Aging and Sarcopenia

Frailty is generally understood as a progressive age-related decline in physiological systems that results in decreased reserves, increasing risk for poor health outcomes including falls, incident disability, hospitalization, and mortality[1]. There are however two distinct concepts that emerge from the clinical and research literature. The first is of a syndrome associated with underlying physiological and metabolic changes that are responsible for driving progressive physical and cognitive impairments through to loss of functional capacity, often helped on the way by acute or chronic disease or injury. As a result, the frail person is at increased risk of disability or death from minor external stresses.[2,3].The second concept underpins a pragmatic approach, which treats frailty as a collection of risk factors for future adverse events, while not necessarily bearing a direct pathophysiological relationship to these outcomes. As discussed later these positions are not incompatible.[23]

Another age-related process is sarcopenia, a term suggested by Rosenberg for the well-recognized loss of muscle with ageing - major component of frailty. The diagnosis, treatment and prevention of sarcopenia is recommended to become part of routine clinical practice. Skeletal muscle accounts for a third or more of total body mass[4]. Along with movement, muscle plays a key role in temperature regulation and metabolism, as muscle is a reservoir for proteins and energy that can be used for the synthesis of antibodies and gluconeogenesis.[2] Low muscle mass is associated with poor outcomes from acute illness, probably because of the reduced metabolic reserve. Sarcopenia is an accelerated loss of muscle mass with decreased function, associated with an increase in falls, functional decline, frailty, and increased mortality. Its main associated risk factor is ageing but is affected by genetics and lifestyle factors. Sarcopenia is becoming an interesting subject of research due to a better understanding of its pathophysiology that allows the development of preventive and therapeutic approaches. The official definition of sarcopenia includes patients with low muscle strength and low muscle mass or quality. It can be acute, secondary to an acute disease or recent immobility, or chronic. Symptoms and events associated with sarcopenia include falls, weakness, slowness, muscle wasting, and difficulty with daily activities. Its diagnosis involves measures of the strength, usually grip strength (in the absence of osteoarthrosis or a neurological condition)[4]. Along with muscle mass, usually measured using dual X-ray absorptiometry which estimates the lean mass. CT, MRI and biometrical impedance analysis can also be used to measure lean muscle mass. Frequent underlying causes of sarcopenia are nutritional such as low calorie and protein intake, micronutrient deficiency, anorexia; inactivity like prolonged bedrest, sedentary lifestyle; diseases that affect musculoskeletal system, cardiovascular diseases, respiratory conditions, neurological diseases and cancer.

Diagnostic criteria-

The evaluation and diagnosis of sarcopenia requires measurements of muscle mass and muscle strength. Numerous methods are currently in use including walking speed, grip strength, calf circumference (CC), bioimpedance analysis (BIA), DEXA and imaging (CT and MRI) but none of these methods are specific for evaluating sarcopenia[5,6].

In 1998, Baumgartner and colleagues[7] proposed a method using DEXA. This method was very similar to the method proposed by the WHO for diagnosing osteoporosis. They proposed using lean body mass, as determined by DEXA, compared with a normal reference population as a standard measure for sarcopenia. His working definition used a cut-off point of [7] standard deviations below the mean of lean mass for gender-specific healthy young adults. This methodology was both practical and predictive for negative outcomes. However, this method has several limitations, other researchers have proposed various methods to account for these limitations; but to date there is no universally accepted method to diagnose sarcopenia [7]. This initial definition of sarcopenia was further modified by the European Society on Clinician Nutrition and Metabolism (ESPEN) special interest groups (SIGs) on geriatric nutrition and on cachexia–anorexia in chronic wasting diseases. Sarcopenia was defined as the following [8]

1. A low muscle mass, greater than 2 standard deviations below that mean measured in young adults (aged 18–39 years in the third NHANES [National Health and Nutrition Examination Survey] population) of the same sex and ethnic background.

