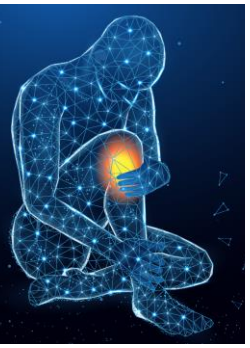
Pharma Nord Academy

Musculoskeletal Health

How nutrition holds the key



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Today's Speaker

Lorraine Nicolle

MSc (Nutr.), PGCHE, BA (hons), Dip. CIM, Dip. BCNH

- Registered Nutritionist (MBANT)
- Registered Nutritional Therapist (CNHC)
- Functional Medicine and Healthy Ageing Specialist
- In clinical practice for 20 years
- Higher education teacher (nutrition science & practice)
- Author/editor of several nutrition books
- Accredited clinical supervisor and mentor for nutrition practitioners

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Learning outcomes for today

1. Review the **musculoskeletal system** (anatomy + physiology)
2. Identify the **underlying drivers** of **musculoskeletal problems**
3. **Intervene nutritionally** in **musculoskeletal conditions**: diet and supplements

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Why is **musculoskeletal health** important?

- In England and Wales, more than 2 million women have **osteoporosis**
- **Joint hypermobility** is estimated to affect approx 10% of the UK population
- In the UK, US, and Europe, the total prevalence of **restless legs syndrome** (RLS) is between 5–10%.
- Estimated that 8.75 million people aged over 45 years in the UK have sought treatment for **osteoarthritis**
- **Rheumatoid arthritis** (RA) is about 1% of the UK population - the most common inflammatory arthritis.

https://cks.nice.org.uk/topics/osteoporosis-prevention-of-fragility-fractures/background-information/prevalence/
Demmler JC, et al. Diagnosed prevalence of Ehlers-Danlos syndrome and hypermobility spectrum disorder in Wales, UK: a national electronic cohort study and case–control comparison. BMJ Open. 2019;9(11):e033365. Published 2019 Nov 4
https://cks.nice.org.uk/topics/restless-legs-syndrome/background-information/prevalence/
https://cks.nice.org.uk/topics/osteoarthritis/background-information/prevalence/
https://cks.nice.org.uk/topics/rheumatoid-arthritis/background-information/prevalence-incidence/

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The musculoskeletal system

A recap

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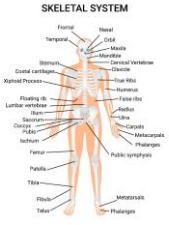
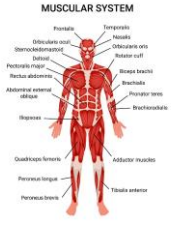
A **complex structure** comprising muscles, bones and connective tissues

Together, they work to provide **a framework and structure** that provides functionality for **stability and movement**.





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Collagen is the primary building block of the M/S system

It provides **structure** to bone, muscle and connective tissues (tendons and ligaments).

- There are numerous **collagen categories** based on their structure and where they're predominantly found *(see image)*

Collagen accounts for approximately **30% of the body's protein**

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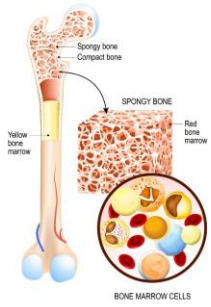

Bone tissue is a **mineralised bone matrix** containing **type 1 collagen**

The two major bone layers are:

- **Compact (cortical) bone** – dense, solid outer layer
- **Spongy (cancellous) bone** – vascular, more metabolically active
  - Houses *bone marrow*

Jagannathan-Bogdan M, Zon LI. Hematopoiesis. *Development*. 2013;140(12):2463-2467. doi:10.1242/dev.083147

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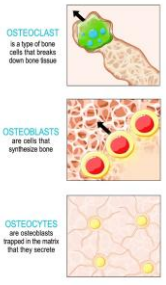
Specialised cells are involved in **bone remodelling**

The continual synthesis and destruction of bone required for **bone growth, maintenance and calcium homeostasis**. These cells include:

- **Osteoblasts** – bone building
- **Osteoclasts** – bone destroying/resorbing
- **Osteocytes** - multiple functions including orchestrating bone remodelling though cell signalling



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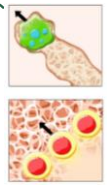
Osteoclasts and osteoblasts come from **different lineages**

Osteoclasts

are differentiated from **haemopoietic stem cells** (HSCs) → immune cells (monocytes/macrophages and dendritic cells)

Stimulated by RANK ligand (more later) i.e., *inflammation*



Osteoblasts

are differentiated from **mesenchymal stem cells** (MSCs)

- MSCs can also differentiate into adipocytes (or chondrocytes or myocytes)
- Physical exercise (and oestrogen) stimulate MSCs to differentiate into osteoblasts at the expense of adipocytes
- Mature osteoblasts can differentiate into bone lining cells (BLC) or osteocytes (Ocy).

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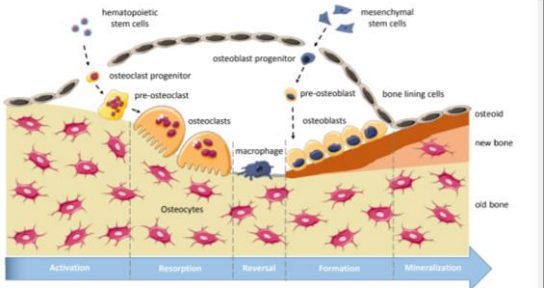
5 stages of bone remodelling



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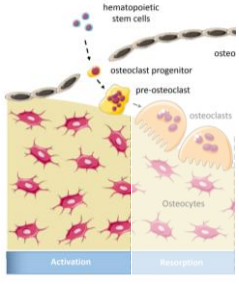
1. **Activation**

- Osteoclast **precursor cells** are recruited from the **circulation**
- Many of these bind to the bone matrix to form **'sealing zones'** around bone-resorbing compartments.
  - This ensures remodelling only takes place in required areas.



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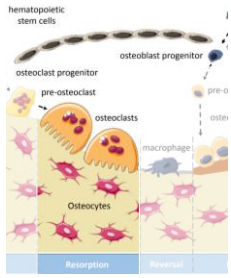
2. **Resorption**

Is triggered by **RANKL** (*see later*)

- Lasts for **approximately 2 weeks.**
- **Activated osteoclasts** pump protons (generated by carbonic anhydrase II) into the compartment which dissolves the bone mineral.
- The collagen rich bone matrix is degraded by protease enzymes such as matrix metalloproteinases and cathepsin K

This phase is terminated by osteoclast's programmed cell death preventing excess resorption



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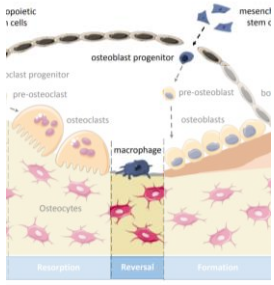
3. **Reversal**

- **Four to five weeks** in duration
- Named **'reversal'** because resorption switches to formation.
- Bone surface is prepared by **macrophages** who **remove unmineralized collagen matrix** (to enhance osteoblastic adherence)



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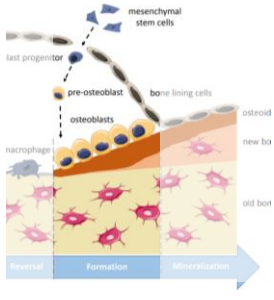
4. **Formation**

- Approx **four months** in duration
- Osteoblasts (differentiated from mesenchymal stem cells) synthesize and secrete collagen rich osteoid matrix (a gelatinous collagen + mucopolysaccharide matrix)



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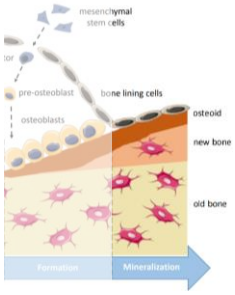
5. **Mineralisation**

Osteoblasts bond minerals to the matrix. Afterwards, they either:

- Undergo **apoptosis**, becoming **bone lining cells**
- Become **entombed** within the bone matrix and differentiate further into **osteocytes** (which signal **the end of remodelling** via secretion of antagonists to osteogenesis),
  - Such as **sclerostin**



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Cartilage is a flexible connective tissue

Cartilage categories include:

- **Hyaline cartilage** – Type II collagen, found in joints, nose, trachea and ribs
- **Elastic cartilage** – More elastic than hyaline, found in the ear and epiglottis
- **Fibrocartilage** – More type I collagen, found in intervertebral discs
- **Articular cartilage** – lines the surfaces of bones

Cartilage is primarily composed of:

- Collagen fibres
- Proteins (Proteoglycans)
- Elastin fibres
- Chondrocytes (specialised cells)

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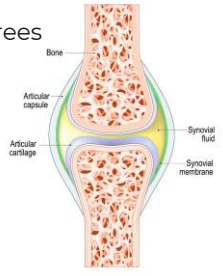
Joints **connect bones together** with varying degrees of movement

Categories of joint **include:**

- **Fibrous joints** (bones connected by dense fibrous connective tissue allowing **minimal movement**, such as in cranial sutures)
- **Cartilaginous joints** with **slightly more** movement than fibrous (i.e., costochondral joints in the sternum)
- **Synovial joints –** freely mobile joints. Bones are not in contact but separated by the synovial capsule, a cavity and a membrane which secretes lubricating **synovial fluid.** (knee, shoulder, elbows)



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Types of **synovial joints**

According to movements they allow, the synovial joints are further subdivided into:

Hinge joints
(e.g. elbow joint)

Condylar (ellipsoid) joints
(e.g. knee joint, 2nd – 5th metacarpophalangeal joints)

Saddle joint
(e.g., carpometacarpal joint of thumb)

Plane joints
(e.g. joints between the carpal bones)

Pivot joints
(e.g. proximal and distal radioulnar joints)

Ball and socket joints
(e.g., hip joint)

Jurgen P, Munjal A, Hubbard JB. Anatomy, Joints. [Updated 2023 Apr 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513293/

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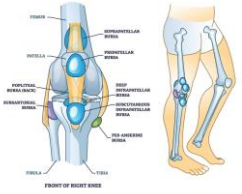
Joints also have **bursae** for additional cushioning

Lined by a synovial membrane, **bursae** are small sacks that **reduce friction between bones, muscles and tendons** by allowing them to slide over each other

Most bursae can be found near large joints of legs and arms



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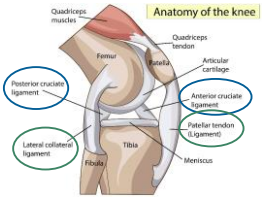
Ligaments are bands of connective tissue that help connect bones to bones

Categories include:

- **Capsular** – thickening of the joint capsule
- **Intracapsular** – reinforce the joint from within; and allow a great range of motion. (Posterior and cruciate ligaments)
- **Extracapsular** – provides the most stability, found on the outside of joint. (Patellar, lateral collateral on outside of knee)



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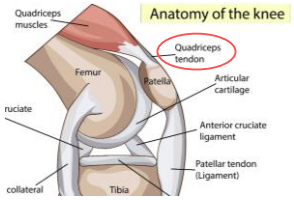
Tendons are bands of connective tissue that attach bone to skeletal muscles

- They are strong and flexible
- They bind muscle to bone and when **skeletal muscle** contracts, tendons pull the bones, **causing movement**



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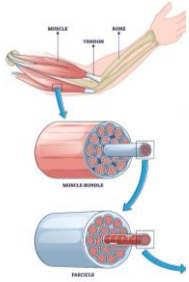
Skeletal muscle structure

Muscles must be able to **contract and stretch without tearing**

- They are comprised of muscle bundles (**fascicles**) enclosed by connective tissue (epimysium)
- Each fascicle is a collection of muscle fibres (aka myocytes / myofibrils) which are elongated, cylindrical cells



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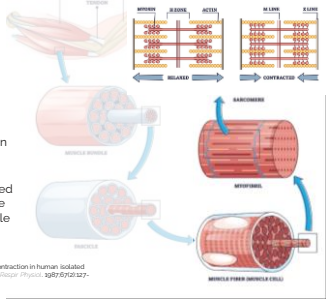
A breakdown of **skeletal muscle** structure

Muscle cells/myofibrils are divided into units called **sarcomeres**, which contain the proteins actin and myosin to facilitate contraction

In response to **acetylcholine** released from nerve endings, calcium ions are released which causes the contractile proteins to rearrange, causing **contraction.**



Marthan R, Savineau JP, Mironneau J. Acetylcholine-induced contraction in human isolated bronchial smooth muscle: role of an intracellular calcium store. *Naspr Physiol*. 1987;67(2):127-135. doi:10.1016/0034-5687(87)90035-1

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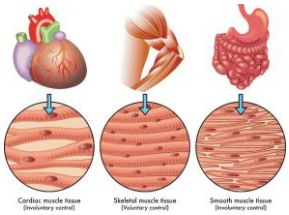
Skeletal muscles are the main functional unit of a broader **muscular system**

There are **over 600 muscles** in the human body, all of which are either:

- **Striated** (skeletal)
- **Cardiac:** the muscular layer of the heart (myocardium)
- **Smooth:** comprises the walls of blood vessels and hollow organs



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Conditions that we will be covering today

- Osteopenia / osteoporosis
- Tissue healing (injury and surgical recovery)
- Hypermobility syndromes
- Restless leg syndrome
- Osteoarthritis
- Autoimmune arthritis (e.g., RA)
- Gout
- Chronic backache

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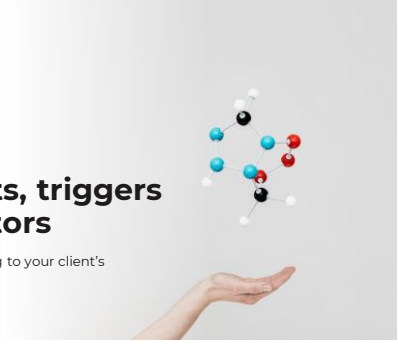
Underlying antecedents, triggers and mediators

These may be contributing to your client's musculoskeletal condition



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Underlying triggers and imbalances to ***consider*** for every patient presenting with a M/S condition

- Structural issues / poor alignment (referral to osteopath / chiropractor)
- Chronic systemic inflammation
- Cardiometabolic disruption (blood glucose/insulin, blood fats)
- Functional gut issues
- Infection (viral / parasitic / mycotoxin)
- Molecular mimicry (and related processes)
- Catabolic state
- Oestrogen disruption (menopause / aromatase inhibitor drugs)
- Oxidative stress and mitochondrial dysfunction
- Poor gamma carboxylation
- Hyperhomocysteinaemia

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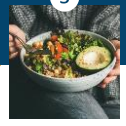
It's a **logical process**

Identify the triggers (both endogenous and environmental) that started the symptoms

Identify the underlying biological imbalances that are driving the symptoms to keep getting worse



Put in diet, lifestyle and supplement interventions to specifically address the underlying factors you've identified

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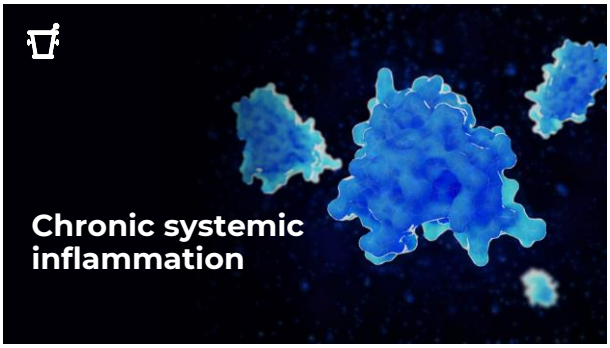

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Inflammation starts with **NF-kB**

- Splits from its inhibitor (IkB)
- Moves from cytosol to nucleus
- Transcribes genes that code for inflammatory proteins (cytokines, eicosanoids, etc)

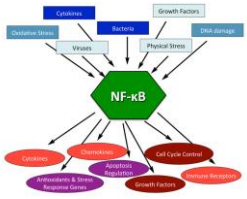

Image: Weizzman Inst Science 2019

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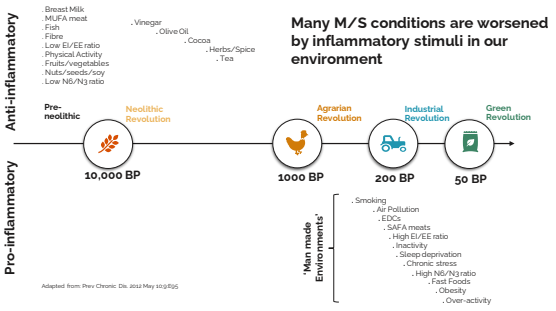
Many M/S conditions are worsened by inflammatory stimuli in our environment



Adapted from: Prev Chronic Dis. 2012 May 10;9:E95

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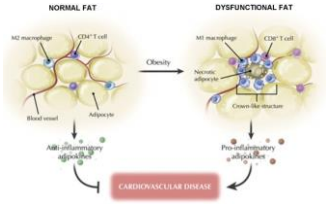
Obesity → chronic inflammation



Nakamura K, Fuster JJ, Walsh K. Adipokines: a link between obesity and cardiovascular disease. J Cardiol. 2014 Apr;63(4):250-9)

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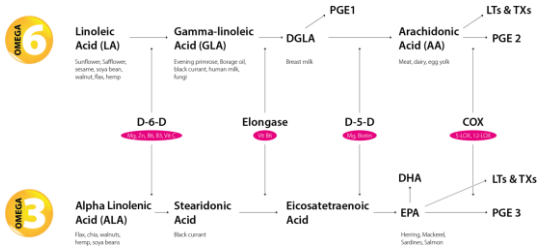
Eicosanoid imbalances can drive M/S inflammation



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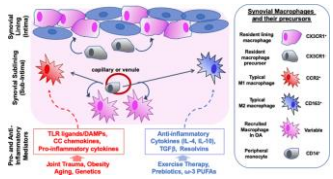
***All* arthritis** is **inflammatory** – *not just autoimmune arthritis*

- We used to think *osteo*-**arthritis** was driven by 'wear and 'tear' and that the inflammation came later
- But now OA has been found to be *driven* **by inflammation** early on…
- …especially from innate IS: macrophages driving synovial inflammation, → the cartilage and bone changes found in OA



Griffin TM, Scanzello CR. Innate inflammation and synovial macrophages in osteoarthritis pathophysiology. Clin Exp Rheumatol. 2019 Sep-Oct;37 Suppl 120(5):57-63

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Inflammation is also the strongest driver of bone loss in **osteoporosis/osteopenia**

- Occurs via the **RANK / RANKL system**
- **Inflammatory triggers** cause osteoblasts (and T cells) to **secrete RANKL**
- RANKL binds to RANK on osteoclast precursors
- This tells **NF-κB** to translocate to the nucleus
- Here, NF-κB turns on genes that instruct bone to **make more osteoclasts**

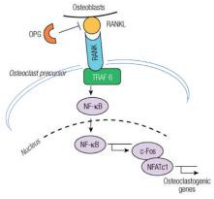

Image from: https://www.researchgate.net/figure/The-RANK-RANKL-system-RANKL-produced-by-osteoblasts-binds-to-RANK-on-the-surface-of_fig2_279828512

