ImproSyn®

Monograph

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Section I: Understanding Muscle Weakness

1. Introduction

Muscle weakness (sarcopenia) is a prevalent condition commonly associated with aging, but it also affects a significant number of younger individuals due to various underlying diseases. Despite its increasing incidence, sarcopenia often remains underdiagnosed and poorly managed. Muscle weakness contributes to a decline in quality of life (QoL), as it is linked to multiple adverse outcomes such as functional impairment, increased risk of disability, falls, and compromised treatment responses. Beyond physical limitations, muscle weakness can also lead to psychological consequences, including depression and anxiety, thereby compounding the overall deterioration in well-being.

Currently, the market is saturated with general protein supplements with or without nonspecific amino acids which are essential for structural muscle protein synthesis that are of dubious efficacy for muscle health. In contrast, this product, ImproSyn offers a muscle-specific formulation that stands apart from conventional supplements. It contains Calcium β-Hydroxy β-Methylbutyrate (CaHMB), L-Carnosine, and Astaxanthin which is designed to support muscle strength, endurance, and recovery by improving muscle protein synthesis, muscle growth and preventing muscle protein breakdown leading to a net muscle gain.

2. Prevalence & Epidemiology of Muscle Weakness

Aging & muscle weakness

Muscle weakness commonly occurs with aging, it also affects a significant proportion of younger individuals due to different disease conditions (Keskin Kavak S, 2025) (Bhat G, 2024) (Chung JY, 2025) (Wasir AS, 2024). An Indian study by Reji et al. (2023) reported a prevalence of muscle weakness in elderly individuals is 63.1% (Reji RE, 2023). Additionally, findings from the Longitudinal Aging Study in India indicated a prevalence of 43.6%, with 19.4% experiencing severe muscle weakness (Rao AR, 2025).

Disease & muscle weakness

Apart from aging, muscle weakness due to disease conditions was found to have a high prevalence of 61.9% (Kalra S, 2025). It is thought to result from a complex interplay of chronic and systemic inflammation, immobilization, and undernutrition. This weakness is often linked to comorbidities that impact the osteo-arthro-muscular triad and the bio-psycho-social triad, further compromising a patient's overall health and mobility.

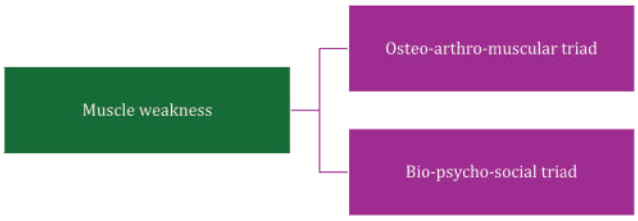


Figure: Comorbidities that impact muscle weakness

For example, in the bio-psycho-social triad, an individual has an underlying disease condition (biological aspect) that leads to psychological disturbances such as depression or anxiety (psychological aspect). This, in turn, causes social withdrawal and isolation (social aspect), creating a vicious cycle of low energy, reduced interest in surroundings, decreased physical activity, inadequate nutrition intake, deteriorating mental health, and worsening muscle weakness considerably compromising quality of life (Dhar M, 2022).

Given the increased prevalence of muscle weakness with aging, comorbid conditions, and age with multiple comorbidities, early intervention is essential to prevent further disease progression, enhance therapeutic efficacy, and improve quality of life (Dhar M, 2022).

3. Impact of Muscle Weakness on Quality of Life & Health Outcomes

Muscle weakness negatively impacts patients' well-being and outcomes by increasing the risk of disability, falls, fractures, hospitalization, reducing the quality of life, and increasing risk of mortality. (Shorter E, 2024). Muscle weakness is significantly prevalent in aging, disease conditions, and further exacerbated by age-related comorbidities impacting mobility, function, and overall quality of life (Keskin Kavak S, 2025) (Kalra S, 2025) (Dhar M, 2022).

4. Complexity of Muscle Weakness

Muscle weakness overt/covert

Muscle weakness can manifest in two distinct forms overt and covert. Overt muscle weakness is easily recognizable through clinical signs assessing the muscle strength, assistance in walking, rising from a chair, climbing stairs, and history of falls which are not routinely assessed (Chung JY, 2025) (Iuliano S, 2022). Whereas the hidden muscle weakness can be intricately intermeshed with the pathophysiology of the disease is often overlooked and undertreated. This results in underestimating muscle dysfunction and increases the risk of complications in both overt and covert muscle weakness (Bhanji RA, 2017) (Ooi H, 2024) (Neelam PB, 2024). The clinical presentation of muscle weakness varies across different diseases, making it complex condition to identify and manage (Saguil, 2005) (Wiedmer P, 2021).

For example, patients with diabetes often visit the clinic with disease-related symptoms, accompanied by overt or covert muscle-specific manifestations. These may include fatigue, muscle weakness, reduced muscle strength, and functional deficiencies affecting activities of daily living, which can impact mobility and overall physical performance (Lien AS, 2018) (Almurdhi MM, 2016).

The loss of muscle mass significantly impairs glucose metabolism, as muscle accounts for over 80% of glucose uptake. With reduced muscle, glucose cannot efficiently enter muscle cells for energy production, leading to elevated blood glucose levels (Alabadi B, 2023) (Merz KE, 2020). This excess glucose is subsequently converted into fat, particularly in the abdominal region, contributing to insulin resistance, hyperinsulinemia, and weight gain. Over time, these metabolic disturbances result in muscle weakness, fatigue, reduced muscle strength, functional impairments resulting in reduced physical activity leading to bedbound conditions (Alabadi B, 2023) (Merz KE, 2020) (Lien AS, 2018) (Almurdhi MM, 2016). Even with anti-diabetic treatment, patients with muscle weakness or low muscle mass often experience persistent poorly controlled diabetes mellitus. This can progress to treatment-resistant diabetes and further accelerates disease progression and creating a vicious cycle (Alfaro-Alvarado FA, 2023) (Scheen, 2017) (Liu Z, 2024) (Zhang X, 2021).

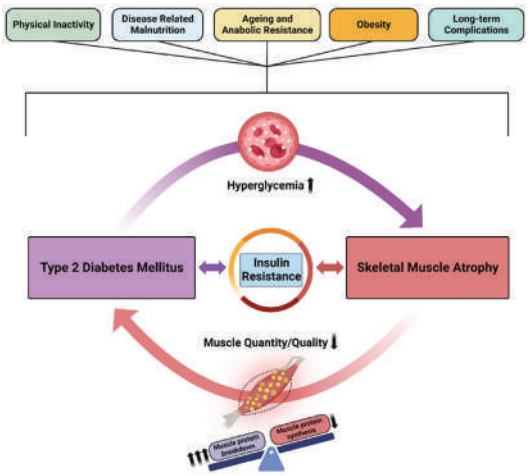


Figure: The vicious cycle of T2DM & muscle weakness (Lopez-Pedrosa JM, 2024)

Muscle weakness, whether overt or covert, should not be under-recognized in clinical practice (Lewis EG, 2025). Early detection and targeted interventions to support muscle health can improve metabolic dysregulation, prevent disease progression, and enhance therapeutic outcomes.

Healthcare professionals play a crucial role in assessing, diagnosing, managing, and preventing muscle weakness in its early stages (Yao XM, 2022). However, patients often present with nonspecific symptoms such as debility, fatigue, or exhaustion, which are linked to muscle weakness but are frequently underestimated as indicators of an underlying pathology (Theodorou DJ, 2012). There are technologically advanced investigations in clinical practice to assess muscle weakness, but none is accurate or considered the gold standard (La Tegola L, 2021). Fortunately, simple clinical tools are available and can be easily implemented in clinical settings for the initial detection of muscle weakness (Locquet M, 2021) such as Calf Circumference, Chair Stand, Leg press/leg extension, Grip strength, Sit-to-Stand test, Mid-arm Circumference, SARC-F

Questionnaire, and Finger-Ring test (Locquet M, 2021) (Buckinx F, 2021) (Guttikonda D, 2021).

Additionally, factors such as time constraints and heavy workloads contribute to these symptoms being ignored and further increases the likelihood of the diagnosis not being considered (Yao XM, 2022) (Morley, 2021). Therefore, increasing awareness about muscle weakness and the application of clinical measures can lead to better diagnosis and, consequently, improved disease management and enhanced therapeutic outcomes (Yao XM, 2022) (Morley, 2021) (Lewis EG, 2025) (Locquet M, 2021).

Currently the physician's main focus is on addressing the primary disease and muscle health related problems are unnoticed. Addressing the muscle health along with (management of primary disease) competing clinical priorities, such as diabetes, with individualized physical activity, and early muscle specific nutritional supplementation is essential for preserving, maintaining, and restoring muscle health, as well as optimizing overall metabolic control (Lopez-Pedrosa JM, 2024).

5. Importance of Early Recognition & Diagnosis

Early identification and accurate diagnosis of muscle weakness are crucial, as poor muscle status can lead to significant health impairments, accelerate disease progression, increase postoperative complications, and prolong hospitalization (Ackermans LL, 2022) (Yuan S, 2023). Muscle weakness, whether overt or covert, is often undertreated or difficult to address in patients with comorbid conditions and is not often routinely performed in current clinical practice (Iuliano S, 2022) (Argilés JM, 2016) (Witham, 2019). Without routine evaluation, it silently progresses, complicating disease management. Currently in clinical practice, there is a lack of interventions to prevent or reverse muscle weakness beyond resistance training; thus, there is little added value to clinicians in making or recording the diagnosis, as doing so does not change treatment (Witham, 2019).

However, failing to address muscle weakness increases the risk of falls, fractures, loss of autonomy, and physical disabilities (Locquet M, 2021). This is where the advantage of early screening, diagnosis, and intervention comes in; it offers the possibility to screen and initiate intervention at an early stage, or a latent phase of a muscle weakness. By detecting and initiating intervention in individuals with co-existing overt or covert muscle weakness before adverse health events arise, clinicians can take proactive measures to prevent further disease progression (Locquet M, 2021) in terms of muscle health and primary disease which is causing it.

6. Diagnostic Challenges & Barriers

Early diagnosis is challenging, as it relies on patients just crossing diagnostic thresholds (Ooi H, 2024). However, the current diagnostic strategies are not disease-specific, and it is not known if different diagnostic strategies may be superior in different populations remains uncertain (Ooi H, 2024). Simple clinical tests, including muscle strength, power, tone, range of motion, and physical performance assessments, can be routinely conducted in clinical settings but are often neglected (Iuliano S, 2022) (Locquet M, 2021). Increasing awareness is essential, as early diagnosis and intervention leads to better disease management and improve long-term outcomes (Lewis EG, 2025) (Yao XM, 2022) (Locquet M, 2021).

7. Clinical Signs & Cues

Different screening tests such as the, Calf Circumference (< 31 cm- muscle weakness), Chair Stand Test (30s-CST ≤ 8 rep, low physical performance), Leg press/leg extension, Grip strength (< 30 kg in men and < 20 kg in women), Sit-to-Stand test (STST- >10s for standing up, >11s for sitting down), Mid-arm Circumference, SARC-F Questionnaire (0 to 10, with ≥4 points indicating muscle weakness), Finger-Ring test can be performed in the clinical settings to identify the persons of muscle weakness (Locquet M, 2021) (Buckinx F, 2021) (Guttikonda D, 2021).

These assessments can detect muscle weakness in its early stages. Given the progressive nature of muscle loss, it is critical to evaluate at risk patients using these tests before sizable and substantial muscle loss occurs. Relying solely on imaging confirmation often represents late-stage detection (Clapauch R, 2023) (Ooi H, 2024) (Locquet M, 2021) (Ooi H, 2024). Early identification of muscle weakness is crucial, as there is a likelihood that the patient may already have muscle weakness (Morley, 2021). Timely diagnosis significantly improves the potential for reversing muscle decline, preserving the functional capacity, and thus improves the primary disease outcomes (Clapauch R, 2023).

Therefore, healthcare providers should incorporate

routine screening and assessment for muscle weakness into standard patient care to ensure early detection, intervention, and optimize disease management (Iuliano S, 2022).

8. Enhancing Physician Awareness

Muscle weakness is often underemphasized due to the lack of appropriate management. Instead, health care providers must recognize and address it as a complex, chronic health condition that can exacerbate existing diseases. Healthcare providers must identify and continue to provide comprehensive management for muscle weakness (Visvanathan R, 2021).

The widespread perception that muscle weakness is natural, inevitable, and irreversible as consequence of aging, comorbidities, and age-associated multiple comorbidities is surprisingly prevalent (Lewis EG, 2025). This misconception is the reason why muscle weakness is often ignored, leading to a loss of muscle mass and strength, which further exacerbates the disease management (Lewis EG, 2025). Currently there is no pharmacologic intervention specific to muscle that will directly treat or reverse muscle weakness.

Effective management requires a multi-modal approach incorporating:

1. Targeted effective nutritional supplementation
2. Structured physical activity
3. Comprehensive therapeutic strategies

This approach demands a clinician's engagement, time, patience, sustained commitment, innovative problem solving, creative thinking (Visvanathan R, 2021).

Below is the list of disease conditions where muscle weakness is prevalent, mechanism by which disease is leading to muscle weakness, and clinical presentation.

9. Terminology and Clinical Relevance of Muscle Weakness in Health and Disease

Muscle weakness is found across many diseases and is recognized as a major health problem (Bhimani R, 2021) (Tarantino G, 2023). Therefore, increasing awareness among healthcare professionals about the serious consequences of poor muscle health is crucial for improving diagnosis, disease management, and patient outcomes (Daly RM, 2024) (Chen YS, 2023). Muscle weakness is present in most cases of the aging population, where there is a higher chance of the co-existence and it also affects a significant proportion of younger individuals in different disease conditions (Keskin Kavak S, 2025) (Bhat G, 2024) (Chung JY, 2025) (Wasir AS, 2024).

Muscle weakness can be present in different forms, starting with

Microvascular changes – Reduction in the number of capillaries in muscle fiber cross-sectional area (Estruch R, 1992)

Macrovascular changes – Muscle atrophy (de Lima EP, 2024)

Symptomatic appearance – Fatigue, muscle weakness, reduced muscle strength, and functional deficiencies affecting activities of daily living, which can impact mobility and overall physical performance, ultimately leading to disease (Lien AS, 2018) (Almurdhi MM, 2016). The different terminologies related to muscle health & muscle weakness are described in the following table.:

Disease	Definition
Sarcopenia	"Age associated skeletal muscle disease- loss of muscle mass, strength, & physical performance However, it is no longer considered a geriatric syndrome, but rather a skeletal muscle disease (muscle failure) that is not always associated with aging, as it can appear in younger people and may be due to diseases other than aging (Sanchez-Tocino ML, 2024)"
Kratopenia	Deficit of muscle power (Sanchez-Tocino ML, 2024)
Dynapenia	Loss of muscle strength (Sanchez-Tocino ML, 2024)
Myopenia	Loss of muscle mass (Sanchez-Tocino ML, 2024)
Cachexia	Complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass (Evans WJ, 2008)
Skeletal muscle atrophy/wasting	Weakening, shrinking, & decreasing muscle mass and fiber cross-sectional area at the histological level (Yin L, 2021)
Asthenia	Lack or loss of strength or energy (Gleeson A, 2015)
Hypotonia	Poor muscle tone resulting in floppiness (Madhok SS, 2025)
Hemiplegia	Severe or complete loss of motor function on one side of the body (https://www.ncbi.nlm.nih.gov/medgen/852561#:~:text=Definition, n.d.)
Hemiparesis	Relatively mild loss of strength in one side of body (https://www.ncbi.nlm.nih.gov/medgen/852561#:~:text=Definition, n.d.)
Paraplegia	Partial or total loss of motor and/or sensory function of the lower half of the body (Alizadeh A, 2019)
Myalgia	Muscle pain or muscle ache (Lee HH, 2023)
Myopathies	Heterogeneous group of disorders affecting the skeletal muscle structure, metabolism, or channel function They usually present with muscle weakness interfering in daily life activities (Nagy H, 2023)
Fibromyalgia	Widespread musculoskeletal pain accompanied by other symptoms such as fatigue (Siracusa R, 2021)
Disuse atrophy	Loss of skeletal muscle mass due to inactivity/lower than 'normal' use (Malavaki CJ, 2015)
Polymyositis	Inflammatory muscle diseases presenting with muscle weakness (Leclair V, 2021)

Even though these conditions are different, the same definition of muscle weakness applies to all the disease conditions listed. Below is a list of common disease conditions where muscle weakness is not only a symptom but also contributes to disease progression and overall outcomes.

The common abbreviations used are:

- CSA- Cross-sectional areas
- SMM- Skeletal muscle mass
- MPS- Muscle protein synthesis
- MPB- Muscle protein breakdown
- LM- Lean mass
- FFM- Fat free mass
- HGS- Handgrip strength
- ALM-Appendicular lean mass
- ASM- Appendicular skeletal muscle
- MyoD- Myogenic Differentiation 1
- MEF-2- Myogenesis-enhancing factor-2
- PI3K- Phosphatidylinositol-3 kinase
- Akt- Protein Kinase B
- ERK- Extracellular signal-regulated kinase
- mTOR-mammalian target of rapamycin
- FOXO3- Forkhead box O3
- PGC-1α- Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
- AMPK- Adenosine monophosphate-activated protein kinase
- IGF- Insulin-like Growth Factor
- UPS- Ubiquitin–proteasome system
- ALS- Autophagy–lysosome system
- AR- Anabolic resistance
- MAFbx/atrogin-1- Muscle Atrophy F-box
- MuRF1- Muscle RING-finger 1
- CS- Citrate synthase
- GLUT4- Glucose transporter 4
- TCA- Tricarboxylic acid
- ETC- Electron transport chain
- PCr- Phosphocreatine
- TUG: The Timed-Up and Go
- SARC-F: Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls
- HG: Grip strength with dynamometry
- SREBF1- Sterol regulatory element binding transcription factor 1
- Pax-7- Paired box protein 7
- MRFs- Myogenic Regulatory Factors

Section II: Disease Associations and Pathology of Sarcopenia

10. Disease Conditions Causing Muscle Weakness

Category	Conditions
Metabolic Disorders (Keskin Kavak S, 2025) (Saguil, 2005)	• Type 2 Diabetes Mellitus (T2DM)
	• Cardiovascular diseases (CVD)
	• Obesity
	• Dyslipidaemia
	• Hypertension
Neuromuscular & Degenerative Diseases	• Stroke-related muscle atrophy (Saguil, 2005)
	• Parkinson's Disease (Saguil, 2005)
	• Spinal cord injury (Saguil, 2005)
	• Spinal muscle atrophy (Saguil, 2005)
	• Hemiplegia (Papadatou, 2020)
	• Hemiparesis (Scherbakov N, 2013)
	• Paraparesis (Cubo E, 2014)
	• Paraplegia (Cubo E, 2014)
	• Neuropathy (Hammi C, 2022)
	• Sarcopenia (Keskin Kavak S, 2025)
	• Amyotrophic lateral sclerosis (Masrori P, 2020)
	• Multiple sclerosis (Gaemelke T, 2025)
	• Systemic sclerosis (Jagtap K, 2022)
	• Lumbar and lumbosacral nerve root compression
	• Herniated disc
Musculoskeletal	• Osteopenia (Saguil, 2005)
	• Osteoporosis (Saguil, 2005)
	• Fibromyalgia (Kapuczinski A, 2022)
	• Dynapenia (Kapuczinski A, 2022)
	• Myopenia (Sanchez-Tocino ML, 2024)
	• Kratopenia (Sanchez-Tocino ML, 2024)
	• Asthenia (Peixoto da Silva S, 2020)
	• Hypotonia (Nickerson BS, 2025)

Endocrine (Saguil, 2005) (Reincke, 2021)	Hyperthyroidism
	Hypothyroidism
	Cushing's Syndrome
	Growth Hormone Deficiency
	Adrenal insufficiency
	Vitamin D deficiency
Chronic Inflammatory & Autoimmune Diseases	Osteoarthritis (Saguil, 2005)
	Gout (Covello A, 2024)
	Cancer cachexia (Anjanappa M, 2020)
	Rheumatoid arthritis (Moschou D, 2023)
	Systemic lupus erythematosus (Bilici R, 2024)
	Polymyositis (Sarwar A, 2023)
	Vasculitis (Jagtap K, 2022)
	Psoriatic arthritis (Takami K, 2025)
	Spondyloarthritis (Hu J, 2024)
	Spinal spondylosis (Kitsuda Y, 2023)
	Lumbar Spondylosis (Gibbons D, 2021)
	Low back pain (Iwahashi S, 2022)
	Axial myopathy (Nanna Witting, 2016)
Renal	Chronic Kidney Disease (CKD) (Shimizu M, 2022)
	Haemodialysis (Shimizu M, 2022)
Respiratory (Keskin Kavak S, 2025)	Chronic obstructive pulmonary disease (COPD)
	Asthma (Karakousis ND, 2022)
	Obstructive sleep apnea (Tao X, 2024)
Surgical	Total knee arthroplasty (Chung JY, 2025)
	Total hip arthroplasty (Sumbal R, 2024)
	Fractures (Mair O, 2024)
	Cervical spine surgery (Tayal A, 2025)
Drug-Induced (Saguil, 2005)	Nonsteroidal anti-inflammatory drugs
	Statins
	Diuretics
	Corticosteroids
	Amiodarone
	Colchicine
	Fibric acid derivatives: gemfibrozil
	Antithyroid agents: methimazole; propylthiouracil
	Antiretroviral medications: zidovudine; lamivudine
	Chemotherapeutic agents
	Interferon
	Leuprolide acetate

Infections (Saguil, 2005)	All infections
	Influenza (Saguil, 2005)
	Dengue
	TB
	Typhoid
	Malaria
	Meningitis (Saguil, 2005)
	HIV (Saguil, 2005)
	Lyme Disease (Saguil, 2005)
Gynaecological	Menopause (Buckinx F, 2022) (Lu L, 2023)
	PCOS (McBreairty LE, 2019)
Liver diseases	Non-Alcoholic Fatty Liver Disease (NAFLD) (Iwaki M, 2023)/ Metabolic dysfunction associated steatotic liver disease (Wong R, 2024)
	Non-alcoholic steatohepatitis (NASH)/ metabolic dysfunction associated steatohepatitis (MASH) (Iwaki M, 2023) (Rinella ME, 2023)
	Cirrhosis (Dhaliwal A, 2020)
	Alcoholic Liver Disease (Dasarathy J, 2017)
	Viral Hepatitis (Coelho MPP, 2023)
Others	Ageing (Paulussen KJM, 2021)
	Debility (Bhimani R, 2021)
	Chronic fatigue syndrome/ muscle fatigue
	Injury/trauma (Paulussen KJM, 2021)
	Immobilization/bedrest/Sedentary behaviour (Paulussen KJM, 2021)
	Hospitalized adults (Shimizu M, 2022)
	Malnutrition (Shimizu M, 2022)

11. Sarcopenia

Sarcopenia classification

Sarcopenia is a progressive age-related loss of muscle mass, reduced muscle strength, and low physical performance. According to its degree of severity it is classified as follows (Sanchez-Tocino ML, 2024) (Wiedmer P, 2021) (Lynch, 2011)

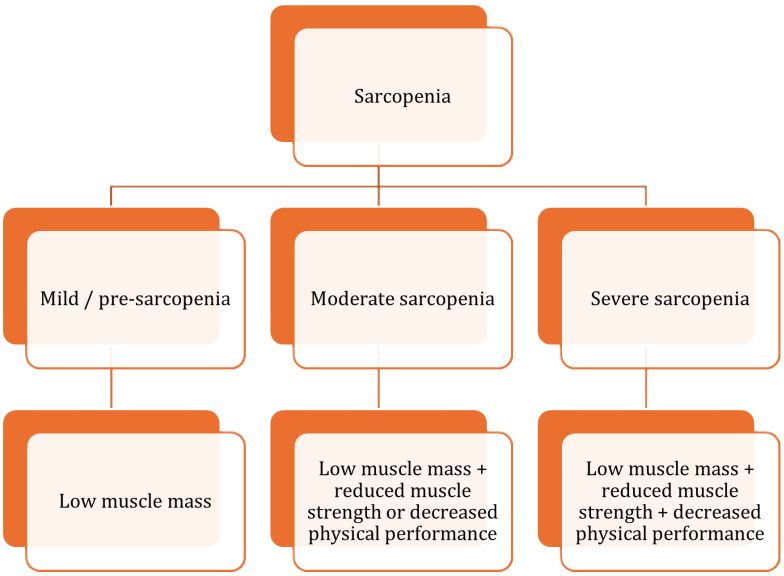


Figure: Classification of Sarcopenia

An Indian consensus on sarcopenia recommends screening for all patients with the following conditions (Kalra S, 2025).

1. The strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F)>4
2. All people > 60 years of age
3. All patients with chronic comorbidities
4. All patients with chronic inflammation
5. All patients with risk factors such as prolonged immobility, critical illness and malnutrition

Causes of sarcopenia

It occurs due to age-related changes in both myogenic and neurogenic components, as outlined below:

Myogenic: (Dowling P, 2023) (Damanti S, 2024)

1. Decrease in size & number of type II fibers
2. Decrease in number & regenerative capacity of satellite cells
3. Reduced protein synthesis
4. Increased proteolysis
5. Mitochondrial abnormalities & dysfunctional energetics
6. Reduced number of actin-myosin cross-bridges formation
7. Lactic acid build-up and muscle weakness
8. Hormonal changes
9. Increased levels of muscle adipocyte fat infiltration
10. Chronic inflammation

Neurogenic: (Kwan, 2013) (Moreira-Pais A, 2022) (Kwon YN, 2017):

1. Nerve denervation
2. Failure of reinnervation
3. Failure of Neuromuscular junction (NMJ)
4. Loss of motor neurons
5. ↓ Presynaptic release of Ach
6. ↑ Axonal thinning
7. ↓ Density of postsynaptic acetylcholine receptors (AChRs)
8. ↑ Fragmentation of the postsynaptic apparatus
9. ↓ Glial cells
10. ↓ Neurotrophic factors
11. Widening of synaptic clefts
12. ↓ Nerve conduction velocity
13. ↓ Excitatory postsynaptic potentials

Complications of sarcopenia

Muscle and bone are metabolically active tissues that undergo continuous remodelling, a process largely dependent on the capacity of mesenchymal stem cells (MSCs) to proliferate and differentiate into myoblasts and osteoblasts. In skeletal muscle, satellite cells initiate myogenesis, leading to the formation of myotubes. Similarly, osteoblast number and activity are critical for bone formation and maintenance (Kirk B, 2021).

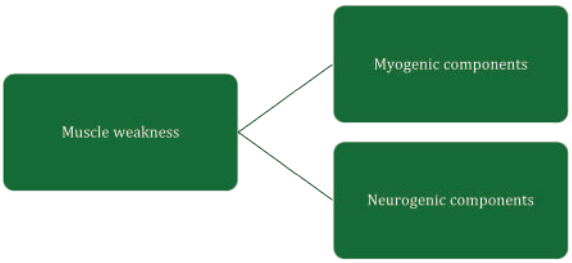
With aging, the regenerative potential of both muscle and bone declines due to impaired MSC function. This is characterized by a reduction in satellite cell populations within muscle fibers and a decreased number and proliferation rate of osteoprogenitor cells in bone. These changes contribute to the development of osteosarcopenia- a condition marked by the concurrent loss of bone and muscle mass and function (Kirk B, 2021).

Furthermore, aging MSCs exhibit a shift in lineage commitment, becoming more prone to differentiate into adipocytes. This leads to fat infiltration within muscle and bone tissues, potentially exerting lipotoxic effects. Notably, this intramuscular and intraosseous fat accumulation can occur independently of overall visceral adiposity. When sarcopenia is accompanied by excess fat deposition, it results in a condition termed sarcopenic obesity, which significantly increases the risk for cardiometabolic disorders such as type 2 diabetes mellitus (T2DM) and atherosclerosis (Zamboni M, 2021) (Sabico S, 2021).

The alterations in muscle power, strength, and function, leading to reduced physical performance, disability, increased risk of fall-related injury, frailty, loss of independence, accelerated progression of diseases, need for long-term care placement, reduced quality of life, and death (Anjanappa M, 2020) (Lang T, 2010). Also, patients often present with nonspecific symptoms such as debility, fatigue, or exhaustion, which are linked to muscle weakness but are frequently underestimated as indicators of an underlying pathology (Theodorou DJ, 2012). So, it is very difficult for physicians to identify the patients with sarcopenia (Theodorou DJ, 2012).

Pathology of sarcopenia/ muscle weakness

Muscle weakness is a condition in which the capacity of a rested muscle to generate force is impaired. It has characteristics of debility, loss of function, and asymmetry. The characteristics of debility include lack of strength, atrophy, and fatigue (Bhimani R, 2021). It is well-accepted that muscle strength is determined by a combination of neurologic and skeletal muscle factors. Therefore, muscle weakness can originate from neurogenic disturbances, myogenic disturbances, or a combination of both.



The myogenic component of muscle weakness includes loss of muscle mass or atrophy which is the main culprit (Vanhorebeek, 2015). The significance of muscle health & quality has long been overlooked and has recently gained attention because loss of muscle mass, strength, and function is strongly associated with frailty, increased risk of falls and fractures, reduced physical fitness, impaired ability to perform activities of daily living, disabilities, diminished quality of life, and loss of independence (Daly RM, 2024) (Cheng AJ, 2021) (Damanti S, 2024). Normally, skeletal muscle proteins are constantly and simultaneously synthesized and degraded with a net synthesis of approximately 1–2%

daily in healthy adult humans (Breen L, 2011) (Kim IY, 2020) (Damanti S, 2024). The Net protein balance is defined as the difference between skeletal muscle protein synthesis (MPS) and breakdown (MPB). Thus, a significant rise in MPS (anabolism) and/or a reduction in MPB (catabolism), such that net protein balance remains positive can result in the accretion of skeletal muscle proteins. Conversely, a negative net protein balance, arising from a reduction in MPS and/or increase in MPB, will result in a loss of skeletal muscle protein (Breen L, 2011) (Kim IY, 2020) (Damanti S, 2024).

Net Protein Balance=MPS−MPB

- When MPS > MPB, there is a positive net balance, leading to muscle growth (hypertrophy)
- When MPS < MPB, there is a negative net balance, resulting in muscle loss (atrophy)
- In healthy adults, MPS and MPB are generally balanced, maintaining muscle mass

The net protein synthesis or muscle mass decreases approximately 3–8% per decade after the age of 30 and this rate of decline is even higher after the age of 60 (Volpi E, 2004). Another study stated that human skeletal muscle mass reaches peak levels between the second and fourth decades of life, and then progressively declines thereafter under relatively sedentary conditions (Aragon AA, 2023)

The factors that affect muscle mass and net protein synthesis are:

1. Age
2. Sedentary lifestyle/ Physical inactivity
3. Immobilization
4. High-intensity exercise
5. Malnutrition
6. Nutrient deficiencies
7. Drugs especially statins, corticosteroids, and anti-retrovirals
8. Diminished and altered microvascular structure
9. Elevated levels of inflammatory mediators
10. Anabolic resistance
11. Decreased anabolic hormonal levels
12. Disrupted protein homeostasis
13. Impaired proteolytic and autophagic pathways
14. Myofiber denervation
15. Decrease in satellite cell number and regenerative capacity or alterations in their proliferation and differentiation abilities
16. Mitochondrial dysfunction (Saguil, 2005) (Damanti S, 2024) (Vanhorebeek, 2015)

All these factors cause imbalance in either a decrease in myofibrillar protein synthesis or an increase in myofibrillar protein breakdown that is higher than any change in the opposite direction (If myofibrillar protein synthesis decreases or protein breakdown increases without an adequate compensatory change, muscle loss occurs) and even little changes as mentioned in the above can contribute to considerable muscle loss over time and lead to atrophy (Damanti S, 2024) (Vanhorebeek, 2015), which results in reduced muscle strength, reduced mass, reduced muscle quantity, and reduced physical performance (Damanti S, 2024) (Kemp PR, 2019) (Dao T, 2020) (Wiedmer P, 2021). All these events lead to: (Yakabe M, 2015)

1. Decreased mobility & function
2. Increased fatigue
3. Increased risk of metabolic disorders
4. Increased risk of falls & skeletal fractures
5. Disability
6. Loss of independence
7. Hospitalization
8. Mortality

Cellular changes that happen in sarcopenic muscle are characterized by (Cho MR, 2022) (Zhu GZ, 2024) (Wiedmer P, 2021) (Dao T, 2020) (Zhang N, 2024) (Buglio AL, 2024) (Frontera, 2022) (M, 2011)

Muscle atrophy can involve either a slow-to-fast or fast-to-slow fiber type transition, depending on the underlying pathological condition. In age-related sarcopenia, a fast-to-slow fiber type shift has been reported

Microanatomy of muscle weakness

Skeletal muscle plasticity

Adult human skeletal myofibers are traditionally classified into slow-twitch (Type I) and fast-twitch (Type II) fibers, which is a result of activity-dependent plasticity (Pette, 2006). These muscle fibers can modify their size and phenotypic characteristics in response to neural input, mechanical loading or unloading, hormonal influences, availability of appropriate nutritional elements or neurotransmitters, and specific patterns of neuromuscular activity (Pette, 2006) (Bhattacharya S, 2022) (Dowling P, 2023) (Jin TE, 2008). These adaptations significantly influence muscle functional properties, including contractile force, shortening velocity, and resistance to fatigue (Schiaffino S, 2006).

