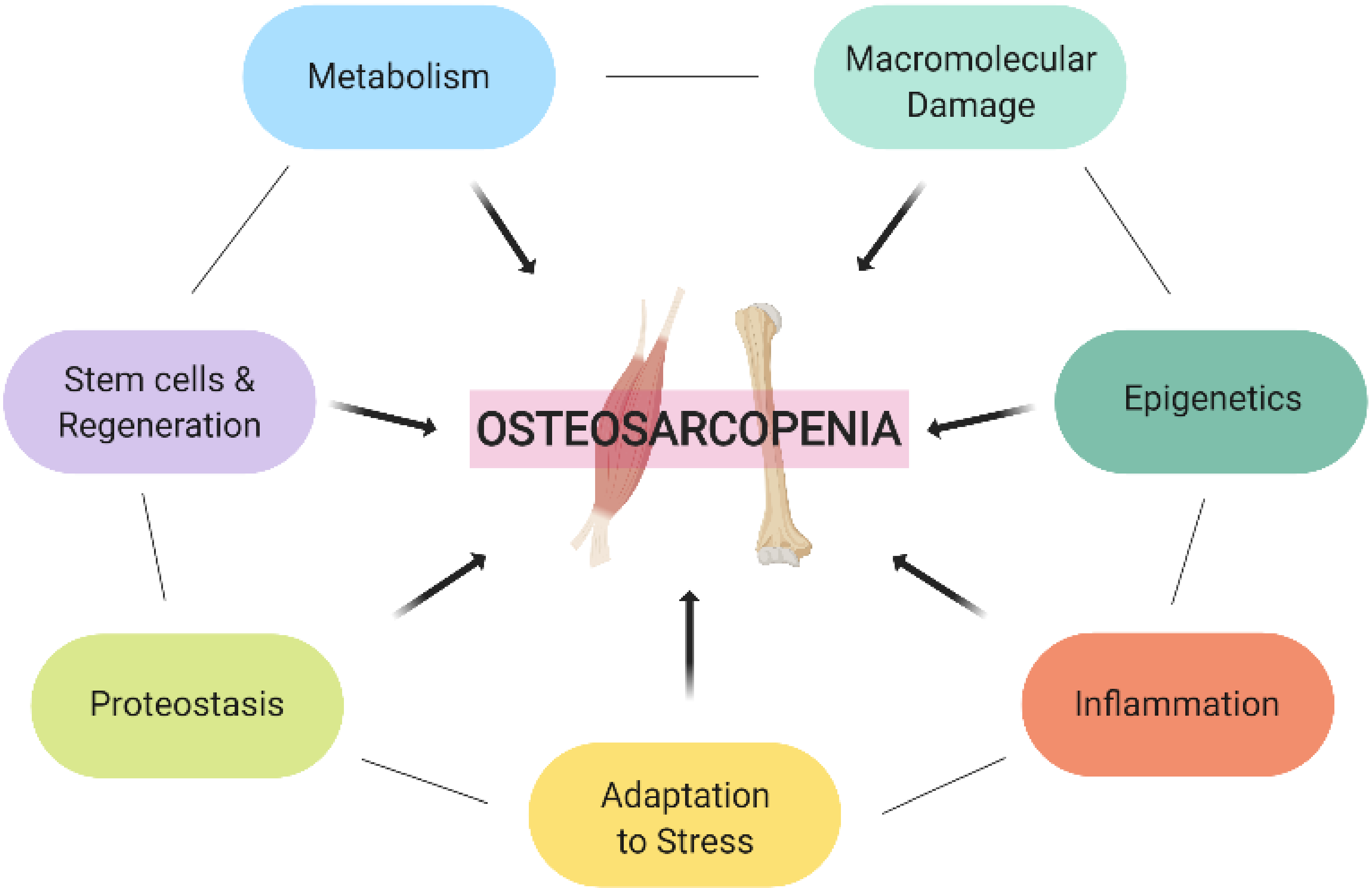
Osteosarcopenia: A growing concept



Source: Pubmed

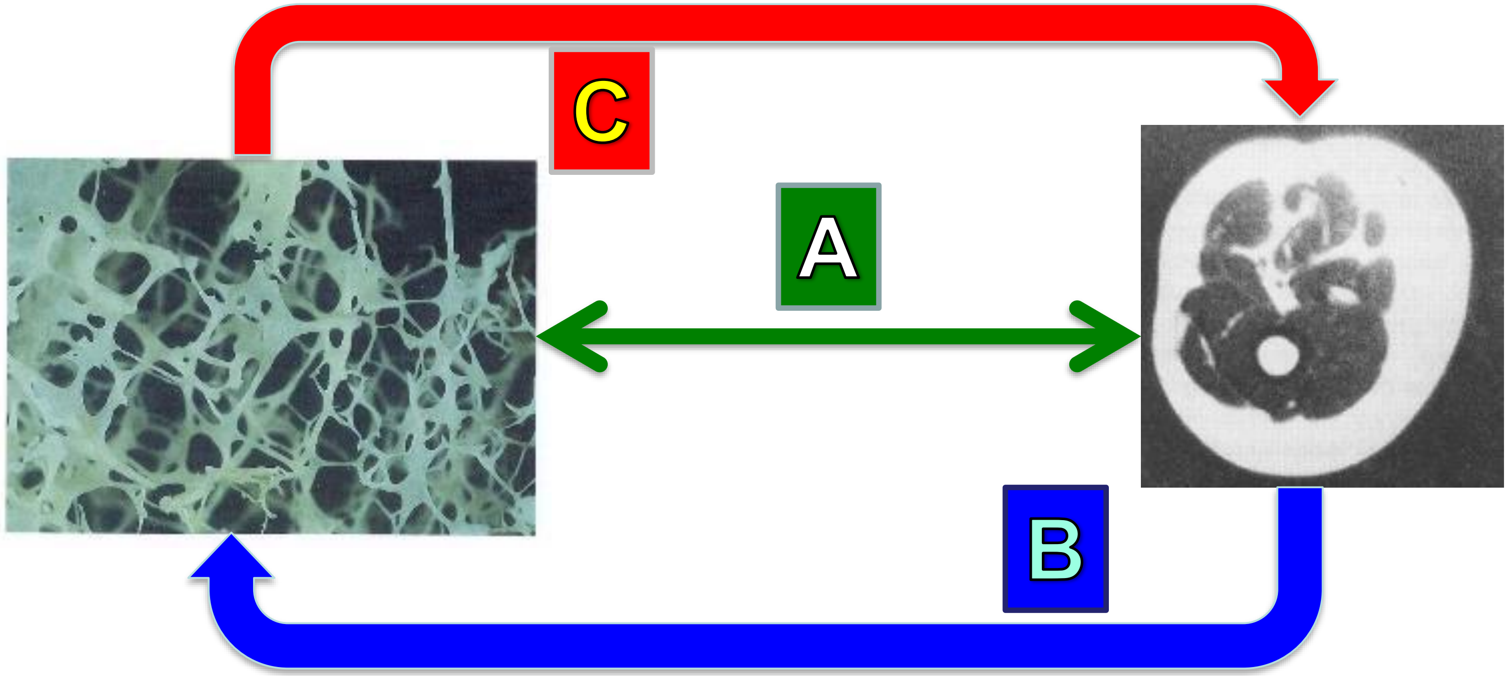
Pathophysiology

Osteosarcopenia: A case of geroscience



Kirk et al, Aging Med. 2019

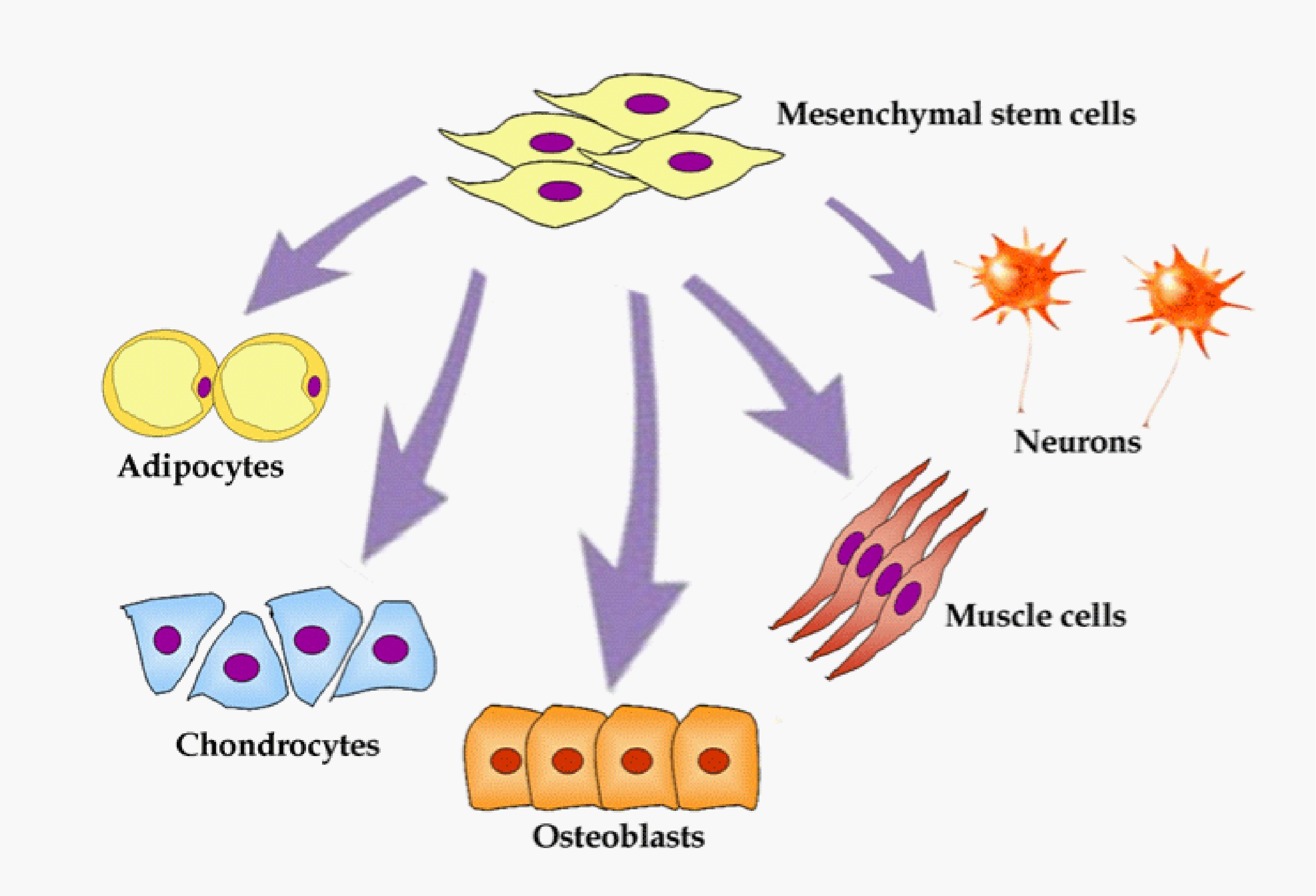
Osteosarcopenia: Muscle and bone interactions



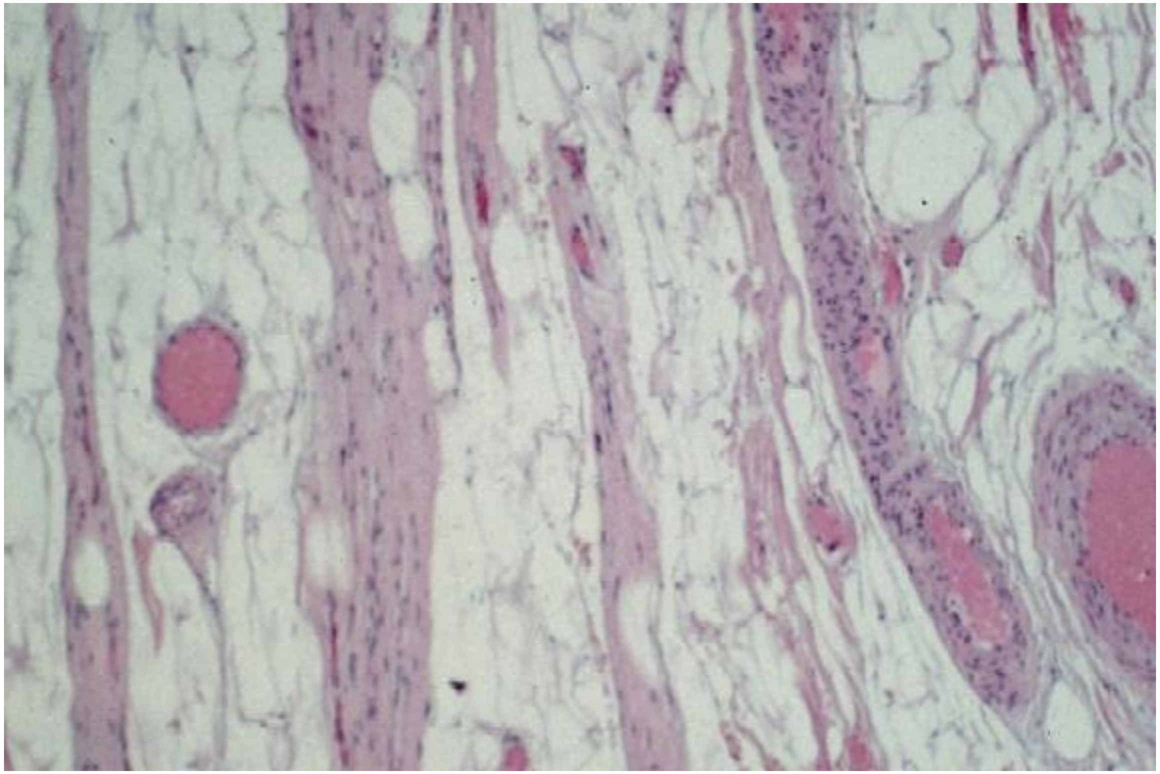
- **A** Common mechanisms
- **B** Defective muscle leads to defective bone
- **C** Defective bone leads to defective muscle

