PERSPECTIVE

Perspective: Creating the Evidence Base for Nutritional Support in Childhood Cancer in Low- and Middle-Income Countries: Priorities for Body Composition Research

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ABSTRACT

There is a striking disparity in survival rates for children in low- and middle-income countries (LMICs) compared with high-income countries (HICs). Many of the contributing factors are preventable, including the comorbidity of malnutrition. There are emerging data that malnutrition, as reflected in body composition changes, impacts survival of cancer. However, not enough priority is given to nutrition management of children with cancer, particularly in LMICs. The primary purpose of this article is to review the current knowledge on childhood cancer and body composition in LMICs and identify priorities for future research into the interlinking associations between cancer, body composition, and clinical outcomes for childhood cancer patients. Evidence will ensure feasible and effective nutrition management is prioritized in childhood cancer centers in LMICs and contribute to improving outcomes for children with cancer. *Adv Nutr* 2020;11:216–223.

Keywords: body composition, childhood cancer, low- and middle-income countries, nutrition support, malnutrition, clinical outcomes

Introduction

More than 429,000 children are diagnosed with cancer each year, with the annual incidence rate of cancer being 155 per million children aged 0–19 y in 2001–2010 (1). Although survival rates for some cancers have reached a 5-y overall survival of ∼80% in many high-income countries (HICs), ∼90% of children and young people with cancer live in low- and middle-income countries (LMICs), where survival rates are currently only 10–30% (2, 3). It is calculated that between 80,000 and 100,000 children die unnecessarily from cancer each year in LMICs, where the most important prognostic factor for a child with cancer is place of birth (4). Low survival rates in LMICs are due to misdiagnosis of cancer, inaccessible treatment, treatment abandonment, coexisting conditions, and paucity of health professionals with specialized training (5). The challenge in childhood cancer is to take the improvements achieved in HICs to all children worldwide, but it is not enough to duplicate HIC strategies: quality research is needed to address the specific needs of childhood cancer centers in LMICs.

One of the influencing factors for lower survival rates in childhood cancer is coexisting malnutrition (6–10). Malnutrition is an imbalance in a person's intake of energy and/or nutrients and importantly refers to both undernutrition and obesity. In the simplest form, malnutrition is reflected in changes in weight, but more clinically relevant changes are reflected in body composition, specifically the proportion and distribution of lean and fat tissues in the body. Body composition is an emerging theme in clinical

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Abbreviations used: ALL, acute lymphoblastic leukemia; BIA, bioelectrical impedance analysis; CINV, chemotherapy-induced nausea and vomiting; FFM, fat-free mass; FM, fat mass; HIC, high-income country; LMIC, low- and middle-income country; MNT, medical nutrition therapy; RUTF, ready-to-use therapeutic food; SCAN, nutrition screening tool for childhood cancer.

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oncology and is increasingly recognized as a key outcome measure (11–13). To effectively manage malnutrition in children with cancer and potentially improve survival rates in LMICs, it is vital to assess body composition as an indicator of malnutrition and understand the interlinking associations between cancer, body composition, and clinical outcomes.

The value of nutritional support in children and young adults is still an underacknowledged topic within pediatric oncology, both in HICs and in LMICs (14, 15). Whereas new cancer therapies are not readily accessible and solutions to improve survival may not be feasible in LMICs, a focus on nutritional management could serve to improve clinical outcomes with simple low-cost nutrition strategies, such as education, assessment, and intervention. Although there is some progress to improve nutrition care for children with cancer (16), more research is needed globally to provide quality evidence to support decision-making. This article explores the current evidence concerning body composition and childhood cancer and identifies research priorities in providing guidance to cancer centers to improve nutritional management of children with cancer in LMICs.

