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Review Article

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The Role of Nutrition in Modulating Myosteatosis and Sarcopenia among Surgical Cancer Patients

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Abstract

Malnutrition and muscle mass loss are common clinical problems in cancer patients. Surgical procedures can also cause weight and muscle loss in patients if nutritional interventions are not initiated early on. Therefore, as with all patients, the nutritional status of surgical patients must be regularly assessed. Recent studies report that muscle quality and density are prognostic indicators, particularly in surgical patients, in terms of postoperative complications and survival. Myosteatosis, defined as intramuscular fat infiltration and associated with decreased muscle quality, occurs prior to sarcopenia, which is characterised by muscle atrophy. Therefore, detecting myosteatosis in the preoperative period is critical for both preventing sarcopenia and reducing surgery-related postoperative complications. The effect of nutrition on muscle mass and function is also well known. The prognostic role of myosteatosis on postoperative complications and survival is a current topic in the literature. However, studies involving nutrition, which clearly affects the body composition, are very limited. The aim of this review is to examine the effects of nutritional status and nutritional interventions on myosteatosis and sarcopenia in cancer surgery patients.

Keywords: Cancer, Malnutrition, Myosteatosis, Nutrition, Sarcopenia, Surgery

1. Introduction

In cancer patients, reduced oral intake, disease progression and systemic inflammation lead to a decrease in muscle mass and can cause changes in body composition. This may lead to progressive undernutrition and functional decline (1). In cancer patients, the decrease in body weight and muscle mass has a significant impact on prognosis and quality of life. These losses in muscle mass, strength, and function are referred to as sarcopenia, while myosteatosis is defined as "intramuscular fat infiltration," a condition that occurs independently of muscle size and is associated with lower muscle strength and mobility (2,3). In myosteatosis, which is associated with decreased muscle quality, physical fitness, and muscle function, there is an abnormal distribution of adipose tissue within and between muscle cells (4). Increased intramuscular fat infiltration is seen in aging, physical inactivity, and many diseases such as diabetes, obesity, chronic obstructive pulmonary disease (COPD), cirrhosis, and cancer. For the relationship between myosteatosis and postoperative complications and higher mortality rates (5,6). Myosteatosis may occur before the development of sarcopenia, a condition that causes muscle atrophy. Therefore, early detection of myosteatosis may also contribute to preventing the development of sarcopenia. However, in clinical practice, routine screenings for myosteatosis or sarcopenia are not performed, so these conditions may be unrecognized (7).

For the detection of myosteatosis and sarcopenia, magnetic resonance imaging (MRI), computed tomography (CT) or ultrasonography (USG) are frequently used in the literature. Among these techniques, CT and MRI are considered the gold standard for assessing body composition, particularly muscle mass and intramuscular fat tissue. In oncology services, CT and MRI are frequently used for diagnosis and monitoring. In abdominal CT scans, the L3 vertebra level is most commonly imaged. This level has recently been established as the standard for muscle mass analysis and has also been reported to be useful for identifying myosteatosis in cancer cases (1,8). Recent studies have reported that myosteatosis in the preoperative period may be a predictive marker for postoperative complications, prognosis, and survival in many types of cancer surgery (1,9-12). Surgical interventions have a curative potential, however postoperative complications can have adverse effects on the patient's quality of life and survival. In recent years, approaches aimed at improving the patient's nutritional and metabolic status during the preoperative and perioperative periods have attracted attention as important practices that support postoperative prognosis (13). However, clinical studies on the effects of nutritional interventions and nutritional status on the modulation of a prognostic marker, myosteatosis, are insufficient. At this point, the aim of this review is to examine the effects of nutritional interventions and the nutritional status of cancer surgery patients on myosteatosis and sarcopenia.