A

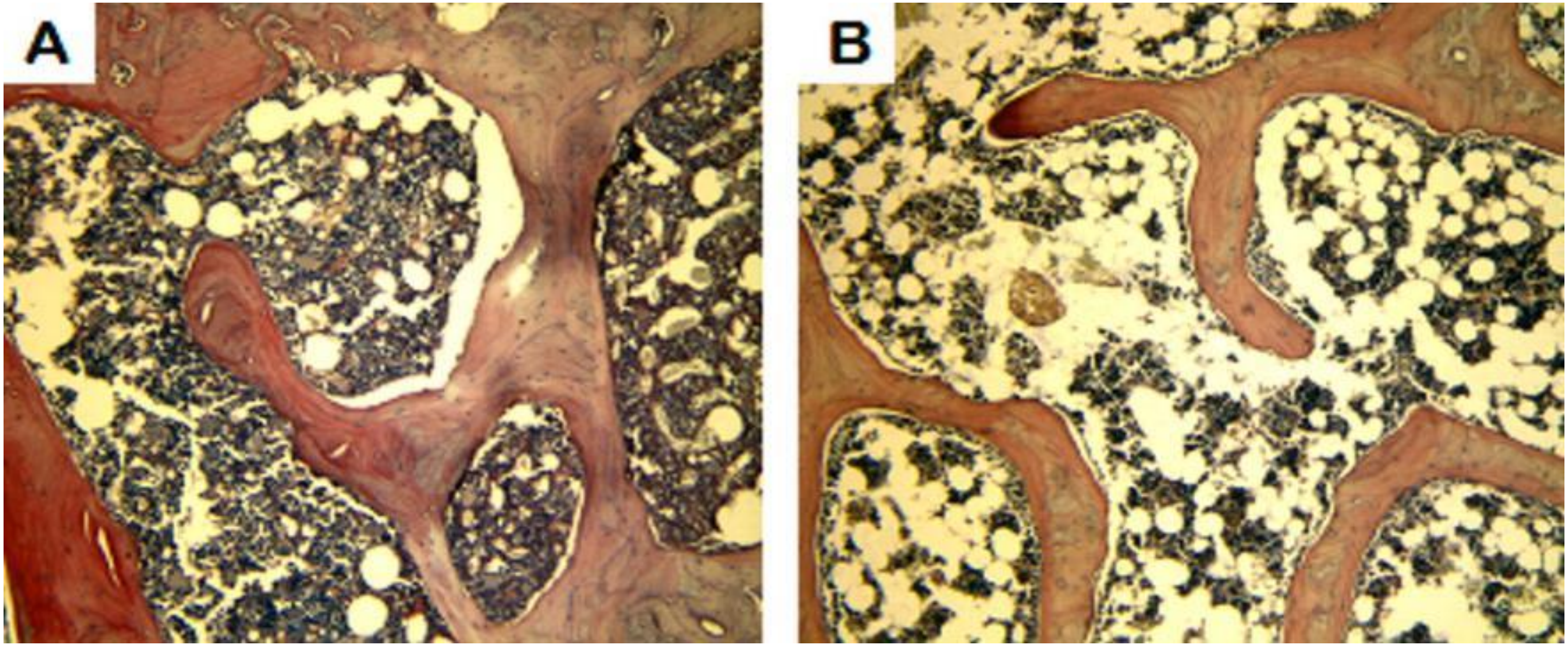
Common mechanisms


Mesenchymal stem cells
Adipocytes
Neurons
Chondrocytes
Muscle cells
Osteoblasts

Fat infiltration of muscle and bone

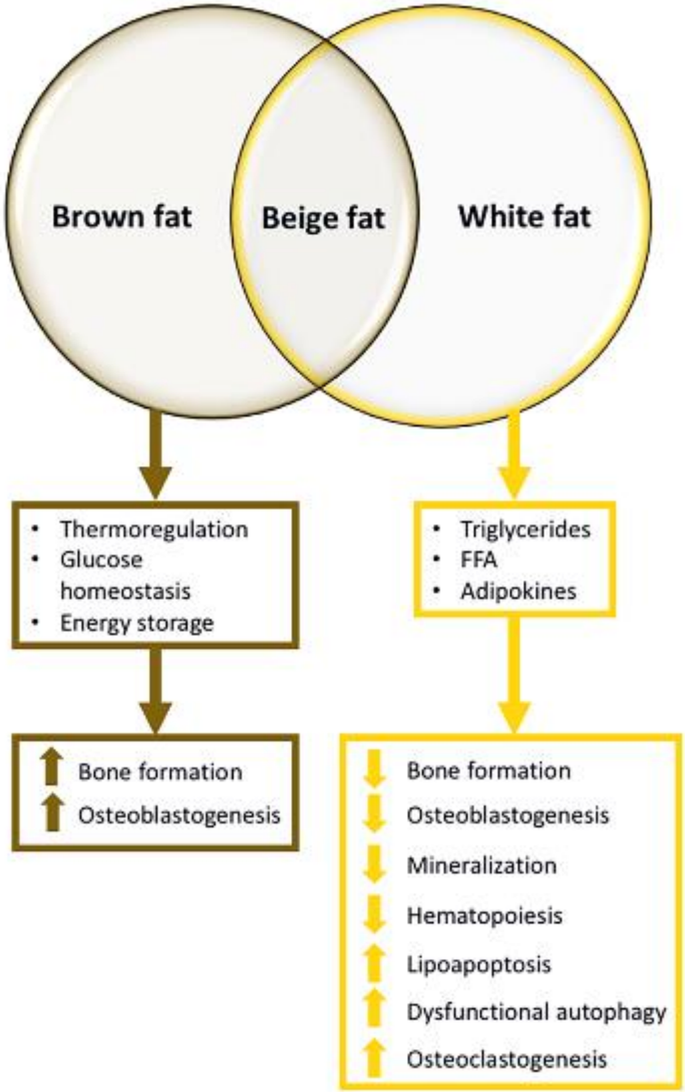


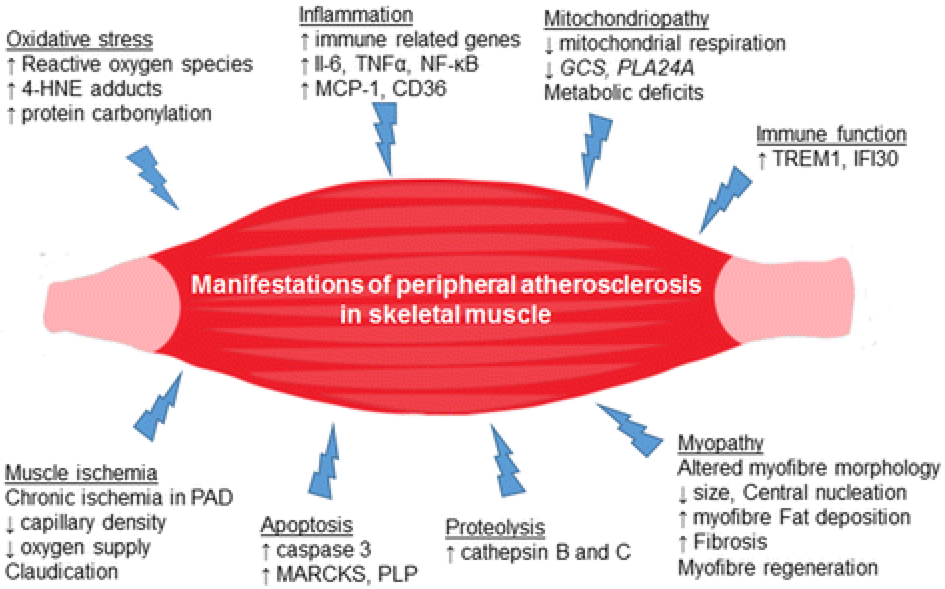
Stewart et al, Exp Cell Res, 2007



Duque G, BoneKey-Osteovision. 2008

Osteosarcopenia as a lipotoxic disease





Sfyri et al, J Biomed Sci. 2017

Duque et al, Curr Osteoporos Rep. 2018

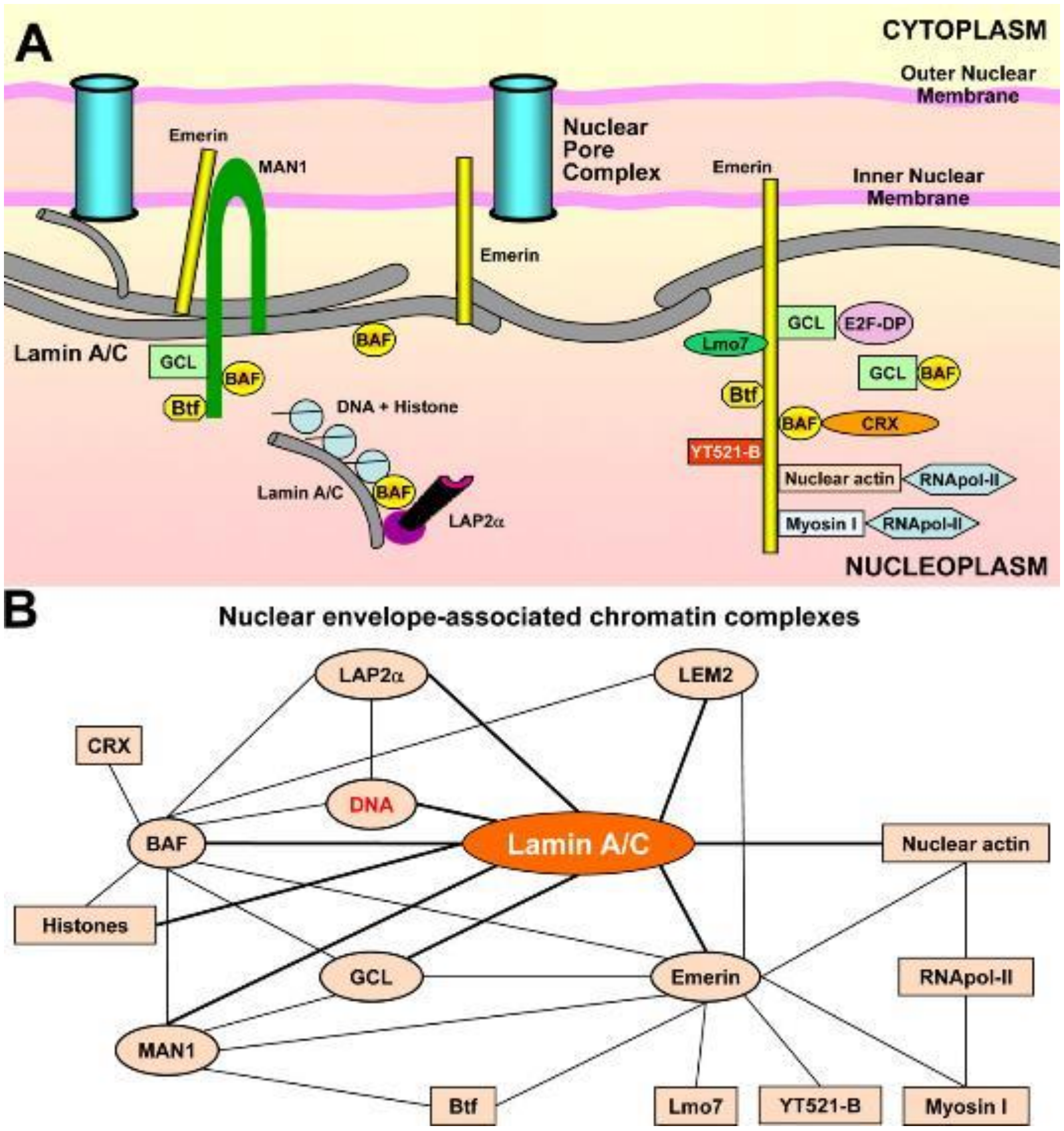
ANNALES
DE GÉNÉTIQUE

Severe bone changes in a case of Hutchinson–Gilford syndrome

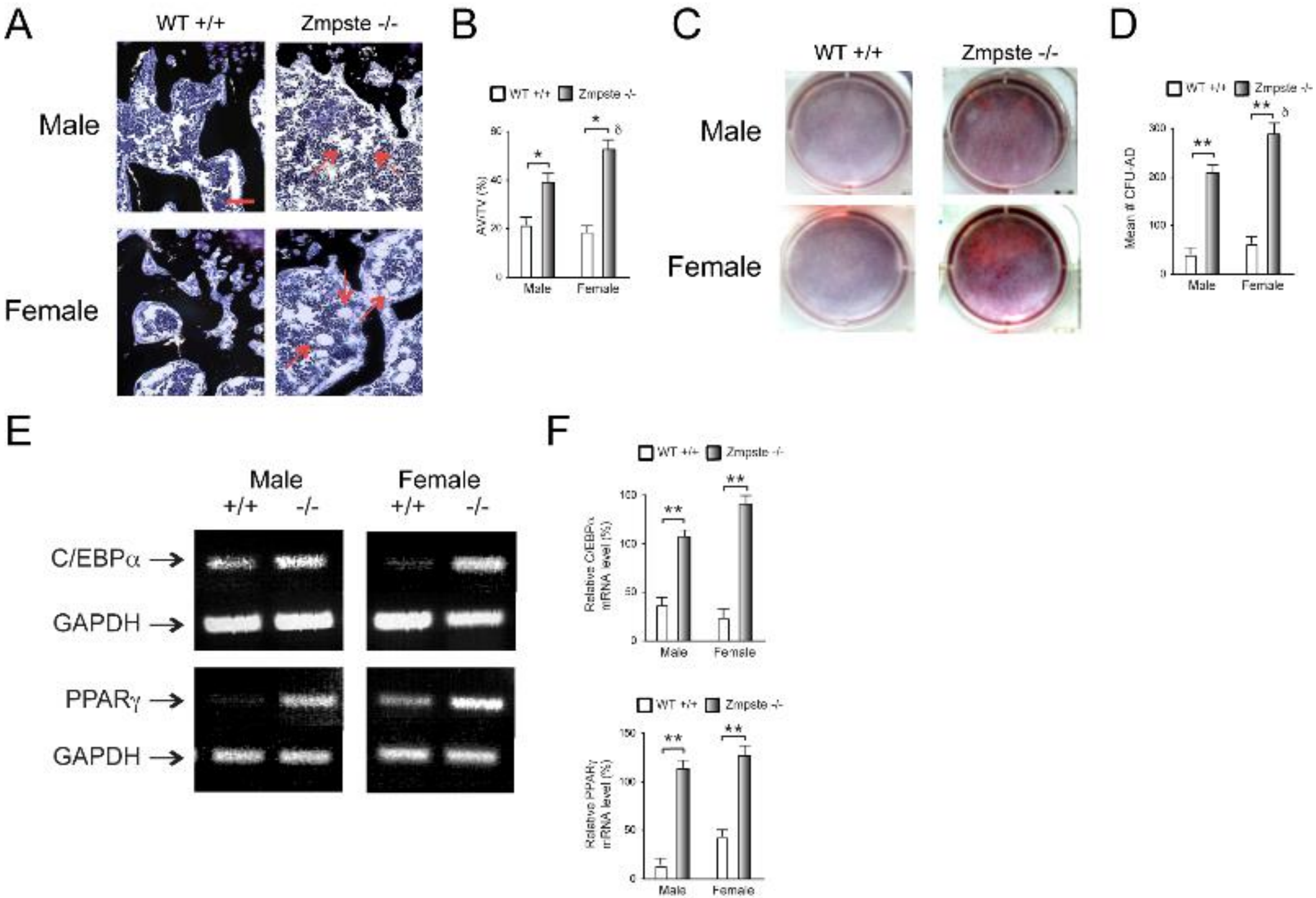
Giselle Helena de Paula Rodrigues [a], Izilda das Eiras Tâmega [a], Gustavo Duque [b,*], Vicente Spinola Dias Neto [a]

[a]Division on Aging, Sorocaba Medical School, Pontifícia Universidade Católica de São Paulo, Brazil
[b]Division of Geriatric Medicine and Calcium Research Laboratory, Royal Victoria Hospital, 687, Pine Avenue West, Room H4-80, McGill University, Montreal, Canada H3A 1A1

