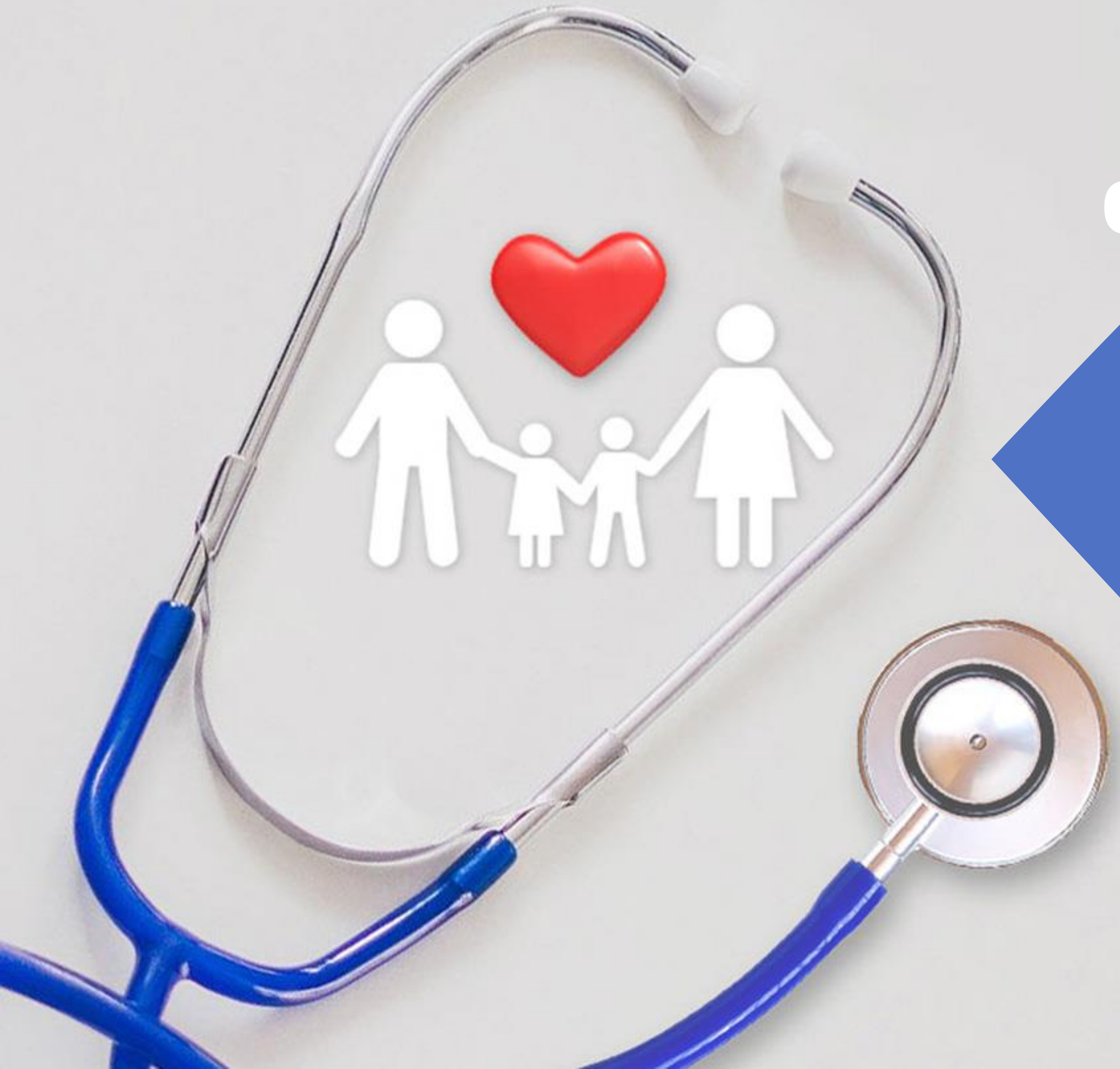

Nutrition in osteoporosis and sarcopenia

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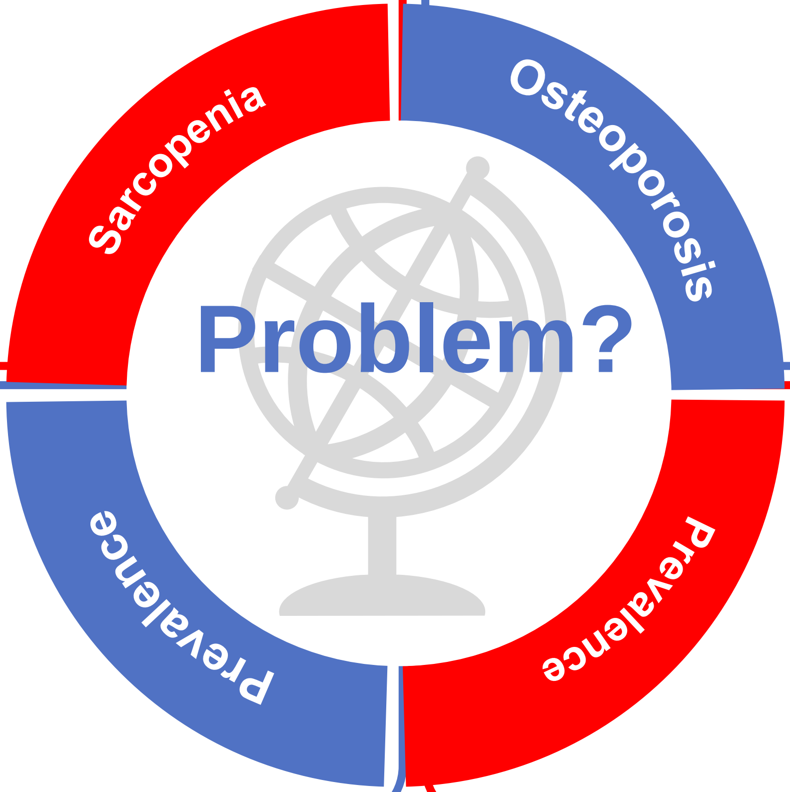
Introduction

Introduction

Age-related progressive loss of skeletal muscle mass, strength, and function.

A systemic skeletal disease characterized by low bone density and microarchitectural deterioration, leading to increased fracture risk.

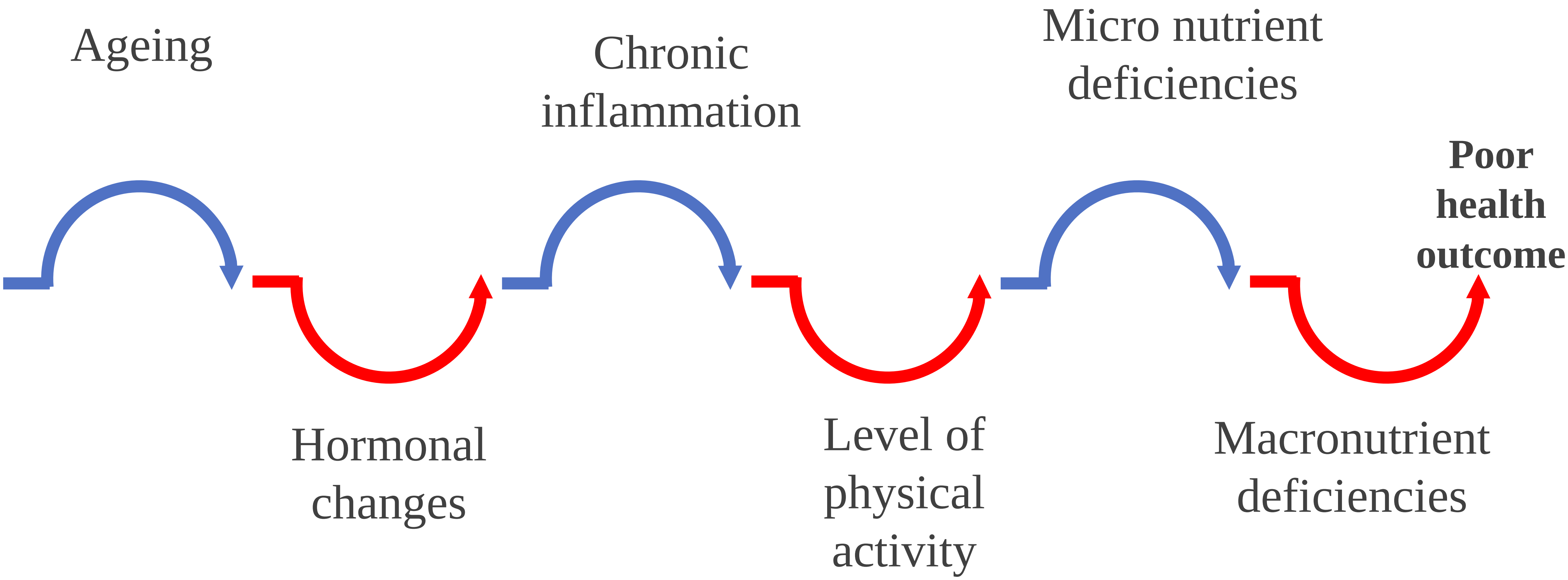


Affects 5-13% of adults over 60, rising to over 50% in those over 80

varied greatly according to countries (from 4.1% in Netherlands to 52.0% in Turkey) and continents (from 8.0% in Oceania to 26.9% in Africa).

Cruz-Jentoft AJ, et al. (2019). Sarcopenia: Revised European consensus on definition and diagnosis. Age and Ageing, 48(1), 16–31.Kanis JA, et al. (2020)
Global, regional prevalence, and risk factors of osteoporosis according to the World Health Organization diagnostic criteria: a systematic review and meta-analysis
,2022

Shared Risk Factors for Sarcopenia and osteoporosis



:Liguori I, et al. (2018). Oxidative stress, aging, and diseases. Journal of Physiology and Biochemistry, 74(1), 31-35.Papadopoulou SK, et al. (2020). Nutritional management of sarcopenia and osteoporosis in older adults. Annals of the New York Academy of Sciences, 1469(1), 52-72.

Cellular Pathophysiology of sarcopenia

Muscle-Bone Crosstalk

Anabolic Resistance (MPS)

Activation of Proteolysis

Mitochondrial Dysfunction

Inflammation

Scicchitano BM, et al. (2018). The physiopathology of skeletal muscle aging: Tissue-specific mechanisms. Journal of Clinical Medicine, 7(10), 332.Powers SK, et al. (2020). Mitochondrial function and oxidative stress in aging skeletal muscle. Cell Metabolism, 31(2), 245-253.