2. Body Composition Changes in Cancer

Malnutrition and cachexia are common in cancer patients. Malnutrition, which is associated with poor clinical outcomes and occurs as a result of cancer-related metabolic changes and reduced food intake, causes muscle loss with or without fat loss. It may be present at the time of diagnosis and may also develop and worsen during the progression of the disease and the treatment (14). On the other hand, cancer cachexia is a systemic catabolic syndrome that occurs in cases of severe malnutrition, characterised by muscle loss and systemic inflammation (15). Sarcopenia is associated with low skeletal muscle mass and strength in elderly individuals, while in cancer patients it is simultaneously linked to disease-specific adverse outcomes. Sarcopenia can develop even without loss of body weight or fat mass; therefore, it is important to assess overweight or obese patients to avoid overlooking the development of sarcopenia. (14). In myosteatosis, the abnormal distribution of adipose tissue inside and between muscle cells is associated with a decrease in muscle quality and function. Myosteatosis is the process of lipid infiltration into both intermuscular and intramuscular areas. (4). Muscle wasting is characterised not only by a reduction in muscle mass, but also by changes in normal tissue structure and composition. It is known that intramuscular fat accumulation or myosteatosis reduces muscle quality. Myosteatosis is more common in obese and elderly patients, but it can also occur in individuals of normal body weight and reflects a chronic inflammatory condition. Myosteatosis is associated with metabolic abnormalities and decreased muscle strength and may lead to a decline in survival (16). Myosteatosis is one of the most important factors contributing to sarcopenia. Sarcopenia, like myosteatosis, predicts overall survival, chemotherapy toxicity, and surgical complications in patients with various types of cancer (17). A recent study has shown that age-related mitochondrial dysfunction and decreased lipid oxidation may increase myosteatosis (18). Furthermore, during ageing, changes in the biochemical and biomechanical microenvironment may lead to an increase in adipogenesis, which contributes to intramuscular fat infiltration. In addition to ageing, some chronic diseases such as cancer, diabetes, COPD and cirrhosis, inflammation,

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hormones, mitochondrial dysfunction, genetic characteristics, obesity, physical inactivity and unhealthy nutrition are among the factors that increase the risk of sarcopenia and myosteatosis. These factors contribute to the impairment of muscle structure and function via mechanisms such as decreased muscle protein synthesis, impaired energy metabolism, fat accumulation in muscle cells, and increased oxidative stress (5,6,18). Factors that increase the risk of sarcopenia and myosteatosis are shown in Figure 1.