Annales de Génétique 45 (2002) 151–155

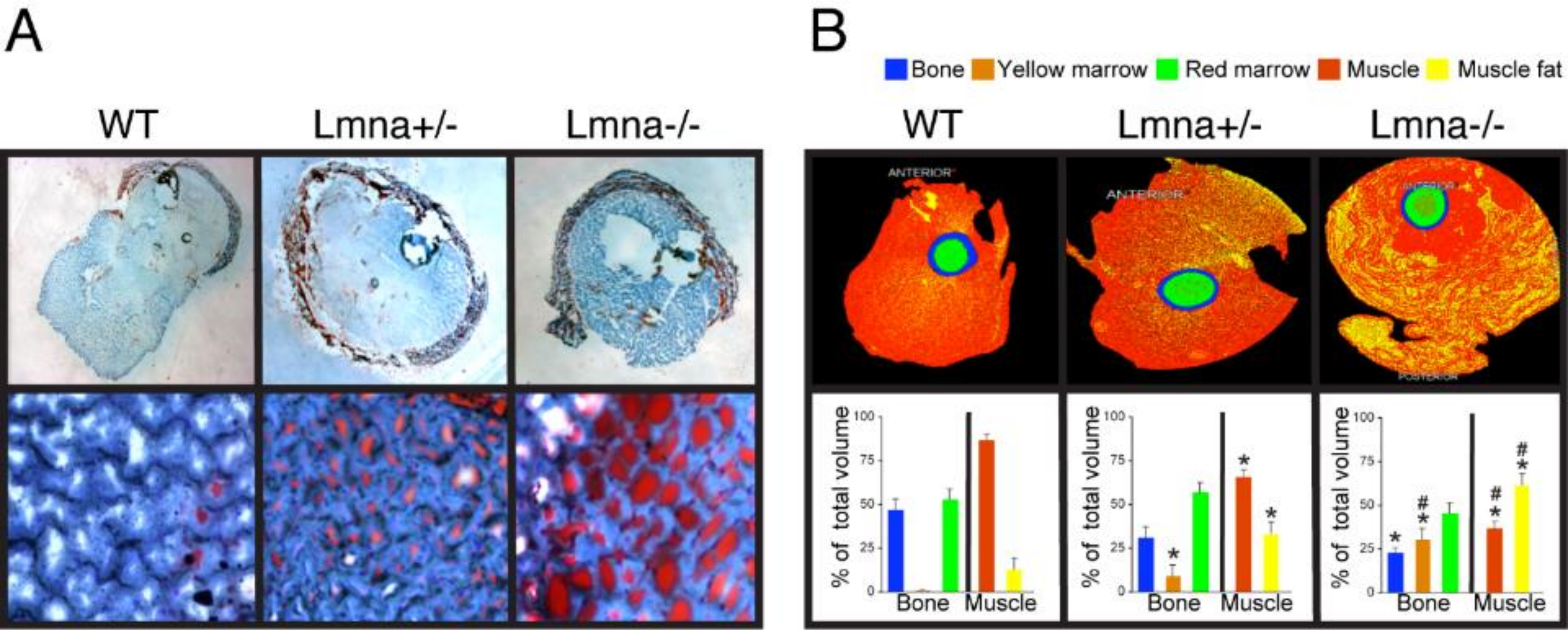


Andrés V , González J M J Cell Biol 2009;187:945-957



Rivas et al, J Gerontol Biol Sci. 2009

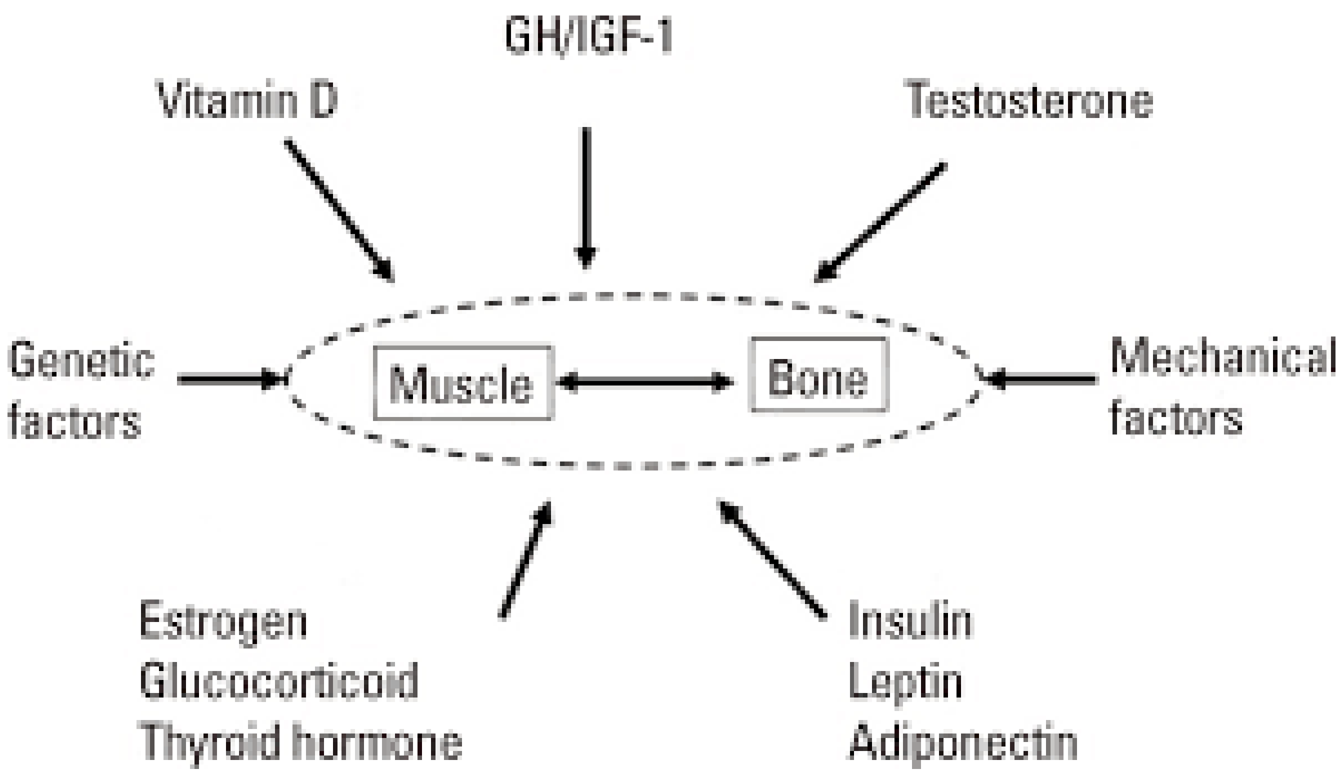
Lamin A/C KO mice as a model of osteosarcopenia



Tong et al., Mech Ageing Dev. 2011

Hormones and common mechanisms of osteosarcopenia

Hormones and osteosarcopenia



Kaji. JBM. 2014

Vitamin D and osteosarcopenia

Low vitamin D → **Falls**

Low vitamin D → **Fractures**

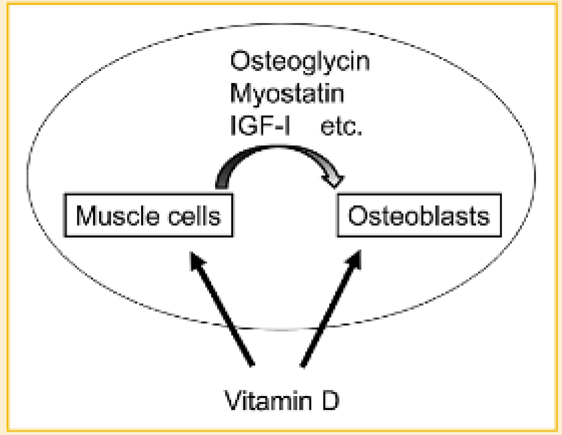
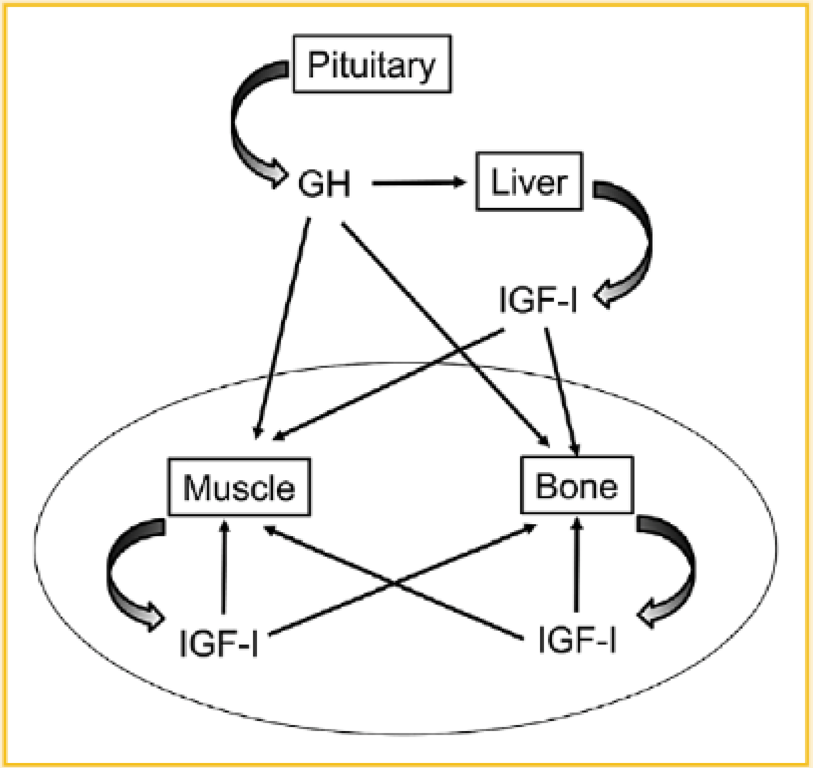


Fig. 2. Vitamin D affects the linkage of muscle to bone.

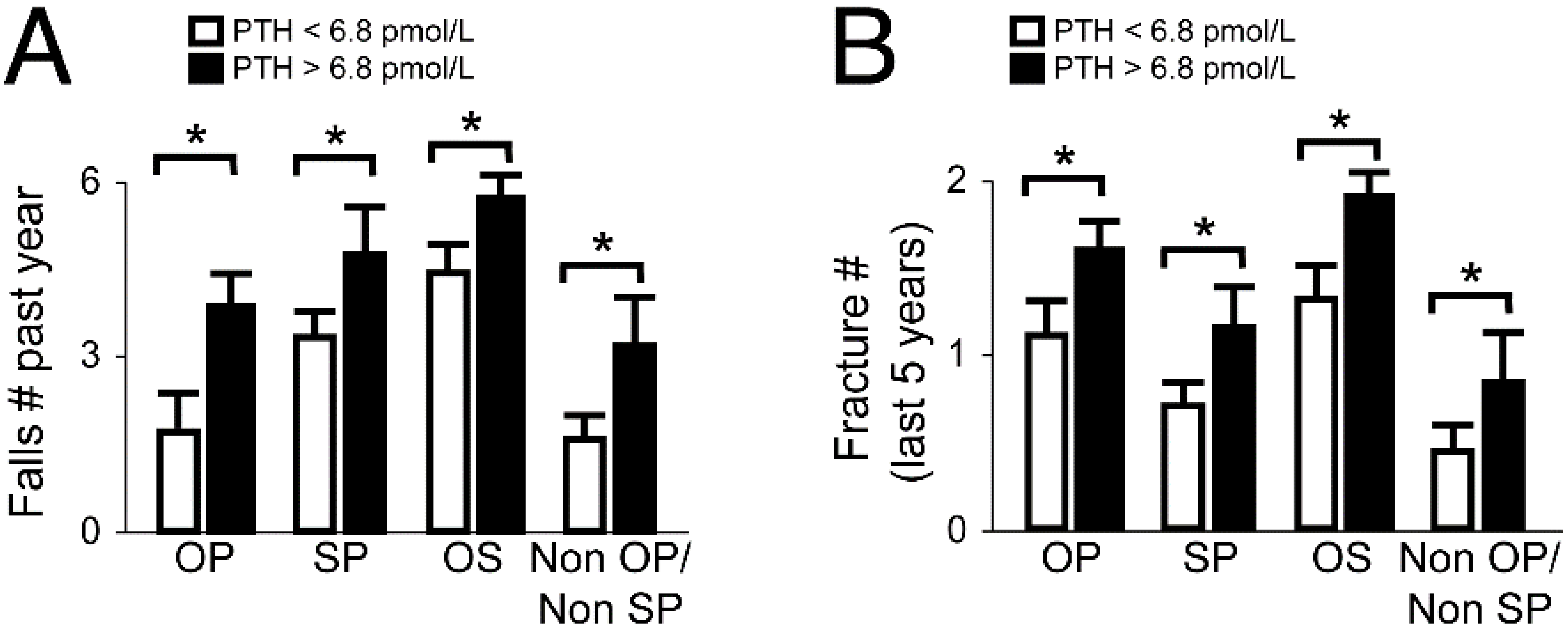
Kawao et al. J Cell Biochem. 2015

IGF-I and osteosarcopenia



Kawao et al. J Cell Biochem. 2015

PTH and osteosarcopenia

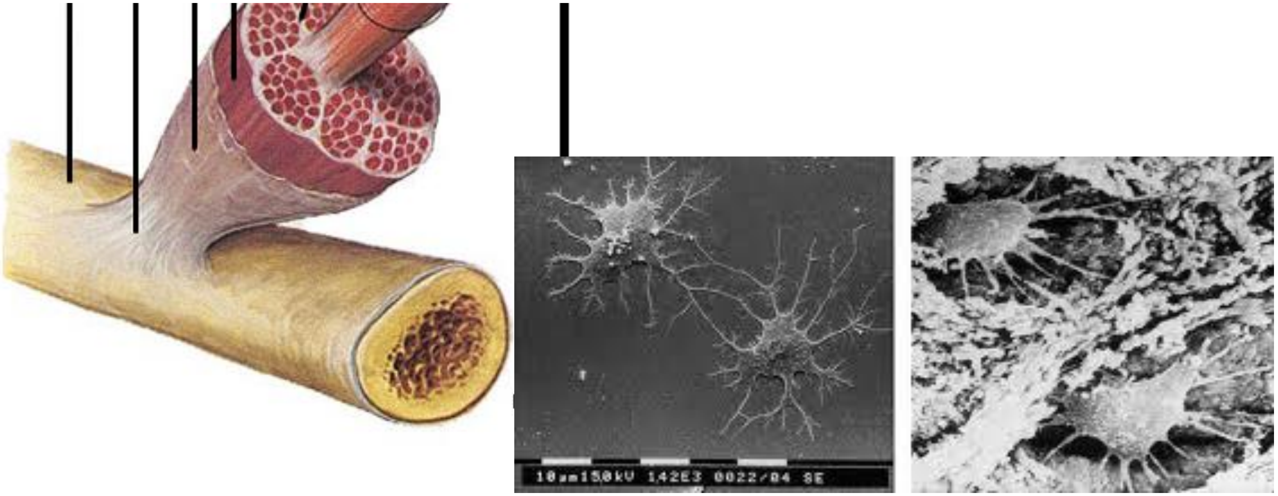


Suriyaarachchi et al. Maturitas. 2018

B

Defective muscle leads to defective bone

Mechanical factors



Myokines

IGF-I, Myostatin, Osteoglycin, FAM5C, Irisin, Osteonectin, FGF2, IL-6, IL-7, IL-15, MMP-2

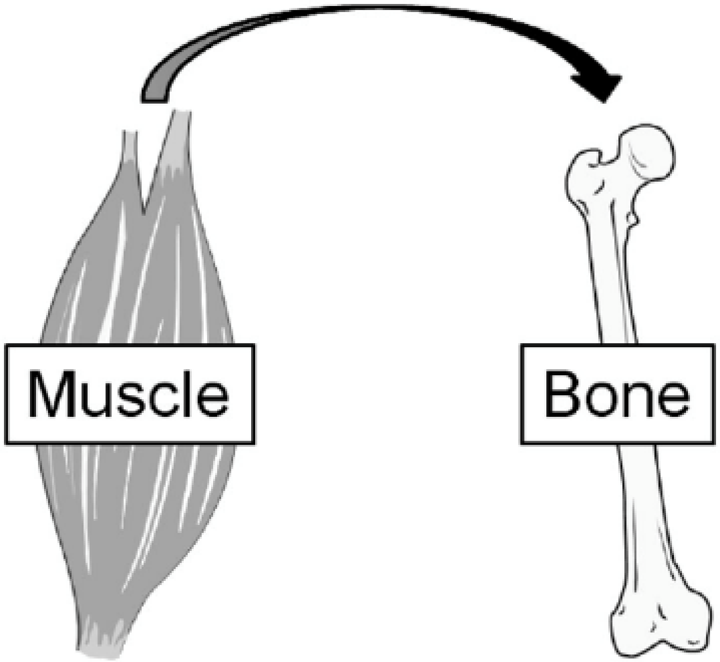


Table 1

Osteogenic factors known to be secreted from myotubes.

