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The evaluation of changes in body mass index (BMI) of children diagnosed with leukemia or lymphoma before and after treatment in consideration of age at diagnosis and patient's lifestyle**

Ocena zmian wartości indeksu masy ciała (BMI) u dzieci z rozpoznaniem białaczek i chłoniaków przed leczeniem i po leczeniu z uwzględnieniem wieku w momencie rozpoznania i stylu życia pacjentów

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Keywords

body mass index (BMI), childhood cancer treatment, acute lymphoblastic leukemia, lymphomas, patient's life style

Słowa kluczowe

wskaźnik masy ciała (BMI), leczenie przeciwnowotworowe w wieku dziecięcym, ostra białaczka limfoblastyczna, chłoniaki, styl życia pacjentów

Conflict of interest
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S u m m a r y

Introduction. In childhood leukemia and lymphoma survivors, after systemic treatment, a significant increase in body mass index (BMI) was reported. Chemotherapy alone did not cause a significant increase in BMI; however, the addition of the steroidotherapy or prophylactic radiotherapy resulted in a significant increase in BMI.

Aim. The purpose of the study was to assess the changes in the body mass index of children with acute lymphoblastic leukemia (ALL) and lymphomas (NHL) at the time of diagnosis, during remission sustaining therapy or after the end of complex treatment and the analysis of the relationship between the body mass index and lifestyle led by the patients.

Material and methods. The study concerned a total of 173 people: the 82 patients who were treated in the Department of Pediatric Hematology, Oncology and Transplantation in Children's University Hospital in Lublin and a noncancer control group of 91 people who were the healthy siblings of those patients. For each of the participants BMI was calculated as a ratio of weight and height (BMI; kg/m^2). These values were obtained from the database of the department in 2007-2014 at the time of diagnosis ALL/NHL and from information obtained from parents in 2016 based on home measurements or from the last medical examination. The parents were interviewed on a telephone and the interview based on a standardized survey included in the prepared B-W (Body-Weight) Questionnaire.

Results. BMI values at the time of the study were significantly higher than the BMI at the time of the diagnosis. In the age group 0-5 years, 5.9% of children were underweight, 70.6% in the normal range of BMI, 3.9% were overweight and for 19.6% obesity was reported at the time of the measurement. There is a significant statistical difference in BMI at the time of the study between the group of patients aged 6-12 years, and a group of patients aged 13 years and more. The study shows that there are no significant differences in BMI both at diagnosis and at the time of the study between girls and boys. BMI-SDS between patients and their siblings are at a similar level and are within the normal range according to WHO pediatric standards. There were no statistically significant effects of the frequency of physical activity and dietary habits on BMI in patients group.

Conclusions. At the moment of the diagnosis most of the children were in the group of normal range, according to WHO pediatric standards. After the end of the therapy their indicators of physical development of most patients normalized with time, especially BMI. In the group of children under study the average BMI value showed no tendency to obesity.

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S t r e s z c z e n i e

Wstęp. U dzieci z rozpoznaniem białaczki lub chłoniaka, które zakończyły systemowe leczenie, obserwowano znaczący wzrost indeksu masy ciała (BMI). Leczenie obejmujące jedynie chemioterapię nie powoduje takiego wzrostu BMI, ale w połączeniu ze steroidoterapią lub profilaktycznym napromienianiem OUN może prowadzić do znaczącego wzrostu BMI.

Cel pracy. Celem pracy była retrospektywna ocena zmian wartości indeksu masy ciała u dzieci z rozpoznaniem ostrej białaczki limfoblastycznej (ALL) i chłoniaka nieziarniczego (NHL) w trakcie leczenia podtrzymującego remisję lub po zakończonym leczeniu kompleksowym oraz analiza zależności między indeksem masy ciała a prowadzonym stylem życia przez pacjentów i środowiskiem rodzinnym.

Materiał i metody. Badaniem objęto w sumie 173 osoby, w tym przebadano 82 pacjentów Kliniki Hematologii, Onkologii i Transplantologii Dziecięcej USD w Lublinie oraz grupę kontrolną liczącą 91 osób, którą stanowiło rodzeństwo pacjentów. U każdego badanego obliczono wskaźnik masy ciała (BMI) jako proporcję masy ciała i wzrostu. Uzyskano te wartości z bazy danych Kliniki z lat 2007-2014 w chwili rozpoznania ALL/NHL oraz z wywiadu z rodzicami w 2016 roku na podstawie pomiarów domowych lub z danych z ostatniej kontroli lekarskiej. Rozmowa z rodzicami pacjentów prowadzona była telefonicznie na podstawie standaryzowanej ankiety zawartej w sporządzonym Kwestionariuszu do oceny Masy Ciała (Kwestionariusz M-C).

