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ARAŞTIRMA YAZISI / ORIGINAL ARTICLE

The Effect of Neutropenic Diet Adherence on Malnutrition and Duration of Hospital Stay in Children with Acute Lymphoblastic Leukemia

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ABSTRACT

Objectives: Neutropenic diet (ND) was once considered to be important for the protection of patients from neutropenia when chemotherapy continued. The nutritional problems that neutropenic patients are struggling with include decreased quality of life, inadequate nutrition, prolonged hospital stay, gastrointestinal complications, avoidance of food and decrease in cell mediated immunity resulting from vitamin deficiencies. This cross-sectional trial aimed to evaluate the effect of ND adherence on malnutrition and hospital stay.

Material and Method: Between 1st July to 1st December 2017, 60 consecutive children with acute lymphoblastic leukemia treated in University of Health Science Kanuni Sultan Süleyman Research and Training Hospital who were between 1 to 18 years of age and of whom 58.3% (n=35) were boys and 41.7% (n=25) were girls included in the study. Baseline data collection included demographic and anthropometric information (body weight, height, mid upper arm circumference, skinfold thickness); medical history and adherence to ND was evaluated with a dietary survey method with questions asking actual dietary adherence based on the frequency of food consumed within limited food categories.

Results: The adherence rate was 61.7% (n=37) for ND. The hospital stay was actually significantly lower in the low ND adherence (p=0.027). Patients in the ND adhering group had no statistically significant difference in malnutrition risk compared to ND incompatible patients (p=0.524).

Conclusion: ND extends the length of stay in the hospital while it does not affect malnutrition status. Dietary guidelines with fewer limitations for children with cancer would be helpful for improving nutritional status and shortening hospital stays.

Keywords: Acute lymphoblastic leukemia, malnutrition, diet

ÇOCUKLUK ÇAĞI AKUT LENFOBLASTİK LÖSEMİ TEDAVİSİ ALAN HASTALARIN NÖTROPENİK DİYET UYUMUNUN MALNUTRİSYONA VE HASTANEDE YATIŞ SÜRESİNE ETKİSİ

ÖZET

Amaç: Nötropenik diyetlerin (ND), kemoterapi tedavisi alan hastalarda sık görülen nötropeni nedeniyle enfekte olma durumuna karşı korunmalarında önemli olduğu düşünülmektedir. Nötropeniyle mücadele eden hastalarda görülen diyete ait zorluklar arasında; yaşam kalitesinin azalması, yetersiz beslenme, hastanede kalış süresinin uzaması, gastrointestinal yan etkiler, yemekten kaçınma ve vitamin eksikliğinden kaynaklanan bağışıklığın zayıflaması sayılabilmektedir. Bu kesitsel çalışmada, nötropenik diyete uyumun malnutrisyona ve hastanede yatış süresine etkisini değerlendirmek amaçlanmıştır.

Gereç ve Yöntem: 1 Temmuz– 1 Kasım 2017 tarihleri arasında Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi'nde tedavi alan Akut Lenfoblastik Lösemi'li %58,3'i (n=35) erkek ve %41,7'si (n=25) kızlardan oluşan 60 çocuk hasta çalışmaya dahil edilmiştir. Demografik bilgi toplanmış ve antropometrik ölçümler (vücut ağırlığı, boy uzunluğu, üst orta kol çevresi, deri kıvrım kalınlığı), tıbbi öykü alınmış ve ND uyumu kısıtlanmış besin katogorileri içinde bulunan besinlerin tüketim sıklığına yönelik bir anket ile sorgulanmıştır.

Bulgular: Nötropenik diyete uyum oranı %61,7 (n=37) olarak saptanmış, hastanede yatış süresi nötropenik diyet uyumu daha az olan hastalarda anlamlı olarak daha düşük bulunmuştur (p=0,027). Nötropenik diyet uyumu ile malnütrisyon riski arasında istatistiksel olarak anlamlı bir sonuç bulunanamıştır (p=0,524).

Sonuç: Nötropenik diyetin hastanede kalış süresini uzattığı ancak malnutrisyona etkisi olmadığı bulunmuştur. Çocukluk çağı kanserleri için kısıtlaması daha az olan diyet önerileri, beslenme durumunun iyileşmesine ve hastanede kalış süresine olumlu katkıda bulunacaktır.