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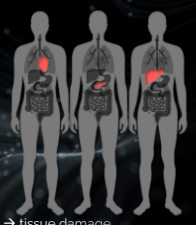
Cardiometabolic disruption



Blood glucose / insulin; blood fats

- Insulin resistance → hyperglycaemia → glycation → tissue damage
- Insulin resistance → hyperinsulinaemia → inflammation
- Hypercholesterolaemia → tendon issues

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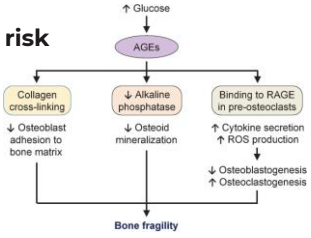
Both **types 1 and 2 diabetes** are associated with **increased fracture risk**

In type 1:

- insufficient anabolic tone from insulin → low BMD

In type 2 *(see graphic)*:

- hyperglycaemia → AGEs → glycation of type 1 collagen in bone → poor bone quality *independent of bone density*



Diabetes Ther. 2021 Jan;12(1):71-86. Clin Calcium. 2016 Jan;26(1):29-41

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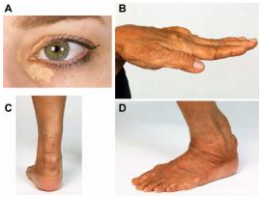
Cardiometabolic issues are associated with **elevated LDL-c (and ApoB)**

Familial hypercholesterolaemia

- prevalence estimated at 1 in 200-250 individuals
- Key clinical sign = **tendon xanthomas**
- extensor (B) and /or Achilles (C, D)



Zubielienė K, Valteryté G, Jonaitienė N, et al. Familial Hypercholesterolemia and Its Current Diagnostics and Treatment Possibilities: A Literature Analysis. Medicina (Kaunas). 2022 Nov 17;58(11):1655. Image: Bell DA, Hooper AJ, Watts GF, Burnett JR. Mipomersen and other therapies for the treatment of severe familial hypercholesterolemia. Vasc Health Risk Manag. 2012;8:651-9

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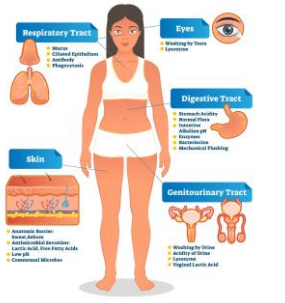
Functional Gut Issues

(But don't forget the other functional barriers throughout the body and brain)



41

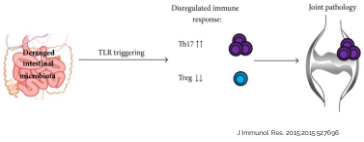
GI problems cause loss of immune **tolerance**

Example 1:

Dysbiosis, even of commensal microbes, drives AI arthritis by promoting Th17 and suppressing Treg cells

Example 2:

molecular mimicry far more like to occur where **gut is leaky** as this allows peptides to reach the underlying GALT and thus trigger inflammatory differentiation of T Cells



J Immunol Res. 2015;2015:527698

Intervention:
support functional GI health

42

Interventions for **intestinal dysbiosis** and **'leaky gut'**

Are the links real?

- Very well discussed in the scientific literature in recent years
- **A 2021 review proposes:**

'The increase in epithelial barrier-damaging agents linked to **industrialization, urbanization and modern life** underlies the rise in allergic, autoimmune and other chronic conditions'

Gut barrier integrity requires:

- Avoidance of NSAIDs, alcohol, gluten
- Anti-inflammatory diet, stress management
- Zinc, folate, vit C, protein (glutamine)

Microbiome balance requires:

- Avoidance of Abx and PPIs unless vital
- Wide variety of plant foods daily

PPI =
Proton pump inhibitors

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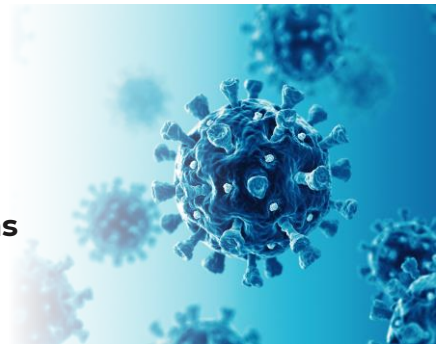
Infections



44

Understanding the Link:
Infections and Musculoskeletal Conditions

Infections as triggers:

- Infections have been found to act as triggers for arthritis, osteomyelitis, and reactive arthritis:
  - Certain microbes can invade M/S tissues, damaging joints and bones.

Infections as mediators:

- Inflammation triggers in response to infections can contribute to the development and progression of existing M/S disorders.

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Common Infections Associated with Musculoskeletal Conditions

Bacterial Infections

Osteomyelitis: Bacterial infection of the bone

Septic Arthritis: (Infectious arthritis) Bacterial infection within a joint

Viral infections

Parvovirus B19: Associated with arthropathy

Hepatitis B and C: Can lead to joint pain, arthritis, and musculoskeletal manifestations.

Fungal infections

Candida albicans: Invasive fungal infection that may affect joints, causing arthritis-like symptoms.

Aspergillosis: Fungal infection that can lead to bone and joint complications

Henry MW, Miller AO, Walsh TJ, Brause BD. Fungal Musculoskeletal Infections. Infect Dis Clin North Am. 2017;31(2):353-368. doi:10.1016/j.idc.2017.01.006

Franssila R, Hedman K. Infection and musculoskeletal conditions: Viral causes of arthritis. Best Pract Res Clin Rheumatol. 2006;20(6):1139-1157. doi:10.1016/j.berh.2006.08.007

Li S, Yu Y, Yue Y, Zhang Z, Su K. Microbial Infection and Rheumatoid Arthritis. J Clin Cell Immunol. 2013;4(5):174. doi:10.4172/2155-9899.1000174

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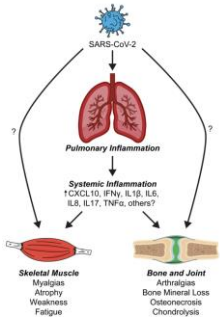
PHARMA NORD ACADEMY

Musculoskeletal Consequences of **COVID-19**

- Myalgias and generalised weakness: occur in up to 50% of symptomatic patients with COVID-19
- The primary respiratory infection → systemic inflammation
- However, it is unknown whether the virus can *directly* infect musculoskeletal tissues



Disser NP, De Micheli AJ, Schonk MM, et al. Musculoskeletal Consequences of COVID-19. *J Bone Joint Surg Am*. 2020;102(14):1197-1204. doi:10.2106/JBJS.20.00847

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Molecular mimicry and related mechanisms

A driver to consider in all autoimmune M/S conditions

Can be more likely with loss of barrier function

So what are these mechanisms?

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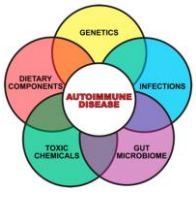
PHARMA NORD ACADEMY

Self-tissue attacking mechanisms

that are triggered by the interaction of the *exposome* with the individual's internal terrain



Vojdani A, Vojdani E. The Role of Exposomes in the Pathophysiology of Autoimmune Diseases I: Toxic Chemicals and Food. Pathophysiology. 2021 Dec 18;28(4):513-543.

Examples:

- *Toxins* can damage self-tissue and cause the release of autoantigens, which can provoke autoimmune response
- *Foods and/or infections* can trigger auto-antibodies via molecular mimicry, in which the food's molecular structure bears a similarity with the structure of one or more self-tissues

Intervention:
detect the trigger, remove it, then repair the damage

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PHARMA NORD ACADEMY

World authorities **warn against toxins**

The US National Institute of Environmental Health Sciences Expert Panel Workshop has concluded that they are 'confident' that:

1) **Crystalline silica** exposure can contribute to the development of several AID
2) **Solvent exposure** can contribute to the development of systemic sclerosis
3) **Smoking** can contribute to the development of seropositive rheumatoid arthritis
4) **(Conversely, an inverse association** exists between **ultraviolet radiation** exposure and the risk of development of multiple sclerosis)

J Autoimmun. 2012 Dec;39(4):259-71

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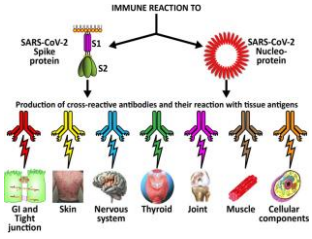
PHARMA NORD ACADEMY

E.g. of **Molecular Mimicry:**

Human Tissues Found to Cross-React with Antibodies Produced to SARS-CoV-2 Infection

- The viral infection stimulates antibodies that may also react against self-tissues because the strings of amino acids (the epitopes) in the virus and the self-tissue are so similar to each other
- Cumulative effect of infections throughout life is more AID-inducing than a single infection



Front Immunol. 2021 Jan 19;11:617089

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PHARMA NORD ACADEMY

Example: **Rheumatoid Arthritis**

Microbes	Clinical association	Animal study	Arthritogenic mechanism
Porphyromonas	Clinical association between RA and periodontitis [6–10]. Presence of *P. gingivalis* DNA in RA patients [17]. Immune responses to *P. gingivalis* in RA patients [34,35]. Increased anti-*P. gingivalis* antibodies in subjects with high risk of RA [36].	Immunization with *P. gingivalis* or *P. gingivalis* enolase induced or exacerbated arthritis [47–49]. *P. gingivalis* facilitated destructive arthritis in CIA mice dependent on its peptidylarginine deiminase [51].	Neo-antigen generation [62]. Molecular mimicry [69]. Bystander activation [47,49]. Direct joint damage [88].
Proteus	Clinical association between RA and urinary tract infection [11]. Immune responses to *P. mirabilis* in RA patients [30–33].		Molecular mimicry [33].
EBV	Clinical association between RA and EBV infection [24]. Presence of EBV DNA and protein in RA patients [21,22]. Immune responses to EBV in RA patients [37,41–43].	EBV induced arthritis in humanized mice [55,56].	Molecular mimicry [70,89]. Superantigen [43,82,83].
Mycoplasma	Presence of DNA [18,19] and glycoglycerophospholipids (GGPL) [29] in RA patients. Immune responses to mycoplasma in RA patients [39,40].	Immunization with mycoplasma arthritidis induced or exacerbated arthritis [46,50,84].	Superantigen [40,50]. Bystander activation [29].

Li S, Yu Y, Yue Y, Zhang Z, Su K. Microbial Infection and Rheumatoid Arthritis. J Clin Cell Immunol. 2013;4(1):174. doi:10.4172/2155-9899.1000174

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Catabolic states

Some key things to remember for M/S health:

- Being **underweight** is linked to **more muscle and bone loss**
- **Hyperactive HPA** function is **catabolic**
- **Hyperactive thyroid** function speeds up metabolism and M/S tissue **catabolism**
- Bones, muscles, tendons and ligaments are made of protein (collagen, osteocalcin, etc)
  - Thus **calorie restriction** and/or **low protein** intake linked to muscle and bone loss

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PHARMA NORD ACADEMY

How **HPA axis** imbalances → **poor M/S health**

- **Long-term elevated cortisol** (hyperactive HPA response) is **catabolic** to muscles, tendons, ligaments and bone
- Conversely, **supressed cortisol** takes the break off **inflammatory processes**
- **DHEA** is the main source of oestrogen post-menopause (converted locally within bone via aromatase)
  - Studies demonstrate a significant association between **DHEA and increased bone mineral density**
  - **DHEA also increases osteoblast activity** and insulin like growth factor 1 (IGF-1) expression for M/S repair

Arch Osteoporos. 2020 Jun 5;15(1):84.

? **DHEA =** Dehydroepiandrosterone

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PHARMA NORD ACADEMY

HPA axis function and **M/S health**

Aim for a **healthy cortisol curve** and **optimal DHEA**

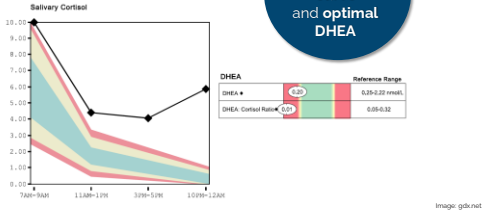

Image: gdx.net

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PHARMA NORD ACADEMY

Calorie restriction is linked to **bone loss**

1. A two-year **RCT** of 218 normal weight adults in their 30s and 40s found that **calorie restriction causes bone loss**
   - CR group practiced 25% reduction in calories vs control
   - Bone loss in the CR group was at all the measured points: lumbar spine, total hip, and femoral neck

2. An earlier RCT of 48 adults reported that participants who **lost weight via CR** also **lost bone mineral density** at common sites of fracture

3. And a more recent review of studies concluded **CR seems to reduce BMD**; and that vegan diets are associated with lower BMD vs. omnivore diets and could, potentially, increase the risk of fractures
   - NB: Bone growth needs IGF-1 from insulin

J Bone Miner Res. 2016 Jan;31(1):40-51. Aging Clin Exp Res. 2019 Jun;31(6):753-758. Arch Intern Med. 2006 Dec 11-25;166(22):2502-10.

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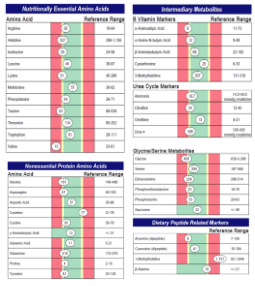
PHARMA NORD ACADEMY

The importance of **protein** for M/S anabolism

- Protein stimulates **IGF-1 for muscles & bones**
- Protein provides **EAAs for collagen**
- Trend towards lower protein diets:
  - Veganism
  - Fasting and/or calorie restriction
  - Fear of mTOR over-expression driving metabolic dxs and cancer
- UK RDA is **0.8g/kg body weight**
  - **Is this optimal?**
- **Urinary amino acids** can indicate protein sufficiency



(Image from GDX.net)

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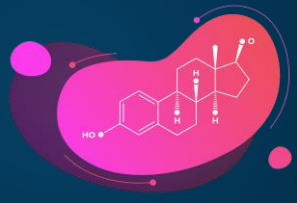
Oestrogen disruption



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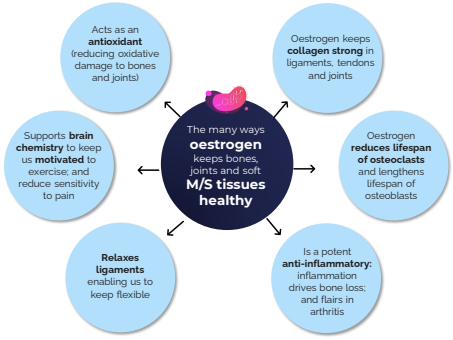

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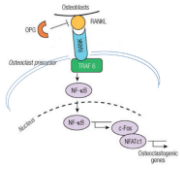
Oestrogen as anti-inflammatory in bone

The **RANKL inflammatory system** (*see earlier*) is triggered during peri-menopause and early menopause because…

- …the sharp drop in oestrogen can **trigger inflammatory cytokines** to rise (TNF-a and IL-6)…
- … → **osteoclast proliferation** (as these are derived from leukocytes)
- And hence also why rheumatoid arthritis is a big risk factor for bone loss



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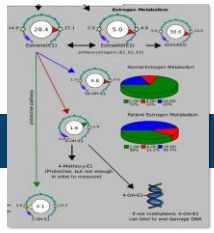
The role of **phase 1 oestrogen *metabolites*** in bone health



- **Studies report:** women with predominant estrogen metabolism through the 2-OH pathway (sometimes termed 'inactive') have lower BMD vs. those with predominant 16a-OH ('active')
- Also, women with a family history of osteoporosis have predominant 2-OH metabolism
- *'Thus, the increased risk of osteoporosis in those with family history may in part be related to inherited differences in estrogen metabolism'*
- Animal studies have shown higher levels of 2-OH oestrogen to reduce the proliferative effects of oestrogen in osteoblasts

J Clin Endocrinol Metab. 2005 Apr;90(4):2035-41. Adv Clin Chem. 2007;43:211-27. J Endocrinol Invest. 2016 Oct;39(10):1149-58.

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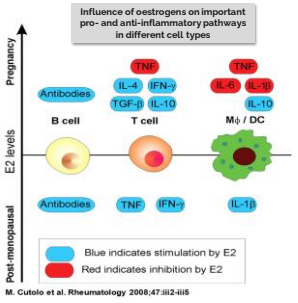
PHARMA NORD ACADEMY

In overt **inflammatory conditions** (e.g. arthritis)

Oestrogen levels strongly influence pro- and anti-inflammatory pathways in different cell types

RHEUMATOLOGY



M. Cutolo et al. Rheumatology 2008;47:iii2-iii5

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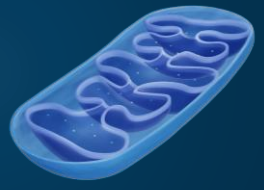
Oxidative stress and **mitochondrial dysfunction**



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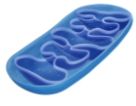
PHARMA NORD ACADEMY

Mitochondrial dysfunction is found in almost all M/S conditions

Mito dysfunction → excessive release of **mtROS** → oxidative stress that leads to **inflammation and catabolism** within the M/S system

- A **review of 36 studies** reported a significant elevation in levels of some markers of oxidative stress, and a reduction in some markers of antioxidant power, in women with postmenopausal **osteoporosis** *vs.* controls
- **Osteoarthritis** is partly driven by mitochondrial dysfunction that then fails to control excessive apoptosis of chondrocytes → tissue destruction



Arch Osteoporos. 2021 Jan 5;16(1):4. Liu H, Li Z, Cao Y, Cui Y, Yang X, Meng Z, Wang R. Effect of chondrocyte mitochondrial dysfunction on cartilage degeneration: A possible pathway for osteoarthritis pathology at the subcellular level. Mol Med Rep. 2019 Oct;20(4):3308-3316

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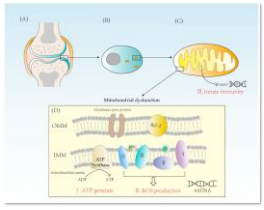
Mito dysfunction → RA

Mito function = essential for the normal survival of chondrocytes and synovial cells

RA: excessive proliferation of synovial and inflammatory cells → cartilage destruction

Driven by mito dysfunction in 4 ways:

1. Disruption of energy supply to keep chondrocytes healthy and functional
2. Increased mtROS that damage chondrocytes
3. Damaged mito fail to control apoptosis of synovial cells
4. Damaged mito release DAMPS that trigger innate immune response

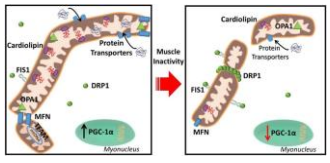


Ma C, Wang J, Hong F, Yang S. Mitochondrial Dysfunction in Rheumatoid Arthritis. Biomolecules. 2022 Sep 12;9(1):216

65

In prolonged muscle inactivity, mitochondrial dysfunction ***is a requirement*** *for* muscle atrophy

- In inactive states, mito demonstrate increased fission, decreased mitochondrial protein import, and decreased cardiolipin
- This then activates proteolytic signalling, causing more muscle wasting/damage
- (PGC-1a – stimulated in exercise - optimises mito biogenesis and mitophagy, fusion and fission)



Hyatt H, Deminice R, Yoshihara T, Powers SK. Mitochondrial dysfunction induces muscle atrophy during prolonged inactivity: A review of the causes and effects. Arch Biochem Biophys. 2019 Feb 15;662:49-60.