CellularPathophysiology of osteoporesis

Muscle-Bone Crosstalk

1. Bone Remodeling Imbalance

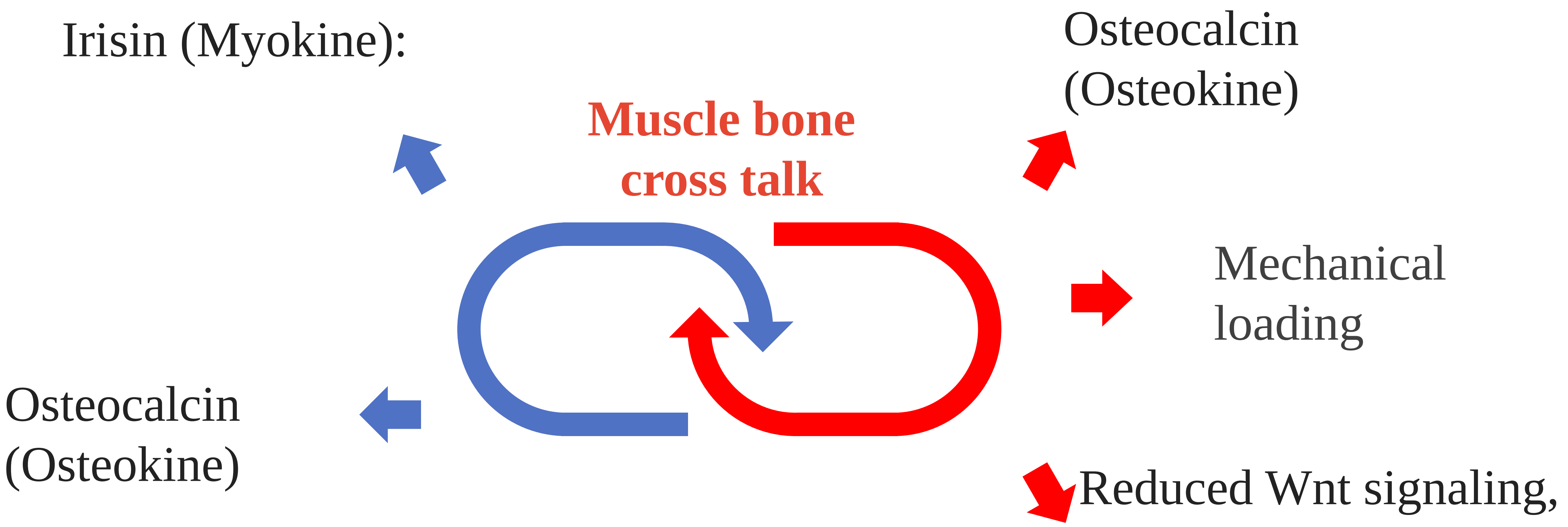
2. RANK/RANKL/OPG Pathway

3. Reactive oxygen species

4. Cellular Senescence

Khosla S, et al. (2018). Cellular and molecular mechanisms of age-related bone loss in humans. Bone, 120, 543-552.Manolagas SC. (2020). Aging, cellular senescence, and osteoporosis.
The New England Journal of Medicine, 383(15), 1447-1457.

Muscle-bone cross talk



Aging leads to reduced Wnt signaling, contributing to sarcopenia and osteoporosis.References:Levinger I, et al. (2017).
The crosstalk between skeletal muscle and bone: Emerging concepts and therapeutic implications. Bone, 94,59-69.Kim BJ, et al. (2020).

Role of Nutrition

A **healthy lifestyle** is crucial for preventing sarcopenia and osteoporosis.

In this section, we will explore how targeted nutritional strategies and healthy lifestyle practices can effectively combat sarcopenia and osteoporosis, ultimately promoting better health outcomes and quality of life for older adults

Calorie and Sarcopenia

calorie

- Older adults require sufficient calorie combined with adequate protein to maintain muscle mass

Balance

- A balance between energy intake and physical activity is key to preserve muscle mass.

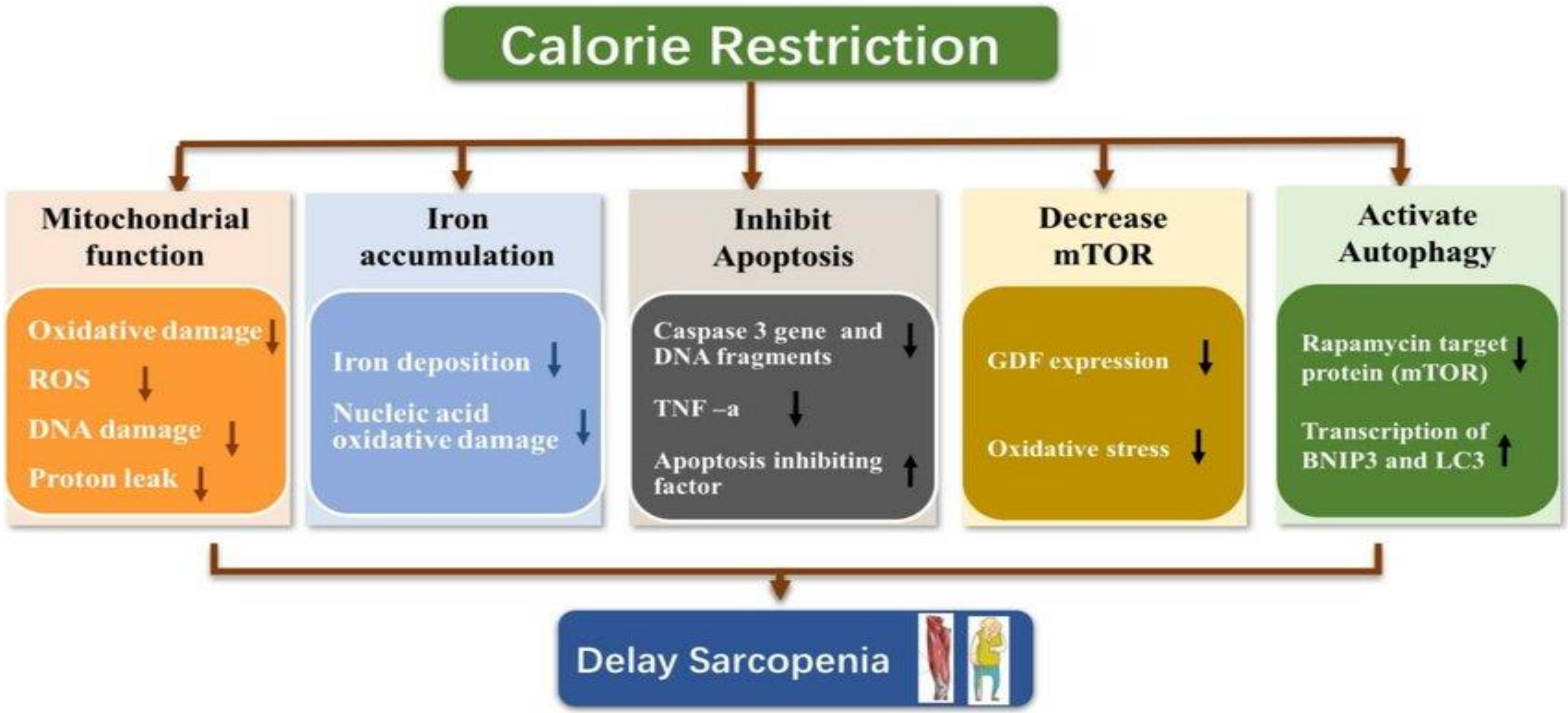
Notice

- **Over restrictive dieting,** particularly in elderly can lead to significant muscle loss even if fat loss is achived.

➡ The evidence supports the recommendations for intakes of protein above the current **guidelines of 0.8 g/kg body weight**/d for the healthy elderly population for weight management in this age group.

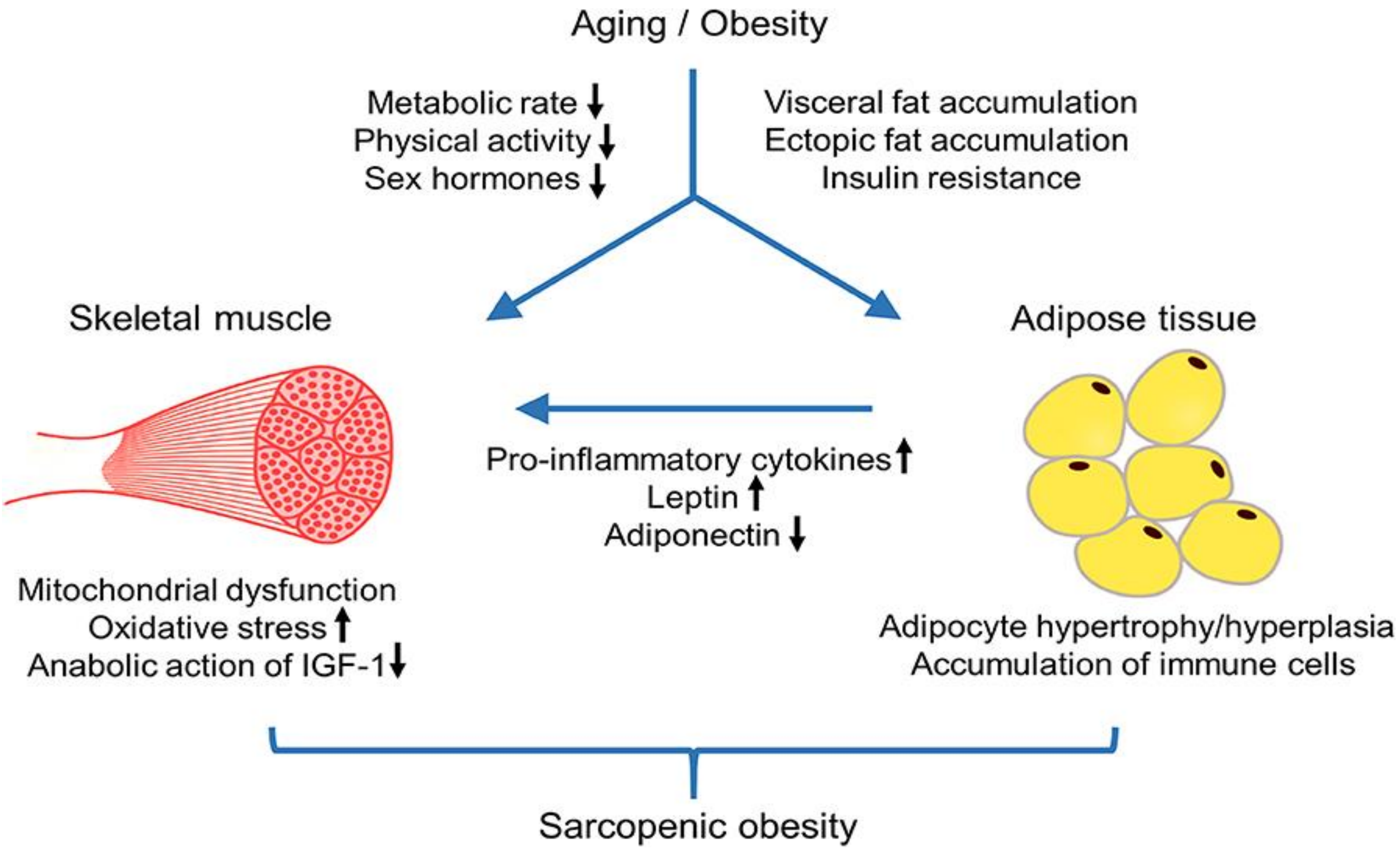
Weight Loss Strategies and the Risk of Skeletal Muscle Mass Loss,2021

How moderate calorie restriction affect sarcopenia



Caloric restriction: implications for sarcopenia and potential mechanisms 2020

Sarcopenic obesity



Health Consequences of Sarcopenic Obesity: A Narrative Review,2020

“Dynapenic obesity

” is characterized by loss of muscle strength due to obesity.

It is associated with limited mobility and contributes to an increased risk of falls

Sarcopenic obesity

is characterized by loss of muscle mass due to obesity. It

is positively associated with an increased risk of falls because of postural instability and reduced physical activity

Dynapenic Abdominal Obesity and Risk of Heart Disease among Middle-Aged and Older Adults: A Prospective Cohort Study,2023

Calorie and osteoporosis

calorie

- Adequate caloric intake supports osteoblast function and bone formation

Balance

- caloric Restriction: May lead to increased bone resorption due to elevated sympathetic nervous system activity and decreased (IGF-1) levels

Notice

- Sclerostin Expression: Increased under caloric restriction, inhibiting the Wnt signaling pathway and osteoblast activity

Zhu, M. and Fan, Z., 2022. The role of the Wnt signalling pathway in the energy metabolism of bone remodelling. Cell Proliferation, 55(11), p.e13309.