Current Status of Knowledge

Assessing body composition in children with cancer in LMICs

Nutrition screening and simple assessments.
It is important that all children with cancer are screened for high risk of malnutrition, especially in LMICs, to ensure that the limited resources available for nutrition support are prioritized for high-risk patients. Screening tools combine parameters that are known to contribute to malnutrition in patients and categorize malnutrition risk. There are several nutrition screening tools for hospitalized children (17, 18) and 1 tool, the nutrition screening tool for childhood cancer (SCAN), that has been developed specifically for children with cancer (19). SCAN considers cancer type, treatment phase, gastrointestinal symptoms, oral intake, weight loss, and observable signs of undernutrition. Translation and cross-cultural adaptations with SCAN are underway (currently in Brazil, China, and Spain) to provide an accurate and feasible tool to identify malnutrition risk for cancer patients in both HICs and LMICs.

Research has shown that most cancer centers in LMICs only use simple assessments of weight, height, and BMI to represent nutritional status in children with cancer (14). BMI is often used as a proxy measure of total adiposity and to categorize nutritional status because it is simple and can be compared with reference standards. However, BMI is a measure of excess or inadequate weight, not excess or inadequate fat mass (FM), and it cannot differentiate between FM and fat-free mass (FFM). The relation between BMI and FM in children is influenced by factors such as age, sex, pubertal status, and ethnicity. In children with cancer, the use of BMI is even more erroneous because weight can be influenced by tumor mass and hydration status. Children with cancer defined as healthy by weight or BMI have been shown to have excess FM and reduced FFM (20–22), so malnourished children may go unrecognized if BMI alone is used to assess for malnutrition. Cancer centers should not use BMI in children with cancer as the sole method of nutrition assessment and should incorporate methods that assess the clinically relevant body composition.

Measurements of arm anthropometry, including upper arm circumference and triceps skinfold thickness, have been used to predict nutritional status in children with cancer (9, 23–27). However, these methods vary as a function of age and body size and are based on several approximations that may limit accuracy and need to be considered. Arm anthropometry is useful as a screening method and for predicting FM, but it is limited in predicting FFM (28, 29). Arm anthropometry is recommended over BMI to identify malnutrition in children with cancer where stunting, tumor masses, and metabolic changes affect interpretation of weight indices, but it is still not a measure of FM and FFM. Further investigation of arm anthropometry against reference body composition techniques in children with cancer should be undertaken in LMICs to develop its potential as a simple technique to identify malnutrition.

Body composition assessment.
Malnutrition is reflected in altered FM and FFM. The FFM contains the metabolically active component of the body, and the preservation of FFM is vital for growth, metabolism, homeostasis, and functional capacity. There is no single in vivo gold standard for the measurement of body composition in children, and only multicomponent models are considered sufficiently accurate to act as criterion methods. Most methods of body composition analysis are indirect and rely on assumptions that have the potential to introduce bias into the results. The use of body composition techniques in children has been explored in detail elsewhere (30, 31). There are several methods available that may be appropriate for use in children with cancer in LMICs, including isotope dilution, DXA, and bioelectrical impedance analysis (BIA). Other methods are valuable in childhood cancer patients, such as total body potassium and air displacement plethysmography, but the availability of these methods in LMICs is currently limited and so they are not discussed further here.

The measurement of body composition using the isotope dilution technique is a well-established methodology in LMICs (32). The isotope dilution technique measures the amount of water in the body, which is an indirect assessment of FFM based on the assumption that body water is only found in the FFM. The isotope dilution technique is established in >70 LMICs and has been used to understand body composition in healthy children and those with acute malnutrition, as well as a reference to validate simple body composition techniques. There have been several studies done in cancer patients using deuterium dilution in HICs to determine body composition (33, 34). However, there is only 1 known study in Mexico that used deuterium dilution to assess body composition in children with cancer (35). With isotope capacity established in many LMICs, cancer centers should collaborate with these facilities to use the isotope method to enhance the knowledge about cancer's impact on body composition, validate simple nutrition methods, and evaluate the impact of interventions on body composition. The advantage of this method for children with cancer is that it is safe, involves no radiation, can be done at bedside or in clinic, requires minimal patient burden, and can be carried out by the clinical staff with limited training. This method is not recommended during intensive treatment phases, in which gastrointestinal symptoms, hyperhydration, or edema may affect the FFM hydration assumptions.