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These processes happen when the **mitochondria sense danger**

Because mito control ATP synthesis and inflammation/innate immunity, they decide whether the cell should focus on 'peacetime' metabolism, or, instead **cellular defence**

- Mito can't do both roles simultaneously
- It's either ATP production, or defence mode (termed **'cell danger response - CDR'** by Naviaux)

Purpose of CDR:
to protect cells from damage

E.g. in infection, to prevent microbes replicating by using mito ATP

- **CDR** manifests as **fatigue**, due to ↓ATP and ↑ immune response/inflammation/oxidation
- Hence during infection we feel **physically and mentally fatigued**
- Body normally gets itself out of CDR but can get stuck in CDR mode in situations of chronic stress/infection

Naviaux RK. Incomplete Healing as a Cause of Aging: The Role of Mitochondria and the Cell Danger Response. Biology (Basel). 2019 May 11;8(2):17

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There is evidence that any of these **lifestyle practices** can trigger CDR

- **Calorie** excess
- **Sedentary** living
- High **starch / sugar / fructose** diet
- Excess **alcohol**
- **Trans/oxidised** fats
- **Smoking**
- Excess time in **traffic / environmental** toxins
- Advanced **glycation** end products in foods or endogenous
- **Polypharmacy** (esp. statins, metformin, certain antibiotics)
- **Poor sleep** / night shifts

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Poor gamma carboxylation

The introduction of a **carboxyl group (-COOH)** or **carbon dioxide (CO_2)** into a specific position (the third position from a designated carbon atom) within a compound or molecule

The key way that the body gets calcium to behave properly

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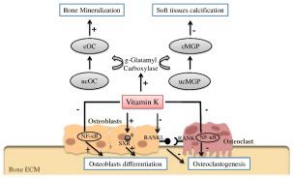
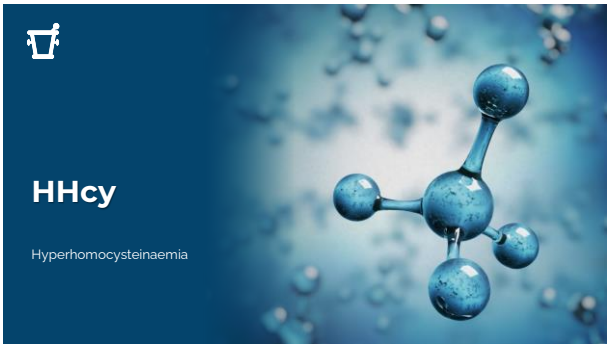
How **gamma carboxylation** helps bone

- Converts the bone protein **osteocalcin to its active form** (by carboxylating OC's glutamic acid residues) → osteocalcin binds to Ca and holds it in place within bone
  - Osteocalcin is the most abundant bone protein after collagen
- Enables the arterial protein **'matrix GLA protein'** to reject Ca and keep it out of arteries, inhibiting vascular calcification
- Thus it directs Ca towards mineralizing bone & away from calcifying soft tissue
- **The limiting factor is lack of vitamin K2** (*see later*)



Metabolism. 2017 May;70:57-71.

70



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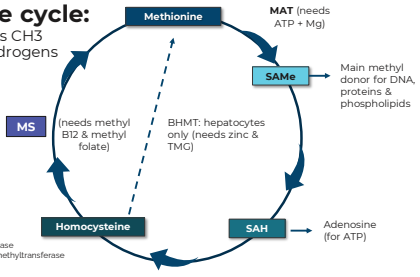
Methionine cycle:

A methyl group is CH3
= 1 carbon + 3 hydrogens



MS: Methionine synthase
MAT: methionine adenosyltransferase
BHMT: Betaine-homocysteine S-methyltransferase

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Hyperhomocysteinaemia in M/S conditions

- In a recent study of 1306 postmenopausal women followed for 9.7 years, higher Hcy was associated increased prevalence and/or progression of **osteoarthritis** in the spine
- HHcy can aggravate normal **muscle maintenance and repair**, increasing fibrosis and wasting, due to its tendency to:
  - Increase ROS and inflammation; and compromise methylation and therefore appropriate gene expression
- HHcy is more frequently found in patients with **rheumatoid arthritis** than in the general population and is thought to be one reason that RA patients are at greater risk of stroke
  - Researchers of one study call for folate supplementation in all RA patients

Veeraraki S, Tyagi SC. Defective homocysteine metabolism: potential implications for skeletal muscle malfunction. Int J Mol Sci. 2013 Jul 18;14(7):15074-91. Ghusnek J.

Wierzowiecka M, Niklas K, Niklas A. The importance of homocysteine in the development of cardiovascular complications in patients with rheumatoid arthritis. Reumatologia. 2020;58(5):282-288. Nakano M.

Nakamura Y, Urano T, Miyazaki A, Suzuki T, Watanabe K, Takahashi J, Shiraki M. Associations of Homocysteine Metabolism With the Risk of Spinal Osteoarthritis Progression in Postmenopausal Women. J Clin Endocrinol Metab. 2021 Nov 19;106(12):3418-3428.

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Elevated **homocysteine** can → **bone loss**

- Elevated Hcy can accumulate in bone tissue, **disturbing collagen cross-linking** and **stimulating osteoclasts**
- Also disturbs osteoblast function, increases oxidative stress and increases advanced glycation end products
- These mechanisms reduce bone density *and also* bone quality

Curr Osteoporos Rep. 2018 Oct;16(5):554-560. Bone. 2012 Sep;51(3):376-82. Clin Chem Lab Med. 2007;45(12):1621-32.

Meta-analysis and systematic review

Suggested that **HHcy significantly increased the risk of fracture**, and the increase was independent of risk factors

Nine studies covering almost 15,000 participants

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Musculoskeletal conditions

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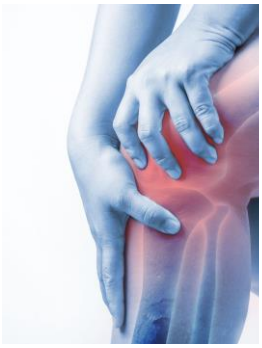
A reminder of the conditions that we will be covering today

- Osteopenia / osteoporosis
- Tissue healing (injury and surgical recovery)
- Hypermobility syndromes
- Restless leg syndrome
- Osteoarthritis
- Autoimmune arthritis (e.g., RA)
- Gout
- Chronic backache



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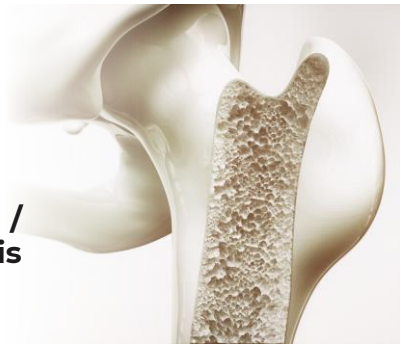
Osteopenia / osteoporosis



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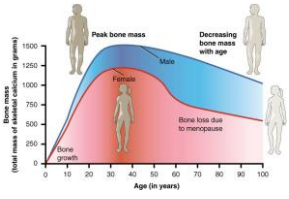
Low bone **density**



- 50% women and 20% men > 50 years old are expected to break a bone
- Diagnosed via a DEXA scan (Dual energy x-ray absorptiometry)
- The 'T score' is given as a standard deviation: the number of units above or below the average BMD of a young and healthy person
  - **Osteopenia -** T score of -1 to -2.5
  - **Osteoporosis -** T score of -2.5 and lower
- 'Z score' is benchmarked against the typical BMD for *age*
- DEXA gives quantity (*vs* quality) measurement only
- Risk of fracture is based not only on BMD, but on the combination of other risk factors, including – see next →

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Acknowledged **risk factors**

- Age
- Female
- Caucasian or Asian
- Smoker
- Alcohol drinker
- Body mass index of <19
- Previous fracture
- Loss of height
- Family history (many genes!)
- Being of a smaller, finer build
- Being prone to falling
- Rheumatoid arthritis
- History of corticosteroids, PPIs, epilepsy medication, aromatase inhibitors, SSRIs, glitazones, antipsychotics
- Coeliac dxs or Crohn's dxs
- History of eating disorders
- Long periods of immobility
- Early menopause / hysterectomy / amenorrhea without HRT
- Hyperthyroidism, parathyroid dxs

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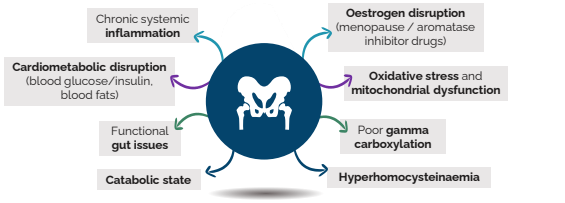
Key underlying drivers
to consider *(described earlier)*



All these have been found in excessive bone loss

80

Nutritional priorities for bone health (1)

- Promote an **anabolic state** (sufficient calories and protein)
- Get **calcium, magnesium and phosphorous**, as these mineralise the bone matrix (to harden and strengthen bone)
- Avoid excessive **mineral binders** in the diet
- Get **vitamins D3 and K2** as cofactors to absorb and direct calcium
- Avoid **inflammatory** foods
- Get **anti-inflammatory fats** and **anti-inflammatory antioxidants**
- Support the **gut microbiome** with plant diversity (inflammation control)

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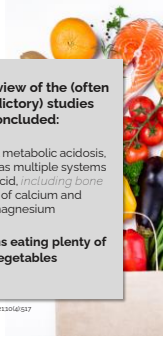
Nutritional priorities for bone health (2)

- **Support blood glucose metabolism** so as not to trigger hypoglycaemic episodes
  - These spike adrenal and cortisol that are catabolic to bone
- **Balance acid-alkaline metabolic load**
  - Bone base helps neutralize some of the dietary net acid load (animal and human studies).



A 2018 review of the (often contradictory) studies concluded:

To prevent metabolic acidosis, the body has multiple systems to buffer acid, *including bone stores* of calcium and magnesium

This means eating plenty of Vegetables

Nutrients. 2018 Apr 21;10(4):513

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Calcium is essential for the normal development and maintenance of bone

If serum Ca is too low, homeostasis is achieved by releasing Ca from the bone reservoir

- A meta-analysis of 8 studies (30,970 participants) showed that **calcium + vitamin D supplementation** produced a **15% reduced risk of total fractures** and a **30% reduced risk of hip fractures**
- Recommended Ca intake is **800-1000mg/day** (**1000mg-1200mg/day for postmenopausal women** with osteoporosis)
- The balance of the evidence is: intake below this amount may increase fragility fracture risk
- Is this possible from diet alone?

Osteoporos Int. 2018 Jan;27(1):367-76.

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Can your client get 1,000mg/day **from diet alone?**

Dairy contains the most Ca

- Best source after dairy is tinned sardines (240mg/Ca per 60g)
- If your client can't tolerate dairy, consider supplementation

FOOD (200 ml)	CALCIUM (mg)
Milk, semi-skimmed	240
Milk, skimmed	244
Milk, whole	236
Milkshake	360
Sheep milk	380
Coco milk	54
Soy drink (non-enriched)	26
Soy drink, calcium-enriched*	240
Rice drink	22
Oat milk	16
Almond milk	90

› Yoghurt

⌄ Cheese

FOOD	SERVING SIZE (g)	CALCIUM (mg)
Hard Cheese (e.g. Cheddar, Parmesan, Emmental, Gruyere)	30	240
Fresh Cheese (e.g. Cottage cheese, Ricotta, Mascarpone)	200	138
Soft Cheese (e.g. Camembert, Brie)	60	240
Feta	60	270
Mozzarella	60	242
Cream Cheese	30	180

Image: International Osteoporosis Foundation)

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Calcium in **plant foods**

Far less in plant foods

- And anti-nutrients that compromise Ca absorption (phytates, oxalates, tannins)
- Thus vegans may be at risk of calcium insufficiency

⌄ Vegetables

FOOD	SERVING SIZE (g)	CALCIUM (mg)
Lettuce	90	19
Kale, Collard greens	50 (raw)	32
Bok Choy / Pak Choi	80 (raw)	20
Broccoli	120 (raw)	112
Gombo/Okra	120 (raw)	77
Cress	120 (raw)	188
Rhubarb	120 (raw)	103
Carrots	120 (raw)	36
Tomatoes	120 (raw)	11

⌄ Nuts & Seeds

FOOD	SERVING SIZE (g)	CALCIUM(mg)
Almonds	30	75
Walnuts	30	28
Hazelnuts	30	56
Brazil Nuts	30	28
Sesame seeds	30	22
Tahini Paste	30	42

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Calcium supplementation, an emotive issue...

- ever since a **2010 meta-analysis concluded caution is needed with Ca supplementation** in the elderly (review found a 30% ↑ed risk of myocardial infarction)
- Since then, results from meta-analyses have been inconsistent...
- ...making some practitioners wary of supplementing Ca for fear of increasing risk of atherosclerosis *(continued next slide)*

BMJ. 2010 Jul 29;341:c3691. EMAS clinical guide. Maturitas. 2018 Jan;107:7-12. Climacteric. 2016 Jun;19(3):303-7.
Nutrients. 2021 Jan 26;13(2):368

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Calcium supplementation, an emotive issue...

But **mechanism studies** have concluded the link between osteoporosis and atherosclerosis is more to do with the common underlying cause being *inflammation* rather than due to calcium supplementation

- And that doses of <2,000mg/day pose no risk
- The most recent review (2021) concluded that *excessive* Ca intake correlated with increased CVD risk
  - But that these studies used calcium dosing *far higher* than the recommended 800-1000mg
  - Approx. 700-1000mg dietary Ca **as well as** approx. 1000mg supplementation
  - Examples on next slide

BMJ. 2010 Jul 29;341:c3691. EMAS clinical guide. Maturitas. 2018 Jan;107:7-12. Climacteric. 2016 Jun;19(3):303-7.
Nutrients. 2021 Jan 26;13(2):368

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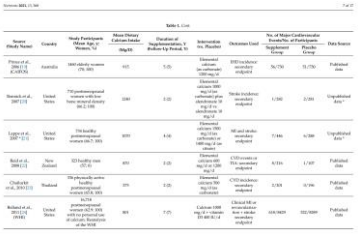
Examples of the studies: dietary + supplemental Ca doses



Nutrients. 2021 Jan 26;13(2):368

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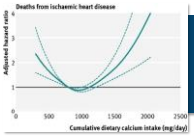
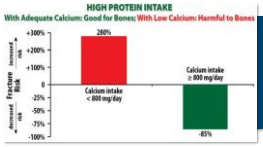
And a **2016 review** concluded calcium is crucial for bones ***and*** CV health



Ca intake for optimal bone and CV health is 1g/day



Animal protein promotes bone strength but only with adequate Ca intake

Open Heart. 2016 Mar 22;3(2):e000395

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Applying this to **clinical practice**

Get *a total* of **800-1000mg/day** elemental Ca

- No more, no less
- This is both necessary for bone, and safe for CV health
- Supplement the minimum needed to get there

Consider ways to **encourage the Ca to behave properly** (go to bone rather than soft tissues like arteries)

- Vitamin K2 (gamma-carboxylation)
- Mg (balances inflammatory effect of unopposed Ca)

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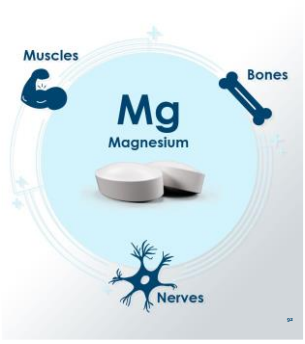
A **handy tool**

A calcium calculator that clients can use to work out how much they are typically getting from their diet:

- https://www.osteoporosis.foundation/educational-hub/topic/calcium-calculator
- Supplement the difference to make the total 1,000mg/d

Magnesium



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Mg in bone health

A major structural component of bone (about 60% of the body's Mg is stored in the bone, another 30% in muscle, less than 1% is extracellular)

- **Observational studies**: low Mg status is a risk factor for osteoporosis; and higher Mg intake is associated with better BMD
- Experimental Mg deficiency in animals causes bone loss, ↓osteoblasts and ↑osteoclasts, ↑ inflammatory cytokines and CRP

Front Med (Lausanne). 2020 Aug 4;7:381. Nutrients. 2013 Jul 31;5(8):3022-33

Mechanisms:

- **Mg taken from bone reservoir** in times of **deficiency**
- Cellular Mg deficit triggers calcium-activated **inflammatory cascades**, even without the presence of typical inflammatory triggers (like injury or pathogens)
- **Mg activates vitamin D** for better calcium absorption

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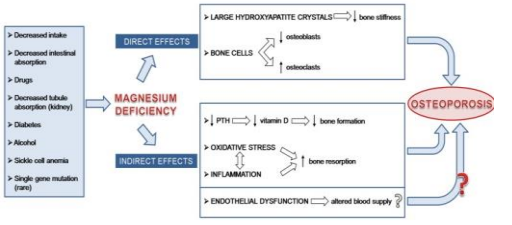
Mg deficiency and osteoporosis:



Nutrients. 2013 Jul 31;5(8):3022-33

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Mg supplementation **studies in osteoporosis**

Some evidence from small-scale studies:

1. A 30 day, open-label, controlled Mg supplementation trial (**1,830mg/day Mg citrate**) showed that **magnesium decreased markers of bone turnover** in post-menopausal women with osteoporosis
2. A 12 months double-blind placebo-controlled study on magnesium supplementation (**300 mg as magnesium oxide**) in children and adolescents with low magnesium intake showed an **increase in bone mineral content**
3. A 2-year open-label trial of 31 post-menopausal women (and 23 controls) were given two to six tablets/day of **125mg Mg hydroxide** for 6 months and two tablets for another 18 months. Reported **significant increases in BMD** vs. controls

Magnes Res. 1993 Jun;6(2):155-63. Biol Trace Elem Res. 2010 Feb;133(2):136-43. J Clin Endocrinol Metab. 2006 Dec;91(12):4855-72.

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Bio-Magnesium formulation

Mg hydroxide & carbonate

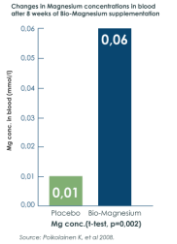
- High elemental mg %

Magnesium acetate

- Organic magnesium
- Ionises other Mg - biologically active mg fraction

Bioavailability evidence

- *Example trial:*
- Participants with low Mg experienced **600% increases** in mg levels after 8 weeks
- 400mg per day (2x200mg)



Paikolainen, K., Alho, H. Magnesium treatment in alcoholics: A randomized clinical trial. Subst Abuse Treat Prev Policy 3, 1 (2008). https://doi.org/10.1186/1747-597X-3-1

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Vitamin D

Contributes to normal immune function, cell division, muscle function and calcium homeostasis

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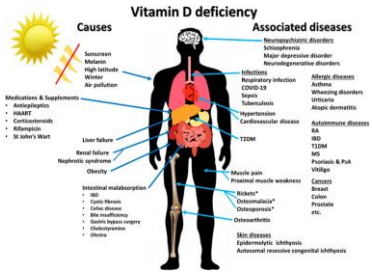
Vitamin D **deficiency**



Nutrients. 2020 Jul 15;12(7):2097.