2. Low gait speed (eg, a walking speed below 0.8 m/s in the 4-minute walking test).

More recently, the European Working Group on Sarcopenia in Older People proposed the following diagnostic criteria for sarcopenia6:

1. Low muscle mass (LMM), assessed by skeletal muscle mass index of no more than 8.90 kg/m2 (men) and 6.37 kg/m2 (women)

2. Low muscle strength (LMS) assessed by handgrip strength less than 30 kg (men) and 20 kg (women)

3. Low physical performance (LPP) assessed by gait speed of no more than 0.8 m/s

A detailed description of methods to determine LMM, LMS, and LPP are well described in the literature[9].The diagnosis of sarcopenia required the presence of LMM plus LMS or LPP. In addition, the EWGSOP suggested staging of sarcopenia into 3 different categories based upon the presence of LMM and the presence or absence of functional impairment [10] (Table 1). These progressive stages of sarcopenia have a dose–response relationship with functional limitations.

Table 1. Staging of sarcopenia

Stage	Muscle Mass	Muscle Strength	Performance
Presarcopenia	Low	Normal	Normal
Sarcopenia	Low	Low	Normal or low
Severe sarcopenia	Low	Low	Low

Pathophysiology-

The pathophysiology of sarcopenia and frailty is intricate involving multiple causes, models and pathways[10] [3](Image1). Neither condition has been completely understood although there is a better understanding of sarcopenia due to it largely involving a single system, neuromuscular system.

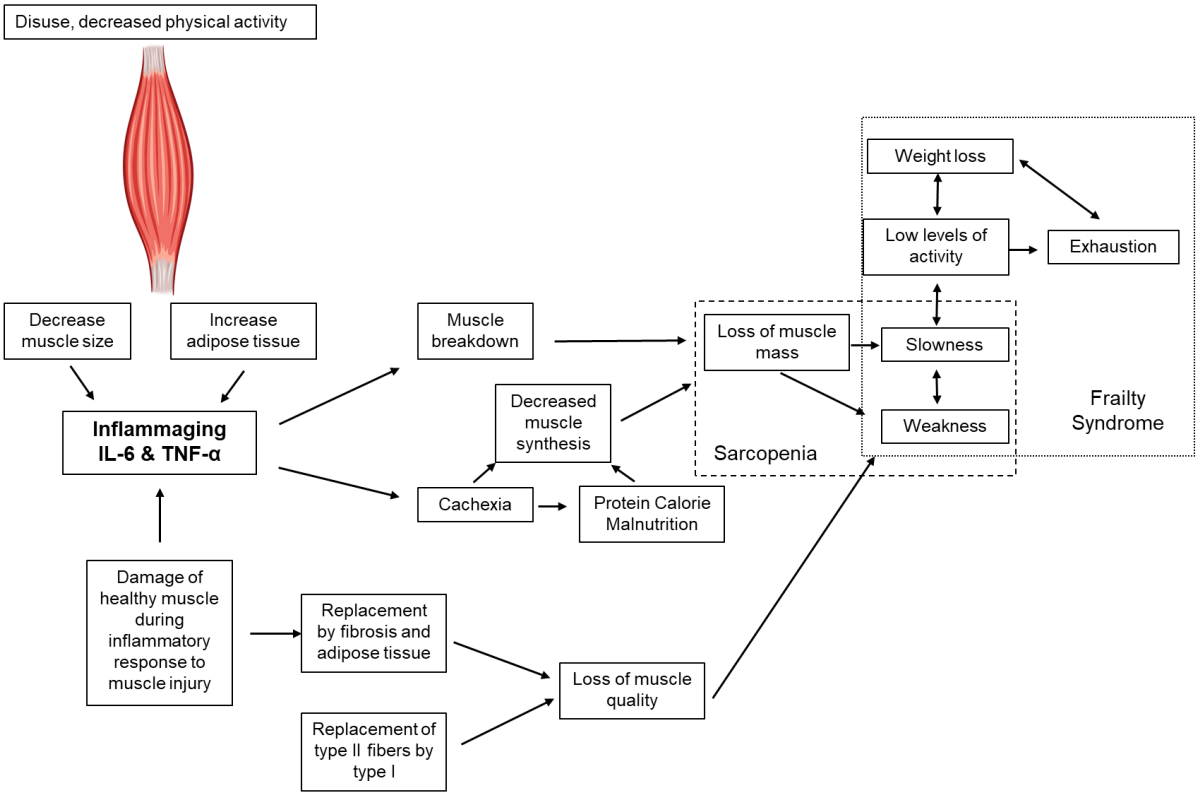

Image 1: Pathophysiology of Sarcopenia adapted from Wilson D. et al. Frailty and sarcopenia: The potential role of an aged immune system