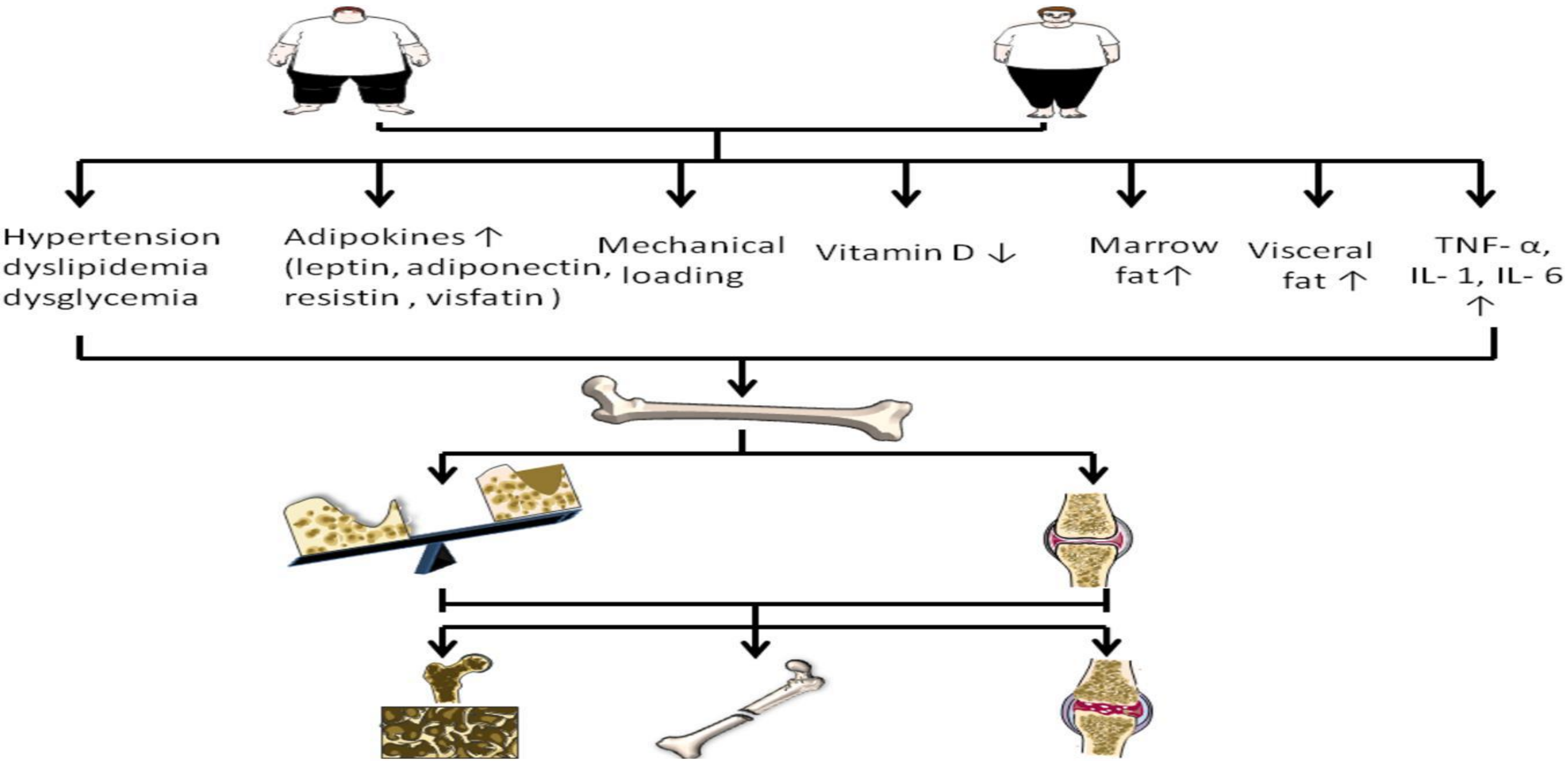
Adverse effect of calorie restriction

Bone Marrow adipose tissue

- BMAT, another type of fat tissue in the bone marrow that accounts for more than 10% of total body fat
- Caloric restriction promotes the differentiation of mesenchymal stem cells (MSCs) toward adipogenesis rather than osteoblastogenesis
- Alteration of mechanical loading and adipokines secretions

New Insights into Calorie Restriction Induced Bone Loss,2023

How does obesity affect bone mineral density



Obesity and Bone Health: A Complex Link,2020

Protein and sarcopenia

01

Enhanced muscle function translates to better physical performance and reduced disability.

02

Recent metanalysis: higher protein intake (≥1.2 g/kg/day) significantly improves muscle mass and strength in older adults.

03

Protein supplementation combined with **resistance training** yields superior outcomes compared to either intervention alone.

04

protein intakes greater **than ~1.6 g/kg/day do not** further contribute to RET-induced gains in FFM.

Morton RW, et al. (2018). A systematic review, meta-analysis and meta-regression of the effect of protein supplementation on resistance training-induced gains in muscle mass and strength in older adults.

CLOSER LOOK

Leucine: Key anabolic amino acid. Supplementation has been shown to stimulate muscle protein synthesis, particularly in older adults (Churchward-Venne et al., 2022)

Studies suggest **evenly distributing protein** across meals improves muscle protein synthesis vs. skewed pattern.(Layman et al.2015)

Generally the **protein quantity** play the most important role rather than distribution (Layman et al.2024)

Resistance exercise combined with adequate protein intake is the most effective strategy to combat sarcopenia (Morton et al,2018)

Clinical studies demonstrated that older adults (>60 years) require meals with at least 2.8 g of leucine (~30 g of protein) to stimulate MPS (Layman,2024)

MPS :muscle protein synthesis

protein synthesis involving ribosomes and mRNAs **decreased in both capacity and efficiency with increasing age**.

Age-related decline in **MPS** could be overcome by increasing the amount of leucine in the meal and suggested that MPS has an upper limit to a meal response.

Activation of mTORC1 requires a **twofold to threefold increase** in plasma and intracellular **leucine** concentrations to stimulate MPS

This metabolic role of **leucine** highlights the difference between the minimum dietary requirement for protein defined by the RDA (2.7 gr/day) versus an optimal metabolic need 7.5 gr/day).