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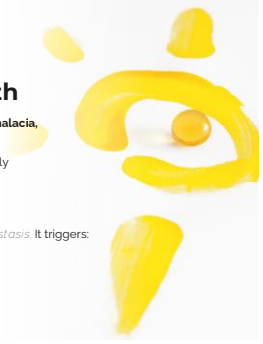
Roles of **vitamin D in bone health**



- Deficiency associated with a risk of **rickets, osteomalacia, osteopenia and osteoporosis**
- Low levels contribute to fractures, esp. in the elderly
- Pleiotropic mechanisms in bone:
- E.g. anti-inflammatory within bone
- But most well-known for its role in *calcium homeostasis*. It triggers:
  - •Ca (and P) absorption in the intestine
  - •Ca reabsorption by the kidneys
  - •Mobilization of Ca from bone

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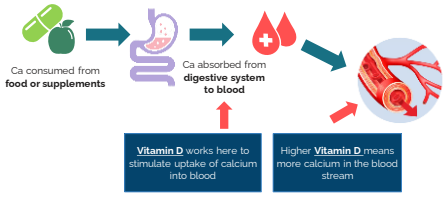
Calcium transport with vitamin D



100

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Hence, for vit D to be *anabolic* to bone, there **must be sufficient Ca *intake***

- In a *negative* **Ca balance**, 1,25(OH)$_2$D triggers **bone** *resorption*
  - via the *direct* mobilization of Ca from bone into the circulation, thus correcting the negative balance
- Conversely, when Ca serum levels are normal, 1,25(OH)$_2$D regulates bone homeostasis *indirectly*
  - By increasing intestinal Ca absorption and renal calcium reabsorption, which maintain normal serum calcium levels
- Thus the **anabolic effects of vit D depend on being calcium-sufficient**
- No point in ingesting vitamin D without getting sufficient Ca
- Vitamin D *toxicity* is mediated through hypercalcaemia (it causes too much bone resorption at too high serum levels)

Biomed Res Int. 2018 May 22;2018:3783580. JAMA Netw Open. 2019 Dec 2;2(12):e1917789. Orthopedic. 2017 Sep;40(5):e725-734.

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D-Pearls – Vitamin D3

- Small, easy to swallow 'pearl' capsules
- Oil-based for optimum absorption
- Featured in clinical trials
- Large range of options:
  - 400 IU
  - 800 IU
  - 1000 IU
  - 1520 IU (**D-Pearls Green** 100% Plant-Based)
  - 3200 IU
  - 5000 IU
  - 20,000 IU (*Practitioner exclusive*)

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Vitamin K2

Contributes to normal blood clotting, vascular health and bone health

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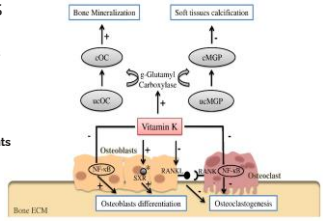
Vitamin K2 works

(As we saw earlier) activating VKDPs (like osteocalcin) via 'gamma carboxylation' to get calcium to behave properly:

1. Gets **Ca to the bones**
2. Keeps **Ca out of arteries + joints**

Vitamin K2 also stimulates the synthesis of osteoblasts…

- … and inhibits osteoclasts



Metabolism. 2017 May;70:57-71.

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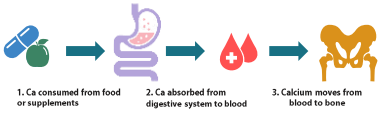
The 'ideal' picture of calcium behaviour in the body



'Expectation'

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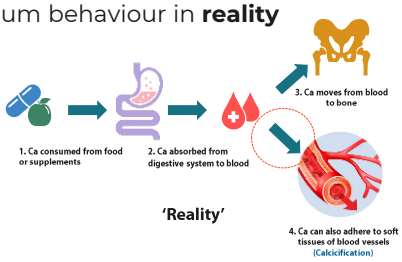
Calcium behaviour in **reality**



'Reality'

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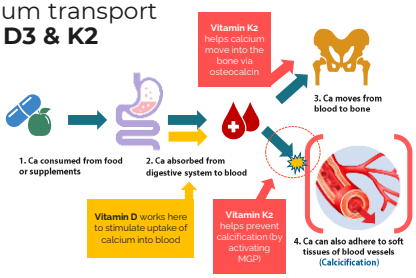
Calcium transport with **D3 & K2**



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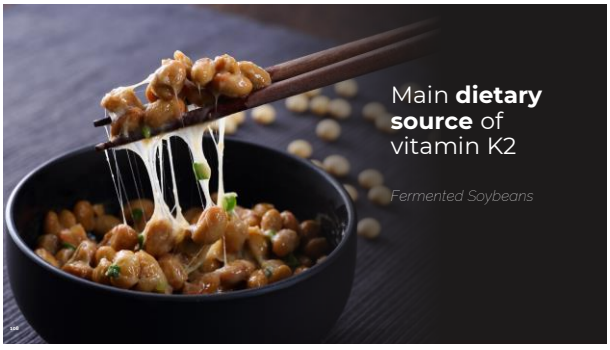

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Food sources of vitamin K2 - 75mcg per day

7kg Beef

8.5 litres or Milk/Yoghurt

14 Egg Yolks

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What the **evidence base** says

1. Activation of osteocalcin may require **vit K at levels 10 X those required for blood clotting** (thus mild insufficiencies common)
2. **Lower vit K intake** is associated with **lower BMD** in women
3. Serum K2 levels are far higher in Eastern Japan, where **natto** is eaten, and this correlates with a **lower rate of hip fracture**
4. Most studies suggest that both **K1 and K2 (MK-7) have a protective effect on bone**
5. Co-supplementation with **calcium** and **vit D** provides better BMD results than vit K alone
6. The evidence for **MK-7 is more useful** because the evidence for MK-4 is at *pharmaceutical* (vs. nutritional) levels

Metabolism. 2017 May;70:57-71. Int J Mol Sci. 2019 Aug 25;20(17):4150

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Practical takeaways for vitamin K

- Shouldn't be difficult to eat sufficient K1 (greens)
- K2 is harder to optimise via diet alone, so could consider supplementing MK-7 at 150-200mcg to replicate the trials for bone health
- Take with fats for optimal absorption – or use an oil-based supplement
- Makes sense to supplement MK-7 if your client is supplementing Ca and/or vitamin D, to optimise the safety and efficacy of the Ca + D
- Ensure the supplement is in the *all-trans* configuration (not cis) as trans is the only biologically active form (that activates OC)

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There are various **forms of vitamin K** with different properties

Vitamin K isoform	Structure	Half-life	Major site of activity	Dietary Sources
Vitamin K1 **(Phylloquinone)**		Approx **3 hours**	Taken up preferentially by the liver	Leafy greens e.g. spinach, kale
Vitamin K2 **(Menaquinone-4)**		Approx **1.5 hours**	Extrahepatic tissues (bones and circulatory system)	Meat and dairy e.g. beef, butter, poultry, soft cheese
Vitamin K2 **(Menaquinone-7)**		Approx **70 hours**	Extrahepatic tissues (bones and circulatory system)	Fermented foods and dairy e.g. natto, hard cheese, sauerkraut

Akbulut AC, Pavlic A, Petsophonsakul P, et al. Vitamin K2 Needs an RDI Separate from Vitamin K1. Nutrients. 2020;12(8):1852. Published 2020 Jun 21. doi:10.3390/nu12061852

Schurgers LJ, Aebert H, Vermeer C, Bultmann B, Janzen J. Oral anticoagulant treatment: friend or foe in cardiovascular disease? Blood. 2004;104(13):3931–3932.

Vitamin K1 has a **short half-life** and is preferentially taken up primarily by the liver, not the extrahepatic tissues

Vitamin K2-MK4 is more likely to circulate and reach the circulatory system and bones, but has a **short half life**

Vitamin K2-MK7 demonstrates the longest half life (due to having the longest chain) and offers the **most consistent carboxylation of K-dependant proteins around the body** due to not being taken up preferentially by the liver

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K-Pearls (Bio-Vitamin K2)

- **Vitamin K2 MK-7**
  - Favoured for higher **bioavailability**
  - Longer-half life, more **carboxylation**
  - Longest isoprenoid (unsaturated hydrocarbon) chain
- **100% active 'trans-isomer'** form
- Derived from flower essential oils (**soy-free**)
- Manufactured under **Danish pharmaceutical control**

Sato T, Schurgers LJ, Uenishi K. Comparison of menaquinone-4 and menaquinone-7 bioavailability in healthy women. Nutr J. 2012;11:93. Published 2012 Nov 12. doi:10.1186/1475-2891-11-93

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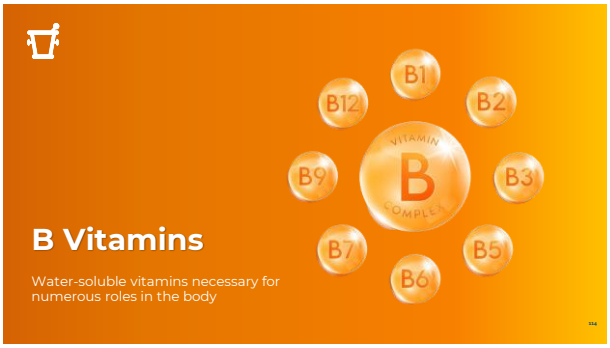

B Vitamins

Water-soluble vitamins necessary for numerous roles in the body

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B vitamin deficiency is bad for bones due to hypermonocysteinemia (HHcy)

A 2022 review of 29 studies reported:

Low serum folate can be a risk factor for reduced BMD and fractures in the elderly, particularly women

- Of the **2 studies on dietary B vit intake**:
  - One (1869 women) showed a positive effect of folate intake on BMD
  - The other (35298 women) demonstrated a dose-dependent inverse relationship between vitamin B6 intake and risk of hip fracture
- Of the **9 studies of B vit supplementation:**
  - All that considered patients with Hhcy or low folate blood levels showed: 'folate supplementation (500mcg- 5mg) is useful in improving BMD'

Conclusion

calls for testing folate and hcy blood levels in elderly patients with osteopenia/osteoporosis to be mandatory;

and supplementation given to those with HHcy and/or low serum folate

Rondanelli M, Tartara A, Fossari F, et al. Adequate Intake and Supplementation of B Vitamins, in Particular Folic Acid, can Play a Protective Role in Bone Health. Curr Aging Sci. 2022;15(2):110-120.

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PHARMA NORD ACADEMY

But: supplementing *high doses* over the ***long-term*** appears to be linked to unwanted bone loss

A prospective cohort study of 75 864 postmenopausal women followed for 20 years, assessed via diet and supplement questionnaires

- Both vitamin B6 (for an intake of ≥35mg/d vs <2 mg/d) and vitamin B12 (for an intake of ≥30 vs <5 µg/d) were associated with increased fracture risk
- Found an almost **50% increased risk of hip fracture** in women with a combined **high intake of both vitamins** (B6 ≥35 mg/d and B12 ≥20 µg/d), compared with women with a low intake of both vitamins (B6 <2 mg/d and B12 <10 µg/d)
  - The RDAs are 1.2mg (B6 for women) and 1.5mcg (B12)
- This was preceded by 2 RCTs that incidentally found higher intakes to correlate with fracture risk

JAMA Netw Open. 2019 May 3;2(5):e193551

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B Vitamins

Bio-B-Complex

A comprehensive B-Complex

- Supports homocysteine metabolism & energy-yielding metabolism
- One-a-day formula
- Suitable for vegetarians & vegans
- Manufactured to pharmaceutical standards

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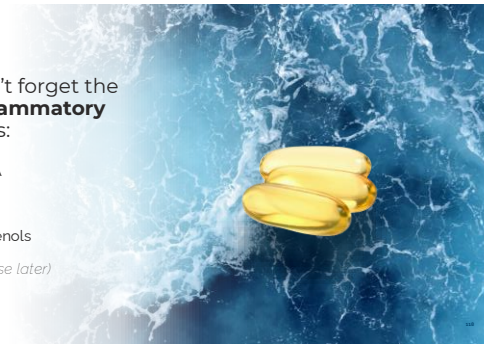
And don't forget the **anti-inflammatory** nutrients:

- EPA/DHA
- Curcumin
- Other phenols

(More on these later)



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Tissue healing

Injury and surgical recovery

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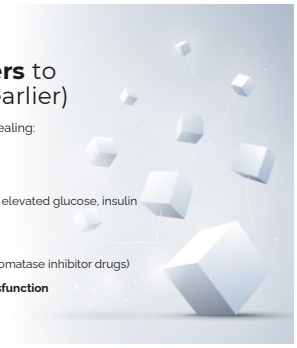

Key **underlying drivers** to consider (described earlier)

Any of these may prevent efficient tissue healing:

- Chronic systemic **inflammation**
- **Immune insufficiency** (infection)
- **Cardiometabolic disruption** (especially elevated glucose, insulin and/or glycation)
- **Catabolic state** (e.g. RED-S)
- **Oestrogen disruption** (menopause / aromatase inhibitor drugs)
- **Oxidative stress** and **mitochondrial dysfunction**

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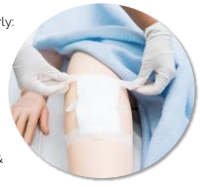
A **holistic approach** to wound healing

Wound healing is **affected by many factors** but particularly:

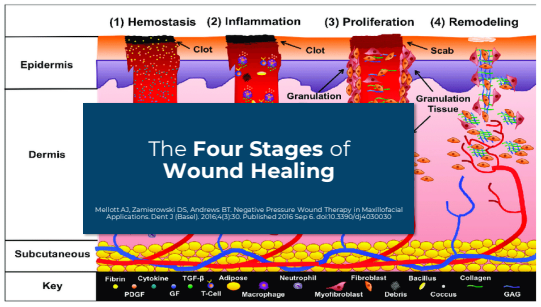
- Wound characteristics
- Infection
- Comorbidities
- Nutritional status of the patient

In addition, **psychological stress & depression** may ↓inflammatory response required for bacterial clearance & so delay wound healing



Adamová Z, Adam Z. Psychological influences on wound healing. Vliv psychiky na hojení ran. Rozhl Chir. 2019;98(8):312-314. doi:10.33699/PIS.2019.98.8.312-314

121



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Haemostasis phase:
lasts from seconds to hours

Main focus is on stopping the flow of blood

Mechanisms:

- Vasoconstriction
- Platelet aggregation
- Leucocyte migration

Nutritional support:

A good general nutritional status is fundamental to this acute phase of skin wounds

e.g. we can support clients before surgery, which is a "planned wound"

Palmieri B, Vadalà M, Laurino C. Nutrition in wound healing: investigation of the molecular mechanisms, a narrative review. J Wound Care. 2019;28(10):683-693. doi:10.12968/jowc.2019.28.10.683

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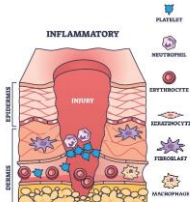
Inflammatory phase:
lasts from hours to days

Pro-inflammatory cytokines such as interleukin (IL)-1α, IL-1β, IL-6, IL-8 & tumor necrosis factor (TNF)-α are crucial during early phases of healing process, & thus for successful resolution of wounds

Their function is to

- Remove damaged tissue
- Limit infection
- Stimulate tissue repair

Adequate wound healing depends on the delicate balance between pro- & anti-inflammatory effects



Meesters A, den Bosch-Meevissen YMCI, Weijzen CAH, et al. The effect of Mindfulness-Based Stress Reduction on wound healing: a preliminary study. J Behav Med. 2018;41(3):385-397. doi:10.1007/s10865-017-9901-8

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Inflammatory phase

Nutritional support for balanced response:

- **Vit A** ↑ cytokine release
- **Vit C** ↑ neutrophil migration & lymphocyte activation

If inflammation is prolonged rule out infection first, then consider:

- **Bromelain** ↓ inflammation & then protein to ↑ tissue repair
- **Fish oils & Vit D**: for anti-inflammatory & immunomodulatory effects
- **Curcumin**: ↓expression of TNF-α & IL-1 & restores the imbalance between ROS production & antioxidant activity

Barchitta M, Maugeri A, Favara G, et al. Nutrition and Wound Healing: An Overview Focusing on the Beneficial Effects of Curcumin. Int J Mol Sci. 2019;20(5):1119. Published 2019 Mar 5. doi:10.3390/ijms20051119

Palmieri B, Vadalà M, Laurino C. Nutrition in wound healing: investigation of the molecular mechanisms, a narrative review. J Wound Care. 2019;28(10):683-693. doi:10.12968/jowc.2019.28.10.683

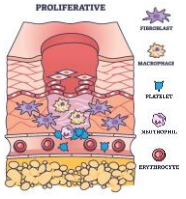
Nouailhetová J, Gál B, Urbánková P, Smíšek P. Can fish oil improve wound healing in surgery?. Vnitr Lek. 2018;64(5):406-412.