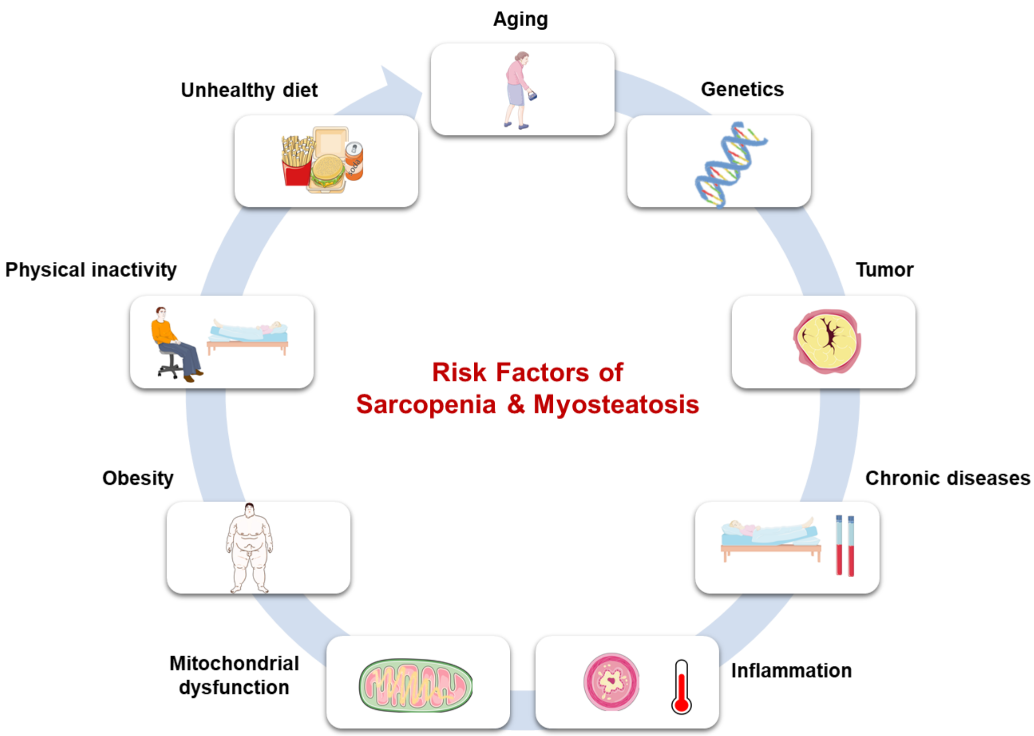

Figure 1 Risk Factors for Sarcopenia and Myosteatosis *(All icons by Servier https://smart.servier.com/ are licensed under CC-BY 3.0 Unported https://creativecommons.org/licenses/by/3.0/)*

Figure 1 shows the main risk factors involved in the development of sarcopenia and myosteatosis. Chronic inflammation, chronic diseases, tumours and oncological treatments, genetics, ageing, hormones, malnutrition, physical inactivity, obesity and mitochondrial dysfunction are among the risk factors.

It is recommended that nutritional assessments be performed regularly for the early diagnosis and treatment of malnutrition, which is associated with adverse outcomes in cancer patients. Some screening tools developed for use in cancer include assessments such as unintentional weight loss, body mass index and reduced food intake. However, assessment of skeletal muscle or metabolic changes may be overlooked (14). Although there are several methods for assessing nutritional status, there is no single parameter that accurately determines nutritional status and muscle mass. It is important to use techniques that are easy to use, specific, accurate and compatible with other nutritional screening tools when assessing nutritional status. Among these techniques, especially CT, is considered a highly accurate tool for assessing body composition (19). CT images enable a multidimensional body composition analysis, including the amount and distribution of skeletal muscle and fat tissue (visceral and subcutaneous), as well as tissue-specific radiodensity values (14). Although the routine use of CT in assessing body composition is not possible due to radiation, images taken for different medical purposes can be used to evaluate body composition (19). In oncology, most patients undergo CT scans primarily for diagnosis or monitoring, which presents an opportunity to examine the CT results from this perspective as well. Also, computed tomography, magnetic resonance imaging, or ultrasonography methods are frequently used in the literature to determine myosteatosis and sarcopenia (1). The abdominal and thigh muscles are most commonly assessed in the diagnosis of myosteatosis (8). Some studies have reported the third lumbar vertebra (L3) level as standard for muscle mass analysis and confirmed the use of CT in assessing body composition in cancer patients (1,8,20,21). However, other images, such as the psoas muscle at the L3 level and all muscles at the T4 level, are also used with similar prognostic efficacy (22). Images obtained from axial computed tomography scans are frequently used for cancer staging and monitoring, making them the primary assessment method for body composition analysis in oncology (17).

Muscle mass assessment using computed tomography generally involves measuring the cross-sectional area of muscle on a single CT image. The cross-sectional area is usually indexed according to the patient's height to obtain the skeletal muscle index (SMI). Sarcopenia is defined as the ratio of the total area of the L3 skeletal muscle (cm^2) to the square of the patient's height (m^2). The assessment of myosteatosis using CT generally obtained by measuring the mean muscle attenuation in the range of -29 HU to +150 HU (23). Table 1 summarises the cut-off points for the assessment of myosteatosis and sarcopenia. The cut-off values for myosteatosis in Table 1 are based on the values reported by Martin et al (24). Also, the normal structure of skeletal muscle and the types of fat infiltration developing in skeletal muscle are shown in Figure 2.

Myosteatosis cut-off values	For BMI <25 kg/m^2, <41 Hounsfield units For BMI ≥ 25 kg/m^2, <33 Hounsfield units
Sarcopenia cut-off values	Women: SMI <41 cm^2/m^2 Men: SMI <43 cm^2/m^2 (if BMI <25 kg/m^2) Men: SMI <53 cm^2/m^2 (if BMI ≥ 25 kg/m^2)

(CSA: muscle cross-sectional area (cm^2), SMI: skeletal muscle index (cm^2/m^2))

Table 1 Determination of sarcopenia and myosteatosis and cut-off points
Table 1 shows how myosteatosis and sarcopenia are determined in CT images and the cut-off values used in evaluating these results.