Wyniki. U dzieci po leczeniu ALL/NHL stwierdzono znaczący statystycznie wzrost wartości BMI. W grupie dzieci w przedziale wiekowym 0-5 lat, które zakończyły leczenie, u 5,9% osób stwierdzono niedowagę, u 70,6% prawidłowe wartości BMI, u 3,9% odnotowano nadwagę, a u 19,6% otyłość. Istotne statystycznie różnice w wartościach BMI w badania występowały pomiędzy grupą pacjentów w przedziale wiekowym 6-12 lat a grupą pacjentów w przedziale wiekowym 13 lat i więcej. Z przeprowadzonych badań wynika, iż nie ma istotnych różnic w BMI zarówno w momencie rozpoznania, jak i w momencie badania pomiędzy dziewczynkami a chłopcami. Wartości BMI pomiędzy pacjentami a ich rodzeństwem są na podobnym poziomie, u większości badanych mieszczą się w zakresie normy według pediatrycznych standardów WHO. Nie wykazano istotnego statystycznie wpływu częstotliwości aktywności fizycznej i nawyków żywieniowych na BMI pacjentów onkologicznych.

Wnioski. W momencie rozpoznania waga większości ocenianych dzieci mieściła się w normie według dziecięcych norm WHO. W wyniku terapii onkologicznej stwierdzono znaczący przyrost masy ciała. Z upływem czasu od zakończenia leczenia u większości pacjentów występuje normalizacja wskaźników rozwoju fizycznego, zwłaszcza BMI. W badanej grupie dzieci po leczeniu ALL/NHL średnia wartość BMI nie wykazywała tendencji do otyłości.

INTRODUCTION

The proper physical development is conditioned by the harmonious interaction of exogenous elements: environmental conditions, nutrition, physical activity and the body's internal factors, such as genetic predisposition or the proper function of various organs and systems. Neoplastic disease as a catabolic process interferes with the normal functions of the body metabolism. Nowadays, due to the complex antineoplastic treatment it is possible to achieve 5-year survival rate of 80% in children, and in cases of acute lymphoblastic leukemia (ALL) even up to 90% (1). Due to the modification of chemotherapy programs, it was possible to improve surgical techniques, the use of modern methods of radiotherapy and in some cases – megachemotherapy with autologous bone marrow transplantation (2).

At the same time, along with advances in anticancer therapy there is an increase in the risk of health problems that may interfere with the psychophysical development of patients. Oeffinger et al. state that one third of people treated with anticancer therapy will experience acute or chronic side effects within 30 years from diagnosis (3). Long-term as it lasts on average approx. 2.5 years remission sustaining therapy, with months in the reduction of physical activity can lead to abnormal energy and endocrine balance of the body. The result of that is improper physical development including fatigue, pain, growth and puberty disturbances, tendency to obesity and osteoporosis (4-6). Health problems after treatment extend on cognitive functions, cardiovascular and neuromusculoskeletal systems, but also they can lead to secondary neoplasms (3).

Some authors state that steroid therapy can cause a tendency to excess weight. These abnormalities are usually observed during or immediately after treatment. Physical development indicators especially the body mass index and the rate of growth (so-called catch-up) are normalized with time since the end of treatment (4-6). However, according to CCSS (Childhood Cancer Survivor Study Group) conducted by the American Society of Clinical Oncology, underwent steroid therapy does not affect the male BMI level or affects, but not significantly, the growth in the level of BMI in women (7). In this study there was a comparison between the BMI's in the group of patients treated for ALL in childhood and their unaffected siblings. The CCSS results lead to observation that the effect on BMI

depended on the type of treatment provided. Chemotherapy alone did not cause a significant increase in BMI; however, the addition of the therapeutic radiation to the protocol resulted in a significant increase in BMI of patients compared to the BMI's of the healthy siblings (7).

Another factor that may influence the value of BMI is physical activity. Tseng-Tien et al. state that exercise are beneficial for the treatment of patients with ALL, especially when they are conducted in a hospital setting, where there is a proper frequency and regularity assured (8). Cox et al. also emphasize the importance of physical activity in the treatment process (9). CCSS research shows that regular activity initiated during therapy and continued for years after treatment can modify and prevent late side effects of anticancer therapy (10).

