Biomedical & Pharmacology Journal, December 2024. Vol. **17**(4), p. 2203-2216

Nutritional Challenges in Paediatric Oncology: Screening and Managing Malnutrition and Sarcopenia

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https://dx.doi.org/10.13005/bpj/3017

(Received: 26 April 2024; accepted: 15 July 2024)

Sarcopenia and malnutrition can coexist in pediatric patients with neoplasia, worsening the patient's prognosis. The classification of primary and secondary sarcopenia may be helpful in clinical practice, as it can help with timely initiation of appropriate and tailored dietary treatments to address it. This review summarizes the current state of the art of assessing skeletal muscle function in children and adolescents with cancer and discusses the role of nutritional interventions in the management of children with cancer. It highlights the urgent need for comprehensive nutritional support and interventions to mitigate the impact of malnutritions on both treatment outcomes and patients' well-being.

Keywords: Cancer; Children; Malnutrition; Natural Products; Sarcopenia.

Cancer is a significant cause of mortality among children and adolescents in the United States, ranking as the second most common cause of death for children aged 1–14 years and the fourth most common cause of death for adolescents aged 15–19 years. This highlights the impact of cancer on young people and the need for continued research and support for pediatric and adolescent cancer patients.

Children who have cancer frequently experience malnutrition. Numerous research investigations indicated that the incidence of this medical condition ranges widely with reports showing that it affects 6–51 % of children admitted to hospitals. Malnutrition in children with tumors is associated with higher energy needs and losses, as well as reduced intake of essential nutrients.[1–5] Tumor-secreted proinflammatory cytokines increase metabolism and catabolism, leading to protein loss and faster oxidation of energy sources.[6-14] Gastrointestinal issues (i.e., vomiting, nausea, etc) from chemotherapy toxicity can also contribute to increased energy losses. Chemotherapy can result in changes in taste, reduced appetite, and lower nutrient absorption, which may result in decreased appetite.[15-28] All of these processes lead to neoplastic cachexia, a metabolic syndrome involving ongoing loss of muscle mass that cannot be fully reversed with typical nutritional aid.[29–32] This results in anorexia,

muscle wasting, fatigue, abnormal biochemical levels, functional decline, and inadequate weight changes. [33-39]

Among other predisposing factors, malnutrition of protein-energy can lead to sarcopenia. Sarcopenia refers to the gradual loss of mass, strength, and skeletal muscle function. Sarcopenia may occur in young people, such as children with cancer, related to malnutrition, aggravating its side effects and increasing patients' sensitivity to various complications.

Sarcopenia, in contrast to malnutrition, is a new term in the pediatric literature. Sarcopenia in adults, which is a component of malnutrition, is defined as a decrease in skeletal muscle mass (SMM) and a decrease in muscle strength or physical performance.[40] However, sarcopenia associated with decreased SMM in pediatrics has only recently been recognized. A pathological condition called sarcopenia is defined by a gradual and widespread loss of muscle mass - both quantitative and qualitative - as well as a deterioration in physical function. It is a leading cause of mortality, poor quality of life, loss of independence and physical disability.[41] After age 50, muscle mass typically declines by 0–1 percent annually in women and 0.5–1 percent in men. This condition is typically associated with age. Nevertheless, certain pathological conditions characterized by systemic inflammation, such as cancer, endocrine disorders and chronic inflammatory diseases, can also lead to early development of sarcopenia due to the catabolic state that inflammatory cytokines induce in skeletal muscle.[42,43] Sarcopenia and malnutrition may coexist in pediatric patients with neoplasia, worsening the patient's prognosis. The co-occurrence of two clinical conditions, malnutrition and sarcopenia syndrome, has been documented in the adult literature, with notable overlap in treatment outcomes and adverse events.[44, 45] Similar concepts regarding loss of muscle mass, changes in muscle function, and inadequate nutrient intake leading to deficits in fine motor skills, cognition, and nutrition are shared in the definitions of malnutrition and sarcopenia.

In this review, we want to emphasize the critical importance of early detection of malnutrition in pediatric cancer patients and the subsequent optimization of nutritional interventions within this population. This highlights the immense significance of regularly assessing the nutritional status and identifying the risk factors for the development of malnutrition. Additionally, the review presents practical tools that are highly applicable in daily clinical practice, further aiding in the battle against malnutrition.