Factor	Abbreviation	Reference
Insulin-like growth factor 1	IGF-1	1, 13, 16, 32
Insulin-like growth factor binding protein 5	IGFBP5	1
Basic fibroblast growth factor	FGF-2	4, 13
Osteonectin	SPARC	1, 4, 18
Transforming growth-factor beta 1	TGFβ1	1
Matrix metalloproteinase 2	MMP-2	1, 3
Leukemia inhibitory factor	LIF	28

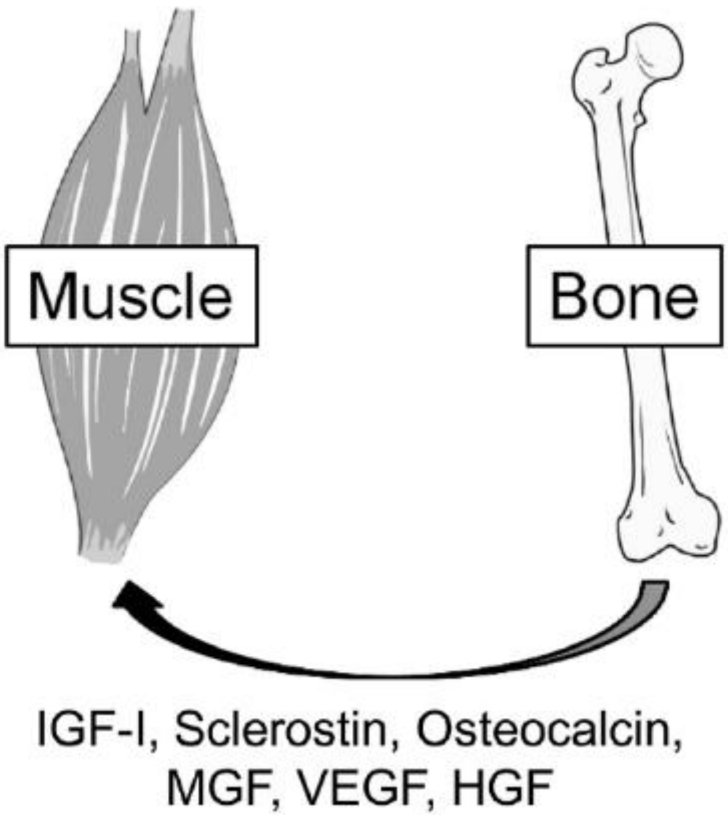
Hamrick MW. Exerc Sport Sci Rev . 2011

Kawao et al. J Cell Biochem. 2015

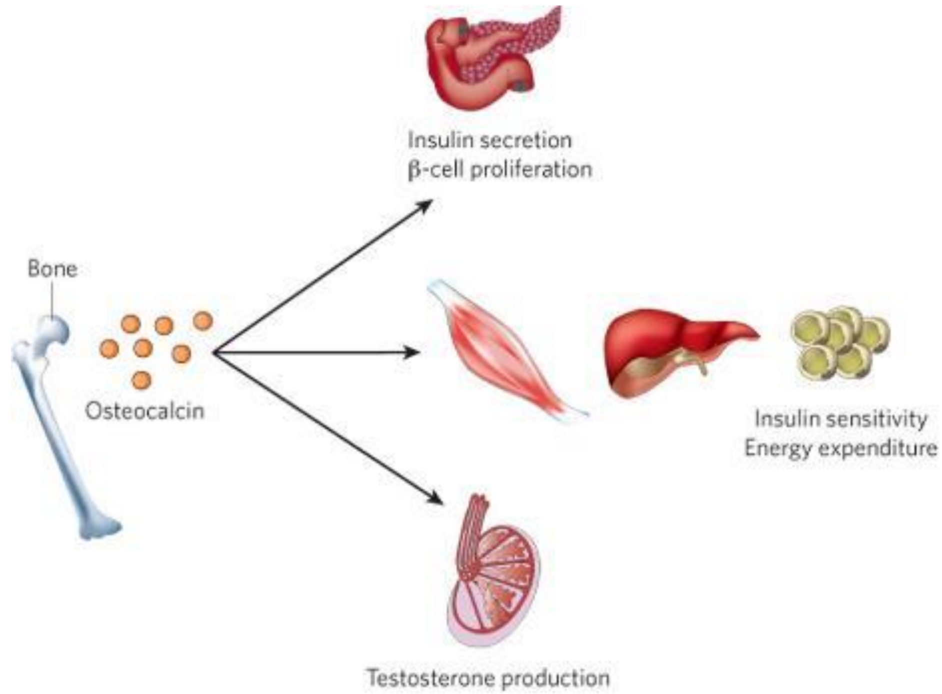
C

Defective bone leads to defective muscle

Osteokines

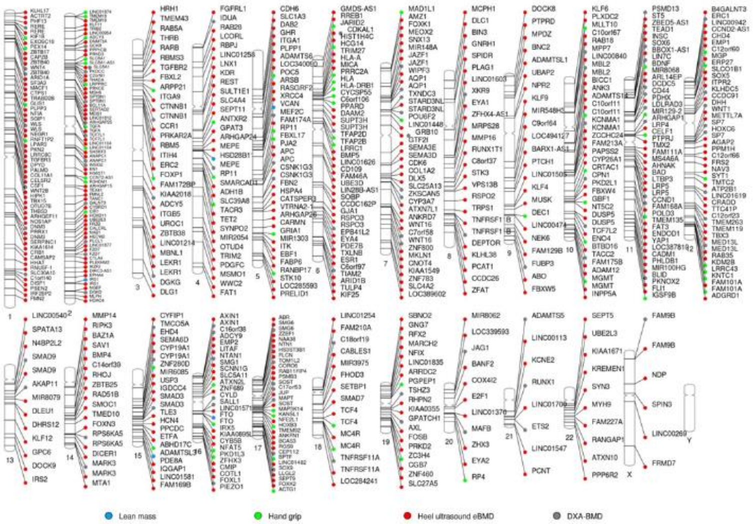


Kawao et al. J Cell Biochem. 2015



Karsenty et al. Nature. 2012

Osteosarcopenia: Genetics



eBMD gene	Muscle-related trait	Reference
AHNAK	Gene expression in human skeletal muscle	Su, Ekman et al. 2015
AQP1	Gene expression in human skeletal muscle	Su, Ekman et al. 2015
ARHGAP26	Positive/mouse skeletal muscle mass KO	Verbrugge, Schönfelder et al. 2018
BCKDHB	Gene expression in human skeletal muscle	Su, Ekman et al. 2015
DAAM2	Gene expression in human skeletal muscle	Su, Ekman et al. 2015
DLEU1	Gene expression in human skeletal muscle	Su, Ekman et al. 2015
GRB10	Negative/mouse skeletal muscle mass KO	Verbrugge, Schönfelder et al. 2018
HMGA2	Positive/mouse skeletal muscle mass KO	Verbrugge, Schönfelder et al. 2018
IGFBP2	Negative/mouse skeletal muscle mass overexpress	Verbrugge, Schönfelder et al. 2018
MMP9	Positive/mouse skeletal muscle mass overexpress	Verbrugge, Schönfelder et al. 2018
MPP7	Gene expression in human skeletal muscle	Su, Ekman et al. 2015
PPARD	Positive/mouse skeletal muscle mass overexpress	Verbrugge, Schönfelder et al. 2018
SMAD3	Positive/ mouse skeletal muscle mass KO	Verbrugge, Schönfelder et al. 2018
SMAD7	Positive/mouse skeletal muscle mass KO	Verbrugge, Schönfelder et al. 2018
SOX6	Positive/mouse skeletal muscle mass KO	Verbrugge, Schönfelder et al. 2018

eBMD estimated bone mineral density, *KO* knock out

Trajanoska et al. Curr Osteoporos Rep. 2019

Osteosarcopenia: Genetics

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-017-00108-3 OPEN

Bivariate genome-wide association meta-analysis of pediatric musculoskeletal traits reveals pleiotropic effects at the *SREBF1/TOM1L2* locus

murine and human osteoblasts, as well as in human muscle tissue. This is the first bivariate GWAS meta-analysis to demonstrate genetic factors with pleiotropic effects on bone mineral density and lean mass.

Medina-Gomez et al. Nat Comm. 2017

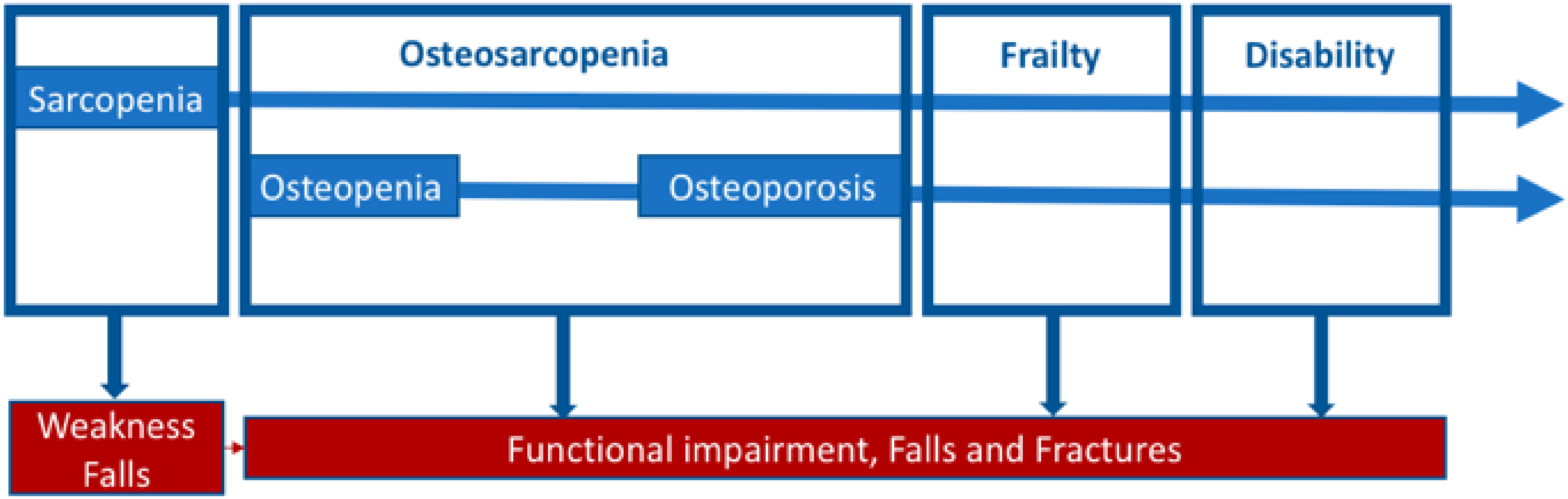
Osteosarcopenia: A phenotype?

Table 1
Demographic and Clinical Characteristics of Participants (Mean ± SD)

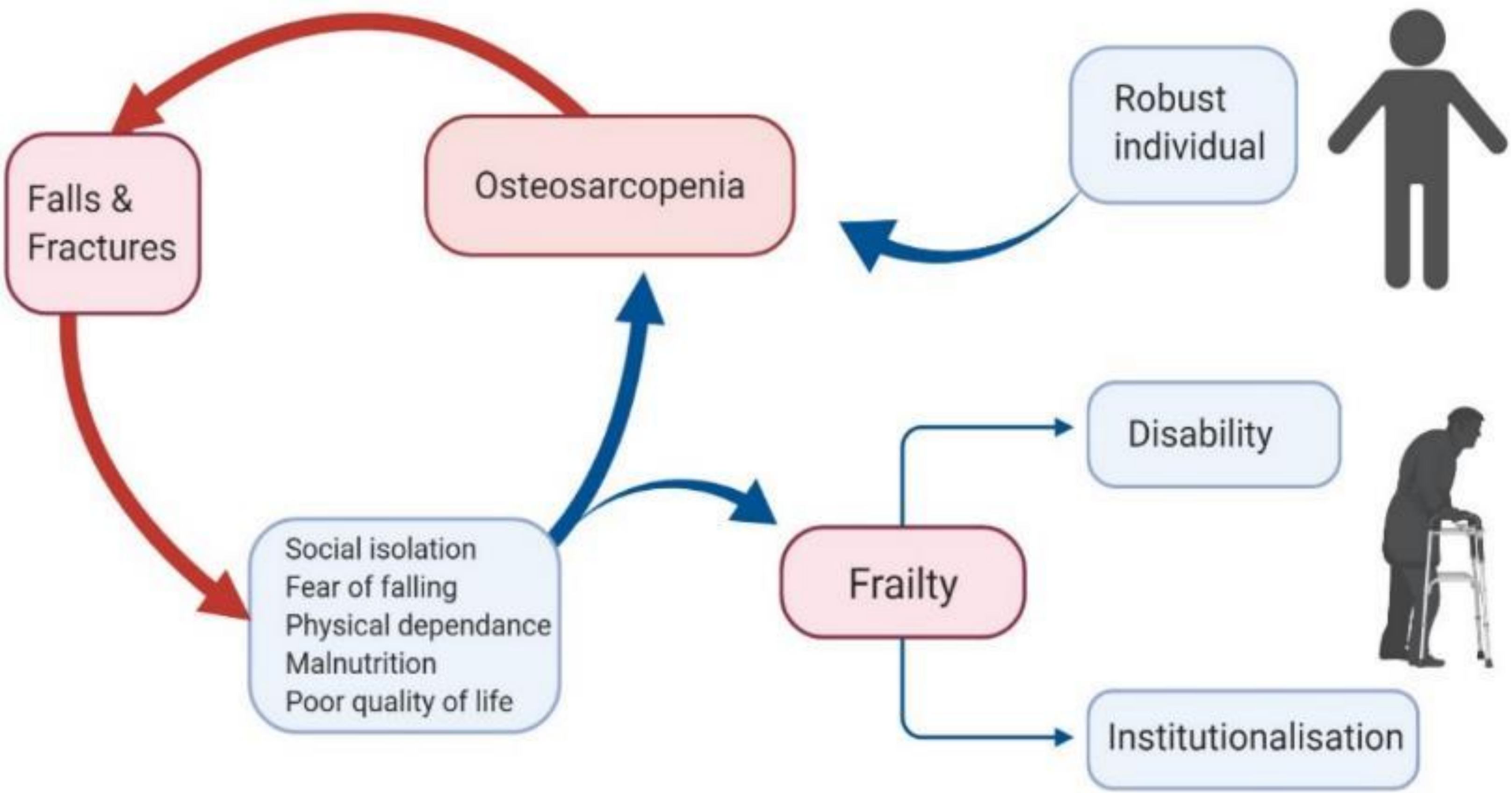
	OS, n = 258	OP, n = 183	SP, n = 87	Nonsarcopenic/Nonosteopenic, n = 151	P*
Age	80.4 ± 7	78 ± 7	79.4 ± 7.2	77.4 ± 7	**.001**
Gender, n (%)					
Male	45 (17)	61 (33)	33 (38)	85 (56)	**<.001**
Female	213 (83)	122 (67)	54 (62)	66 (43)	**<.001**
BMD, T-score, femoral neck	−2.31 ± 0.77	−2.05 ± 0.67	0.088 ± 0.85	0.14 ± 1.02	**<.001**
Grip strength, kg	16.6 ± 5.9	21.8 ± 9.2	18.7 ± 6.2	27.2 ± 10.2	**<.001**
Gait velocity, cm/s	57.1 ± 15.2	87.6 ± 22.5	56.5 ± 16.2	90 ± 23.7	**<.001**
Current smoker, n (%)	16 (6.2)	13 (7.1)	4 (4.5)	5 (2.8)	.11
Current drinker, n (%)	28 (11)	31 (17)	11 (12)	23 (15)	.14
On oral steroids, n (%)	21 (8)	10 (5)	6 (7)	7 (5)	.32
BMI, kg/m^2	27.2 ± 6.2	27.2 ± 6.4	29 ± 6.6	29.5 ± 5	**.001**
Been fractured, n (%)	102 (39)	81 (44)	26 (29)	33 (21)	**<.001**
Menopause age	43 ± 7	45 ± 5	43 ± 5	44 ± 6	.23
Used HRT, n (% of female)	35 (24)	31 (25)	14 (25)	21 (31)	.99
HRT years	10.4 ± 10	7.8 ± 10	8.1 ± 7	11.2 ± 10	.59
Hematological results					
Vitamin D, nmol/L	63 ± 30	73.7 ± 74	64 ± 29	62 ± 29	.17
eGFR, mL/min	66.3 ± 17	66.2 ± 18	63.3 ± 19	66.8 ± 16	.57
PTH, pmol/L	6.6 ± 5.6	6.7 ± 6.2	6.4 ± 4.3	5.7 ± 2.7	.42

Huo et al. JAMDA. 2014

Osteosarcopenia: A continuum?

