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The impact of oral nutritional supplementation in children treated for cancer

Uğur Demirsoy [1], Feza Kırbıyık [2], Ali Evrim Doğan [2], Funda Çorapçıoğlu [1]

[1] Kocaeli University, Faculty of Medicine, Department of Pediatric Oncology, Kocaeli, Turkey
[2] Medical Department, Danone Nutricia Specialized Nutrition, Istanbul, Turkey

ORCID ID of the author(s)

UD: 0000-0002-5424-7215
FK: 0000-0001-7933-2814
AED: 0000-0002-9040-2737
FÇ: 0000-0003-3514-084X

Corresponding Author
Ali Evrim Dogan
Medical Department of Danone Nutricia Specialized Nutrition, Besiktas, Istanbul, Turkey
E-mail: ali.dogan@nutricia.com

Ethics Committee Approval
All procedures involving study participants were approved by Kocaeli University Non-interventional Clinical Research ethics committee, Istanbul on 19.06.2019 with session number 1037. Authors state that they have obtained the required informed patient consents prior to the study. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Malnutrition is a dangerous comorbidity in children with cancer that can affect tolerance to treatment modalities such as chemotherapy and radiotherapy. It also adversely affects the treatment outcome and overall survival. It has been known that low Z score of body mass index (BMI) indicates malnutrition. This study aims to underline the effects of oral nutritional supplementation (ONS) on pediatric oncology patients.

Methods: All records were collected from Kocaeli University Hospital, Department of Pediatric Oncology, Kocaeli, Turkey, and analyzed. Weight, height, and BMI status of sixty patients who received ONS with cancer treatment were recorded during visits up to 8 months after the start of ONS. Statistical analyses were maintained on the whole cohort as well as on following tumor sub-groups: CNS tumors (13.3%), lymphoma (18.3%), other tumors (68.3%).

Results: Sixty malnourished pediatric oncology patients (64.6% male, 35.4% female) were included in the study cohort. BMI values of the majority (60%, $P<0.05$) of patients increased after ONS treatment while those of 40% decreased. BMI values also increased in the case of other tumors and lymphoma sub-groups ($P<0.001$ and $P=0.012$, respectively).

Conclusion: This study underlined the benefits of ONS treatment in terms of BMI status among pediatric oncology patients. The recovery rate of nutritional status depends on malignancy, cancer type and location.

Keywords: Pediatrics, Malnutrition, Cancer, Body mass index

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Introduction

Poor nutrition is detrimental for all stages of life including childhood [1] and under-nutrition is linked to lower survival rates among children in low- and middle-income countries [2]. The presence of malnutrition as a comorbidity with severe disease states such as malignancy can critically influence the outcome. The underlying oncologic pathology as well as the adverse effects of treatment regimens such as chemotherapy and radiotherapy lead to weight loss and malnourishment in pediatric oncology patients [3]. Weight loss and malnutrition in cancer is hypothesized to be induced by insufficient energy intake and inflammation [4]. Inadequate energy intake leads to loss of fat mass whereas inflammation mostly leads to loss of muscle mass. An additional risk factor is cachexia in these patients, possibly resulting from depletion of body protein mass [5]. Collectively, these factors affect tolerance to treatment modalities such as chemotherapy and radiotherapy, lead to discontinuation of the treatment more frequently [6-8] and ultimately adversely influence the treatment outcome and overall survival [9, 10].

Body mass index (BMI), a formula based on weight and height, is a widely accepted measurement of nutritional state along with conventional measurements, such as ideal body weight (IBW) and weight-for-height (WFH). It is known that negative and positive Z scores of BMI indicate malnutrition and overnutrition, respectively [11, 12]. BMI is also accepted by World Health Organization (WHO) as a significant and cost-effective measurement for monitoring the nutritional state [13, 14].

Not only under-nutrition but also over-nutrition may result in poor clinical outcomes such as increased rate of relapse and mortality in patients treated for cancer [15]. While survivors of most childhood cancers are at risk for weight loss, survivors of some malignancies such as ALL and brain tumors have been shown to be at risk for weight gain due to the treatment they received for cancer [16].