Anahtar sözcükler: Akut lenfoblastik lösemi, malnutrisyon, diyet

Cancer is the second widespread reason for death in children. Thanks to specific diagnostic procedures and implementations additionally to the continuous improvement of multimodal treatment strategies. In the past decades, the likelihood of treatment being successful has markedly increased (1).

Cancer and its treatment may cause neurocognitive, psychosocial, and physical, symptoms and problems that influence somebody's functions (2). Children with cancer are particularly at risk as childhood cancer emerges during the crucial period of growth and development (3). Therefore, for this population, meeting the increased energy requirement during disease progression is important. Nutrition is a particularly essential factor for children diagnosed with cancer to get the adequate nutrients they require (2). The nutritional requirements of children with cancer differ from child to child and the use of an appropriate dietary regimen before, during, and after therapy may help a child stay healthy and feel better (2).

A perfect emphasis is settled on the accurate balance of the nutrition of patients treated in hematology-oncology clinics (4). The nutritional status of patients diagnosed with cancer may worsen rapidly during hospitalization (3). Childhood cancer patients' nutritional status may further be worsened due to intestinal inflammation and malabsorption (5). As achievements in the therapy of children's cancers continue to proceed, led to ascended survival incidence, the effect of nutrition has become progressively significant in terms of treatment associated morbidity, quality of life and supportive care (6). Maintenance of good nutritional status throughout cancer treatment might improve a pediatric cancer patient's tolerance to chemotherapy and quality of life and decrease their risk of infection (5).

The diagnosis of cancer in children is a life-altering event for themselves and their parents. The cancer disease and its treatments cause changes, particularly in nutrition, appetite and eating habits (2). Besides, patients commonly present with insufficient nutrient intake owing to anorexia, vomiting, nausea, and changes in smell and taste (3).

Current data shows that most commonly experienced problems during cancer therapy are related to malnutrition. Malnutrition in children with cancer might be influenced by some factors; such as hospital environment, alterations in routines, an unfamiliar environment, the necessity of adherence to a special diet, inadequate knowledge about problems other than the treatment and the disease (2).

Throughout the years, many techniques have been in use in order to try reducing the risk of infection in this population such as contact preventions, using masks, preventative antibiotics, environment safety, central venous catheter maintenance, hand hygiene, colony stimulating components, personal sanitation practices, oral care as well as dietary limitations (7). The allegedly; the more contacts a child has in the kindergarten environment, he/she is more likely to develop new infection: Childcare center or kindergarten is considered as a surrogate criterion for determining the incidence of exposure to infection (8). However, research in kindergarten as well as leukemia showed no distinction in incidence, or more frequently decreased frequency of infection in comparison with controls (9).

The attempts to protect from important bacterial infections in the cancer population include dietary limitations (10). Dietary limitations implemented to patients with cancer at risk for neutropenia are called NDs (9). These diets are in a purpose to reduce infections in neutropenic patients, was designed to decrease the entrance of bacteria into the intestine by the limitations of special foods, particularly fresh fruits as well as vegetables (11). The NDs are occasionally called a "low bacterial diet", as cooking devastates the bacteria as well as other organisms related to these foods (7).

Whether slacking up on foodstuff limitations would indeed enhance the quality of life in malignant diseases (7). The current literature about the ND has demonstrated its contradictory models for utilization as it has limited diversity in food groups and there is a necessity to create blood-based dietary guidelines for neutropenic cancer patients (11). Hence, the procedure of several institutions has suspended NDs practices, for example in the Northwestern Memorial Hospital in 2006. Nonetheless, there is a deficiency of clinical proof, some clinics resist using NDs and it is important to be careful in immune-suppressed cases with low microbial-bacterial diets, which results in higher dietary limitations (12). In spite of the limited evidence sustaining the practice of ND in patients treated with chemotherapy or stem cell transplantation (SCT), a lot of centers continue to apply this diet (11, 13, 14). With all these considered; our study aimed to investigate the effect of ND adherence on malnutrition and duration of hospital stay in children with acute lymphoblastic leukemia (ALL).

Material and Method

Ethical considerations

Approval by Yeditepe University Clinical Research and Ethics Committee was obtained with the number KAEK 737 and date 08.06.2017 before the initiation of the study.