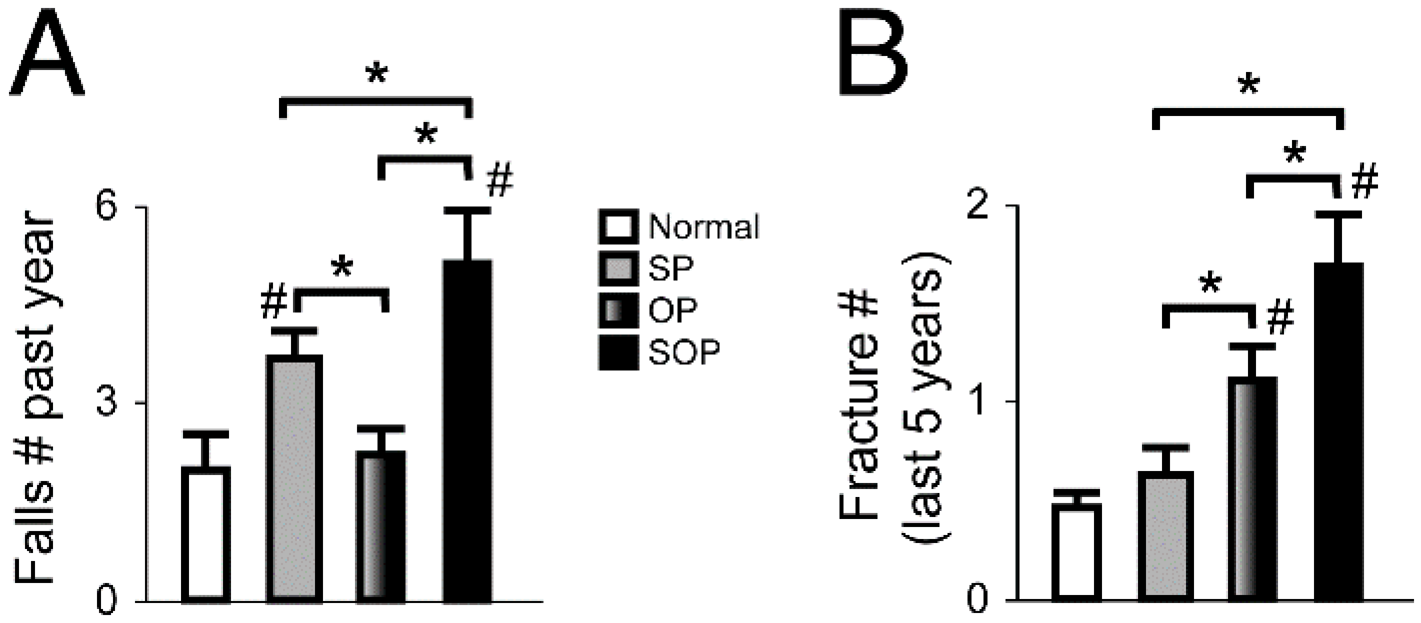


Osteosarcopenia: A dynamic syndrome?

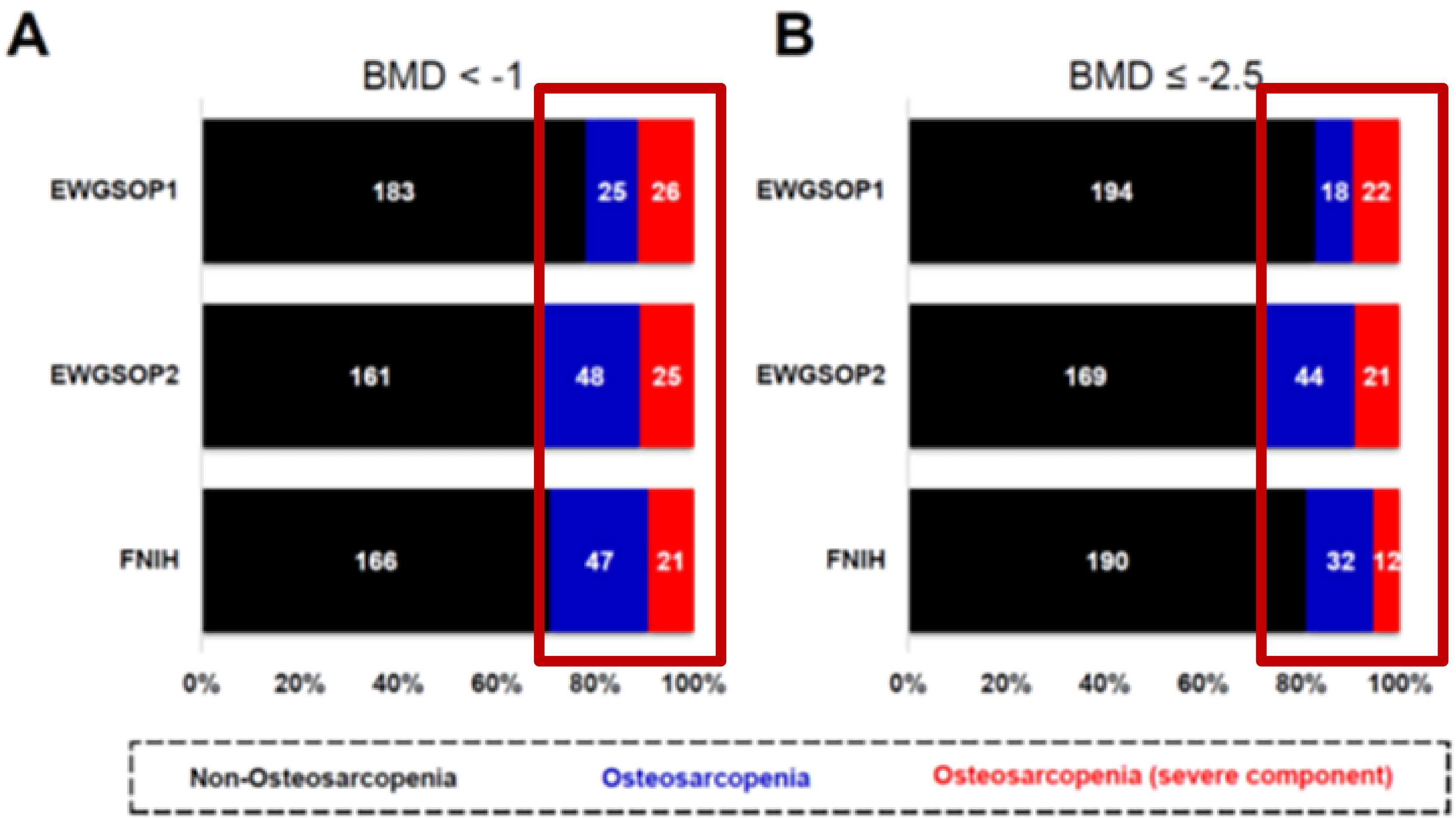


Clinical outcomes

Clinical outcomes in osteosarcopenia



Huo et al. JNHA 2015



Sepulveda-Loyola et al., JAMDA. 2019

THE UNIVERSITY OF MELBOURNE

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JAMDA

journal homepage: www.jamda.com

Original Study

The Joint Occurrence of Osteoporosis and Sarcopenia (Osteosarcopenia): Definitions and Characteristics

Walter Sepúlveda-Loyola MSc[a,b,c], Steven Phu MSc[a,b], Ebrahim Bani Hassan PhD[a,b], Sharon L. Brennan-Olsen PhD[a,b], Jesse Zanker MPHTM[a,b], Sara Vogrin PhD[a,b], Romy Conzade MSc[a,b,d], Ben Kirk PhD[a,b], Ahmed Al Saedi PhD[a,b], Vanessa Probst PhD[c], Gustavo Duque MD, PhD[a,b,*]

[a] Australian Institute for Musculoskeletal Science (AIMSS), University of Melbourne and Western Health, St Albans, Victoria, Australia
[b] Department of Medicine—Western Health, Melbourne Medical School, University of Melbourne, St Albans, Victoria, Australia
[c] Masters and PhD Programme in Rehabilitation Sciences, Londrina State University (UEL) and University North of Paraná (UNOPAR), Londrina, Brazil
[d] Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Institute of Epidemiology, Neuherberg, Germany

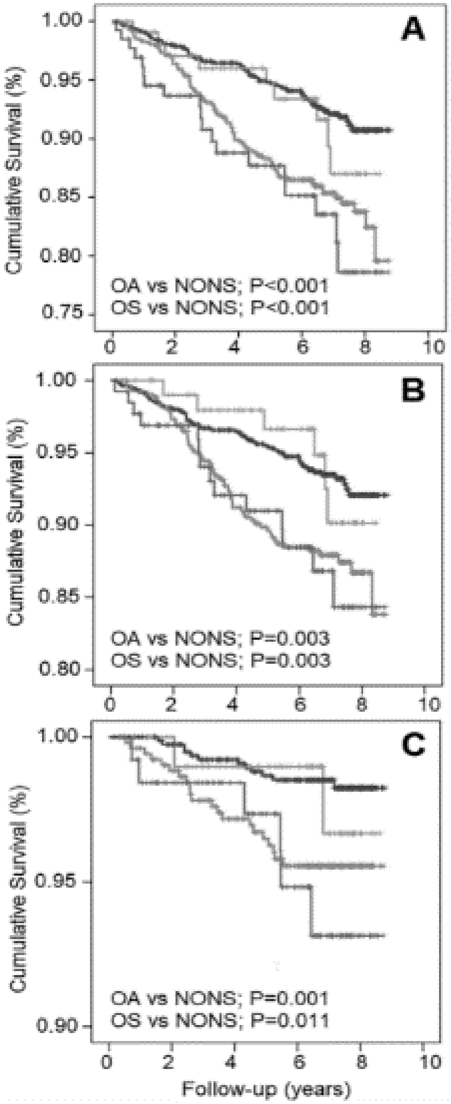
PROOF

Conclusions and Implications: Compared with the nonosteosarcopenic group, those with osteosarcopenia had greater impairment of physical performance and balance. The EWGSOP2 and FNIH criteria resulted in the strongest associations with physical performance and self-reported falls and fractures.

Sepulveda-Loyola et al., JAMDA. 2019

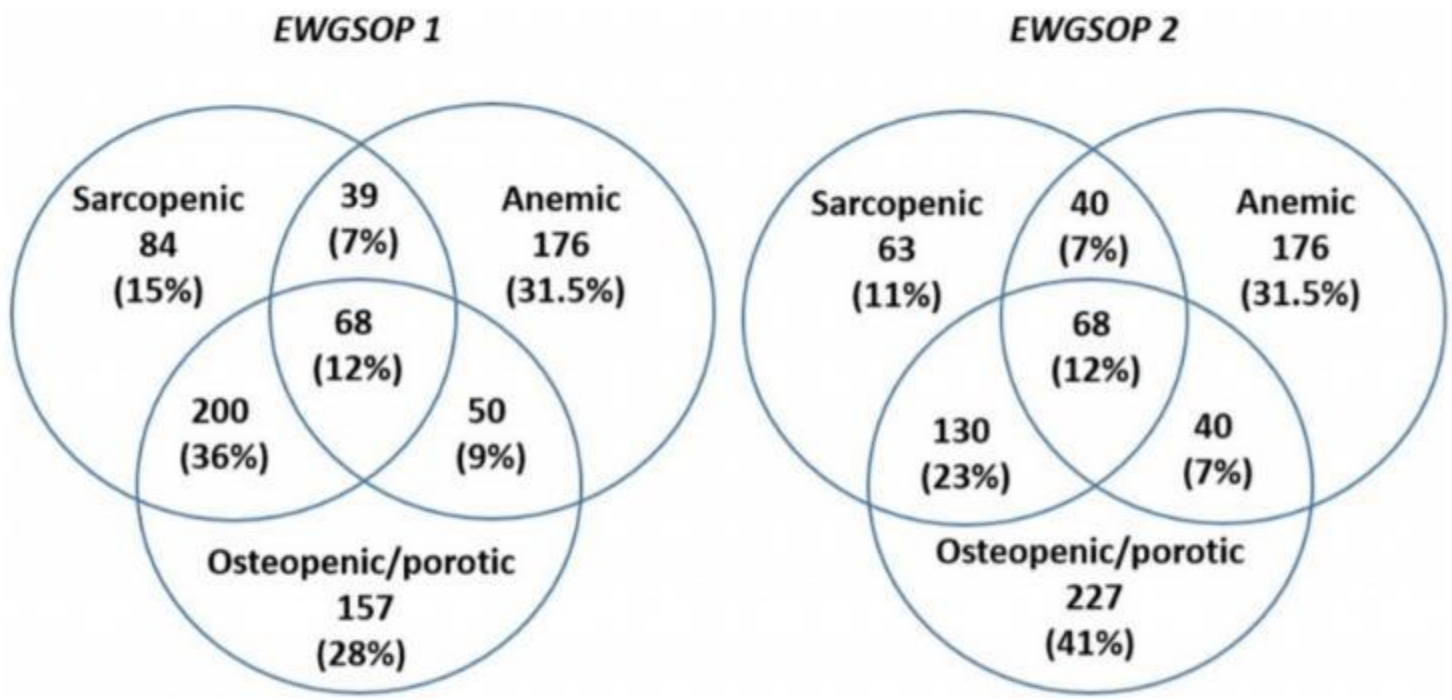
aimss Australian Institute for Musculoskeletal Science