This pathophysiology is triggered when ageing alters the balance between hypertrophy and regeneration due to an imbalance in the protein anabolic and catabolic metabolism. There is a reduction in the size and number of myofibrils, fat infiltration and altered mitochondrial integrity. Sarcopenic muscle has a reduced number and elasticity of myofibers, mainly type II, sometimes with fat infiltration and fibrotic changes. There are also fewer satellite cells (the stem cells of the skeletal muscle) which This decline results in loss of the regenerative capacity of muscle fibers and an inability to compensate for loss of fibers due to aging[11].

The regeneration of myofibers from satellite cells are regulated by transcription factors, Myf5 and PAX7 are the central regulators. PAX7 additionally regulates the myoblast proliferation and their return to a quiescent state as satellite cells. MyoD controls myoblast proliferation and differentiation. And finally, myogenin regulates the final differentiation into fusion competent myocytes.[12]

There is a significant overlap between PAX7, MyoD and Myogenin since those participate along the myoblast proliferation and the early and late differentiation of the There is a significant overlap between the functions of PAX7, MyoD and Myogenin since they are involved in myoblast proliferation and the early and late differentiation of the myocytes[12].

Factors and conditions where these factors are disturbed or affected can disturb the myogenic process. Immune cell infiltrating cells (mainly macrophages), vascular pericytes and fibro/adipogenic precursors participate in the muscle repair and regeneration.

The muscle regeneration is additionally driven by extracellular elements released by damaged muscle tissue, secreted by immune cells and extracellular matrix components.

At the molecular level of myofiber metabolism it is proposed that a disturbance in protein degradation and intracellular organelle disposal pathways ~~in~~ which include insulin like growth factor 1/ protein kinase B (Akt)/ mTOR/ fork head box O and macroautophagy pathways leading to failure in protein and organelle quality control which could contribute to muscle atrophy.

Physical exercise and calorie restriction are also involved in the sarcopenia process. In normal conditions both increase mitochondrial calcium uniporter expression levels improving mitochondrial performance of aging muscle. Exercise induces a moderate level of oxidative stress that up regulates PGC1α, a protein required for mitochondriogenesis and oxidative fiber formation. This increases muscle mass and strength, resistance to muscle wasting, and augments the early steps in the activation of muscle stem cells. However, in sarcopenia there is altered PGC1α expression in the muscle secondary to age related enhanced ROS production due to altered mitochondria number and function[13,14].

Another transcription factor family involved is FoxO, which are necessary for muscle atrophy, they coordinate stress response genes including autophagy and ROS detoxification in catabolic conditions.

A family of genes denominated as atrophy genes, including atrogin-1 and MuRF-1 also participated in the process. And myogenin is upregulated and required for the maximal activation of these genes, by binding to their promoters.

Aging muscle tissue has defective activity or abundance of Nrf2, antioxidant factor, fundamental in maintenance of the intracellular redox homeostasis. Event that can be counteracted by regular exercise. Sulforaphane, an Nrf2 activator, attenuates muscle fatigue by reducing oxidative stress caused by exhaustive exercise.

Neurotrophin 3 influences the protein synthesis and metabolic remodeling, activation of TrkC/Akt/mTORC1 causing muscle hypertrophy with fast-twitch, type II glycolytic muscle fibers[12].

Recent work in humans has showed that elevated levels of myogenin along with less vigorous response in Nrf2 levels and higher levels of HSPA1A[12](stress-induced chaperone acting on misfolded proteins) results in reduced cellular defense factors, increased level of misfolded

proteins, disturbed mitochondrial function in healthy elderly sarcopenic muscle may cause accumulation of ROS which negatively impact muscle trophism and function[12].

Myokines, which are secreted by muscle tissue with autocrine, paracrine, and endocrine effects, include IL-15 which stimulates myofiber hypertrophy, IL-8 inducer of angiogenesis, IL-6 which increases glucose uptake and fatty acid oxidation and decorin which inhibits myostatin inhibitory effects on muscle trophism. It has been seen this secretion increases due to exercise, making of it the most efficient approach to confront sarcopenia[12].