MATERIALS AND METHODS

Pathogenesis

Sarcopenia can be caused by various factors and progress through different mechanisms such as muscle fat content, neuromuscular integrity, proteolysis, and protein synthesis. Understanding these mechanisms and their causes can help in designing intervention trials. Some individuals may have a clear cause for sarcopenia, while others may not. Thus, primary and secondary classifications are used in clinical practice. Age-related sarcopenia is classified as secondary, while sarcopenia with additional causes is classified as primary. The multifactorial nature of sarcopenia in older adults may make classification challenging for each individual.[46-56]

Classification

The European Working Group on Sarcopenia in the Elderly (EWGSOP) recommends using the terms "presarcopenia", "sarcopenia", and "severe sarcopenia" to classify stages of muscle mass loss in the elderly. Presarcopenia, with low muscle mass but no impact on strength or performance, requires precise measurement methods for diagnosis. Sarcopenia is marked by low muscle mass, strength or performance, while severe sarcopenia meets all three criteria. Understanding these stages aids in selecting appropriate treatments and recovery goals. [57,58] EWGSOP has identified acute and chronic sarcopenia as subcategories, with acute cases lasting less than six months and chronic cases lasting longer. Regular evaluation is crucial to monitor progression and enable early intervention to prevent or slow the effects of sarcopenia (Figure 1).

Evaluation

Early and sufficient nutritional intervention can help hospitalized children avoid growth arrest, increase therapy tolerance, improve their quality of life, and shorten their hospital stay.[59,60]

Screening tools

To identify children at risk and establish an appropriate nutritional support plan, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and ESPEN recommend screening for nutritional risks at the time of hospital admission.[61,62] Despite the fact that a number of pediatric nutritional risk assessments have been reported in research, screening for nutritional disorders is often not performed and there is no consensus on the "optimal" screening tool.[63] Currently, there are seven primary screening tools for childhood nutritional risk: PNRS, SGNA, STAMP, PYMS, STRONGkids, and PNST. Patients at risk of malnutrition must undergo a specific nutritional assessment following the nutritional risk assessment. It is important to examine growth curves, the onset of puberty, psychomotor development, motor skills and swallowing ability, gastrointestinal complaints, weight fluctuations, medication intake, eating habits, dietary habits, allergies and food intolerances.[64-66]

Physical examination

The physical examination assesses the patient's general health and looks for evidence of specific nutritional deficiencies. Although no single laboratory test can provide a comprehensive assessment of nutritional status, laboratory data plays a complementary role in the assessment process. An inflammatory state is often associated with disease-related malnutrition, which may reduce the benefit of nutritional interventions. In acute inflammation or catabolic states, levels of acute phase proteins are increased, whereas albumin, prealbumin, retinol-binding protein and transferrin are reduced.[67-73]

Anthropometric Measurements

Although weight is a measure of a person's overall nutritional status, a number of factors, including age, gender, daily intake and fluid intake, can affect a person's weight. Standing patients older than two years should be weighed using a digital scale or a platform scale with movable weights. For patients who cannot stand, we use wheelchair or bed scales. When weighing a child under two years of age, it is best to place them on a scale on their back and make sure the weight is evenly distributed in the center of the scale.[74] A critical metric for tracking long-term nutritional status is height, whether measured as length, height, or another variable. When measuring a child under two years old, he should lie on his back and use an infantometer. If possible, a vertical stadiometer mounted on the wall is used for children aged two and over. The head circumference of babies as young as 36 months can be measured using a flexible tape measure that is wrapped around the head. Head size should be viewed as a measure of nutritional status and brain development.

Weight-for-height, which corresponds to BMI in patients over two years of age, can be used as an evaluation measure in children under two years of age. The formula for calculating BMI is BMI=weight(kg)/height^2 (m2). Due to the variability of age and gender, different specific BMI values are available for children. BMI can be used to determine obesity or overweight in children. The World Health Organization (WHO) has approved the use of BMI to measure thinness in adolescents, but underweight in children is defined as "low weight for age" and is not determined by BMI. Furthermore, because BMI ignores variations in body composition, it should not be the sole measure of a child's nutritional status under clinical conditions. Mid upper arm circumference (MUAC) is a simple measurement that can be taken using a flexible tape measure positioned perpendicular to the extended axis of the arm. The midpoint of the upper arm, which is located between the olecranon and the acromion, is measured and marked. In patients with edema, MUAC is a more accurate measure of body composition than BMI because it is unaffected by fluid intake.