Study population

Between 1st July to 1st December 2017, 60 consecutive children with ALL; who were between 1 to 18 years of age and were treated in accordance with ALL-IC BFM 2009 protocol in University of Health Science Kanuni Sultan Süleyman Research and Training Hospital were included. Interviews lasted an average of 20 minutes and were conducted in Turkish. Firstly; the purposes of the study were clarified to the parents and written consent form was received. The study was conducted in hospitalized patients and outpatient chemotherapy setting. Inclusion criteria included age 1 to 18 years, diagnosis of ALL, and being voluntary. Exclusion criteria included the patients who could not tolerate oral feeding and had additional metabolic diseases that required specialized diets.

Data collection

Baseline data collection included demographic and anthropometric information (age, birth weight, breastfeeding duration, sex, body weight, height, mid upper arm circumference, skinfold thickness); medical history (date of diagnosis, risk classification, date of treatment initiation, treatment phases); and adherence to ND.

Nutritional status at diagnosis in children with leukemia was assessed according to different anthropometric indicators weight-for-age (WFA), height-for-age (HFA) and weight-for-height (WFH) and they were classified with National Center for Health Statistic classification, 2000 Centers for Disease Control and Prevention (CDC) growth charts, and the World Health Organization (WHO) malnutrition classification and Screening Tool for Risk On Nutritional status and Growth ($STRONG_{kids}$) were used as indicators of malnutrition (15, 16). Children with a $STRONG_{kids}$ score of 0 were classified as being at low risk for malnutrition, those with a score between 1 and 3 were at moderate risk, and children with a score ≥4 were considered at high risk for malnutrition. According to WHO classification, patients were categorized as underweight, severely underweight, stunted and severely stunted, and wasted or severely wasted according to WFA, HFA, and WFH/BMI anthropometric indicators, respectively, and percentile ranged from ≥-2 to – 2.9 and ≥-3 (16).

The following variables were included as covariates in the initial model: age at diagnosis (1–6, 6.1–12, and >12 years), sex (girl/boy), treatment phase (Protocol IA, IB, Protocol M, (HR1–1, HR2–1, HR3–1, HR1–2, HR2–2, HR3–2 for high risk group), Protocol II, ALL-IC BFM 2009 protocol (standard/intermediate/high). Protocol I'A is designed for the induction therapy of SR patients with BCP-ALL only, whereas Protocol IA should be used for induction in all the others. The protocol included 3 phases, induction phase:'The protocol included 7-drug regimen for 6 weeks. Protocol IB; all SR patients will have it as early intensification. It starts on day 36 of protocol I'A or IA. The protocol included a 7-drug regimen for 4 weeks. Protocol M; as it was used in ALLIC 2002, this treatment element, with a period of 56 days, is designed for consolidation therapy of both SR and IR patients with BCP ALL (17).

Calibrated body composition analyzer (Tess 300 kg, model no: pfhlcd) was used for weight and height measurement. The food record was measured using the 24-hour diet recall method. This method and format have been validated in men, women, and children (11).

Risk group determination

Patients were stratified into 3 risk groups according to the ALL-IC BFM 2009 protocol risk criteria (17). The standard risk (SR) group was defined as aged more than 1 year and less than 6 years, with an initial white blood cell (WBC) count of <20.000/mm^3 and peripheral leukemic blasts <1.000/mm^3 on day 8 and minimal residual disease (MRD) <0.1% on day 15. The high-risk (HR) group was defined as patients with t (9; 22), or t (4; 11), or hypodiploidy ≤45 chromosomes, peripheral leukemic blasts ≥1.000/mm^3 on day 8 and MRD >10% on day 15. WBC >100.000. All patients with T-cell or pre– B-cell ALL that did not meet the SR or HR criteria were considered intermediate risk (IR) patients (17).

Survey

The survey consists of four parts; Part 1 contains the demographic information, risk group of ALL, birth weight, duration of breastfeeding, common nutritional problems and duration of hospitalization; Part 2 is about the patient's adherence to ND which consists of 13 questions (survey); Part 3 (survey) is about the malnutrition screening tool and Part 4 is a 24-hour dietary recall. Daily food intake was measured with the '24 hour recall' technique for three times. Those three days consisted of two weekdays and one day on the weekend. In this measurement period, measurements were taken based on the last 24 hours and all food and beverages consumed by the participants were recorded. The average daily consumption of energy and nutrients has been identified with the food consumption obtained by the '24-hour recall' method by evaluating with BeBis v3.4 (Nutrition Information System version 3.4 for Windows) software. Average daily consumptions were compared with recommended daily amounts of nutrients (RDA) of the Food and Nutrition Institute of the United States Department of Health (18). The survey was developed by a pediatric hemato-oncologist and dietitians from a modified article by Lehrnbecher et al. (19). Patients were questioned regarding hospital admissions and the duration of hospital stay; however, the researchers verified all admission information via hospital database review. No compensation was offered for participation and survey responses were anonymous.