Osteosarcopenia in men



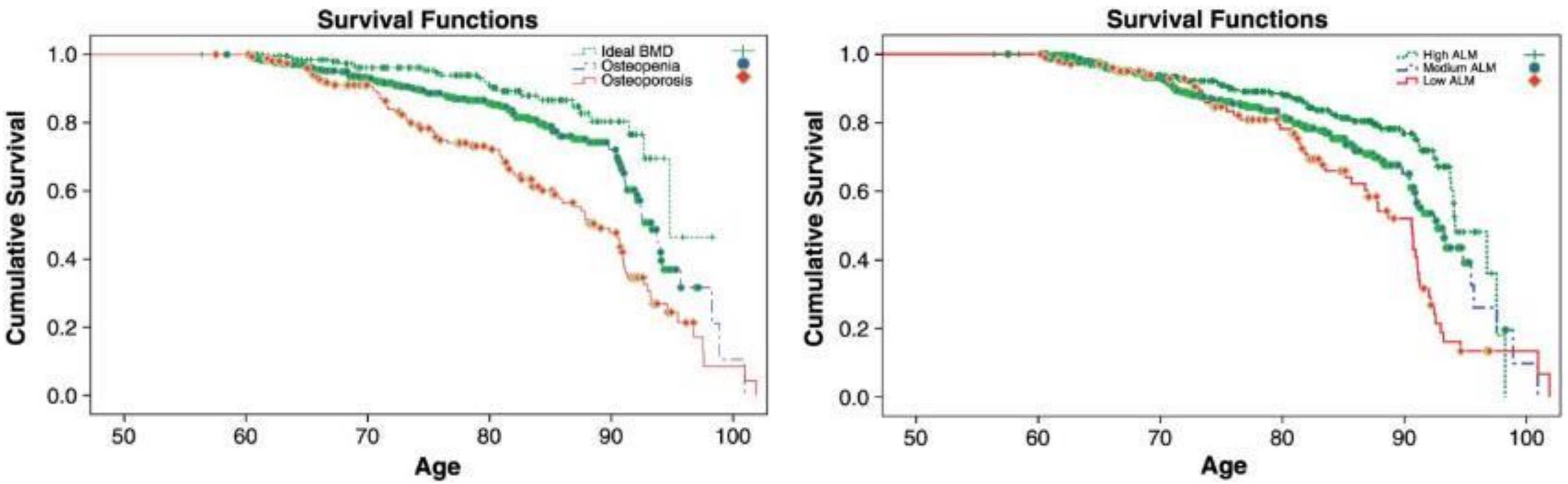
Scott et al. J Gerontol: Med Sci. 2018

Osteosarcopenia and anemia



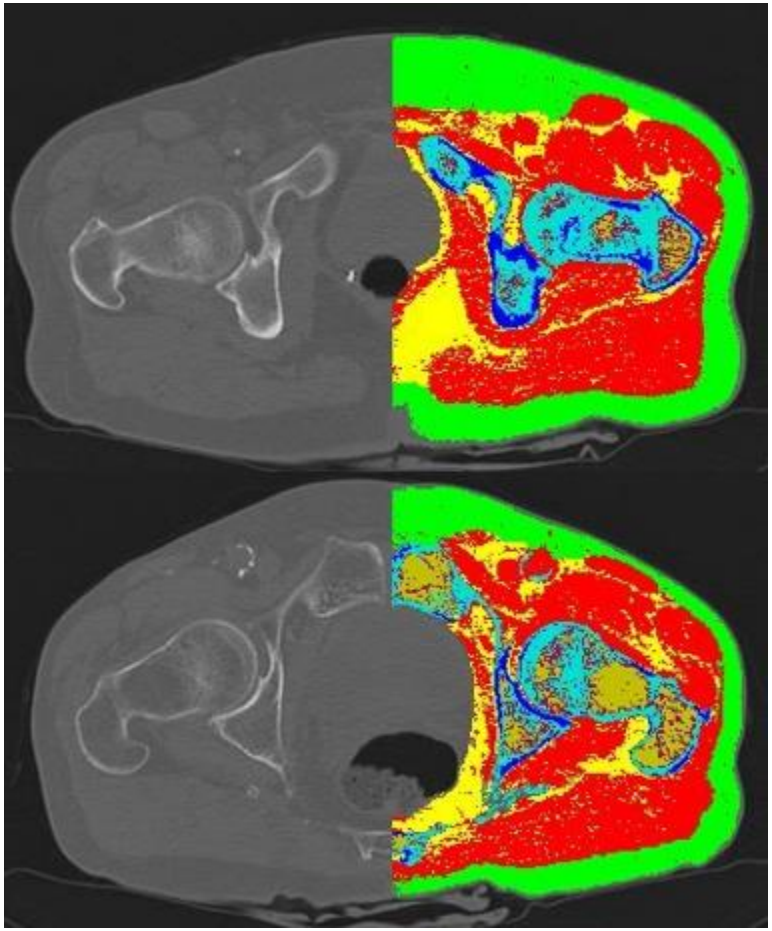
Bani Hassan et al. Calc. Tissue Int. 2020

Osteosarcopenia and mortality

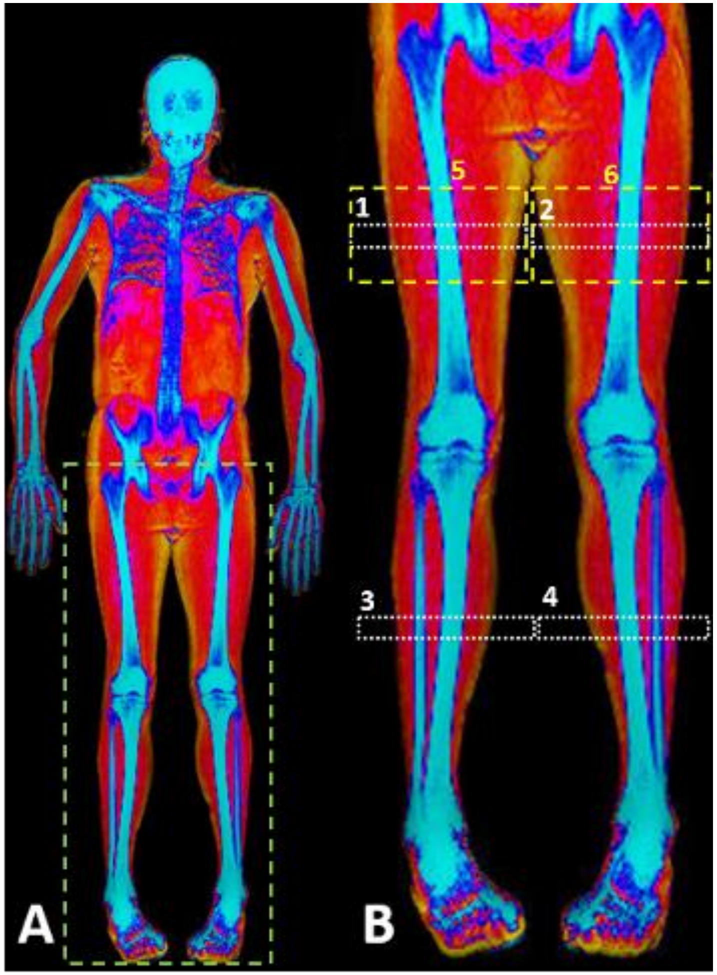


Pasco et al. J Cachexia Sarcopenia Muscle. 2017

How to Diagnose Osteosarcopenia? Imaging



Bani Hassan et al. Curr Osteoporos Rep. 2019



Bani Hassan et al. Calc Tissue Int. 2019

Therapeutic interventions for osteosarcopenia

- **Pharmacological:**
  - Growth hormone
  - Androgens
  - SARMs
  - Vitamin D
  - Activin signaling inhibitors
- **Non-pharmacological:**
  - Exercise
  - Protein supplementation
- **Future directions**
  - FAS Inhibitors
  - Myokines/Osteokines?

Curr Osteoporos Rep. 2014 June ; 12(2): 142–153. doi:10.1007/s11914-014-0204-5.

Therapies for Musculoskeletal Disease: Can we Treat Two Birds with One Stone?

Christian M. Girgis,
Garvan Institute of Medical Research, 384 Victoria St, Darlinghurst, Sydney NSW, Australia; Faculty of Medicine, University of Sydney, Sydney, NSW, Australia

Nancy Mokbel, and
Garvan Institute of Medical Research, 384 Victoria St, Darlinghurst, Sydney NSW, Australia

Douglas J. DiGirolamo
Department of Orthopaedic Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Non-pharmacological interventions

Vitamin D as an anabolic

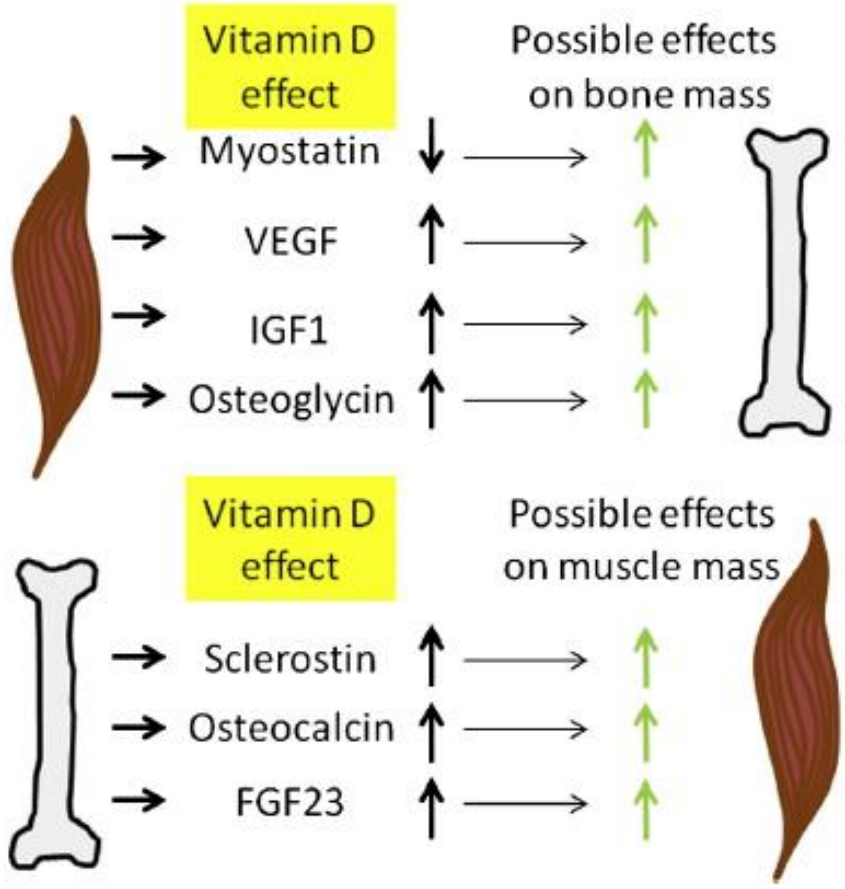
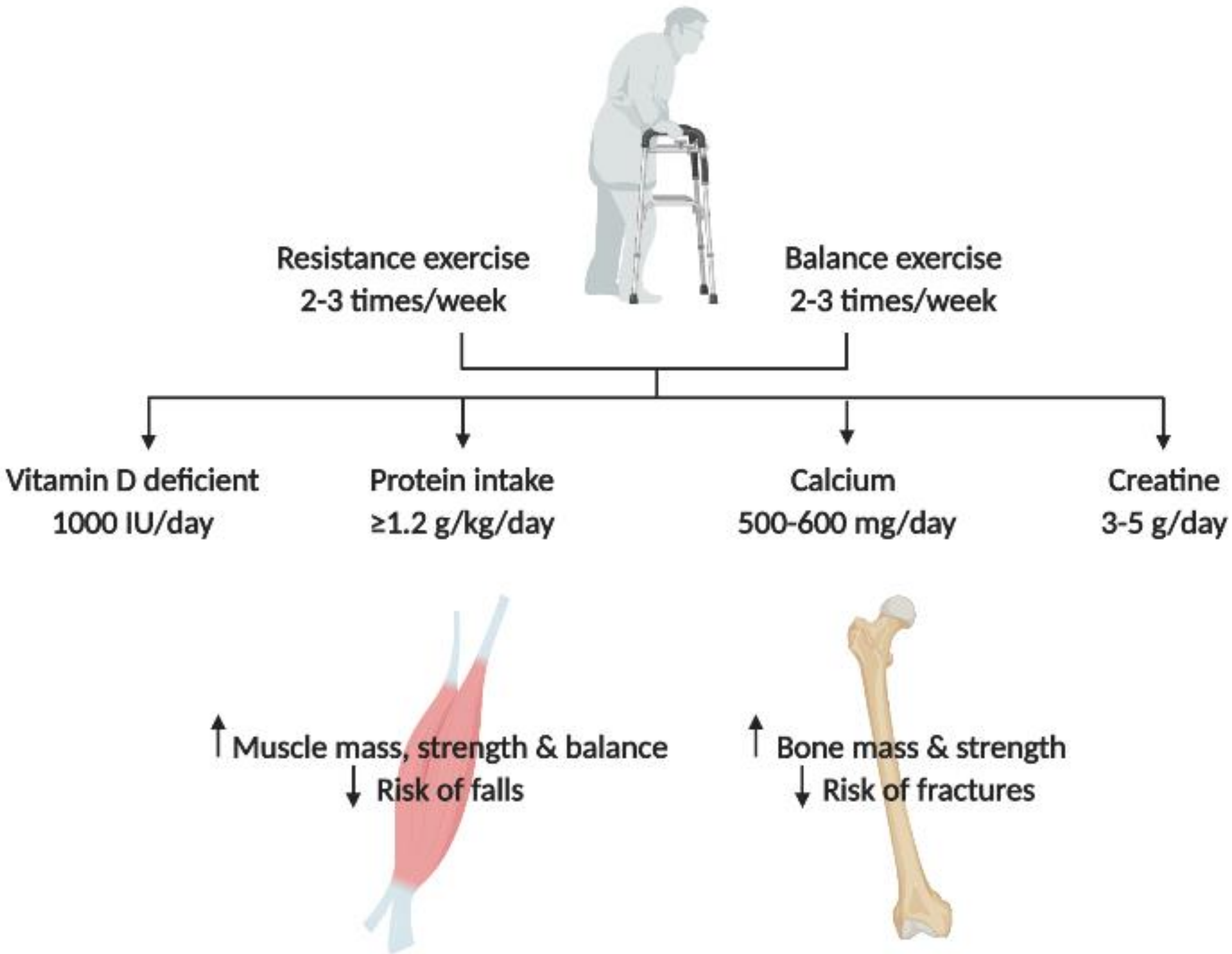


Fig. 1. Potential vitamin D mediated mechanisms of bone–muscle cross-talk.