Ageing also has an effect on satellite cells, reducing their ability to maintain muscle mass. Once satellite cells are activated, they tend to accumulate ROS, due to altered mitochondrial function or defective ROS management. This ROS imbalance might cause leading to aberrant MAPK activity, deregulated expression of cell proliferation inhibitor p16, deregulated JAK/STAT signaling and defective autophagy which has been detected is aged SCs, causing altered proliferation and differentiation properties. The accumulation of ROS in myofibers may be attributed to a sedentary lifestyle leading to reduced muscle strength along with other comorbidities and poor food habits, smoking and alcohol consumption might be one of the causes. Myostatin has been shown to increase ROS and TNF-α production in myoblasts, and elevated TNF-α in turn causes increased myostatin expression resulting in catabolism of intracellular proteins[12].

A summary of these different pathways is depicted in Figure 2.

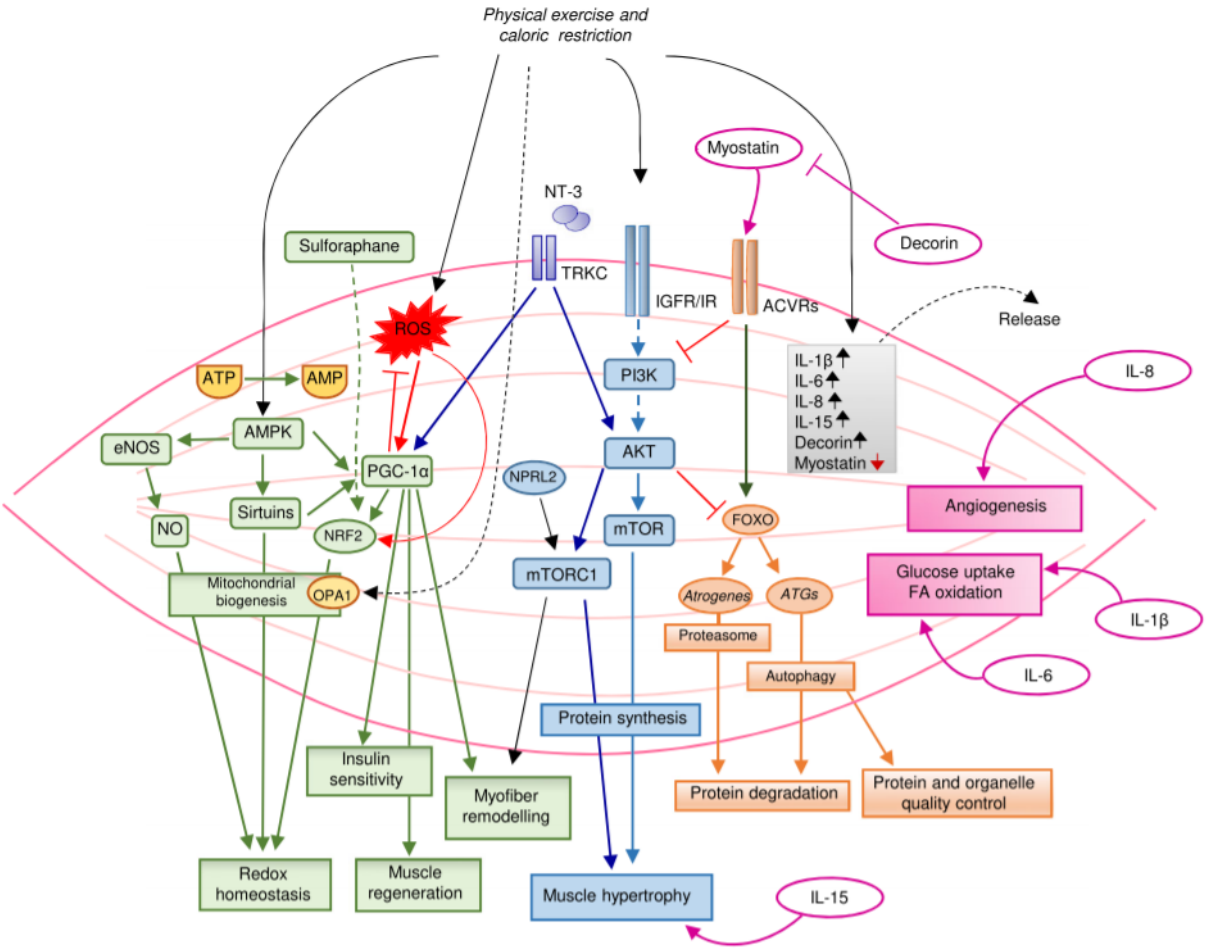

Figure2 – Image taken from Riuzzi, F et al (2018) Cellular and molecular mechanisms of sarcopenia: the S100B perspective. Journal of Cachexia, Sarcopenia and Muscle, 9: 1255– 1268

