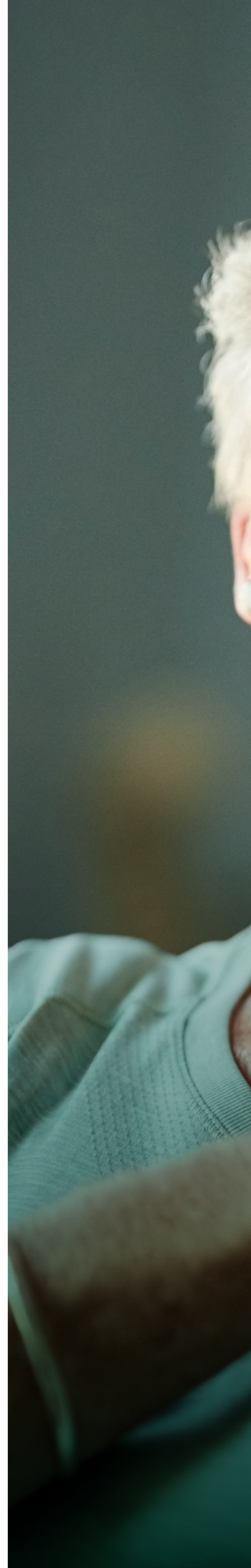


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# Nutritional lipids in medical nutrition: maintaining muscle health in elderly and cancer patients

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# Introduction

People worldwide are living longer. This has led to a notable increase in the risk and prevalence of chronic diseases, such as type-2 diabetes and cancer, as well as 'diseases of aging', like sarcopenia and osteoporosis, and the associated healthcare expenditure required to manage and treat these conditions.<sup>1,2,3</sup> Muscle health is critical for normal physical movement and its role in supporting the overall health of an individual is becoming increasingly recognized. For example, low muscle mass and strength may contribute to adverse health outcomes, including longer recovery times and increased risk of mortality, particularly in individuals presenting with sarcopenia or cancer cachexia (a common wasting disorder associated with cancer). Preserving muscle health and decreasing the risk of muscle loss is therefore becoming increasingly relevant as the number of sarcopenia and cancer cachexia

cases rise worldwide. But to date, pharmacological intervention aimed at slowing the progression of sarcopenia and muscle wasting due to disease, or reversing it, has generally failed – indicating an opportunity to develop more innovative medical nutrition solutions.<sup>4,5</sup>

This whitepaper outlines the emerging role of the omega-3 long-chain polyunsaturated fatty acids (LCPUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in supporting individuals experiencing muscle loss as the result of aging or disease. While the whitepaper will discuss EPA and DHA inclusion in medical nutrition solutions, it does not include recommendations for their use in pharmaceutical medications, nor does it advise using medical nutrition solutions without the consultation of a medical professional.



# Muscle loss in the senior population

Muscle loss is a natural part of the aging process, thought to start around the age of 30 when the balance between muscle growth and break down shifts more towards the latter. While age-associated muscle loss is normal, sarcopenia is “a progressive and generalized skeletal muscle disorder that involves the accelerated loss of muscle mass and function”, contributing to gradual frailty and loss of independence, and even dementia in some cases<sup>6,7,8,9</sup>

Sarcopenia is associated with major clinical problems and health consequences which can have devastating effects on quality of life, survival rates and healthcare costs.<sup>10,11</sup> Previously accepted as an inevitable geriatric syndrome, independent of other diseases, there is now increasing evidence

to suggest that muscle loss in the elderly is highly dependent on physical activity levels and/or underlying pathological conditions.<sup>12</sup> Physical inactivity are proven to accelerate loss of muscle mass and strength, for instance, which may lead to impaired mobility, higher risk of falls and increased mortality.<sup>13</sup> As such, sarcopenia is recognized as a disease by the World Health Organization (WHO) and represents a major health problem among older adults.<sup>14</sup> Thought to already affect around 10% of individuals worldwide depending on the diagnostic tools and definition used for the disease, the number of people suffering from sarcopenia is expected to increase further by 2050 due to the aging population.<sup>15,16,17</sup>

# Muscle loss in cancer patients

The loss of muscle due to disease or chronic illness, so called muscle wasting or cachexia, is a prevalent condition in cancer patients that have malignant tumor growth. Associated with extreme weight loss and wasting of the body, as well as decreased ability to fight infection and withstand treatments, cachexia often leads to reduced survival rates.<sup>18,19</sup> Cancer cachexia is a complex, multifactorial syndrome defined by clinical experts as “an ongoing loss of skeletal muscle mass (with or without wasting of fat tissue) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.”<sup>20</sup>

The disease-related malnutrition observed in cancer, and consequent alterations to body composition and physiological functions, usually results from a combination of increased resting metabolic expenditure but reduced energy intake, low physical activity, pharmacological treatment and varying degrees of acute or chronic inflammation.<sup>21,22,23,24</sup> It is also well accepted that systemic inflammation plays an important role in the development of cachexia.<sup>25</sup> In patients with cancer cachexia for instance, it has been widely