Satellite Cell–Mediated Myoneural Regeneration

Satellite cells (SCs), which are muscle-resident stem cells, play a pivotal role in muscle repair and regeneration. These cells are more abundant in slow-twitch fibers and tend to localize near neuromuscular junctions and capillaries (Gillespie MA, 2006). Beyond repairing damaged myofibers, SCs also help restore vascular and neural components of muscle tissue. During regeneration, they coordinate the angio-myogenic process and secrete axon-guidance molecules such as Semaphorin 3A (Sema 3A), which facilitates axonal regrowth and reinnervation after short-term denervation. This molecule is thus crucial for directing intramuscular neuronal outgrowth and successful reinnervation during muscle recovery. So within the muscle fiber, there is an inbuilt system that supports both muscle and nerve growth, enabling efficient muscle coordination and regeneration (Naldaiz-Gastesi N, 2019) (Tatsumi R, 2009) (Gigliotti D, 2016).

Muscle atrophy can involve either a slow-to-fast or fast-to-slow fiber type transition, depending on the underlying pathological condition. In age-related sarcopenia, a fast-to-slow fiber type shift has been reported, which is also seen in many other conditions where muscle regeneration and recovery occurs (Dumitru, 2018).

Myogenic components

Decrease in size, number in type II muscle fibers & shift to type I fibers

In sarcopenia, several reports show that aging, disease, lack of physical activity (activity-related sarcopenia), or inadequate dietary intake of protein (nutrition-related sarcopenia) causes muscle fiber-type tran¬sition due to "Use It or Lose It" phenomenon", problems in denervation and reinnervation of type II fibers, reduced Sema3A secretion, reduced presynaptic release of ACh, thinning of axons, and reduction in neuromuscular junction (NMJ) maintenance, which is characterized by a gradual decrease of both type II fiber number and size with age, suggesting a fast to slow fiber-type shift (Dao T, 2020). This twitch in fiber-type transition can be explained by

A. "Use It or Lose It" Phenomenon

With aging, sedentary lifestyles, and conditions of muscle disuse individuals engage in fewer explosive movements, leading to reduced activation of fast motor units (type II fibers). As a result, type II fibers are more prone to atrophy and degeneration, contributing to muscle weakness (Kwan P. , 2013) (Grgic, 2022) (Lang T, 2010)

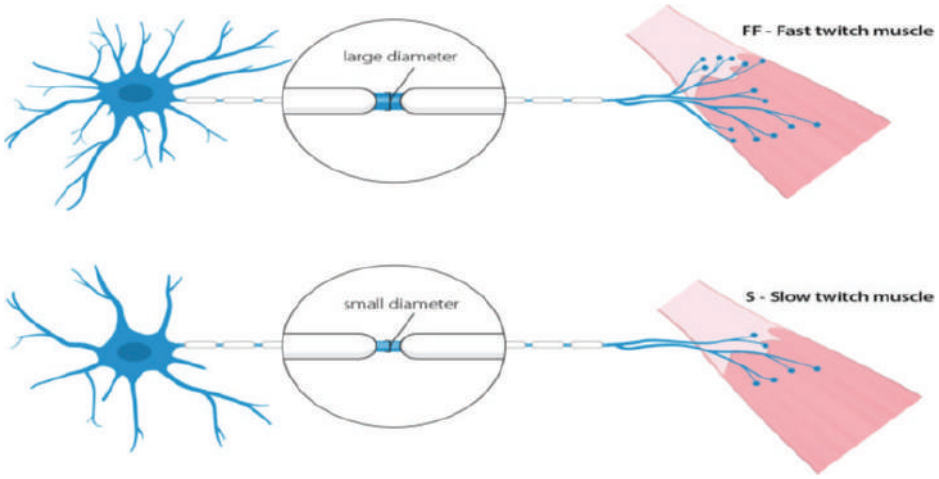
A study found that:

- Quadriceps muscle cross-sectional area (CSA) was 14% smaller in older men compared to younger ones
- Type II fiber size was 29% smaller in the elderly (Nilwik R, 2013)

Another study in patients with hip fractures reported an age-related decline in type IIx fibers in the vastus lateralis, along with a positive correlation between handgrip strength and type IIx fiber density—highlighting the critical role of these fibers in maintaining functional strength (Tian J, 2024).

All these findings indicate a reduction in type II fibers, suggesting a possible shift in muscle fiber composition with age and disuse (Nilwik R, 2013)

B. Denervation and Reinnervation of Type II Fibers



- As shown in the figure, fast-twitch, fast-fatigable (FF) fibers are innervated by fast-firing motor neuron (MNs). One MN in an FF motor unit typically innervates (far) over 300 muscle fibers, reaching up to 2,000 in the big muscles of the limbs. But, slow-twitch, fatigue-resistant (S) typically innervates less than 200 muscle fibers (Nijssen J, 2017).
- Skeletal muscle regeneration is functionally successful only if the motor nerve terminal and a post-synaptic region of regenerating fibers are correctly connected by NMJ development, which is essential for functional contractility.
- In skeletal muscle, a specific semaphorin signal, Sema3A, is involved in the restoration and remodelling of nerve-muscle connections, thus emphasizing its plausible role to ensure the success of muscle regeneration.
- During aging, the SCs reservoir declines, and its crosstalk with the surrounding microenvironment becomes impaired, thereby disrupting the overall muscle regeneration process.
- This age-related dysfunction may also compromise the regulated release of Sema3A by SCs, which plays a critical role in guiding axonal regrowth. As a result, the coordination required for effective muscle-nerve communication and reinnervation may be disrupted in the elderly, contributing to impaired muscle repair and functional decline (Fard D, 2024).
- In addition, a sedentary lifestyle leads to the preferential denervation of type II muscle fibers, resulting in the loss of their motor neuron connections and reduced force generation. This results not only in muscle atrophy, rapid weight loss, and muscle weakness, but also impairs muscle metabolic function. Over time, the affected muscle tissue is largely replaced by fibrous connective tissue and fat (Carlson, 2014).
- A study reported that after 28 days of denervation, the soleus muscle underwent approximately 40% atrophy, accompanied by a decrease in GLUT4 transporter expression. This reduction in GLUT4 was associated with the development of insulin resistance (Kostrominova, 2022).
- These denervated fibers are then reinnervated by collateral sprouting from slow-twitch motor neurons in a process called motor unit remodelling which is a critical adaptive process, leading to their conversion from type II (fast-twitch) to type I (slow-twitch) fibers (Coletti C, 2022) (Wiedmer P, 2021).
- However, this reinnervation does not always occur. While collateral sprouting and motor unit remodelling can help restore connections in early or moderate stages of muscle denervation, this process becomes increasingly limited in the late stages of disease or in cases of severe nerve damage (Carlson, 2014).
- In such conditions, the nerve's ability to regenerate is minimal, and the muscle undergoes progressive morphological atrophy, where muscle fibers shrink and are gradually replaced by fibrous tissue and fat (Larsson L, 2019) (Carlson, 2014).

Table: Fiber-Type Characteristics (Lang T, 2010) (Nijssen J, 2017)

Feature	Type I (Slow-Twitch)	Type II (Fast-Twitch)
Motor Neuron Diameter	Small	Large
Function	Sustained, low-intensity activities like posture	Rapid, forceful contractions
Mitochondria/Myoglobin	High	Low
Capillary density	High	Low
Metabolism	Oxidative (aerobic)	Glycolytic (anaerobic)
Fatigue Resistance	High	Low
Colour	Red	White

2. Decrease in number & regenerative capacity of satellite cells

Muscle can maintain its size and function through regeneration following severe injury or stress. This regenerative capacity is primarily attributed to muscle SCs, which reside between the sarcolemma and the basement membrane of muscle fibers. These SCs act as muscle stem cells and play a crucial role in repairing damaged tissue by proliferating and differentiating into new muscle fibers (Alway SE, 2014) (Huo F, 2022).

Mechanisms of Satellite Cells (SCs) Activation Following Injury

Under normal resting conditions, SCs remain in a quiescent state, characterized by the expression of paired homeobox transcription factor Pax7 (Pax7) and the absence of myogenic differentiation 1 protein (MyoD) expression (Fu X, 2015). In response to muscle injury, these quiescent SCs become activated, re-enter the cell cycle, and begin expressing MyoD. They migrate to the site of injury with the help of a complex combination of signals generated by damaged myofibers, blood vessels, and immune cells, which serve to activate quiescent satellite cells (SCs). These signals include hepatocyte growth factor (HGF), nitric oxide (NO), chemokines, cytokines, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), fibroblast growth factors (FGFs), as well as neuromuscular activity and the activation of key signaling pathways such as Notch and Wnt (Fu X, 2015).

Importantly, calcium ions (Ca^{2+}) also act as critical messengers in myogenesis, regulating satellite cell activation, proliferation, and differentiation by modulating calmodulin-dependent kinases. The increase in intracellular Ca2+ is crucial for activating myosatellite cells and regulating myoblast migration and fusion during myogenesis and muscle regeneration, which is essential for proper muscle repair after injury, muscle growth, and recovery after atrophy (Dong M, 2025) (Schiaffino S P. T., 2008).

Activated satellite cells either fuse with damaged myofibers or differentiate into myogenic progenitor cells (Alway SE, 2014). Notably, a subset of activated satellite cells downregulates MyoD and resists the differentiation process, thereby maintaining a mitotically inactive state like quiescence, a process depending on Sprouty1 (Schmidt M, 2019). During differentiation, myogenin expression is upregulated, and myogenic progenitor cells elongate into myocytes and fuse into multinucleated myotubes, supporting muscle repair (Alway SE, 2014) (Wiedmer P, 2021) (Sousa-Victor P, 2016). In addition to these physiological and molecular cues, satellite cells are also responsive to external factors such as nutrition and exercise. Collectively, these stimuli contribute to increased myofibrillar number (hyperplasia), enlarged myofibrillar size (hypertrophy), enhanced myofibrillar content, and ultimately result in increased muscle mass and greater muscle fiber cross-sectional area (Rehman SU, 2023) (Nastasi T, 2008) (Gillespie MA, 2006).

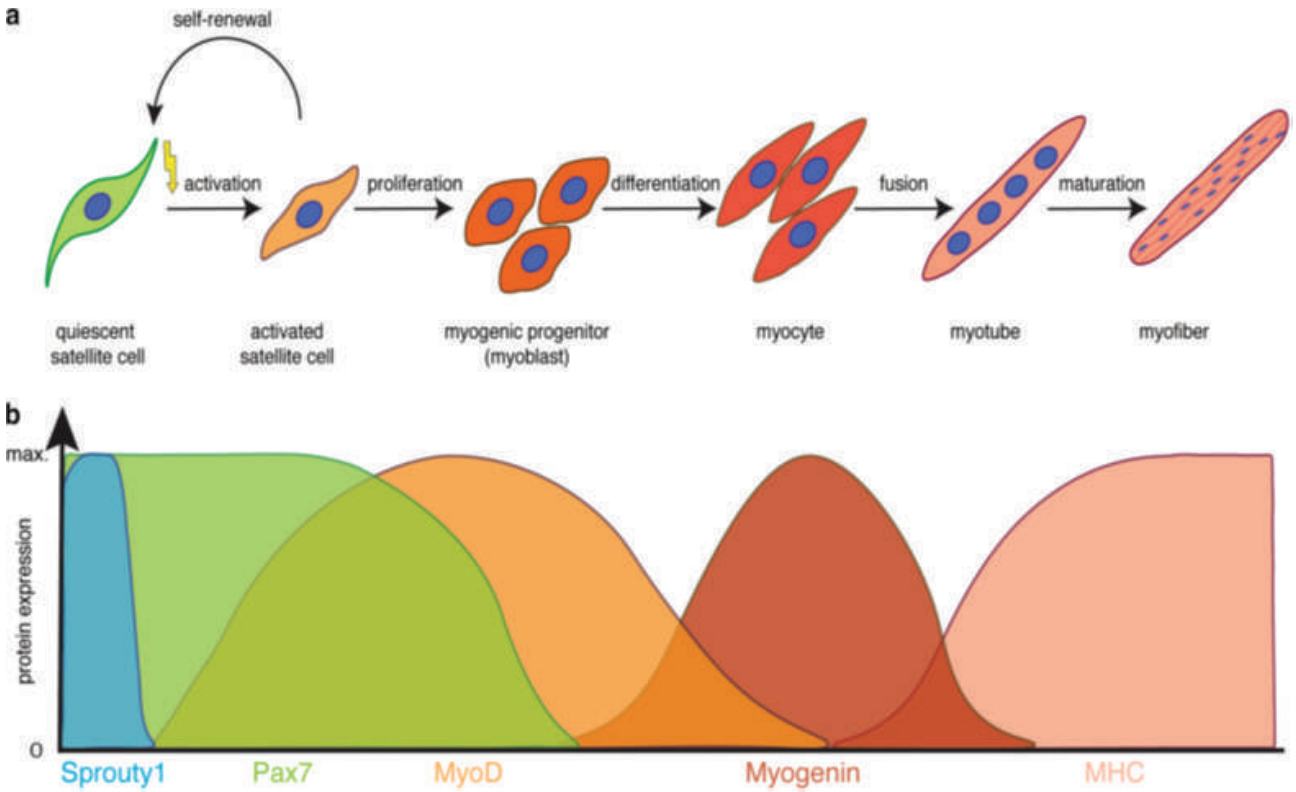


Figure: Myogenic lineage progression & expression profile of key modulators of myogenic lineage progression (Schmidt M, 2019).

1. Signaling Pathways Regulating Satellite Cell Activation
2. The Notch signaling pathway plays a pivotal role in regulating satellite cell (SC) activation, proliferation, and lineage determination during skeletal muscle regeneration (Russell AP, 2010). Under normal resting conditions, high levels of Notch are in quiescent SCs to maintain the stem cell pool and prevent premature activation (Schmidt M, 2019) (Russell AP, 2010) (Pagano AF, 2019). Following muscle injury or mechanical loading (stimuli), Notch signaling is upregulated, triggering SCs sproliferation and self-renewal to support regeneration (Wiedmer P, 2021).
3. Once enough activated SCs is established, the Wnt/β-catenin signaling pathway becomes predominant. This transition serves to downregulate Notch activity, allowing SCs to exit the proliferative phase and proceed toward differentiation into mature myofibers (Wiedmer P, 2021) (Sousa-Victor P, 2016).
4. However, this signaling coordination becomes disrupted with aging. Diminished Notch activation in aged muscle results in impaired SCs proliferation and a reduced regenerative capacity (Pagano AF, 2019). Simultaneously, hyperactivation of Wnt signaling has been implicated in the pathological conversion of myogenic progenitors to fibrogenic fate, contributing to muscle degeneration and fibrosis seen in age-related muscle diseases (Gioftsidi S, 2022) (Wiedmer P, 2021).
5. In addition, to age, sarcopenia, factors such as elevated transforming growth factor-β (TGF-β) and chronic Wnt pathway activity further suppress Notch signaling, exacerbating SCs dysfunction. Therefore, a precise balance between Notch and Wnt signaling is essential for effective and timely muscle regeneration (Sousa-Victor P, 2016).
6. Therefore, restoring the age-associated dysregulation of Notch and Wnt signaling during skeletal muscle repair through physiological stimuli and appropriate nutritional interventions has shown promise in rejuvenating aged muscle and represents a potential therapeutic strategy for managing sarcopenia (Arthur ST, 2012) (Montenegro KR, 2019).

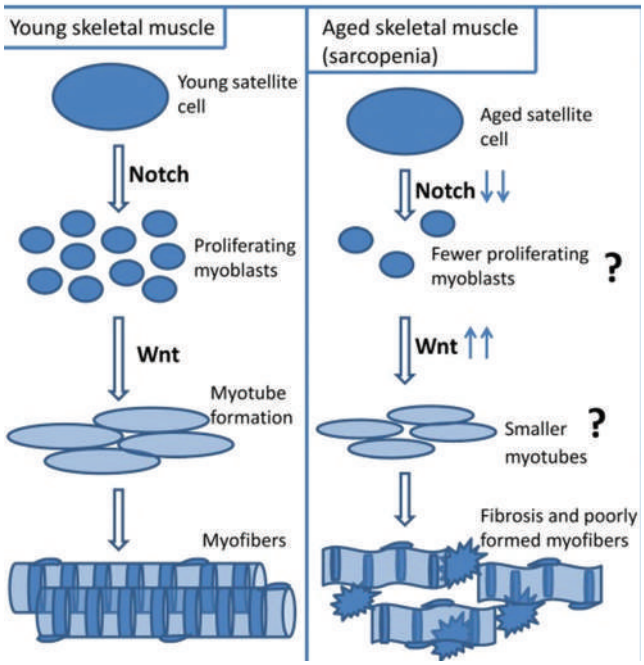


Figure: The effect of aging & physiological stimuli on Notch and Wnt signaling (Arthur ST, 2012)

Satellite Cells in Growth and Aging

Evidence shows that after birth, muscle growth, or myogenesis, includes a notable increase in muscle fiber size along with a rise in the number of myonuclei. These observations provide support for an active role of satellite cells during childhood muscle development (Fry, 2019). Indeed, satellite cells in developing muscles appear more "active" than those found in mature muscles, through observation of a well-developed granular endoplasmic reticulum, indicative of enhanced protein synthesis. Fewer ribosomes are present in the satellite cells of adult mammals, consistent with the reduced metabolic activity. Which means, in adulthood, satellite cells show reduced protein synthesis activity, making muscles more dependent on external support for muscle health (Fry, 2019).

Restoring Balance in Aging Muscle/ Sarcopenia

Despite an aging-related decreased number, the remaining resident SCs should be able to activate and sustain an adequate regenerative process. Indeed, it has been revealed that SCs retain their ability to respond to growth-promoting stimuli, undergo differentiation, fuse into myotubes, and produce a reservoir of cells throughout an individual's lifespan, suggesting that impaired regeneration may be due to aging-dependent alteration of the environment rather than inherent SCs dysfunctions (Fard D, 2024).

This means these stem cells will always be present, and they will continue to function, therefore activation of satellite cells will always revert the situation in diseases like sarcopenia. Therefore, in sarcopenia, early recognition and intervention through external support (such as muscle specific nutrition) can "prime" satellite cells. This priming effect enhances their responsiveness to injury or stress, leading to increased proliferation and contributing to the maintenance of muscle health. The result is an increase in myofibrillar number (hyperplasia), enlargement of myofibrillar size (hypertrophy), enhanced myofibrillar content, and ultimately, increased muscle mass and greater muscle fiber cross-sectional area (Alway SE, 2014) (Kim KY, 2025).

Pathological changes in sarcopenia, muscle disuse, & aging leads to:

A. Decline in Satellite Cell Function

- There is fewer satellite cells and a reduction in their density within muscle fibers.
- Satellite cell proliferation capacity diminishes, partly due to replicative senescence in type II muscle fibers.
- This process leads to telomere attrition and DNA damage, further limits the regenerative potential of skeletal muscle (Alway SE, 2014) (Huo F, 2022).
- However, even under these conditions, early recognition and intervention through nutrition can "prime" satellite cells. This priming effect can enhance their responsiveness to stimuli, leading to increased proliferation and contributing to the maintenance of muscle health (Alway SE, 2014) (Kim KY, 2025).

B. Disruption in Signaling Pathways

- Aging and muscle disuse cause an imbalance in the Notch and Wnt pathways
- Notch signaling activity decreases, reduces satellite cell proliferation and self-renewal. In contrast, Wnt signaling becomes hyperactive, prevents proper muscle differentiation and instead promotes myogenic to fibrogenic fate conversion.
- This shift promotes excess connective tissue formation (fibrosis) and alters the extracellular matrix (ECM) by stimulating fibroblasts, leading to increased collagen production and muscle

stiffness. These changes impair functional muscle regeneration, diminish mechanical properties, and ultimately reduce the muscle's regenerative capacity (Wiedmer P, 2021) (Sousa-Victor P, 2016) (Cai L, 2023)

- Although the proliferation of satellite cells is critical for muscle regeneration after injury, proliferation without adequate differentiation does not contribute to increased muscle mass (Alway SE, 2014).
- Therefore, restoring the age-associated dysregulation of Notch and Wnt signaling during skeletal muscle repair through physiological stimuli and appropriate nutritional interventions has shown promise in rejuvenating aged muscle and represents a potential therapeutic strategy for managing sarcopenia (Arthur ST, 2012) (Montenegro KR, 2019).

C. Chronic Fibroblast Growth Factor (FGF2 & 23) Production & Impaired Stem Cell Quiescence

- Satellite cells continuously produce FGF2, even in the absence of injury
- This disrupts stem cell quiescence, leads to premature depletion of satellite cell pools, further impairs muscle repair (Alway SE, 2014) (Huo F, 2022).
- FGF23 secreted by osteocytes in the bone, with emerging evidence highlighting its systemic effects on skeletal muscle. Elevated levels of FGF23 have been shown to induce the release of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. These inflammatory mediators contribute to muscle catabolism through direct activation of the ubiquitin-proteasome system and the NF-κB signaling pathway. Additionally, FGF23 indirectly promotes muscle degradation by inhibiting insulin/IGF-1 signaling, further exacerbating protein breakdown and contributing to skeletal muscle wasting (Afsar RE, 2023).
- Moreover, chronically elevated FGF23 levels have been implicated in the deterioration of the musculoskeletal system, particularly in older adults. This hormonal dysregulation is associated with reduced muscle strength, impaired physical performance, slower gait speed, and increased risk of falls, reflecting a decline in overall mobility and functional capacity (Egund L, 2023).

D. Reduced Expression of Myogenic Regulatory Factors

- MyoD and myogenin, which are critical for satellite cell activation and muscle regeneration, show reduced expression in atrophied and aged muscles
- This contributes to the overall decline in muscle repair efficiency, regenerative capacity, accelerates muscle degeneration, and weakness (Kwan P. , 2013) (Alway SE, 2014) (Huo F, 2022) (Wiedmer P, 2021) (Sousa-Victor P, 2016).
- Furthermore, a pathophysiological disconnection between sarcolemmal excitation and muscle contraction may occur with aging and sarcopenia. This includes alterations in the voltage-gated Ca^{2+}release mechanism, decreased myoplasmic Ca^{2+} elevation in response to membrane depolarization, reduced calcium supply to the actomyosin apparatus, and overall diminished contractile strength. Abnormal calcium handling is therefore believed to contribute significantly to the loss of skeletal muscle force during aging and sarcopenia (O'Connell K, 2011).

These alterations collectively impair muscle mass, strength, and functional capacity, thereby exacerbating sarcopenia, increasing the risk of muscle injury, and contributing to the progression or worsening of other comorbid conditions (Alway SE, 2014).

Hence, in sarcopenia, early recognition and intervention—particularly through nutritional supplementation can "prime" satellite cells, enhancing their responsiveness to regenerative stimuli and supporting muscle health (Alway SE, 2014) (Kim KY, 2025). Moreover, age-related dysregulation of Notch and Wnt signaling pathways during muscle repair can be modulated by physiological stimuli and targeted nutritional strategies. These approaches show promise in rejuvenating aged muscle and offer a potential therapeutic strategy for managing sarcopenia (Arthur ST, 2012) (Montenegro KR, 2019).

Aspect	Mechanism/Change	Consequence	Reference
Satellite Cell Function	↓ Satellite cell density & reduced proliferation capacity	↓ Muscle regeneration potential and impaired repair	(Alway SE, 2014) (Huo F, 2022).
Replicative Senescence in Type II Fibers	Leads to telomere attrition and DNA damage	Further limits satellite cell regenerative potential	(Alway SE, 2014) (Huo F, 2022).
Notch Signalling Pathway	↓ Notch signalling activity	↓ Satellite cell proliferation & self-renewal	(Wiedmer P, 2021) (Sousa-Victor P, 2016)
Wnt Signaling Pathway	↑ Wnt signalling activity	Promotes myogenic-to-fibrogenic fate conversion → Fibrosis	(Wiedmer P, 2021) (Sousa-Victor P, 2016)
FGF2 Production	Continuous FGF2 secretion even without injury	Disrupts stem cell quiescence → Premature satellite cell depletion	(Alway SE, 2014) (Huo F, 2022)
Myogenic Regulatory Factors	↓ Expression of MyoD and myogenin	Impaired satellite cell activation, reduced muscle regeneration	(Kwan P. , 2013) (Alway SE, 2014) (Huo F, 2022)
Muscle Fibrosis	↑ Wnt signalling & ↓ Notch signalling promote excess connective tissue formation	Reduces functional muscle regeneration capacity	(Wiedmer P, 2021) (Sousa-Victor P, 2016)
Aging and Disuse-Related Changes	Imbalance in regenerative pathways, impaired quiescence, & reduced myogenic factor expression	Accelerates muscle degeneration, weakness, & atrophy	(Kwan P. , 2013) (Alway SE, 2014) (Huo F, 2022) (Wiedmer P, 2021) (Sousa-Victor P, 2016)

Reduced protein synthesis

Metabolic functions of muscle

Muscle's primary role is contraction, but its substantial mass and high protein content also make it a key reservoir for protein synthesis and energy, especially when other resources are limited (Argilés JM, 2016). It is essential for glucose uptake and stores glucose as glycogen, enabling rapid energy production during contraction even in the absence of dietary glucose. During increased energy demand, muscle undergoes proteolysis to release amino acids for energy. This process also occurs during prolonged starvation or protein-energy malnutrition, even when immediate energy needs are minimal (Argilés JM, 2016).

Aging, sarcopenia, and a sedentary lifestyle are associated with progressive alterations in muscle metabolism and a decline in functional capacity, often resulting in reduced independence. These metabolic changes are linked to structural modifications in muscle, accompanied by a loss of muscle mass and decreased insulin sensitivity (Shur NF, 2021).

Consequence of muscle loss

Muscle loss due to aging, sarcopenia, or a sedentary lifestyle result in muscle atrophy and the depletion of a vital amino acid reservoir. This progressive decline in muscle mass has significant clinical implications (Argilés JM, 2016).

Muscle Mass Loss	Clinical Consequences
10% loss	↓ Immunity, ↑ risk of infections
20% loss	↓ Wound healing, ↑ muscle weakness, ↑ risk of infections
30% loss	Difficulty sitting, ↑ risk of pressure ulcers & pneumonia, inability to heal
40% loss	Significantly increased risk of death

Preserving muscle mass is therefore critical for maintaining overall health, resilience, and survival (Argilés JM, 2016).

Muscle protein synthesis

Skeletal muscle protein synthesis is a highly regulated and dynamic process, influenced by nutritional status such as availability of amino acids, vitamin D, mechanical stimuli, repair mechanisms, hormones, growth factors, oxygen levels, and energy status. Among these, Insulin-like Growth Factor-1 (IGF-1) and availability of amino acids plays a pivotal role in regulating both anabolic and catabolic pathways (Dao T, 2020) (Graber TG, 2019) (Chen X, 2023).

All these promote muscle protein synthesis (MPS) via the phosphatidylinositol-3 kinase (PI3K)/ Protein Kinase B (Akt)/mammalian target of rapamycin (mTOR pathway), where:

- Akt activation stimulates mTOR, a key regulator of muscle growth.
- mTOR activation enhances ribosomal protein translation, leading to increased muscle protein synthesis.
- This process ensures muscle growth, repair, and adaptation to physical stimuli such as exercise.

Nutritional status, availability of amino acids, mechanical stimuli, repair mechanisms, hormones, growth factors, oxygen levels, & energy status

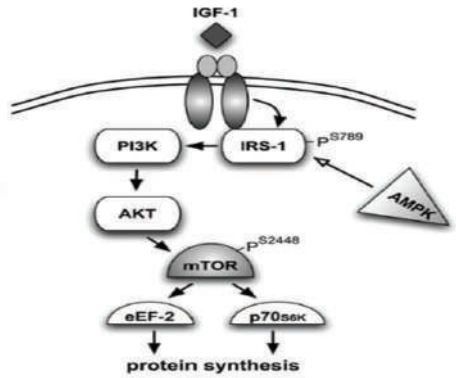


Figure: mTORC signaling pathway & muscle protein synthesis (Chambers MA, 2009)

Abbreviations: IGF-1- Insulin-like Growth Factor-1, IRS-1- Insulin Receptor Substrate-1, PI3K- Phosphoinositide 3-Kinase, AKT- Protein Kinase B, mTOR- mammalian Target of Rapamycin, eEF-2- eukaryotic Elongation Factor 2, p70S6K- p70 Ribosomal S6 Kinase

Other pathways for protein synthesis include:

- IGF-1 levels activate p70 ribosomal S6 kinase (p70S6K) which stimulates mRNA translation by phosphorylating ribosomal protein S6 (rpS6) and activation of eukaryotic elongation factor (eEF) 2 thereby activating muscle protein synthesis (Timmer LT, 2018).
- IGF-1 increases protein levels of β-catenin-a transcription factor involved in skeletal muscle growth by phosphorylation of glycogen synthase kinase 3 beta (GSK3β), which prevents atrophy and can even induce hypertrophy (Timmer LT, 2018).

Pathological Changes Affecting Muscle Protein Synthesis Leading to Muscle Weakness

A. Immobilization and Muscle Disuse

- Skeletal muscle disuse (bed rest, injury, or immobilization) reduces Akt and mTOR signalling, leading to a decline in muscle protein synthesis.
- More prolonged periods of bed rest have resulted in 30% reduction of muscle volume, particularly in muscles of the lower limbs (Rom O, 2012)
- After 15 days of unilateral lower limb immobilisation, vastus lateralis CSA decreased by ~15%, while muscle strength declined more markedly by 31%. Additionally, motor unit potential (MUP) size reduced by 11–24%, and motor unit firing rate decreased by 8–11% (Inns TB, 2022).

- Even brief periods of muscle disuse, such as 5 days, can lead to significant losses in skeletal muscle mass and strength, accompanied by reductions in quadriceps muscle CSA, leg lean mass, and an increase in muscle myostatin expression (Wall BT, 2014)
- Interestingly, evidence from disease-related disuse conditions shows that muscle atrophy is not limited to the affected limb alone reductions in lean body mass have also been observed in the unaffected limbs, which may be related to disrupted synaptic transmission of the muscle innervating motor neurons and lead to the reduction of motor unit numbers. So, which means even if not for the affected limb, the unaffected limb, which is having disuse atrophy, also needs to be supplemented. (Nakanishi N, 2021) (Scherbakov N D. W., 2011).
- Peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC-1α) which leads to upregulation of mitochondrial gene expression and an increase in mitochondrial DNA in tissues such as skeletal muscle is greatly influenced by levels of physical activity.
- During muscle atrophy and sarcopenia, there is a denervation of nerve fibers accompanied by a decline in PGC-1α expression
- In aging muscles, mitochondrial autophagy is reduced, leading to impaired clearance of damaged mitochondria. This is accompanied by a decline in neuromuscular innervation, reduced levels of PGC-1β which is critical for maintaining basal mitochondrial function, and decreased expression of mitochondrial transcription factor A (TFAM), an essential protein that binds mitochondrial DNA (mtDNA) to regulate transcription initiation and control mtDNA copy number (Hepple, 2010)
- There is also increased activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and glycogen synthase kinase 3 beta (GSK3β) pathways, which inhibit protein synthesis and muscle growth (Timmer LT, 2018) (Wiedmer P, 2021).
- All these results in muscle atrophy and loss of strength, as the rate of protein breakdown surpasses protein synthesis (Chen X, 2023) (Sakuma K, 2015) (Rom O, 2012).