Finally, gut microbiota can affect amino acid availability and participate in the short chain fatty acid generation such as butyrate, propionate and acetate. Gut microbiota plays a role in maintaining a balance between pro and anti-inflammatory response[12]. Butyrate is not only an energy source, but it also works in the gut as anti-inflammatory molecule regulating host metabolism and immunity[15].

Management-

Early recognition and intervention are key to improved outcomes in patients with sarcopenia. Screening patients for impairment in their physical function and activities of daily living (ADLs) should be a routine part of health care visits for the elderly. Patients with impaired ADLs should undergo more specific testing for sarcopenia. Assessment of patients' environments for fall hazards and implementation of precautionary safety measures should be part of the treatment strategy[16]. According to the pathophysiological factors involved in the pathogenesis of

sarcopenia, we can identify different treatment strategies that are mainly aimed to correct behavioral and endocrine causes.

Nonpharmacological Treatments-

Exercise

Physical inactivity and disease are both highly prevalent in the elderly and are the main contributors to the decline of muscle mass and function[17] Both resistance and aerobic training have been shown to increase muscle strength and improve physical function[18]. Progressive resistance exercise training (PRT) helps in increasing muscle strength, muscle size, and functional capacity in the elderly[17,19]In PRT, subjects exercise their muscles against an increasing external force, and this is undertaken at least 2–3 times a week the duration of sessions and number of exercises increases gradually over time based on each individual's capability and improvement[18].PRT should be considered a first-line treatment strategy for managing and preventing sarcopenia and its adverse health outcomes. Although it is under used due to lack of easy accessibility to the equipment and trained therapists[18].

Nutrition

Malnutrition undoubtedly is involved in the pathogenesis of sarcopenia, it contributes to the poor muscle function observed in many older adults, particularly in frail elderly patients.104 Food intake declines progressively between 20 and 80 years by ~1.300 and 600 kcal in men and women, respectively. The prevalence of malnutrition ranges from 5% to 20% in community-dwelling older adults and exceeds 60% in the institutionalized elderly[20]. These findings have led to the proposition of nutritional as effective treatment in preventing and/or reversing sarcopenia[21]. The main nutritional strategies proposed for the treatment of sarcopenia include: – Increased protein intake An increase in protein intake above 0.8 g/kg/day, has been identified as the minimum amount required to maintain muscle mass in old age[22],[23]Increased protein intake may enhance muscle mass and function[24]. Moreover, essential amino acids are the primary stimulus for protein synthesis. Thus, elderly patients should be recommended to consume protein sources containing a relatively high proportion of amino acids.

Vitamin D supplementation- Serum levels of vitamin D decline with aging and approximately over one billion people worldwide have vitamin D deficiency or insufficiency[25]. Moreover, vitamin D influences muscle metabolism and tropism and its deficiency is related to sarcopenia[26]. It is currently recommended to measure serum levels of 25-hydroxy vitamin D in all sarcopenic patients and to prescribe vitamin D supplements (800 IU [20 µg]/day) to those with values lower than 100 nmol/L (40 ng/mL)[26]

Creatine monohydrate Creatine (Cr) monohydrate has emerged as an efficient nutritional supplement capable of improving muscle mass and performance in older adults when combined with resistance exercise[26]. Therefore, short-term Cr supplementation (5–20 g/day of Cr

monohydrate for 2 weeks) may be advisable in older persons engaged in strength-training programs[27].

Antioxidants - According to the "oxi-inflamm-aging" theory of aging[28] and the involvement of oxidative stress in the pathogenesis of sarcopenia, the administration of antioxidative agents (i.e., selenium, vitamin E, and vitamin C) has been proposed for the management of sarcopenia[26].