Neutropenic diet adherence

ND adherence was measured with a dietary survey method. Questions were asked about actual dietary adherence based on the frequency of food consumed. The adherence rates were determined for participants with respect to each of the food category limit. Qualitative and quantitative analyses were performed on the data collected during the exit interview to determine the adherence of the ND recommendation provided for participants.

The adherence score was based on thirteen questions related to diet limitation. Each question regarding frequency of consumption was given a score of 0 (lowest score) to 2 (highest score). "Food restriction score" is a semi-quantitative scoring system ("always prefers", 2 points; "sometimes prefers", 1 point; "certainly does not prefer", 0 points) and calculated using a triple answer option on 13 questions. These factors are evaluated through the compatibility of a general adherence score (total score, with answers, normalized in questions). A score of more than 35% of the scores indicates incompatibility (19). As the ND adherence decreased, the score increases.

The sensitivity analysis that was performed to further evaluate the effect of the included tap water by deleting it from the analysis, was powerful.

Statistical analysis

Statistical analysis was conducted with SPSS 22 for Windows (IBM Corp. 2013). Descriptive statistics were initially carried out to determine the population's demographic characteristics. Demographic parameters were summarized as means and ranges for continuous variables, or frequency and percentages for categorical variables. Comparisons between categorical variables were carried out using the chi-squared test as appropriate. The rates of adherence were described with point estimates and 95% confidence intervals (CI). Differences between groups were analysed by paired t-test and student t-test. Bivariate associations between variables were assessed by Pearson's correlation test. A probability value ≤0.05 was considered as the criterion of statistical significance.

Results

Of the 60 patients, 35 (58.3%) were boys and 25 (41.7%) were girls, with a boy to girl ratio of 1.4:1. The median age of the population was 8.3±4.8 years: the mean age of boys was 9.0±5.0 years (range, 2.9 to 17 y) and the mean age of girls was 7.2±4.3 (range, 2.9 to 18.3 y). 40 (66.6%) children were younger than 10 years and 20 children (33.3%) were 10 years or older. A total of 35% (n=21) were diagnosed before 5 years of age. In our cross-sectional study, patients had a mean birth weight of 3.2 kg (range 1.8–4.7 kg) and patients had a mean breastfeeding duration of 19.7 months (between 2–54 months) and breastfeeding frequency was slightly higher in boys (57.7%) than in girls (42.3%). Patients had a mean hospitalization duration of 94.5 days (range 14–228 days).

The number of patients with anthropometric criteria weight and height under 10 percentile or below normal range at oncological treatment is 25%, 13.3% respectively. Mid-upper arm circumference measurement was allowed in 23 patients and skinfold thickness in 20 children. The number of patients with the mid-upper arm circumference anthropometric criterion under 10 percentile or below normal range at oncological treatment is 15%.

According to the ALL-IC BFM 2009 risk classification, 7 patients (11.7%) were defined as standard risk, 31 patients (51.7%) as intermediate risk as well as 16 patients (26.7%) as high risk. 3.2% of the boys were SR, 58.1% were IR, 38.7% were HR and 26.1% of the girls were SR, 56.5% were IR, 17.4% were HR. There were notable differences between the genders in the distribution of ALL risk groups (p=0.025). The least common risk class in boys is SR (3.2%), the least common risk class in girls is HR (17.4%). There were notable differences between the age in the distribution of ALL risk groups (p=0.001). In the analysis, with using birthweight <2500 g as a reference, having a birthweight ≥2500 g was not associated with an increased risk for the development of ALL risk groups. Similarly, we did not find any association with an increased risk for the development of ALL risk groups when a birthweight ≥4000 g was considered. There were no statistically significant differences observed between the risk of ALL regarding breastfeeding frequency (p=0.092) (Table 1).