Increased fat infiltration in muscle results in lower muscle radiodensity on CT images (8,25). Tissue radiodensity decreases with the presence of excessive triglycerides within the tissue. Myosteatosis, has been reported to be an important predictor of reduced overall survival in cancer (14). In a study, reduced skeletal muscle mass was reported as an independent prognostic indicator of decreased survival in patients with lung and gastrointestinal malignancies (24). Meta-analysis studies have also shown that sarcopenia (35.3%) and myosteatosis (48%) are common in patients with solid tumours and that myosteatosis significantly increases the risk of all-cause mortality. Furthermore, myosteatosis has been found to have exceptional prognostic value in seven different tumour types ((gynaecological (endometrial and ovarian), renal, periampullary/pancreatic, hepatocellular, gastro-oesophageal, colorectal carcinomas and lymphoma)) (17,26).

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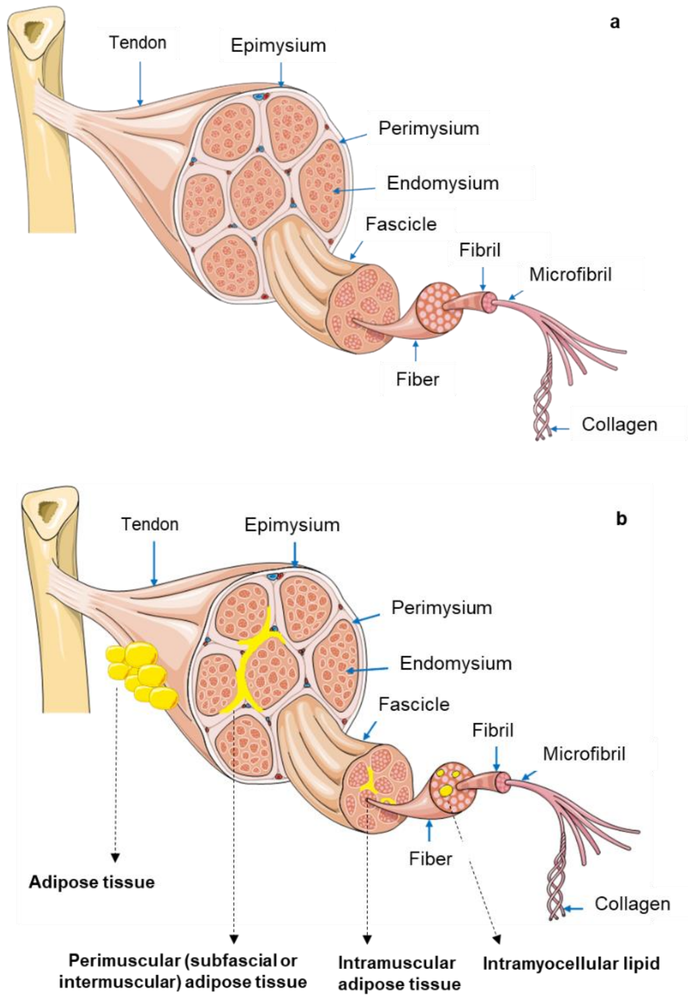

Figure 2 Normal structure of skeletal muscle and types of fat infiltration

(Icons "muscle-tendon", "adipocyte-1", "adipocyte-2" adapted from Servier https://smart.servier.com/ is licensed under CC-BY 3.0 Unported https://creativecommons.org/licenses/by/3.0/)

Skeletal muscle consists of fascicles connected to each other by intramyocellular myofibrils, muscle fibres, and successive layers of thickening connective tissue (endomysium, perimysium, and epimysium). Figure 2-B shows three areas of fat infiltration in the muscle (i) perimuscular (subfascial or intermuscular) adipose tissue refers to extracellular adipose tissue located under the fascia between muscle fascicles; (ii) intramuscular adipose tissue refers to extracellular adipose tissue located between muscle fibres within the same muscle fascicle; (iii) intramyocellular lipid refers to protein-coated lipid droplets inside the cytoplasm of muscle fibres.