AIM

The purpose of the study was to assess the changes in the body mass index of children with acute lymphoblastic leukemia (ALL) and lymphomas (NHL) at the time of diagnosis, during remission sustaining therapy or after the end of complex treatment and the analysis of the relationship between the body mass index and lifestyle led by the patients.

Following research questions were investigated:

1. Does the history of oncological treatment in childhood affect the body mass index (BMI)?
2. Does the level of BMI of patients after treatment for ALL/NHL significantly differ from the level of BMI of their healthy siblings?
3. Do the patient's lifestyle have a significant impact on the value of BMI of children treated for ALL/NHL?

MATERIAL AND METHODS

Design of the study

The plan of the research has been carried out in several stages. Using the hospital INFO MEDICA database we pre-selected 198 patients who have been treated for ALL or non-Hodgkin lymphoma in the Department of Hematology, Oncology and Transplantation, Children's University Hospital in Lublin in 2007-2014. We chose patients with these two particular diagnoses due to the use of therapeutic protocols that included chemotherapy and steroid therapy.

The following inclusion criteria have been established: 1. The age of child at the time of the study must have been over 6 years due to the compulsory school attendance; 2. The initial measurement of weight and height must have been registered in the INFO MEDICA system during the admission to the hospital of the child with the suspicion of cancer; 3. The capability of telephone contact with a parent; 4. The consent to participate in the study.

We excluded a total of 116 people: 50 of them due to a lack of current phone number, 2 people who did not agree to participate in the study, 46 patients without preliminary measurements of weight and height registered in the INFO MEDICA system, 15 children who at the time of the study were less than 6 years and 3 people who died.

The control group consisted of the healthy siblings of the children who underwent anticancer therapy.

The survey was carried on a telephone. Before the start of the interview the information about the purpose of the study and a request for a consent to participate in the research have been provided. The body mass index (BMI) for each patient has been calculated based on the body weight and height obtained from the INFO MEDICA database registered at the time of diagnosis of a disease entity and at the time of the study on the basis of information obtained from the parents of the patients based on the authors' questionnaire to assess the body weight (B-W Questionnaire). The measurements at the time of the diagnosis were performed in the hospital, while the ones at the time of the study were performed by their parents at home or taken and recorded during the last medical examination. The measurements of the body weight and height of the healthy siblings were made by parents at home. Information about the children were given by their parents.

As an indicator for the assessment of the physical development, the ratio of body weight in kilograms and height in meters were chosen. BMI was adjusted for age and gender providing BMI SDS (z-score) using WHO growth reference data for children aged 5-19 years. For children aged 0-5 years growth charts were used related to the child's age and sex. The obtained BMI values were related to the standards of the World Health Organization (WHO) that divides it into four categories: underweight (< -2SD), normal value, overweight (> +1SD), obesity (> +2SD).

Study group

Finally, the study involved 82 children who were treated for leukemia or lymphoma in the Department of Hematology, Oncology and Transplantation, Children's University Hospital in Lublin in 2007-2014. The standard treatment protocols for ALL/NHL were used. In the study group were not children undergoing stem cell transplantation. The analysis of BMI values involved 39 girls (48%) and 43 boys (52%), and were provided also in three age groups: 0-5 years, 6-12 years, and 13+ years. At the time of the diagnosis the average age of the patients was 6.1 ± 4.2 years. Most of the respondents were from urban centers with more than 25 thousand residents (57%), while the rest from the rural or suburban areas.

The interviews were mainly carried out with the mothers of the patients (94%).

Control group

The control group consisted of the 91 healthy siblings of the patients. The average age in this group was 11.9 years. The analysis of BMI values involved 54 boys (59%) and 37 girls (41%).

Body Weight Questionnaire

In order to assess dietary habits, physical activity of patients, the presence of complications after cancer treatment and approach to physical activity of medical staff a standardized survey based on questions included in the Questionnaire to assess Body-Weight (B-W Questionnaire) has been carried out with the parent of each patient. The questionnaire consisted of 24 questions: 4 questions were related to the siblings of the patient (sex, age, height and weight at the present moment) and 20 questions were related to the patients including 13 closed questions (with answers yes or no) and 7 closed questions with several variants of possible answers. Within these questions 8 were related to eating habits: regularity and quantity of meals, eating fast food and sweets, focus on health while choosing food, counting calories and a frequency of weight measurements. The next 7 questions related to physical activity: participation in physical education classes and in extracurricular sports activities, the number of hours of physical activity a week, and changes in physical functions compared to the period before the disease. In addition, the questionnaire included one question on the presence of complications after anticancer treatment and 4 questions about the approach of medical staff and parents to the physical activity.