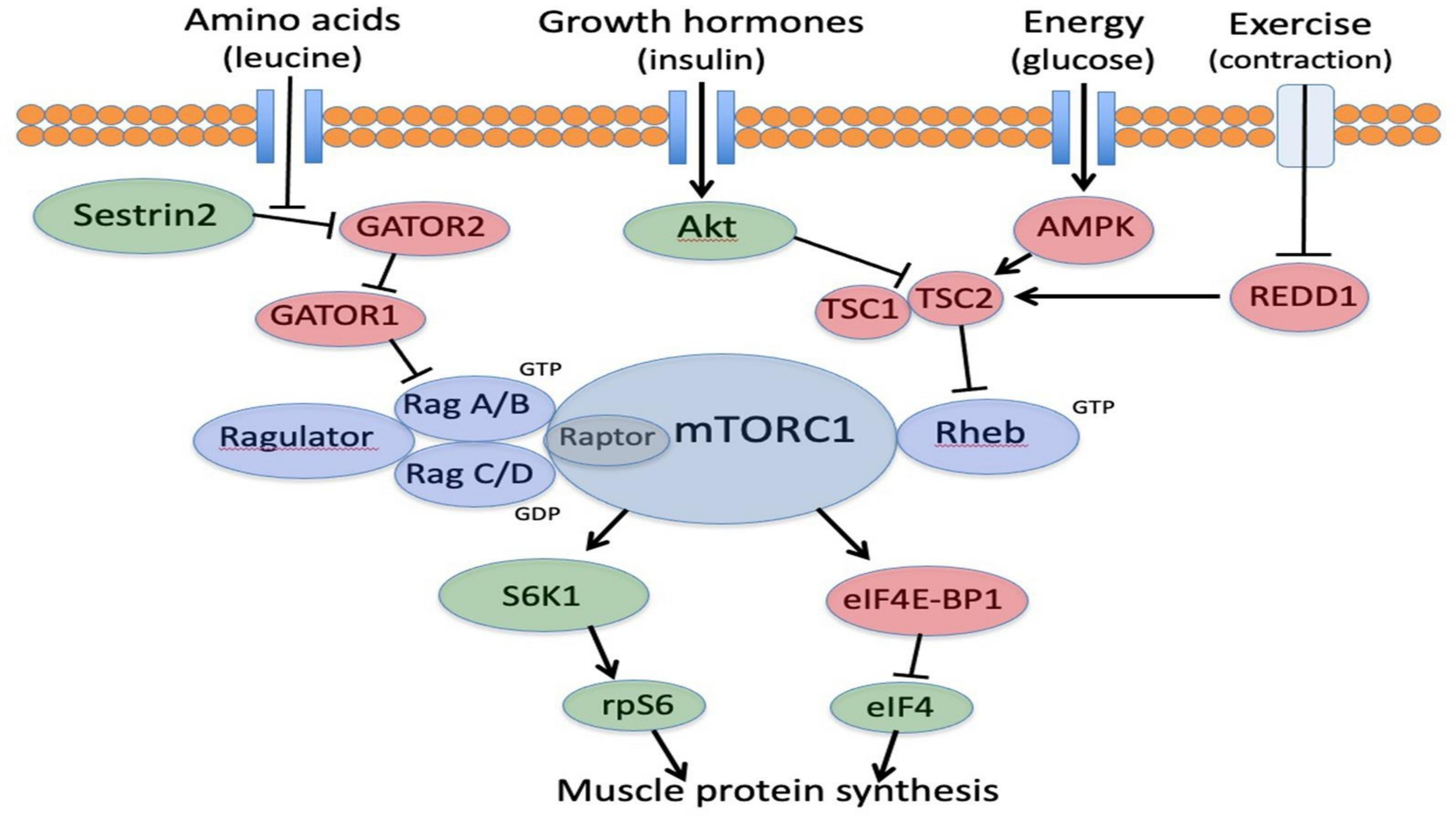
Protein and sarcopenia

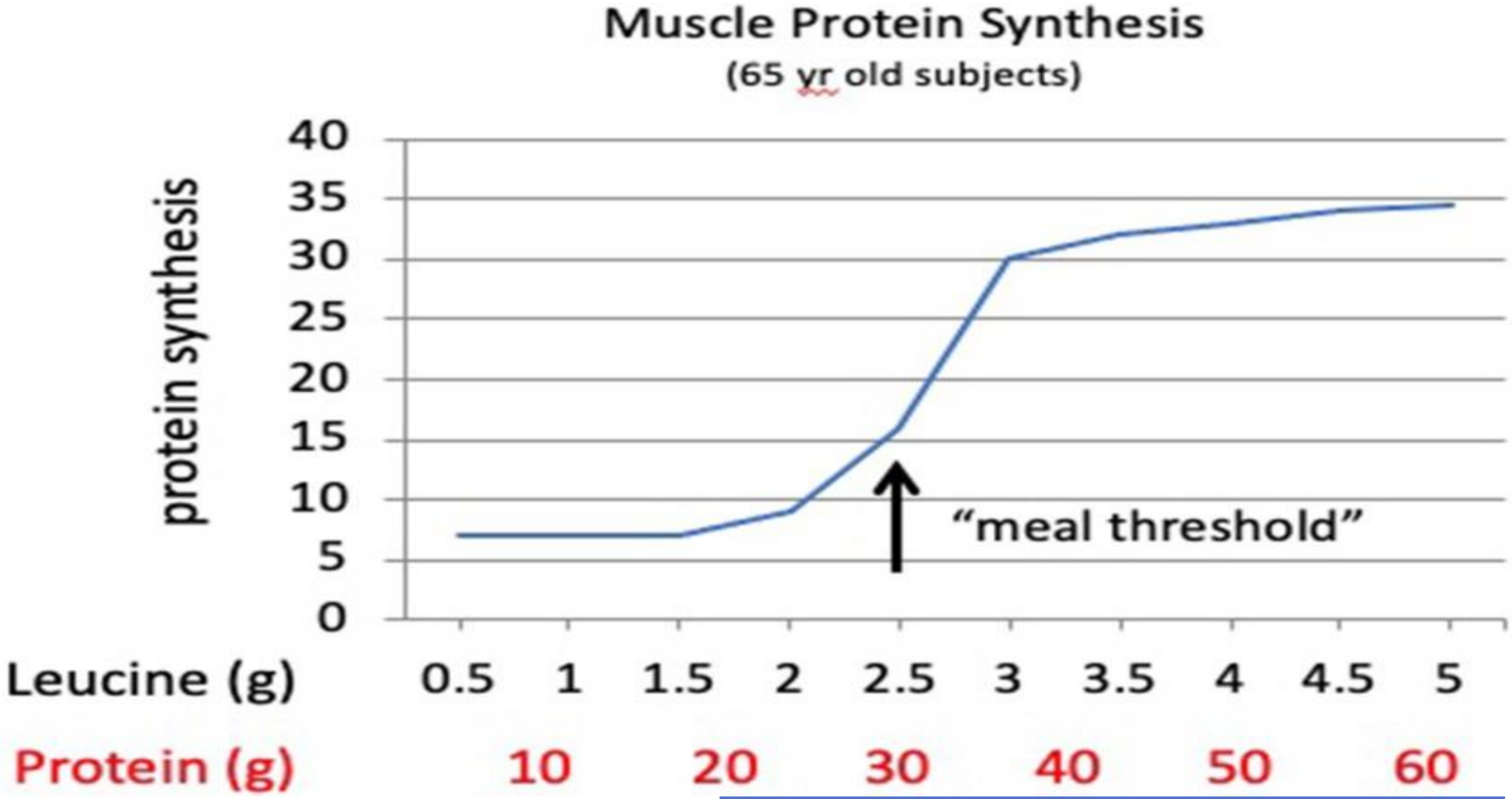
Leucine stimulates mTOR signaling, a critical pathway for muscle protein synthesis.

The recommended protein intake for the elderly is 25–30 g at main meals, with at least 2500–2800 mg of leucine at each meal.

Older adults often have reduced protein digestion and absorption, making high-quality protein critical

Differential regulation of mTORC1 activation by leucine and β-hydroxy-β-methylbutyrate in skeletal muscle of neonatal pigs,2020
Protein and Leucine Intake at Main Meals in Elderly People with Type 2 Diabetes,2023


Amino acids
(leucine)
Growth hormones
(insulin)
Energy
(glucose)
Exercise
(contraction)
Sestrin2
GATOR2
Akt
AMPK
GATOR1
TSC1
TSC2
REDD1
GTP
Rag A/B
Ragulator
Raptor
mTORC1
Rheb
GTP
Rag C/D
GDP
S6K1
eIF4E-BP1
rpS6
eIF4
Muscle protein synthesis


Muscle Protein Synthesis
(65 yr old subjects)
protein synthesis
40
35
30
25
20
15
10
5
0
"meal threshold"
Leucine (g)
0.5 1 1.5 2 2.5 3 3.5 4 4.5 5
Protein (g)
10 20 30 40 50 60

Layman,2024

- **Omega 3 fatty acids and muscles**

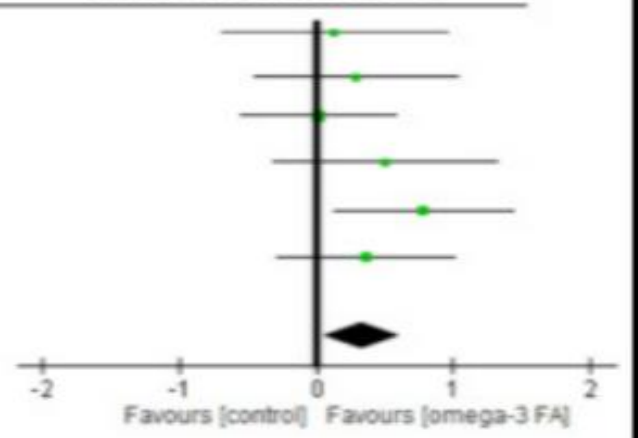
- Omega-3 polyunsaturated fatty acids (PUFAs), particularly EPA and DHA, enhance muscle protein synthesis by activating the **mTOR signaling pathway** and increasing the availability of amino acids for muscle repair and growth.

- Meta analysis: Omega-3 fatty acid supplements at more than 2 g/day may contribute to muscle mass gain (0.67 kg; 95% CI: 0.16, 1.18) and improve walking speed, especially more than 6 months of intervention.

- **Unresolved inflammation may be a key factor in driving muscle catabolism!**
- **Chronic low-grade inflammation**

Non-critical care settings: Oral doses of EPA + DHA in the range of **2.5–5 g/day** increase muscle protein synthesis, decrease muscle protein breakdown, and preserve muscle mass.

Effects of Omega-3 Fatty Acids on Muscle Mass, Muscle Strength and Muscle Performance among the Elderly: A Meta-Analysis.2020Combining proteins with n-3 PUFAs (EPA + DHA) and their inflammation pro-resolution mediators for preservation of skeletal muscle mass,2024



Study	Experimental(n-3 FAs) Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cornish 2009(F)	0.7	2.09	11	0.4	2	12	11.8%	0.14 [−0.68, 0.96]
Cornish 2009(M)	1.2	2.64	14	0.4	2.63	14	14.3%	0.29 [−0.45, 1.04]
KS 2015	0.08	1.09	30	0.06	1	20	24.8%	0.02 [−0.55, 0.58]
Logan 2015	1.6	1.74	12	0.6	2.09	12	12.0%	0.50 [−0.31, 1.32]
Murphy 2011	0	0.52	16	−0.9	1.39	24	18.4%	0.78 [0.12, 1.44]
Strandberg 2015	0.21	0.48	20	0.04	0.44	17	18.7%	0.36 [−0.29, 1.01]
Total (95% CI)			**103**			**99**	**100.0%**	**0.33 [0.05, 0.62]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.36$, df = 5 (P = 0.64); $I^2 = 0\%$

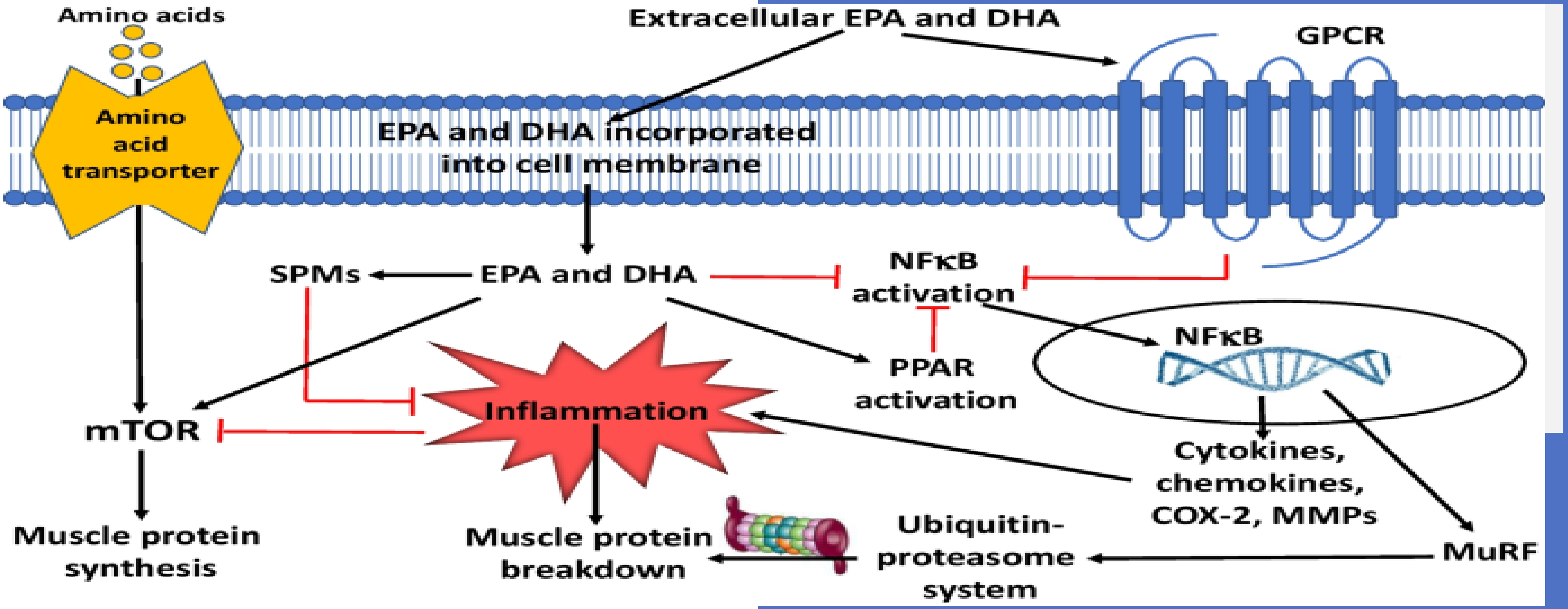
Test for overall effect: Z = 2.32 (P = 0.02)

See this image and copyright information in PMC

Figure 4 Forest plot of the effect of n-3 PUFA supplementation on muscle mass. IV: inverse-variance method. Random: random effect. Weight (in %), the influence of an individual study on the pooled result.

Huang YH, Chiu WC, Hsu YP, Lo YL, Wang YH. Effects of Omega-3 Fatty Acids on Muscle Mass, Muscle Strength and Muscle Performance among the Elderly: A Meta-Analysis. Nutrients. 2020 Dec 4;12(12):3739. doi: 10.3390/nu12123739. PMID: 33291698; PMCID: PMC7761957.