B. Anabolic Resistance (AR)

- With aging, conditions like obesity, sedentary lifestyle, immobilization or bedrest muscle becomes resistant to anabolic stimuli, including IGF-1, mechanical loading, and protein intake—a phenomenon termed anabolic resistance (AR) (Paulussen KJM, 2021)
- Impairment of mTOR/AKT signalling may confer anabolic resistance, thus insensitivity to anabolic signals may reduce protein synthesis leading to reduction in muscle mass (Tan KT, 2020) (Tezze C, 2023)
- Branched-chain amino acids (BCAAs), particularly leucine, are known to activate the PI3K/Akt/mTOR signaling pathway in muscle fibers by activating mTOR, which stimulates protein synthesis by activating S6 kinase 1 (S6K1) (Ferrucci L, 2021).
- Low levels of BCAAs can diminish activation of this pathway, leading to reduced protein synthesis. Over time, this contributes to the accumulation of damaged proteins and progressive loss of muscle mass (Ferrucci L, 2021).
- This contributes to muscle mass loss, weakness, and physical frailty, increasing the risk of sarcopenia (Dao T, 2020) (Chaudhuri, 2024).
- In addition, to anabolic resistance, nutrient deficiencies like higher prevalence of vitamin D deficiency, reduced vitamin D receptor (VDR) expression in various tissues with aging can also leads to muscle atrophy, weakness, and a reduction in type II muscle fibers, contributing to inactivity, increased fall risk, and frailty (Das AK, 2025).

C. Insulin Resistance and Metabolic Dysregulation

- Physiologically, IGF-1 interacts with its tyrosine kinase receptor to phosphorylate insulin receptor substrate (IRS)-1 and activates PI3K/Akt signalling
- Thereafter, phosphorylated Akt activates mTOR which is tightly regulated by availability of amino acid to the cells. This inhibits forkhead box O3 (FoxO3-induces expression of genes involved in protein degradation pathways) resulting in phosphorylation of ribosomal protein S6 kinase which promotes protein synthesis (Kim J, 2023).
- In conditions like type 2 diabetes, metabolic syndrome, resting state, and aging insulin signalling is impaired, leading to reduced glucose uptake & muscle protein synthesis in skeletal muscle.
- Low IGF-1 levels can reduce cellular ATP

production, disrupting the ATP/AMP ratio and activating Adenosine monophosphate-activated protein kinase (AMPK). This inhibits mTOR activation, leading to the suppression of muscle protein synthesis (Marcotte-Chénard A, 2023)

- Low IGF-1 levels impair muscle protein synthesis by deactivating p70 ribosomal S6 kinase (p70S6K), which normally phosphorylates ribosomal protein S6 (rpS6) and activates eukaryotic elongation factor 2 (eEF2) to stimulate mRNA translation. Additionally, low IGF-1 fails to inhibit glycogen synthase kinase 3 beta (GSK3β), allowing it to remain active and further suppress protein synthesis pathways (Timmer LT, 2018) (Yoshida T, 2020).
- This exacerbates muscle loss and weakness, further contributing to metabolic dysfunction and frailty (Wiedmer P, 2021) (Chen X, 2023) (Chaudhuri, 2024) (Dao T, 2020) (Feng LT, 2024).

Table: Pathological Aspects and Their Mechanisms

Pathological Aspect	Mechanism
Immobilization & Muscle Disuse	↓Akt/mTOR signalling →↓ Muscle protein synthesis; ↓ PGC-1α expression → ↓ Mitochondrial gene expression
	↑ MAPK pathway, ↑ NF-κB, & ↑ GSK3β pathways →↓ protein synthesis
Anabolic Resistance (AR)	Impaired mTOR/Akt signalling → Insensitivity to anabolic stimuli like IGF-1, mechanical loading, & protein intake
Insulin Resistance and Metabolic Dysregulation	Impaired IGF-1/IRS-1/PI3K/Akt signalling → ↓ Glucose uptake & ↓ Muscle protein synthesis; Low IGF-1 → ↓ ATP production → AMPK activation → ↓ mTOR activity

4.Increased proteolysis

Skeletal muscle atrophy is driven by two major proteolysis systems: the ubiquitin–proteasome system (UPS) and the autophagy–lysosome system (ALS). Under conditions such as aging, injury, chronic disease, reduced muscle use, bed rest, immobilization, a sedentary lifestyle, and an anabolic resistance, the UPS becomes significantly activated, leading to disruptions in protein homeostasis and the accumulation of protein aggregates (Dao T, 2020).

A. Ubiquitin–Proteasome System (UPS) and Muscle Degradation

The UPS is a key regulator of muscle protein degradation, responsible for breaking down of damaged proteins. The major muscle-specific E3 ubiquitin ligases involved in muscle atrophy are:

- Muscle Atrophy F-box (MAFbx/atrogin-1)
- Muscle RING-finger 1 (MuRF1)

These ligases tag muscle proteins for degradation, contributing to muscle wasting and loss of function (Kim J, 2023) (Wu J, 2023)

B. Autophagy–Lysosome System (ALS) and Its Role in Protein Clearance

The autophagy–lysosome system (ALS) complements the UPS by degrading misfolded and aggregated proteins that are not efficiently processed by the proteasome. Within lysosomes, an acidic pH environment, combined with hydrolases and proteases, enables the effective breakdown of dysfunctional cellular components.

However, in the above-mentioned conditions, the clearance capacity of the ALS declines, leading to:

- Insufficient removal of damaged proteins and dysfunctional organelles
- Increase oxidative stress, which further damages muscle cells (Kim J, 2023) (Wu J, 2023) (Jiao J, 2017)

Studies have shown that autophagy defects in satellite cells impair their regenerative ability, contributing to muscle loss, strength, and weakness. This decline in autophagy diminishes the muscle's ability to repair itself (Wu J, 2023). As a result, muscle fiber degeneration occurs, and the progression of muscle dysfunction has been shown to negatively impact motor neurons, which can ultimately lead to sarcopenia (Kanova M, 2022).

Conversely, activating autophagy promotes muscle regeneration by (Wu J, 2023) (Jiao J, 2017):

- Clearing senescent cells before they accumulate and impair muscle function
- Maintaining satellite cell function, which is crucial for muscle repair and recovery

Mitochondrial abnormalities & dysfunctional bioenergetics

Mitochondria are essential organelles that regulate skeletal muscle metabolism, ensuring optimal energy production, oxidative capacity, and muscle strength (Kim J, 2023). The maintenance of mitochondrial structure and function is crucial for preserving muscle fitness, which is achieved through a balance of mitochondrial dynamics (fusion and fission), biogenesis, and mitophagy (Kim J, 2023) (Chen X, 2023).

Mitochondrial fusion allows damaged mitochondria to merge with healthy ones, compensating for defects and ensuring efficient ATP production. In contrast, fission facilitates the formation of new mitochondria while also isolating dysfunctional parts for removal via mitophagy, a selective autophagy process that degrades damaged mitochondria to prevent oxidative stress. Meanwhile, mitochondrial biogenesis, primarily regulated by PGC-1α, ensures the continuous generation of new mitochondria, maintaining mitochondrial content and energy supply (Chen X, 2023) (Kubat GB, 2023).

In addition to these dynamic processes, mitochondrial function is supported by key enzymes such as citrate synthase (CS), which plays a vital role in the tricarboxylic acid (TCA) cycle and cellular ATP production. Under steady-state conditions, mitophagy and biogenesis occur at balanced rates, ensuring that mitochondrial turnover supports metabolic demands while preserving muscle health. This continuous renewal and adaptation allow skeletal muscle to efficiently meet energy requirements, maintain oxidative capacity, and resist fatigue. The proper regulation of mitochondrial homeostasis is essential for skeletal muscle fitness, strength, and metabolic efficiency, allowing skeletal muscle to function optimally during both rest and activity (Standley RA, 2020) (Kim J, 2023).

Pathological Changes in Muscle Disuse and Sarcopenia

In conditions of muscle disuse, such as prolonged inactivity due to hospitalization, bed rest, a sedentary lifestyle, or injury, mitochondrial homeostasis is disrupted, leading to (Alizadeh Pahlavani H, 2022) (Standley RA, 2020) (Kim J, 2023) (Bellanti F, 2021)

A. Decline in Mitochondrial Biogenesis:

- PGC-1α expression is reduced, leading to fewer new mitochondria, impairing muscle energy metabolism.
- Low BCAAs availability also directly impacts mitochondria by a deficit in mitochondrial metabolism by under expression of PGC-1α, a master regulator of mitochondrial biogenesis (Ferrucci L, 2021).
- This results in a decline in mitochondrial content and ATP production capacity.

B. Dysfunctional Mitophagy and Increased Mitochondrial Damage:

- Mitophagy becomes impaired, leading to the accumulation of damaged, non-functional mitochondria.
- Fission-related removal of defective mitochondria is disrupted, causing oxidative stress and mitochondrial inefficiency.

C. Reduced Enzymatic Activity and Oxidative Capacity:

- Citrate synthase (CS) activity decreases, compromising the electron transport chain (ETC) and reducing oxidative phosphorylation efficiency.
- This leads to low ATP production, increasing muscle fatigue and weakness.

D. Increased Oxidative Stress and ROS Production:

- Dysfunctional mitochondria generate excessive reactive oxygen species (ROS), leading to mtDNA damage, protein degradation, and muscle fiber apoptosis.
- This oxidative damage exacerbates mitochondrial dysfunction, further accelerating muscle loss.

Reduced in the number of actin–myosin cross-bridges formation

Immobilization, muscle disuse, and sarcopenia reduce the concentration of myosin, the motor protein essential for muscle contraction. Since myosin plays a crucial role in forming cross-bridges, its depletion leads to fewer cross-bridges per muscle fiber area,

reducing the muscle's ability to generate force (Frontera WR, 2012) (Miljkovic N, 2015). Muscle injury usually is also associated with disruption of the actin/myosin filaments resulting in rupture of the myofiber and tearing of the sarcolemma (Gillespie MA, 2006). Damage to the muscle fiber compromises its ability to maintain calcium homeostasis, increasing intracellular calcium levels, which in turn activates the M-calpain protease system and leads to degradation of myofibrils (Faulkner JA, 2011).

In addition to myosin reduction, glycogen depletion further impairs muscle performance. Reduced glycogen reserves decrease ATP cleavage, limiting energy production needed to power cross-bridge cycling. Moreover, intermyofibrillar glycogen is believed to fuel the release of calcium (Ca^{2+}) from the sarcoplasmic reticulum, which activates tropomyosin active sites. Consequently, glycogen depletion hampers calcium release, further impairing muscle contraction (Knuiman P, 2015) (Mukul Kansal, 2024) (Frontera WR, 2012) (Miljkovic N, 2015).

Furthermore, a pathophysiological disconnection between sarcolemmal excitation and muscle contraction may occur with aging and sarcopenia. This includes alterations in the voltage-gated Ca^{2+}release mechanism, decreased myoplasmic Ca^{2+} elevation in response to membrane depolarization, reduced calcium supply to the actomyosin apparatus, and overall diminished contractile strength. Abnormal calcium handling is therefore believed to contribute significantly to the loss of skeletal muscle force during aging and sarcopenia (O'Connell K, 2011).

Lastly, aging complexes these issues by promoting both myosin loss and glycogen depletion. Additionally, the decline in physical activity associated with aging further exacerbates these effects, contributing significantly to muscle weakness and functional decline. This combined impact of immobilization, muscle disuse, glycogen depletion, and aging creates a powerful synergy that severely compromises muscle strength and cause muscle weakness function (Knuiman P, 2015) (Mukul Kansal, 2024) (Frontera WR, 2012) (Miljkovic N, 2015).

Lactic acid build-up and muscle weakness

Lactate formation is a process that occurs both at rest and during physical activity. During muscle contraction, ATP is rapidly consumed by myosin ATPase to power the cross-bridge cycle between actin and myosin filaments, enabling force production. Since ATP stores are limited, muscles initially rely on phosphocreatine (PCr) to regenerate ATP quickly. As PCr stores decline with continued muscle activity, glycogenolysis is activated to provide glucose for energy. This glucose enters the glycolytic pathway, producing pyruvate and ATP. In low-intensity exercise, pyruvate is primarily directed into the mitochondria for aerobic metabolism, supporting efficient energy production. However, during high-intensity exercise, mitochondrial capacity may be overwhelmed, causing excess pyruvate to be converted into lactate with the help of enzyme lactate dehydrogenase (LDH) and is directly associated with the production of H^+ ions in the myoplasm (Cairns, 2006).

Pathological Impact of Excessive Lactate Accumulation

A. Intracellular pH Decline:

- With intense glycolysis, accumulating hydrogen ions (H^+) lower the intracellular pH.
- A reduced pH impairs the excitation-contraction coupling mechanism, disrupting calcium binding and weakening muscle contractions (Myers J, 1997).

B. Increased Recruitment of Type IIb Fibers:

- As fatigue develops, the body compensates by recruiting more Type IIb fibers, which are heavily glycolytic.

This intensifies:

- Glycogenolysis leads to accelerated glucose breakdown.
- Lactate production leads to further lactate accumulation

C. Calcium Displacement and Muscle Dysfunction:

- Excessive H^+ ions compete with calcium ions (Ca^{2+}) within muscle fibers, disrupting calcium binding to troponin.

- This interferes with the actin-myosin cross-bridge cycle, reducing muscle force generation
- This combined effects of impaired calcium handling, reduced pH, and rising lactate levels result in muscle fatigue, weakness, and decreased endurance and performance (Seow KN, 2022) (Myers J, 1997) (Todd, 2014) (Surenkok O, 2006) (Bartoloni B, 2024).

Mechanisms for impaired muscle function with lactic acid build-up

Myofilament function	↓Maximum force (↓maximum cross-bridge cycling)
	↓ Ca^{2+} sensitivity (↓ Ca^{2+} binding to troponin)
	↓ Maximum velocity of shortening (↓ myosin ATPase activity)
Excitation-contraction coupling	↓ Ca^{2+} release by SR
	↓ Ca^{2+} uptake by SR

Increased levels of LDH in sarcopenia can be understood as a reflection of muscle damage, chronic inflammation, metabolic stress, and metabolic dysfunction especially in patients with chronic inflammation or comorbid conditions. All these suggest that LDH could reflect muscle injury and impaired energy metabolism in patients with sarcopenia (Sun Y, 2025).

Neurogenic components

Voluntary force is the result of a coordinated process that begins in the brain which involves signals from the motor cortex that activate motor neurons, followed by motor neuron discharge, transmission across the neuromuscular junction (NMJ), and the resulting muscle contractile response. These signals trigger muscle fibers to contract, ultimately producing force. This entire pathway from brain activation to muscle contraction works in coordination to generate voluntary movement (Venturelli M, 2022).

It is well-established that potential candidates for age-related decline in voluntary force or sarcopenia include the reduction in the number of motor neurons, alterations in motor unit (MUs) structure and function, reduced motoneuron firing rate, failure of NMJ, decreased density of postsynaptic acetylcholine receptors, and decreased neurotrophic factors causing attenuated skeletal muscle contractility leading to muscle weakness and reduced force generation (Venturelli M, 2022) (Kwan, 2013) (Moreira-Pais A, 2022) (Kwon YN, 2017).

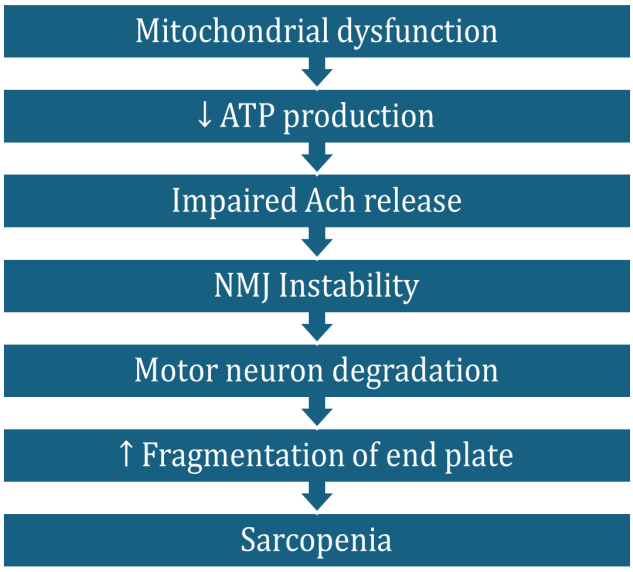
Common pathophysiology shared between the Nervous System and the Muscular system in muscle weakness

Interestingly, several factors contribute to this process, including mitochondrial dysfunction, increased oxidative stress, inflammaging, disrupted protein turnover, and reduced levels of hormones & growth factors. A decline in essential nutrient intake and reduced physical activity or muscle disuse can further worsen the issue. These changes are not unique to the muscular system but are also applicable to the nervous system (Kwan, 2013). The same are discussed in detail in the myogenic components of muscle weakness.

Mitochondrial dysfunction:

Mitochondria are present at both pre- and post-synaptic sites of the neuromuscular junction (NMJ), where they play a critical role in maintaining synaptic function. Mitochondrial dysfunction leads to reduced ATP production, impaired acetylcholine release, and dysregulation of calcium and reactive oxygen species (ROS) (Miao Y, 2024) (Hyatt HW, 2021).

These disturbances compromise NMJ stability and synaptic transmission, contribute to motor neuron degeneration, and increase fragmentation of the motor endplate. Consequently, there is activation of atrogenes, enhanced proteolysis, and reduced protein synthesis, collectively driving the progression of sarcopenia (Miao Y, 2024) (Hyatt HW, 2021)



Oxidative stress & inflammation

Reactive oxygen species (ROS) such as peroxynitrite, superoxide, and lipid hydroperoxides generated by mitochondria—particularly under conditions of aging or disease—contribute significantly to motor neuron damage, leading to denervation and loss of innervation. This disrupts the structural and functional integrity of the neuromuscular junction (NMJ), impairing muscle activation and increasing muscle protein breakdown. As a result, sarcopenia develops, characterized by progressive muscle weakness and a decline in contractile function. While acute denervation, such as that caused by oxidative stress, is often followed by compensatory reinnervation, this process becomes increasingly inefficient with age. Repeated cycles of denervation and reinnervation alter the spatial arrangement of motor units and can shift muscle fiber type composition to type 1. However, in aging and sarcopenia, the failure of adequate reinnervation leads to persistent denervation, exacerbating muscle atrophy and further compromising muscle contractility and reduced force output (Xu H, 2024) (Thoma, 2020) (Meng SJ, 2010).

Decreased Hormones & Growth Factors

Decline in sex hormones, including androgens and estrogens, may negatively impact neuronal health since they have neuroprotective effects (Kwan, 2013). In addition to this, hormonal changes lead to a reduction in key growth factors that are critical for maintaining the health of both muscle cells and neurons. For instance, growth hormone (GH) regulates the synthesis of IGF-1, which supports neuronal survival. Following a nerve injury, local IGF-1 levels increase and promote axonal sprouting into denervated muscle, facilitating neuromuscular repair. Similarly, ciliary neurotrophic factors (CNTFs) act as important hypertrophic and neurotrophic agents, supporting the maintenance and re-innervation of muscle fibers by motor neurons after muscle or nerve injury. The decline in these hormones and growth factors may therefore have significant consequences on both the muscular and nervous systems, contributing to impaired neuromuscular connectivity and ultimately leading to sarcopenia (Kwan, 2013) (Slavin BR, 2021).

Loss of MUs

During aging, sedentary lifestyle, and in sarcopenia, the loss of motor neurons is attributed to a decline in the synthesis of ciliary neurotrophic factor (CNTF)—a critical protein that supports motor neuron survival and differentiation (Narici MV, 2010) and compromised release of Sema3A by SCs, which plays a critical role in guiding axonal regrowth. As a result, the coordination required for effective muscle-nerve communication and reinnervation may be disrupted in the elderly, contributing to impaired muscle repair and functional decline (Fard D, 2024) By the seventh decade of life, healthy older adults have approximately 40% fewer motor units (MUs) compared to young individuals. A study reported that muscle mass, motor unit number, and maximal muscle strength were significantly reduced across aging groups: reductions of 8%, 30%, and 44% in muscle mass; 33%, 47%, and 50% in MU number; and 34%, 39%, and 49% in maximal strength were observed in non-sarcopenic, pre-sarcopenic, and sarcopenic older men, respectively (Kirk B P. M., 2021).

As motor neurons are lost, denervated muscle fibers may be reinnervated by neighboring slow-twitch motor neurons through collateral sprouting. This process, known as motor unit remodeling, is a crucial adaptive response that preserves muscle function by converting denervated fast-twitch (type II) fibers into slow-twitch (type I) fibers (Coletti C, 2022) (Wiedmer P, 2021). However, this reinnervation is not always successful. While collateral sprouting can restore neuromuscular connections in the early and moderate stages of denervation, its capacity becomes limited in later stages of aging or in the presence of severe nerve damage (Carlson, 2014). In such cases, the ability of motor neurons to regenerate is minimal, leading to progressive muscle atrophy, where muscle fibers shrink and are gradually replaced by fibrous tissue and fat (Carlson, 2014). In sarcopenia, this reinnervation process fails, resulting in no significant expansion of motor unit size. Therefore, the inability to remodel and enlarge motor units effectively distinguishes sarcopenic muscles from those in the pre-sarcopenic stage. This suggests that loss of reinnervation capacity is a key turning point in the progression from healthy aging to sarcopenia. All of these reduce muscle force, strength, and the force output required to perform activities of daily living (ADL) (Piasecki M, 2018).

Loss of Muscle Fibers

The loss of MUs largely correlates with the loss of muscle fibers in aging. Autopsy work comparing the quadriceps muscle of younger and older men demonstrated a substantial reduction in the number of muscle fibers (~214000) in the latter cohort (Kirk B P. M., 2021) (Lexell JA, 1983). Studies have shown that the CSA of the quadriceps muscle using CT have shown decrements of around 25–35% between older subjects and young normal controls (Lang T, 2010). It should be noted that total muscle atrophy may not be specific to the loss of type II fibers alone; however, the loss of type II fibers is suggested to occur at a more rapid rate, which is likely a direct consequence of the neuromuscular remodeling phenomenon leading to muscle weakness and atrophy (Kirk B P. M., 2021).

Reduced firing capacity of motoneuron

Motor unit (MU) firing rates have been shown to decline significantly with age, with reductions of approximately 30–35% observed in older adults compared to younger individuals during both submaximal and maximal intensity contractions. This decline in firing capacity is largely attributed to age-related motor unit remodeling, which includes the loss of larger, high-threshold muscle fibers that possess the greatest force-generating capacity and fastest discharge rates. Concurrently, there is a phenotypic shift toward slower type I muscle fibers, further contributing to reduced motor output (Kirk B, 2021).

Such impairments in neural activation directly affect the ability to perform activities of daily living (ADLs). For example, the effort required to rise from a chair increase from 42% of maximal strength in young adults to 80% in older adults. Similarly, ascending and descending stairs demand significantly higher relative effort in older individuals (78% and 88%, respectively) compared to their younger adults (54% and 42%). Electromyographic data indicate that knee extensor and flexor muscle activation during these tasks is 2-fold and 1.6-fold higher, respectively, in older adults (Kirk B, 2021).

Furthermore, evidence suggests that older adults with low skeletal muscle mass (presarcopenia) demonstrate abnormal motor unit firing patterns, deviating from the normal hierarchical recruitment order observed in healthy individuals. This indicates that neuromuscular dysfunction in aging is not limited to muscle atrophy but also involves altered neural input and coordination (Hirono T, 2024).

In support of this, Wages et al. (2024) reported that weak older adults exhibited an approximate 3 Hz reduction in motor unit firing rates compared to their non-weak adults during contractions at 80% of maximal voluntary contraction (MVC). Computational modeling predicted that such a reduction corresponds to an 11–26% loss in muscle strength. Moreover, slower MU firing rates were significantly associated with poorer neuromuscular quality, reduced voluntary activation, longer chair rise times, and diminished stair climbing power. These findings underscore a mechanistic link between impaired motor unit firing and clinically meaningful leg extensor weakness in older adults (Wages NP, 2024).

Failure of Neuromuscular Junction (NMJ) & Decreased Ach Receptors

The neuromuscular junction (NMJ) is a specialized synapse where motor neurons communicate with skeletal muscle fibers to initiate contraction through the release of acetylcholine (ACh). This process depends on the efficient activation of ACh receptors (AChRs) on the postsynaptic membrane. Notably, muscle fibers also send signals that support motor neuron survival, emphasizing the importance of bidirectional communication between nerve and muscle (Moreira-Pais A, 2022).

With aging and in conditions like sarcopenia, this communication becomes impaired due to structural and functional deterioration of the NMJ. Such disruption contributes to progressive muscle weakness and atrophy (Moreira-Pais A, 2022).

Morphological hallmarks of NMJ degeneration observed in aging and sarcopenia include:

- Thinning of motor axons
- Dysfunctional Schwann cells
- Reduced synaptic vesicle density
- Degeneration and elongation of junctional folds
- Widening of the synaptic cleft
- Increased axonal sprouting
- Fragmentation and mislocalization of AChR clusters
- Lower postsynaptic AChR density
- Synaptic detachment and fragmentation of the postsynaptic apparatus

Studies in intercostal muscles from individuals revealed fragmented postsynapses, degenerated junctional

folds, and an increased number of smaller, disorganized AChR conglomerates, rather than a single dense cluster. These findings strongly indicate progressive NMJ and muscle fiber degeneration (Moreira-Pais A, 2022).

Such anatomical remodeling of the NMJ can impair synaptic efficiency, leading to a faster decline in endplate potential strength during repeated neuronal stimulation, further compromising muscle function (Kwon YN, 2017) (Moreira-Pais A, 2022).

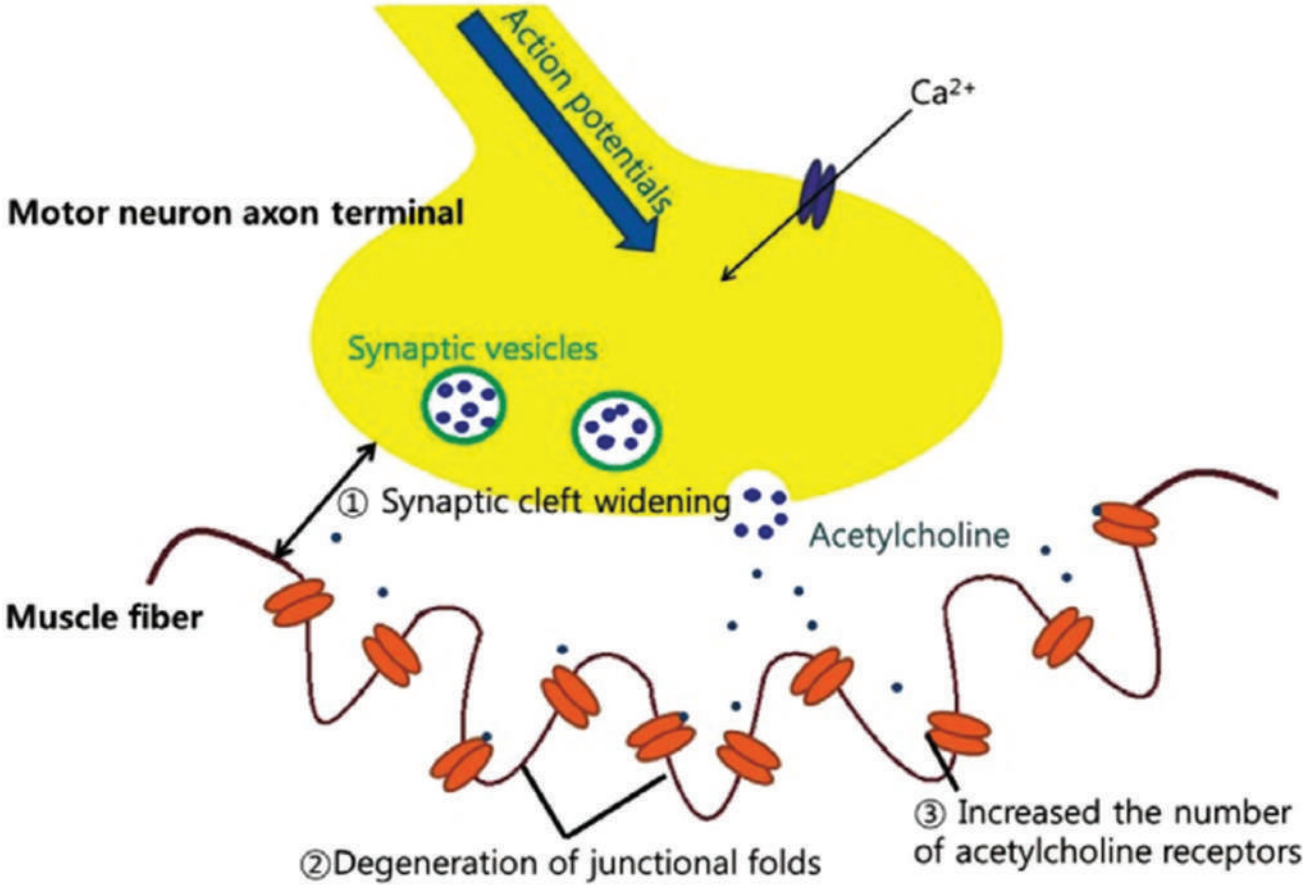
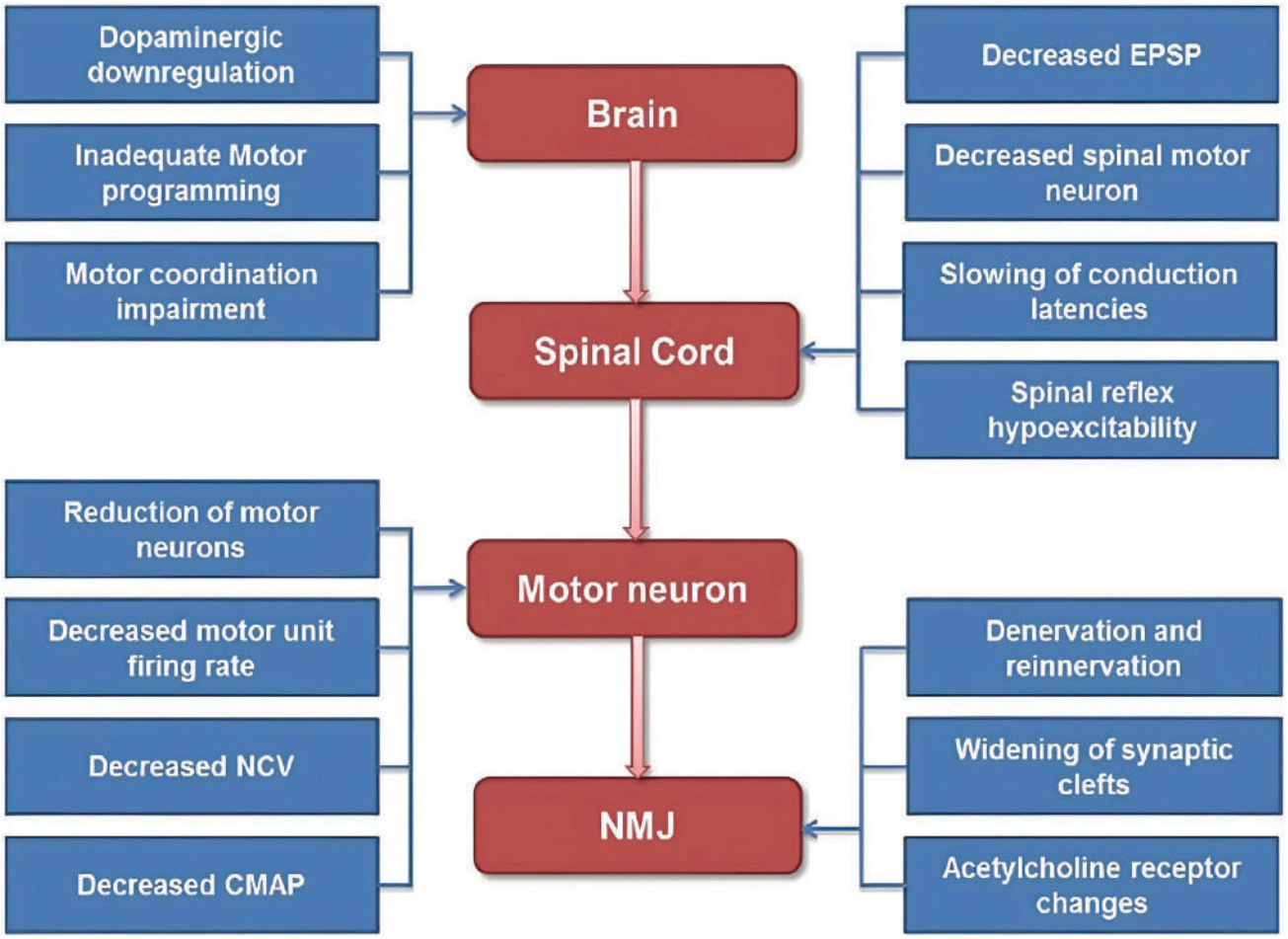


Figure: Anatomical remodelling of NMJ (Kwon YN, 2017).