To measure the thickness of the triceps skinfold, place your thumb and index finger between the skin and subcutaneous fat over the MUAC point. Although it can also be helpful in identifying body fat depots in patients, this parameter is widely used in research. A cost-effective, non-invasive method for assessing the functional status of muscles is the handgrip test, which is performed using a portable dynamometer. The patient uses the dynamometer to subject their hand and forearm muscles to a series of movements designed to replicate their maximum strength. Grip strength is a useful tool for detecting malnutrition in children because dietary changes affect muscle function before muscle mass.

A child's weight, length, height, weight length, or BMI are expressed as a percentile for

age and sex on a bell-shaped reference curve constructed from population data. To compare a child's position with a population of other children similar to him or her in terms of age and gender, a percentile is used to indicate the percentage of the population that remains above or below the measured value. However, according to the WHO, Z-scores would be a better way to express anthropometric measurements because percentiles do not accurately reflect the extent of the patient's deviation from population norms. Z-scores, which compare each individual anthropometric measurement to data from reference age groups, are more sensitive than percentiles because they express the child's deviation from the mean in standard deviation (SD).[74]

Body composition asssessment

Body composition can be routinely determined using several methods, including bioimpedance (BIA), dual-energy x-ray absorptiometry (DXA), and whole-body potassium counting (TBK).[75,76] Despite the common use of these reference methods, each has certain practical limitations. A non-invasive technique for measuring body composition that can be used in patients of all ages is dual-energy X-ray absorptiometry (DXA). It is a quick, cost-effective and radiation-safe procedure.[77] Another safe, noninvasive, and widely used technique for indirectly determining body composition is bioimpedance analysis (BIA). Its basis is the idea that the body's ability to conduct an alternating electrical current can find a contact resistance (impedance) that is inversely proportional to the concentration of electrolyte and water.

Fat mass, lacking water and electrolytes, shows strong resistance to high impedance, while free-fat mass, composed of well-hydrated cells, exhibits lower impedance. Air within the lungs, parenchymal organs, and bones are not considered to be effective conductors and are therefore disregarded. Both resistance (R) and reactance (Xc) are components of the impedance (Z) that affects the flow of current through the body. Fat mass and extracellular water (ECW) are the main factors that primarily affect R. Xc, which is the capacity of normal cell membranes to take in an electric charge and then later discharge it, serves as a representation of the cellular mass in the body. The early detection of sarcopenic status can help with timely initiation of appropriate and tailored dietary treatments to address it. Different techniques are available in the medical field to assess muscle mass and diagnose sarcopenia.[80] Anthropometric measurements like weight, BMI, mid-arm circumference, and triceps skinfold thickness can be easily influenced by illness and therapy and may not provide an accurate evaluation of body composition. Bone densitometry (DXA), bioelectrical impedance analysis (BIA), and air displacement plethysmography (ADP) are more accurate methods for body composition assessment, but their usage is restricted due to the need for specialized staff and equipment.[81,82]

CT and MRI are the top choices for measuring skeletal muscle mass in adults, with CT being the preferred method despite its high radiation levels. The radiation exposure from standard CT scans is a significant disadvantage when evaluating sarcopenia in children. Although MRI does not involve radiation, it is pricier than CT and might not be as easily accessible for regular monitoring. Yet, kids with chronic illnesses frequently undergo imaging as a component of their routine healthcare, enabling the assessment of muscle mass without any extra expenses or radiation exposure. [83,84]

RESULTS AND DISCUSSION

Examining the general development is essential when evaluating body composition in pediatrics, as it can influence the evaluation of sarcopenia in children. In puberty, there are significant differences in skeletal muscle mass and fat mass proportions, despite similar lean and fat mass in young boys and girls. During puberty, it has been observed that males typically see a larger boost in lean muscle mass due to hormonal factors like growth and sex hormones (estrogens, testosterone), whereas females tend to accumulate more fat mass. [85,86] At present, there is no definitive tool for assessing the decline in motor function in children undergoing evaluation for sarcopenia. Assessing muscle function in infants with standardized methods is difficult due to several factors influencing their motor performance, including postural control development, coordination, core stability, and ability to perform specific movements.