Cellular mechanisms by which EPA and DHA impact muscle protein synthesis and breakdown



Combining proteins with n-3 PUFAs (EPA + DHA) and their inflammation pro-resolution mediators for preservation of skeletal muscle mass,2024

Vitamin D and muscle

- **118 people with both sarcopenia and vitamin D deficiency:**
- 10,000 IU given 3 times a week vs. the nutritional supplement alone

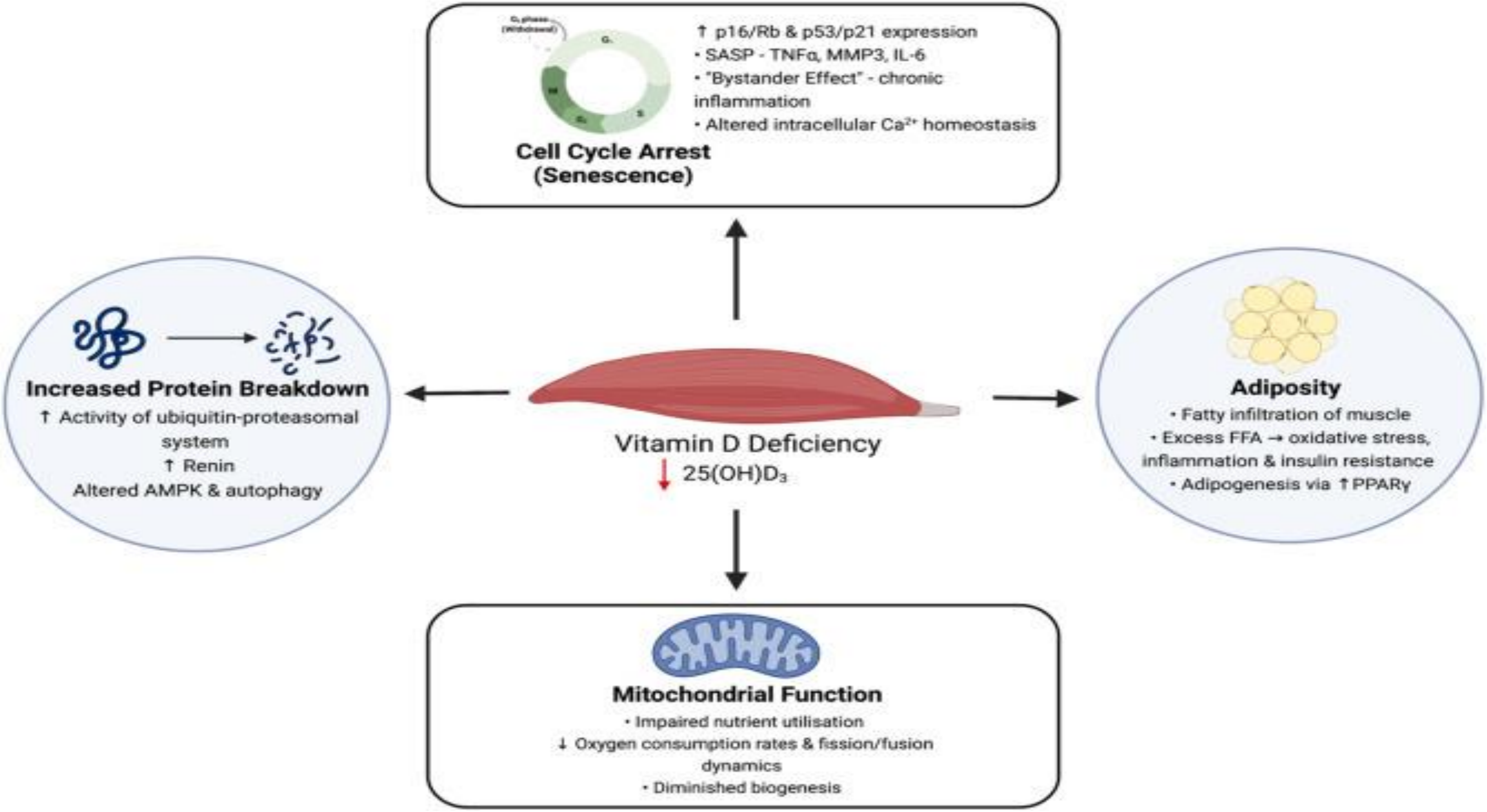
  Muscle mass but not grip strength after 6 months.

- Gender was a significant predictor of muscle mass in normal-weight subjects, it was not a significant predictor in obese patients

- **A meta-analysis of 35 studies with more than 6628 participants:**

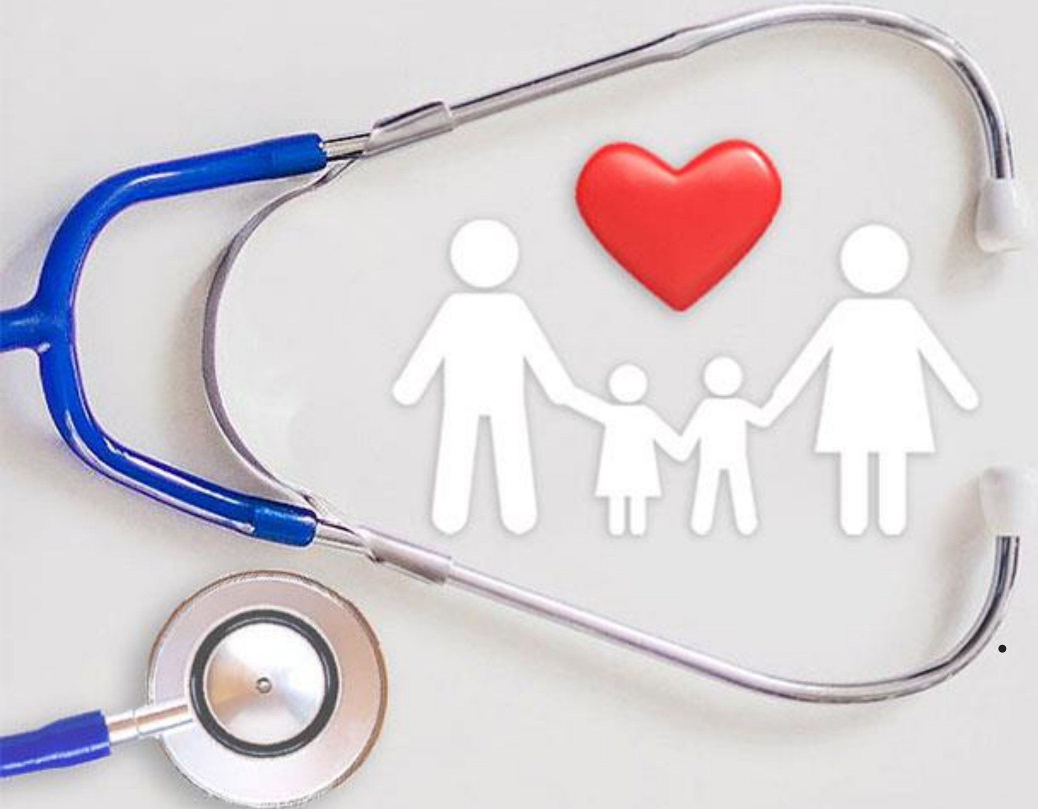
- No significant results were observed on muscle mass size, strength and function.

El Hajj, C.; Fares, S.; Chardigny, J.M.; Boirie, Y.; Walrand, S. Vitamin D supplementation and muscle strength in pre-sarcopenic elderly Lebanese people: A randomized controlled trial. *Arch. Osteoporos.* **2019**, *14*, 4.
Widajanti N, Hadi U, Soelistijo SA, Syakdiyah NH, Rosaudyn R, Putra HBP. The Effect of Vitamin D Supplementation to Parameter of Sarcopenia in Elderly People: a Systematic Review and Meta-Analysis. Can Geriatr J. 2024 Mar 1;27(1):63-75. doi: 10.5770/cgj.27.694. PMID: 38433884; PMCID: PMC10896205.



The Vitamin D/Vitamin D receptor (VDR) axis in muscle atrophy and sarcopenia,2022

Ca and sarcopenia



01

- Daily calcium intake was positively correlated with appendicular skeletal muscle mass in 1339 older Korean adults

02

- after controlling for age, sex, BMI, total energy intake, and daily lifestyle factors, individuals in the highest had an odds ratio for sarcopenia **of 0.29 when compared to the lowest tertile**

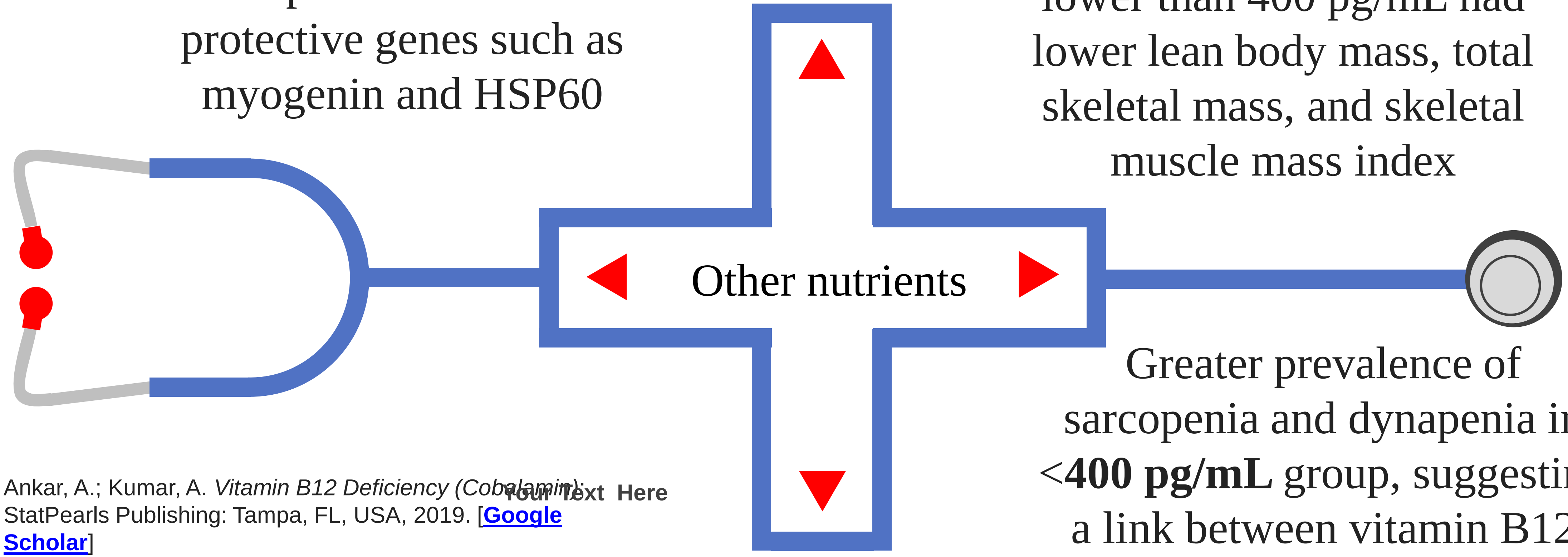
03

- The effect of daily calcium intake on sarcopenia is overall unclear and needs to be studied more in the future.

- Seo, M.H.; Kim, M.K.; Park, S.E.; Rhee, E.J.; Park, C.Y.; Lee, W.-Y.; Baek, K.H.; Song, K.-H.; Kang, M.I.; Oh, K.W. The association between daily calcium intake and sarcopenia in older, non-obese Korean adults: The fourth Korea National Health and Nutrition Examination Survey (KNHANES IV) 2009. *Endocr. J.* **2013**, *60*, 679–686..

Compared to marginal B6 deficiency, consuming the RDA of vitamin B6 upregulates the expression of several protective genes such as myogenin and HSP60

Compared to elderly patients with levels of **vitamin B12 > 400 pg/mL**, patients with lower than 400 pg/mL had lower lean body mass, total skeletal mass, and skeletal muscle mass index



Greater prevalence of sarcopenia and dynapenia in <**400 pg/mL** group, suggesting a link between vitamin B12 levels and the development of sarcopenia

Your Text Here

Ankar, A.; Kumar, A. *Vitamin B12 Deficiency (Cobalamin)*; StatPearls Publishing: Tampa, FL, USA, 2019. [Google Scholar]

Bulut, E.A.; Soysal, P.; Aydin, A.E.; Dokuzlar, O.; Kocyigit, S.E.; Isik, A.T. Vitamin B12 deficiency might be related to sarcopenia in older adults. *Exp. Gerontol.* **2017**,.