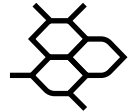
observed that the rate of muscle protein catabolism increases whilst anabolism of new proteins decreases, resulting in net protein breakdown i.e. muscle wasting.<sup>26</sup> This imbalance of protein synthesis and degradation is one of the most obvious disruptions to metabolism in cancer patients. Although observed in many medical conditions, the wasting pathway is exacerbated in cancer, which is why muscle loss is particularly rapid in these patients.<sup>27</sup>

While estimated to affect 50–80% of all patients with cancer, and despite the devastating toll it has on patients, cachexia is still largely an underrated and untreated condition.<sup>28</sup> Therapies targeting the metabolic pathways affected by cachexia may prove promising, but current strategies are typically inadequate due to the fact that the mechanisms underlying the development of cancer cachexia are not completely understood. To further complicate matters, the reversal of cachexia symptoms is difficult once the condition progresses beyond a certain level, making the development of early intervention solutions and prevention strategies key.<sup>29</sup>

# Three ways EPA and DHA positively impact muscle health

Maintaining healthy muscles is important for overall health and wellbeing. But evidently, protecting healthy muscle mass, muscle strength and functionality is particularly critical in clinical settings as it can impact patient outcomes and quality of life. The health benefits of EPA and DHA are well-documented, with more than 36,000 scientific papers, including 4,000 human trials, dedicated to their research.<sup>30</sup> Some of the current research has been devoted to their role in supporting muscle health, where they have been shown to influence key modulators of muscle mass, strength and function, including metabolic pathways, inflammatory factors and insulin resistance. Below, we highlight the latest scientific evidence indicating EPA and DHA are important for healthy muscles, especially in patients with sarcopenia or cancer cachexia.

## 1. Plasma membrane modulation



Phospholipids are the major constituents of cell membranes and their composition determines the structure and function of the cell. The incorporation of EPA and DHA into biological membranes for instance, modifies the membranes composition, affecting the cells permeability and fluidity and influencing the activity of specific enzymes and proteins. In doing so, EPA and DHA modulate multiple cellular and signaling pathways; helping to support and influence normal biological processes. But in many clinical settings, including sarcopenia and cancer cachexia, impaired metabolic health due to dysregulation of such processes is observed.

Research indicates that dietary EPA and DHA might help to restore the levels of omega-3 LCPUFAs in cell membranes, mitigating metabolic dysfunction and consequent muscle loss in certain diseases. For example, one trial showed that enrichment of EPA and DHA in the membrane phospholipids of older adults was linked to enhanced rates of muscle protein synthesis and decreased expression of factors that regulate muscle protein breakdown.<sup>31</sup> A recent report supports these findings, demonstrating that EPA and DHA can slow normal decline of muscle mass and strength in older adults by promoting muscle protein synthesis.<sup>32</sup> This indicates that medical nutrition solutions including EPA and DHA may help to address the increased nutritional requirements of individuals experiencing sarcopenia or cancer cachexia, combat metabolic dysfunction and thereby slow down or even prevent the loss of muscle in clinical settings.



## 2. Anti-inflammatory properties



While inflammation is an essential part of our immune response, sarcopenia and cancer cachexia involve excessive and/or prolonged inflammation that is damaging to tissues and organs. For instance, in cancer cachexia, the lower rate of muscle protein synthesis and elevated rate of protein breakdown is often induced by a hyperinflammatory state. Because of this, the mitigating influence of EPA and DHA on inflammation has been gaining increasing interest in the medical field.<sup>33</sup>

EPA and DHA serve as the substrates for the production of anti-inflammatory and inflammation resolving mediators (including resolvins, protectins and maresins), whilst simultaneously inhibiting the transcription of proinflammatory genes.<sup>34</sup> In conditions like cancer cachexia, EPA and DHA could therefore help to reduce inflammation.<sup>35,36</sup> Although results vary, in some clinical settings EPA and DHA have been shown to improve the immune response of patients too, helping individuals to fight infection, support the effects of cancer therapies, maintain lean body mass and prevent cachexia.<sup>37,38,39</sup> Furthermore, EPA and DHA may also help to stabilize and improve appetite and food intake, leading to improved lean body mass and body weight.

In sarcopenia, the anti-inflammatory effects of EPA and DHA could be beneficial in mitigating the loss of muscle strength and physical performance associated with aging by targeting the age-related low-grade inflammation that contributes to the development of the disease.<sup>40</sup> Given the effects of EPA and DHA on the immune system, taken together with their positive influence on muscle protein synthesis and appetite, it is clear why medical professionals should be interested in their inclusion in medical nutrition solutions that support healthy aging and help prevent disease-related malnutrition. Omega-3 LCPUFAs (with EPA levels at 2-2.5 g/day) have already been used in anti-inflammatory and anti-catabolic nutritional therapy to combat the pro-inflammatory burden of cancer cachexia, with outcomes including increased lean body mass, improved physical function and quality of life.<sup>41,42,43,44</sup> While exact dosage, frequency and use (alone or combined) in the treatment and prevention of sarcopenia still needs further exploration, reports conclude that there is also growing evidence for the beneficial effects of omega-3 supplementation in sarcopenic older adults.<sup>45,46</sup> This is promising, but more knowledge of the inflammatory pathways caused by aging and disease is needed in order to innovate further in this field.