DXA is an X-ray imaging technique for calculating bone mineral density and total and regional body composition with minimal exposure to ionizing radiation (36). DXA is more commonly being utilized to describe the body composition of children with cancer in both HICs and LMICs (37–39). The benefits of DXA include that it is quick and allows the reporting of both regional body composition and bone density. However, it is not the gold standard of body composition and has measurement limitations, including that it is not suitable for field or bedside measures; there is exposure to small amounts of radiation, which limits longitudinal measurements; and FM and FFM are only estimated, not measured, in areas close to bone.

BIA is a body composition method based on the principle that electrical currents flow at different rates through the body depending on its composition. FFM, which is high in water and electrolytes, has minimal impedance, whereas FM contains nonconducting materials that provide resistance to the flow of electric current. BIA is portable, inexpensive, and simple to perform, so it has potential in LMICs for estimation of body composition in cancer patients. However, currently available equations do not provide accurate estimations of body composition in children with cancer (40, 41). New BIA prediction equations specifically developed for children with cancer are needed to allow reliable assessment of body composition to be used in LMICs.

Opportunities should be taken to integrate body composition measures into oncology care to guide clinical decision-making. Any method used to screen for low FFM or excess FM in LMIC cancer centers will need to be predictive of important cancer outcomes, feasible, affordable, and easily implemented within existing clinical workflows. Future studies should validate simple body composition techniques that could be used in LMICs to identify changes in FM and FFM and guide clinical care. A current limitation for the integration of body composition assessment into clinical care is the lack of healthy pediatric body composition reference curves that are region specific. While international efforts continue in collecting reference body composition data, body composition should be assessed against available reference data and, importantly, evaluated longitudinally for each patient.

Understanding the impact of cancer on body composition

Cancer-induced body composition changes may be caused by multiple factors impacting energy balance, including side effects, host tumor response, and altered physical activity. Food intake in children with cancer may be affected by numerous treatment side effects, such as nausea, change in taste and smell, mucositis, vomiting, and pain. A study from Mexico demonstrated that 90% of the children admitted to hospital with cancer demonstrated a feeding-related symptom, such as reduced appetite and fear of feeding due to pain (42). In Turkey, the most common nutritional problems experienced by children were loss of appetite (85.5%), nausea (84.1%), vomiting (81.2%), fatigue (79.7%), and mucositis (66.7%) (43). The host response to tumor also causes a variety of complex metabolic and endocrine changes increasing energy losses. Cytokines, such as TNF-α, IL-1, IL-6, IFN-γ, and leukemia inhibitory factor, may elicit many host changes seen in cancer-induced FFM loss, including loss of appetite, loss of body weight, and the induction of acute-phase protein synthesis (12, 44, 45). Although the resting energy expenditure of children with cancer may be increased due to the metabolic activity, physical activity levels will be reduced during periods of hospitalization and fatigue. Reduced physical and muscle activity in children may contribute to a progressive decline in FFM. The contribution of these different mechanisms to changes in body composition in children will depend on factors such as cancer type and treatment, and it needs to be elucidated further.

There are very few studies in childhood cancer patients assessing the impact of cancer on body composition. In HICs, children undergoing treatment for various cancers appear to have lower FFM and higher FM compared with their healthy peers (21, 22, 46–48). There is less evidence from LMICs on the impact of cancer and treatment on body composition (**Table 1**). At diagnosis, patients in Mexico with acute lymphoblastic leukemia (ALL) had normal body composition (39), but in Romania, patients with a variety of cancers had increased total body water and decreased FM compared with healthy children (49). Longitudinal studies have shown that in Mexico, children with lymphoma had an increase in FM during the first 6 mo of treatment (35), whereas in India, children with ALL had FFM decreases during induction (50). The knowledge of how FM and FFM are affected by the various cancer-related mechanisms is important to guide interventions and ensure clinical outcomes are not affected by poor nutritional status.