3. The Role of Nutrition in Myosteatosis and Sarcopenia in Cancer Surgery

Nutritional support in cancer surgery patients aims to prevent malnutrition and the occurrence of postoperative complications associated with malnutrition. Malnutrition and trauma due to major surgery may trigger immunosuppression, systemic inflammation and intestinal dysfunction in patients (27). Losses in skeletal muscle mass and quality have been reported to be associated with systemic inflammatory response and survival in surgical candidates with colorectal cancer. Some studies have reported that sarcopenia and myosteatosis are negative factors for survival in cancer patients. (1,9-

12,28). The quantitative and qualitative assessment of muscle mass in surgical patients offers an innovative perspective for personalised treatments aimed at improving clinical outcomes and reducing postoperative mortality rates (20). In the past, nutritional support was primarily focused on maintaining metabolic homeostasis. Today, in addition, enhancing the immune response, reducing inflammation and protecting the intestinal mucosa are also priorities in nutritional therapy (27). Since the 1990s, ERAS (Enhanced Recovery After Surgery) protocols, which have become a key focus of perioperative care and include nutritional protocols as a fundamental principle, aim to improve perioperative care, minimise complications and accelerate recovery (29,30). While early oral nutrition is preferred in ERAS protocols, not providing any nutritional therapy to the patient leads to the risk of malnutrition in the postoperative period following major surgery. Considering that nutritional status is a risk factor for postoperative complications, this is particularly important for patients at nutritional risk. Therefore, ERAS guidelines recommend the use of pre- and postoperative oral supplements. Furthermore, ERAS protocols also support early oral intake for the return of bowel function (31).

In surgical cancer patients, adequate energy and protein intake is important for maintaining muscle mass and supporting the recovery process. For most cancer patients, it is recommended that daily energy intake is 25-30 kcal/kg/day and protein intake is 1-1.5 g/kg/day (32). Inadequate energy and protein intake may lead to decreased muscle radiodensity and increased myosteatosis. In a study in patients undergoing radiotherapy for lung cancer, it was reported that pre-treatment inadequate energy and protein intake was associated with a decrease in post-treatment muscle radiodensity and the development of myosteatosis (33). In a study conducted on elderly women suffering from sarcopenia, it was reported that moderately higher-protein diets (20-25% of energy from protein) resulted in improvements in muscle mass composition and muscle strength, and decreases intermuscular and subcutaneous fat tissue, compared to those receiving normal protein (34). In an observational study of women with metastatic breast cancer, it was reported that patients had inadequate protein intake and exercise levels, and that myosteatosis and impaired physical function were common (35). In another study conducted on patients with colorectal cancer, it was found that as the percentage of myosteatosis increased, the frequency of unintentional weight loss (one of the parameters of frailty) also increased. This study reported that body fat and speed of walking are determinants of intramuscular fat infiltration percentage, and that the presence of four or more frailty criteria is associated with myosteatosis and muscle weakness in obese patients with colorectal cancer (6). In a prospective observational study in overweight and obese patients diagnosed with gastrointestinal, lung, or head and neck cancer, the presence of sarcopenia and myosteatosis was investigated in different nutritional risk statuses determined by the Patient Generated Subjective Global Assessment Short Form (PG-SGA SF). In this study, it was found that sarcopenia and myosteatosis were commonly present in patients at different levels of nutritional risk, and that in multivariate survival analysis, sarcopenia, myosteatosis, and PG-SGA scores ≥9 predicted reduced survival (14). In a study on elderly patients who underwent surgery for bile duct cancer, it was found that patients with myosteatosis had a lower prognostic nutritional index (PNI). In addition, preoperative myosteatosis and low PNI were reported as independent prognostic factors for overall survival (36).