Statistical analysis

To compare the studied parameters between the two groups t-test was used. For comparison of the examined parameters among the three groups ANOVA test with Fisher's least significant difference (LSD) test as post-hoc analysis was used. The statistical analysis was performed using STATISTICA 12.5 program. Three levels of confidence limits were accepted: $p < 0.05$, $p < 0.01$ and $p < 0.001$.

RESULTS

The diagnosis of ALL/NHL in children before 6 years of age that is before the compulsory school attendance was established in 68.3%. From the moment of the diagnosis to the time of the survey it had passed on average 5.0 ± 2.0 years. At the time of the study the mean age of the patients was 11.1 ± 4.2 years. Average BMI values in the entire studied population of the children at the moment of the diagnosis of neoplastic disease were 16.4 ± 2.7. The mean body weight was 25.0 ± 16.7 (kg) and the mean height was 115.6 ± 27.6 (cm). In contrast, the mean BMI values at the time of the study in the same children after treatment were 18.7 ± 3.5, with the mean weight of 39.8 ± 17.0 (kg) and the mean height of 141.9 ± 20.5 (cm). However, in the control group that comprised of the healthy siblings, the mean body mass index was 19.85 (tab. 1). There was no significant statistical difference between the mean values of BMI between the groups of children who underwent anticancer treatment and a group of their healthy siblings (fig. 1).

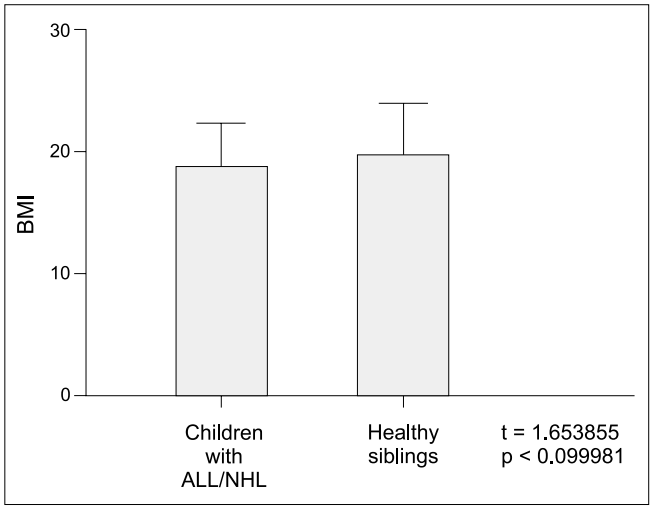

Fig. 1. BMI of the children after treatment ALL/NHL in comparison to their healthy siblings

Tab. 1. BMI of the children with ALL/NHL before and after treatment compared to their healthy siblings

Analyzed group	Children with ALL/NHL	Healthy siblings	p
Sample size	82	91	
% girls % boys	48 52	41 59	
Mean age at the time of study/years ± SD	11.1 ± 4.2	11.9 ± 6.9	
Mean BMI at diagnosis ± SD	16.4 ± 2.7	Not studied	
Mean weight (kg) and height(cm) at diagnosis ± SD	25.0 ± 16.7 115.6 ± 27.6	Not studied	
Mean BMI at the time of study ± SD	18.7 ± 3.5	19.85 ± 4.2	0.0999
Mean weigh (kg) and height (cm) at the time of study ± SD	39.8 ± 17.0 141.9 ± 20.5	45.4 ± 24.3 144.1 ± 32.9	0.0815 0.6011
BMI at the time of study % underweight % normal range % overweight % obesity	 2.4 65.06 20.48 10.84	 7.61 59.78 16.30 16.30	 0.0674 0.9806 0.5042 0.0627

At the time of the study 2.4% of people with the history of ALL/NHL were underweight, 65.06% in the normal range of BMI and in one third, overweight (20.48%) and obesity (10.84%) was reported. In the group of the healthy siblings 7.61% were underweight, 59.78% within normal range of BMI and 32.6% were overweight and obese.

We have demonstrated a significant statistical differences in the value of BMI depending on the stage of the treatment. BMI of children with ALL/NHL at the time of the study, that is after anticancer treatment were significantly higher than the BMI values at the moment of the diagnosis (fig. 2).