Table 1. Patient distribution according to the ALL-IC BFM 2009 risk classification

	Standard risk		*Intermediate risk*		*High risk*		*p*
	n	*%*	*n*	*%*	*n*	*%*	
General	7	13	31	57.4	16	26.7	
Gender							0.025*
Girl	6	26.1	13	56.5	4	17.4	
Boy	1	3.2	18	58.1	12	38.7	
Age (year)							0.001*
1–6	7	26.9	17	65.4	2	7.7	
>6	0	0	14	50.0	14	50.0	
Birth weight (kg)							0.510
<2.5	1	12.5	5	62.5	2	25	
≥2.5	4	10.5	23	60.5	11	28.9	
≥4	2	40.0	2	40.0	1	20.0	
Breastfeeding duration (month)							
0–6	0	0	3	11.1	4	30.8	
7–12	1	16.7	5	18.5	0	0	
13–18	0	0	4	14.8	2	15.4	0.092
19–24	3	50	8	29.6	6	46.2	
>24	2	33.3	7	25.9	1	7.7	

*p<0.05 is accepted as statistical significance.

The adherence rate for the ND was 61.7% (n=37). Girls were found to be more adhered to ND compared to boys, but there was no statistically significant difference between genders (p=0.083). The correlation analysis of age was actually significantly lower in the ND adhering patients compared to the ND incompatible patients (r=0.377, p=0.003). Patients in the ND adhering group had no statistically significant difference in malnutrition risk compared to ND incompatible patients (p=0.524) (Table 2).

The ND adhered children were younger than incompatible children (p=0.047). The average age of ND adhering patients was 6.8 years (range=2.9–17y). The average age of incompatible patients was 10.5 years (range=3.3–18.3 y). Results for hospitalization duration days showed that it was actually significantly higher in the ND adhering patients compared to the ND incompatible patients (p=0.027). There was a negative correlation between hospitalization duration and ND adherence score (r=-0.310, p=0.016). Mean initial treatment weight was 22.7±15.3 kg and 39.9±24.0 kg, current mean weight was 24.0±15.3 kg and 40.2±22.6 kg in ND adhering and incompatible patients, respectively. Patients in the ND adhering group had a significant difference in weight compared to ND incompatible patients (p=0.001). In a univariate analysis, factors significantly influencing ND adherence included age and hospitalization duration (p=0.003, p=0.027; respectively). Recommended Dietary Allowances (RDA) express the daily average amount of a nutrient that is considered sufficient to satisfy the needs of children. Regarding RDA, ND adhering children received an average of 79% of the recommended amount of energy and ND incompatible children received 70.1% of the recommended amount of energy. There was no statistically meaningful significant difference (p=0.308) (Table 3).

Table 2. Distribution rates of patients according to the ND adherence

	Adhering Patients (Score=0–9)		*Incompatible Patients (Score=9.1–26)*		*p*
	n	*%*	*n*	*%*	
General	37	61.7	23	38.3	
Sex					
Girl	18	72.0	7	28.0	0.083
Boy	19	54.3	16	45.7	
Age					
1–6 y	21	75.0	7	25.0	0.047*
>6 y	16	50	16	50	
Malnutrition Risk Groups					
Moderate Risk	27	64.3	15	35.7	0.524
Severe Risk	10	55.6	8	44.4	

*p<0.05 accepted as statistically significant.

Table 3. Comparison of ND adhering and incompatible patients (mean ± SD)

	Adhering patients	*Incompatible patients*	*p*
Age (years)	6.8±4.0	10.5±5.1	0.003*
Body weight (kg)	23.9±14.4	40.2±22.6	0.001*
Hospitalization duration (days)	105±51.2	77.7±33.0	0.027*
Comparison of RDA (%)	79±30.2	70.1±36.4	0.308

*p<0.05 is accepted as statistically significant.

ND adhering patients failed most often to adhere to the limitations concerning dried fruit (50% of total children) and sweet and coloured chewing gum (41.7% of total children). There was a trend toward a difference in the consumption of dried fruit (p=0.015). On the other hand, sweet and coloured chewing gum was not statistically significant.

Patients on the ND most often succeed to adhere to the limitations concerning tap water (98.3%), unpackaged milk and milk products (80%) as well as unpacked sugar and products (88.3%).

Moderate and severe malnutrition risk at diagnosis was 70% and 30%, respectively. Children in the 1–6 age range were in the high risk group at a percentage of 22.2%, and 77.8% of children older than 6 years were in the severe risk group. The risk for malnutrition was significantly associated with age, with a higher risk in older children (p=0.013). There was no significant difference between the malnutrition risk classifications and hospitalization duration (p=0.291). Of the 70% in moderate malnutrition groups who had ALL diagnosis, 10.3% had SR, 25.6% had IR, and 1.3% had HR according to the ALL-IC BFM 2009 risk classification; of the 30% in severe malnutrition groups, who had ALL diagnosis, 20% had standard, 40% had intermediate, and 40% had high risk according to the ALL-IC BFM 2009 risk classification. We found no significant difference between the ALL risk classification rates of malnourished and adequately nourished groups (p=0.310). The most common nutritional problems children experienced were like 35% had a loss of appetite and 40% had none. There was a correlation between the risk for malnutrition and common nutritional problems but it was statistically insignificant (p=0.059). Mid-upper arm circumference and skinfold thickness were not significantly associated with the risk of malnutrition (p>0.05). There were no statistically significant differences observed between the risk of malnutrition regarding breastfeeding frequency (p=0.411) (Table 4).