All these above processes involve the selective denervation of type II (fast-twitch) muscle fibers, followed by collateral reinnervation by type I (slow-twitch) motor units. While this adaptation preserves some muscle mass, it results in a shift toward slower muscle function and a decline in overall muscle power, as fast-twitch fibers are primarily responsible for generating strength and speed (Kwon YN, 2017). In addition, central nervous system changes such as reduced dopamine levels, decreased postsynaptic dopamine receptor density, and impaired presynaptic dopamine transport negatively affect reward processing and motivation for physical activity. This dopamine dysregulation further contributes to reduced movement and subsequent muscle atrophy (Kwon YN, 2017). Moreover, spinal cord degeneration, including axonal demyelination, diminishes excitatory postsynaptic potentials and promotes fibrotic changes. These alterations impair neuromuscular signaling and further exacerbate declines in muscle strength, mass, and physical performance seen in aging and sarcopenia (Kwon YN, 2017).



Abbreviations: EPSP- Excitatory postsynaptic potentials; NCV- Nerve conduction velocity; CMAP- Compound muscle action potentials; NMJ- Neuromuscular junction.

Figure: Summary of neurological mechanisms of sarcopenia (Kwon YN, 2017)

Section III: ImproSyn Product Information

11. Product Based Scientific Information

In all the above discussed conditions, muscle weakness and atrophy arise from a combination of reduced protein synthesis and increased protein degradation. Therefore, an ideal supplementation strategy would be one that enhances protein synthesis, promotes muscle mass, and inhibits protein breakdown. While the underlying disease is addressed through primary therapy, there remains a critical need for muscle-specific supplementation to counteract muscle loss and improve muscle strength. Such an approach can support better functional outcomes, including the attenuation of muscle mass loss, decline in strength, and impaired muscle function, ultimately optimizing the overall effectiveness of the primary treatment (Cretoiu SM, 2018)

Composition of ImproSyn

Ingredient	Dose
Calcium β-Hydroxy β-Methyl Butyrate (CaHMB)	750 mg
L-Carnosine	150 mg
Astaxanthin 10%	10 mg

Calcium β-Hydroxy β-Methyl Butyrate (CaHMB)

Beta-hydroxy-beta-methylbutyrate (HMB) is a naturally produced metabolite of the essential amino acid leucine in humans (Holeček, 2017). It has emerged as a promising agent for muscle health and its benefits are discussed below (Holeček, 2017) (Bideshki MV, 2025).

HMB

- **Increases:** Muscle mass, muscle strength, muscle growth, muscle quality, lean body mass, functionality, & endurance
- **Reduces:** Muscle loss in disuse conditions, muscle damage, & muscle soreness, & fatigue
- **Supports/Maintains:** Muscle contraction, muscle repair, muscle recovery after disease, preserve muscle mass

It exerts positive effects both in healthy (reducing exercise-related muscle damage) and pathological conditions (i.e. preserving and increasing muscle mass). HMB is unique in its dual mechanism by reducing protein degradation and enhancing protein synthesis, thus improving the net muscle protein buildup, protecting muscle strength, survival, and stability during times of inactivity to help maintain physical independence with proven safety and no significant adverse effects (Molfino A, 2013).

Figure: Benefits of HMB

HMB mechanism of action (Landi F, 2021) (Bideshki MV, 2025) (Molfino A, 2013) (Arazi H, 2019) (Kim D, 2022) (Arazi H T. B., 2018)

Mechanism	Effect
↑ mTOR pathway	↑ Protein synthesis
↑ Growth hormone/IGF-1axis	↑ Protein synthesis
↓ Autophagy	↓ Apoptosis
↑ Mitochondrial biogenesis (↑ PGC-1α, ↑ Citrate synthase)	↑ ATP synthesis, ↑ Protein synthesis
↑ HMG-CoA synthesis	↑ Tissue repair & enhance sarcolemma integrity
↓ Ubiquitin/proteasome system	↓ Proteolysis
↑ Calcium release from SR	↑ Excitation and contraction coupling
↑ Proliferation of satellite cells (↑ MRFs such as MyoD and MEF2 & activation of the MAPK/ERK and PI3K/Akt pathways)	↑ Tissue repair & improves the repair of sarcolemma after contractile activity
Improves aerobic capacity	↑ Mitochondrial biogenesis & fat oxidation
	↑ Hormone-sensitive lipase (HSL) gene and protein expression in white adipose tissue → ↑ GH levels, leading to ↑ lipolysis
Delaying acute muscle fatigue	Increasing the content of mitochondrial acetyl-CoA through the conversion of HMG-CoA into acetoacetyl-CoA
Increasing ATP and glycogen content in skeletal muscle	Accelerating the TCA cycle, increasing malate-aspartate shuttle, and providing needed carbon for glycogen synthesis
↓Levels of pro-inflammatory cytokines	Antioxidant & ↓ oxidative stress

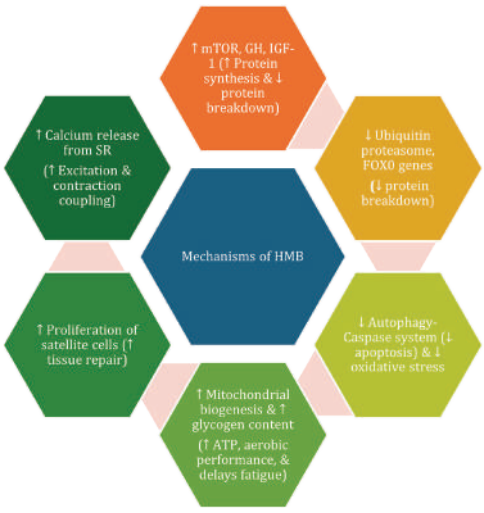


Figure: An overview of potential pathways of HMB (Landi F, 2021) (Arazi H T. B., 2018)

- HMB enhances myofibrillar protein synthesis via the mTOR pathway and the growth hormone/ IGF-1axis pathway (Landi F, 2021)
- It enhances mitochondrial energy production by increasing the levels of PGC-1α, and citrate synthase (Molfino A, 2013)

- It prevents muscle protein breakdown via the ubiquitin proteasome, autophagy–lysosome systems, down-regulation of caspases, decreasing the apoptosis of myonuclei and inhibiting MuRF-1 expression and atrogenes by phosphorylation of FoxO1 (Landi F, 2021) (Arazi H T. B., 2018)
- It increases the SCs proliferation, by enhancing the MRFs (Landi F, 2021) (Arazi H T. B., 2018)
- On the other hand, the HMB hampers inflammation and reduces the protein degradation process. In particular, the HMB hinders the stimulation of caspase-8, nuclear factor kappa B (NFκB) & atrogenes, thus inhibits the downregulation of protein synthesis. Hence, HMB preserves protein synthesis and counteracts additional protein degradation (Landi F, 2021)
- It improves aerobic capacity by ↑ mitochondrial biogenesis & fat oxidation, ↑ hormone-sensitive lipase (HSL) gene and protein expression in white adipose tissue, → ↑ GH levels, enhances lipolysis, and increases lipid availability (Arazi H T. B., 2018)
- It delays acute muscle fatigue by increasing the content of mitochondrial acetyl-CoA through the conversion of HMG-CoA into acetoacetyl-CoA (Arazi H T. B., 2018)
- It increases ATP and glycogen content in skeletal muscle by accelerating the TCA cycle, increasing malate-aspartate shuttle, and providing needed carbon for glycogen synthesis (Arazi H T. B., 2018)
- Overall, HMB has been demonstrated to stabilize the muscle cell membrane by increasing HMG-CoA synthesis, downregulate the protein degradation, and upregulate the protein synthesis (Landi F, 2021)
- The use of HMB in one's regimen has the potential to accelerate the recovery process and boost muscular hypertrophy by mitigating muscle injury

Metabolism of HMB

Once HMB is taken, it is absorbed through the small intestine and enters the bloodstream (Ribeiro HR, 2024). It is then distributed to peripheral tissues, primarily skeletal muscle, where it performs its physiological roles as discussed in the above section. During this process, HMB also contributes to the production of a small amount of cholesterol, which is utilized locally within the muscle tissue (Ribeiro HR, 2024) without increasing circulating cholesterol levels (Mccullough PA, 2015). The locally produced small amount of cholesterol is primarily used to support the stabilization and repair of the muscle cell membrane (sarcolemma), especially during periods of muscle damage (Mccullough PA, 2015). The dosage of HMB, used is 1.5 grams, which is small and sufficient to meet the muscle's need with small amount of localized cholesterol production, contributing to muscle integrity and repair without significantly affecting systemic cholesterol levels (Mccullough PA, 2015).

Therefore, when supplemented directly, HMB bypasses the need for conversion from leucine (which gives only a small quantity of HMB), allowing for more targeted and efficient physiological effects on muscle. This direct route of action highlights why HMB supplementation cannot be fully substituted by leucine, especially when the goal is to achieve specific anti-catabolic and anabolic outcomes.

Receptor & entry into muscle cells

HMB is a monocarboxylate and is transported into skeletal muscle through monocarboxylate transporters, such as H^+coupled monocarboxylate transporters (MCTs), particularly MCT1 and MCT4, as well as sodium-coupled transporters like SMCT1 (Ogura J, 2019). However, HMB uptake in skeletal muscle primarily occurs through H^+ coupled monocarboxylate transporters (MCTs), which are more abundantly expressed than SMCT1, the latter being present at much lower levels in muscle tissue. Therefore, MCTs are likely the major pathway for HMB accumulation in skeletal muscle (Ogura J, 2019).

Under normal physiological conditions, plasma lactate levels (~1 mM) are higher than those of HMB (~0.5 mM with supplementation), and since both are transported via the same MCTs, they naturally compete for entry into muscle cells. At first glance, this might suggest that lactate would outcompete HMB. However, a key physiological mechanism known as trans-stimulation by intracellular lactate ensures efficient HMB uptake (Ogura J, 2019).

Trans-stimulation by intracellular lactate

During muscle activity, lactate accumulates inside muscle cells, especially under anaerobic conditions. This internal lactate can stimulate MCT activity from the opposite side (the bloodstream), promoting the influx of HMB — a phenomenon known as trans-stimulation. This mechanism allows HMB to enter muscle cells more efficiently, even without a strong proton gradient or despite external competition from lactate (Ogura J, 2019).

This suggests that when adequate HMB is not available for uptake into muscle cells, lactate accumulates within the muscle tissue, leading to muscle pain and fatigue. This also suggests, in muscles, where lactates are produced in higher quantities, HMB may outcompete this mechanism and supersede to reduce lactate levels biochemically, through restoration of healthy muscle biology, and through improvement in muscle bulk.

Dose of HMB

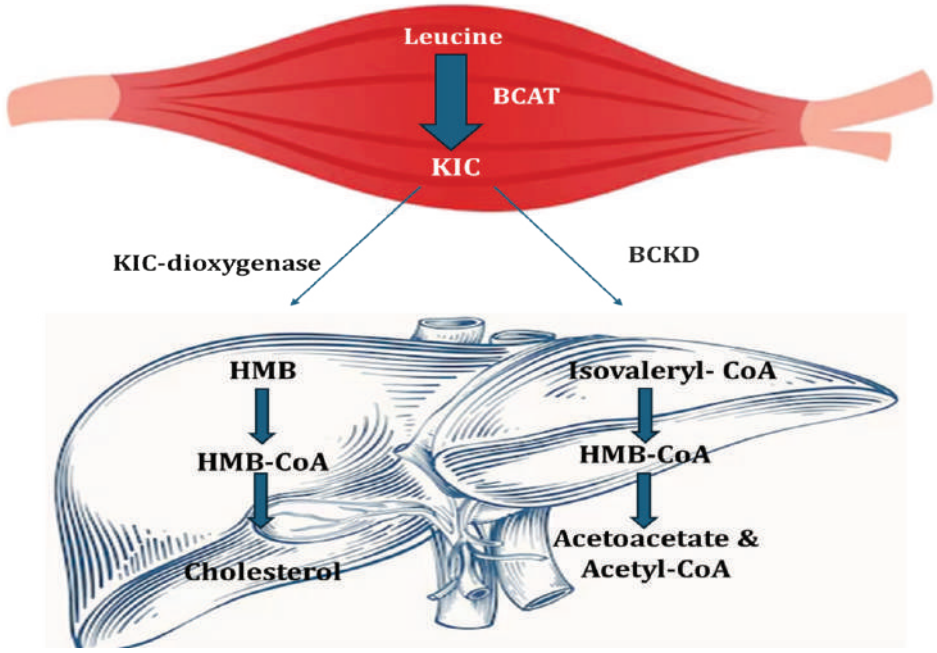
Several studies have been published globally on HMB (1-6 grams), and currently in India, a dosage range of 1.5 to 6 grams per day is approved by the regulatory authorities. This dosage regimen is supported by multiple clinical studies. Notably, most of the studies recommended higher HMB doses involving HMB as a single active ingredient (Rathmacher JA, 2025) (Jacob M Wilson, 2013) (Tsuchiya Y, 2021). Whereas Improsyn is a combination of myotrophic ingredients consisting of HMB, L-Carnosine, and Astaxanthin.

BCAAs in the muscle growth and maintenance

Leucine is recognized as a most potent and widely used amino acid supplement, due to its central role as the primary driver of muscle protein synthesis (MPS) (Li G, 2024).

Leucine, a branched-chain essential amino acid (BCAAs), is primarily metabolized in skeletal muscle. The metabolic process begins with the reversible transamination of leucine to α-ketoisocaproate (KIC), catalyzed by the enzyme branched-chain amino acid aminotransferase (BCAT), which is highly active in skeletal muscle and further leading to formation of HMB in the liver. Unlike many other amino acids, leucine and the other BCAAs are not extensively metabolized in the liver due to its low expression of BCAT (Landi F, 2021) (Holeček, 2017).

Subsequently, KIC is irreversibly converted into isovaleryl-CoA, through the action of the branched-chain α-keto acid dehydrogenase (BCKD). In the next step, isovaleryl-CoA is further metabolized to β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) leading to cholesterol synthesis (Landi F, 2021) (Holeček, 2017). The cholesterol synthesized (small amounts) from HMG-CoA in muscle tissue is used locally, playing a crucial role in maintaining and repairing the muscle cell membrane (sarcolemma), particularly during episodes of muscle damage or stress (Mccullough PA, 2015).



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Is Leucine Alone Sufficient to Meet HMB Requirements?

Although small amounts of HMB are naturally present in some foods, only about 5% of dietary leucine is converted to HMB in the body. In a healthy adult weighing 70–80 kg, this conversion results in the endogenous production of approximately 0.2–0.4 grams of HMB per day, which may not be sufficient to support metabolic needs during times of catabolic stress and healing (Landi F, 2021).

Leucine Supplementation and BCAA Imbalance: A Double-Edged Sword

Supplementation with leucine alone can also result in decreased concentrations of isoleucine and valine in both plasma and muscle. This occurrence is attributed to ketoisocaproate, a product of leucine transamination, which enhances BCKA dehydrogenase activity, thereby accelerating BCAA catabolism (Li G, 2024).

Additionally, aging muscle is less sensitive to lower doses of amino acids than the young and may require higher quantities of protein to acutely stimulate equivalent muscle protein synthesis (Breen L, 2011).

Several expert groups have nutritional recommendations to maintain and/or improve lean body mass and function in old age, suggesting that daily protein intakes of at least 1.0-1.2 g/kg BW in healthy persons, 1.2-1.5 g/kg BW in those with acute or chronic diseases, and up to 2.0 g/kg BW in cases of severe illnesses, injuries, or malnutrition. So, it means for an average acute or chronic disease patients, total protein intake per day is 60–75 gms, which is practically impossible (Calvani R, 2023).

All these increase BCKD activity, accelerates the oxidation of not only leucine but also valine and isoleucine, leading to a depletion of these essential amino acids in body fluids. This imbalance in BCAAs concentrations may have adverse effects on protein metabolism all over the body leading to protein breakdown and muscle wasting (Holeček, 2017). Therefore, leucine, which typically promotes anabolic signaling, may paradoxically contribute to muscle protein breakdown when it excessively activates BCKD, leading to increased BCAAs catabolism (Holeček, 2017) (Rathmacher JA, 2025) (Jacob M Wilson, 2013) (Molfino A, 2013) (Edwards SJ, 2020).

Introducing HMB in Tablet Form – A New Era in Muscle Health Support

For the first time, HMB (β-hydroxy β-methylbutyrate) is now available in a convenient tablet dosage form, offering a significant advancement in muscle specific supplementation. Unlike conventional approaches that rely on nonspecific combinations of amino acids or broad-spectrum nutritional blends, this formulation is designed specific to muscle, where the physiological demand for muscle growth, endurance, support, and repair is better.

This includes avoiding unnecessary stimulation of the BCKD pathway, which is often triggered by excess intake of BCAAs. Activation of this pathway can lead to metabolic imbalances and unintended muscle degradation over time a process that often progresses silently and remains clinically undetected until functional decline becomes apparent.

Unlike leucine, which serves as a precursor to HMB but converts only a very small fraction (approximately 5%) into active HMB, direct supplementation with HMB offers a more efficient and reliable pathway to achieve its physiological benefits on muscle health. This approach bypasses the metabolic step required for conversion, ensuring it reaches the muscle tissue where it is most needed.

Clinical evidence

HMB is not only the most clinically proven ingredient for the attenuation of muscle loss but has more than 30 years of clinical research, 150+ human studies, 100+ review articles, and 14 meta-analyses showing effectiveness and safety. We have tabulated important studies below which are more relevant to clinical practice, highlighting HMB's proven role in preserving muscle mass, enhancing strength, and supporting recovery—especially in aging populations and conditions of muscle wasting.

Study design	Materials & Methods	Subjects	Result	Reference
Indian Consensus	NA	NA	Specialized nutrients such as HMB should be recommended	(Kalra S, 2025).
Umbrella Review of Meta-Analyses	11 studies	NA	Increased muscle mass, muscle strength & fat-free mass (FMM)	(Bideshki MV, 2025)
Systematic review & meta-analysis	5 studies	872 in patients with sarcopenia	Higher SMI & elevated handgrip strength (HGS)	(Gu WT, 2025)
Systematic review	21 studies	1935	Improved appendicular skeletal muscle mass, HSG, five-time chair stand test & gait speed	(Nan Li, 2025)
Review	NA	NA	Positive effects on muscle mass, strength, power, endurance, & recovery after muscle damage (creatine kinase & lactate dehydrogenase)	(Ren Y, 2025)
Systematic review & meta-analysis	5 studies	257 elderly patients with sarcopenia	Increased gait speed, five-time chair stand test, FFM & fat mass	(Li T, 2024)
Systematic review & meta-analysis	6 studies	NA	Improved HGS, gait speed, FFM, & skeletal muscle index (SMI)	(Su H, 2024)
Review	14 studies	NA	Improved muscle strength & functional outcomes	(Mendes J, 2024)
Meta-analysis	NA	NA	Reduced CK, LDH, FM & increased FFM	(Rahimi MR, 2024)
Prospective cohort study	NA	1290 persons community-dwelling older people	Endogenous levels of HMB correlated with the markers of weakness (strength, BMI, exhaustion & weight loss)	(Molina-Baena B, 2024)
Randomized, double-blind, placebo-controlled trial	12-week	32 in post-acute geriatric rehabilitation unit	Improved physical performance & handgrip strength	(Meza-Valderrama D, 2024)
A Randomized, Double-Blind, Placebo-Controlled Study	12-week	12-week intervention in older adults with sarcopenia	Improved handgrip strength, gait speed, five-time chair stand test, muscle quality, and reduced tumor necrosis factor like weak inducer of apoptosis	(Yang C, 2023)

Systematic review	15 studies	Cancer patients	Beneficial effect on muscle mass, function, hospitalization outcomes & survival	(Prado CM, 2022)
Meta-Analysis	9 studies	896 elderly people	Improved muscle strength	(Lin Z, 2022)
Double-blind, parallel group, randomized controlled trial	12 weeks	43, Malnourished Cirrhotic Patients	Upward trend in handgrip strength was observed	(Espina S, 2022)
Randomized, single-blind, placebo-controlled pilot trial.	12 weeks	24, Patients with Liver Cirrhosis	Increased muscle function (chair stand test & six-minute walk test) Increased Quadriceps muscle mass	(Lattanzi B, 2021)
Review of Clinical Trials	6 studies	NA	Improved strength & body composition in people over 65 years, especially in bed rest/sedentary & untrained conditions	(Costa Riela ND, 2021)
Randomised, double-blind, placebo-controlled, parallel design study	2 weeks	20	Inhibited reduction in muscle strength & range of motion	(Tsuchiya Y, 2021)
Randomised, Double-Blind, Placebo-Controlled Crossover Study	12 weeks	42, Combat Sports Athletes	Increased FFM, reduced FM Improved endurance, better performance, greater recovery response	(Durkalec-Michalski K, 2017)
Systematic Review	18 articles	203 Older persons	Improved lean muscle mass, preserves muscle strength & function	(Oktaviana J, 2019)
Systematic review and meta-analysis	15 studies	2137	Increase in muscle mass & strength was observed	(Bear DE, 2019)
Review	NA	NA	↑Resistance to fatigue, minimized muscle damage, and atrophy	(He X, 2016)
Review	NA	NA	Improves muscle growth, strength Reduces muscle damage Improves aerobic performance & lean body mass	(Holeček, 2017)
Open Label Randomized Controlled Trial	8 weeks	80 healthy old women	HMB improved muscle strength, endurance & density	(Berton L, 2015)

Systematic review and meta-analysis	7 studies	287 older adults	Greater muscle hypertrophy, preserves muscle mass & prevents muscle atrophy induced by bed rest	(Wu H, 2015)
Randomized, controlled, double-blinded, parallel-group design	8 weeks	24 healthy older subjects confined to complete bed rest for 10 days	Prevented acute decline in muscle mass & maintained muscle strength/function during extended immobilization	(Deutz NE, 2013)
Systematic review	37 studies	NA	Prevents exercise-related muscle damage in healthy trained & untrained individuals, muscle loss during chronic diseases	(Molfino A, 2013)

L-Carnosine

L-Carnosine & function

Carnosine is a dipeptide composed of beta-alanine (BA) and L-histidine which is highly abundant in skeletal muscle. It performs multiple physiological roles, including hydrogen ion (H^+) buffering, enhancement of calcium sensitivity, improvement of antioxidant activity, & antiglycation effects (Perim P, 2019) (Jukić I, 2021) (Blancquaert L, 2017).

Synthesis of L-Carnosine & types of carnosinase enzymes

Carnosine is synthesized from BA and L-histidine in a reaction catalyzed by the non-specific enzyme carnosine synthase (CARNS), an enzyme located in skeletal muscle. Serum carnosinase (also known as carnosinase-1) is highly specific for carnosine while carnosinase found in tissue (also known as carnosine-2) has a broader substrate specificity. Importantly, beta-alanine has a high affinity for carnosine synthase along with a low muscle content; histidine, on the other hand, is found in high concentration in muscle but has a low affinity for carnosine synthase. These findings establish BA as the rate-limiting amino acid in muscle carnosine synthesis (Perim P, 2019) (Mahomoodally MF, 2022).

Absorption of L-Carnosine

When Carnosine is consumed it is absorbed via Peptide/Histidine Transporter 1 (PHT1) and Peptide transporter-1 (PEPT1) transporters. However, not all the carnosine we consume remains intact and a lot of it is broken down into β-alanine and L-histidine inside the gut itself by an enzyme called carnosinase-2 (Perim P, 2019) (Mahomoodally MF, 2022) (Matthews JJ, 2019).

After entering the bloodstream, any intact carnosine is rapidly hydrolyzed by carnosinase-1 into β-alanine and L-histidine. These free amino acids then reach the skeletal muscle, where they are transported into muscle cells via Taurine Transporter (TauT)/ Proton-coupled Amino acid Transporter 1 (PAT1) for β-alanine and PHT1 for histidine transporters (Perim P, 2019) (Mahomoodally MF, 2022).

Inside the muscle fiber, carnosine synthase recombines β-alanine and L-histidine to resynthesize carnosine, which is then stored within the muscle. Stored carnosine plays a crucial role in pH buffering, antioxidant defense, and protection against fatigue and oxidative stress, thereby supporting enhanced muscle performance (Perim P, 2019) (Mahomoodally MF, 2022).

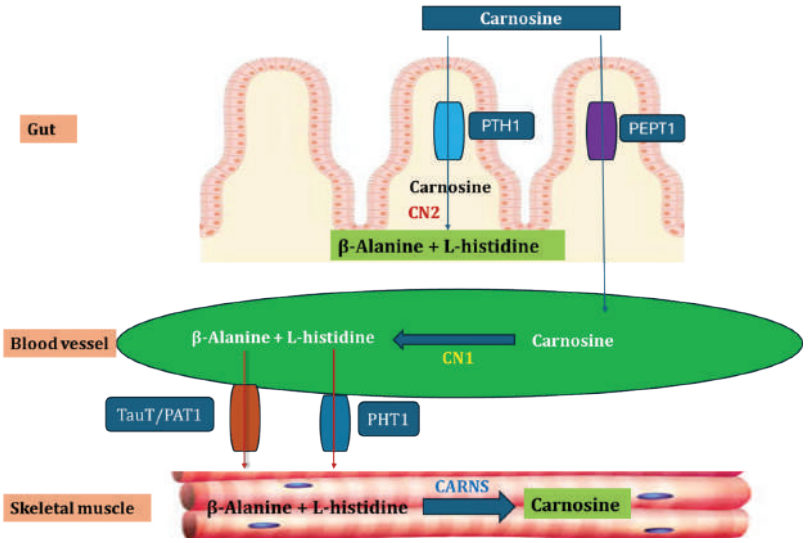

Figure: Metabolism of muscle carnosine

Mechanism of action

During intense muscle contraction, metabolites like lactate and H^+ accumulate in the skeletal muscle. An increase in H^+ ions lead to a reduction in muscle pH, which directly impairs muscle function and reduces power output. This accelerates the onset of fatigue (Landis J, 2012).

L-Carnosine is a potent intracellular buffer of H^+ ions and helps maintain muscle excitation–contraction coupling (Landis J, 2012). It contributes to muscle contractile efficiency by buffering H^+) ions and regulating calcium (Ca^{2+}) availability. During intense exercise, increased H^+ competes with Ca^{2+} for binding sites on troponin, impairing contraction. L-Carnosine helps mitigate this effect by binding excess H^+, thereby increasing Ca^{2+} availability to support continued muscle activation (Jukić I K. N.-R.-K., 2021). In less acidic conditions, carnosine may bind Ca^{2+}, aiding in its redistribution. This dynamic buffering supports effective excitation–contraction coupling and can contribute to more efficient muscle protein turnover. By optimizing this process, carnosine can potentially aid both muscle protein synthesis and breakdown, which are essential for muscle growth, repair, and overall function (Jukić I K. N.-R.-K., 2021). It also promotes faster relaxation by facilitating Ca^{2+} dissociation from troponin, enhancing its movement toward the sarcoplasmic reticulum (SR), and improving reuptake via Sarcoplasmic Reticulum Calcium ATPase (SERCA) pumps (Jukić I K. N.-R.-K., 2021). It also reduces pro-inflammatory mediators such as TNF-α & IL-6 which are involved in atrophy (Caruso G, 2023).

An experimental study reported that carnosine may promote muscle growth by activating the Akt/mTOR signaling pathway, which is essential for muscle regeneration and development. Additionally, it supports the proliferation of SCs, thereby contributing to muscle repair and regeneration (Shen W, 2022). It also inhibits the protein breakdown by reducing Ubiquitin/proteasome system/atrogenes formation (Agrawal A, 2022) (Md Mizanur Rahman, 2024).

By attenuating muscle acidosis, L-Carnosine can delay the onset of fatigue by 15% to 30%, increase the anaerobic (lactate or ventilatory) threshold by 10% to 15%, and improve exercise capacity by 15% to 20% (Landis J, 2012). It works by following these mechanisms (Gasmi A, 2025) (Kumar A, 2024):

Study design	Materials & Methods	Subjects	Result	Reference
Review	NA	NA	Improves muscle strength, endurance, & recovery	(Gasmi A, 2025)
Review	NA	NA	Improves muscle function & power output	(Kumar A, 2024)
Review	NA	NA	Improves muscle strength, endurance, & recovery Supports in falls & sarcopenia	(Wang Q, 2024)
RCT	4-week	27	Enhanced muscle endurance & power	(Cimadevilla-Fernández-Pola E, 2024)
Systematic Review	5	163	Improved muscle endurance	(de Camargo JBB, 2024)
Review	NA	NA	Improves muscle power, performance, & delayed fatigue	(Antonio J, 2024)
Review	NA	NA	Improves physical performance, capacity, muscle recovery & quality of life	(Cesak O, 2023)
Review	NA	NA	Prevents intramuscular acidification by decreasing lactate accumulation, regulate muscles energy metabolism, enhance muscle performance, & functions	(Caruso G, 2023)
Systematic Review	7 studies	138	Improved muscle strength, power, & endurance, Recovery from physical exertion Increased lean mass & decreased fat mass	(Fernández-Lázaro D, 2023)
Review	NA	NA	Improves muscle performance, output & reduce fatigue	(Jukić I K. N.-R.-K., 2021)

Randomized, double-blinded, placebo-controlled trial	10 weeks	18	Reduced muscle fatigue and improved muscle endurance	(Milioni F, 2019)
Randomized, controlled study	5 Weeks	30	Improved muscle power & strength	(Maté-Muñoz JL, 2018)
Randomized, double-blind, crossover design	23 days	16	Improved muscle endurance & reduced lactate concentration	(Santana JO, 2018)
Randomized, placebo-controlled trial	28 days	26	Attenuated fatigue	(Varanoske AN, 2017)
Randomized, placebo-controlled trial	24-weeks	25	Improved muscle endurance	(Saunders B, 2017)
Review	NA	NA	Improved muscle strength, endurance, & fatigue	(Trexler ET, 2015)
Double blind, randomized study	28 days	22	Increased muscle endurance & lactate threshold thereby reduced fatigue	(Gray M, 2015)
Review	NA	NA	Improves muscle power, endurance, reduces fatigue	(Blancquaert L E. I., 2015)
Randomized, placebo-controlled study	12 weeks	60	Improved physical working capacity, muscle quality, & function	(McCormack WP, 2013)
Review	NA	NA	Improves endurance, delays fatigue, promotes gain in lean body mass, & increased time to exhaustion	(Culbertson JY, 2010)
Review	NA	NA	Improves muscle endurance, power output, & reduces fatigue	(Sale C, 2010)
Review	NA	NA	Improved muscle endurance, delayed fatigue, & anaerobic threshold	(Artioli GG, 2010)
Double-blind, placebo-controlled study	8 months	18	Improved muscle endurance	(del Favero S, 2012)

Astaxanthin

Astaxanthin is a naturally occurring xanthophyll and a potent antioxidant. It effectively scavenges free radicals, boosts the body's antioxidant defenses, and helps reduce oxidative stress (Wong SK, 2020) (Shibaguchi T, 2016). Since the majority of molecular and cellular changes involved in muscle degeneration are mediated by oxidative stress, astaxanthin can serve as a potential adjunct therapy for muscle weakness due to its antioxidant properties (Wong SK, 2020).

Mechanism

Astaxanthin also appears to shift substrate metabolism towards fatty acid oxidation and away from carbohydrate oxidation, thereby preserving endogenous glycogen stores and mitigating a rise in lactate and hydrogen ion accumulation, which can prevent a muscle-acidifying effect thereby reducing fatigue (Waldman, 2024).