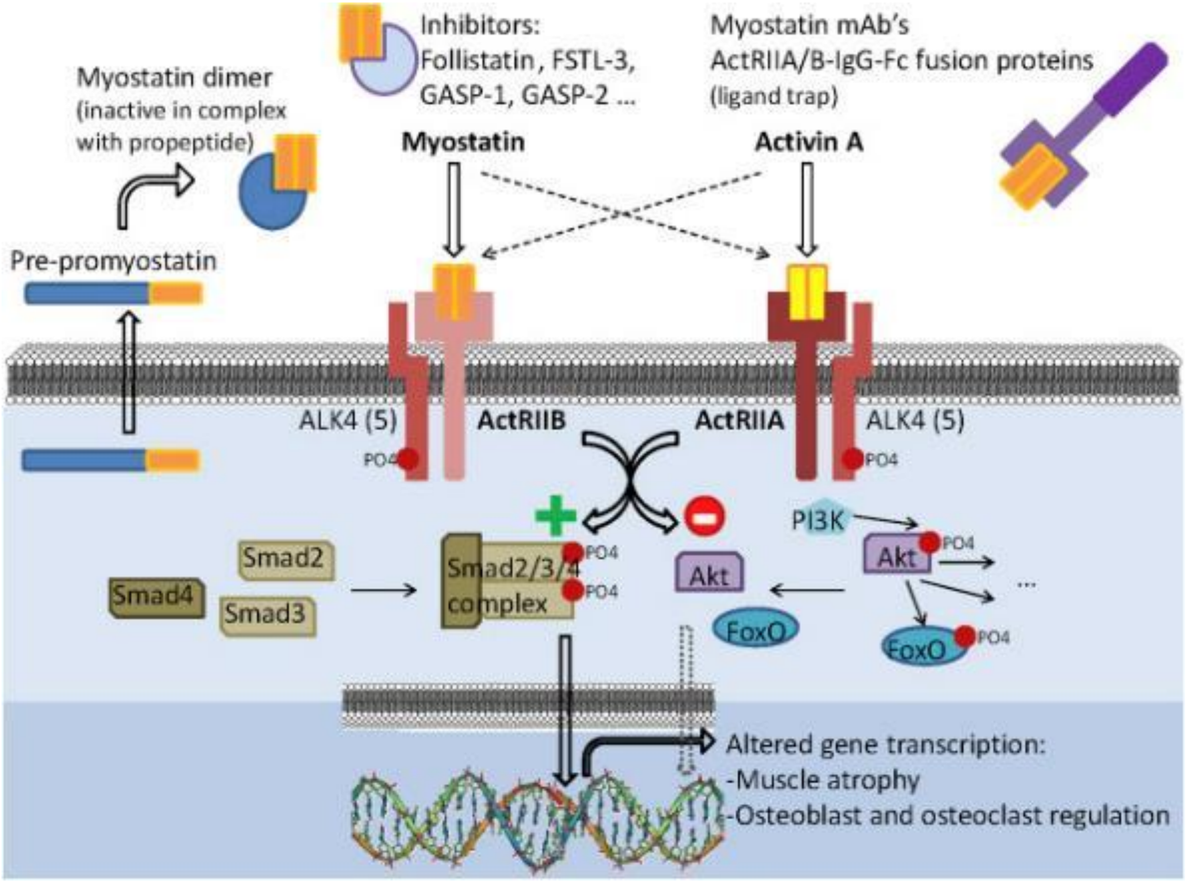
Gunton JE, et al, Bone muscle interactions and vitamin D, Bone (2015), http://dx.doi.org/10.1016/j.bone.2015.02.029



Kirk et al. J Cachexia Sarcopenia Muscle. 2020

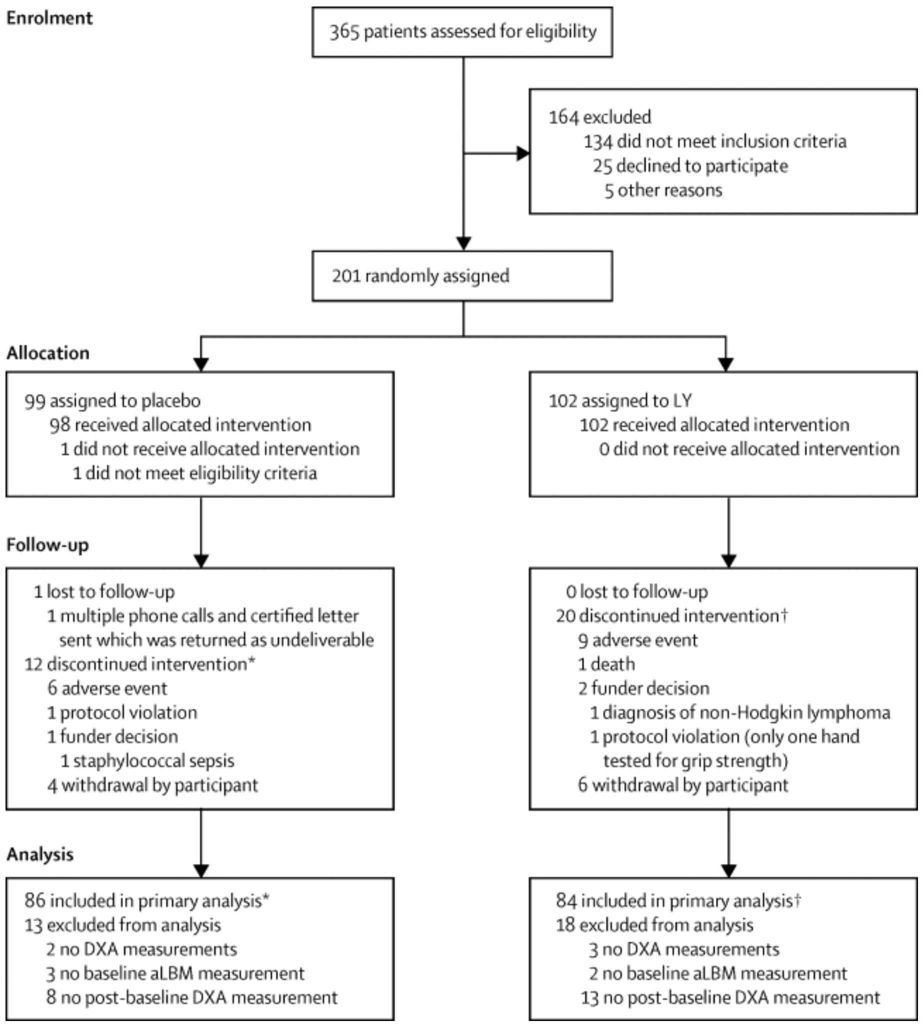
Pharmacological interventions

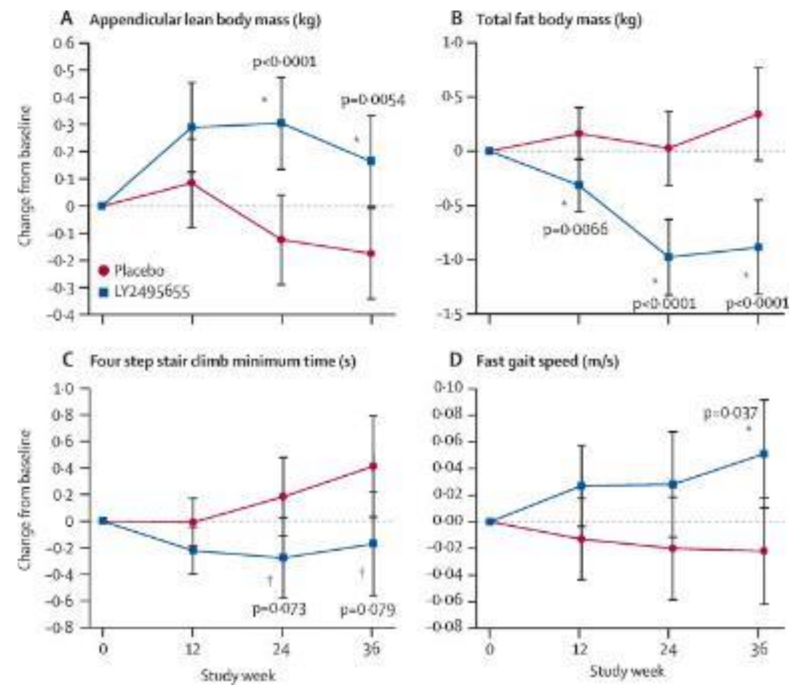
Activin signalling inhibitors



Laurent MR, et al. Mol Cell Endocrinol. 2016 Sep 5;432:14-36

Myostatin Antibody LY2495655





Becker et al. Lancet Diabetes and Endocrinology, 2015

Myostatin inhibition – ACE031

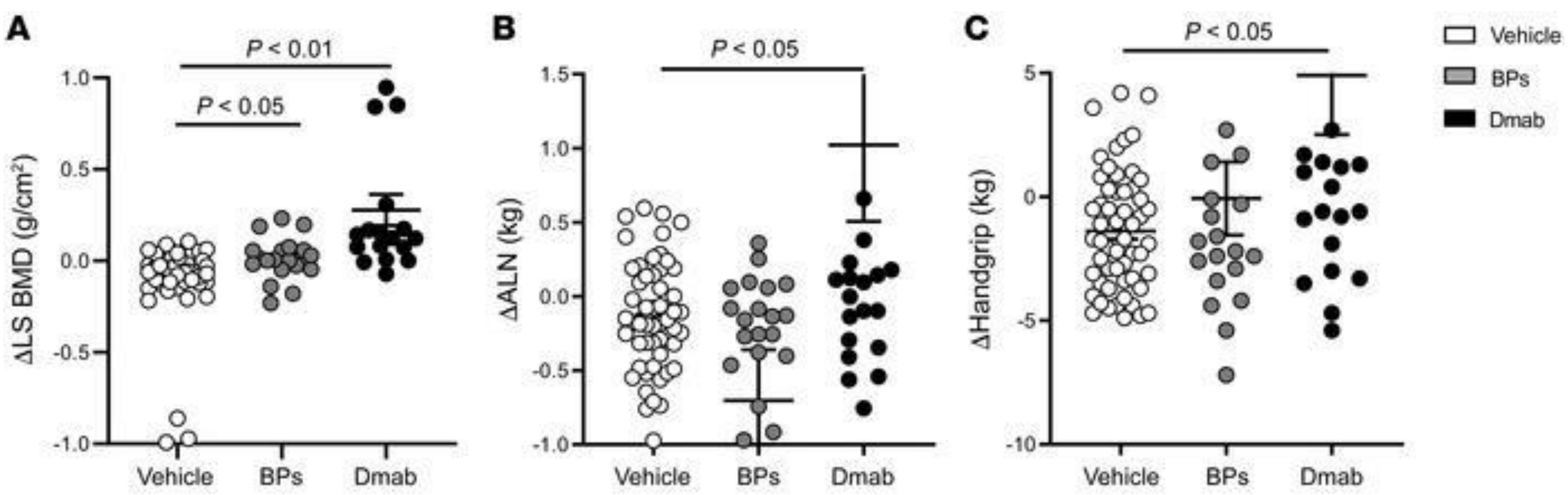
Table 4. Mean (SD) percent change from baseline to days 15, 29, and 57 in serum fat and bone biomarkers for the placebo and 1 mg/kg and 3 mg/kg ACE-031 groups.

Parameter	Study day	Placebo (n=12)	ACE-031 treatment group: 1 mg/kg (n=6)	ACE-031 treatment group: 3 mg/kg (n=6)
Adiponectin	15	−3.9 (22.8)[a]	25.1 (26.1)	39.6 (27.6)[*,†]
	29	13.7 (12.2)[a]	19.4 (22.1)	51.3 (17.6)[*,†]
	57	9.1 (17.1)[a]	6.1 (34.0)	35.1 (26.6)[*]
Leptin	15	−2.9 (44.0)[a]	−5.0 (30.7)	−24.1 (40.1)
	29	44.3 (50.4)[a]	28.8 (44.7)	−27.7 (24.1)[*,†]
	57	9.6 (22.6)	58.6 (48.2)	10.1 (30.4)
BSAP	15	5.6 (4.0)[*]	14.1 (15.8)	22.7 (10.4)[*]
	29	11.0 (10.3)[*]	33.6 (16.5)[*,†]	33.9 (11.6)[*,†]
	57	11.7 (10.6)[*]	16.3 (13.7)[*]	24.1 (14.3)[*,†]
CTX	15	8.9 (24.0)	−19.4 (9.3)[*,†]	−23.9 (35.1)[†]
	29	10.0 (16.8)	−22.7 (13.1)[*,†]	−34.2 (15.6)[*,†]
	57	12.3 (21.9)	−4.5 (14.6)	−33.0 (13.1)[*,†]

[*]P < 0.05 for the mean change from baseline.
[†]P < 0.05 for the comparison of mean change vs. placebo.
[a]n=4.

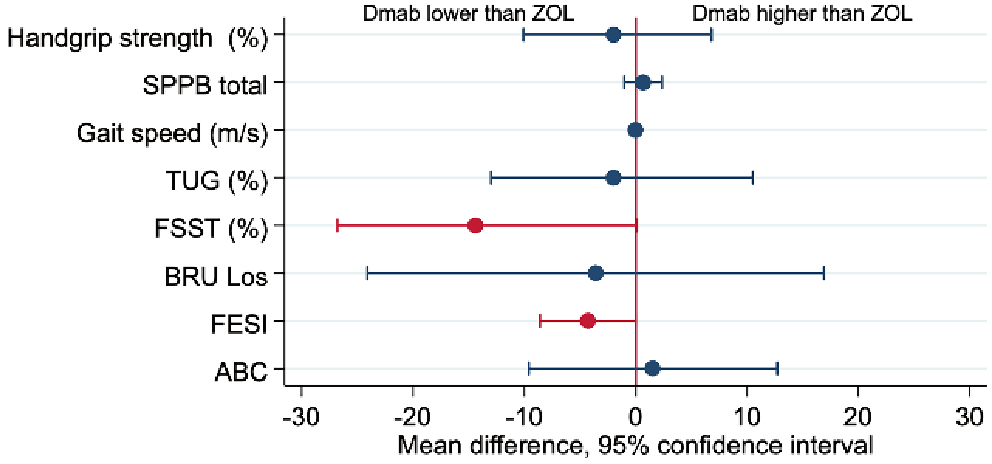
Attie et al. Muscle & Nerve. 2012

Denosumab and muscle



Bonnet et al. JCI. 2019

Dmab (n = 51) or ZOL (n = 28), combined with vitamin D supplementation



"Dmab displayed positive effects on balance, function, and fear of falling, which may underlie reductions in fall rates."