PHARMA NORD ACADEMY

Proliferative phase:

lasts from days to 1 or 2 weeks

- Adequate intake of **carbohydrates** to support fibroblast migration
- **Vit A** ↑epithelial cell differentiation
- **Vit C** ↑collagen synthesis
- **Glucosamine** ↑hyaluronic acid production
- **Aloe vera** ↑ the generation of granulation tissue (from the inside of the wound outwards)
- **Curcumin** facilitates collagen synthesis, fibroblast migration & differentiation
- **Zinc** required for DNA & protein synthesis, & cell division (formation of new skin tissue)



Barchitta M, Maugeri A, Favara G, et al. Nutrition and Wound Healing: An Overview Focusing on the Beneficial Effects of Curcumin. Int J Mol Sci. 2019;20(5):1119. Published 2019 Mar 5. doi:10.3390/ijms20051119

Palmieri B, Vadalà M, Laurino C. Nutrition in wound healing: investigation of the molecular mechanisms, a narrative review. J Wound Care. 2019;28(10):683-693. doi:10.12968/jowc.2019.28.10.683

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Remodelling phase:

lasts from 1 or 2 weeks to months

Nutritional considerations

Requirements of chronic wound patients may rise by:

- 250% (protein)
- 50% (energy)

- Amino acids & proteins play a key role in wound scar stabilisation
- Whey protein powders, arginine and/or glutamine show benefit

Thiruvoth FM, Mohapatra DP, Kumar D, Chittoria SRK, Nandhagopal V. Current concepts in the physiology of adult wound healing. Plast Aesthet Res. 2015;2:250-6. http://dx.doi.org/10.4103/2347-9264.158851

PHARMA NORD ACADEMY

Foundational approach: **Supporting blood glucose levels**

It is well documented that **uncontrolled blood glucose** levels (e.g. In diabetes Type 1 & 2 patients) can → further **circulatory damage**, which impedes the wound healing process & often results in chronic wounds that do not heal

- Introduce all that you know about managing blood glucose levels as a foundational approach to wound healing
- see our webinars on this topic in the Webinar recordings section @ www.pharmanord.co.uk/pro

Winterbottom C. Diabetic leg and foot ulcers: how district nurses can promote wound healing through blood glucose control. *Br J Community Nurs.* 2022;27(Sup6):S12-S18. doi:10.12968/bjcn.2022.27.Sup6.S12

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PHARMA NORD ACADEMY

Summary: **nutritional support** for **all phases** of wound healing

Nutritional can be considered as epigenetic signals influencing each of the wound healing steps

Palmieri B, Vadalà M, Laurino C. Nutrition in wound healing: investigation of the molecular mechanisms, a narrative review. *J Wound Care.* 2019;28(10):683-693. doi:10.12968/jowc.2019.28.10.683

- Normalise blood glucose and insulin
- Vits A, B, C, D, E, beta-carotene
- Zinc
- Selenium
- Curcumin
- Iron (if deficient: needed for haemoglobin)
- Ensure adequate hydration (>1.5l fluid/day)
- Increase calorie intake, especially protein *(see previous slide)*

Barchitta M, Maugeri A, Favara G, et al. Nutrition and Wound Healing: An Overview Focusing on the Beneficial Effects of Curcumin. *Int J Mol Sci.* 2019;20(5):1119. Published 2019 Mar 5. doi:10.3390/ijms20051119
Palmieri B, Vadalà M, Laurino C. Nutrition in wound healing: investigation of the molecular mechanisms, a narrative review. *J Wound Care.* 2019;28(10):683-693. doi:10.12968/jowc.2019.28.10.683

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PHARMA NORD ACADEMY

Psychological health & wound healing

Preoperative psychological ill-health is a significant risk factor for adverse wound outcomes after surgery for 4 of the procedures most commonly performed in England

English observational study 2009-2011 of 176,827 patients undergoing

- 59,410 **hip** replacements
- 64,145 **knee** replacements
- 38,328 hernia repairs
- 14,944 varicose vein operations

Results

- Patients with **moderate anxiety or depression** before their operations had an increased probability of wound complications

Brittoon P, Cullum N, Sutton M. Association between psychological health and wound complications after surgery. *Br J Surg.* 2017;104(6):759-776. doi:10.1002/bjs.10474

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PHARMA NORD ACADEMY

Psychological health & wound healing

In patients with chronic or acute wound pain, psychological interventions can have a positive effect on analgesic requirements; & patient-centred & clinical outcomes

Often used alongside analgesics or anaesthetics and are classified as:

- **Procedural:** informing patients of wound or surgery procedures
- **Sensory:** describing how the wound or procedure will feel
- **Behavioural:** advising patients what to do to facilitate procedures or recovery

Continued on next slide.

Bolton L. Psychological Methods of Managing Surgical Pain. *Wounds*. 2021;33(2):57-59.

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PHARMA NORD ACADEMY

Psychological health & wound healing

- **Cognitive:** coaching patients how to think more positively about the wound or procedure
- **Relaxation:** systematic muscle relaxing and/or breathing techniques
- **Hypnosis:** suggesting changes in patient perceptions
- **Mindfulness:** techniques based on meditation or contemplation
- **Emotional:** methods of coping with stress related to the wound or procedure
- **Patient-generated narratives** focusing on the procedure or wound

Bolton L. Psychological Methods of Managing Surgical Pain. *Wounds*. 2021;33(2):57-59.

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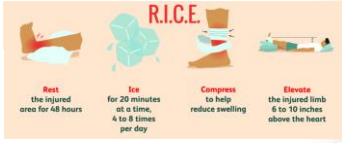
PHARMA NORD ACADEMY

Anything further specific for the healing of ***sports*** **injury?**

1. Everything discussed for general tissue healing applies
2. Don't forget **RICE** ->
3. Referral to appropriate allied musculoskeletal health professional (physiotherapist / osteopath / chiropractor / myofascial bodyworker / podiatrist, etc)
4. Take care of protein intake (see next →)



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Prevention / treatment of **muscle** injuries

- *Additional* protein intake (to an already protein-sufficient diet) will not prevent muscle injury nor reduce post-exercise muscle soreness.
- But increasing protein may be **beneficial after an injury** in helping to:
  - Attenuating muscle atrophy; and promoting repair
  - (This is because limb immobilization reduces resting muscle protein synthesis)
- Data is from lab studies and has not been explored in human trials but researchers recommend increasing protein to help attenuate the **'immobilisation-induced anabolic resistance'** in muscles
- Studies for maximising muscle synthesis *generally* (not in injury) have used **2 – 3 times the RDA of 0.8g/kg body weight**

Nutrients. 2020;12(8):2249. *International Journal of Sport Nutrition and Exercise Metabolism.* 24, 543-552. Int J Sport Nutr Exerc Metab. 2013 Mar 1;23(2):189-197

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Muscle injury: specific nutrients

Int J Sport Nutr Exerc Metab. 2019 Mar 1;29(2):189-197

a journals.humankinetics.com

Nutritional Strategies Claimed to Help With Skeletal Muscle Injuries in Athletes

Micronutrient	Rationale for supplement	Suggested dose	Key research
Vitamin D	It is well established that many athletes are vitamin D deficient due to a lack of sunlight exposure. Emerging evidence suggests that vitamin D deficiencies can impair muscle regeneration following damaging exercise both in vitro and in vivo.	2,000–4,000 IU D_3 taken daily during the winter months to ensure serum 25(OH)D is greater than 75 nmol/L with sensible sun exposure in the summer.	Owens et al. (2015, 2018)
Vitamins C and E	It has been claimed that increased free radical production increases the magnitude of muscle damage following exercise and, therefore, supplements with vitamins C and E could increase recovery time. Literature, however, indicates that vitamins C and E have limited ability to attenuate muscle damage or promote recovery.	No need for additional supplementation.	Close et al. (2005); Cobley et al. (2015); Owens et al. (2018)
Polyphenols	It is claimed that polyphenols may attenuate muscle damage caused by inflammation and increase free radical production. Montmorency cherries (*Prunus cerasus*) are suggested to help improve rate of muscle function recovery after damage as well as reduce muscle soreness and inflammation, especially in athletes consuming a low polyphenol diet.	A diet rich in polyphenols (fruit and vegetables) may be the best strategy to augment recovery from damaging exercise rather than specific supplementation.	Bell et al. (2015); Peeling et al. (2018)
Creatine	Creatine monohydrate is one of the most widely used supplements to support gains in strength and lean mass. Supplementation has been shown to attenuate loss of upper arm muscle mass and strength during limb immobilization, as well as increase muscle hypertrophy following lower leg immobilization.	20 g/day for 5 days followed by 5 g/day thereafter.	Hespel et al. (2001); Johnston et al. (2009)

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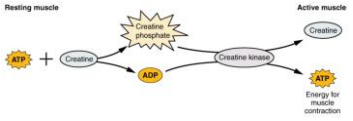
Creatine

A 2021 review of 1322 papers on creatine supplementation concluded many roles for improving health, including that..

- ..Creatine supplementation prior to and following injury may **reduce immobilisation-related atrophy** and/or enhance rehabilitative outcomes in a number of populations

The phosphocreatine system

creatine donates a phosphate group to ADP to recycle ATP



Nutrients. 2021 Jan 29;13(2):447.

Betts, J. Gordon Betts, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix, et al. "10.3 Muscle Fiber Contraction and Relaxation - Anatomy and Physiology." *Openstax*, https://openstax.org/books/anatomy-and-physiology/pages/10-3-muscle-fiber-contraction-and-relaxation.Accessed 26 July 2023

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Bone, tendon and ligament injury: nutrients for prevention/treatment

Evidence is primarily from lab studies rather than human trials

Stress fractures:

- Sufficient **protein and calories** to prevent RED-S (Relative Energy Deficiency in Sport Syndromes)
- **All micronutrients for bone health** (see earlier) and considering dermal loss of minerals through perspiration

Tendon and ligament injuries:

- **Glycine** (cell and animal studies)
- **Collagen** (RCT 10g hydrolysed collagen in athletes decreased knee pain from standing and walking)
- Collagen co-factors: **vitamin C, copper** (sufficiency; no evidence for loading)
- Progressive mechanical loading is also crucial to stimulate collagen synthesis

Int J Sport Nutr Exerc Metab. 2019 Mar 1;29(2):189-197. *Current Medical Research & Opinion* 2008; 24, 1485–1496

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Omega-3 fatty acids

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Omega-3 fatty acids

1

Fish oil at 5g/day (3,500mg EPA + 900mg DHA) for at least 2 weeks has had some success in reducing **inflammation in muscle injury**

But such high doses are not generally recommended: not been studied over the longer term

2

May be helpful in **DOMS**: 2021 study found **3000 mg per day of omega-3** (study does not say what types) through anti-inflammatory action **reduced muscle soreness associated with exercise**

Placebo controlled trial but only 14 participants

3

May be helpful in muscle adaptation: previous studies have found **omega-3 fatty acids to increase the anabolic response to insulin and amino acids**

E.g. 2011 study reported 4000mg omega-3 FAs (1860mg EPA + 1500mg DHA for 8 weeks) to improve anabolism in healthy adults, facilitating muscle protein synthesis

Smith GI, Atherton P, Reeds DN, et al. Omega-3 polyunsaturated fatty acids augment the muscle protein anabolic response to hyperinsulinaemia-hyperaminoacidaemia in healthy young and middle-aged men and women. Clin Sci (Lond). 2011;121(6):267-278. doi:10.1042/CS20100597

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Omega-3 supplements

Triglyceride form versus free fatty acid form:

- Triglyceride form is found most commonly in nature
- Free fatty acid form is 1.6x more bioavailable than triglyceride & does not require lipase

el Boustani S, Colette C, Monnier L, Descomps B et al. Enteral absorption in man of eicosapentaenoic acid in different chemical forms.. Lipids 1987 22, no. 10, pp. 711-4.

Bio-Marine Plus

- ✓ Free fatty acid form
- ✓ Screened for heavy metal content
- ✓ Small and easy to swallow source of DHA & EPA
- ✓ Featured in human clinical trials

Bio-Fish Oil

- ✓ Pure fish oil with natural lemon flavour
- ✓ Screened for heavy metal content
- ✓ Small and easy to swallow source of DHA & EPA
- ✓ Featured in human clinical trials

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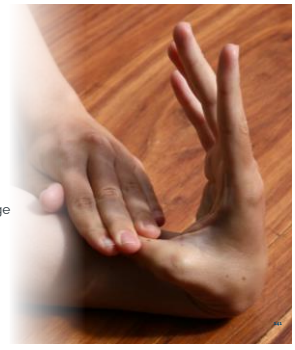
Hypermobility Spectrum Disorders (HSD)

Primarily defined as an unusually wide range of joint motion, plus joint instability

- Flexibility of joints is measured using the Beighton score
- Individuals may describe themselves as "double-jointed"



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Joint **Hypermobility**

- Affects approx. **1 in 30 people,** usually children & young people (can improve with age)
- **Genetic condition**, either inherited (from 1 or both parents) or arising spontaneously
- There is **no known cure or prevention**. Rare, severe types can be life-threatening
- Ligaments are weak due to **issues with collagen**

Individuals typically experience **a multitude of systemic manifestations**, requiring interdisciplinary team care

NHS (2023) *Joint Hypermobility Syndrome* https://www.nhs.uk/conditions/joint-hypermobility-syndrome/

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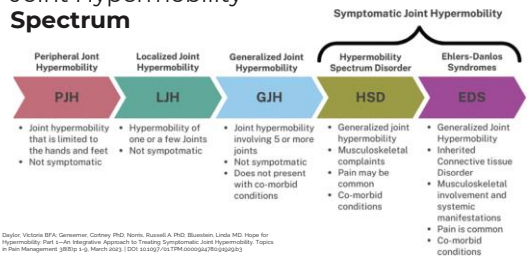
Joint Hypermobility **Spectrum**



Daylor, Victoria BFA; Gensemer, Cortney PhD; Norris, Russell A PhD; Bluestein, Linda MD. Hope for Hypermobility: Part 1—An Integrative Approach to Treating Symptomatic Joint Hypermobility. Topics in Pain Management 38(8):p 1-9, March 2023. | DOI: 10.1097/TPM.0000000000000303

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PHARMA NORD ACADEMY

Ehlers-Danlos (EDS) subtypes

- In 2017 the International EDS Consortium proposed a revised EDS classification, recognizing 13 subtypes
- Diagnosis requires confirmation by molecular testing

Name of EDS Subtype	*IP**	*Genetic Basis*	*Protein Involved*
		Major: *COL5A1, COL5A2*	Type V collagen
Classical EDS (cEDS)	AD	Rare: *COL1A1* c.934C>T, p.(Arg312Cys)	Type I collagen
Classical-like EDS (clEDS)	AR	*TNXB*	Tenascin XB
Cardiac-valvular EDS (cvEDS)	AR	*COL1A2* (biallelic mutations that lead to *COL1A2* NMD and absence of pro α2(I) collagen chains)	Type I collagen
		Major: *COL3A1*	Type III collagen
Vascular EDS (vEDS)	AD	Rare: *COL1A1* c.934C>T, p.(Arg312Cys) c.1720C>T, p.(Arg574Cys) c.3277C>T, p.(Arg1093Cys)	Type I collagen
Hypermobile EDS (hEDS)	AD	Unknown	Unknown
Arthrochalasia EDS (aEDS)	AD	*COL1A1, COL1A2*	Type I collagen
Dermatosparaxis EDS (dEDS)	AR	*ADAMTS2*	ADAMTS-2
Kyphoscoliotic EDS (kEDS)	AR	*PLOD1*	LH1
		FKBP14	FKBP22
Brittle cornea syndrome (BCS)	AR	*ZNF469*	ZNF469
		PRDM5	PRDM5
Spondylodysplastic EDS (spEDS)	AR	*B4GALT7*	b4GalT7
		B3GALT6	B3GalT6
		SLC39A13	ZIP13
Musculocontractural EDS (mcEDS)	AR	*CHST14*	D4ST1
		DSE	DSE
Myopathic EDS (mEDS)	AD or AR	*COL12A1*	Type XII collagen
Periodontal EDS (pEDS)	AD	*C1R*	C1r

The Ehlers-Danlos Society (2023) EDS Types Chart https://www.ehlers-danlos.com/eds-types/

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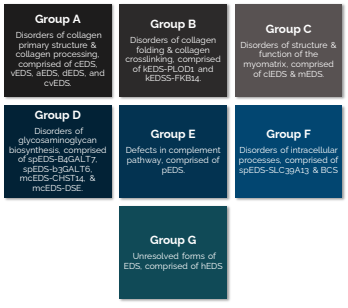
PHARMA NORD ACADEMY

Genetic classifications of the Ehlers-Danlos syndromes

EDS is sub-categorised into groups according to similarities in the way the responsible genes affect the body:



The Ehlers-Danlos Society (2023) EDS Types Chart https://www.ehlers-danlos.com/eds-types/

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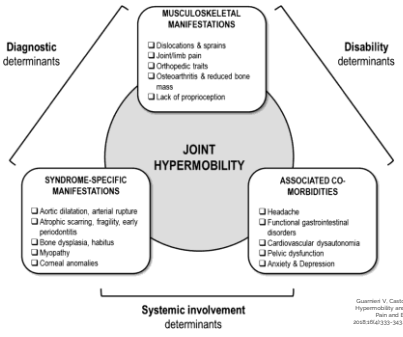

Guerriet V, Castori M. Clinical Relevance of Joint Hypermobility and Its Impact on Musculoskeletal Pain and Bone Mass. Acta Myol. 2018;37(4):333-343. doi:10.36185/2532-1900.2018.37.333-343

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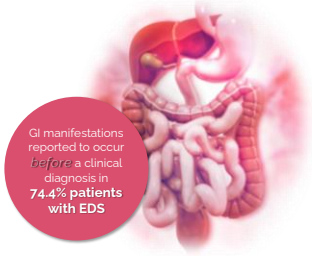
Comorbidities: **GI manifestations**

Largest GI focused study (134 EDS patients):

- **84%** had functional bowel disorders
- **48%** diagnosed with irritable bowel syndrome (IBS)
- **36%** with functional constipation
- **68.7%** with gastroesophageal reflux disease (GERD)



Daylor, Victoria BFA; Gensemer, Cortney PhD; Norris, Russell A PhD; Bluestein, Linda MD. Hope for Hypermobility: Part 1—An Integrative Approach to Treating Symptomatic Joint Hypermobility. Topics in Pain Management 38(8):p 1-9, March 2023. | DOI: 10.1097/01.TPM.0000934780.91919.b3

Zeitoun JD, Lefèvre JH, de Parades V, et al. Functional digestive symptoms and quality of life in patients with Ehlers-Danlos syndromes: results of a national cohort study on 134 patients. PLoS One. 2013;8(11):e80321. Published 2013 Nov 22. doi:10.1371/journal.pone.0080321

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Comorbidities: **other manifestations**

Other manifestations include, but are not limited to:

- fragile skin
- easy bruising
- abnormal wound healing
- sleep disturbances
- psychologic disorders
- anxiety
- depression
- chronic fatigue syndrome
- Raynaud's phenomenon
- recurrent hernias
- neurodivergence (eg, ADHD, autism spectrum disorder, social anxiety, dyslexia, dyspraxia, among other conditions)
- immunologic disorders, such as mast cell activation disorder (MCAD). Further research is needed to fully understand the relationship between connective tissue & mast cells

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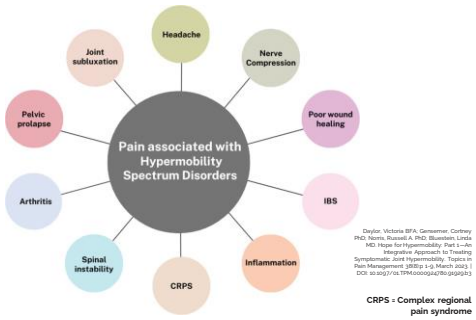

Daylor, Victoria BFA; Gensemer, Cortney PhD; Norris, Russell A. PhD; Bluestein, Linda MD. Hope for Hypermobility: Part 1—An Integrative Approach to Treating Symptomatic Joint Hypermobility. Topics in Pain Management 38(8):1-9, March 2023. | DOI: 10.1097/01.TPM.0000934780.95919.b3

CRPS = Complex regional pain syndrome

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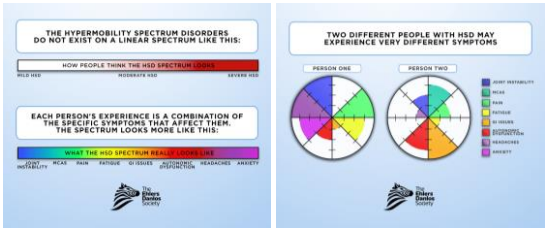
HSD Spectrum



The Ehlers-Danlos Society (2023) What is HSD? https://www.ehlers-danlos.com/what-is-hsd/

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Treatment is therefor **highly individual**

Depending on the patient's complaints a wide **range of specialists may be required**, including but not limited to

- Gastroenterologist
- Immunologist
- Cardiologist
- Neurologist
- Ophthalmologist
- Psychologist
- Psychiatrist
- Orthopaedist
- Pain management specialist