Combination therapy

Author	Population	Intervention	Results of Supplemental Protein + Vitamin D vs. Placebo	With Exercise?
Bauer 2015 [92]	*n* = 380 (297 completed), age ≥ 65 years, with class I or II sarcopenia.	20 g whey protein, 3 g leucine, 800 IU VitD supplement vs. isocaloric placebo supplement for 13 weeks.	Nonsignificant differential increase in SPPB performance and hand-grip strength in both groups. Significant increase in chair-stand test performance in experimental group vs. placebo group. Experimental group also gained more appendicular muscle mass than control.	No.
Rondanelli 2016 [93]	*n* = 130, age ≥ 65 years, relative muscle mass Z score ≤ 2.	Nutritional supplement: 22 g whey protein, 100 IU vitD. Groups: Supplement group vs. isocaloric placebo for 12 weeks	Significant differential increase in fat-free mass, relative skeletal muscle mass, and hand-grip strength in the intervention group.	Yes, both groups received physical activity training.
Chanet 2017 [94]	*n* = 24, age ≥ 65 years, men with BMI between 20 and 30.	Nutritional supplement: 21 g leucine-enriched whey protein + 800 IU vitD$_3$. Groups: Nutritional supplement vs. noncaloric placebo before breakfast for 6 weeks.	Significant differential improvement in mixed muscle protein fixed synthesis rate (FSR) as well as appendicular lean mass growth in the intervention group, mainly as lean leg mass.	No.
Abe 2016 [95]	*n* = 38, age ≥ 65 years, resided in nursing home and required special care from helper.	Nutritional supplement: L-leucine (1.2 g), vitD$_3$ (20 ug). Groups: Leucine supplement (LD) + 6 g Medium Chain Triglycerides (MCTs) vs. Leucine supplement + 6 g Long Chain Triglycerides (LCTs) vs. isocaloric placebo for 3 months.	Significant differential improvement in bodyweight, grip strength, and walking speed in the LD + MCT group only.	No.

Author	Population	Intervention	Results of Supplemental Protein + Vitamin D vs. Placebo	With Exercise?
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Vit C

1. **One of the factors potentially implicated in the mechanism of sarcopenia is oxidative stress**

2. Studies have shown mixed results:

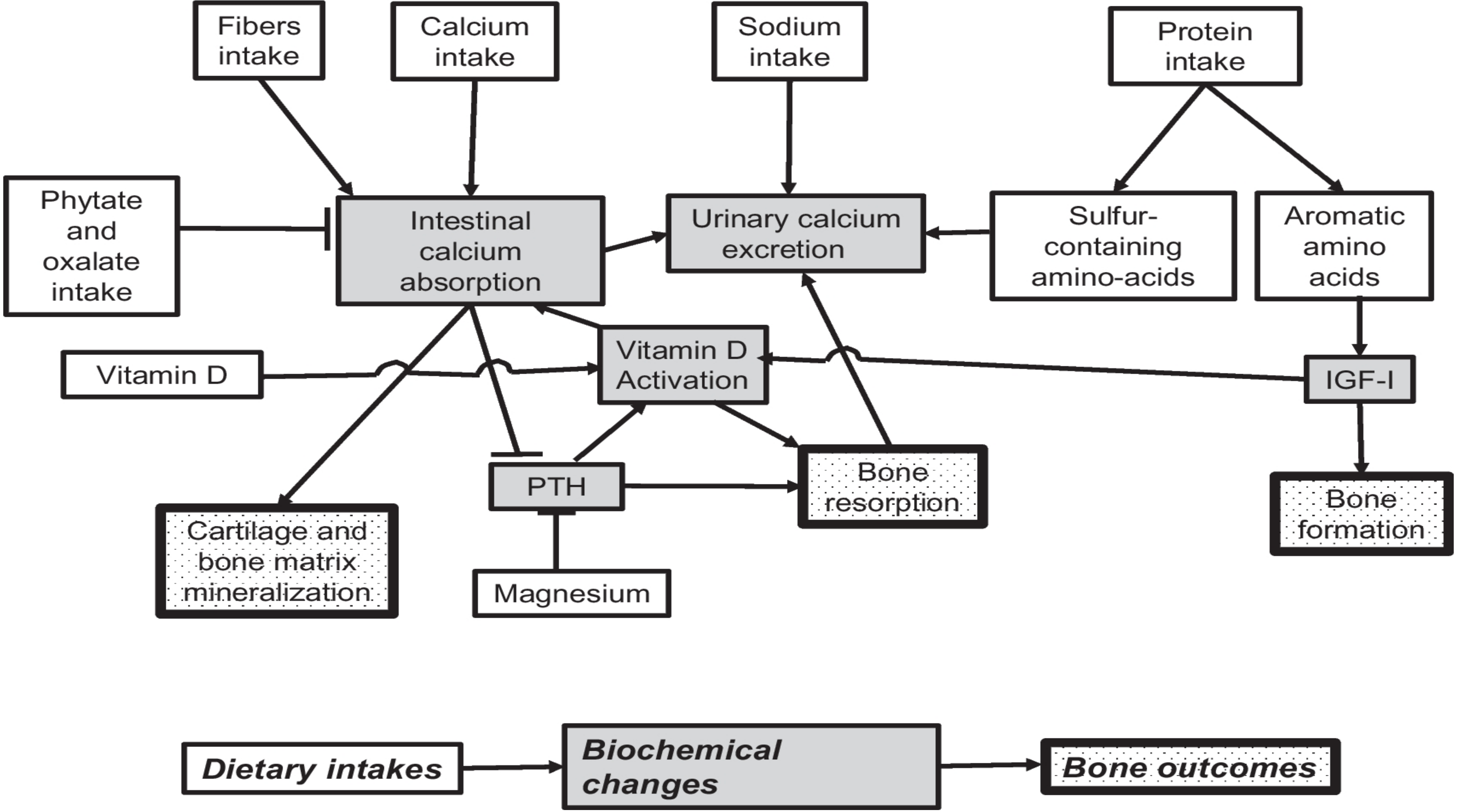
3. A large study involving 1433 subjects (658 men and 775 women) over the age of 60 **years found no association between vitamin** C and sarcopenia.

4. High doses of antioxidant supplementation (vitamin C + E) have been shown to constrain total lean mass gains in a study involving 34 elderly **males** randomized to either an antioxidant or placebo group

Nutrition and Sarcopenia—What Do We Know,2020

The effect of vitamin C dietary intakes and supplementation should be further studied in both men and women.

Nutrition and Bone Health



Rizzoli R, Biver E, Brennan-Speranza TC. Nutritional intake and bone health. Lancet Diabetes Endocrinol. 2021;9:606–21.

Protein and osteoporosis

01

Increasing IGF-1 (a key regulator of bone growth

02

possible reduction in hip fractures when protein intake was over RDA (0.8 g/kg/day)

03

Excessive protein intake without adequate calcium can increase calcium excretion,.

04

increased protein intake (>1.2 g/kg body mass/day) by postmenopausal, non-active women for three years is negatively correlated with BMD and BMC

Wallace, T.C.; Frankenfeld, C.L. Dietary Protein Intake above the Current RDA and Bone Health: A Systematic Review and Meta-Analysis. *J. Am. Coll. Nutr.* **2017**, *36*, 481–496.
Rossato LT, Nahas PC, de Branco FMS, Martins FM, Souza AP, Carneiro MAS, Orsatti FL, de Oliveira EP. Higher Protein Intake Does Not Improve Lean Mass Gain When Compared with RDA Recommendation in Postmenopausal Women Following Resistance Exercise Protocol: A Randomized Clinical Trial. Nutrients. 2017 Sep 12;9(9):1007. doi: 10.3390/nu9091007. PMID: 28895933; PMCID: PMC5622767.

Literature insight

One trial: high-protein drink containing **30 g of protein** compared with a placebo with 2.1 g of protein for 2 Years in healthy postmenopausal women

ere

No significant differences in hip and femoral neck BMD

3-week vitamin D, calcium and leucine-enriched whey protein supplementation

increased total body BMD (0.02 g/cm^2; ~2%) in sarcopenic non-malnourished older adults

Hill TR, Verlaan S, Biesheuvel E, Eastell R, Bauer JM, Bautmans I, et al. A vitamin D, calcium and leucine-enriched whey protein nutritional supplement improves measures of bone health in sarcopenic non-malnourished older adults: The PROVIDE study. *Calcif Tissue Int* 2019;105:383–391

Zhu K, Meng X, Kerr DA, Devine A, Solah V, Binns CW, et al. The effects of a two-year randomized, controlled trial of whey protein supplementation on bone structure, IGF-1, and urinary calcium excretion in older postmenopausal women. *J Bone Miner Res* 2011;26:2298–2306

Physical activity and protein adjustment

The effect of high protein intake is strictly related to lifestyle (including exercise)

an increased protein intake in patients during bed rest causes a rise in bone resorption markers

whether PA combined with the increased supply of protein can provide better results in decreasing the risk of osteoporosis.

Thus, PA can diminish the potential negative impact of protein intake on bone mineralization in inactive patients

PA: physical activity, Impact of Dietary Protein on Osteoporosis Development,2023

Omega3 and bone formation

oblast activity and inhibit osteoclastogenesis, leading to increased bone formation and reduced bone resorption.

2022 meta-analysis reported:

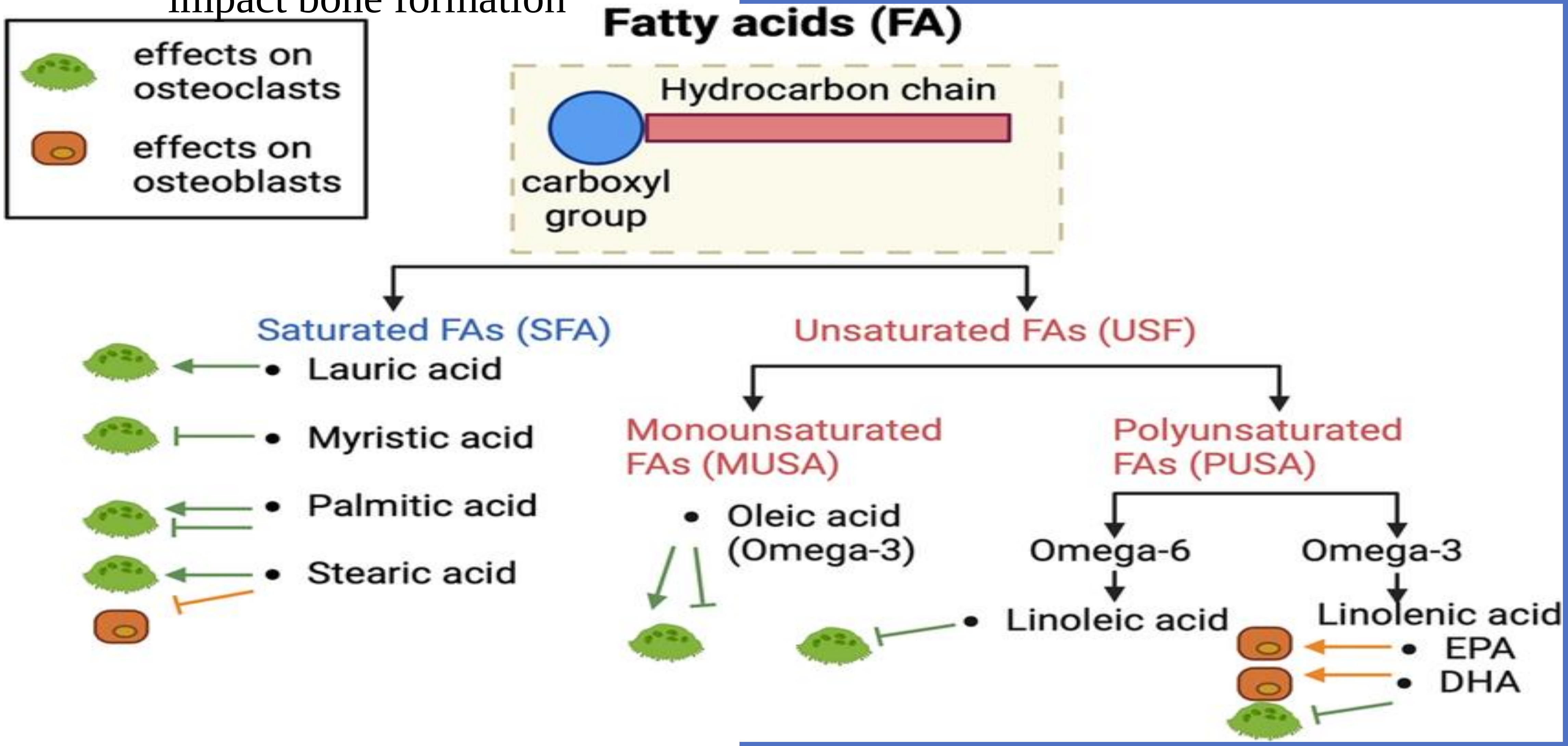
n-3 PUFAs could slightly enhance the level of bone mineral density (BMD) (0.005 g/cm2; 95% CI, 0.000-0.010).

the supplementation form of **α-linolenic** rather than EPA and DHA acid significantly increased the content of BALP (0.396 µg/L; 95% CI, 0.069-0.724).