Phu et al., JAGS. 2019

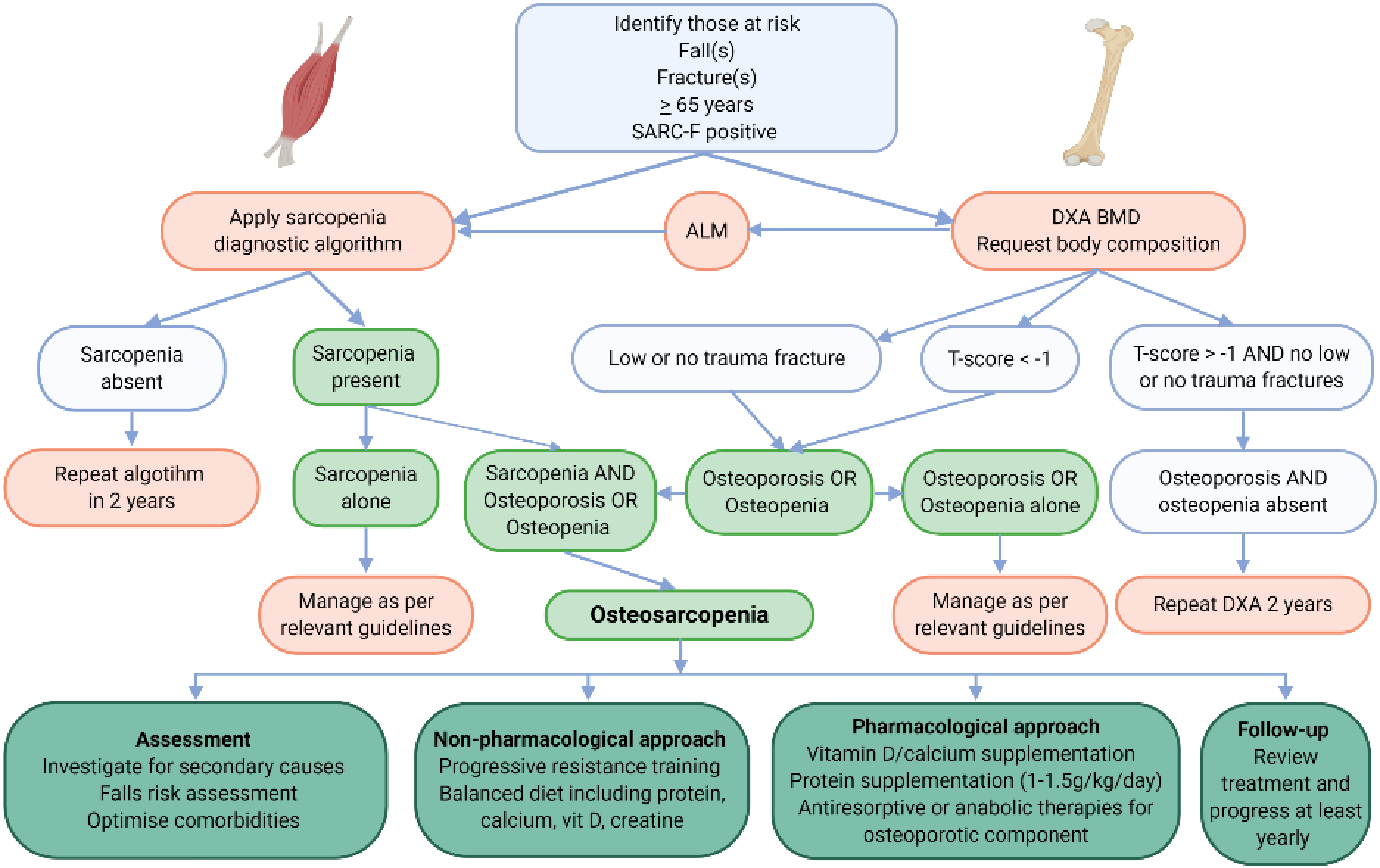
Osteosarcopenia: treatment

Table 7. Summary of the evidence regarding the effect of pharmacological agents on osteoporosis and sarcopenia related outcomes.

Pharmacological agent	Osteoporosis	Sarcopenia
Denosumab	Meta-analysis of 4 RCTs, investigating the effect of denosumab on BMD reported significant improvement in BMD at lumbar spine, hip, and radius.[73]	Reduction in falls in the Denosumab treatment group of the FREEDOM Study. No evidence of effect on muscle function.[74] Improves muscle strength and insulin sensitivity in osteoporotic humans.[75]
Testosterone	Intramuscular testosterone increased lumbar spine bone density in men.[76]	Testosterone in older men with decreased testosterone levels and muscle weakness can improve muscle mass, strength and physical performance.[65]
Growth hormone	Meta-analysis of 7 RCTs and one extension trial concluded that growth hormone may not improve bone density but decrease fracture risk in women with age related bone loss.[77]	Low growth hormone levels with age contribute to decrease in lean body mass and increase adipose tissue.[78]
Antimyostatin antibodies	Antimyostatin antibody in combination with resistance exercise improved bone health in rats.[79]	(1) Antimyostatin antibodies increased muscle mass and strength in mice.[80] (2) Antimyostatin antibodies increased lean mass and may improve functional measures of muscle power.[81]

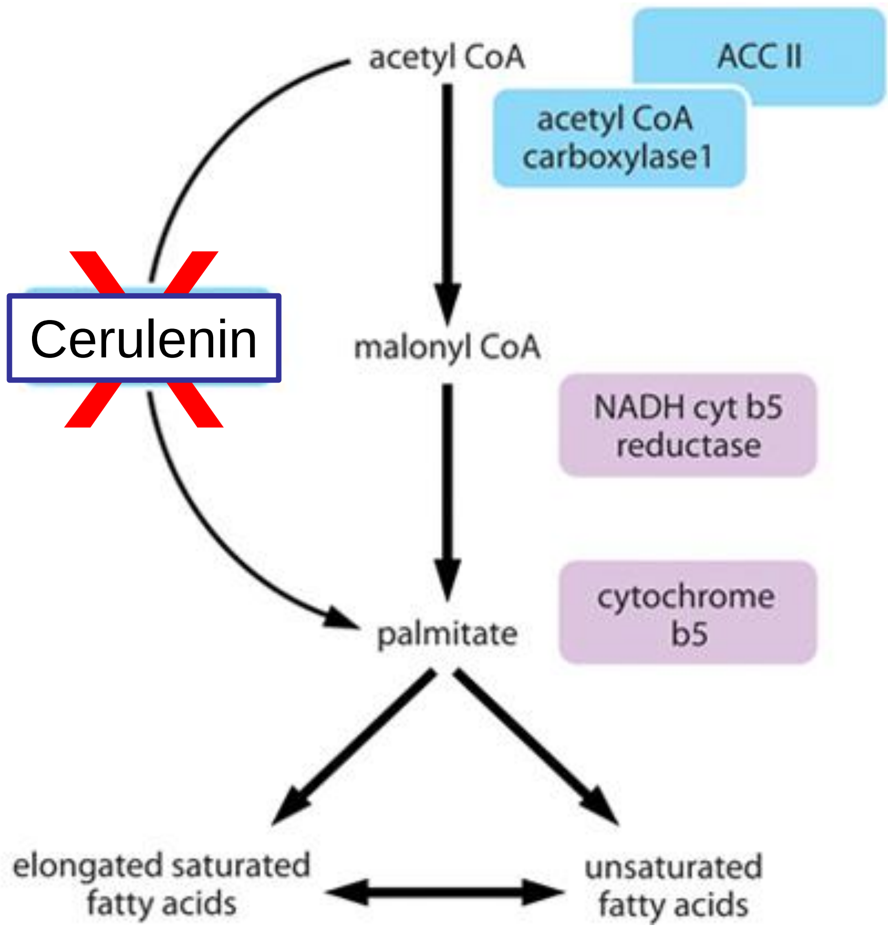
BMD, bone mineral density; RCT, randomized controlled trial.

Fatima et al, Ther Adv Musculoskelet Dis. 2019

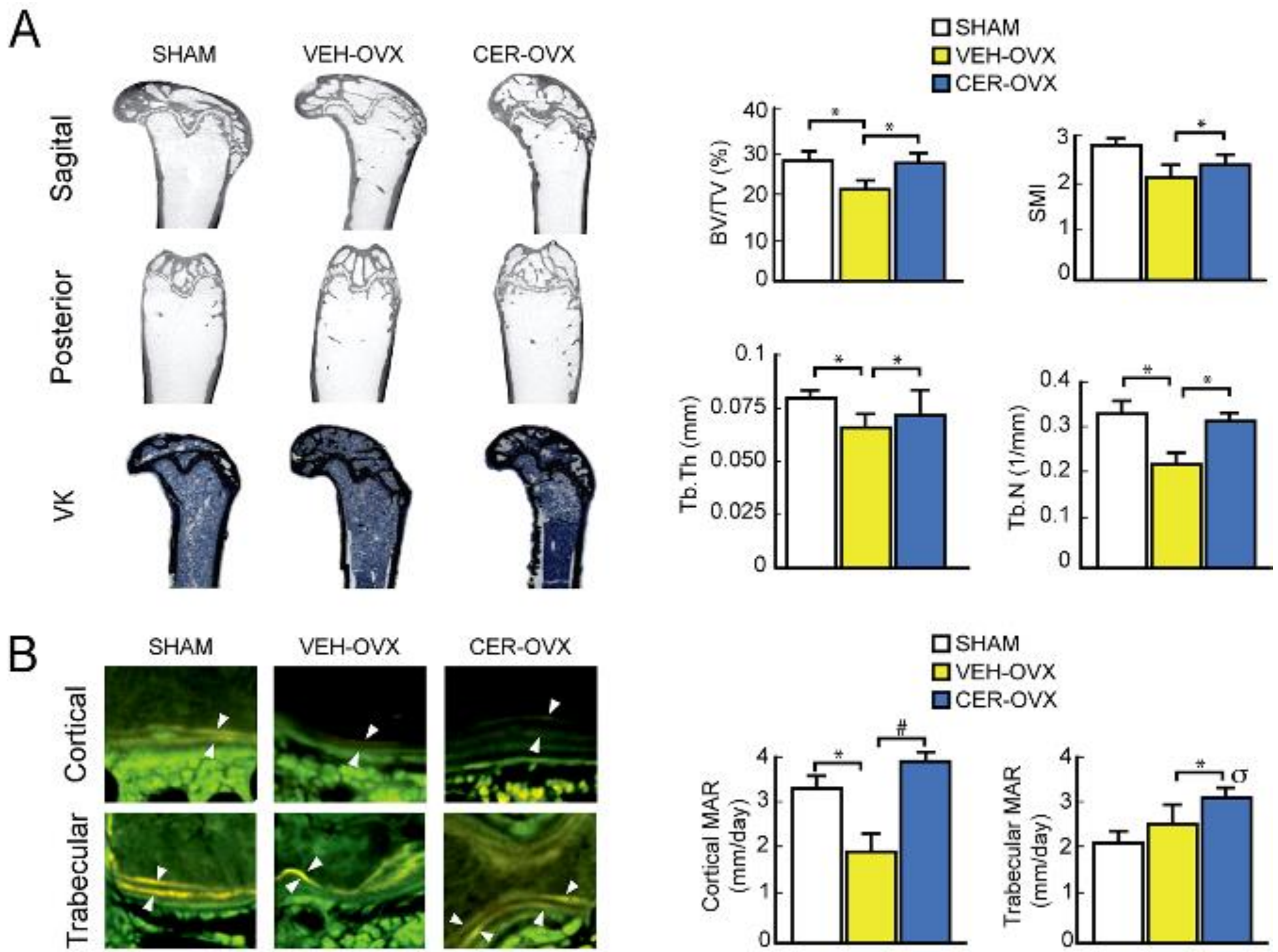


Kirk et al. J Cachexia Sarcopenia Muscle. 2020

Future Directions

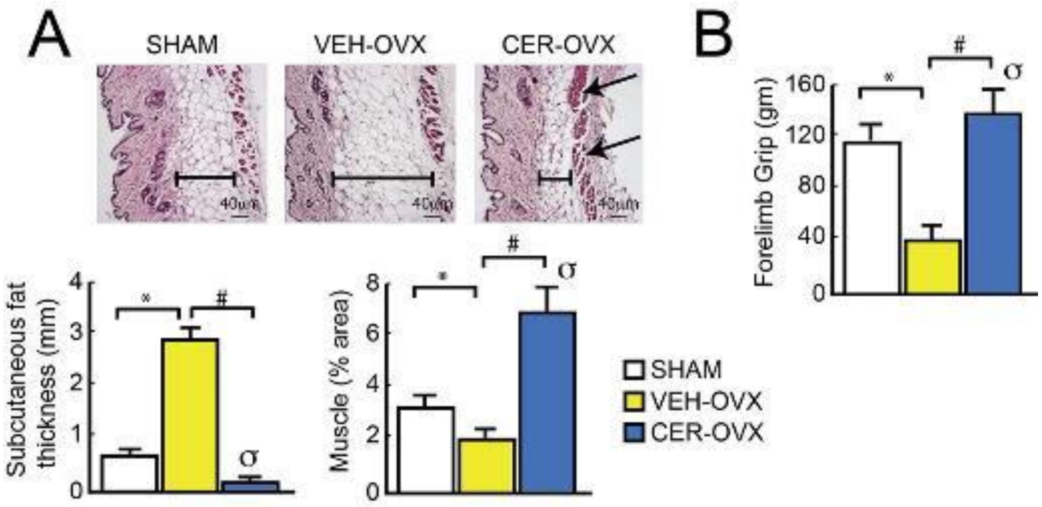

acetyl CoA
ACC II
acetyl CoA carboxylase1
Cerulenin
malonyl CoA
NADH cyt b5 reductase
palmitate
cytochrome b5
elongated saturated fatty acids
unsaturated fatty acids

Inhibition of fatty acid synthase increases bone mass

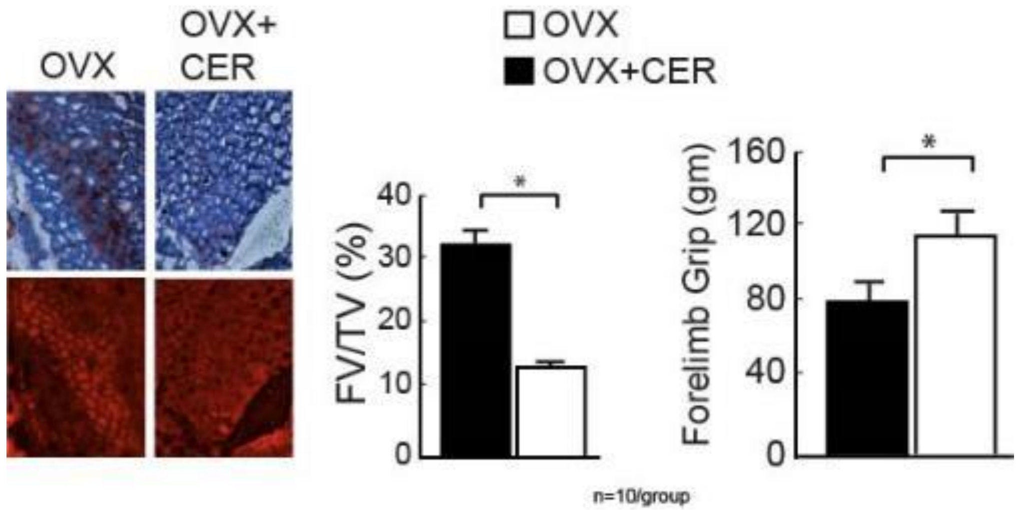


Bermeo et al. Bone, 2019

Inhibition of fatty acid synthase improves muscle mass and strength

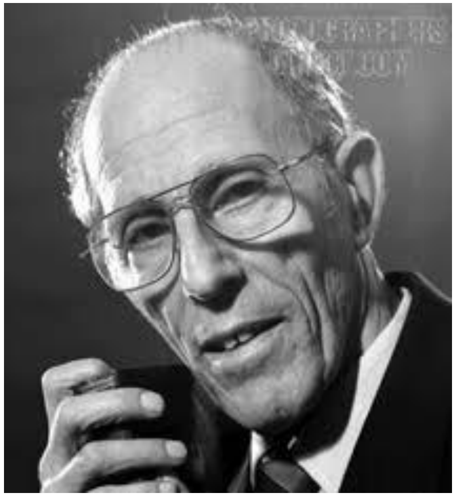


Bermeo et al. Bone, 2019



Bermeo et al. Submitted data

Osteosarcopenia: A geriatric giant



Geriatric Giants

- Instability
- Immobility
- Incontinence
- Intellectual impairment

Bernard Isaacs

Osteosarcopenia: A new geriatric syndrome

Ebrahim Bani Hassan, Gustavo Duque

AFP, 2018

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THANK YOU

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