Enteral feeding is safe and effective in pediatric oncology patients, leads to weight gain and corrects nutritional status. However, the correlation between oral feeding and the magnitude of the benefit in different cancer types has not been fully investigated [17]. This is a retrospective study aiming to demonstrate the probable impact of oral nutritional supplementation (ONS) in BMI scores in children with heterogenous malignancies.

Materials and methods

A retrospective cohort was formed from pediatric oncology patients aged between 0-18 years who were treated for cancer in Pediatric Oncology department of Kocaeli University, Medical Faculty. Appropriate oncology patients were identified by a retrospective scan of the medical records. Study inclusion criteria consisted of oncology patients who received a conventional anti-cancer treatment.

Weight, height and BMI statuses of the patients who received nutritional support along with cancer treatment were followed up for a period of 8 months post-ONS [18]. Tumor sub-groups were organized as follows: CNS tumors, lymphoma, and other tumors with the majority being Wilms tumor, Ewing sarcoma, neuroblastoma, and rhabdomyosarcoma with the addition of less frequent tumor types.

Initially, sixty-five patients were identified from the medical records. Five patients who discontinued treatment were excluded. Patients less than 2 years of age were excluded from the BMI-z score analysis but were included in BMI analysis. Diagnosis of malnutrition was based on weight-for-height (WFH) -2 SD threshold, coherent with WHO. Gender age and adjusted z-scores were calculated using raw BMI values according to growth charts for patients between 2–18 years of age. In the case of measurements belonging to patients <24 months of age, BMI scores were replaced with length-for-weight (LFW) [19].

Ethical Approval

All procedures involving study participants were approved by Kocaeli University Non-interventional Clinical Research ethics committee, Istanbul on 19.06.2019 with session number 1037. Informed patient consents were obtained from the legal guardians of all patients prior to the study.

Statistical analysis

All statistical analyses were maintained by MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013) program. Normality of the data was checked with the Shapiro-Wilk test. Wilcoxon test was used to evaluate the statistical relationship between two dependent non-parametric data sets. Parametric data were assessed with repeated measures ANOVA, followed by Wilks' lambda multivariate test. Bonferroni correction ($P<0.05$) was used in pairwise analysis in repeated measures ANOVA. Statistical significance was evaluated at $P<0.05$.

Results

Study cohort consisted of sixty malnourished pediatric oncology patients (64.6% male, 35.4% female). Statistical analyses were performed on the whole cohort as well as on following tumor sub-groups: CNS tumors (13.3%), lymphoma (18.3%), other tumors (n=41, 68.3%), which included Wilms tumor, Ewing sarcoma, neuroblastoma, rhabdomyosarcoma, and less frequent tumor types.

Mean overall ONS treatment period was 3 months. The BMIs of 36 (60%, $P<0.05$) patients increased while that of 24 patients (40%) decreased after ONS treatment (Figure 1 and Table 1). BMIs mostly increased in patients with other tumors (BMI increase in 24 patients versus BMI decrease in 17 patients, $P<0.001$) and lymphoma (BMI increase in 8 patients versus BMI decrease in 3 patients, $P=0.012$) sub-groups. Despite the insignificant result obtained in the CNS sub-group ($P=0.068$), it showed a p value close to the threshold of significance ($P<0.05$) in terms of BMI improvement (BMI increase in 4 patients versus BMI decrease in 4 patients, $P=0.068$) (Table 2).