Illnesses can hinder the capability to perform specific muscle evaluations. Even though studies on sarcopenia in children are ongoing, evaluations in early childhood still do not include assessments of motor function. Handgrip and 6-minute walk tests are frequently employed among older children and teenagers to assess upper body strength and overall exercise capacity. These evaluations align with the suggested tests for detecting muscle function deficiencies in adults diagnosed with sarcopenia. While other tests for strength and performance have been used with children, their effectiveness is limited due to the lack of standardized protocols. [87-92]

Measuring the psoas muscle area (SMA) from abdominal computed tomography (CT) images at the L3-L4 and L4-L5 levels is a quick, efficient, and reliable way to determine muscle mass.[93,94] The skeletal muscle index (SMI) is calculated by multiplying the patient's height squared (m2) by the SMA (cm^2). Sarcopenia may be present if the SMI is below 55 cm^2/m^2 for men and 39 cm^2/m^2 for women. Examining the muscle mass of adult cancer patients, patients undergoing regular axial tomography re-evaluation scans, patients with liver disease, critically ill patients, and surgical patients has become a frequent occurrence. [95-101] Sarcopenia diagnosis has been used in patients with pediatric cancer, inflammatory bowel diseases, type 2 diabetes, end-stage liver disease, and intestinal failure.[102-112] Recently, age- and sex-specific curves for total area of psoas muscle (tPMA) have been developed for pediatric patients aged 1 to 16. These curves allow for a quick assessment of sarcopenia and calculation of Z-Scores for PMA.[113–119] Lurz et al. found that when examining tPMA at the L3–L4 and L4–L5 levels, the psoas muscle has a rounder shape, allowing for a more accurate contour design. As a result, tPMA at the L4–L5 level seems to be more important in pediatric patients. Additionally, a measurement taken at the L4-L5 reference level gives a reliable assessment of skeletal muscle and adipose tissue, as this level is commonly used to assess visceral adipose tissue.[120-125] In more recent times, MRI has been used to measure the thickness of the temporal muscle as a way to detect sarcopenia, especially in patients with brain tumors.[126-128]

Clinicians should combine nutrition assessment with screening for sarcopenia to properly evaluate these two connected nutritional issues and ultimately enhance patients' clinical outcomes. Several malnutrition screening tools are accessible, including the Malnutrition Screening Tool (MST), Malnutrition Universal Screening Tool (MUST), the short version of the Mini-Nutritional Assessment (SF-MNA), and Nutrition Risk Screening-2002 (NRS-2002).[129-132]

Indicators of history and physical examination are often seen in both tools, such as unintentional weight loss, reduced food consumption, digestive issues, and impairment in

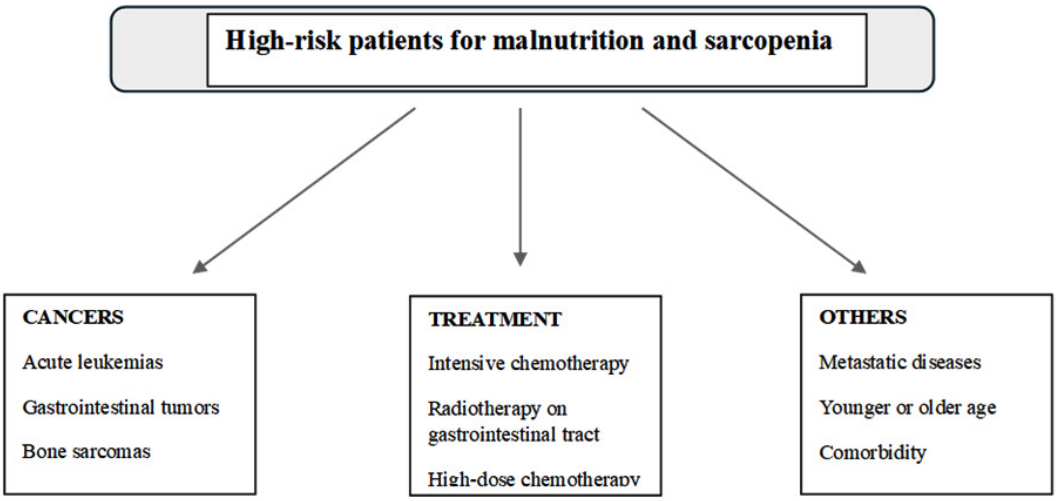

Fig. 1. Detection of high-risk patients for malnutrition and sarcopenia

daily functioning. Additional studies are needed to establish the accuracy and effectiveness of this evaluation tool among various patient groups and environments.

Recent advances in muscle biology have unveiled new insights into the molecular mechanisms of sarcopenia and potential nutritional treatments. While the conventional recommendation for preventing age-related muscle weakness and loss involves a combination of resistance training and amino acid-containing supplements, it's been found that protein-only supplements have little impact on sarcopenia symptoms. Candidate substances like catechins, soy isoflavones, and ursolic acid show promise in combating sarcopenia. These compounds have a crucial role in regulating proteins responsible for aging and inflammation-related signalling pathways. This regulation is key in the development of sarcopenia and its associated pathogenesis. Understanding these pathways and how they are affected by these compounds can provide valuable insights into potential interventions for sarcopenia and age-related inflammation.