Other nutritional strategies - Several novel dietary candidates and nutrition strategies against sarcopenia include β-hydroxy β-methylbutyrate a metabolite of leucine (117), Ornithine α-ketoglutarate the precursor of several amino acids (ie, glutamate, glutamine, arginine, and proline) and of other bioactive compounds (ie, polyamines, citrulline, α-ketoisocaproate, and nitric oxide) that are important modulators of muscle protein metabolism and hemodynamics [26] ,Omega-3 fatty acids have been showed to improve muscle protein synthesis and grip strength[29],[30]suggesting that an adequate intake of omega-3 fatty acids could represent an effective nutritional remedy for sarcopenia.

Caloric restriction (CR) and regular physical exercise exert beneficial effects on overall health and muscle homeostasis in advanced age[31]However, long-term CR could induce a weight loss that may be harmful, thereby accelerating muscle loss[32]. Recent studies have detected dietary-derived "CR mimetics" (CRMs) and "exercise mimetics" (EMs) in plant sources although promising the field of CRMs and EMs is still under investigation[26].

Gut microbiome- The human gut microbiota is composed of more than a thousand microorganisms[33]. Alterations in the gut microbiota could contribute to the pathogenesis of sarcopenia, because it does have an influence on systemic inflammation, anabolism, insulin sensitivity, and energy production[26]. Malnutrition and physical inactivity may influence microbiota composition[34] One randomized controlled trial, investigated the benefits on skeletal muscle outcomes of the administration of a prebiotic formulation (fructo-oligosaccharides and inulin) versus placebo for 13 weeks, showing unexpectedly that the treatment group experienced improvement in two outcomes of muscle function: exhaustion and handgrip strength[35] This supports the possible presence of a "gut–muscle axis" and this hypothesis needs to be further investigated[34].

Pharmacological Therapies-

Testosterone

Testosterone levels decline by approximately 1% per year from 30 years of age, this is associated with a reduction in muscle mass and strength[24]. Numerous studies have shown the beneficial effects of testosterone supplementation on muscle and bone tissues[24]. In lower doses, testosterone increases protein synthesis, thereby resulting in an increase in muscle mass[36] and, in high doses, testosterone activates satellite cell recruitment and reduces adipose stem cells increasing myogenesis and decreasing adipogenesis[24]. Although there are several possible side effects associated with testosterone replacement, such as cardiovascular disease, fluid retention,

gynecomastia, worsening of sleep apnea, polycythemia, and acceleration of benign or malignant prostatic disease[37].

Selective androgen receptor modulators (SARMs)

They are a class of androgen receptor ligands that show androgenic effects in some tissues (eg, muscle and bone) and without effects on other organs, such as the prostate or skin, thereby limiting adverse effects such as prostate growth or androgenization[26]. Based on their structure they can be classified into steroidal and non-steroidal SARMs[38]. Steroidal SARMs are modified testosterone and have similar side effects[24]. Several steroidal and non-steroidal SARMs have undergone Phase I–III trials[39]. A Phase II clinical trial conducted to evaluate GTx-024 (enobosarm) showed a dose-dependent improvement in total lean body mass (LBM) and physical function and was well tolerated[40]. Another, 21-day ascending dose study of LGD-4033 (ligandrol) in healthy young men showed that the drug was well tolerated, had a favorable pharmacokinetic profile, and increased LBM and leg press strength[41]. Another SARM, MK-773produced statistically significant increases in LBM compared to placebo, but no significant improvement in strength or function[42]. SARMs appear to be safe and effective in increasing LBM and possibly strength and function but their effects on muscle mass and function have not been as significant in comparison to high doses of testosterone[43].

Growth Hormone (GH)/Insulin Growth Factor -1 (IGF-1)

Treatment with GH increases LBM but not muscle strength in the elderly, and it is associated with a variety of side effects including joint and muscle pain, edema, carpal tunnel syndrome, and hyperglycemia[44]. As for IGF-1 administration, an increase in side effects and risk of CVDs[45] was observed in a single small study in elderly subjects.