Alterations in body composition also persist as a long-term effect of cancer and its treatment. Survivors of childhood cancer in HICs have increased prevalence of obesity (51, 52), with increased FM and decreased FFM (34, 53, 54). Nutritional status alterations and increased metabolic risk symptoms in childhood cancer survivors are supported in limited studies from LMICs (55–57). One study from Brazil showed survivors of childhood ALL had an increase in body fat and an alteration of fat distribution, which was

TABLE 1 Impact of childhood cancer on body composition in LMICs[1]

Reference, year	Country	Cancer type (no. of subjects)	Assessment time points	Assessment method	Body composition findings
Barbosa-Cortés et al. (35), 2007	Mexico	Lymphoma ($n = 8$) Solid tumor ($n = 9$)	After first chemotherapy course; 2 mo; 6 mo	Isotope dilution	Lymphoma group—FM, FFM, and TBW increased during first 6 mo of treatment Solid tumor group—no changes
Jaime-Pérez et al. (39), 2008	Mexico	ALL ($n = 102$)	Diagnosis	DXA	20.5% reduced, 24.5% increased, and 55% same body composition as reference values
Kumar et al. (50), 2000	India	ALL ($n = 25$)	Diagnosis; completion of induction	Ultrasound	56% of patients had reduced FFM and 96% of patients had increased subcutaneous FM over study period
Chincesan et al. (49), 2016	Romania	All cancer types ($n = 43$)	Diagnosis	BIA	Increased TBW and decreased FM compared with controls
Siviero-Miachon et al. (56), 2013	Brazil	ALL survivors ($n = 56$)	At least 2 y post-therapy	DXA	Survivors with cranial radiation had increased FM and abdominal adipose tissue

[1] ALL, acute lymphoblastic leukemia; BIA, bioelectrical impedance analysis; FFM, fat-free mass; FM, fat mass; LMIC, low- and middle-income country; TBW, total body water.

related to cranial radiotherapy (56), but more research about FM and FFM changes in long-term survivors from LMICs is required. As the number of cancer survivors increases in LMICs, it is important that there is evidence supporting their long-term nutritional health needs and minimizing comorbidities.

Due to the scarcity of evidence, research should aim to understand why and how cancer impacts FM and FFM in children with cancer. Whereas in HICs, it appears that cancer treatment decreases FFM and increases FM across the spectrum of treatment, there will be additional factors that influence nutritional status in LMICs. By understanding what cancer-related mechanisms affect body composition, nutrition management can be prioritized to the high-need patients and treatment phases.

Understanding the impact of body composition on childhood cancer outcomes

To ensure that nutrition support is a priority in cancer centers, there must be evidence that body composition has clinical significance. There is emerging evidence in adults that it is the reduced FFM and increased FM, not just weight alterations in cancer patients, that are linked to survival and clinical outcomes (58, 59). However, studies in childhood cancer have predominately only examined weight and BMI and its relation to clinical outcomes.

Underweight children with cancer have been shown to have reduced tolerance to therapy, with more toxicities, longer duration of therapy, treatment delays, and prolonged periods of hospital stays in both HICs (60, 61) and LMICs (9, 62–64). Several studies in LMICs have shown that undernutrition, as determined by simple nutrition measures, is related to increased infections and length of hospital stays in several different cancer types. In patients with Burkitt's lymphoma in Malawi, low arm muscle area was associated with a significantly higher rate of neutropenia, independent of clinical stage of disease, bone marrow involvement, and HIV infection (65). In Bangladesh, ALL patients with lower weight for age were more likely to suffer infections and consequently had longer hospital stays (62). In childhood cancer patients in Iran, there was an association between albumin, prealbumin, and BMI and duration of neutropenic fever and length of hospital stay (66).