Table 4. Distribution rates of patients according to the malnutrition risk

	Moderate risk		*Severe risk*		*p**
	n	%	*n*	%	
General	42	70	18	30	
Age					
1–6 y	24	57.1	4	22.4	0.013*
>6 y	18	42.9	14	77.8	
ALL risk classification					
Standard risk and intermediate risk	29	70.4	9	60.0	0.310
High risk	10	25.6	6	40.0	
Common nutritional problems					
Loss of appetite	13	61.9	8	38.1	
Nausea-vomiting	3	75.0	2	25.0	
Oral mucositis	1	20.0	4	80.0	0.059
Over nutrition	3	100	0	0	
None	21	87.5	3	12.5	

*p<0.05 is accepted as statistically significant.

In our study, 47.3% of the food records which were analysed did not achieve the recommended daily intake of energy. In addition, 52.5% of the analysed food records did not achieve the recommended daily intake of carbohydrates, 70% of fat and 53.3% of protein.

Discussion

Given that ND does not show a lower microbiological burden and implements various dietary constraints, it results in low nutritional quality, compared to the consumption of a regular diet prepared with good hygiene care in pediatric cancer cases (20). There is little and limited evidence about the benefit of the use of an ND for newly diagnosed acute leukemia (21). Besides the lack of evidence related to ND, there may be adverse effects on the limitation of foods in children diagnosed with cancer. Particularly, in the context of gastrointestinal toxicity induced by chemotherapy including nausea, vomiting, and mucositis, food unwillingness and alterations in smell and taste, strict dietary guidelines may also endanger the nutritional status and quality of life of children with cancer (8). Paltiel et al. (22) showed no remarkable differences between genders in the distribution of nutritional status (22). We also did not find a significant difference between boys and girls regarding nutritional status.

A study reported that the most notable feature is the increase of the "acute lymphocytic leukemia"peak in children between the ages of 2 to 6 (9). The Surveillance, Epidemiology and End Result (SEER) at diagnosis of ALL reported a peak incidence at ages 2–3 (23). Ladas et al. (24) found a childhood ALL predominance at younger age at diagnosis (72%, ≤8 years old) (24). According to our data; there were notable differences between ages at diagnosis in the distribution of ALL. The risk categorization and age distribution were similar to those recorded worldwide. According to our data, there were remarkable differences between genders in the diagnosis of ALL. Unlike, in the United States, ALL is less widespread in girls than in boys

(25). Similarly, Ladas et al. (24) reported that the demographics included a slight boy's predominance (56%) with childhood ALL (24).

In pediatric acute lymphoblastic leukemia, the effect of body mass index (BMI) on the outcome of the patient has been reported to be contradictory. The spreading of the Western lifestyle and diet causes a clear rising in the incidence of childhood overweight and obesity. Obesity is related to overexpression of insulin and insulin-like growth factor I and II, which can affect both leukemia induction events and the phase of the disease (26). Results show that obesity is a factor commonly encountered in pediatric oncology, with significantly increased percentages of obese patients, especially among older children (27). According to WHO reports, in 2016, children and adolescents aged between 5–19 were overweight and obese 18.5%, 7%, respectively. Our results showed that 13.6% and 6.8% of the children were overweight and obese, respectively. Research have (or A research has) shown that a higher BMI is positively related to both the prevalence of leukemia and leukemia linked mortality, in adults. In children, discussion continues about whether childhood obesity may similarly influence leukemia treatment and survival (26).