The most frequently used oral supplements in cancer patients include specific nutritional components such as glutamine, arginine, leucine, beta-hydroxy beta-methylbutyrate (HMB) and other protein derivatives, omega-3 polyunsaturated fatty acids (n-3 PUFA) and antioxidants. It is thought that nutritional support enriched with immunomodulatory agents during the surgical period may have positive effects on the nutritional status of cancer patients. The European Society for Parenteral and Enteral Nutrition (ESPEN) strongly recommends oral or enteral immunonutrition (containing arginine, n-3 fatty acids, nucleotides) in patients with upper gastrointestinal cancer undergoing surgical resection as part of traditional perioperative care (32). Previous clinical studies suggest that HMB, arginine, and glutamine support the maintenance of lean body mass (37). Furthermore, a clinical study conducted on patients with head and neck cancer reported that glutamine, HMB, and arginine exhibited inhibitory properties against chemotherapy-induced mucositis and the progression of cancer cachexia (38). As a leucine metabolite, HMB is frequently used to improve body composition. Previous studies have shown that HMB supplementation can preserve total lean body mass and appendicular lean body mass in hospitalised elderly patients (39). In a study in patients with oesophageal cancer undergoing surgery, it was demonstrated that skeletal muscle mass, nutritional status, and postoperative outcomes improved in the group receiving pharmaconutritional intervention containing glutamine, arginine, and HMB during the perioperative period compared to the control group (40). In a preclinical study conducted by Wang et al. (2020) on sarcopenic mice with age-related muscle loss, the combined application of HMB and vibration therapy was shown to increase grip strength, significantly reduce myosteatosis, and suppress adipogenic differentiation (41).

Omega-3 polyunsaturated fatty acids exhibit anti-inflammatory effects that promote muscle anabolism by enhancing communication between skeletal muscle and immune system cells (42). Improvements in muscle composition have also been observed in cancer patients taking omega-3 supplements (43,44). In an in vitro study investigating the effect of PUFAs on myosteatosis in muscle cells, myosteatosis was induced by palmitic acid exposure in C2C12 myoblasts. The cells were also incubated with PUFAs (ALA: α-linolenic acid, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid, ARA: arachidonic acid) for 48 hours. Incubation with DHA or ARA provided protection against palmitic acid-induced anabolic resistance and cell death, preventing myosteatosis and lipotoxicity (45). In an another preclinical study, long-term (one week prior to tumour implantation) and adjuvant (at the start of chemotherapy) fish oil administration reduced tumour and chemotherapy-induced increases in neutral lipid accumulation and total muscle triglycerides, and reduced adipogenic transcription factors, thus showing efficacy in reducing myosteatosis. Furthermore, in rats treated with fish oil, muscle fibre cross-sectional area was maintained, whereas an atrophic decrease was observed in the control group (46). In a study conducted on cervical cancer patients, the low-radiodensity skeletal muscle index and high-radiodensity skeletal muscle index values were maintained in the intervention group receiving 2.5 g/day omega-3 supplementation. However, in the control group, the low-radiodensity skeletal muscle index increased and the high-radiodensity skeletal muscle index decreased, which are associated with myosteatosis (47). In a pilot study conducted on patients with early-stage lung cancer, no significant difference in muscle characteristics was observed in the intervention group receiving multimodal prehabilitation, which included nutritional supplements (fish oil containing vitamin D3 + whey protein with leucine), exercise and relaxation techniques, compared to the standard care group (48).

4. Conclusions and Recommendations

Myosteatosis is a current topic open to emerging innovations in the field of nutrition science. Current studies have focused on the important role of certain nutrients, such as HMB and omega-3 fatty acids, in reducing myosteatosis in cancer patients, in addition to adequate energy and protein intake. However, the data is insufficient to reach a definitive consensus. As with all patients, regular assessment of nutritional status in cancer patients is important for the early detection of sarcopenia and myosteatosis, as well as malnutrition. Surgical procedures, particularly when ERAS protocols are not adopted and adequate nutritional intake is not ensured in the early stages, can lead to weight and muscle loss, complications, and poor prognosis. Therefore, assessing nutritional status before surgery and implementing nutritional interventions in high-risk patients is crucial for surgical cancer patients. Future nutrition-based clinical studies on myosteatosis are important for understanding the effects of nutrition on muscle radiodensity. These studies may help clarify whether myosteatosis, which is considered a prognostic marker, can also serve as a predictor of nutritional status.

- Consent for publication

There is no obstacle for publication approval

- Competing interests

The author declares that she has no conflict of interest.

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