Daylor, Victoria BFA; Gensemer, Cortney PhD; Norris, Russell A. PhD; Bluestein, Linda MD. Hope for Hypermobility: Part 2—An Integrative Approach to Treating Symptomatic Joint Hypermobility. Topics in Pain Management 38(9):pp 1-10, April 2023. | DOI: 10.1097/01.TPM.0000933968.28098.59

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Nutritional interventions

This includes how we eat: eg. sitting down, eating slowly & mindfully activates the **parasympathetic nervous system (PNS)** allowing ↑ **absorption of nutrients**

Daylor, Victoria BFA; Gensemer, Cortney PhD; Norris, Russell A. PhD; Bluestein, Linda MD. Hope for Hypermobility: Part 2—An Integrative Approach to Treating Symptomatic Joint Hypermobility. Topics in Pain Management 38(5):1-10, April 2023. | DOI: 10.1097/01.TPM.0000933968.28098.59
Solano F. Metabolism and Functions of Amino Acids in the Skin. Adv Exp Med Biol. 2020;1265:187-199. doi:10.1007/978-3-030-46398-2_11

- **nutrient deficiencies** should be **identified & targeted** in each individual
- ↑ **fibre:** may reduce diarrhoea and/or increase stool frequency as relevant
- **low FODMAP** (Fermentable Oligo-, Di-, Mono-saccharides, And Polyols): may ease irritable bowel syndrome (IBS) symptoms
- **gluten-free diet**: may reduce abdominal discomfort even in individuals without coeliac disease
- **anti-inflammatory diet**: may reduce pain & other inflammatory signs & symptoms: see later
- **ensure adequate protein**: amino acids are building blocks of keratins, collagen & elastin

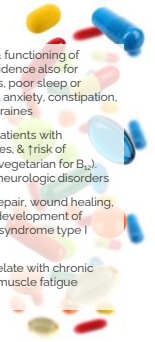
Nutritional supplements (hypothetical)

No research specific to Symptomatic Joint Hypermobility (SJH) is conclusive due to the highly individualised nature of the condition

Recommendations need to be related to specific sxs but may include

Daylor, Victoria BFA; Gensemer, Cortney PhD; Norris, Russell A PhD; Bluestein, Linda MD. Hope for Hypermobility: Part 2—An Integrative Approach to Treating Symptomatic Joint Hypermobility. Topics in Pain Management 38(5):1-10, April 2023. | DOI: 10.1097/01.TPM.0000933968.28098.59

- **Mg:** protein synthesis & functioning of extracellular matrix. Evidence also for fatigue, muscle spasms, poor sleep or memory, inflammation, anxiety, constipation, menstrual cramps, migraines
- **B vits**: B_1, B_2, & B_{12} for patients with dysautonomia, migraines, & ↑risk of deficiency (eg. vegan/vegetarian for B_{12}). B_{12} deficiencies cause neurologic disorders
- **Vit C:** supports tissue repair, wound healing, may help prevent the development of complex regional pain syndrome type I (CRPS-I)
- **Vit D**: deficiencies correlate with chronic pain, delayed healing, muscle fatigue



Nutritional supplements (hypothetical)

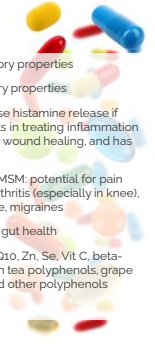
(contd.)

Daylor, Victoria BFA; Gensemer, Cortney PhD; Norris, Russell A PhD; Bluestein, Linda MD. Hope for Hypermobility: Part 2—An Integrative Approach to Treating Symptomatic Joint Hypermobility. Topics in Pain Management 38(5):1-10, April 2023. | DOI: 10.1097/01.TPM.0000933968.28098.59

Do T, Diamond S, Green C, Warren M. Nutritional Implications of Patients with Dysautonomia and Hypermobility Syndromes. Curr Nutr Rep. 2018;7(4):334-339. doi:10.1007/s13668-018-00273-1

Vollmer DL, West VA, Lephart ED. Enhancing Skin Health: By Oral Administration of Natural Compounds and Minerals with Implications to the Dermal Microbiome. Int J Mol Sci. 2018;19(10):3059. Published 2018 Oct 7. doi:10.3390/ijms19103059

- **EPA & DHA**: anti-inflammatory properties
- **Curcumin**: anti-inflammatory properties
- **Quercetin**: may help stabilise histamine release if relevant. Therapeutic effects in treating inflammation from rheumatoid arthritis or wound healing, and has neuroprotective properties
- **Glucosamine**, chondroitin, MSM: potential for pain relief when treating osteoarthritis (especially in knee), inflammatory bowel disease, migraines
- **Prebiotics & probiotics**: for gut health
- **Skin support:** collagen, CoQ10, Zn, Se, Vit C, beta-carotene, astaxanthin, green tea polyphenols, grape seed proanthocyanidins and other polyphenols



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Restless legs syndrome is a neurological disorder associated with...

Unpleasant sensations in legs, including an irresistible urge to move them

- Symptoms are reported to worsen in late afternoon/evening

Musculoskeletal pain

- Two studies (2015 and 2020) observed increased reporting of M/S pain in young males and females (respectively) with RL

RLS suffers may also report

- Periodic limb movement of sleep → disrupted sleep → daytime **fatigue**
- Impaired psychological wellbeing including **depression** and **anxiety**
- Impaired cognition including **memory and concentration**

Hoogerzaal SJ, Paananen MV, Smith AJ, et al. Musculoskeletal pain is associated with restless legs syndrome in young adults. BMC Musculoskelet Disord. 2015;16:294. Published 2015 Oct 14. doi:10.1186/s12891-015-0795-1
Amorim RAE, Moreira GA, Santos FH, et al. Sleep and restless legs syndrome in female adolescents with idiopathic musculoskeletal pain. J Pediatr (Rio J). 2020;96(6):763-770. doi:10.1016/j.jped.2019.09.007

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Most reported cases of RLS are classified as **primary** *(idiopathic)*

Proposed **mechanisms include**

Disruption to the dopaminergic system

- Dopamine is involved in co-ordinating movement; and dopamine disruption can cause involuntary movements (such as in Parkinson's)
- Dopamine levels decline during the day, which correlate to the worsening of RLS symptoms
- Some SSRIs which affect dopamine activity may trigger RLS

Iron deficiency

increasing evidence for this as a primary cause (measure ferritin levels) in disrupting dopamine

A genetic component

Has been indicated in some research, and RSL appears to run in families

RLS associated with another condition or state (such as the following) is known as **secondary RLS:**

- Diabetes
- Neuropathy
- Kidney failure
- Parkinson's disease
- Pregnancy
- Rheumatoid arthritis

Amir A, Masterson RM, Halim A, Nava A. Restless Leg Syndrome: Pathophysiology, Diagnostic Criteria, and Treatment. Pain Med. 2022 May 4;23(5):1032-1035. doi: 10.1093/pm/pnab253. PMID: 34402902

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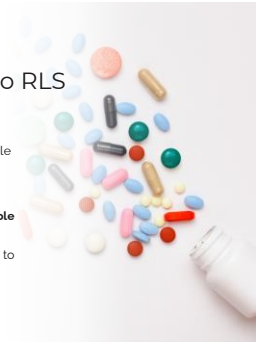
The **medical approach** to RLS



Medications for:

- Managing the primary condition where applicable (e.g. T2DM or PD)
- Regulating or stimulating dopamine:
  - Dopamine agonist medications include **ropinirole and pramipexole**
- Supporting sleep – and a review of medications to avoid those that disrupt sleep.

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Diet & Lifestyle factors may be associated with RLS

Common advice is to **avoid dietary stimulants** (especially in the evening) including caffeine, tobacco and alcohol

In a 2016 cohort study of 12,812 men and 42,728 women, the following **lifestyle factors** were associated with lower RLS risk:

- Normal weight
- Physically active
- Non-smokers

Batool-Anwar S, Li Y, De Vito K, Malhotra A, Winkelman J, Gao X. Lifestyle Factors and Risk of Restless Legs Syndrome: Prospective Cohort Study. *J Clin Sleep Med.* 2016;12(2):187-194. doi:10.5664/jcsm.5482

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Nutrients that may support RLS

D3

Vitamin D

- RLS patients demonstrate lower levels of vit D than healthy controls
- Proposed that that vit D deficiency → reduced dopamine (and associated metabolites) in the brain
- In a 2021 analysis, lower levels of vit D were associated with more severe RLS symptoms, less quality sleep and greater depression
- A 2023 review concluded that correcting vit D deficiency may improve sxs but trials are limited to small numbers

Fe

Iron

(if deficiency is suspected)

- Those with iron deficiency may be at higher risk of RLS
- A Cochrane review of 10 studies (428 total participants, followed for 2-16 weeks) concluded: *'Iron therapy probably improves restlessness and RLS severity in comparison to placebo.'*

Cochrane Database Syst Rev. 2019 Jan 4;1(1):CD007634. *Front Neurol.* 2021;12:781585. Tremor Other Hyperkinet Mov (N Y). 2023 Apr 6;13:12

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Magnesium for RLS?

Mg

Magnesium

- Magnesium supplementation is often suggested for RLS based on anecdotal evidence
- However, a review of eight studies (one RCT, 3 case series and 4 case studies) did not find a significant treatment effect of Mg (although the authors say it may have been underpowered)

'It is not clear whether magnesium helps relieve RLS, nor in which patient groups any benefit might be seen'.

Sleep Med Rev. 2019 Dec;48:101218. Mayo Clin Proc. 2021;96(7):1921–37

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Mg in **musculoskeletal cramping**

Commonly occur as an isolated phenomenon (idiopathic) or may be disease-associated (including metabolic derangements associated with liver and/or kidney failure, thyroid and parathyroid disorders; and/or neuromuscular disorders).

J Musculoskelet Neuronal Interact. 2021;21(1):1-3

- Usually associated with electrolyte imbalance, including hypomagnesaemia
- Mg is one of the minerals required by human body for **nerve transmission and muscle contraction**
- Experimental studies suggest Mg administration may enhance glucose uptake and limit lactate accumulation in skeletal muscle thus improving exercise performance
- However, Cochrane review of 11 trials (735 patients) found no effect of Mg supplementation (dosage 100-520mg elemental; or IV) on sxs in *healthy* adults

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Osteoarthritis

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OA – Pathophysiology

The pathophysiology of osteoarthritis involves a complex interplay of various factors, including biomechanical, biochemical, and genetic factors.

Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum*. 2012;64(6):1697-1707. doi:10.1002/art.34453

1. **Cartilage Degeneration:** initial breakdown of articular cartilage. Aging, mechanical stress, joint instability and inflammation contribute.
2. **Synovial Inflammation:** Synovial membrane becomes inflamed in response to cartilage damage.
3. **Changes in Subchondral Bone:** Subchondral bone undergoes structural changes
4. **Alterations in Joint Mechanics**: Joint misalignment, ligamentous instability, and abnormal loading patterns.
5. **Genetic and Metabolic Factors:** Genetic variations can predispose individuals to cartilage degeneration
6. **Joint Trauma:** Previous joint injuries

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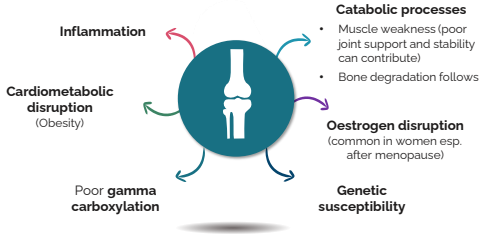
Key drivers of OA



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Obesity exacerbates OA

Mechanisms by which obesity leads to or exacerbates OA

Thomas, Sally et al., What is the evidence for a role for diet and nutrition in osteoarthritis?, *Rheumatology*, Volume 57, Issue suppl_4, May 2018, Pages iv61–iv74, https://doi.org/10.1093/rheumatology/key011

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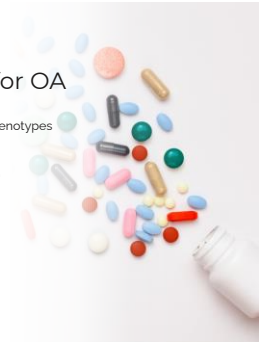
Allopathic treatments for OA



Current OA drugs target several proposed OA phenotypes

Treatments targeting:

- Cartilage (inhibition of degradation & regeneration)
- Subchondral bone
- Inflammatory processes
- Pain processes
- Metabolic syndrome

Grässel S, Muschter D. Recent advances in the treatment of osteoarthritis. *F1000Res*. 2020;9:F1000 Faculty Rev-325. Published 2020 May 4. doi:10.12688/f1000research.22115.1

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What is the evidence **for nutrition in osteoarthritis?**

This review suggests that for the *metabolic* OA phenotype - driven by adipokines, hyperglycaemia and endocrine imbalance - these **dietary interventions** are recommended:

- **Weight reduction** in overweight patients (taking weight off the joints)
- **Lipid modification** - increase in Omega 3s (anti-inflammatory role)
- **Management of cholesterol** levels – fibre, plant sterols, increased PUFAs and MUFAs, reduce SFAs, sugar, starch
- Optimal levels of **key antioxidant nutrients** and **vits D and K**

Thomas, Sally et al., What is the evidence for a role for diet and nutrition in osteoarthritis?, *Rheumatology*, Volume 57, Issue suppl_4, May 2018, Pages iv61–iv74, https://doi.org/10.1093/rheumatology/key011

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OA and the **Mediterranean Diet**

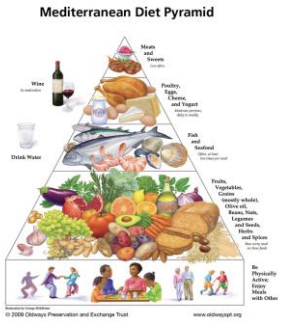
Systematic Review (2018)

Found positive associations between MD and improved quality of life in participants with OA

- Biomarkers of inflammation and cartilage degradation were lower in the diet group.

Review concludes that MD may reduce the prevalence of OA and improve the quality of life in these patients because of its anti-inflammatory effects.

Morales-Ivorra I, Romera-Baures M, Roman-Viñas B, Serra-Majem L. Osteoarthritis and the Mediterranean Diet: A Systematic Review. *Nutrients*. 2018; 10(8):1030. https://doi.org/10.3390/nu10081030



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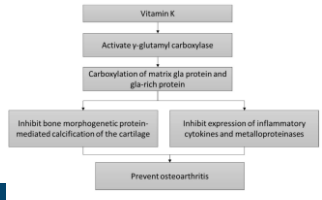
Vitamin K and OA

Mechanism of action –

- Vitamin K activates matrix GLA proteins → inhibit bone cartilage calcification
- Cartilage calcification contributes to pathogenesis of OA, so could vit K help?

Observational studies show that **vitamin K could prevent OA** but evidence from clinical trials is limited



Chin KY. The Relationship between Vitamin K and Osteoarthritis: A Review of Current Evidence. Nutrients. 2020;12(5):1208. Published 2020 Apr 25. doi:10.3390

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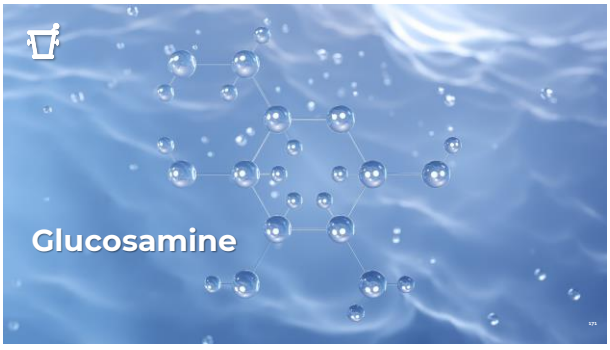

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Chondroitin and glucosamine are often prescribed synergistically to treat **osteoarthritis pain**

Glucosamine

- Produced endogenously – **a key 'building block' of joints**
- Needed for production of **glycosaminoglycan compounds (GAGs)** such as **hyaluronic acid**.
- These molecules (such as proteoglycans) necessary for the **maintenance and repair** of:
  - Joint cartilage and related tissues
  - Ligaments
  - Tendons
- Glucosamine shown to inhibit the action of the enzymes which break cartilage down.

Chondroitin

- An important **structural component of cartilage**; provides much of its resistance to compression
- Maintains the **elasticity and structural integrity** of cartilage
- A sulphated glycosaminoglycan (GAG)
- Helps **stimulate** the synthesis of **proteoglycans and hyaluronic acid,** and decrease the catabolic activity of chondrocytes
- And inhibits the synthesis of proteolytic enzymes and other substances that damage the cartilage matrix

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Multicentre, randomised, double-blind, non-inferiority trial (2014)

Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib

Aim	To compare the efficacy of chondroitin sulfate plus glucosamine hydrochloride versus celecoxib in knee osteoarthritis and severe pain
Patients	**606 patients** with grades 2-3 knee **osteoarthritis** and moderate-to-severe pain
Methods	Patients - randomised to receive • 400 mg CS plus 500 mg GH three times a day or • 200 mg celecoxib every day for 6 months

Hochberg MC, et al., MOVES Investigation Group. Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. Ann Rheum Dis. 2016 Jan;75(1):37-44. doi: 10.1136/annrheumdis-2014-206734. Epub 2015 Jan 14. PMID: 25589511; PMCID: PMC4717339.

Glucosamine and Chondroitin vs drug

Results:

- Both groups elicited **a reduction >50% in the presence of joint swelling**
- **CS+GH = comparable efficacy to celecoxib** in reducing **pain, stiffness, functional limitation and joint swelling/effusion** after 6 months in patients with painful knee osteoarthritis, with a good safety profile.

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RCT (2017)

Pharmaceutical-grade Chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: the CHONdroitin versus CElecoxib versus Placebo Trial (CONCEPT)

Aim	Chondroitin sulfate 800 mg/day (CS) pharmaceutical-grade in the management of symptomatic knee osteoarthritis consistent with the European Medicines Agency guideline
Patients	**604 patients** with **knee osteoarthritis**
Methods	**Study:** Participants with inflammatory knee conditions were split into three groups: • A placebo group • A group receiving 200mg of the anti-inflammatory drug Celecoxib (NSAID) • A group receiving 800mg of pharmaceutical grade chondroitin sulphate.

Reginster, J., Dudler, J., Blicharski, T. and Pavelka, K. (2017). Pharmaceutical-grade Chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: the CHONdroitin versus CElecoxib versus Placebo Trial (CONCEPT). Annals of the Rheumatic Diseases, 76(9), pp.1537–1543.