Figure 1: Impact of oral nutritional supplementation on body mass index in pediatric cancer patients

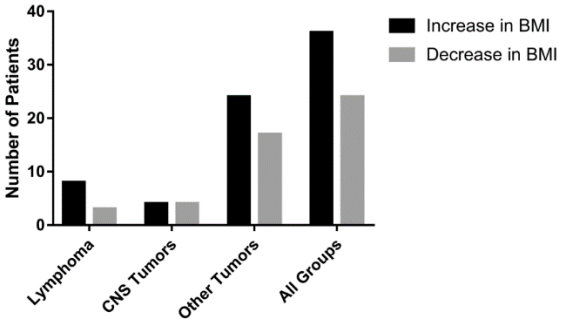

Table 1: First visit versus last visit BMI values of pediatric cancer patients in different tumor sub-groups according to BMI increase or decrease after nutritional intervention

Group	Disease type	Pre-ONS BMI n=60	Post ONS BMI (8th Month) n=60
BMI Increase	Lymphoma, mean (SD)	15.8 (3.1)	16.6 (3.0)
	Med. (Min.-Max.)	15.3 (11.1-20.1)	16.5 (11.7-20.2)
	CNS Tumors, mean (SD)	15.6 (1.9)	16.4 (1.8)
	Med. (Min.-Max.)	15.6 (13.2-18.1)	16.1 (14.5-18.8)
	Other Tumors, mean (SD)	15.5 (2.7)	17.1 (3.6)
	Med. (Min.-Max.)	14.8 (11.7-24)	15.9 (11.9-29.7)
	All Patients, mean (SD)	15.6 (2.6)	16.9 (3.2)
	Med. (Min.-Max.)	15.2 (11.1-24)	16.0 (11.7-29.7)
BMI Decrease	Lymphoma, mean (SD)	18.7 (4.6)	17.7 (4.9)
	Med. (Min.-Max.)	17.9 (14.6-23.7)	17.3 (13-22.8)
	CNS Tumors, mean (SD)	15.7 (2.1)	14.6 (1.9)
	Med. (Min.-Max.)	15.4 (13.7-18.3)	14.9 (12.2-16.5)
	Other Tumors, mean (SD)	17.2 (2.8)	16 (2.9)
	Med. (Min.-Max.)	16.7 (13.8-24.0)	15.8 (11.3-23.3)
	All Patients, mean (SD)	17.1 (2.9)	16.0 (3.0)
	Med. (Min.-Max.)	16.7 (13.7-24)	15.8 (11.3-23.3)
P-value	All Patients	0.037	
	BMI increase, n (%) versus BMI decrease, n (%)	36 (60%) versus 24 (40%)	

SD: Standard deviation, Med: median, CNS: central nervous system

Table 2: First visit versus last visit BMI z-score values and their p values of pediatric cancer patients in different tumor sub-groups according to BMI increase or decrease after nutritional intervention

Group	Disease Type	Pre-ONS BMI n=60	Post ONS BMI (8th Month) n=60	*P*-value
BMI Z-score Increase	Lymphoma, mean (SD)	-0.7 (1.9)	0.37 (1.5)	0.028
	Med. (Min.-Max.)	-0.8 (-3.4-2.3)	0.22 (-1.05-2.6)	
	CNS Tumors, mean (SD)	-1.9 (1.4)	0.46 (1.4)	0.109
	Med. (Min.-Max.)	-2.3 (-2.9--0.4)	-0.27 (-0.49-2.1)	
	Other, mean (SD)	-1.8 (2.2)	-0.9 (2.0)	<0.001
	Med. (Min.-Max.)	-1.3 (-9.1-0.8)	-0.53 (-7.8-1.5)	
	P-value [2]	0.531	0.321	
BMI Z-score Decrease	Lymphoma, mean (SD)	-0.06 (0.9)	-0.72 (1.0)	0.068
	Med. (Min.-Max.)	-0.1 (-1-0.98)	-0.68 (-1.79-0.24)	
	CNS Tumors, mean (SD)	0.48 (0.9)	-1.12 (2.0)	0.068
	Med. (Min.-Max.)	0.95 (-1-1.04)	-0.6 (-3.9-0.55)	
	Other, mean (SD)	-0.17 (1.5)	-1.21 (2.1)	0.001
	Med. (Min.-Max.)	-0.23 (-2.8-1.9)	-1.21 (-5.6-1.67)	
	P-value [2]	0.705	0.953	