With regarding to ALL, substantially more literature has not found a relationship between ALL risk and breastfeeding as well as breastfeeding duration. Results from previous studies showed that length of breastfeeding greater than 6 or 12 months has been founded to have a protective effect (23). However, there are studies in the literature that do not support this hypothesis. A number of studies have investigated the relationship between childhood leukemia risk and breastfeeding with inconsistent consequences; however, the common idea suggests a protective effect (28, 29). A case study found that breastfeeding for longer than 6 months had a protective influence on Hodgkin Lymphoma (HL) but not on ALL and Acute Myeloid Lymphoma (AML) (29). In studies investigating the relationship between early childhood nutrition forms and breastfeeding with the risk of childhood ALL, breastfeeding duration was not found to be related to the risk of ALL (28, 30). In our cross-sectional study, we did not find a correlation between breastfeeding and ALL risk.

The birth weight is not only impacted by genetics but also by the exposure to some intrauterine environment factors as well, it is assumed to be related to acute leukemia in children. However, more recent research has demonstrated that accelerated fetal growth is more decisive in childhood leukemia rather than high birth weight (31). The results demonstrate a moderate relationship between relatively convenient birthweight and AML and for ALL. The birth weight higher than 3500 g is a risk factor for ALL and AML and in addition to, the results of birth weight >4000 g were associated with an increased risk for ALL (32). According to epidemiological studies resulted in an increased prevalence of leukemia and cancer in diabetic patients and high birth-weighted children (26, 28). A study found that low birth weight was not related to ALL, but to AML (33). Similarly, we did not find any association between ALL risk groups and a birthweight ≥4000 g.

Previous studies have found that children with low weight or overweight have worse results than well-fed children in the diagnosis (34, 35). But, according to a study result, no relationship was observed between malnutrition at diagnosis during the first 3 and 6 months of treatment (15). Our findings showed no significant difference between the ALL risk classification and malnourished risk categories. A study result found that no association between malnutrition and hospitalization duration in ALL patients (36). Our results supported this study.

In the study by Sala et al. (33), 57% of patients were severely malnourished according to an algorithm based on arm anthropometry (33). Our results showed no correlation between arm anthropometry and malnutrition risk. This could be caused by the study population number, technical difficulties and differences of arm circumference measurements.

Children with cancer explained that food was less pleasant to them because of their decreased appetite, alterations in smell and taste perception, emetogenic chemotherapy, as well as limitations in food selections. Dietary limitations enforced by the medical personnel also limited the possibility of children to take pleasure in food (37). Furthermore, applying those diet limitations in some cultures may cause an exclusion for a critical part of daily food intake in which vegetables, fresh fruits and uncooked meats, are frequently consumed. The ND types are limited, intervene with the patient's common food selections, as well as thereby have the possibility to bring about insufficient nutrient consumption throughout chemotherapy (7). Moreover, more dietary limitations bring out higher nutritional risk as well as enhancement of the requirement of nutritional support, hence raise the costs as well as the nutritional risk for the patient. As the patient's diet is limited, malnutrition risk increases. Hence, there can be a greater need for nutritional supplementation (12).

According to the current literature, social isolation for infection risk as well as limited activities as a result of a special diet are distinctive to the children with cancer and also isolate their lives from the environment of other healthy children (37). Additionally, the germ-free surroundings, as well as intestinal purification, were suspended from universal practice for many causes including high cost, adverse effect on the quality of life and severe side effects (11).

The nutritional pattern of the hard ND was found to be lower in vitamin C as well as fiber compared to the regular diet, thereby it is thought to be symbolizing low nutritional insufficiency like fresh fruits as well as vegetables that are limited in ND (20). The cooking methods may also trigger nutritional deficiencies and a diet with poor nutritional quality (20). Vitamin C (ascorbic acid), with its significant characteristics as an antioxidant, is one of the most degraded nutrients in cooked fruits and vegetables. The limitation of vegetables and fruits may impair the fragile balance of the intestine flora and enhance the risk of bacterial translocation and overgrowth (38). In addition, dietary fiber may aid in increasing immune functions in cancer patients by reducing bacterial translocation and maintaining gut flora (7). One can agree that the inclusion of raw fresh fruits and vegetables may virtually be beneficial, as they are a perfect source of dietary fiber. Fiber can be considered as a helpful dietary ingredient for cancer populations. Insoluble fibers have a strong relationship with decreased prevalence of constipation and improved intestinal transit, as well as soluble fibers might help controlling diarrhea and enhance immune function (10).

Many patients define their weight and appetite as factors within their controls, and the foodstuffs are seen as a nutritious and relaxing field of life. Food may also be a source of relish and specific limitations may aggravate sensitive emotional states (12). Disclaimer of desired foodstuffs, for example, fresh fruits and fast food may result in decreased adherence to ND (11). Patients with cancer diagnosis are facing many stressors, an unknown future and fears, so removing ND limitation may make patients feel more powerful to gain control over a very critical effect of their lives (10).