Glucosamine sulphate vs drug

Results

- **800mg of chondroitin sulphate significantly reduced pain** in arthritis sufferers versus placebo
- Found to be similar to Celebrex with less risk of adverse events

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Glucosamine and Chondroitin

knee/hip OA

	Meta-Analysis of 30 trials (2018)	Meta-Analysis including 8 RCTs (2022)
Aim	To assess the symptomatic effectiveness and safety of chondroitin, glucosamine, and combination treatment on the treatment of knee and/or hip osteoarthritis	To evaluate the efficacy and safety of the combination of glucosamine (GS) and chondroitin (CS) in knee osteoarthritis (KOA) treatment. **3793 patients; 1067 receiving G+C**
Results	Chondroitin could alleviate pain symptoms and improve function Glucosamine proved significant effect only on stiffness improvement However, the combination therapy did not have enough evidence to be superior to placebo (caveat of limited combination studies included)	*"Our study confirmed that the combination of glucosamine and chondroitin is effective and superior to other treatments* [not specified in the abstract] *in knee osteoarthritis"*
	Zhu X, Seng L, Wu D, Rong J, Jiang L. Effectiveness and safety of glucosamine and chondroitin for the treatment of osteoarthritis: a meta-analysis of randomized controlled trials. J Orthop Surg Res. 2018;13(1):170. Published 2018 Jul 6. doi:10.1186/s13018-018-0871-5	Meng Z, Liu J, Zhou N. Efficacy and safety of the combination of glucosamine and chondroitin for knee osteoarthritis: a systematic review and meta-analysis. Arch Orthop Trauma Surg. 2023 Jan;143(1):409-421. doi: 10.1007/s00402-021-04376-9. Epub 2022 Jan 13. PMID: 35024908

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Pharma Nord Formulations

Glucosamine & Chondroitin

All manufactured under Danish **pharmaceutical control**

Bio-Glucosamine Super

- 675 mg of glucosamine sulphate per tablet

Bio-Glucosamine MEGA

- 500 mg of glucosamine sulphate per tablet
- 40 mg chondroitin sulphate per tablet

Bio-Glucosamine + MSM cream

- MSM improves glucosamine absorption
- Japanese Mint & Butcher's broom

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Curcumin

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Curcumin Supplementation OA

Turmeric contains bioactive compounds with beneficial properties called **curcuminoids**, the most studied of which is **curcumin**.

- **Curcumin:** Anti-inflammatory mechanism – stimulated NrF2 and interferes with NF-kB and therefore, inflammatory cytokine release

Study: 2021 meta-Analysis of 15 trials, 1621 participants, curcumin in the management of OA

Findings: Compared with non-steroidal anti-inflammatory drugs (NSAIDs), Curcuma longa extract/curcumin supplements have similar effects on:

- Joint pain
- Joint function/Mobility
- Stiffness

Safety profile: The side-effects of the curcumin groups were lower in terms of adverse events

Zeng L, Yu G, Hao W, Yang K, Chen H. The efficacy and safety of Curcuma longa extract and curcumin supplements on osteoarthritis: a systematic review and meta-analysis. Biosci Rep. 2021;41(8):BSR20210817. doi:10.1042/BSR20210817

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Curcumin Supplementation OA

Study: Double-blind placebo, 90 days trial, 2019

Participants: Knee - osteoarthritis patients given:

- 2x 400mg/d SLCP (**solid lipid curcumin particles**), providing total of 160mg actual curcumin (i.e. the active ingredient comprises approx. 20% of total)
- V.s. Ibuprofen 400mg/d

Findings:

- Significant improvements in OA sxs.
- 160 mg daily was found to be effective and safe in alleviating symptoms in patients suffering from knee osteoarthritis when administered for 90 days
- *'Comparable efficacy of SLCP in alleviating pain with Ibuprofen'.*

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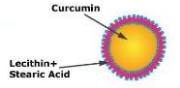
Considerations when supplementing with curcumin

- **Absorption** (see box)
- **Metabolism**
  - Glucuronidation is the liver pathway used to make curcumin water soluble
  - Makes standard curcumin less effective and excreted faster

Requesting product-specific evidence can be helpful, due to wide variance of bioavailability of curcumin formulations



Longvida® extract – utilises 'Solid Lipid Curcumin Particles' (SLCP) to encapsulate the curcumin compound in a fatty sphere ('liposome matrix' or 'micelle') for effective delivery

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Bio-Curcumin

Extract-specific research

- Including reduction of muscle pain & osteoarthritis

Patented delivery form

- Patented Solid Lipid Curcumin Particle (SLCP)
- Encapsulates curcumin compound in a fatty sphere ('liposome matrix' or 'micelle')
- Helps prevent glucuronidation & improve delivery
- Documented high bioavailability – no black pepper required

400 mg patented SLCP in each capsule - 20% curcuminoids

Gota VS, Maru GB, Soni TG, Gandhi TR, Kochar N, Agarwal MG. Safety and pharmacokinetics of a solid lipid curcumin particle formulation in osteosarcoma patients and healthy volunteers. J Agric Food Chem. 2010;58(4):2095-2099. doi:10.1021/jf9034850

Gupte PA, Gramkar SA, Hatke SM, et al. Evaluation of the efficacy and safety of Capsule Longvida® Optimized Curcumin (solid lipid curcumin particles) in knee osteoarthritis: a pilot clinical study. J Inflamm Res. 2019;12:145-153. Published 2019 Jun 5. doi:10.2147/JIR.S205350

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Auto-immune arthritis

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Umbrella term for many inflammatory M/S conditions

- **Rheumatoid arthritis** (used as the main example here re. evidence)
- Psoriatic arthritis
- IBD-related arthritis
- SLE-related arthritis
- Ankylosing spondylitis
- Juvenile arthritis
- Chronic Lyme-related arthralgia
- Some types of long-COVID-related arthritis

Note there are many other types of autoimmune M/S conditions, e.g.:

- **Multiple sclerosis** (aside from the nerve pain, there can be pain from damaged muscles, tendons, ligaments caused by changes in posture or sitting for long periods)
- **Scleroderma** (can case Raynaud's and muscle pain/fatigue)
- **Sarcoidosis** (can cause muscle/joint/bone pain)
- **Myositis** (inflamed, weak muscles)

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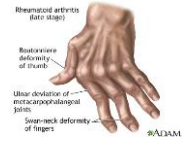
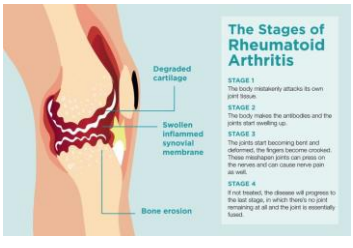


Images from: medlineplus.org and creakyjoints.org



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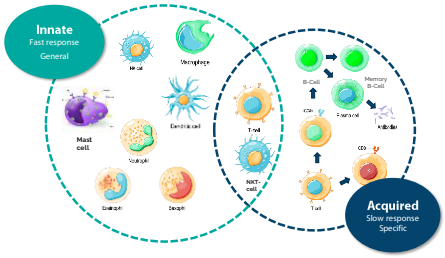
In autoimmunity
the adaptive/acquired immune system becomes confused



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Key **underlying drivers** to consider *(described earlier)*

All these have been found in autoimmune M/S conditions:

- Genetic predisposition triggered by environmental inputs, e.g.
  - **Infection**: viral, parasitic, fungal or bacterial
  - **Dietary antigens** (gluten, casein, lectins, excess sodium chloride)
  - **Toxic stress** (chemicals, pollutants, metals)
- Functional **gut issues**
- **HPA** dysfunction
- **Oestrogen** disruption
- **Molecular mimicry** and similar processes (→ T-cell dysfunction: *see next*)
- **Eicosanoid** imbalance
- **Oxidative stress** and **mitochondrial dysfunction**
- **Obesity** (hypertrophic adipocytes trigger adipokines; excessive calories block T-reg
- All driving **chronic inflammation**

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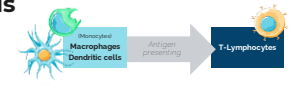
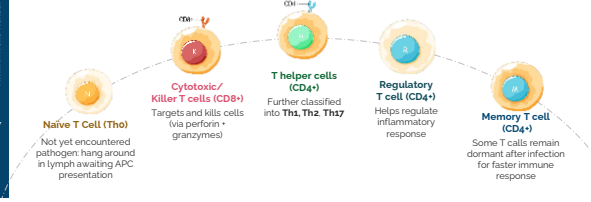
Too many naïve T cells are differentiated to inflammatory Th cells *vs.* T-reg





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Dietary interventions

Diet should be *personalised* but usually involves some sort of *exclusion*

- **Autoimmune Paleo Diet (AIP)** is increasingly popular
- Almost all evidence to-date is *in vitro*
- Human (pilot) studies have shown benefit in IBD and Hashimoto's thyroiditis but not trialled yet in M/S AID
- Details of AIP on next slide

Taking rheumatoid arthritis as an example of a common M/S AID:

- **A 2021 review of 70 human trials** concluded benefits from restricting sodium; transient subjective improvements from fasting; improvements in some RA disease activity measures from the Mediterranean diet; and individualized responses from food elimination, vegetarian diets and/or elemental diets
- The review also reported **benefits from supplementing EPA/DHA** and **vitamin D**
- Another 2021 review (of 20 trials) reported vegetarian diets, Med and elemental diets may help alleviate sxs but that the studies are too heterogeneous for firm conclusions

Cureus. 2019 Apr 27;11(4):e4656. Inflamm Bowel Dis. 2017 Nov;23(11):2054-2060. Nutr Rev. 2021 Mar 9;79(4):410-428. Nutrients. 2021 Oct 4;13(10):3506.

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Paleo diet exclusions

- All grains including pseudo-grains
- All animal dairy
- Legumes
- Added sugars
- Vegetable/seed oils

AIP additional exclusions

- Eggs
- Nuts, seeds, cocoa, coffee
- Nightshades
- Alcohol
- NSAIDS
- Stevia
- Emulsifiers, thickeners
- Algae (chlorella, spirulina, etc)

Foods to eat

- Vegetables, fruits
- Roots
- Organ and other meat
- Bone broth
- Seafood
- Healthy fats (avocado, coconut, olive, ghee)
- Fermented foods
- Herbs

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AIP in MS

- Small pilot study in secondary progressive multiple sclerosis
- **'The Wahl's Protocol':** a modified AIP
- Also, electrical nerve stimulation, meditation. (Supplements varied)
- Significant improvement in fatigue in those who completed the study

Food item	Instruction	Recommended daily intake
Green leafy vegetables	Recommended	3 cups cooked/6 cups raw=3 servings
Sulfur-rich vegetables	Recommended	3 cups raw or cooked=3 servings
Intensely colored fruits or vegetables	Recommended	3 cups raw or cooked=3 servings
Omega-3 oils	Encouraged	2 tablespoons
Animal protein	Encouraged	4 ounces or more
Plant protein	Encouraged	4 ounces or more
Nutritional yeast	Encouraged	1 tablespoon
Milks: soy, almond, peanut, rice, and coconut	Encouraged	According to subject choice
Kelp	Encouraged	¼ teaspoon powder or 2 capsules
Spirulina/chlorella/klamath blue–green algae	Encouraged	¼ to 1 teaspoon or 4 to 8 capsules
Gluten-free grains/starchy food	Allowed	Only two servings per week
Gluten-containing grain	Excluded	
Dairy	Excluded	
Eggs	Excluded	

J Altern Complement Med. 2014 May;20(5):347-55

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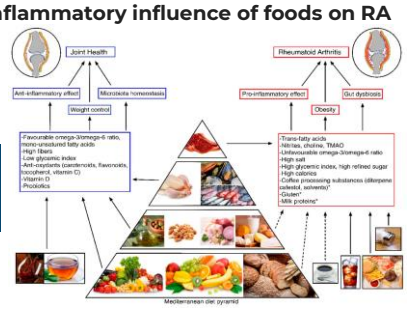
Example of inflammatory influence of foods on RA

Nutrients & their food sources involved in the development & progression of RA

Key:

*Nutrients with less defined evidence

TMAO: trimethylamine-N-oxide



Gioia C, Lucchino B, Tarsitano MG, Iannuccelli C, Di Franco M. Dietary Habits and Nutrition in Rheumatoid Arthritis: Can Diet Influence Disease Development and Clinical Manifestations? Nutrients. 2020; 12(5):1456. https://doi.org/10.3390/nu12051456

'Gold standard' evidence for **fish oil and vitamin D**

The first large scale DBRCT to investigate preventive measures against autoimmunity

- Compared the number of cases of AID that arose in 25,871 older adults
- 4 groups: took either **vitamin D** (2,000iu), or **omega 3** (460mg EPA + 380mg DHA), or **both**, or **placebo** every day for 5 years

Reported that:

- Vitamin D, with or without omega 3 fatty acids reduced autoimmune disease by 22%
- Omega 3 fatty acid supplementation with or without vitamin D reduced the autoimmune disease rate by 15% (not statistically significant)
- Both treatment arms showed larger effects than the placebo arm

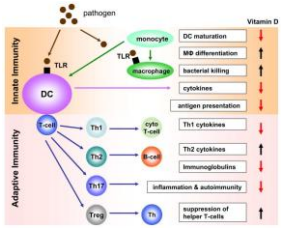
BMJ. 2022 Jan 26;376:e066452

Vitamin D **mechanisms** in AID

Autoimmunity is often characterised by low T-reg, resulting in imbalances in Th1, Th2, Th17

- **Intervention:** T-reg is promoted by commensal gut microbes, n-butyrate (from soluble fibre), vitamins D and A
- Vitamin D also reduces antigen presentation by dendritic cells to T-helper cells
- And preserves tight junction integrity

Vitamin D's anti-inflammatory roles



Endocrinol Metab Clin North Am. 2010; 39(2):365-79

Coenzyme Q10

A vital compound found chiefly in the **mitochondria** of the cell

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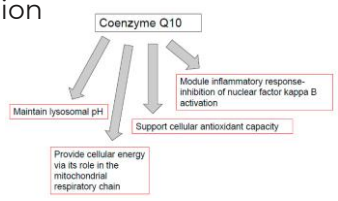
CoQ10 modulates immune function

- Promotes robust immune reaction against infections
- Prevents chronic inflammatory NF-kB activation
- Found to ameliorate AI arthritis in mice by rebalancing Th17/T-reg



Antioxidants (Basel). 2021 May 11;10(5):759. Immunol Lett. 2015 Aug;166(2):92-102

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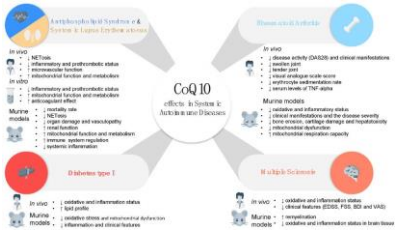
Q10 in autoimmunity

'Numerous studies comprising in vitro analysis, preclinical murine models and randomized controlled clinical trials have demonstrated the capacity of CoQ_{10} to improve the main clinical features of each disease, through both immunomodulatory and antioxidant effects'



Antioxidants (Basel). 2021 Apr 13;10(4):600

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Considerations for Q10 Supplementation

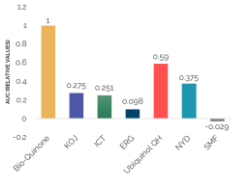
Q10 **does not ordinarily absorb well**

Bio-Quinone is developed to ensure **superior bioavailability**

Bio-Quinone has been used in clinical trials for over 30+ years

The formulation involves development of a 'snowflake' structure which maximises surface area for absorption

Graph Adapted from:
Bioavailability of coenzyme Q10 supplements depends on carrier lipids and solubilization



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Coenzyme Q10

Bio-Quinone Q10

- **102 clinical studies** of the safety, absorption, bioavailability, and efficacy of Bio-Quinone Q10 over 30+ years
- Patented superior bioavailability
- Reference product of the International Coenzyme Q10 Association

Also available in new plant-based 'Q10 Green Bio-Quinone'

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Selenium

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Selenium

In the form of **selenoproteins**, Se has powerful antioxidant and anti-inflammatory roles

A review (2019) of 32 studies reported:

- Lower Se status in patients with autoimmune dxs
- Sxs improvement with Se supplementation compared to controls

A narrative review (2021)

- highlights the AO potential of Se in managing RA and reports evidence that Se supplementation can reduce disease progression by managing its clinical symptoms

Curr Rheumatol Rev. 2013;9(2):123-134. J Trace Elem Med Biol. 2021 Jul;66:126737

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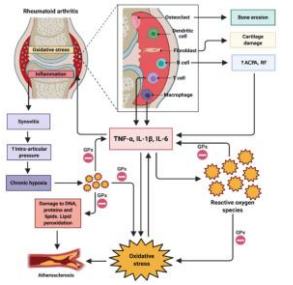
Selenium in RA: **mechanisms**

- Activation of immune cells in synovial tissue → proinflammatory cytokines that induce ROS
- ROS activate NF-κB, generating more inflammatory cytokines that positively feed back the presence of ROS in the joints and lead to the translocation of NF-κB in the other immune cells infiltrated in synovial tissue
- Joint pressure generates chronic hypoxia that (in this inflammatory environment) causes oxidative stress
- **Selenoenzyme GPx can reduce inflammation through decreasing ROS; and NF-kB**



ACPA, autoantibodies against citrullinated peptides; RF, rheumatoid factor; GPx, glutathione peroxidase. Tumubistes-Hernández F.J, Márquez-Sandoval. YF, González-Estevez G, Reyes-Castillo Z, Muñoz-Valle JF. The Relevance of Selenium Status in Rheumatoid Arthritis. Nutrients. 2020 Sep 30;12(10):3007.

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Selenium-yeast

SelenoPrecise

- The highest documented selenium absorption
- Contains more than 30 organically bound selenium compounds
- Used in more than 40 published scientific trials
- EFSA approved for bioavailability & safety

Bio-Selenium + Zinc:

An antioxidant complex with SelenoPrecise plus, zinc and vitamins C, E & B6

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Curcumin

Huge body of data demonstrating its anti-inflammatory and antioxidant effects

Front Immunol. 2022 Aug 1;13:896476
J Ag Food Chem. 2010, 58(4) 2095-2099

A systematic review and meta-analysis (this year) of 31 RCTs reported:

- Curcumin and turmeric extract to reduce sxs in a wide range of AID
- Particularly strong data for use in psoriasis, UC and RA
- Turmeric extract useful where inflammation is within the GI tract (UC, Crohn's, Coeliac) but
- ..where GI absorption is crucial (for systemic inflammation such as RA or SLE), curcumin modified for optimal absorption is recommended
  - E.g. a 'solid lipid curcumin particle'
  - At least 67 times better absorbed than standard 95% curcumin

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Human trials of curcumin in RA

A 2020 systematic review of 6 studies (259 patients with RA of 6-12 weeks duration)

- Curcumin significantly reduced disease activity scores in 4 out of 5 studies and pain in all 3 studies that measured pain
- Inflammatory markers ESR and CRP were significantly reduced in 4 studies
- Rheumatoid factor (RF) was significantly reduced in all 3 relevant studies

Adv Exp Med Biol. 2021;1291:251-263

- Several other reviews report similar outcomes
- Doses vary across trials and depend on mode of delivery (bioavailability)

ESR =
Erythrocyte sedimentation rate

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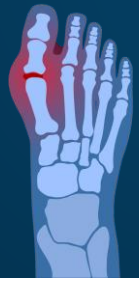
Gout



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Gout – **Pathophysiology**

Severe debilitating inflammatory arthritis → deposition of mono-sodium urate crystals in the joint space and soft tissues = **inflammation and pain**

- Urate is the by-product of **fructose overload** and/or **purine degradation**
- Mostly from **endogenous liver synthesis**, but also from **purine-rich foods,** or **excessive fructose** consumption
- Humans lack **uricase**, and therefore rely on other mechanisms of elimination
- Hyperuricemia more common from decreased renal urate excretion (under-excretors)
- Hyperuricemia → a serum urate level of 6.8 mg/dl (0.360 mmol/l) or greater = central risk factor for developing gout

Golenbiewski, J., Keenan, R.T. Moving the Needle: Improving the Care of the Gout Patient. Rheumatol Ther 6, 179–193 (2019). https://doi.org/10.1007/s40744-019-0147-5

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Gout - **Progression**

Four pathophysiological stages:

1. Hyperuricemia without evidence of monosodium urate crystal deposition or gout
2. Crystal deposition without symptomatic gout
3. Crystal deposition with acute gout flares
4. Advanced gout characterised by tophi, chronic gouty arthritis, and radiographic erosions

Natural history of an acute gout attack typically lasts 7–10 days.