It prevents muscle atrophy, muscle degeneration, myoblast apoptosis, oxidative stress, capillary regression, protein degradation by inhibiting FOX genes, ubiquitin-proteosome, calpain pathways and inflammation, promotes mitochondria regeneration, formation of blood vessels, protein synthesis, increases muscle strength and endurance by activating mTOR pathway and by ↑ PGC1α levels and SCs number (Wong SK, 2020) (Yoshihara T, 2018) (Chen M, 2024) (Toshinori Yoshihara, 2019).

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Study design	Materials & Methods	Subjects	Result	Reference
Review	NA	NA	Improves muscle endurance, performance, lactate accumulation, & recovery	(Waldman, 2024)
Randomized, double-blind, placebo-controlled	4 Week	19	Reduced muscle pain & enhance recovery	(Barker GA, 2023)
Review	NA	NA	Protective action on muscle atrophy	(Alugoju P, 2023)
Randomized, double-blind, placebo-controlled study	3 Months	42	Improved fat oxidation, carbohydrate sparing, muscle capillarization, increased exercise endurance	(Sophia Liu Z, 2021)
Review	NA	NA	Enhances muscle performance, counteracts muscle disuse, & improves chronic inflammation	(Wong SK, 2020)
Randomized, double-blind, placebo-controlled study	4 months	42	Improved muscle strength, force, endurance, & CSA	(Liu SZ, 2018)
Review	NA	NA	Improves muscle endurance & recovery	(Brown DR, 2018)
Randomized, double-blind, placebo-controlled study	3 months	29	↓ Derivatives of reactive oxygen metabolites (D-ROM), improved physical performance, endurance, & ↓ blood lactate levels	(Fujino H, 2016)
Randomized, double-blind, placebo-controlled study	3 months	32	Prevented free-radical production, CK and AST levels were significantly reduced & prevents muscle damage & atrophy	(Djordjevic B, 2012)
Randomized, Double-blind, Parallel design	4 Weeks	21	Increased muscle endurance & performance	(Earnest CP, 2011)
Double Blind Placebo Controlled Study	6 months	20	Improved muscle endurance & performance	(Malmsten CL, 2008)

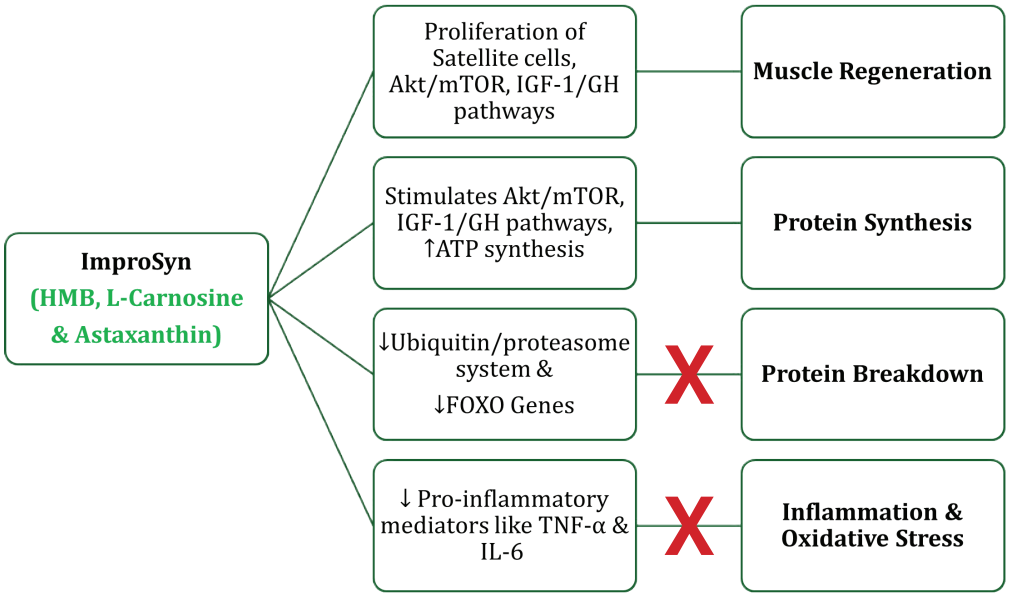
12. Combined Effect of HMB, L-Carnosine, & Astaxanthin on Muscle Health

ImproSyn is a combination of Beta-hydroxy-beta-methylbutyrate (HMB), L-Carnosine, and Astaxanthin, specifically designed to support and improve muscle health. It is particularly beneficial for individuals experiencing muscle loss, reduced muscle strength, or deterioration of muscle tissue architecture, commonly associated with aging and co-morbid conditions. It helps support muscle protein synthesis, prevent muscle breakdown, and helps in muscle regeneration by preventing inflammation and oxidative

Benefits	HMB	L-Carnosine	Astaxanthin
Supports muscle protein synthesis	Via the mTOR, IGF-1/GH pathways	Via the Akt/mTOR pathway	Via the mTOR pathway
	(Landi F, 2021) (Arazi H T. B., 2018)	(Shen W, 2022)	(Wong SK, 2020) (Yoshihara T, 2018)
	Regulates muscle excitation contraction coupling		
	↑ PGC-1α→ ↑ mitochondrial activity →↑ATP synthesis	By buffering and supports protein synthesis	↑ PGC-1α → ↑ mitochondrial activity→ ↑ATP synthesis
	↑ PGC-1α → ↑ATP synthesis	↑ PGC-1α → ↑ATP synthesis	Mitigate rise in lactate & hydrogen ion
	Increases aerobic capacity & delays fatigue	Increases aerobic capacity & delays fatigue	Increases aerobic capacity & delays fatigue
	(Landi F, 2021) (Arazi H T. B., 2018) (He X, 2016)	(Landis J, 2012) (Jukić I K. N.-R.-K., 2021) (Wang Q, 2024)	(Waldman, 2024) (Wong SK, 2020)
Prevents muscle protein breakdown	↓Ubiquitin/proteasome system	↓Ubiquitin/proteasome system	↓Ubiquitin/proteasome system
	↓FOXO Genes	↓FOXO Genes	↓FOXO Genes
	(Landi F, 2021) (Arazi H T. B., 2018)	(Agrawal A, 2022) (Md Mizanur Rahman, 2024)	(Toshinori Yoshihara, 2019) (Wong SK, 2020)
Muscle regeneration	↑ Proliferation of Satellite cells	↑ Proliferation of Satellite cells	↑ Proliferation of Satellite cells
	(Landi F, 2021) (Arazi H T. B., 2018)	(Shen W, 2022)	(Wong SK, 2020) (Yoshihara T, 2018)
Prevents inflammation & oxidative stress	Antioxidant, reduces pro-inflammatory mediators like TNF-α & IL-6	Antioxidant, reduces pro-inflammatory mediators like TNF-α & IL-6	Antioxidant, reduces pro-inflammatory mediators like TNF-α & IL-6
	(Arazi H, 2019) (Hamid Arazi, 2018) (Hoffman JR, 2016)	(Chen M W. Y., 2022)	(Chen M W. Y., 2022)

Abbreviations: mTOR - Mammalian Target of Rapamycin, ATP - Adenosine Triphosphate, IGF-1 - Insulin-like Growth Factor 1, GH - Growth Hormone, Akt - Protein Kinase B, PGC-1α - Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha, FOXO genes - Forkhead Box O transcription factors, S6K- Ribosomal protein S6 kinase

Table: Role of ImproSyn in preventing muscle weakness



The combined effect of HMB, L-Carnosine, and Astaxanthin provides a comprehensive approach to muscle health by targeting muscle strength, endurance, pain, fatigue, recovery, and protection at both cellular and metabolic levels:

HMB

Supports muscle protein synthesis

- Acts via the mTOR and IGF-1/GH pathways, which promotes muscle growth and repair (Landi F, 2021) (Arazi H T. B., 2018)

Prevents muscle protein breakdown

- Inhibits the ubiquitin-proteasome system & FOXO genes, reducing muscle atrophy (Landi F, 2021) (Arazi H T. B., 2018)

Supports muscle regeneration

- Stimulates the proliferation of satellite cells, key for muscle repair and hypertrophy (Landi F, 2021) (Arazi H T. B., 2018)

Increases aerobic capacity & delays fatigue

- Helps regulate muscle excitation-contraction coupling, enhances mitochondrial function, and ultimately boosts ATP synthesis. This improves aerobic capacity and delays fatigue (Landi F, 2021) (Arazi H T. B., 2018) (He X, 2016)

Prevents inflammation & oxidative stress

Acts as a potent antioxidant, reducing levels of TNF-α and IL-6 (Arazi H, 2019) (Hamid Arazi, 2018) (Hoffman JR, 2016)

L-Carnosine

Supports muscle protein synthesis

Acts via the Akt/mTOR signaling pathway, which promotes protein synthesis and muscle hypertrophy (Shen W, 2022)

Prevents muscle protein breakdown

Inhibits the ubiquitin-proteasome pathway and FOXO gene expression, reducing muscle degradation (Agrawal A, 2022) (Md Mizanur Rahman, 2024)

Supports muscle regeneration

Promotes proliferation of satellite cells, key for muscle repair and regeneration

(Shen W, 2022)

Increases aerobic capacity & delays fatigue

- Acts as a buffer to reduce muscle acidosis
- Supports protein synthesis & ↑PGC-1α → ↑ATP synthesis thereby regulates muscle-excitation contraction coupling & enhances endurance (Landis J, 2012) (Jukić I K. N.-R., 2021) (Wang Q, 2024)

Prevents inflammation & oxidative stress

- Acts as a potent antioxidant, reducing levels of TNF-α and IL-6, key pro-inflammatory cytokines (Chen M W. Y., 2022)

Astaxanthin

- Supports muscle protein synthesis
- Works via the mTOR pathway, enhancing protein synthesis and muscle mass (Wong SK, 2020) (Yoshihara T, 2018)

Prevents muscle protein breakdown

- Inhibits the ubiquitin-proteasome system & FOXO gene activity, minimizing muscle protein catabolism (Toshinori Yoshihara, 2019) (Wong SK, 2020)

Supports muscle regeneration

- Stimulates satellite cell proliferation, aiding in muscle repair and hypertrophy (Wong SK, 2020) (Yoshihara T, 2018)

Increases aerobic capacity & delays fatigue

- Enhances PGC-1α expression, improves mitochondrial efficiency, and helps mitigate lactate and H^+ accumulation, delaying muscle fatigue and increasing aerobic performance (Waldman, 2024) (Wong SK, 2020)

Prevents inflammation & oxidative stress

- Functions as an antioxidant & reduces inflammatory markers such as TNF-α and IL-6 (Tabassum M, 2025)

13. Expected Clinical Outcomes with Improsyn

Effects	Mediated by	Clinical Outcomes
Supports muscle protein synthesis	mTOR pathway	↑ Muscle mass, strength, endurance, preserves lean body mass, range of motion, & recovery from damage
Prevents muscle protein breakdown	Inhibiting ubiquitin-proteasome system & FOXO gene activity	↓ Muscle loss & muscle wasting, ↑muscle bulk, strength, endurance, range of motion, & recovery from damage
Supports muscle regeneration	Proliferation of satellite cells	Enhances muscle tissue repair, recovery, muscle strength, endurance & range of motion
Mitigate muscle lactate & H^+ accumulation	↑PGC-1α expression, mitochondrial ↑ efficiency, improves muscle-contraction-excitation coupling, accelerates malate-aspartate shuttle, & TCA cycle	↑ Glycogen stores, improves aerobic performance, delays fatigue, & ↓ muscle pain
Prevents inflammation & oxidative stress	↓ Pro-inflammatory mediators & ROS	↓ Muscle loss, muscle wasting, ↑ muscle bulk, strength, endurance, range of motion, & recovery from damage

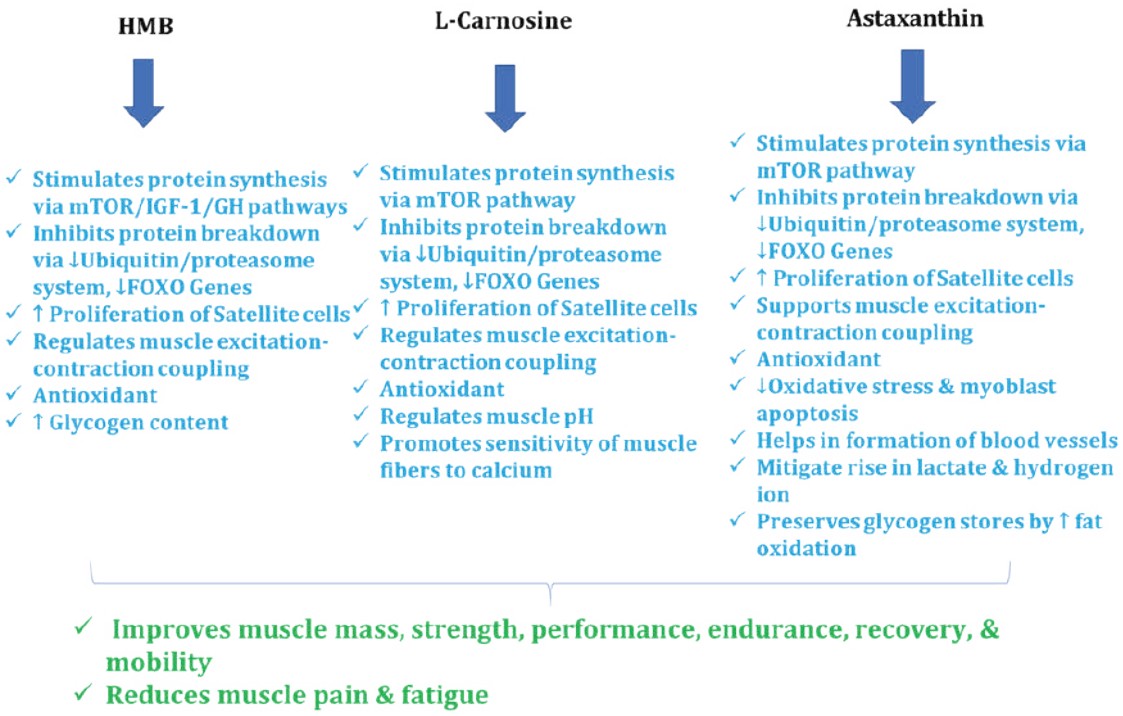


Figure: Role of ImproSyn in preventing muscle weakness

Together, these three ingredients offer complementary and multi-targeted muscle specific support by:

- Enhancing muscle mass and strength
- Stimulating muscle regeneration
- Improving performance and endurance
- Accelerating recovery
- Reducing pain, inflammation, and fatigue

14. Long Term Safety of ImproSyn

Available safety and toxicity data indicate that chronic oral supplementation with HMB is well-tolerated in humans for at least one year in length (Rathmacher JA, 2025). While long-term data on L-Carnosine supplementation beyond one year is currently lacking, its endogenous production suggests a low potential for adverse effects (Trexler ET, 2015). Astaxanthin has demonstrated a favorable safety profile with no significant adverse events reported for up to 24 months of use (Brendler T, 2019). Based on these findings, ImproSyn can be considered safe for use for at least 1 year, with longer durations advised under clinical supervision.

Safety in Pregnancy and Lactation

HMB: Not recommended for use by pregnant women and lactating mothers because of the lack of specific research on its effects during pregnancy and lactation in humans (FSSAI) (Tomczyk-Warunek A, 2021) (Pascual VC).

L-Carnosine: There is not enough reliable information about the safety of taking carnosine during pregnancy or breastfeeding.

Astaxanthin: Should not be consumed by pregnant women and during breastfeeding (EFSA NDA Panel (EFSA Panel on Dietetic Products, 2014) (Pascual VC).

Therefore, ImproSyn is not recommended for use during pregnancy & lactation

Safety in Renal Problems

HMB: Consuming up to 6 g of HMB-Ca per day up to

8 weeks did not lead to any changes in biochemical parameters of renal function and was not associated with any adverse events or changes in renal function (Rathmacher JA, 2025) (Ikeda T, 2023) (GALLAGHER PM, 2000) (Pérez AN, 2022).

L-Carnosine: It has a promising potential for the treatment and prevention of kidney diseases and is well-tolerated with no serious side effects (Narongrit Siriwattanasit, 2021) (Elbarbary NS, 2018) (Kilis-Pstrusinska, 2020) (Cesak O, 2023)

Astaxanthin: Has been shown to reduce kidney damage, alleviate inflammation, and rescue kidney function in different experimental models and has been demonstrated to be safe (Shukla G, 2022) (Chang MX, 2020) (Huang J, 2023) (Brendler T, 2019). In renal transplant patients, astaxanthin administered over a period of 12 months did not show any adverse events (Brendler T, 2019). Astaxanthin, even at doses up to 12 mg/day for 16 weeks, showed no adverse events or renal function abnormalities (Ng QX, 2021).

Therefore, ImproSyn is considered safe for consumption in patients with renal problems.

Cardiac Safety

HMB: It can be taken safely in patients with cardiac diseases (Ikeda T, 2023) (Arazi H, 2019) (Nissen S, 2000)

L-Carnosine: It is usually well tolerated, safe and no specific concerns have been raised till now as regards its use as a dietary supplement (Cicero AFG, 2020) (Feehan J, 2022).

Astaxanthin: Used in the treatment and prevention of cardiovascular disorders (López-Cervantes J, 2019). There have been no adverse events of any consequence associated with astaxanthin (Fassett RG, 2012) (Kato T, 2020)

Note: Elevated INR & bleeding complications occurred after astaxanthin was added to the patient's warfarin regimen. Therefore, Astaxanthin should be used with caution or make dosage adjustments in such patients (Santiyanon N, 2019).

Therefore, ImproSyn is considered safe for consumption in patients with cardiac disorders.

Hepatic Safety

HMB: Consuming up to 6 g of HMB-Ca per day up to 8 weeks did not lead to any changes in biochemical parameters of hepatic function and was not associated with any adverse events or changes in hepatic function (Rathmacher JA, 2025) (GALLAGHER PM, 2000). It is well tolerated in patients with liver cirrhosis, and no adverse events have been documented (Lattanzi B, 2021).

L-Carnosine: Carnosine is safe with no reported adverse effects; however, a limited number of human studies exist (Wang Q, 2024) (Doğru-Abbasoğlu S, 2018).

Astaxanthin: Used in the treatment and prevention of hepatic disorders (López-Cervantes J, 2019). After 24 weeks of astaxanthin supplementation, liver functions remained unchanged in patients with Nonalcoholic Steatohepatitis (NASH) (Sayuti NH, 2023). However, limited clinical data are available (Arefpour H, 2024) (Li J, 2020).

Therefore, ImproSyn is considered safe for consumption in patients with hepatic disorders.

Gastrointestinal Safety

HMB: It is Generally Recognized as Safe (GRAS), and no serious adverse events have been reported. However, mild adverse GI effects like abdominal pain and constipation have been reported within doses of 1.5 to 3 gms/day (Berton L, 2015) (Espina S, 2022) (Zhou S, 2025).

L-Carnosine: No major adverse events have been reported; however, side effects such as dry mouth, constipation, and nausea were reported within a dose of 400-800 mg (Tharoor H, 2023).

Astaxanthin: It has been generally recognized as safe (GRAS), has demonstrated a good safety profile, and no adverse events have been reported in any clinical studies (Giannaccare G, 2020) (Rizzardi N, 2022) and is used in the treatment and prevention of gastrointestinal disorders (López-Cervantes J, 2019).

Common Side Effects

HMB: Gastrointestinal effects such as nausea, vomiting, abdominal pain, constipation, itching (Espina S, 2022) (Berton L, 2015)

L-Carnosine: Dry mouth, constipation, nausea, itching, short-term paresthesia or numbness at high doses (Tharoor H, 2023) (Cimadevilla-Fernández-Pola E, 2024) (Cesak O, 2023)

Astaxanthin: Red-colored stool, increased bowel movements (Brendler T, 2019)

15. Musculoskeletal and Orthopaedic Indications

Osteosarcopenia

Muscle weakness, a silent process caused by bone degeneration, nutrient deficiencies, medications, sedentary lifestyles, or sarcopenia, reduces mechanical loading, impairs bone remodeling, and accelerates bone loss. Muscle weakness is intricately linked with osteoporosis due to the shared developmental origins and functional interdependence of muscle and bone. Both tissues originate from mesenchymal stem cells (MSCs) in the mesoderm and are part of the motor system, where muscles exert mechanical forces on bones, stimulating bone remodeling and maintaining bone mineral density (BMD). Adequate blood supply is essential for muscle function and bone health, as it delivers oxygen and nutrients to muscle tissues while also supporting bone remodeling. Impaired

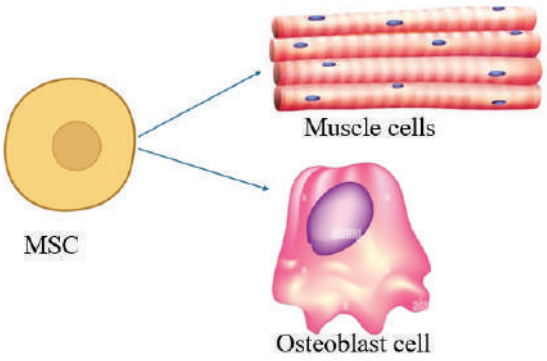


Fig: MSCs differentiate to muscle & bone cells

circulation can cause muscle weakness, compromising muscle & bone health, leading to atrophy, increasing fracture risk and osteosarcopenia. (Martins-Neves, Sampaio-Ribeiro, & Gomes, 2023), (Bianchi, Gaiero, & et.al, 2021), (Lu, Zhang, & et.al, 2022)

1. Does Muscle Weakness Coexist with Osteoporosis?

Osteosarcopenia:

The term "osteosarcopenia" occurs in ageing populations, who is suffering with both sarcopenia and osteoporosis due to various factors, such as ageing, hormonal changes, comorbid disease conditions, and physical inactivity. Studies indicate that younger populations (ages 18-21) may exhibit early signs of osteosarcopenic elements (increased fat mass, hsCRP levels, lower muscle & bone masses) in their blood samples, and older adults also show high prevalence of osteosarcopenia—men (14.3% at 60-64 years to 59.4% at ≥75 years) and women (20.3% at 60-64 years to 48.3% at ≥75 years) (Franulic, Salech, Rivas, & Duque, 2024), (Huang, et al., 2023), (Stefanaki, Peppa, Boschiero, & Chrousos, 2016).

Several diagnostic criteria for muscle health exist, with muscle weakness diagnosed by low muscle mass and low muscle function (either low strength and low physical performance) or by low whole-body or appendicular fat-free mass combined with poor physical performance. Sometimes individuals exhibit some signs of muscle loss or weakness, experiencing a decline in their ability to perform physical activities, even for minimal physical exertion, without any diagnosis of low muscle mass, low muscle strength, or low physical performance (key diagnostic criteria for sarcopenia). This condition is known as "subclinical sarcopenia". Recognising subclinical sarcopenia allows for early intervention strategies, such as exercise and nutritional support, which can help slow or even reverse the progression of muscle loss (Conforto, 2024), (Kirk, Zanker, & Duque, 2020), (Bauer, Cruz-Jentoft, & Fielding, 2019), (JafariNasabian, Inglis, Kelly, & Ilich, 2017), (Ormsbee, et al., 2014).

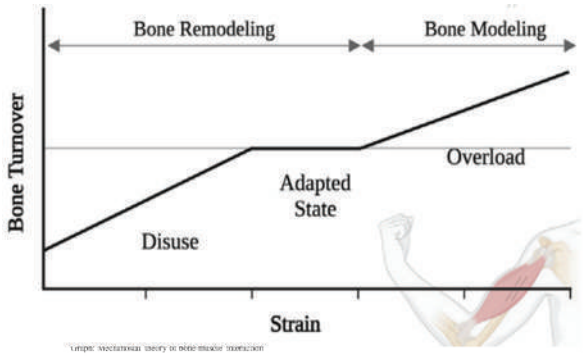
Comorbid Disease Conditions:

Studies have explored the direct link between osteosarcopenia and cardiovascular disease risk factors, such as BMI, high-fat mass, and diabetes. The association between increased adipocyte levels, insulin resistance, and chronic low-grade inflammation can alter the microenvironment, and reducing myogenesis and osteogenesis. This leads to the production of localized adipokines, free fatty acids, and intramuscular lipid accumulation, which induces local lipotoxicity, muscle mass and strength loss, limiting physical activity, and increases the risk of falls, fractures, and physical frailty. Osteosarcopenia is inversely associated with high-fat mass but directly associated with lean muscle mass.

Osteosarcopenia is more likely to occur in diabetic men, as they tend to have more skeletal muscle mass than women. Elevated LDL-C, total cholesterol (TC), and triglycerides (TG), along with decreased HDL-C, suppress osteoblast differentiation, impair blood flow to muscles, increase insulin resistance, and reduce muscle utilization of glucose, resulting in reduced bone mineral density (BMD). Furthermore, elevated levels of non-esterified fatty acids (NEFAs) contribute to lipotoxicity, inhibiting osteoblast differentiation & function, promoting oxidative stress & inflammation, ultimately impairing both muscle and bone health and disrupting normal cellular function, thereby exacerbating the risk of osteoporosis and sarcopenia. Chronic increase of cortisol levels is frequently seen in a variety of comorbid diseases. Prolonged cortisol imbalance can worsen muscle weakness, bone loss, and general metabolic dysfunction, all of which can lead to poor health outcomes. Elevated cortisol levels can also lead to impaired body composition, alter muscle protein synthesis, increase insulin resistance, reduce adequate blood flow, and potentially cause osteosarcopenic adiposity syndrome (OSA), a condition characterized by bone loss, muscle loss, and excess fat. Nutritional restriction exacerbates these situations. These factors are detrimental to both bone and muscle health and function, leading to a decline in endurance capacity (Franulic, Salech, Rivas, & Duque, 2024), (Conforto, 2024), (Kirk, Zanker, & Duque, 2020).

The Mechanostat Model:

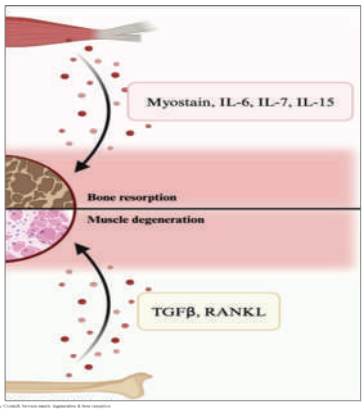
The Mechanostat graph describes how bones adapt their strength and mass in response to mechanical loads, primarily stimulated by muscles. According to the Mechanostat model, bone growth and loss are influenced by local mechanical deformation caused by muscle forces. The bone adapts its mechanical properties in response to the strains



induced by muscle contractions. Therefore, reduced muscle strength leads to diminished mechanical loading on bones, which is a critical stimulus for maintaining bone mass (Castoldi, 2025), (Hart, Nimphius, Rantalainen, & Ireland, 2017), (Tyrovola, 2015).

Muscle-Derived Myokines:

Additionally, muscle-derived myokines (e.g., myostatin, irisin, leptin, interleukins) play a key role in bone metabolism by promoting osteoblast activity and inhibiting osteoclast-mediated bone resorption.



Atrophied muscles produce fewer osteoprotective myokines (irisin) which increase Receptor Activator of Nuclear Factor kappa-B/ Osteoprotegerin (RANK/OPG) ratios, favouring osteoclastogenesis over osteoblast activity. Increased serum irisin or RANK may serve as indicators for identifying patients at higher risk for osteosarcopenia-related fractures. A decline in muscle mass or strength disrupts the crosstalk, further contributing to osteoporosis progression (Franulic, Salech, Rivas, & Duque, 2024), (Conforto, 2024), (Huang, et al., 2023), (Kirk, Zanker, & Duque, 2020).

2. Can muscle weakness contribute to OP/ OP treatment outcomes?

Pathophysiological Relationship Between Muscle Weakness and Osteoporosis Muscle

Aging-related changes: Aging leads to DNA damage and metabolic derangements, resulting in impaired satellite cell functions. Aged satellite cells exhibit reduced self-renewal, proliferation, and differentiation, leading to diminished regenerative capacity of muscle tissue. This negatively affects bone health, as muscle tissue supports bone mass.

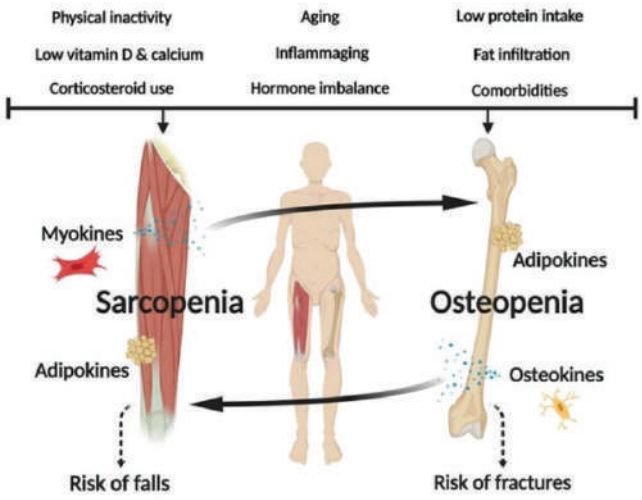


Fig: Both osteoporosis & sarcopenia are observed in ageing

(Franulic, Salech, Rivas, & Duque, 2024), (Conforto, 2024), (Huang, et al., 2023), (Kirk, Zanker, & Duque, 2020)

Endocrine factors: Endocrine disorders, particularly those affecting sex hormones (estrogen, testosterone, growth factors (IGF-1), thyroid, and parathyroid glands, significantly contribute to both muscle weakness and osteoporosis, leading to increased fracture risk and decreased bone density (Franulic, Salech, Rivas, & Duque, 2024), (Conforto, 2024), (Huang, et al., 2023), (Kirk, Zanker, & Duque, 2020).

- Declining sex hormones and growth factors (IGF-1) impair muscle protein synthesis, contributing to muscle atrophy and negatively impacting bone strength and increasing bone loss.
- Abnormal parathyroid hormone and calcium uptake are involved in muscle and bone kinetics. Excessive parathyroid hormone causes muscle weakness and fatigue due to energy metabolism disorders and skeletal muscle catabolism, leading to muscle weakness and osteoporosis.
- Hyperthyroidism causes muscle weakness and the loss of lean body mass, resulting in muscle fiber atrophy and altering muscle fiber types, contributing to muscle weakness.
- During menopause, the decline in estrogen levels significantly impacts both osteoporosis and muscle weakness, decreasing bone density and muscle mass and strength, making postmenopausal women more vulnerable to falls and fractures.

Physical inactivity: Sedentary behavior reduces mechanical loading essential for muscle hypertrophy that supports bone strength. When muscles aren't regularly used, they weaken and waste away, which increases the risk of falls and injuries and contributes to weak muscles and bones (Huang, et al., 2023), (Kirk, Zanker, & Duque, 2020).

Collagen Degeneration & Extracellular Matrix Disruption: The extracellular matrix, which provides structural support and regulates cell functions, plays a critical role in both muscle and bone health. Sarcopenic muscle increases matrix metalloproteinase activity (especially MMP-2, MMP-9), leading to collagen degradation and further progression of osteoporosis (Huang, et al., 2023), (Kirk, Zanker, & Duque, 2020).

Abnormal muscle protein synthesis: Disruptions in amino acid metabolism affect muscle protein synthesis, which disrupts bone matrix formation, reduces osteoblast differentiation, and increases osteoclast proliferation, worsening osteoporosis (Huang, et al., 2023), (Kirk, Zanker, & Duque, 2020).

Chronic inflammation & oxidative stress: Elevated inflammation and oxidative stress promote muscle protein catabolism and accelerated bone resorption, contributing to the progression of osteoporosis (Franulic, Salech, Rivas, & Duque, 2024), (Martins-Neves, Sampaio-Ribeiro, & Gomes, 2023), (Bianchi, Gaiero, & et.al, 2021).

Consequences of Untreated Muscle Weakness in Osteoporosis

- Untreated muscle weakness contributes to declining physical activity, further reducing mechanical stimulation, which accelerates bone loss and osteoporosis progression.
- Adequate muscle function provides essential

blood supply and growth factors that support bone health. Muscle weakness leads to the release of myokines that reduce pro-osteogenic factors and increase inflammatory cytokines, negatively impacting bone remodeling.

- Sarcopenia demonstrates higher rates of adverse effects from osteoporosis medications, leading to reduced adherence and discontinuation.
- Muscle-derived growth factors are necessary for optimal osteoblast response to anabolic agents like teriparatide, explaining reduced treatment efficacy in sarcopenic patients.
- Patients with significant muscle weakness often cannot perform exercises efficiently or with sufficient intensity to stimulate osteogenesis. Balance training interventions show reduced effectiveness in preventing falls when baseline muscle function is severely compromised. Furthermore, nutritional interventions alone (calcium, vitamin D) show minimal BMD improvements in the absence of adequate mechanical loading from functioning muscles.