SD: Standard deviation, Med: median, CNS: central nervous system, BMI z-score: BMI-for-age percentile

Discussion

Prevalence of malnutrition at diagnosis in children with cancer ranges between 10-50% in industrialized countries and reach levels as high as 50% in developing countries [3]. Furthermore, frequent complications of chemotherapy and radiotherapy such as oral and GI mucositis complicate the attempts to correct the nutritional status via oral feeding and lower the quality of life for the children [20]. The risk of developing these complications depend partly on specific combination of chemotherapeutic agents utilized in the treatment for specific cancers [21] and partly on the specific cancer type being treated [22]. Timely and accurate identification of changes in BMI during treatment will facilitate the implementation of preventive measures and improve the outcome. This is also important as nutritional status at diagnosis is a predictor of weight outcome at final height in patients who received radiotherapy or chemotherapy [23].

Brinksma et al. [24] showed that the greatest changes occur in the BMIs of children under treatment for hematological, solid and brain malignancies within 3 months of diagnosis. Decreased level of activity and tube feeding were both identified as significant contributing factors to increased fat mass percentage (FM) and BMI, respectively. In our study, we observed that significantly more patients have shown an increase in BMI than those who have shown a decrease when treated with oral nutritional supplementation. This finding is in line with previous observations for benefits of enteral feeding in pediatric oncology patients [17]. However, it should be kept in mind that low initial BMI at the time of diagnosis in cancer patients can contribute to relative increases in BMI. This may also be due to exceedingly increased energy intake relative to energy requirements. For example, low level of activity is associated with increased body weight in patients treated with cancer, mainly due to increased FM [27, 28]. Furthermore, in this study, patients with brain malignancies showed an increase in BMI that started immediately after diagnosis; whereas patients with hematological and solid malignancies showed an initial decrease followed by an increase later in the course. Stagnation of growth in height was also a contributing factor to BMI increase. In contrast, other studies reported an increase in BMI from the start of treatment in patients with ALL [18-22, 24, 25] and craniopharyngioma [26].

Protein needs must be met to treat or prevent under-nutrition in these patients while energy intake must be well balanced with the level of physical activity. Corticosteroid use as part of anti-cancer regimens is another contributing factor that should be considered in persons with increased BMI, as corticosteroids change body composition [29-31]. In children with lymphoma whose treatment regimen included corticosteroids, FM increased in the first 6 months of the treatment whereas in patients with solid tumors, FM remained the same [31]. Moreover, in lymphoma, the incidence of oral mucositis and associated gastrointestinal adverse events such as anorexia, diarrhea and dysphagia are high, which negatively effects both the nutritional status and the quality of life of the patient [20].

The reason that we could not detect a change in BMI among patients with CNS tumors may be because change in body composition is more valid for CNS tumors and thus, only measuring body weight and height is not enough; body composition by fat free mass (FFM) and FM should be measured in this group [24, 32]. Low FFM may result in loss of muscle strength, intolerance to chemotherapy, increased susceptibility to infections and poor treatment outcome.

Limitations

The number of patients included in the study is low, which negatively effects the statistical significance of the results. We acknowledge that FFM is an important factor when assessing nutritional status in patients with cancer and absence of FFM is a limitation to our study. As the design of our study is retrospective, some of the missing measurements in patient records such as triceps skin fold thickness (TSFT) that estimates fat mass (FM) and mid-upper arm circumference (MUAC) that estimates lean

body mass (LBM) [2, 5] have limited our results. Tools such as Bio-electrical impedance assessment (BIA) and dual energy x-ray absorptiometry (DXA), which would be more precise in showing these variables, are not currently in use in routine clinical practice in the country.

Conclusion

This study underlined the benefits of ONS treatment in terms of BMI status among pediatric oncology patients. However, it should be noted that the recovery rate of nutritional status depends on the malignancy type and location. Further studies with larger cohorts are required to demonstrate the rate of improvement for each tumor sub-group to estimate the type of the nutritional intervention more fittingly.

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