First presentation- often defined by podagra (gouty inflammation of the big toe), can also involve the feet, ankle, knees, hands, wrists, or elbows.

Golenbiewski, J., Keenan, R.T. Moving the Needle: Improving the Care of the Gout Patient. Rheumatol Ther 6, 179–193 (2019). https://doi.org/10.1007/s40744-019-0147-5

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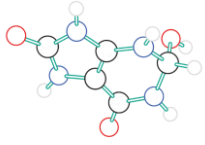
Key **underlying drivers** to consider (described earlier)

- Inflammation
- Acid-base balance
- Renal impairment
- Cardiometabolic
- Liver: excess fructose
- Genetic predisposition
- Being male
- Being older



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Allopathic treatments

Three potential pharmacologic mechanisms for achieving target serum uric acid

Xanthine Oxidase Inhibitors
- Aim is to inhibit urate production
- Main class of medications used
- Drugs such as Allopurinol

Uricosuric Agents - Aim is to increase renal uric acid excretion

Uricase - Metabolism of urate to the more water-soluble and readily excretable allantoin through use of recombinant uricase

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Any of these can **elevate uric acid**

- Complex interplay of genetic and environmental factors
- Excessive dietary **purines** and/or **alcohol**
- A systematic review and meta-analysis of studies of 125,299 white health professionals reported a **higher incidence of gout** with **higher fructose intake** in a dose-response fashion

Jamnik J, Rehman S, Blanco Mejia S, et al. Fructose intake and risk of gout and hyperuricemia: a systematic review and meta-analysis of prospective cohort studies. BMJ Open. 2016 Oct 5;6(10):e013191.

- Can be a side-effect of some **meds** (diuretics, aspirin, immunosuppressants)
- Associated with obesity, metabolic syndrome and hypertension, due to glycation, inflammation and oxidation damaging delicate blood vessels in the kidneys → compromised urate excretion
  - Gout is often caused by *poor urate excretion* rather than simply overconsumption

Purine Dietary Sources
organ meats, game meats and some seafood

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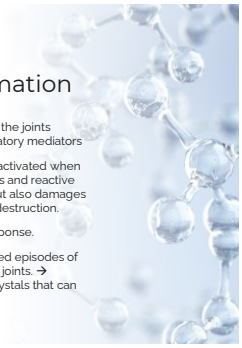
Key Imbalances - Inflammation



1. **Acute Inflammatory Response**: Uric acid crystals in the joints triggers an immune response → release of inflammatory mediators
2. **Neutrophil Activation and Phagocytosis**:, become activated when they encounter uric acid crystals → release enzymes and reactive oxygen species (ROS) to break down the crystals. But also damages the surrounding tissues → inflammation and tissue destruction.
3. **Cytokine Release**: Perpetuate the inflammatory response.
4. **Chronic Inflammation and Tissue Damage**: Repeated episodes of acute inflammation→ tissue damage in the affected joints. → formation of tophi, which are deposits of uric acid crystals that can be seen and felt as lumps under the skin.

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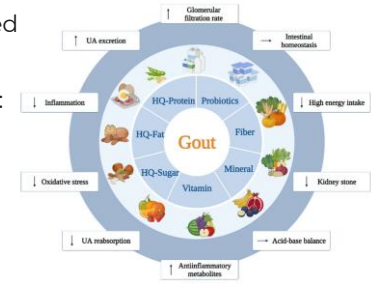
Recommended food-derived **nutritional interventions**:

- Fibre
- Vitamins and Minerals
- High quality fats and carbs
- Proteins – plant and animal based
- Probiotics



Zhang Y, Chen S, Yuan M, Xu Y, Xu H. Gout and Diet: A Comprehensive Review of Mechanisms and Management. Nutrients. 2022;14(17):3525. Published 2022 Aug 26. doi:10.3390/nu14173525

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Gout and **vitamin C**

A higher level of vitamin C in the serum has a positive effect on purine metabolism and favours the **reduction of uric acid levels**

- thus **reducing the risk of monosodium urate crystal deposition in joints** structures and soft tissue
- But **too little evidence** of a beneficial effect of ascorbic acid supplementation in the prevention and treatment of gout, as well as for its usefulness during an exacerbation of the disease

Brzezińska O, Styrzyński F, Makowska J, Walczak K. Role of Vitamin C in Prophylaxis and Treatment of Gout-A Literature Review. Nutrients. 2021;13(2):701. Published 2021 Feb 22. doi:10.3390/nu13020701

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Magnesium and Gout

Study (2018):

- To assess the association between dietary magnesium intake and hyperuricemia in 26,796 US adults aged 20-85 yrs old
- 24h dietary recall (accuracy?)

Findings:

- Our results indicated that increased magnesium intake was associated with decreased hyperuricemia risk (adjusting for confounding variables).
- The biological mechanism underlying the association may be inflammation


nutrients

Dietary Magnesium Intake and Hyperuricemia among US Adults

Zhang Y, Qiu H. Dietary Magnesium Intake and Hyperuricemia among US Adults. Nutrients. 2018;10(3):305. Published 2018 Mar 2. doi:10.3390/nu10030305

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Randomised Controlled Trial (2021)

71 volunteers (35-80 yrs)

> Vitamin D supplementation lowers serum uric acid in prediabetic patients with hyperuricaemia, and supplementation might be considered to help alleviate hyperuricaemia in these patients. 2 groups: weekly dose D2 - 20,000IU and D3 – 15,000IU

Nimitphong H, Saetung S, Chailurkit LO, Chanprasertyothin S, Ongphiphadhanakul B. Vitamin D supplementation is associated with serum uric acid concentration in patients with prediabetes and hyperuricemia. *J Clin Transl Endocrinol*. 2021;24:100255. Published 2021 Apr 2. doi:10.1016/j.jcte.2021.100255

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CoQ10 and Gout

Udhaya Lavinya B, Bardhan I, Evan Prince S. Efficacy of Coenzyme Q10 in inhibiting monosodium urate crystal-induced inflammation in rats. *Eur J Pharmacol*. 2016;791:589-594. doi:10.1016/j.ejphar.2016.09.036

Murine study (2016):

- Looked at the anti-arthritic effect of (CoQ10) on monosodium urate crystal-induced inflammation in rats and compared it with that of the non-steroidal anti-inflammatory drug, indomethacin.

Findings:

- CoQ10 (10 mg/kg/b.w. orally) treated monosodium urate crystal-induced rats showed near normal activities of lysosomal enzymes, reduced levels of lipid peroxidation, near normal paw volume and antioxidant status.
- CoQ10 was also able to minimize mononuclear cell infiltration and damage to articular cartilage.
- Current study indicates that CoQ10 possesses anti-inflammatory effect against gouty arthritis and can be used to treat acute form of gouty arthritis.

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Is there a role for **cherries?**

Systematic Review (2019):

Assessed the effectiveness of cherries in reducing uric acid levels associated with gout in 6 different studies

Chen, P. E., Liu, C. Y., Chien, W. H., Chien, C. W., & Tung, T. H. (2019). Effectiveness of cherries in reducing uric acid and gout: a systematic review. *Evidence-Based Complementary and Alternative Medicine*, *2019*.

Findings:

Overall observed a positive correlation between the consumption of tart cherry juice and a decrease in serum uric acid concentration.

"Note however that we were unable to conduct effective meta- analysis due to a lack of relevant studies and a high degree of variation in the methodologies and metrics used in previous studies."

Previous studies have attributed the suppression of gout-related inflammation to the antioxidant and anti-inflammatory effects of anthocyanin in cherries which inhibits IL-1β secretion.

The anthocyanin levels in cherry are far higher than those in most other fruits.

Chronic back pain

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Back pain

NHS advice for back pain:

- stay active & try to continue with daily activities (don't stay in bed for long periods of time)
- take anti-inflammatory medicine like ibuprofen – paracetamol on its own is not recommended for back pain but may be used with another painkiller
- use an ice pack (or bag of frozen peas) wrapped in a tea towel to reduce pain & swelling
- use a heat pack (or hot water bottle) wrapped in a tea towel to relieve joint stiffness or muscle spasms
- try doing some exercises & stretches for back pain: physiotherapy is recommended

Back pain is the leading cause of disability worldwide

NHS (2023) *Back Pain* https://www.nhs.uk/conditions/back-pain/

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NICE guidelines for chronic low back pain

Consider a **combined physical & psychological programme, incorporating a cognitive behavioural approach** (preferably in a group context that takes into account a person's specific needs & capabilities), for people with persistent low back pain or sciatica:

- when they have significant psychosocial obstacles to recovery (for example, avoiding normal activities based on inappropriate beliefs about their condition) **or**
- when previous treatments have not been effective
- .. but only as part of a treatment package including exercise, with or without manual therapy (spinal manipulation, mobilisation or soft tissue techniques such as massage)
- **Other options to consider:** epidural injections of local anaesthetic & steroid, radiofrequency denervation, spinal decompression, surgical intervention

NICE guideline [NG59] (2018, updated 2020) Low back pain and sciatica in over 16s: assessment and management

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Causal & risk factors to consider

Causes of mechanical lower back pain include:

- Muscle strain
- Ligament sprain
- Herniated nucleus pulposus
- Osteoarthritis
- Spinal stenosis
- Spondylolisthesis
- Scoliosis
- Sciatica

Altug Z. Lifestyle Medicine for Chronic Lower Back Pain: An Evidence-Based Approach. Am J Lifestyle Med. 2021;15(4):425-433. Published 2021 Jul 21. doi:10.1177/15598276211031547

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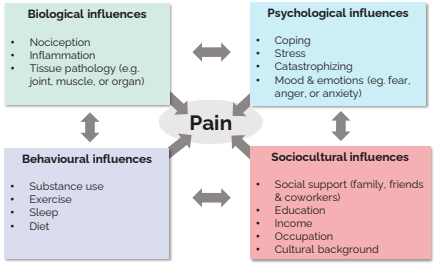
Biopsychosocial Model of Pain



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cross-sectional, correlational study (2022)

Pro-inflammatory diet associated with low back pain in adults aged 50 & older.

Objective	Investigate association between pro-inflammatory diets & low back pain in nationally representative sample of Korean adults
Participants	6th Korea National Health and Nutrition Examination Survey: 7346 respondents. Most were middle-aged, married, & non-/ex-smokers, lived in 2+ person households, consumed alcohol < once a week, & had no allergies or underlying medical conditions.
Methods	Health interviews, examinations, and nutritional surveys. Dietary inflammatory index scores were generated based on 24-hour dietary recalls. Respondents were asked if they had experienced low back pain for at least 30 days in the past three months

Shin D, Hong SJ, Lee KW, Shivappa N, Hebert JR, Kim K. Pro-inflammatory diet associated with low back pain in adults aged 50 and older. Nutr Res Pract. 2022;16(1):63-74. doi:10.4162/nrp.2022.16.1.63. Epub 2022 Jan 31.

Pro-inflammatory diets & back pain

Respondents in highest inflammatory diet quintile were nearly 25% more likely to report low back pain than those in lowest quintile

- **Conclusions:** Results from this study indicate a role of pro-inflammatory diets in the development of low back pain
- "Nurses can screen for those consuming pro-inflammatory foods and thus are vulnerable to back pain, and aid in the delivery of tailored nutritional education.
- Future studies should investigate how diet affects low back pain diagnosis and chronicity relative to pain phenotypes."

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High levels of immunoglobulin G (IgG), especially IgG4, may activate inflammatory processes

Research suggests that intestinal inflammation is involved in the onset & evolution of chronic pain diseases & thus **an exclusion diet could be beneficial in patients with chronic pain** (in this study, 17 with lower back pain, total sample 54 patients – 43 women, 11 men)

More than 5 foods had to be excluded in 87% of subjects.

- highest IgG4 values were eggs, dairy products, cereals (spelt & wheat), and nuts (hazelnuts & almonds)

After 4 wks of personalised exclusion diets, pain visual analogue scale (VAS) morning readings decreased by 50%

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Blinded randomized controlled trial (2022)

The effect of intermittent diet and/or physical therapy in patients with chronic low back pain

Objective	Investigate the effect of intermittent diet and/or physical therapy in patients with chronic low back pain
Participants	60 sedentary volunteers with chronic low back pain, residing in Turkey
Methods	Body weight and body mass index (BMI) were measured. Pain severity was assessed using Visual Analogue Scale (VAS) and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), while assessment of disability was done using Barthel Index (BI).

Torlak MS, Bagcaci S, Akpinar E, Okutan O, Nazli MS, Kuccukturk S. The effect of intermittent diet and/or physical therapy in patients with chronic low back pain: A single-blinded randomized controlled trial. *Explore (NY)*. 2022;18(1):76-81. doi:10.1016/j.explore.2020.08.003

Weight loss improves back pain

Results:

- Weight & BMI were reduced after treatment with diet only & diet + physical therapy
- Pain severity was reduced in all the treated groups
- BI (assessment of disability) was increased in the group treated with only physical therapy

Conclusion:

- The present study indicated that intermittent diet and/or physical therapy are beneficial to patients with chronic low back pain in terms of pain sensation & daily activities

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Cross-sectional study (2020)

Altered Gut Microbiota Composition Is Associated With Back Pain in Overweight and Obese Individuals

Objective	To determine if alterations in intestinal microbiota contribute to the pathogenesis of back pain through metabolites affecting immune and inflammatory responses
Participants	36 overweight or obese individuals with or without self-reported back pain in the preceding month
Methods	Participants were characterized for anthropometry; bone health; metabolic health; inflammation; dietary intake; and physical activity

Dekker Nitert M, Mousa A, Barrett HL, Naderpoor N, de Courten B. Altered Gut Microbiota Composition Is Associated With Back Pain in Overweight and Obese Individuals. *Front Endocrinol (Lausanne)*. 2020;11:605. Published 2020 Sep 2. doi:10.3389/fendo.2020.00605

Gut microbiota & back pain

Results

- Demographic, clinical, biochemical characteristics, diet & physical activity were similar between participants with (*n*=14) or without (*n*=22) back pain
- Individuals with back pain had a higher abundance of the genera *Adlercreutzia*, *Roseburia*, & *Uncl. Christensenellaceae* than those without back pain.
- *Adlercreutzia* abundance remained higher in individuals with back pain in the past 2 weeks, 6 months, & 1 year
- *Adlercreutzia* was positively correlated with BMI, serum adipsin (raised in IR as it increases insulin) & serum leptin

Conclusion

- Back pain is associated with altered gut microbiota composition, possibly through ↑ inflammation

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Pycnogenol
A sustainably grown **pine-bark extract** with a consistent content of polyphenols
40+ years of evidence with actions in numerous areas of health
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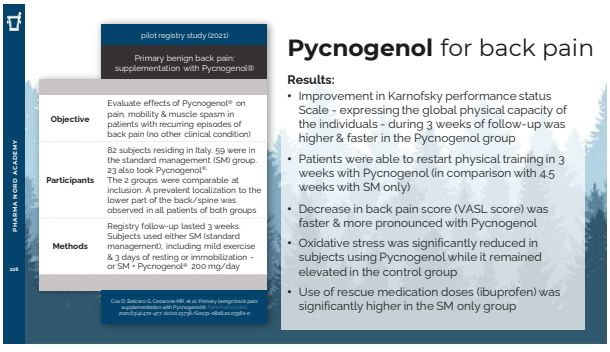
PHARMA NORD ACADEMY
pilot registry study (2021)
Primary benign back pain: supplementation with Pycnogenol®
Objective
Evaluate effects of Pycnogenol® on pain, mobility & muscle spasm in patients with recurring episodes of back pain (no other clinical condition)
Participants
82 subjects residing in Italy. 59 were in the standard management (SM) group. 23 also took Pycnogenol®. The 2 groups were comparable at inclusion. A prevalent localization to the lower part of the back/spine was observed in all patients of both groups
Methods
Registry follow-up lasted 3 weeks. Subjects used either SM (standard management), including mild exercise & 3 days of resting or immobilization - or SM + Pycnogenol® 200 mg/day
Cos D, Belcaro G, Cesarone MR, et al. Primary benign back pain supplementation with Pycnogenol®.
Pycnogenol for back pain
Results:
• Improvement in Karnofsky performance status Scale - expressing the global physical capacity of the individuals - during 3 weeks of follow-up was higher & faster in the Pycnogenol group
• Patients were able to restart physical training in 3 weeks with Pycnogenol (in comparison with 4.5 weeks with SM only)
• Decrease in back pain score (VASL score) was faster & more pronounced with Pycnogenol
• Oxidative stress was significantly reduced in subjects using Pycnogenol while it remained elevated in the control group
• Use of rescue medication doses (ibuprofen) was significantly higher in the SM only group
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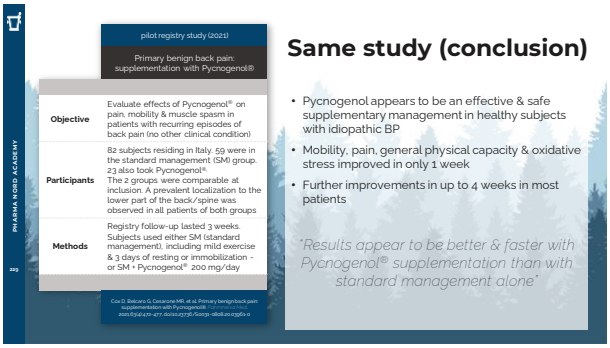
PHARMA NORD ACADEMY
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Cos D, Belcaro G, Cesarone MR, et al. Primary benign back pain supplementation with Pycnogenol®.
Same study (conclusion)
• Pycnogenol appears to be an effective & safe supplementary management in healthy subjects with idiopathic BP
• Mobility, pain, general physical capacity & oxidative stress improved in only 1 week
• Further improvements in up to 4 weeks in most patients
"Results appear to be better & faster with Pycnogenol® supplementation than with standard management alone"
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Bio-Pycnogenol

A research-driven & sustainable pine bark extract

- 40mg of Pycnogenol per tablet
- Consistent levels of plant compounds from batch to batch
- Over 40 years of research in various areas of health
- Produced under pharmaceutical quality

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Summary

1. Health conditions affecting bones, joints, muscles, ligaments and tendons are common
2. Many specific nutritional interventions have been found helpful
3. The most effective approach is to identify the **underlying drivers** for the individual patient and address these, rather than following a protocol for the condition
4. Nutrients that feature in many studies include protein, Ca, Mg, Zn, Se, B vits, vits C, D and K2, glucosamine, chondroitin, Co Q10, curcumin and Pycnogenol

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Thank you!

Please email

pro@pharmanord.co.uk

For any queries!

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