For postmenopausal women, it presented a significant decreasing level of CTX (-0.393 µg/L; 95% CI, -0.651 to -0.135) and NTX (-2.082 µg/L; 95% CI, -2.970 to -1.195) within their bodies.

Effect of n-3 polyunsaturated fatty acid on bone health: A systematic review and meta-analysis of randomized controlled trials. 2022

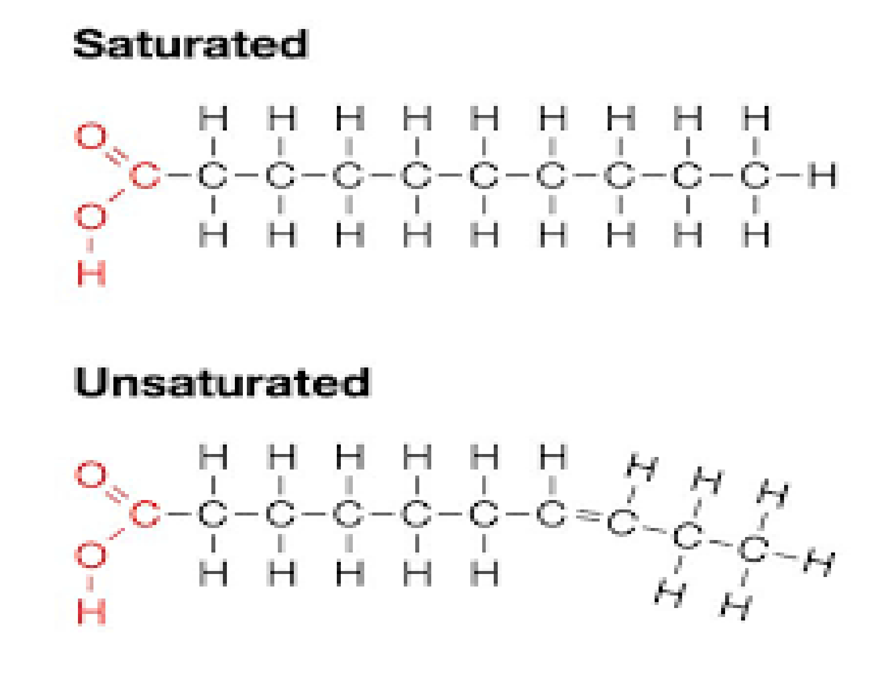
Cellular mechanisms by which fatty acids impact bone formation



Bone metabolism – an underappreciated player,2020

Fatty acids

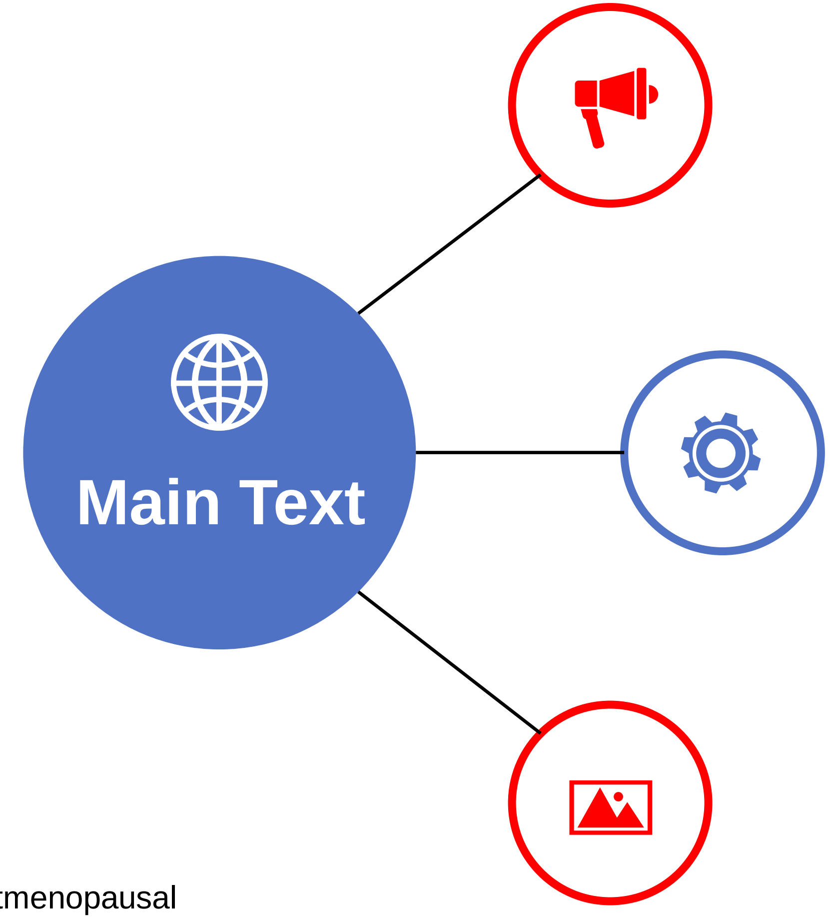
- SFA **decreases** intestinal epithelia cells' membrane fluidity, thereby reducing calcium uptake by small intestinal brush border cells.
- SFA suppresses the differentiation of rat bone marrow mesenchymal stem cells.
- **Oxidized lipids** increase osteoclast cell differentiation. Therefore, people who eat an SFA-enriched diet (mostly from animal fats) are more at risk for osteoporosis



skari A., Naghizadeh M.M., Homayounfar R., Shahi A., Afsarian M.H., Paknahad Increased serum levels of IL-17A and IL-23 are associated with decreased vitamin D3 and increased pain in osteoarthritis. PloS one. 2016; 11 (11) : e0164757 .

Emerging role of alpha lipoic acid

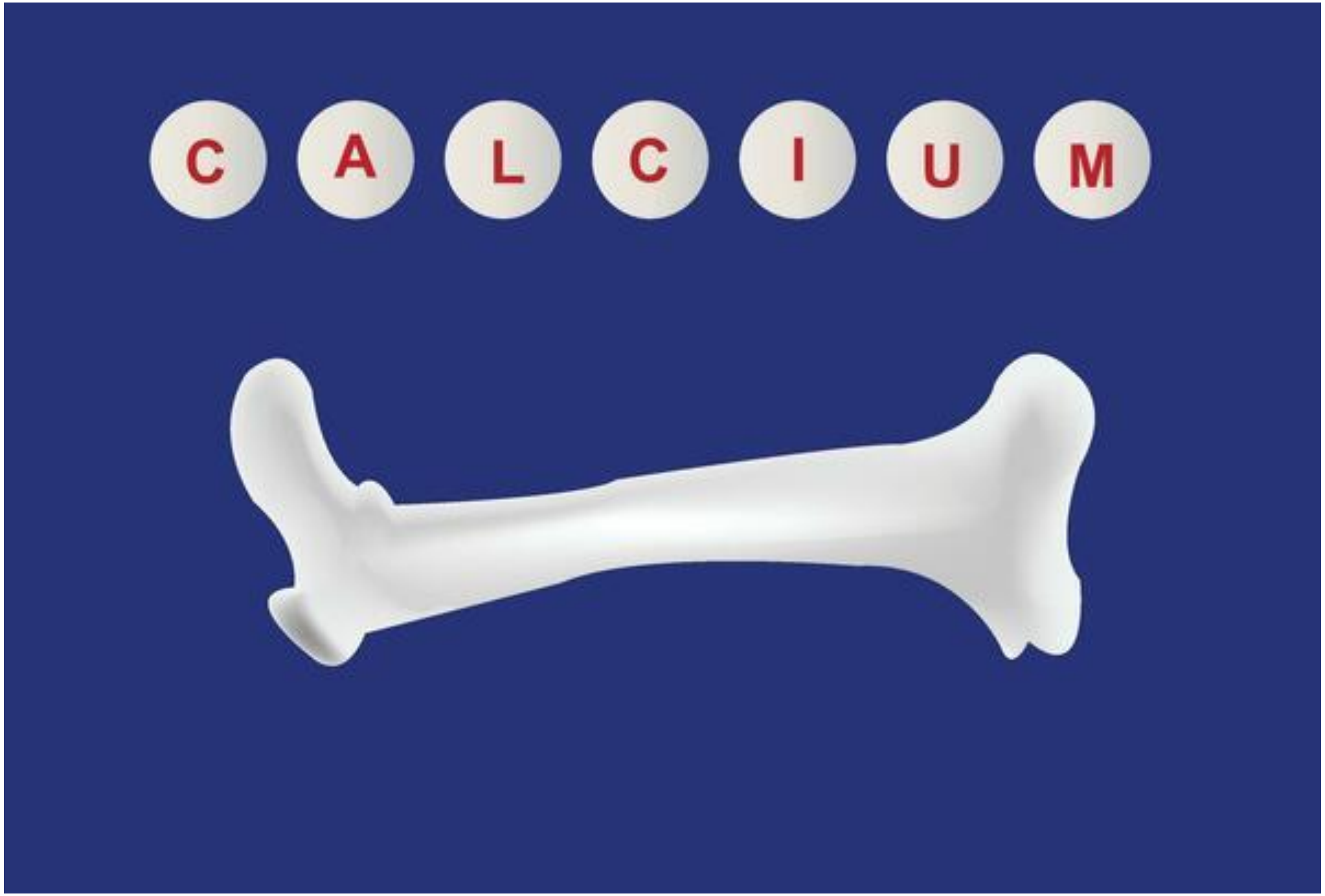
LA inhibited oxidative stress, suppressed apoptosis and improved osteopenia by promoting the expression of osteogenesis markers, including ALP, COL-I, OCN, BMP-2, RUNX2 and OSX



ALA exerts potent protective effects against bone loss in T2DM and postmenopausal osteoporosis coexisting conditions by modulating the YAP/Glut4 pathway.

Alpha-lipoic Acid Prevents Bone Loss in Type 2 Diabetes and Postmenopausal Osteoporosis Coexisting Conditions by Modulating the YAP/Glut4 Pathway.2024

Foods to Improve Bone Density - Nutrition and Bone Health


CALCIUM

The most important sources of calcium in the diet are dairy products (milk, yogurt, and cheese), fish (especially sardines with bones), pulses, and a few vegetables and fruits (particularly nuts and seeds).