## 3. Insulin resistance



Normal healthy skeletal muscle tissue is key for whole body insulin sensitivity. Where muscle tissue is diminished, like it is in sarcopenia and cancer cachexia, or metabolically impaired, muscle insulin resistance can therefore develop. This can affect whole body insulin sensitivity leading to overall insulin resistance, which is a major health risk to individuals.<sup>47</sup>

Both human and animal studies demonstrate that insulin resistance is present in catabolic diseases where there is inflammation and significant muscle wasting.<sup>48,49,50,51</sup> When insulin sensitivity is compromised in cancer patients, skeletal muscle mass is adversely affected and protein degradation occurs because it is through this pathway that insulin controls muscle protein metabolism. There is growing evidence to suggest that EPA and DHA may improve insulin sensitivity, especially in individuals with metabolic disorders, with studies indicating that these nutrients have an anabolic effect on muscle and reduce insulin resistance.<sup>52,53,54</sup>

EPA and DHA have clear roles in decreasing insulin resistance and inflammation, and facilitating normal function of metabolic pathways. But they also have additional benefits, including stimulation of mitochondrial function and muscle strength. This evidence suggests that EPA and DHA omega-3 LCPUFAs have the potential to alter the trajectory of several human diseases, including cancer and the physical decline associated with aging.

# Why a multimodal approach to therapy is important

Clearly, medical nutrition solutions – that include protein and/or amino acids as a substrate for muscle protein to stimulate muscle protein synthesis – are important for supporting healthy aging and preventing disease-related malnutrition. However, as muscle wasting syndromes tend to be complex and multifactorial, particularly cancer cachexia, a multimodal approach to therapy is essential.

Solutions containing EPA and DHA could boost the quality of life and clinical outcomes of patients globally, and lower healthcare costs, when used in combination with other interventions, such as:



1  
A high  
protein diet



2  
Drug  
Therapies



3  
Exercise

While good nutrition is essential, exercise has just as significant a role to play in maintaining muscle mass as it improves muscle function and stimulates the growth of muscle mass. In cancer cachexia, recent therapies to combat this accompanying syndrome involve increased physical activity and targeted nutritional strategies. To date, these agents have been reported to improve survival rates and quality of life, indicating that nutrition, combined with exercise, plays an important role in clinical settings.<sup>55</sup> In sarcopenia though, it would be more effective to take a preventative approach rather than reversing the condition. Here, offsetting the effects of sarcopenia in old age via exercise and nutrition throughout life may help to slow its development.

The management of muscle loss in conditions like sarcopenia and cancer cachexia often requires an integrated or multimodal treatment approach that will target the different factors involved in its pathophysiology. But routine screening for malnutrition, including signs of muscle function loss in clinical settings, is also important as it would help to identify disease-related malnutrition early on. This way, solutions aimed at managing malnutrition could be implemented sooner, therefore helping to prevent progression of a condition and promoting better patient outcomes.

The Global Leadership Initiative on Malnutrition (GLIM) is dedicated to the identification, harmonisation and endorsement of criteria for the diagnosis of malnutrition. It advocates a scheme that will diagnose malnutrition in adults in clinical settings on a global scale.



# dsm-firmenich: working in partnership

dsm-firmenich recognizes the importance of medical nutrition for elderly individuals and patients and is passionate about improving care through the development of tailored, scientific concepts that can be combined with promising exercise programs. dsm-firmenich provides a broad range of proven nutritional ingredients and custom premixes that meet the highest safety and quality requirements. From vitamin straightshots as individual ingredients, including vitamins as active pharmaceutical ingredients (APIs) for parenteral nutrition, to nutrients such as omega-3 fatty acids – including EPA and DHA from marine and microalgae sources – dsm-firmenich's ingredients can be used in a range of medical nutrition formulations.


But, creating purpose-led medical nutrition solutions takes more than ingredients. It takes a company that is inspired by consumers to continuously innovate to meet their needs. That's why dsm-firmenich is committed to adding value at every stage of development, from concept to consumption. When you partner with

dsm-firmenich, you not only get access to a broad portfolio of science-backed products and customized solutions, but also its expert services aimed at supporting your entire product life cycle. These services support the development of medical nutrition solutions that successfully address the needs and format preferences of the elderly and patients under medical supervision.

Taking a human-centric approach to innovation is important as it helps to address individual needs and ensure that consumer preferences are implemented into new medical nutrition products. Consumer insights are therefore critical in supporting product innovation for improved patient centricity and quality of life. As an innovation partner to its customers and a purpose-led company, dsm-firmenich strongly advocates this and continues to invest in future research and insights to meet the ever-evolving nutritional needs of elderly adults, patients and individuals at risk of non-communicable diseases.

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