Abnormal body weight or size has been shown to reduce survival in both leukemia and solid tumor patients (6, 67–72). In Guatemala, children with ALL who had severely depleted nutritional status were ~2.5 times more likely to die <6 mo from diagnosis (26); this finding was similar to that of a study in Mexico, in which undernourished children were 2.6 times more likely to die during initial treatment (10). In Nicaragua, pediatric oncology patients with malnutrition at diagnosis experienced increased treatment-related mortality (8). In Pakistan, underweight children with ALL were at higher risk of relapse and mortality compared with normal-weight children (71). Although the relation between weight/body size and survival is supported across HICs and LMICs by meta-analyses and review articles (68, 72, 73), several studies have concluded that there is no relation between weight/body size and survival (74–77). The reason for the discrepancy in results is likely due to the different classification of malnutrition based on weight and body size, and this highlights the need for studies to assess the link between FM and FFM and survival in children with cancer in LMICs.

Malnourished children with cancer may experience poor clinical outcomes due to multiple factors, including altered drug pharmacokinetics. Alterations in body composition may affect drug absorption; alter drug protein binding; decrease oxidative metabolism; and reduce glomerular filtration rate, thereby increasing plasma concentrations of drugs and potentially increasing toxicity (78). The FFM compartment is concerned with metabolic activity in the body; therefore, reduced FFM leads to altered drug metabolism. Dosing as per body surface area is dependent on body weight, and children with sarcopenic obesity (increased FM and decreased FFM) tend to receive drug doses that are possibly higher than what their depleted FFM can metabolize (79). Future research in childhood cancer should look beyond weight and focus on pharmacology studies of bioavailability of chemotherapeutic agents as related to FM and FFM and also the implications for treatment outcomes and toxicity.

Current studies linking malnutrition with clinical outcomes in childhood cancer use weight and BMI, and considering the limitations of these simple methods in children with cancer, it must be a priority to establish a link between clinical outcomes and malnutrition using body composition methods. The physiological mechanisms that link body composition with clinical outcomes are multifactorial and not fully understood. Research is necessary to determine if the effects of body composition on clinical outcomes are causal and, more important, remedial with nutritional interventions.

Nutrition support for childhood cancer in LMICs

The primary goals of medical nutrition therapy (MNT) in pediatric oncology are minimizing loss of FFM, promoting appropriate growth and development, and ensuring a good quality of life (80). MNT for children with cancer includes provision of nutritious food, nutrition education, diet modification, supplementation, appetite stimulation, and nutrition support including enteral and parenteral nutrition. As MNT needs to be overseen by a trained health-care professional, capacity building in LMICs is crucial for the successful delivery of MNT for children with cancer.

Increasing oral food intake through provision of food and education.

Ensuring adequate oral intake to meet energy requirements is the preferred method of nutrition support for children with cancer. Providing healthy meals and nutrition education should be standard of care throughout therapy, regardless of nutrition risk. There is a need for organized efforts from hospitals and support groups to provide quality and safe meals for children and their caregivers in LMIC cancer centers. Provision of healthy and balanced meals could be a simple method of maintaining body composition for low-nutrition-risk patients during inpatient and outpatient treatment. Meals for children with cancer should be high in energy, high in protein, and tailored for the individual considering side effects such as taste changes, mouth sores, nausea, and poor appetite.

All children and caregivers should be educated about the importance of good nutrition during cancer therapy, symptomatic management of side effects impacting nutrition intake, and food safety. In a survey of 96 LMICs, only 35% of institutions reported that nutrition education was provided to patients and families (14). Diet education for patients and families in LMICs is complicated by low literacy, limited availability of trained personnel, and a lack of materials (81). To provide successful education for low-literacy patients and caregivers, culturally appropriate instruments and pictorial-based material must be developed; this has been successfully done in several LMICs (82–84). To ensure that food provision and nutrition education are prioritized in LMIC cancer centers, research should be conducted to demonstrate if these low-cost and low-resource measures can effectively improve body composition and clinical outcomes.