Ghrelin and ghrelin receptor agonists

Ghrelin increases appetite and GH secretion[24]. Several studies involving ghrelin or ghrelin receptor agonists (ie, anamorelin and capromorelin) have shown an increase in food intake and muscle mass and function. 2More trials are needed to understand the safety and efficacy of these drugs.

Angiotensin-converting enzyme inhibitor (ACE-I)

ACE-Is are under investigation for skeletal muscle preservation. Particularly Perindopril has shown to increase physical performance, in a double-blind randomized controlled trial, perindopril improved exercise capacity, showing improvement equivalent to that reported after 6 months of exercise training[46].

Future therapeutic approaches-

Recent developments in sarcopenia therapeutic interventions have evaluated several promising agents. Given the role of the pro-inflammatory cytokines (i.e., TNF- α, IL-1, IL-6) and myokines in the pathogenesis of sarcopenia, as well as anti-inflammatory agents, such as the monoclonal

antibodies infliximab, tocilizumab, and bimagrumab, appear promising[47]. However, these agents have shown significant impact on reversal of skeletal muscle loss but have limited effect on physical function[48]. Another promising alternative therapeutic approach includes utilizing stem cells to stimulate myogenesis. To date, little success has been achieved using different stem cells (e.g., satellite cells, muscle-derived, perivascular, embryonic, and induced pluripotent stem cells) for skeletal muscle repair and, the clinical utility of stem-cell-based approaches show technical, economic, and regulatory difficulties[49]. These approaches could provide improved outcomes for patients suffering from age-related muscle loss but are still under investigation.

There are certain currently FDA approved medications such as Metformin or experimental compounds like PPAR-y agonist or rapamycin that can have a role in sarcopenia and ageing. In the case of metformin its mechanism is linked to the activation of autophagy due to increase of AMPK activity, this induces the mitochondrial biogenesis improving the redox homeostasis, also inproves muscle regeneration, myofiber remodeling and muscle hypertrophy[50]. Rapamycin has shown to increase autophagy due to inhibition on mTORC1, and an increase in protein biosynthesis which in muscle cells would imply an improvement in muscle regeneration. Whereas PPAR-y agonist can increase PGC-1a, increasing mitochondrial biogenesis. These mitochondrial changes improve the cell handling of the ROS, the accumulation of which is associated with ageing of the muscle cells and sarcopenia[50].

Another treatment target being used in ageing medicine is SIRT-1, one of its known agonist resveratrol is known to improve insulin resistance but has also shown improvement in lifespan[47]. In the long-term the treatment has shown an improvement in ability to exercise that could be explained by its effects on the sirtuins that impact the redox balance[51].

In animal models these molecules have been linked to an increase in lifespan of the animal model, neuro, and cardio-protection, one of the reasons why it would be promising to explore their roles in muscle cells as a way to prevent ageing and sarcopenia.

Conclusion

Sarcopenia is a condition associated with significant morbidity due to the increase risk of falls, decrease in functional capacity with repercussions in increased mortality. Its main risk factor is ageing but it should be differentiated from a normal ageing process without pathological consequences. The main findings are decrease in muscle mass, muscle strength and performance. And the presence of changes in all three components implies a significant severity in the condition. These changes in conjunction with cognitive changes are part of the frailty syndrome which in turn implies additional increase in the risk of morbidity and mortality.
The pathophysiology of sarcopenia represents a imbalance between the anabolic and catabolic pathways which in turn drives increased muscle breakdown and a decrease in muscle synthesis. The underlying process driving this phenomenon is multifactorial including a decreased pool of stem cells for proliferation and regeneration and increased ROS due to diminished antioxidant

capacity facilitating inflammatory changes. Leading to a decrease in the activation of hypertrophy signaling pathways.

Therapeutic approaches include nonpharmacological measures where physical activity and exercise seem to be the most effective due to its role in prevention and management of the condition and their impact on several of the pathways described previously. In the pharmacological approaches different strategies have been test with varied levels of effectiveness accompanied by potential concerning side effects. New promising targets related to inflammatory pathways are being explored however there is a requirement to further evaluate their impact. Additional pathways including the Akt/mTOR pathway could be explored in the future due to its importance in the proliferation/regeneration/hypertrophy process, there are currently drugs approved for various other conditions that might be worth to evaluating as a potential sarcopenia reversal drug which would potentially decrease mortality in at risk population.

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