Changes in muscle mass and strength typically precede and predict subsequent changes in BMD. Physicians should consider screening for muscle weakness when diagnosing osteoporosis, as the presence of both conditions significantly increases fracture risk and functional impairment compared to either condition alone. The coexistence of muscle weakness and osteoporosis underscores the need for comprehensive assessment and management of both conditions (Martins-Neves, Sampaio-Ribeiro, & Gomes, 2023), (Bianchi, Gaiero, & et.al, 2021), (Lu, Zhang, & et.al, 2022), (Lin, Jewell, & et.al, 2017).

3. Can muscle weakness management improve OP outcomes?

Addressing muscle weakness through a comprehensive approach, including resistance exercise, nutritional support, and muscle-strengthening therapies, can lead to enhanced bone mineral density (BMD), reduced risk of fractures, and improved osteoporosis outcomes (Franulic, Salech, Rivas, & Duque, 2024), (Bianchi, Gaiero, & et.al, 2021), (Lu, Zhang, & et.al, 2022), (Lin, Jewell, & et.al, 2017).

Improved Bone Density and Strength: Muscle-strengthening therapies help enhance osteoblast activity that increases mechanical loading on bones and promotes bone remodelling, which helps in improving bone mineral density (BMD) (Bianchi, Gaiero, & et.al, 2021), (Lu, Zhang, & et.al, 2022), (Lin, Jewell, & et.al, 2017).

Enhanced Muscle Mass and Strength: Muscle-strengthening therapies help build muscle mass and strength, improving functional capacity and postural stability. Stronger muscles protect bones by reducing the risk of falls and improving balance and coordination (Bianchi, Gaiero, & et.al, 2021), (Lu, Zhang, & et.al, 2022).

Reduced Risk of Falls and Fractures: Strengthening muscles enhances balance, stability, and mobility, thereby reducing the risk of falls and fractures. This is especially important in osteosarcopenic patients (Bianchi, Gaiero, & et.al, 2021), (Lu, Zhang, & et.al, 2022).

Synergy with Osteoporosis Medications: When combined with osteoporosis medications, muscle-strengthening therapies can improve overall treatment outcomes. Exercise and strengthening programmes support bone health by promoting bone formation and reducing bone resorption. This synergy helps maximise the effectiveness of osteoporosis treatments, making it a comprehensive approach to managing bone health (Conforto, 2024), (Huang, et al., 2023), (Bianchi, Gaiero, & et.al, 2021), (Lu, Zhang, & et.al, 2022).

Prevention of Osteosarcopenia: Muscle-strengthening therapies can help prevent or delay the onset of osteosarcopenia by addressing subclinical sarcopenia while simultaneously improving bone health. This combined approach prevents further deterioration of both muscle and bone mass (Bianchi, Gaiero, & et.al, 2021), (Lu, Zhang, & et.al, 2022).

In conclusion, managing muscle weakness is crucial for improving osteoporosis outcomes. It not only strengthens bones directly through mechanical loading but also reduces the risk of falls and fractures, supports the efficacy of osteoporosis treatments, and improves overall functional capacity (Bianchi, Gaiero, & et.al, 2021), (Lu, Zhang, & et.al, 2022).

4. What are the possible outcomes muscle strengthening regimen (Nutrition+Exercise) with primary therapy?

Enhanced Therapy Outcomes when Combined with Exercise, Nutritional support, and Muscle-strengthening Therapies: When a muscle-strengthening regimen (including targeted exercises and supportive nutraceuticals) is added to primary therapy, it helps fully address muscle weakness and

prevent further decline in muscle mass. This combined approach not only improves bone health by enhancing mechanical loading but also prevents osteosarcopenia or reverses subclinical sarcopenia, which could otherwise have a detrimental impact on both muscle and bone health. The regimen helps preserve muscle strength and optimizes the effectiveness of primary therapy, ensuring that bone health is maintained or improved while addressing the underlying muscle deterioration (Huang, et al., 2023), (Martins-Neves, Sampaio-Ribeiro, & Gomes, 2023), (Bianchi, Gaiero, & et.al, 2021), (Lu, Zhang, & et.al, 2022).

Long-Term Benefits of Integrating Muscle Therapy: The inclusion of muscle-strengthening interventions alongside nutraceuticals and exercise results in better functional outcomes, reduced risk of falls, and improved mobility, particularly in aging populations. Without a comprehensive muscle therapy regimen, the benefits of primary bone treatments may be suboptimal, and the risk of complications such as fractures or disability may increase. A muscle-strengthening regimen provides a healthy environment that supports bone and muscle health, reduces the risk of osteosarcopenia, and delays the progression of osteosarcopenia (Martins-Neves, Sampaio-Ribeiro, & Gomes, 2023), (Bianchi, Gaiero, & et.al, 2021), (Lu, Zhang, & et.al, 2022), (Kirk, Zanker, & Duque, 2020).

Preventing Future Decline and Optimizing Bone Health: If muscle health is not effectively managed, bone health can further deteriorate, resulting in increased fracture risk and physical frailty. A muscle-strengthening regimen ensures long-term protection of bone health, reduces the need for intensive treatments in the future, and supports continuous muscle recovery, reducing the risk of falls and fractures while improving physical frailty and preventing future deterioration of both muscle and bone health (Martins-Neves, Sampaio-Ribeiro, & Gomes, 2023), (Bianchi, Gaiero, & et.al, 2021), (Lu, Zhang, & et.al, 2022).

Nutraceuticals

Therefore, integrating a muscle-strengthening regimen with exercise and nutraceuticals enhances muscle function and bone health. While nutraceuticals and exercise alone provide partial benefits, they do not fully address muscle weakness, increasing the risk of osteosarcopenia. Adding muscle therapy prevents muscle and bone deterioration, optimizes primary bone therapies, and improves long-term health outcomes. This comprehensive approach is crucial for preventing osteoporosis-related complications and ensuring sustained strength and mobility (Martins-Neves, Sampaio-Ribeiro, & Gomes, 2023), (Bianchi, Gaiero, & et.al, 2021), (Lu, Zhang, & et.al, 2022).

Bone Fracture and Post-Fracture Recovery

Bone fractures are common musculoskeletal injuries that require comprehensive management for optimal recovery. Muscle weakness is increasingly recognized as a significant factor in fracture pathophysiology, recovery, and long-term outcomes. Understanding and managing muscle weakness is essential for both fracture prevention and improved healing after fractures (Rahmati, Haffner, Lee, Leach, & Saiz, 2024), (Szulc, 2020), (Shah, Majeed, Jonason, & O'Keefe, 2013).

1. Does muscle weakness co-exist with bone fracture?

Muscle and bone interact closely, and conditions affecting one often impact the other. Muscle weakness is evident in fractures, where significant muscle damage occurs, such as in traumatic fractures (resulting from force, falls, or sports injuries) or those involving substantial soft tissue injury. Multiple studies demonstrate significant pre-existing muscle weakness in 60-80% of elderly patients (41- 79 years of age) with hip, vertebral, and distal radius fractures. Followed by atypical femoral fractures which exhibit concurrent muscle weakness, particularly in 3-5 years bisphosphonate users. Athletes with lower extremity stress fractures show 30-50% reduced muscle strength compared to matched controls without fractures. The biochemical and clinical factors related to muscle weakness (MW) and bone fractures are mentioned below (Niwczyk, et al., 2023), (Arai, Kirk, & Duque, 2023), (Jiang, et al., 2022), (Wong, et al., 2019).

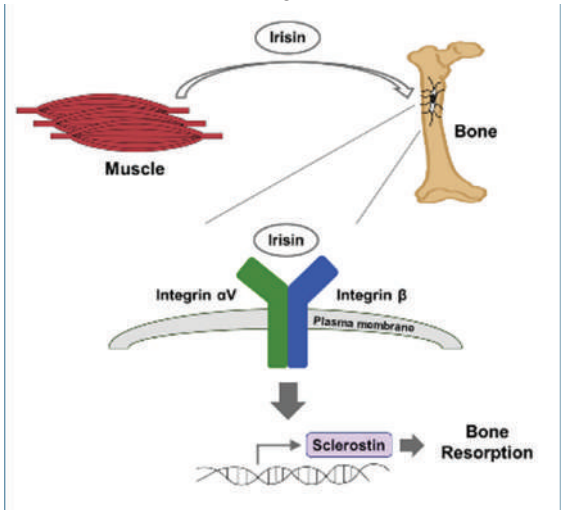
Mechanobiology Pathways

Mechanotransduction Integration: Both bone and muscle tissue respond to mechanical loading through similar mechanoreceptors. Mechanical stimulation through these shared receptors is crucial for sensing joint position, muscle tension, and the speed of limb movements. Therefore, progressive muscle weakness reduces receptor stimuli, leading to bones becoming increasingly susceptible to fracture due to diminished mechanoreceptor activation (Stewart, Darwood, Masouros, Higgins, & Ramasamy, 2020), (Entezari,

Swain, Gooding, Roohani, & Li, 2020), (Goodman, Hornberger, & Robling, 2015).

- Cellular deformation sensors (integrins, stretch-activated channels) operate in parallel systems. Dysfunction in cellular deformation sensing will concurrently reduce myogenesis & osteogenesis, affecting both muscle and bone adaptation processes by synchronously declining in both muscle strength and bone fragility (Entezari, Swain, Gooding, Roohani, & Li, 2020), (Goodman, Hornberger, & Robling, 2015).

Figure: Irisin is secreted by muscle, increases with exercise, shown to have beneficial effects against abnormal bone remodelling



65-75% overlap in mechanotransduction signalling pathways (cells translate mechanical stimuli into biochemical signals) between osteocytes and myocytes. Therefore, systemic conditions (inflammation, hormonal changes) can simultaneously degrade both muscle and bone tissue through common molecular targets, leading to muscle weakness and bone integrity (Stewart, Darwood, Masouros, Higgins, & Ramasamy, 2020), (Goodman, Hornberger, & Robling, 2015).

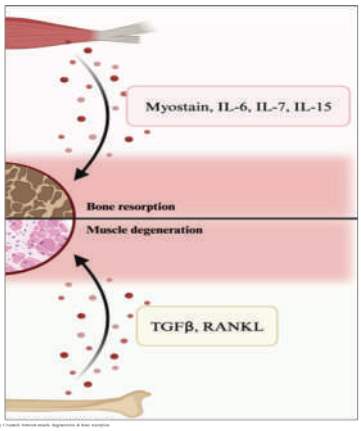


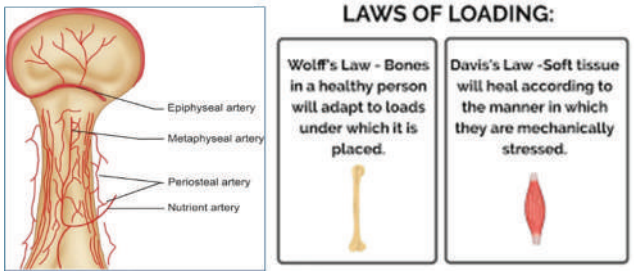
Figure: Crosstalk between muscle degeneration & bone resorption

Wolff-Davis Principle Extension: Wolff's law (bone adaptation to loading) and Davis' law (soft tissue adaptation) operate synergistically. Reduced mechanical stimulation affects both tissues simultaneously. A decrease in muscle force correlates with a reduction in bone formation activity (Finnegan, 2020), (Herrmann, et al., 2020), (Ruff, Holt, & Trinkaus, 2006).

Vascularity & Fracture

The lower extremities have relatively less dense vascular circulation compared to the upper body. Bone receives its blood supply primarily through surrounding muscles.

In the lower limbs, this limited circulation can affect bone repair following fracture. Epiphyseal, metaphyseal, periosteal, and nutrient arteries supply blood to bone tissue and work with muscle-derived flow to support osteoblast function, mineralization, and fracture repair.



Therefore, osteoblastic activity is dependent on the surrounding muscle health (Ahsan & Alzahrani, 2024), (Heyland, et al., 2023), (Wirayuni & Arista, 2021), (Darak & Karthikbabu, 2020), (Elniel & Giannoudis, 2018). The calf muscle acts as a venous pump, helping push blood against the gravity that is back towards the heart and improving circulation in the lower limb. During fracture recovery, immobilization and muscle disuse weaken the venous pump, slowing blood flow and delaying healing. Adequate muscle strength & health can lead to good venous return supporting oxygen and nutrient delivery, reduce swelling, and aid fracture healing (Tauraginski & et.al, 2025), (Yuan, et al., 2025), (Yang, et al., 2025), (Liu, He, Song, & Li, 2025), (Yang, et al., 2025).

Muscle mass plays a critical role in delivering sufficient blood flow to bone. Adequate muscle volume ensures better vascular support, enhancing the healing environment. Muscle mass applies mechanical load on bone, stimulating bone formation and maintaining density.

It also supports joint stability and alignment. Muscles enhance blood flow to the fracture site, supplying oxygen and nutrients for healing. They also release growth factors that activate osteoblasts, promoting bone regeneration. In contrast, pre-existing muscle weakness can reduce local blood supply, especially in the lower limb, contributing to delayed healing and risk of non-union, malunion, or recurrent fractures. This condition may extend the hospital stay and compromise recovery, such as muscle atrophy & imbalance, delay healing, abnormal bone fixation, joint stiffness & contraction, and impaired functional recovery. This highlights the importance of supporting muscle health as part of comprehensive care to aid in fracture healing and achieve optimal fracture recovery outcomes (Spiegel & Banskota, 2020), (Elniel & Giannoudis, 2018).

Muscle health directly influences osteoblast activity. Well-perfused, healthy muscle tissue supports osteoblast function, promoting bone formation and proper fracture healing. Osteoblast activity is highly dependent on oxygen and nutrient availability through the blood supply from the surrounding muscle. Local muscle weakness causes poor perfusion, which creates a hypoxic condition. This effects in reduced osteoblast proliferation resulting in delayed callus formation & mineralisation and further slow recovery. Therefore, supporting muscle health can positively influence osteoblast function, helping to promote optimal fracture outcomes (Mandal & Saha, 2024), (Heyland, et al., 2023), (Spiegel & Banskota, 2020), (Do & Yim, 2020), (Elniel & Giannoudis, 2018).

A 12-year prospective cohort study in 823 men aged 60–87 found that those with fractures had a 41% greater decline in grip strength and worsened balance and mobility, even in areas away from the fracture, showing the broad impact of fractures on muscle function (Szulc, Lewis, & Chapurlat, 2024).

A randomized controlled trial on 100 sarcopenic patients with femoral fractures showed that those with muscle strengthening regimen had better muscle strength, faster fracture healing, and shorter hospital stays compared to the control group (Nie, et al., 2023).

A 25-year prospective study of 1184 individuals who had at least one low-trauma fracture after the age of 50 years indicated that muscle weakness is an independent risk factor for post-fracture mortality. The study concluded that early intervention to improve muscle strength in the older population may influence improving BMD and reducing pro-fracture mortality risk (Pham, et al., 2017).

A cohort study of 82 individuals aged 75–80 found that lower pre-fracture muscle strength was linked to a higher risk of mortality after the fracture. Those in the lowest third of muscle strength had a 4.4-fold increased risk of death compared to those with the highest strength (Rantanen, Sakari-Rantala, & Heikkinen, 2002).

A study involving 830 men with low-trauma fractures found that pre-fracture muscle strength and physical performance predicted post-fracture mortality but not subsequent fractures. Annual declines in grip strength and gait speed were linked to a higher risk of mortality, independent of other factors (Alajlouni, et al., 2022).

These studies collectively emphasize the integral role of muscle strength and function in fracture outcomes, highlighting the need for interventions targeting muscle health to improve recovery and reduce mortality risks associated with fractures.

Immobilization during fracture healing leads to disuse of surrounding muscles, especially in the lower limb where circulation is already less dense. Immobilization exacerbates muscle deterioration and weakness. This muscle inactivity delays recovery compared to the upper limb due to reduced blood flow and slower local muscle recovery. Prolonged immobilization and reduced muscle activity post-fracture increase DVT risk, compromising venous return and local circulation. Impaired blood flow can also lead to osteonecrosis, especially in fractures near joints (e.g., femoral neck), were disrupted microvascular supply causes muscle and bone tissue death. Muscle atrophy negatively impact oxygen delivery and cellular repair processes, ultimately delaying effective bone regeneration after discharge. Supporting muscle health during fracture treatment and periods of immobilization can accelerate bone healing and help patients return to their pre-fracture activity levels more quickly and effectively (Huang, Liao, Yang, & Zhang, 2024), (Yuan & Song, 2021), (Herrmann, et al., 2020).

Therefore, healthy muscle is crucial for optimal fracture outcomes. It also enhances joint stability and facilitates efficient load transfer across bones and joints. Adequate blood supply through this healthy local muscle promotes bone remodelling stimulating osteogenic activity. Additional benefits may include decreased pain, earlier weight-bearing

capacity, reduced incidence of complications, such as DVT, muscle atrophy and joint stiffness, and overall enhancement of mobility and quality of life (Mandal & Saha, 2024), (Heyland, et al., 2023), (Spiegel & Banskota, 2020), (Do & Yim, 2020).

Endocrine Regulation

Shared Hormonal Influences: Sex hormones (estrogen, testosterone) regulate both muscle protein synthesis and bone mineral density. The growth hormone/IGF-1 axis modulates both myoblast and osteoblast activity. Thyroid hormones regulate metabolic activity in both tissue types. Therefore, age-related hormonal changes synchronized decline in both muscle strength and bone integrity often observed in elderly populations (Niwczyk, et al., 2023), (Mills, et al., 2021).

Synchronized Sensitivity: Age-related endocrine changes affect both tissues with similar temporal patterns (changes and arrangements). Both tissue types show parallel declines in hormonal receptor sensitivity; endocrine disorders (e.g., hyperparathyroidism, hypercortisolism) affect both systems simultaneously. (Bonewald, 2020).

Integrated Neurovascular Supply

Vascular Coupling: Shared microcirculation networks supply adjacent muscle and bone. Muscle contraction drives 80-85% of bone blood flow for their nourishment and maintenance. Vascular pathologies compromise both tissue perfusion systems by impairing blood flow to muscle & bone. Abnormal blood vessels impact bone fracture healing, potentially leading to complications like delayed healing, non-union, or avascular necrosis (bone death) (Qin, et al., 2022), (Morton, Jacobsen, & Segal, 2019), (Gliemann, Hansen, Rytter, & Hellsten, 2019).

Neural Coordination: Common proprioceptive feedback loops are sensory-motor feedback systems that allow the body to monitor and adjust its movements, posture, and balance in real-time. When the loop is compromised, the brain may not receive the necessary feedback to properly regulate muscle activity, leading to muscle weakness and joint instability. Proprioceptive feedback also plays a role in bone healing by influencing muscle activity that can help realign fractured bone fragments. Disrupted proprioception can interfere with this natural realignment process. Neuromuscular junction integrity affects mechanical protection of adjacent bone structures (Ahsan & Alzahrani, 2024), (Heyland, et al., 2023), (Qin, et al., 2022), (Morton, Jacobsen, & Segal, 2019).

Exposure to chronic inactivity or immobilization causes a disproportionate loss of muscle strength and muscle mass that can reduce bone strength. Alterations in neurotransmitter release or action at the neuromuscular junction can significantly contribute to muscle atrophy & bone fracture (Qin, et al., 2022), (Gliemann, Hansen, Rytter, & Hellsten, 2019), (Morton, Jacobsen, & Segal, 2019).

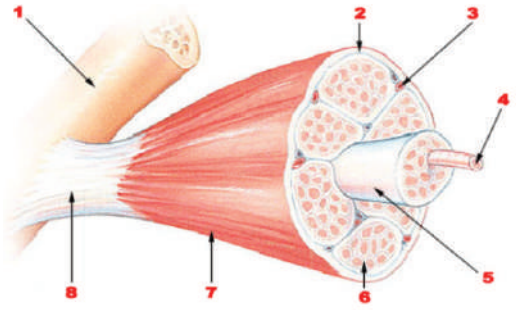


Fig.: Skeletal Muscle: Skeletal muscle: 1] Bone, 3] Blood vessel, 4] Muscle fiber

Nutritional and Metabolic Interdependence

Resource Competition and Sharing: Both tissues require similar amino acid profiles and micronutrients. Protein malnutrition affects muscle before bone due to higher turnover rates. Vitamin D deficiency impairs both muscle function and bone mineralization simultaneously (Rahmati, Haffner, Lee, Leach, & Saiz, 2024), (Szulc, 2020).

Energy Allocation Systems: Muscle serves as an amino acid reservoir for acute protein needs, including fracture healing. Bone marrow fat interacts with adjacent muscle metabolism. Mitochondrial dysfunction affects both tissues with similar patterns of impairment (Rahmati, Haffner, Lee, Leach, & Saiz, 2024), (Szulc, 2020).

Muscle health significantly influences bone fracture patterns through various mechanisms that differ by fracture location and type (Alajlouni, Bliuc, Tran, Blank, & Center, 2023) (Alajlouni, Tran, Bliuc, & Blank, 2021), (Erinç, Bazca, Özdemir, Yahşi, & Çakırtürk, 2020), (Visser, 2000).

2. Can muscle weakness contribute to bone fracture/treatment outcomes?

Muscle weakness increases the risk of non-union, malunion, or recurrent fractures by impairing

balance, reducing impact absorption, and decreasing mechanical loading on bones. It also worsens fracture healing by weakening osteoblast stimulation, delaying callus formation, and limiting mobility needed for recovery. Poor muscle strength is linked to longer healing times, higher risk of complications, and reduced functional outcomes after fracture (Ahsan & Alzahrani, 2024), (Rahmati, Haffner, Lee, Leach, & Saiz, 2024), (Heyland, et al., 2023), (Darak & Karthikbabu, 2020), (Elniel & Giannoudis, 2018).

- **Pre-existing muscle weakness**, such as in sarcopenia, increases non-union, malunion, or recurrent fractures and predicts poorer healing outcomes.
- **Post-fracture muscle weakness**, especially around the injured site, limits joint stability and delays rehabilitation.
- **Muscle disuse during immobilization** contributes to rapid atrophy, further impairing bone healing and functional recovery.

Direct Contributions

Muscle weakness can increase the risk of non-union, malunion, or recurrent fractures through multiple biomechanical and physiological mechanisms. Additionally, a decrease in grip strength reflects overall muscle weakness, particularly in the upper limbs, and is a strong predictor of reduced functional capacity and frailty. Lower grip strength is associated with poorer balance, slower reflexes, which contribute to a higher likelihood of joint stiffness, chronic pain, impaired functional recovery, delaying fracture healing, —especially in the elderly. Moreover, muscle weakness diminishes proprioceptive feedback, leading to impaired balance and coordination—patients with sarcopenia have been shown to experience falls at a rate 1.5 to 2.3 times higher than those without muscle loss. Muscle weakness also contributes to long-term skeletal fragility by reducing the mechanical loading necessary to maintain bone health. A reduction in muscle strength has been linked to annual loss in bone mineral density (BMD), further compounding the risk of osteoporosis, impaired functional recovery, chronic pain, stiffness, etc (Mandal & Saha, 2024), (Ahsan & Alzahrani, 2024), (Darak & Karthikbabu, 2020).

Indirect Mechanisms

In conditions of muscle dysfunction, the elevated release of inflammatory cytokines such as IL-6 and TNF-α can negatively affect bone remodelling by enhancing bone resorption and suppressing bone formation. At the same time, shared nutritional deficiencies—particularly inadequate protein, vitamin D, and calcium intake—undermine both muscle integrity and bone strength, gradually weakening the entire musculoskeletal system. Additionally, endocrine disorders such as thyroid dysfunction, diabetes, or sex hormone deficiencies can simultaneously impair muscle and bone health. These systemic influences collectively create a biological environment where fractures delay in healing, abnormal bone fixation, muscle atrophy & imbalance, impaired functional recovery, joint stiffness & contraction (Ahsan & Alzahrani, 2024) (Rahmati, Haffner, Lee, Leach, & Saiz, 2024), (Heyland, et al., 2023), (Elniel & Giannoudis, 2018).

3. Impact of Muscle Weakness on Post-Fracture Healing Outcomes

Muscle weakness plays a critical role in determining the quality of recovery following a bone fracture, often leading to poorer post-healing outcomes. Patients with pre-existing muscle weakness, particularly those with sarcopenia, experience significantly worse outcomes following bone fractures. In individuals with muscle weakness-whether due to aging, disuse, or underlying conditions like sarcopenia—this mechanical loading is significantly reduced, resulting in diminished osteoblastic activity and delayed callus formation. Additionally, weakened muscles compromise joint stability, reduce mobility & higher rate of fixation failure, due to reduced support from surrounding musculature and impaired osteogenic signalling. These compromised outcomes making it more difficult for patients to engage in early weight-bearing and rehabilitation, both of which are crucial for optimal fracture healing. The situation is further compounded by impaired balance and proprioception loop, which increase the risk of fractures delay in healing, abnormal bone fixation, muscle atrophy & imbalance, impaired functional recovery, joint stiffness & contraction during the recovery phase. Moreover, muscle weakness is often accompanied by systemic inflammation and nutritional deficiencies, which can further impair tissue repair and slow down healing. Clinically, this manifests as prolonged recovery times, reduced functional independence, and a higher likelihood of complications such as non-union, malunion, or recurrent fractures. Therefore, muscle weakness significantly compromises the biological and functional environment required for

efficient and successful fracture healing (Niwczyk, et al., 2023), (Arai, Kirk, & Duque, 2023), (Jiang, et al., 2022), (Darak & Karthikbabu, 2020).

4. Can muscle weakness management improve fracture outcomes?

Muscle-derived mechanical stimuli are essential for activating osteoblasts—the bone-forming cells responsible for producing collagen (via collagen type I synthase) and mineralizing the bone matrix with enzymes such as alkaline phosphatase (ALP). In the absence of sufficient muscle contraction, osteoblastic activity declines, leading to weaker callus formation and delayed union. Simultaneously, muscle regeneration is compromised due to reduced activity of myoblasts, which are critical for muscle repair and interact with bone through biochemical signalling molecules like IGF-1 and myokines such as irisin. This biological deficiency is reflected in clinical practice: sarcopenic patients tend to have longer hospital stays, as impaired muscle repair delays mobilization and increases post-operative complications. Moreover, a significant reduction in functional recovery is observed in patients with muscle weakness, partly due to suboptimal muscle-bone crosstalk and impaired neuromuscular coordination. The extended recovery time is further illustrated by the prolonged duration required to return to activities of daily living (ADLs), significantly increasing patient dependency and overall healthcare burden. These outcomes underscore the critical roles of osteoblasts, myoblasts, and their associated enzymatic machinery in orchestrating effective optimal bone healing, accelerate fracture healing, muscle growth & balance, proper bone fixation, joint flexibility & extension, optimal functional recovery, decreased pain, earlier weight-bearing capacity, and reduced incidence of complications following fracture (Niwczyk, et al., 2023), (Arai, Kirk, & Duque, 2023), (Jiang, et al., 2022), (Do & Yim, 2020), (Darak & Karthikbabu, 2020), (Elniel & Giannoudis, 2018).

Adequate muscle strength is essential not only for stabilizing the skeletal system but also for generating the mechanical forces that stimulate bone remodelling during the fracture healing process for optimal fracture outcomes.

5. What is the possible outcomes muscle strengthening regimen (Nutrition + Exercise) with primary therapy?

Incorporating a Muscle Strengthening regimen alongside primary therapy significantly enhances post-fracture recovery by promoting multiple positive outcomes. Nutritional support, including adequate protein, calcium, and vitamin D, plays a crucial role in accelerating bone healing and tissue repair. Targeted exercises help prevent muscle atrophy, promote hypertrophy, and restore neuromuscular balance, which improves overall strength and stability. Controlled mechanical loading during exercise stimulates bone remodelling, supporting proper bone alignment and fixation. Additionally, regular movement and stretching enhance joint mobility, prevent stiffness and contractures, and maintain flexibility. Together, these interventions contribute to faster healing, better functional recovery, and an earlier return to daily activities (Qin, et al., 2022), (Szulc, 2020), (Morton, Jacobsen, & Segal, 2019), (Shah, Majeed, Jonason, & O'Keefe, 2013).

Joint Replacement Surgery Recovery

Muscles around a joint play a critical role in recovery after surgery. They provide stability and help maintain proper joint alignment during movement. Post-surgical joints rely on periarticular muscles to restore normal biomechanics and facilitating mobility (Szulc, 2020), (Davis, et al., 2015), (Shah, Majeed, Jonason, & O'Keefe, 2013).

There are adequate evidence linking pre-existing muscle weakness to poor functional outcomes after joint surgeries:

- A 2023 study reported a 14% prevalence of sarcopenia among elderly patients undergoing joint surgery. Muscle loss (sarcopenia) and frailty were linked to more complications after surgery. Patients with pre-existing muscle weakness had longer hospital and ICU stays. Slow walking speed and weak handgrip before surgery were associated with a higher risk of adverse outcomes. Among those who died within a year, 80% had severe sarcopenia. Of the patients who were re-hospitalized, 43% showed signs of muscle loss or frailty (Salles, et al., 2023).
- This study of 162 total hip arthroplasty (THA) patients found that the 91 patients with pre-existing muscle weakness and lower energy had significantly poorer functional outcomes one year after surgery, despite increased physical activity. The findings suggest that sufficient preoperative nutritional intake, particularly protein, along with

exercise, is a key factor in improving muscle health recovery and is important for preventing prolonged muscle weakness following total hip arthroplasty (Ikeda, et al., 2022).

- Another observational study reviewed the effects of sarcopenia in patients aged 60–80 years undergoing joint replacement surgery and concluded that sarcopenia is a progressive muscle disorder strongly associated with poor surgical outcomes and complications, including re-hospitalization, delayed recovery, and increased dependence (Longo, et al., 2023).
- A 2019 observational study evaluated lower-functioning patients aged 40–90 years undergoing total knee arthroplasty (TKA) and found that those with significantly weaker preoperative knee extensor strength, slower gait speed, and higher pain scores had poor postoperative recovery compared to both older and younger higher-functioning patients. The study stated that pre-existing muscle weakness in young individuals undergoing joint surgery is prevalent and is associated with suboptimal surgical outcomes. It concluded that preoperative rehabilitation strategies (nutrition & exercise) can effectively improve muscle strength and physical performance, ultimately leading to better functional outcomes after surgery (Christensen, et al., 2019).

Pre-existing muscle weakness disrupts joint mechanics, which increases stress on the repaired area and can lead to further joint damage and restricted movement. Immobilization and restricted movement often led to disuse of the affected muscles. This can significantly reduce muscle mass and strength, resulting in muscle atrophy and weakness. This disuse atrophy further worsens muscle inhibition and weakness, alters joint stability and mechanics delays recovery and makes functional recovery difficult (Kitamura, Murata, Shigemura, & Yamamoto, 2024), (Wijk, et al., 2021).

As this cycle continues, both joint function and muscle strength deteriorate, creating a vicious circle where weakness and joint stress perpetuate and intensify each other (Hegde & Ranganath, 2021), (Canu, et al., 2019).

Conversely, improving muscle strength helps restore joint mechanics, reduces stress on the repair site, and breaks this negative loop, supporting better recovery and function. Even local muscles can become weakened or atrophied during surgery due to mechanical forces, tissue handling, and surgical trauma at the operative site. This contributes to immediate post-operative muscle shrinkage and delayed recovery. Additionally, muscle weakness can worsen after surgery due to immobilization, pain, and reduced activity — this is referred to as post-surgical muscle weakness. It leads to abnormal joint loading, further increasing strain on surgical repairs or implants (Rahmati, Haffner, Lee, Leach, & Saiz, 2023), (Szulc, 2020).

Poor muscle integrity limits joint control and stability, reducing the effectiveness of rehabilitation. This contributes to post-surgical muscle atrophy, poor fixation, delayed mobilization, increased complications, and impaired functional recovery. As a result, complete functional recovery is compromised due to muscle weakness. Strengthening muscles (by exercise & nutrition) before and after surgery is very important. It helps enhance mobility, restore range of motion, improve muscle endurance and strength, reduce hospital stays, enable earlier physiotherapy, promote greater independence, accelerate healing & improve complete functional recovery (Alajlouni, Bliuc, Tran, Blank, & Center, 2023), (Szulc, 2020), (Visser, Harris, & Fox, 2000).