Certain compounds derived from plants or food, known as phytochemicals, have been attracting attention for their remarkable antioxidant properties. Numerous in vivo and in vitro studies have unveiled the potential of phytochemicals, particularly polyphenols, in facilitating muscle recovery and potentially serving as a treatment for muscle atrophy. In various models of muscle damage, whether caused by pathological conditions or exhaustive exercise, compounds like curcumin and sulforaphane (SFN) have demonstrated their effectiveness in preventing or minimizing injuries to skeletal muscle mass. These remarkable compounds activate cytoprotective signaling pathways and trigger an optimal antioxidant response, combating inflammation and promoting the restoration of skeletal muscle. Specifically, curcumin has shown promising results in preventing muscle atrophy by inhibiting protein synthesis, primarily by regulating ubiquitin ligases.

Moreover, curcumin has demonstrated remarkable myogenic and mitochondrial qualities in both in vitro and in vivo studies. Currently, a variety of natural compounds, including terpenoids (such as ursolic acid, celastrol, and tanshinone IIA), polyphenols (like resveratrol, curcumin, and urolithin A), flavonoids (such as quercetin and apigenin), alkaloids (like tomatidine and magnoflorine), and vitamin D, are known for their ability to enhance muscle strength, increase muscle mass, facilitate muscle stem cell differentiation, promote mitochondrial biogenesis, and reduce hydrogen peroxide production and inflammation in skeletal muscles. These compounds have pleiotropic functions, but some of them also have specific targets and can regulate distinct signaling pathways. For instance, ursolic acid, resveratrol, curcumin, berberine, and others stimulate AMPK-mediated PGC-1á expression, inhibit the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-êB), and activate mitogen-activated protein kinase (MAPK) pathways associated with protein catabolism, thereby facilitating muscle myogenesis. Despite these promising findings, the efficacy of natural products compared to synthetic drugs is hindered by the limited research on their molecular mechanisms, bioavailability, and clinical trials. Nevertheless, herbal medicines and their purified components, such as polyphenols and alkaloids, continue to hold significant potential in the realm of muscle recovery and overall well-being. Additionally, further research is needed to fully elucidate the mechanisms involved and to identify specific compounds that can effectively target these pathways.[133-139] One limitation of using natural products is that the studies often use amounts that exceed what would be consumed through typical food sources. This means that the effects observed may not accurately represent real-life scenarios. Additionally, the issue of bioavailability, such as in the case of curcumin, must be taken into account. However, this is not a concern with SFN found in broccoli, as other factors like preparation and cooking play a role. Lastly, it is crucial to conduct more studies involving human subjects. While research on cell lines and animal models is valuable for understanding the mechanisms of action, it is imperative to fully comprehend how these active compounds affect the human biological system.[140]

CONCLUSIONS

Malnutrition in cancer patients significantly impacts survival rates by lowering disease-free survival, increasing treatment-related

mortality, and reducing chemotherapy tolerance. Malnutrition also negatively affects physical, emotional, and social well-being, hindering recovery and making cancer treatment more challenging.

Distinguishing between primary and secondary sarcopenia can be beneficial in a clinical setting, as it can aid in promptly starting suitable and personalized dietary interventions to manage it. This review outlines the current status of evaluating skeletal muscle function in children and adolescents with cancer and explores the impact of nutritional strategies in treating pediatric cancer patients.

Comprehensive nutritional support is crucial to alleviate these negative impacts and improve treatment outcomes and patient well-being.

ACKNOWLEDGEMENT

The authors thank "Fondazione per l'Oncologia Pediatrica ONLUS" for their dedicated patient care and scientific support.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest

The author(s) do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required

Clinical Trial Registration

This research does not involve any clinical trials

Author contributions

Stefano Mastrangelo, Antonio Ruggiero: Conceptualization, Methodology, Writing – Original Draft; Alberto Romano, Palma Maurizi, Daniela Rizzo, Giorgio Attinà: Data Collection, Analysis, Writing – Review & Editing; Antonio Ruggiero, Giorgio Attinà, Daniela Rizzo, Alberto Romano: Visualization, Supervision, Project Administration; Antonio Ruggiero, Stefano Mastrangelo: Funding Acquisition, Resources, Supervision

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