The participants declared that they had the most hassle owing to the limitation of fresh fruit as well as adherence to the diet took too much time (11). Some of the reasons that the ND is found to be unimplementable for a long time include 'take out foods' and 'too much to do' (11).

Braun et al. (13), conducted a study in 2014 in which 57% of pediatric oncology physicians reported implementing the ND at their institution, 40% of the physicians reported they do not practice the ND and 3% did not know (13). According to our study with 60 pediatric ALL diagnoses of patients showed that; 37 children (61.7%) adhered to the rules of the ND while 23 children (38.3%) did not obey the rules of ND. Patients on the ND reported difficulties adhering to the list of food limitations (10).

Patients on ND usually did not obey to adhere to the limitations regarding take-out food (2.4%) and raw fruit (2.9%). There were disregarded amounts (<1%) of food consumed in the categories of, raw vegetables, undercooked meats, cold meat cuts and fast food (11). According to our data, ND adhering children usually did not obey to adhere to the limitations regarding dried fruit (50% of total children) and a considerable majority of patients were successful in not drinking tap water (98.3%).

Braun et al. (13), reported that the factors which considerably affect the implementation of ND on girls are; fewer years of fulfilment, larger centers with 150 and more new diagnoses per year, centers that perform allogeneic SCTs as well as academic centers. The analysis consequence with a multivariable logistic regression showed that being an SCT center was the only factor considerably correlated with the implementation of the ND in a univariate analysis (13). Our analysis showed that; girls have been found to be more adhering to ND compared to boys, but we did not find any statistical significance. This may be due to the fact that our study had a limited population.

In a study conducted on adults receiving hematopoietic SCT, those were who treated with ND experienced a noteworthy higher incidence of diarrhea compared to those consuming a standard hospital diet (39). Our patients in the ND adhering patient group had no difference in common nutritional problems compared with ND incompatible patients. In a study, it was reported that the main incidence of death and major infection, the rates of grade 3 to 4 mucositis or diarrhea, the two major outcomes, were alike in patients consuming raw or cooked diets (21).

Gardner et al. (21) investigated the effects of cooked and uncooked diet in pediatric acute myeloid leukemia and showed a weight loss of 5 lbs at the end of induction (21). According to our results; in both of the ND adhering patients and incompatible patients there was no significant weight loss.

Taken together, these studies showed that a limited neutropenic or "low bacterial"diet is described as mutable and does not exactly provide an important advantage to the patients (10). Our findings showed a positive relationship between the ND adherence and hospitalization duration; however, these patients had more malnutrition risk but it was not statistically significant.

There are data investigating the continuous practice of the ND either in outpatient or inpatient cancer populations with infection risk. A trial demonstrated that in population with cancer on ND are at higher risk of infection, particularly following adherence of ND (7). In a study, it is showed that strict ND as well as strict procedures are related to limitations of social contacts (for example school attendance) and limitations of pets at home throughout severe chemotherapy for pediatric AML which do not reduce the incidence of infections. Therefore, alterations in this strict procedure might improve the patients' quality of life without the ascending risk of infectious complications (40). In a prospective multi-centered randomized controlled trial, it has been shown that ND is useless in decreasing neutropenic infections in children with cancer populations (8).

Conclusion

Consequently; the clinical importance in this cross-sectional study is associated with the assessment that adhering to ND gave the multiplicity of adverse effects of cancer and treatments. The primary outcomes included tolerability of the ND adherence and its effect on malnutrition and hospitalization duration. The secondary outcomes are; evaluation of nutritional status; with weight, height, triceps skinfold thickness, mid upper arm circumference, malnutrition, nutritional problems and daily energy intake.

Institutions have supported changeover from the ND to a more standardized opinion of safe food processing to let for a less limited diet in the existence of neutropenia as well as immunosuppression (13). In a trial, it was found that the liberalization of the diet of cancer patients is reasonable and that it is necessary to focus on safe food processing methods by changing the focus to prevent food-borne infections (7).

This study may help to enrich the current literature about the importance of improving dietary guidelines for children with cancer with fewer limitations and without side effects. Allowing patients to follow fewer limited dietary procedures with focusing on safe food processing may enhance interest in food thus increase the intake of protein and calories, resulting in less unintentional weight loss.

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