1. Does Muscle Weakness Co-exist with Joint Surgery?

Muscle weakness around a fractured joint can arise from three distinct but interrelated conditions:

Pre-existing muscle weakness: Poor muscle condition prior to a fracture or surgery provides less support to the joints, making them more vulnerable to muscle atrophy and delaying the healing process. Disuse or inactivity—often due to aging, a sedentary lifestyle, chronic pain, or comorbidities—leads to a reduction in muscle mass (atrophy) and deterioration in muscle quality (sarcopenia). These changes weaken periarticular muscles, reduce overall muscle strength & mass, and impair neuromuscular coordination. As a result, limb function is compromised, leading to prolonged post-operative rehabilitation and increased dependency & rehospitalization. Patients with pre-existing muscle weakness tend to experience slower recovery, reduced joint stability, increased joint stiffness, worsening local muscle health, and a higher risk of surgical complications or failure. Prehabilitation, or targeted muscle strengthening before surgery, can significantly enhance surgical readiness and improve post-operative functional outcomes (Rahmati, Haffner,

Lee, Leach, & Saiz, 2023), (Alajlouni, Bliuc, Tran, Blank, & Center, 2023), (Szulc, 2020), (Shah, Majeed, Jonason, & O'Keefe, 2013; Kostenuik & Mirza, 2017).

Surgery-induced muscle trauma: During joint surgery, muscles surrounding the operative site are often exposed to significant mechanical stress, causing intraoperative muscle weakness. Surgical access frequently involves retraction, manipulation, or incision through muscle tissues, which can cause localized trauma. Mechanical handling during the procedure—including stretching, compression, or the use of surgical instruments—can lead to micro-tears in muscle fibers, reduced blood flow, and temporary loss of neuromuscular function. In some cases, electrocautery or prolonged retraction can damage local nerves or disrupt the vascular supply to muscle tissue. This intraoperative stress contributes to immediate post-surgical muscle weakness, even in muscles that were otherwise healthy before surgery. The result is reduced local muscle strength, delayed activation, and compromised support to the joint during early recovery. Early muscle damage from surgery further limits functional mobility and delays the start of effective physiotherapy (Singh, Dhaniwala, Jadawala, Suneja, & Batra, 2024), (Gao, Huang, Chen, & et, 2023),(Canosa-Carro, Bravo-Aguilar, Abuín-Porras, & Almazán-Polo, 2022), (Schlussel & Maykel, 2019), (Peake, Nosaka, Gatta, & Neubauer, 2017).

Although robotic systems ensure accurate implant placement, the surrounding muscles must stabilize and support that implant during recovery. If the muscles are weak, they cannot maintain proper joint alignment, which may compromise the precision benefits of robotic surgery (Sun, Cappellari, Lan, & Abayazid, 2025), (Younis, et al., 2025), (Bahrami, Nikparto, & Bador, 2024), (Koganezawa, 2014).

Muscle strengthening and activation strategies during the early post-operative period are essential to restore muscle integrity and accelerate recovery.

Post-Surgical Muscle Weakness from Immobilization and Disuse: After joint surgery, muscle weakness often worsens due to post-operative immobilization, muscle disuse, and reduced activity. While temporary rest is necessary for healing, prolonged inactivity can have significant negative effects on muscle health and joint recovery. Immobilization leads to disuse atrophy, where muscles rapidly lose mass and strength due to lack of contraction. This process begins within days of inactivity. Additionally, neuromuscular deconditioning occurs, where communication between the brain and muscles weakens, further impairing muscle activation. Pain, joint swelling, and inflammation after surgery can also inhibit voluntary muscle contraction—a phenomenon known as atherogenic muscle inhibition. As a result, even when the patient is willing to move, the muscle cannot generate normal force. Reduced movement also impairs blood circulation, especially in the lower limbs, increasing the risk of complications such as deep vein thrombosis (DVT), particularly in older adults. Together, these factors delay functional recovery, increase stiffness, and limit the effectiveness of post-operative rehabilitation. Early and progressive muscle activation, under guided physiotherapy, is essential to prevent further muscle loss, restore joint function, and reduce post-surgical complications (Monsegue, Emans, van Loon, & Verdijk, 2024), (Chen, Yu, Wang, & et, 2024), (Konnyu, Pinto, Cao, & et, 2023), (Park & Kim, 2023).

Each condition contributes uniquely to compromised recovery and highlights the need for targeted muscle strengthening strategies.

2. Can Muscle Weakness Contribute to Joint Surgery Outcomes?

Muscle weakness is a key factor that can negatively impact the outcomes of bone and joint surgeries. Muscles surrounding bones and joints provide essential support, stability, and movement. When these muscles are weak-before, during, or after surgery—they significantly compromise recovery, rehabilitation, and surgical success (Rahmati, Haffner, Lee, Leach, & Saiz, 2023), (Alajlouni, Bliuc, Tran, Blank, & Center, 2023), (Szulc, 2020).

Reduced Joint and Implant Stability: Weak muscles fail to stabilize the surgical area. This places extra strain on the bone or implant, increasing the risk of loosening, misalignment, or fixation failure.

Delayed Mobilization: Muscle strength is necessary for early movement after surgery. Weakness delays mobilization leads to stiffness, and prolongs hospital stay.

Impaired Functional Recovery: Without strong muscles, essential movements like walking or lifting become difficult. This limits the patient's ability to regain independence.

Impact of Preexisting Sarcopenia: Patients with sarcopenia have weaker muscles. This increases the

risk of complications after joint surgery. They often stay longer in the hospital. Recovery and rehabilitation are slower. Weak muscles give less support to the joint. This can lead to poor recovery function after surgery. Sarcopenia also reduces joint stability. It increases stress on the implant and may shorten its lifespan. Managing sarcopenia before surgery is important. This includes muscle strengthening and good nutrition. These steps help improve recovery and reduce complications.

Increased Risk of Complications: Prolonged inactivity from weak muscles increases the risk of complications such as DVT, muscle atrophy, and post-operation pain, increased risk of dependence.

Poor Surgical Outcomes: Ultimately, weak muscles compromise mechanical support, leading to delayed bone healing, implant failure, or recurrence of injury.

Impact of muscle weakness on Upper and Lower Limb Surgery Outcomes: In both, weak muscles delay recovery and reduce surgical success rates (Bolletta, Corrado, & Chen, 2019).

In lower limb surgeries (hip, knee, ankle), weak muscles reduce weight-bearing capacity and balance, increasing recurrent fracture and slowing rehabilitation.

In upper limb surgeries (shoulder, elbow, wrist), muscle weakness limits arm function, affecting daily activities.

Surgical Precision and Recovery: Patient's muscle condition plays a key role in precision and faster healing. If periarticular muscles are weak, early mobilization becomes difficult. This limits functional gains and may lead to joint stiffness or instability, reducing the overall effectiveness of the surgery, even in robotic surgeries (Sun, Cappellari, Lan, & Abayazid, 2025).

The muscles around the spine, especially the deep cervical flexors, extensors, and paraspinal stabilizers, are essential for spinal alignment and movement. These muscles stabilize the operated segment and provide active neuromuscular control. They absorb and distribute axial and shear loads, improving head control, balance, and posture. After spinal surgeries like cervical disc replacement or facet joint replacement, muscle function is even more critical for recovery. Strengthening cervical and paraspinal muscles is vital after cervical spine surgery. This muscle strengthening supports joint protection, motion preservation, implant longevity, enhanced functional recovery, and reduced rehospitalization. Prehabilitation and rehabilitation should focus on deep muscle activation, isometric control, and progressive loading for optimal surgical outcomes and complete functional recovery (Robertson, et al., 2024), (Tu, Wang, Chen, & Wu, 2023), (Boddapati, Lee, Mathew, & al., 2021), (Chang, Huang, Wu, & Mummaneni, 2018).

Joint surgery can increase lactic acid levels due to tissue trauma and reduced oxygen supply. High lactic acid after surgery increases pain and joint stiffness, which can lead to immobilization, further muscle disuse, and eventual muscle atrophy. A structured muscle strengthening regimen, including nutritional intake and recovery exercises, helps lower lactic acid levels. Reducing lactic acid through muscle strengthening nutritional intake supports better physiotherapy outcomes, pain relief, functional recovery while also preventing muscle atrophy.

Muscle weakness significantly contributes to suboptimal bone surgery outcomes by reducing stability, delaying mobility, and impairing healing, extending hospitalization, slower healing, impairing functional recovery, implant fixation, imbalance, and muscle atrophy. A structured muscle strengthening regimen with nutrition before and after surgery is essential to improve recovery and achieve better long-term results (Singh, Dhaniwala, Jadawala, Suneja, & Batra, 2024), (Rahmati, Haffner, Lee, Leach, & Saiz, 2023), (Alajlouni, Bliuc, Tran, Blank, & Center, 2023), (Szulc, 2020).

3. Can Muscle Weakness Management Improve Joint Surgery Outcomes?

Addressing muscle weakness through targeted interventions may enhance surgical outcomes. Preoperative muscle strength plays a crucial role in postoperative recovery by improving muscle strength and joint function. Management of muscle weakness-through exercise, nutrition, and rehabilitation-can significantly enhance surgical results (Sun, et al., 2023), (Casaña, et al., 2019), (Calatayud, et al., 2017).

Muscles around the hip and knee, such as the gluteus, quadriceps, and hamstrings, are essential for load bearing, shock absorption, and mobility (Functioning/ADL). These large muscle groups maintain joint alignment, control dynamic motion, and prevent falls during walking, stair climbing, and transfers. Preoperative weakness in these muscles leads to abnormal joint mechanics, increased wear on prostheses, prolonged immobility, and functional

decline. Optimizing muscle health perioperatively enhances joint control and reduces postoperative inflammation. Therefore, after surgery, if the surrounding muscles are healthy, they can improve the joint coordination, torque, integrity. This further restores stable movement patterns to ensure perfect implant fixation results in faster recovery, reduced rehospitalisation, and lower revision rates (Uhlrich, Jackson, Seth, & Kolesar, 2022), (Maestroni, et al., 2020), (Hasson, Caldwell, & van Emmerik, 2008), (Prilutsky, 2000).

Muscles around the small joint surgeries (ankle, elbow, wrist) provide fine control, stability, and functional positioning for balance or dexterity. Atrophied muscles fail to support precise joint movement or protect healing structures. After surgery due to muscle atrophy, results in poor grip, unstable gait, or limited range of motion, affecting activities of daily living. Targeted muscle strengthening improves neuromuscular control, proprioception, and tissue repair. Strengthening these muscles supports faster recovery of function, balance, and joint motion. This results in better functional scores, fewer complications, and greater patient independence (Hong, Lee, & Lee, 2024), (Kacmaz & Unver, 2023), (Nigg, Baltich, Federolf, Manz, & Nigg, 2017), (Aman, Elangovan, Yeh, & Konczak, 2015), (Tripp, Jacobs, & Faust, 2009).

Prehabilitation: Enhancing Recovery Through Exercise

Prehabilitation, involving structured exercise programs before surgery, has shown promise in improving postoperative outcomes (Rhim, et al., 2024), (Vergara-Merino, Lira, Liquitay, González-Kusjanovic, & Morales, 2023), (Casaña, et al., 2019), (Calatayud, et al., 2017).

A systematic review and meta-analysis encompassing 48 trials with 3,570 participants reported that prehabilitation significantly improved preoperative function, muscle strength, and health-related quality of life in patients undergoing orthopaedic procedures (Punnoose, et al., 2023).

A study performed 8-weeks preoperative and 1-month postoperative muscle rehabilitation in 44 end-stage OA patients. The study concluded that improving muscle strength by training during the preoperative period reduces pain and improves lower limb muscle strength, range of motion, and functional task performance before surgery, resulting in a reduced length of stay at the hospital and a faster physical and functional recovery after TKA (Calatayud, et al., 2017).

Preoperative high muscle intensity strengthening regimen on 44 subjects (mean age 66.7 ± 3.9 years) is effective for improving postural control before and early after TKA. The study recommended to include preoperative muscle improvement regimen for proper balance, to speed-up recovery of postural control after TKA (Casaña, et al., 2019).

A review article supports preoperative muscle strengthening on patients undergoing foot and ankle surgery. The study stated that healthy muscles around the foot and ankle support joint stability, protect healing tissues, and enable proper movement patterns after surgery. They enhance neuromuscular control and proprioception, reducing the risk of imbalance and reinjury during rehabilitation. Healthy muscles help absorb load and minimize stress on surgical repairs, supporting tissue healing and implant fixation. Ultimately, accelerates functional recovery, shortens hospital stay, and improves surgical outcomes (Rhim, et al., 2024).

Nutritional Optimization: A Complementary Approach

Adequate nutritional intake is vital for muscle maintenance and recovery. In all joint surgeries, undernourished patients have higher risks of wound complications, delayed rehabilitation, and hospital readmissions. Adequate nutritional supplementation pre- and post-surgery supports muscle repair and enhances surgical outcomes (George, Holderread, Lambert, Harris, & McCulloch, 2024), (Hideki, Narihiro, Yukihide, Yoshiki, & Hiroaki, 2023), (Hirsch, Wolfe, & Ferrando, 2021).

A systematic review analyses beneficial effects of oral nutritional supplementation on postoperative muscle atrophy and patient outcomes following orthopaedic surgery. It reported improved functional outcomes and faster achievement of rehabilitation milestones. Oral nutritional supplementation effectively mitigates muscle atrophy in the postoperative period after ACL reconstruction (ACLR), total hip arthroplasty (THA), total knee arthroplasty (TKA), and surgical treatment of hip fractures. These benefits often correlate with enhanced functional performance and quicker rehabilitation progress (George, Holderread, Lambert, Harris, & McCulloch, 2024).

A double-blind randomized controlled trial evaluated 60 patients undergoing unilateral total knee arthroplasty for primary knee osteoarthritis. Participants received essential amino acid (EAA) supplementation from 1 week prior to surgery until 2 weeks post-surgery. Perioperative EAA supplementation contributed to the recovery of rectus femoris muscle volume and quadriceps strength over the postoperative period. Muscle volume was assessed via ultrasonography, and strength was measured using a handheld dynamometer preoperatively and at periodic intervals up to 2 years postoperatively (Hideki, Narihiro, Yukihide, Yoshiki, & Hiroaki, 2023).

This review highlights oral nutrition strategies that can be implemented before and after major surgery to minimize muscle atrophy and the resulting loss of function. Adequate nutritional intake is essential to address the surgical stress response and reduce the loss of muscle mass, strength, and functionality. Emphasizing nutritional intake throughout the surgical process helps reduce muscle breakdown and preserve function (Hirsch, Wolfe, & Ferrando, 2021).

4. What Are the Possible Outcomes of Muscle Strengthening Regimen (Nutrition+Exercise) with Primary Therapy?

Combining exercise and nutritional optimization before surgery has been shown to reduce postoperative complications. Implementing structured prehabilitation programs may accelerate healing and improve functional recovery. Strengthening exercises restore muscle tone, while supplementation (e.g., protein, EAA, calcium, antioxidants, vitamin D, etc) supports muscle function and aids joint stabilization (Sun, et al., 2023), (Hashizaki, et al., 2023), (Hirsch, Wolfe, & Ferrando, 2021), (Casaña, et al., 2019), (Calatayud, et al., 2017).

- Promotes muscle repair and energy metabolism, helps maintain muscle-joint synergy
- Prevents imbalanced muscle loading, altered biomechanics, and joint stress
- Reduces systemic inflammation; supports anti-inflammatory effects, reduces persistent inflammation
- Activates anabolic pathways (e.g., mTOR), and protein turnover, which accelerates tissue repair and reduces prolonged muscle weakness
- Improves motor unit engagement and supports neuromuscular signalling
- Prevents impaired joint coordination and promotes faster motor recovery
- Improves joint torques, integrity and balance, thereby enhancing proprioception and accelerating mobilization
- Helps lower lactic acid levels, supports pain relief, enhances physiotherapy outcomes & improves functional recovery

Managing muscle weakness through preoperative interventions, including strength training and nutritional optimization, can significantly improve outcomes in joint surgery patients. Strengthening muscles around the joint facilitates faster recovery of function, balance, and joint mobility. Moreover, a targeted muscle strengthening regimen helps restore stable movement patterns, which supports optimal implant fixation and contributes to accelerated recovery, reduced rehospitalization rates, and lower incidence of revision surgery. Consequently, patients achieve improved functional outcomes, experience fewer complications, and gain greater independence, ultimately leading to a more complete and timely functional recovery (George, Holderread, Lambert, Harris, & McCulloch, 2024) (Hirsch, Wolfe, & Ferrando, 2021).

Spinal Cord Injury (SCI) and Degenerative Spinal Disorders

Spinal disorders represent a broad spectrum of musculoskeletal conditions that affect the spinal cord, associated musculature, and supporting structures (Suo M, 2023). Emerging clinical and imaging studies have highlighted the critical role of paraspinal muscle atrophy and degeneration in the development and progression of spinal disorders. These key muscles are responsible for spinal stabilization, posture maintenance, and functional movement (Suo M, 2023) (Noonan AM, 2021) (Mamatha H, 2024). Degeneration of these muscles can lead to structural alterations, impaired spinal biomechanics, and compromised function. Such changes are commonly observed in a variety of spinal pathologies such as (Suo M, 2023) (Mamatha H, 2024) (Sakamoto N, 2025)

- Cervical/lumbar spondylosis
- Degenerative scoliosis
- Degenerative lumbar spondylolisthesis
- Lumbar spine stenosis
- Lumbar disc herniation

- Degenerative lumbar kyphosis
- Low back pain
- Cervical myelopathy
- Spinal cord injuries/surgery
- Idiopathic scoliosis
- Mixed Connective Tissue Disease

Individuals with SCI/disorders frequently rely on their unaffected limbs for daily activities, resulting in overuse injuries. This can lead to chronic pain and functional decline, as the overused side becomes susceptible to injuries due to repetitive strain and show considerable muscle weakness (Vives Alvarado JR, 2021) (Lee KS, 2022). On the other hand, the affected side experiences muscle disuse and weakness, leading to muscle atrophy and decreased strength, which further limits mobility and independence (Vives Alvarado JR, 2021) (Huang H, 2021). If the muscle weakness is neglected it leads to lack of muscular tone (hypotonicity), and loss of reflexes (areflexia) which can further increase disease progression and increase the risk of complications (Peterson DB, 2009).

Therefore, muscle weakness is a common feature across all the above-mentioned conditions.

SCI/disorders lead to loss of innervation of skeletal muscle, decreased motor function, and significantly reduce load on skeletal muscle, resulting in atrophy. This impairs muscle strength, endurance, recovery, and metabolic health (Xu X, 2023). These changes not only limit physical function but also worsen clinical outcomes, delay rehabilitation, and increase the risk of secondary complications such as insulin resistance, thromboembolism, obesity, dyslipidemia, osteoporosis, fractures, and cardiovascular diseases (Fenton JM, 2023) (Gater DR, 2020). Therefore, understanding the impact of muscle loss in patients with SCI and related disorders is essential for improving patient care and clinical outcomes. If not addressed, muscle weakness can escalate the progression of spinal disorders and its complications. Hence, integrated interventions combining resistance training with muscle-specific nutritional support can significantly enhance muscle strength, endurance, recovery and overall treatment outcomes in patients with SCI/disorders (Gherle A, 2024) (Xu X, 2023) (Hagen, 2015) (Kabrhel C, 2011).

1. Does Muscle Weakness Coexist with Spinal Cord Injury and Other Disorders?

Patients with SCI and related disorders are prone to significant muscle weakness both generalized and in the paraspinal muscles especially in cases of high-level spinal injury, prolonged bed rest, & poor nutritional status (Feng T, 2025) (Xu X, 2023). This leads to loss of skeletal muscle innervation, reduced motor function, and decreased mechanical loading on muscles, resulting in atrophy and paraplegia or tetraplegia, which affects mobility and muscle control (Xu X, 2023) (Zhifei Li, 2025) (Debenham MIB, 2024).

Following SCI, skeletal muscle atrophy can range from 30–60%, with associated changes including decreased muscle mass, strength, function, and endurance along with increased fatigability (Binyang Wang, 2024). A rapid decline in muscle cross-sectional area (CSA) has been reported, with reductions of approximately 18–46% within the first 6 weeks (Xu X, 2023), and progressive atrophy occurring within 1–17 months post-injury (Gherle A, 2024).

In SCI, specifically, the muscle weakness observed is multifactorial. Contributing factors include (Xu X, 2023) (Gorgey AS, 2014) (Adams MM, 2005):

- Conduction of peripheral nerves innervating skeletal muscle will be interrupted or blocked
- Muscle denervation
- Decreased motor function & apoptosis
- Reduced acetylcholinesterase content & increased spasticity
- Degeneration of neuromuscular junctions (NMJ)
- Flaccid paralysis particularly if combined with low physical activity
- Decreased secretion of anabolic hormones
- Apoptosis of muscle cells triggered by inflammatory cytokines such as TNF-α, and the overexpression of IL-1 and IL-6
  - » Increased non-esterified fatty acids (NEFA) influx into muscles
  - » Insulin resistance & hyperglycaemia
- A reduction in mitochondrial number, along with mitochondrial damage caused by reactive oxygen species (ROS), impairing the muscle's ability to resist oxidative stress

Collectively, these neurogenic, musculoskeletal, and cellular/molecular changes lead to a more rapid and severe progression of muscle atrophy in individuals with SCI/disorders (Gherle A, 2024). SCI/disorders not only hinder the recovery of motor function but is also closely related to many systemic dysfunctions, affecting the prognosis of patients with SCI/disorders (Xu X, 2023).

2. Can Muscle Weakness Contribute to spinal Cord Treatment Outcomes?

Muscle loss, both generalized and localized (particularly in the paraspinal muscles), contributes to delayed recovery, prolonged hospital stays, poor surgical outcomes, decreased mobility, increased dependency, fatigue, worsened functional recovery, higher risk of in-hospital complications, lower cumulative survival, and ultimately, a poorer overall prognosis (Invernizzi M, 2021) (Xu X, 2023) (Kuo YK, 2020) (Ali Otom, 2021).

Sarcopenia, involving the erector spinae (ES) muscles, of paraspinal muscles are associated with increased risks of proximal junctional kyphosis (PJK) and proximal junctional failure (PJF) in patients undergoing surgery for adult spinal deformity (ASD) (Park JS, 2024). These findings emphasize the need for preoperative assessment of muscle volume and quality as a preventive strategy against postoperative complications like PJK/PJF (Park JS, 2024). Reduced relative cross-sectional area (RCSA) of erector spinae (ES) muscles is a key risk factor for diminished strength, tension, and range of motion, contributing to spinal deformities, disc degeneration, and cervical spine alignment (Cho, 2024) (Lee D, 2022) (Zhifei Li, 2025). In lumbar degenerative diseases (LDD), sarcopenia both generalized and localized to paraspinal muscles is associated with increased pain, disability, poor posture, worsened disc degeneration, and treatment outcomes. This highlights the impact of muscle quality on spinal health and its treatment outcomes (Feng T, 2025) (Evans AR, 2024).

Immobilization and physical inactivity in patients with SCI/disorders contribute to increasing the risk of coagulation disorders, venous stasis, obesity, dyslipidemia, insulin resistance, T2DM, and cardiovascular disease ultimately impairing rehabilitation outcomes and functional recovery (Gherle A, 2024) (Sisto SA, 2014) (Hagen, 2015) (Kabrhel C, 2011) (Fenton JM, 2023) (Gater DR, 2020).

Exercise and nutritional support strategies that include muscle strengthening are essential to prevent further muscle loss and promote functional recovery (Gherle A, 2024). They have been shown to improve muscle strength, endurance, power, voluntary contraction, supports metabolic health, and reduces the risk of secondary complications (Santos LV, 2022) (Fenton JM, 2023).

3. What Are the Changes in Muscle After SCI/ Disorders?

The spinal cord maintains both functional and nutritional connections with skeletal muscles via peripheral nerves. Spinal motor neurons transmit action potentials to the motor endplate, thereby initiating muscle contraction (Xu X, 2023) (Otzel DM, 2021) (Johnston TE, 2011).

Neurological changes

Following a SCI/disorder, the conduction of signals through peripheral nerves innervating skeletal muscles becomes disrupted or blocked, leading to impaired motor function and, in many cases, partial or complete muscle paralysis. As a result, some motor neurons undergo apoptosis, and the skeletal muscles they innervate begin to exhibit atrophy and fibrosis (Xu X, 2023) (Nemeth C, 2024) (Thomas CK, 1997).

In addition, the motor endplate degenerates, and levels of acetylcholinesterase (AChE) significantly decrease (Xu X, 2023). This reduction in AChE impairs the breakdown of acetylcholine, allowing it to accumulate at the synaptic cleft. The sustained presence of acetylcholine causes excess calcium influx through acetylcholine receptor channels on the postsynaptic membrane (Xu X, 2023).

This calcium overload activates intracellular proteases within skeletal muscle cells, leading to protein degradation and apoptosis through the upregulation of muscle-specific E3 ubiquitin ligases, namely Atrogin-1 and MuRF1 (Xu X, 2023).

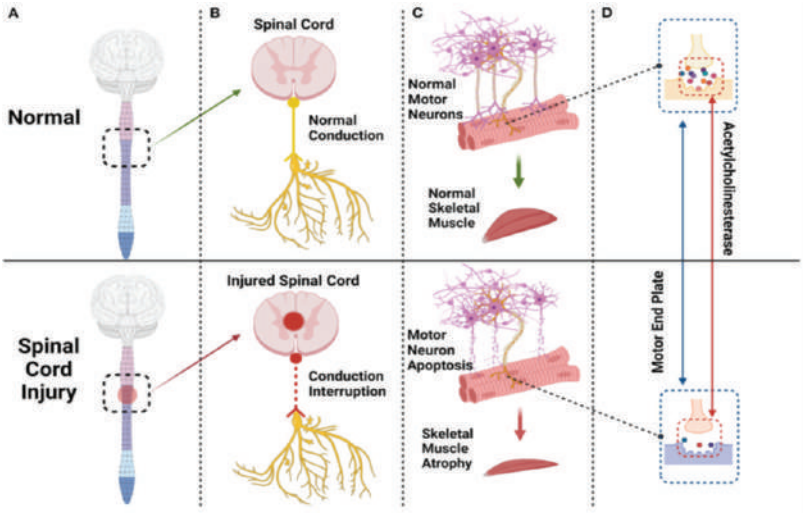


Figure: Spinal cord injury and muscle atrophy (Xu X, 2023)

After a spinal cord injury (A) the conduction of peripheral nerves innervating skeletal muscle will be interrupted or blocked (B) and some motor neurons innervating skeletal muscle will undergo apoptosis (C) Endplates degenerate, and acetylcholinesterase content of synapses will decrease significantly (D) eventually leading to skeletal muscle atrophy (C).

Neuroendocrine changes

SCI/disorders not only disrupt neuromuscular signaling but also impairs the neuroendocrine axis, leading to a reduction in anabolic hormones that are essential for maintaining skeletal muscle mass. This hormonal imbalance further contributes to muscle wasting and functional decline (Xu X, 2023).

Muscle fiber type transition

Following SCI/disorders, a transition in muscle fiber type occurs, where type I (slow-twitch, endurance) fibers are progressively replaced by type II (fast-twitch, glycolytic) fibers. These type II fibers are adapted for rapid and forceful contractions, but they exhibit reduced endurance capacity and are more prone to fatigue (Xu X, 2023) (Otzel DM, 2021) (Johnston TE, 2011). In addition to neural and hormonal disruption, several pathophysiological factors—including mechanical unloading (disuse), hormonal fluctuations, chronic inflammation, and oxidative stress—accelerate skeletal muscle atrophy in individuals with SCI (Xu X, 2023).

Metabolic changes

Following SCI/disorders, reduced physical activity and increased fat accumulation, particularly in the trunk and lower extremities, significantly impair carbohydrate and lipid metabolism (Xu X, 2023). The accumulation of excess adipose tissue leads to elevated levels of NEFAs due to enhanced lipolysis. These elevated NEFAs readily infiltrate muscle and liver cells, promoting intramyocellular and hepatic triglyceride accumulation, which contributes to the development of hepatic insulin resistance (Xu X, 2023).

Moreover, SCI/disorders-induced systemic inflammation is associated with a shift in macrophage polarization from the M2 (anti-inflammatory) to the M1 (pro-inflammatory) phenotype. This transition exacerbates insulin resistance by reducing insulin sensitivity, impairing glucose uptake, and promoting a pro-inflammatory environment (Xu X, 2023) (Li H).

NEFAs further impair glucose utilization in both muscle and liver tissues, intensifying insulin resistance. In the liver, fat accumulation exacerbates metabolic dysfunction by enhancing gluconeogenesis and increasing hepatic glucose output, ultimately leading to hyperglycemia—a central feature in the progression to T2DM (Gorgey AS, 2014) (Rachek, 2014).

Inflammatory changes

The inflammatory response triggered by SCI/disorders plays a pivotal role in driving skeletal muscle atrophy. Elevated levels of proinflammatory cytokines—including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6)- can directly induce apoptosis of muscle cells and promote the accumulation of reactive oxygen species (ROS). This oxidative stress contributes to mitochondrial dysfunction, further impairing muscle cell health (Xu X, 2023). TNF-α also activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, which upregulates the expression of muscle-specific E3 ubiquitin ligases, such as Atrogin-1 and MuRF1. These molecular markers are key mediators of protein degradation, promoting muscle proteolysis and amplifying inflammatory pathways, thereby accelerating muscle loss (Xu X, 2023).

Collectively, all these changes compromise the muscle strength, endurance, power, recovery, range of motion, and voluntary contraction in people with SCI/disorders, contributing to long-term functional decline (Santos LV, 2022).

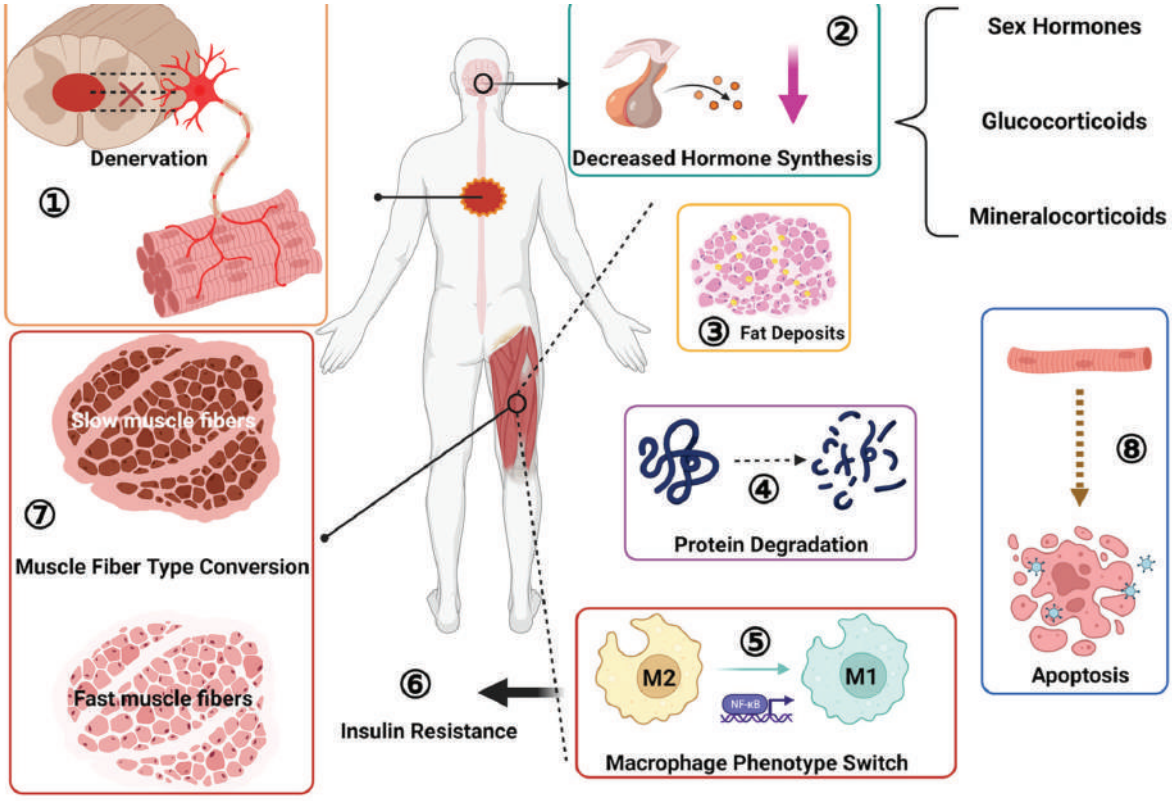


Figure: Spinal cord injury and muscle atrophy (Xu X, 2023)

After a spinal cord injury (A) the conduction of peripheral nerves innervating skeletal muscle will be interrupted or blocked (B) and some motor neurons innervating skeletal muscle will undergo apoptosis (C) Endplates degenerate, and acetylcholinesterase content of synapses will decrease significantly (D) eventually leading to skeletal muscle atrophy (C).