Large cohort study: significant 8% reduction in the risk of hip fracture for each daily serving of milk, in men and women combined

Milk intake : Reduce the risk of osteoporotic fractures by 5–15% in an individual patient especially in older patients (80 years or more).

A cohort of postmenopausal healthy women:

the daily consumption of milk fortified with calcium and vitamin D Improved D status and BMD at the femoral neck, and glucose and lipid profiles improvement

Feskanich D., Meyer H.E., Fung T.T., Bischoff-Ferrari H.A., Willett W.C. Milk and other dairy foods and risk of hip fracture in men and women. Osteoporos. Int. 2018;29:385–396. doi: 10.1007/s00198-017-4285-8

Reyes-Garcia R., Mendoza N., Palacios S., Salas N., Quesada-Charneco M., Garcia-Martin A., Fonolla J., Lara-Villoslada F., Muñoz-Torres M. Effects of daily intake of calcium and vitamin D-enriched milk in healthy postmenopausal women: A randomized, controlled, double-blind nutritional study. *J. Women's Health.* 2018;27:561–568. doi: 10.1089/jwh.2017.665

A large RCT in 7195 vitamin D-replete older (mean age 86 years) individuals living in nursing homes.

Dairy group increased their calcium intake from 700 to 1142 mg/day and protein intake from 0.8 to 1.1 g/kg daily

Reduction of 33% in all fractures, of 46% of hip fracture and of 10% of falls. Mortality was not influenced

Iuliano S, Poon S, Robbins J, Bui M, Wang X, De Groot L, Van Loan M, Zadeh AG, Nguyen T, Seeman E. Effect of dietary sources of calcium and protein on hip fractures and falls in older adults in residential care: cluster randomised controlled trial. BMJ. 2021;375:n2364

Nutrient contents per 100 g of commonly used products.

Source	Calcium (mg)	Phosphorous (mg)	Potassium (mg)	Vitamin D (IU)	Protein (g)
Whole fat milk	119	93	151	*	3.3
Skimmed milk	122	101	156	*	3.4
Swiss cheese	791	567	77	20	26.9
Cheddar cheese	721	512	98	24	24.9
Cream cheese	98	106	138	*	5.9
Yogurt low fat	183	144	234	*	5.3
Ice cream	128	105	199	0	3.5
Wild salmon	9	0	360	600–1000	38
Eggs	56	197	138	20	12.5

Rizzoli R., Bischoff-Ferrari H., Dawson-Hughes B., Weaver C. Nutrition and bone health in women after the menopause. Women's Health (Lond. Engl.) 2014;10:599–608. doi: 10.2217/WHE.14.40

Calcium and osteoporosis controversy

NHANES III population-based**: No correlation between calcium intake and BMD at** the hip site, and the correlation was more applicable for subjects with higher levels of 25(OH)D

Women's Health Across the Nation (SWAN) recently tried to demonstrate the benefits of dairy intake for bones, but its results were not positive for long-term bone health

1. Role of vitamin D fortification

2. Attention to different ethnicity

3. NO **large randomized clinical** trials evaluating dairy intake over long periods of time are available

Willett W.C., Ludwig D.S. Milk and Health. *N. Engl. J. Med.* 2020;382:644–654. doi: 10.1056/NEJMra1903547

Wallace T.C., Jun S., Zou P., McCabe G.P., Craig B.A., Cauley J.A., Weaver C.M., Bailey R.L. Dairy intake is not associated with improvements in bone mineral density or risk of fractures across the menopause transition: Data from the Study of Women's Health Across the Nation. *Menopause.* 2020

Hip fracture	Duration	Dose
The combination of vitamin D and calcium demonstrated a significantly beneficial effect	Beneficial effect was consistent for 3 years, which underpins a positive structural impact on bone formation	minimum effective dose of calcium is 1200 mg while vitamin D should not be below 800 IU.

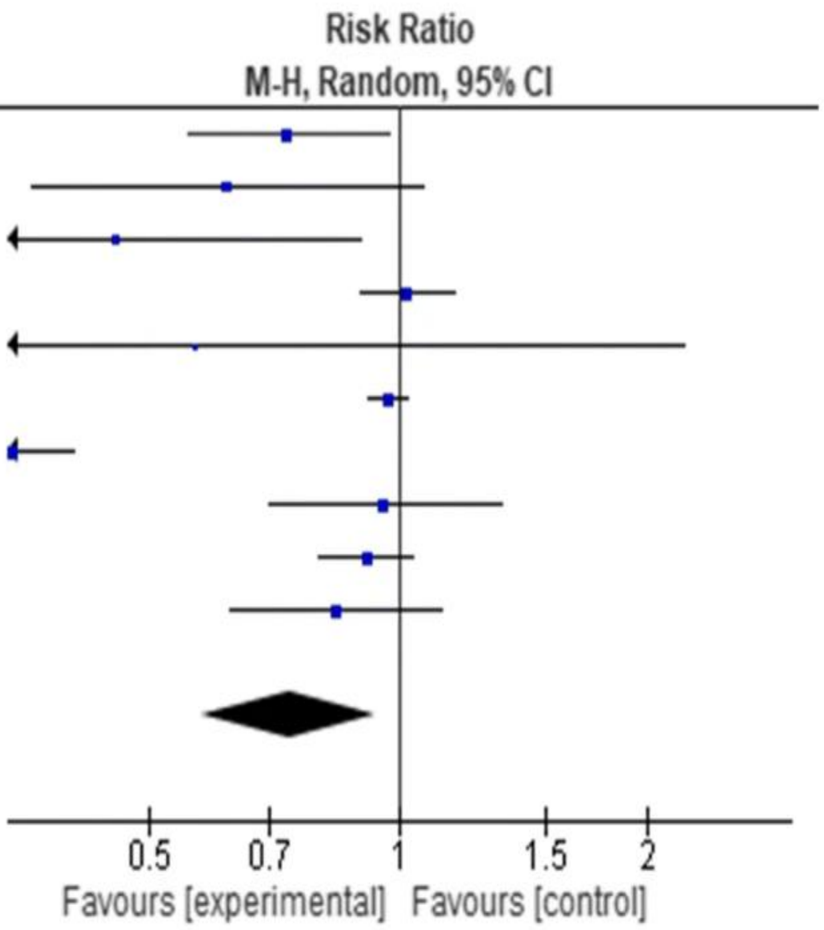
A systematic review and meta-analysis of vitamin D and calcium in preventing osteoporotic fractures,2020

From: A systematic review and meta-analysis of vitamin D and calcium in preventing osteoporotic fractures

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Chapuy et al, 1992 [7]	80	1387	110	1403	11.1%	0.74 [0.56, 0.97]
Chapuy et al, 2002 [16]	27	393	21	190	7.9%	0.62 [0.36, 1.07]
Dawson-Hughes et al, 1997 [21]	11	187	26	202	6.5%	0.46 [0.23, 0.90]
Grant et al, 2005 [8]	387	2649	377	2643	12.6%	1.02 [0.90, 1.17]
Harwood et al, 2004 [19]	3	39	5	37	2.5%	0.57 [0.15, 2.22]
Jackson et al, 2006 [14]	2102	18176	2158	18106	13.0%	0.97 [0.92, 1.03]
Larsen et al, 2004 [18]	217	4957	270	2116	12.3%	0.34 [0.29, 0.41]
Porthouse et al, 2005 [22]	58	1321	91	1993	10.6%	0.96 [0.70, 1.33]
Prentice et al, 2013 [17]	405	7530	458	7801	12.6%	0.92 [0.80, 1.04]
Salovaara et al, 2010 [20]	78	1586	94	1609	11.0%	0.84 [0.63, 1.13]
Total (95% CI)		**38225**		**36100**	**100.0%**	**0.74 [0.58, 0.94]**
Total events	3368		3610			

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 140.55$, df = 9 (P < 0.00001); $I^2 = 94\%$

Test for overall effect: Z = 2.45 (P = 0.01)



Total Fractures (RR RE)

In the women's health initiative trial, a statistically significant increase in urinary and renal tract stones was reported.

Bolland et al. suggested an increase in cardiovascular risk, following use of the combination of calcium and vitamin D

Prentice RL, Pettinger MB, Jackson RD, Wactawski-Wende J, Lacroix AZ, Anderson GL et al (2013) Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporos Int 24(2):567–580
Jenkins DJA ET AL. (2018 Jun 5) Supplemental vitamins and minerals for CVD prevention and treatment. J Am Coll Cardiol

potasium

- **A meta nalysis, Suplementation with alkaline potassium** :

  Reduction in renal calcium excretion and acid excretion. lowered the bone resorption marker cross-linked N-telopeptides of type I collagen (NTX)

Vitamin K

- **Systematic review**:
- Clinical use of oral vitamin K antagonists as part of anticoagulant therapy was neither related to nor reduced BMD, nor was it associated with an increased risk of fracture

Vitamin C

- **Meta-analysis**:
- Strongly reinforces the idea that increasing dietary vitamin C intake could decrease the risk of hip fractures in both males and females

Lambert H., Frassetto L., Moore J.B., Torgerson D., Gannon R., Burckhardt P., Lanham-New S. The effect of supplementation with alkaline potassium salts on bone metabolism: A meta-analysis. Osteoporos. Int. 2015;26:1311–1318. doi: 10.1007/s00198-014-3006-9

. Veronese N., Bano G., Bertozzo G., Granziera S., Solmi M., Manzato E., Sergi G., Cohen A.T., Correll C.U. Vitamin K antagonists' use and fracture risk: Results from a systematic review and meta-analysis. *J. Thromb. Haemost.* 2015;13:1665–1675. doi: 10.1111/jth.13052

Sun Y., Liu C., Bo Y., You J., Zhu Y., Duan D., Cui H., Lu Q. Dietary vitamin C intake and the risk of hip fracture: A dose-response meta-analysis. *Osteoporos. Int.* 2018;29:79–87. doi: 10.1007/s00198-017-4284-9

Vegetarian diets

From: Nutrition and Osteoporosis Prevention

Author, year	Participants	Fracture risk	
		All fractures	Hip fracture
Ignacel, 2019 [58]	4 combined studies		
	Vegans (*n* = 5,690) vs regular meat eaters (*n* = 37,173)	RR: 1.44 (1.05–1.98)	NA
	5 combined studies		
	Vegetarians (*n* = 23,645) vs regular meat eaters (*n* = 42,658)	RR: 1.25 (0.92–1.71)	NA
Key, 2022 [61]	EPIC-Oxford (*n* = 65,000) + Oxford Vegetarian study (*n* = 11,000) men and women		
	Vegans vs regular meat eaters	HR: 1.50 (1.26–1.78); 1.43#	HR: 2.64 (1.90–3.67); 2.31#
	Vegetarians vs regular meat eaters	HR: 1.11 (1.02–1.21); 1.09#	HR: 1.34 (1.12–1.61); 1.25#
Webster, 2022 [59]	UK Women's Cohort study (*n* = 26,318, 822 hip fractures)		
	Vegetarians (*n* = 4,393) vs regular meat eaters (*n* = 13,984)	NA	*HR: 1.33 (1.03–1.71)
Webster, 2023 [60]	Middle-aged UK Men and Women		
	Vegetarians (*n* = 7,638) vs regular meat eaters (*n* = 258,765)	NA	*HR: 1.50 (1.18–1.91)

RR Relative risk (95% CI); *HR* Hazard ratio (95% CI); *NA* Not available; # Adjusted for BMI; *Multivariable-adjusted HR

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Thank you

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