Increasing oral nutrition through supplements and drug therapy.

Liquid nutrition supplements are available in LMICs and are commonly used in pediatric oncology to prevent weight loss, increase dietary calories, or as meal replacement. Protein- and energy-dense liquid supplements have been found to be effective in reversing weight loss in malnourished children with cancer in LMICs. A study in Nicaragua reported that supplementation with polymeric formulas resulted in 55% of patients with leukemia and 35% of patients with solid tumors improving their nutritional status or remaining well-nourished (85). In Turkey, protein- and energy-dense oral nutritional supplements (86) and those containing eicosapentaenoic acid (87) were effective for preventing weight loss in malnourished children with cancer. In LMICs, in which commercial liquid supplements are not readily available, homemade shakes made with high-protein and energy-dense ingredients can serve as alternatives.

In LMICs, in which child undernutrition is common, ready-to-use therapeutic food (RUTF) is available and can be used during anticancer treatment to improve the nutritional status of patients. The advantage of RUTF is that it is a ready-to-use paste that does not need to be mixed with water, thereby avoiding the risk of bacterial proliferation in case of accidental contamination. There are commercially available RUTFs, but it can also be locally produced, with the aim of the supplement to increase protein and energy intake through local ingredients. One study on the use of RUTFs in children with cancer demonstrated that a peanut-based RUTF increased weight (88), but whether RUTFs improve FFM is unknown. Research should prioritize investigating if homemade shakes and RUTFs are beneficial for increasing FFM in children with cancer and if their provision should be standard care in LMIC cancer centers.

Chemotherapy-induced nausea and vomiting (CINV) can negatively impact a child's ability to maintain a nutritious diet and should be addressed as a priority in treating children (89). Algorithms can be developed to prioritize interventions based on the emetogenic potential of chemotherapy (90). Although medications often used in HIC cancer centers to address CINV may be cost prohibitive in LMICs, more economical alternatives can be considered while also advocating for the inclusion of antiemetics in essential medicine lists for children with cancer in LMICs (91, 92).

Providing nutrition support with enteral and parenteral nutrition.

Due to lack of trained staff, lack of resources, and high risk of complications, enteral nutrition and parenteral nutrition are not commonly used in countries with limited resources. The enteral route is the safest way of providing nutrition to children with a functional gastrointestinal tract. However, the availability of appropriate nasogastric tubes and pumps is often inadequate in LMICs. Low-resource alternatives for providing enteral nutrition include using suction tubes to administer enteral nutrition or gravity feeding if feeding pumps are not available. Another complication of enteral nutrition in LMICs is the poor availability of enteral feeds and the high cost of commercial enteral formulas. Homemade blenderized diets can reduce cost and can be used with good results in LMICs, especially for children who must remain on tube feeding postdischarge from the hospital. The feasibility, safety, and effectiveness of local blenderized foods in improving body composition in children with cancer in LMICs should be evaluated to provide guidelines for cancer centers.

Conclusions

There are numerous challenges to improving nutritional care in children with cancer globally. The major challenge is that nutrition support needs to be recognized as playing a significant role in improving clinical outcomes for children with cancer so that the provision of nutrition support is prioritized with increased education, funding, and resources. To improve nutritional care in LMICs, we need to provide the evidence for effective interventions that improve body composition and clinical outcomes. The scientific priorities for nutrition and childhood cancer should include *1*) utilizing body composition to represent malnutrition in children with cancer, *2*) validating simple nutrition assessment techniques against body composition methods, *3*) determining the cancer-related mechanisms that impact body composition, *4*) understanding the impact of body composition on clinical outcomes in children with cancer, and *5*) evaluating the effectiveness of nutrition interventions to improve body composition.

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