4. In What Way Does Muscle Influence SCI/ Disorders Outcomes?

Muscle atrophy following SCI/disorders leads to significant impairment of skeletal muscle function. This reduced capacity for physical activity often results in disuse sarcopenia, contributing to functional limitations, reduced quality of life, increased frailty, and a heightened risk of falls, fractures, and osteopenia/ osteoporosis (Gherle A, 2024) (Giangregorio L, 2006).

Targeted rehabilitation and nutritional support, particularly strategies that include muscle strengthening are essential to prevent further muscle loss and promote functional recovery (Gherle A, 2024). Such interventions have been shown to improve muscle strength, endurance, power, and voluntary contraction in individuals with SCI/disorders (Santos LV, 2022). However, barriers limit exercise and physical activity in individuals with SCI/disorders. Given the barriers to exercise, research focused on nutritional intervention in patients with SCI/disorders (Farkas GJ, 2021). Notably, β-hydroxy β-methylbutyrate (HMB) supplementation has demonstrated positive effects in preserving muscle mass, even in bedridden but otherwise healthy elderly individuals who are unable to perform resistance training. These findings highlight the potential of HMB as an effective nutritional intervention for patients with limited physical activity, such as those with SCI or similar debilitating conditions (Su H, The effects of β-hydroxy-β-methylbutyrate or HMB-rich nutritional supplements on sarcopenia patients: a systematic review and meta-analysis., 2024). Other supplements such as omega-3 Fatty Acids, zinc, & magnesium, has been shown to reduce inflammation, oxidative stress, improve neuronal repair, increase locomotor function, and improve function in both experimental and clinical trials (Abbaszadeh F, 2024) (Li Z W. X., 2025). It was reported that supplementation with calcium and vitamin D was associated with decreased risk of fracture, improved physical performance,

mobility, & bone health in persons with an SCI (Le B, 2024) (Mohammadi H, 2023). Therefore, nutritional supplementations provide functional improvements, also support metabolic health, and reduce the risk of secondary complications associated with SCI/ disorders (Fenton JM, 2023) by contributing to better bone mineral density, fat-free mass, adequate force production, and improved glucose metabolism. These physiological benefits collectively enhance treatment outcomes. Therefore, mitigating muscle deconditioning and providing nutritional support are key clinical priorities and remain central goals of treatment in patients with SCI/disorders (Sisto SA, 2014).

5. Can Muscle Weakness Management Improve SCI/Disorder Outcomes?

Combining physical activity, such as resistance training and aerobic exercise, with targeted nutritional support alongside appropriate pharmacological treatment has been shown to significantly mitigate muscle atrophy and enhance functional outcomes in individuals with SCI/disorders (Hernández-Lepe MA, 2023) (Keogh, 2013) (Gater DR, 2020). Muscle morphometry and composition have demonstrated prognostic value across various spine pathologies. For instance, in degenerative cervical myelopathy, improved outcomes have been associated with reduced muscle asymmetry, & increased fat-free muscle mass (Evans AR, 2024).

Additionally, a position paper from the Italian Spinal Cord Injury Network Rehabilitation Centers concluded that patients with SCI are at significant risk of malnutrition. Hence, regular monitoring of nutritional status and timely interventions are critical to improve prognosis, quality of life, & reduce the risk of complications in these patients (Areni A, 2024).

Nutritional interventions, including supplements like creatine, β-hydroxy-β-methylbutyrate (HMB), carnosine, whey protein, and vitamin D, have shown benefits in:

- Promoting muscle protein synthesis
- Reducing muscle protein breakdown
- Increasing muscle mass and strength
- Enhancing endurance and neuromuscular coordination
- Reducing inflammation and sarcopenia

In young and adult individuals, satellite cells (SCs) are highly active and support muscle repair. Although their function declines with age, they retain the ability to respond to growth signals, differentiate, and contribute to muscle regeneration (Huo F, 2022). This suggests that age-related muscle loss, such as in sarcopenia, is more due to changes in the surrounding environment than a loss of SC potential (Fard D, 2024). Hence, even in older adults, satellite cells can be reactivated to support muscle repair (Alway SE, 2014) (Kim KY, 2025).

However, with aging, satellite cells become senescent and adopt a Senescence-Associated Secretory Phenotype (SASP), releasing inflammatory mediators like Growth Differentiation Factor 15 (GDF15), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interleukin-32 (IL-32), and Transforming Growth Factor Beta 1 (TGFB1) (Podraza-Farhanieh A, 2025). These factors not only impair muscle function but also promote senescence in neighbouring healthy cells, worsening muscle degeneration, contributing to chronic inflammation, and muscle weakness (Podraza-Farhanieh A, 2025).

Therefore, in sarcopenia, early recognition and intervention through external support (such as muscle specific nutrition) can "prime" satellite cells and contribute to the maintenance of muscle health by activating the residual satellite cells and by preventing the acquisition of SASP (Alway SE, 2014) (Kim KY, 2025). When nutritional supplements are combined with exercise programs, the benefits are synergistically amplified (Hernández-Lepe MA, 2023) (Keogh, 2013). (Hernández-Lepe MA, 2023) (Keogh, 2013). Additionally, supplementation with essential amino acids or vitamin D in older adults has been linked to improved walking speed, enhanced muscle function, and a reduced risk of falls in patients with SCI/disorders (Lee D, 2022).

This integrated strategy contributes to substantial improvements in muscle strength, endurance, power, voluntary muscle contraction, and recovery in SCI/ disorder patients (Santos LV, 2022). Furthermore, it helps minimize muscle damage and functional decline, reduces biomarkers of muscle injury, inflammation, alleviates pain, supports protein synthesis, and accelerates recovery from fatigue and exercise-induced muscle damage (An YH, 2020) (Di Paola R, 2011).

6. What Are the Possible Outcomes of a Muscle Strength Regimen (Nutrition + Exercise) Along with Primary Therapy?

The primary therapeutic strategies to counteract muscle loss in individuals with SCI and related disorders include nutritional supplementation, pharmacological interventions, and physical exercise. Improving nutrition support may be a more accessible and practical approach for many individuals with SCI/ disorders, especially since exercise may not be feasible for all due to physical limitations (LaVela SL, 2024).

Nutritional interventions, particularly those involving essential and branched-chain amino acids like leucine, have shown significant benefits when combined with resistance exercise. Leucine and its metabolite, beta-hydroxy-beta-methylbutyrate (HMB), have demonstrated strong anabolic effects on protein metabolism, enhancing muscle mass and endurance capacity in both healthy, elderly individuals and those with muscle-wasting conditions. This multidimensional approach integrating nutritional support and structured exercise has shown promising outcomes in improving muscle strength and functional capacity in patients with SCI/disorders (Invernizzi M, 2021). Evidence has shown that combining both nutrition and exercise can significantly improve physical performance and back muscle function in cases of spinal sarcopenia by improving muscle quality, fiber type, architecture, neuromuscular activation, and aerobic capacity (Seungcheol Kim, 2023) (Invernizzi M, 2021) (Kuo YK, 2020). Overall, a comprehensive regimen that includes nutrition and exercise helps to reduce muscle atrophy, enhance strength and endurance, improve neuromuscular coordination, and support recovery and quality of life in individuals with SCI/disorders.

Psoriatic Arthritis (PsA)

Psoriatic arthritis (PsA) is an autoimmune chronic inflammatory disease characterized by joint inflammation and skin lesions, along with muscle damage, stiffness, atrophy & weakness (Bilski, Kupczyk, & Woźniak, 2024). Muscle weakness (MW) is a common but often overlooked comorbidity in PsA patients. PsA increases muscle protein breakdown, mitochondrial dysfunction, reduces satellite cell activity, and oxidative stress – all of which interact to drive muscle weakness and increased susceptibility to muscle fatigue. As a result, patients experience loss of muscle mass and strength and impairment of the muscle's ability to repair and maintain itself (Slavin, Khemraj, & Hood, 2024), (Wu, Shieh, Qin, & Guo, 2024), (Lian, Chen, Wu, Deng, & Hu, 2022), (Aoxuan, Na, Yujia, Yonghuan, & Yang, 2022). Additionally, corticosteroids, which are often used to manage PsA, can also cause muscle weakness (corticosteroid-induced myopathy). This is a common side effect, particularly with long-term or high-dose use (Surmachevska & Tiwari, 2025), (Kourakis, et al., 2021). Other cornerstone therapies, such as methotrexate and immunotherapies also contribute to muscle weakness and fatigue through their effects on muscle metabolism and immune modulation. Muscle weakness significantly impacts the prognosis of PsA, as it is a common manifestation of the disorder that can escalate to disease progression if not addressed. Addressing muscle weakness through targeted interventions may enhance overall disease management and patient outcomes in PsA (Tabra, Shintenawy, Hassan, & Elshintenawy, 2024) (Careccia, Mangiavini, & Cirillo, 2023), (Barone, et al., 2018), (Krajewska-Włodarczyk, Owczarczyk-Saczonek, & Placek, 2017), (Sirabella, De Angelis, & Berghella, 2013), (Schoels, et al., 2010).

1. Does Muscle Weakness Co-exist with PsA?

Joint pain and swelling are hallmark symptoms of PsA. Joints may feel stiff and harder to move, reducing range of motion. Loss of muscle mass (sarcopenia) is more common in people with PsA and can contribute to muscle weakness and an increased risk of falls. Muscle stiffness may occur, especially if immobility is prolonged due to joint discomfort. These symptoms can vary in severity and may worsen over time. Early recognition and treatment are important to improve joint movement, strengthen muscles, and enhance quality of life. Below are a few studies demonstrating that muscle weakness coexists with PsA:

1. A study evaluating sarcopenia in patients with rheumatic diseases found that approximately 20% of PsA patients exhibited sarcopenia, with an additional 25.7% displaying presarcopenia (Barone, et al., 2018).
2. Another research revealed significant reductions in muscle volume in PsA patients: 16% in male patients and 30% in female patients, particularly emphasising the effect of PsA on muscle health in females. This is often influenced by hormonal factors and ageing (Friedberger, et al., 2020), (Krajewska-Włodarczyk, Owczarczyk-Saczonek, & Placek, 2017).

3. In a study of 51 postmenopausal women with PsA, the prevalence of sarcopenia was found to be 43.1%, while bone mineralization disorders were observed in 72.7% of participants (Krajewska-Włodarczyk, Owczarczyk-Saczonek, & Placek, 2017).

4. An observational cohort study found a significant prevalence of Insulin Resistance (IR) (16%) among patients with PsA. The reason is persistent low-grade systemic inflammation in the joints and in the adipose tissue of patients with PsA (Haroon, Gallagher, Heffernan, & FitzGerald, 2014).

In summary, muscle weakness coexists with PsA in many patients. It is caused by inflammation, inactivity, and metabolic issues. Identifying and addressing muscle weakness early is important to improve muscle function and outcomes (Mogyoróssy, et al., 2023).

2. Can Muscle Weakness Contribute to PsA or Its Treatment Outcomes?

a. Joint Instability and Abnormal Mechanics: Weak muscles fail to stabilize joints, increasing abnormal joint loading, leading to greater mechanical wear and inflammation in synovial tissue. Enhancing muscle health strengthens and supports the muscles, helping to stabilize joints, particularly those in the knees and hips (Silva Santos Ribeiro, Willemen, & Eijkelkamp, 2022), (Pistone, La Vecchia, Pistone, & Bongiorno, 2014).

b. Increased Mechanical Stress on Inflamed Joints: Lack of muscular support transfers more load directly to joints. Higher compressive and shear forces accelerate cartilage degradation and promote synovitis (Abrar, et al., 2020). Strong muscles help absorb forces, protect joints from excessive wear and tear, and reduce the risk of injuries. Healthy muscles play a crucial role in providing optimal support and stability to joints, which is important for proper joint loading and function (Veen, Montefiori, Modenese, Mazzà, & Viceconti, 2019), (Belasco & Wei, 2019).

c. Reduced Shock Absorption: Muscles act as shock absorbers during movement. Muscle weakness reduces shock absorbers during movement. Strong muscles act as dynamic shock absorbers, attenuating impact forces and preventing excessive stress on bones (Belasco & Wei, 2019). Maintaining healthy muscles is crucial for preventing and mitigating microtrauma to joint structures (Damasco, et al., 2024),(Belasco & Wei, 2019).

d. Decreased Lymphatic and Blood Flow: Muscle contraction aids lymphatic return and circulation. Weak muscles impair circulation, leading to inadequate nutrient and oxygen availability to the bones (Cantatore, Maruotti, Corrado, & Ribatti, 2017). Therefore, optimizing muscle health enhances circulation in the environmental milieu and improves arthritis (Damasco, et al., 2024).

e. Inhibited Anti-inflammatory: PsA is an inflammatory disease, and arthritis limits muscle activity, which further releases inflammatory mediators. Active muscles release anti-inflammatory myokines (e.g., IL-6 in its anti-inflammatory role) and modulate systemic inflammation (Lian, Chen, Wu, Deng, & Hu, 2022) Improving the health of muscles can reduce disease progression (Slavin, Khemraj, & Hood, 2024).., (Silva Santos Ribeiro, Willemen, & Eijkelkamp, 2022), (Pistone, La Vecchia, Pistone, & Bongiorno, 2014).

f. Fatigue-Induced Cortisol Dysregulation: Muscle weakness contributes to fatigue, muscle tension & pain, which may increase flare frequency or intensity. Muscle fatigue from weakness alters cortisol rhythm. These factors contribute to HPA-axis imbalance, increase inflammatory flares and worsen PsA symptoms (Kaerts, Swinnen, Dankaerts, Vlam, & Neerinckx, 2024), (Nikhilesh, Sandhya, Dutta, & Chetan, 2023), (Silva Santos Ribeiro, Willemen, & Eijkelkamp, 2022), (Haugeberg, Michelsen, & Kavanaugh, 2020).

Sarcopenia-Driven Immune Dysregulation: Chronic muscle loss is associated with immune ageing and dysregulation. It impairs immune tolerance and promotes chronic low-grade inflammation that aggravates PsA symptoms (Barone, et al., 2018), (Krajewska-Włodarczyk, Owczarczyk-Saczonek, & Placek, 2017).

Limited Participation in Rehabilitation: Weak muscles make it harder for patients to participate in exercise programmes. Poor compliance with physical therapy delays functional recovery and exacerbates joint deformities. Therefore, maintaining good muscle health is crucial for providing the structural support needed for rehabilitation and optimal joint outcomes (Perrotta, et al., 2021).

Based on the above points, it can be said that muscle weakness coexists with PsA and plays a significant role in exacerbating PsA, undermining treatment

outcomes through interconnected pathways. Muscle weakness also hinders rehabilitation adherence, delaying functional recovery. Addressing muscle health – via targeted strength training, anti-inflammatory strategies, and improved physical therapy engagement – can stabilize joints, modulate inflammation, and enhance treatment efficacy.

3. What are the changes in muscle after PsA?

Chronic inflammation contributes to muscle breakdown. PsA involves high levels of inflammatory cytokines like TNF-α, IL-17, and IL-6. These cytokines promote muscle catabolism and inhibit muscle repair & regeneration. Over time, this leads to loss of muscle mass and strength. Muscle atrophy and inflammation exacerbate pain and reduce mobility (Balulu, et al., 2024), (Lee & Moon, 2024), (Naredo, et al., 2011).

Metabolic factors also play a role: Patients with PsA often present with multiple comorbidities, including dyslipidaemia, obesity, cardiometabolic syndrome, and insulin resistance. These conditions are independent risk factors for muscle weakness (Radić, et al., 2025), (Leite, et al., 2020). The underlying pathological mechanisms include low-grade systemic inflammation, mitochondrial dysfunction, oxidative stress, and hormonal imbalances (Williams, et al., 2024). When combined with PsA, these comorbidities increased sedentary behaviour, which can further worsen muscle health and accelerate muscle degradation (Leite, et al., 2020). As a result, muscle mass, strength, quality, and physical performance are impaired. Muscle endurance and recovery are also significantly reduced in PsA patients and create systemic complications (Aljohani, 2022), (Karmacharya, Ogdie, & Eder, 2021), (Ferguson, Linge, Leinhard, & Woodward, 2020), (Rodríguez-Cerdeira, et al., 2019), (Eder, Chandran, Cook, & Gladman, 2017), (Gelfand & Yeung, 2012).

Fatigue further reduces activity levels. Many PsA patients suffer from persistent fatigue. This leads to lower physical effort and reduced muscle stimulation. Chronic underuse of muscles leads to a shift in muscle fibre composition, reduced neuromuscular activation, and mitochondrial dysfunction (Silva Santos Ribeiro, Willemen, & Eijkelkamp, 2022). Over time, these changes result in muscle atrophy, decreased strength & endurance, and functional decline (Jin, et al., 2024), (Diaz, et al., 2023), (Silva Santos Ribeiro, Willemen, & Eijkelkamp, 2022), (Krajewska-Włodarczyk, Owczarczyk-Saczonek, & Placek, 2017).

DRUGS USE FOR PSA

Steroid use can worsen muscle wasting. Glucocorticoids are often used to manage inflammatory diseases, such as PsA. However, while steroids can provide symptom relief, long-term use can cause muscle protein breakdown. This contributes to further muscle weakness in PsA (Surmachevska & Tiwari, 2025), (Bayrak & Aktas, 2024), (Vincken, Balak, Knulst, Welsing, & Laar, 2022), (Reichardt, et al., 2021), (Sato, et al., 2017), (Krajewska-Włodarczyk, Owczarczyk-Saczonek, & Placek, 2017). Incorporating muscle-strengthening interventions as an add-on therapy can counteract steroid-induced muscle loss, enhance muscle mass and strength, and ultimately improve functional outcomes. By enhancing muscle health alongside primary therapy, these interventions help maintain mobility, reduce disability, and promote a better quality of life for individuals with PsA.

Immunotherapy:

Immunotherapy helps control inflammation in PsA. It works by calming an overactive immune system. Biologics like TNF inhibitors and IL inhibitors are commonly used to reduce joint pain and skin symptoms. But they can also suppress the immune system too much. They trigger immune-related muscle problems such as myositis (Miyake, et al., 2024), (Ogdie, Hernandez, Shaw, Stolshek, & Michaud, 2022), (Amy, Molinares, Guo, Fu, & Bruera, 2021). Long-term immune suppression may also slightly increase the risk of infections that affect muscles leading to fatigue or muscle weakness (Suquia, et al., 2024), (Ogdie, Hernandez, Shaw, Stolshek, & Michaud, 2022), (Rakshit & Molina, 2020). Adding muscle-strengthening exercises can help. These improve strength, support joint function, and reduce fatigue. This leads to faster functional recovery and quality of life in PsA.

Methotrexate (MTX):

Methotrexate is a common drug for PsA. It helps reduce joint inflammation and skin symptoms. (Lindström, et al., 2023). But methotrexate may cause tiredness and muscle pain in some people (Ogdie, Hernandez, Shaw, Stolshek, & Michaud, 2022). It can lower folate levels, which are essential for DNA synthesis and muscle cell repair (Coates, Merola, Grieb, Mease, & Duffin, 2020). At the cellular level, MTX inhibits rapidly dividing cells, including satellite cells involved in muscle regeneration. It can also lead to mitochondrial dysfunction and increased oxidative stress, reducing muscle strength

and endurance (Pirkmajer, et al., 2015), (Alsubaie, et al., 2018). Muscle-strengthening therapy may reduce these side effects. It helps improve muscle function, balance, and physical activity. This supports strength and independence in people with PsA.

Topical treatments (e.g., Tacrolimus): Topical drugs in PsA is used on affected skin areas. It reduces inflammation and itching and usually do not affect muscles when used as directed. However, long-term or excessive use of topical drugs can cause skin thinning and may be absorbed systemically in some cases, especially with high-potency steroids (Zheng, et al., 2020). Systemic absorption may lead to muscle protein breakdown by suppressing anabolic pathways and increasing catabolic activity (Seixas, et al., 2022), (Vattemi, et al., 2014). This can reduce muscle mass and strength over time. This shows a requirement of muscle-strengthening therapy, supporting mobility and function in PsA.

Stress and Fatigue Cycle: Psoriasis flares are often linked to physical and psychological stress. Muscle weakness contributes to fatigue, muscle tension & pain, which may increase flare frequency or intensity (Kaerts, Swinnen, Dankaerts, Vlam, & Neerinckx, 2024), (Nikhilesh, Sandhya, Dutta, & Chetan, 2023), (Silva Santos Ribeiro, Willemen, & Eijkelkamp, 2022), (Haugeberg, Michelsen, & Kavanaugh, 2020).

Systemic Inflammatory Autoimmune Disease: Psoriasis and PsA can be associated with systemic inflammatory autoimmune disease. This autoimmune attack on muscle fibres causes muscle inflammation and weakness. Additionally, inflammatory cytokines promote muscle catabolism and inhibit muscle repair and regeneration (Elnady, et al., 2019), (Zabotti, et al., 2017).

Therefore, addressing muscle weakness is essential. Ignoring MW in PsA can worsen disease outcomes. MW can exacerbate PsA symptoms and negatively impact treatment outcomes. Weak muscles may lead to joint instability, increased pain, and reduced physical function. Furthermore, MW can hinder the effectiveness of rehabilitation programmes aimed at improving joint mobility and overall function.

4. Can Muscle Weakness Management Improve PsA Outcomes?

Managing muscle weakness can improve outcomes in PsA. PsA patients often lose muscle strength due to inflammation, pain, and inactivity (Kaerts, Swinnen, Dankaerts, Vlam, & Neerinckx, 2024). PsA increases muscle protein breakdown, mitochondrial dysfunction, reduces satellite cell activity, and oxidative stress – all of which interact to drive muscle weakness and increased susceptibility to muscle fatigue (Ahmad Jamil & Abdul Karim, 2024). Addressing this weakness can make muscles stronger, improve muscle strength, better muscle function, accelerate functional recovery (Ahmad Jamil & Abdul Karim, 2024), (Lian, Chen, Wu, Deng, & Hu, 2022). Targeted management strategies with exercise & nutritional intake can strengthen muscles and improve muscle function (Ahmad Jamil & Abdul Karim, 2024), (Lian, Chen, Wu, Deng, & Hu, 2022). Stronger muscles reduce load on inflamed joints by absorbing mechanical forces. Therefore, support joints and reduce mechanical stress (Kacprzak & Stańczak, 2024), (Sarvazyan, Rudenko, Aglyamov, & Emelianov, 2014). Muscle strength improves neuromuscular control and coordination during movement. This improves mobility, posture, and daily functioning (Holm, et al., 2024), (Roger-Silva, Meireles, Brumini, & Natour, 2023). PsA is an autoimmune and chronic inflammatory disease. Nutritional support & regular exercise may increase anti-inflammatory cytokines (like IL-10).., complementing drug effects. Regular exercise increases mitochondrial efficiency, reducing fatigue and muscle pain, and as a result improve muscle health (Kessler, et al., 2021), (Oliveira & Hood, 2019). Muscle-strengthening nutritional support can enhance treatment response. Better muscle function enhances physical capacity and reduces reliance on assistance (Lubrano, et al., 2023). That can improve quality of life and independence in PsA patients (Slavin, Khemraj, & Hood, 2024), (Wu, Shieh, Qin, & Guo, 2024).

5. What Are the Possible Outcomes of a Muscle Strengthening Regimen (Nutrition + Exercise) with Primary Therapy of PsA?

Combining muscle-strengthening exercise and proper nutrition with standard PsA therapy leads to multiple benefits. Protein intake and amino acid supplementation regulate exercise recovery and performance. This integrated approach can (Bilski, Kupczyk, & Woźniak, 2024), (Lian, Chen, Wu, Deng, & Hu, 2022):

Build and preserve muscle mass: Exercise activates mTOR signalling, which stimulates muscle protein synthesis. Adequate intake of protein and amino acid-rich foods supports this process, preserving and building muscle mass & strength (Torre-Villalvazo,

Alemán-Escondrillas, Valle-Ríos, & Noriega, 2019).

Improve endurance, strength, and joint stability: Exercise improves oxidative metabolism and enhances muscle control, stabilizing joint movement. Vitamins, minerals and antioxidants support oxygen transport, ATP production, and muscular performance. Muscle-strengthening regimen by improving oxidative metabolism, improve muscle endurance, strength and stabilizes joint motion through better muscle control (Hargreaves & Spriet, 2020).

Reduce inflammation and disease activity: Physical activity reduces pro-inflammatory cytokines (e.g., TNF-α, IL-6) and increases anti-inflammatory mediators (e.g., IL-10) Additionally, omega-3 fatty acids, vitamins, and antioxidants help modulate the immune response and further lower systemic inflammation. Therefore, the Muscle-strengthening regimen reducing pro-inflammatory cytokines (e.g., TNF-α, IL-6) and boosts anti-inflammatory mediators in PsA (Lubrano, et al., 2023).

Enhance effects of drugs & medicines: Exercise improves tissue perfusion and drug delivery to inflamed areas, enhancing treatment efficacy. Anti-inflammatory nutrients may act synergistically with pharmacologic therapies to enhance treatment outcome (Leite, et al., 2020).

Improve recovery and immune function: Exercise triggers muscle repair pathways and boosts immune surveillance. Amino acids, minerals, vitamins, and antioxidants maintain immune defence and support muscle repair (Perrotta, et al., 2021).

Lower fatigue, improve mood, and reduce MetS: Physical activity increases endorphins and improves insulin sensitivity and vascular health. Adequate nutrient intake—amino acids and antioxidants—supports energy metabolism, neurotransmitter function, and inflammation control, helping to reduce fatigue, improve mood, and lower the risk of metabolic syndrome (Lubrano, et al., 2023), (Lubrano, et al., 2023).

Promote long-term function and reduce disability: Muscle-strengthening regimen maintains balance, muscle mass, and coordination, reducing the risk of falls and injuries. Adequate nutrients support musculoskeletal health, helping preserve independence over time (Diaz, et al., 2023) (Diaz, et al., 2023).

Therefore, while exercise helps improve muscle strength, endurance, and joint stability, adequate nutrient intake is essential to complement these effects. Together, exercise and nutrition can (Aoxuan, Na, Yujia, Yonghuan, & Yang, 2022), (Tiwari & Brent, 2024) (Mogyoróssy, et al., 2023), (Silva Santos Ribeiro, Willemen, & Eijkelkamp, 2022), (Krajewska-Włodarczyk, Owczarczyk-Saczonek, & Placek, 2017):

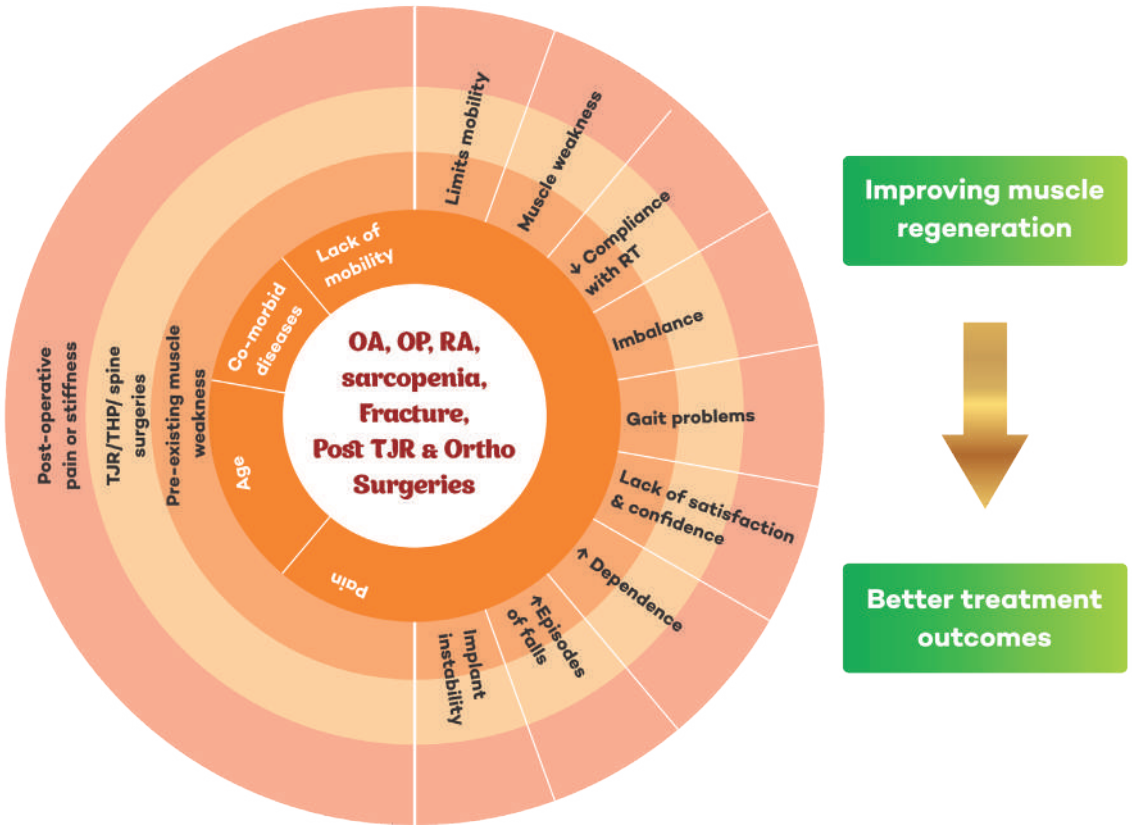
- Reduce inflammation and oxidative stress through anti-inflammatory nutrients and enhanced mitochondrial function
- Improve the muscle environment by supporting muscle repair, and improving oxygen and nutrient delivery to muscle, skin, and bone
- Enhance drug treatment outcomes by lowering systemic inflammation and improving tissue perfusion, which may help medications work more effectively

In addition, this combined approach can (Aoxuan, Na, Yujia, Yonghuan, & Yang, 2022), (Tiwari & Brent, 2024), (Krajewska-Włodarczyk, Owczarczyk-Saczonek, & Placek, 2017):

- Improve mood and energy levels
- Reduce weakness and fatigue
- Increase muscle strength and physical endurance
- Support overall musculoskeletal health
- Decrease arthritis symptoms
- Lower the risk of falls and fractures

These benefits are most effective only when exercise is combined with sufficient nutritional support, making it a vital component of comprehensive PsA management.

Benefits of muscle strengthening supplementation (ImproSyn)



Summary

Muscle weakness and atrophy arise from a combination of reduced muscle structural protein synthesis and increased muscle protein degradation. It can be observed in patients with osteoarthritis, osteosarcopenia, bone fracture and post-fracture surgery, joint replacement surgery, spinal cord injury/ degenerative diseases/spine surgeries, and psoriatic arthritis and even in cases of rheumatoid arthritis.

ImproSyn is a muscle-specific formulation that contains Calcium β-Hydroxy β-Methylbutyrate (CaHMB)- 750 mg, L-Carnosine- 150 mg, and Astaxanthin- 10 mg that helps to improve muscle regeneration, prevents muscle breakdown, and provides muscle specific amino acids for structural protein regeneration by stimulating satellite cells, activating Protein Kinase B (Akt)/ Mechanistic Target of Rapamycin (mTOR) for muscle protein synthesis, boosting Insulin-like Growth Factor 1 (IGF-1) & Growth Hormone (GH) levels for muscle growth, enhancing ATP biogenesis, and preventing muscle breakdown by blocking ubiquitin-proteasome system (UPS activity), suppressing Forkhead Box O (FOXO) genes, reducing inflammation (TNF-α & IL-6), reducing lactic acid accumulation, and relieving muscle pain. Thereby, ImproSyn improves muscle bulk, strength, recovery, power, endurance, and exercise tolerance. ImproSyn can be considered safe for use for a continued use for at least 1 year, with longer durations advised under clinical supervision.

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