There were no significant differences in BMI depending on the gender of the children in both situations: at the moment of the diagnosis and at the time of the study (fig. 3).

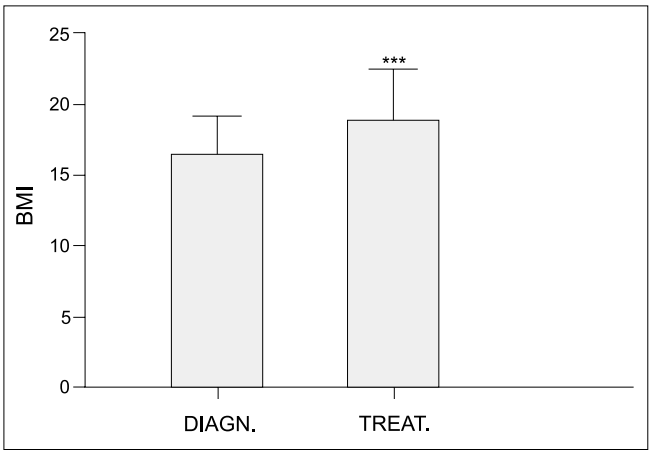

Fig. 2. The value of BMI of the children with ALL/NHL at the moment of diagnosis (DIAGN.) and after treatment (TREAT.)
***There is statistically significant difference lower than p = 0.001 between groups

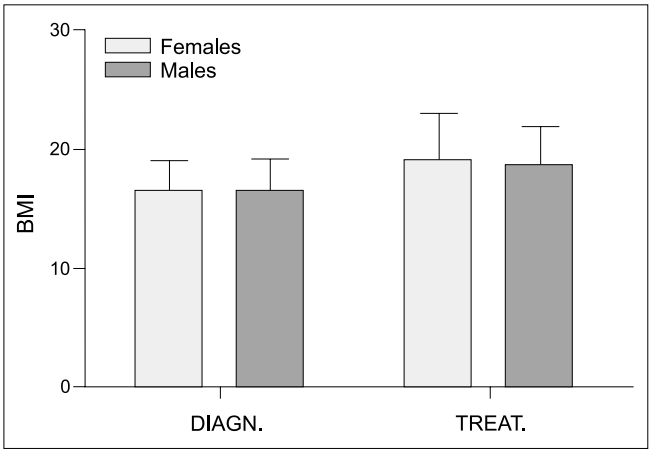

Fig. 3. The values of BMI of the children with ALL/NHL in relation to their gender

In addition, we have conducted the analysis of BMI – SDS values with the consideration of three age groups: 0-5 years, 6-12 years and above 13 years (13+). The lowest average BMI at the moment of the diagnosis was found in the group of children 6-12 years whereas the highest average BMI in the age group 13+. At the moment of the diagnosis most of the children were in normal weight range. The highest percentage of overweight and obese children occurred in 13+ years group, but number of analyzed samples was small. Table 2 shows the mean values of BMI depending on the age at onset of the disease.

In majority of 6-12 years age group (in over than 80%), normal range of BMI was observed both at the time of the diagnosis and at the time of the study. The highest percentage of overweight and obese children was in the youngest age group (0-5 years) of ALL/NHL survivors. In 13+ age group, 12.5% of children were overweight and 12.5% were obese both at the moment of the diagnosis and at the time of the study.

The mean BMI at the study increased in the all age groups comparing to the mean BMI at the moment of the diagnosis. Statistically significant differences are found

Tab. 2. The BMI values of the children with ALL/NHL before and after treatment depending on the age of onset of the disease

Age at diagnosis	0-5 years	6-12 years	13+ years
N patients	51	23	8
T from DIAGN. till TREAT./years	5.2	5.04	3.6
Mean BMI at diagnosis	16.1	15.6	20.7
BMI at diagnosis			
% underweight	5.88	8.70	12.50
% normal range	70.59	86.96	62.50
% overweight	3.91	4.35	12.50
% obesity	19.61	0.00	12.50
Mean BMI at the study	18.7	19.1	22.9
BMI at the study			
% underweight	0.00	8.70	0.00
% normal range	56.86	82.61	75.00
% overweight	27.45	8.70	12.50
% obesity	15.69	0.00	12.50

between the age groups: 6-12 and 13+ years and the age groups 0-5 and 13+ years. Mean BMI values both at the moment of the diagnosis and in the time of the study are significantly higher in the 13+ age group comparing to other groups. In the age group 13+ there was no significant differences in the changes of BMI between the moment of the diagnosis and the time of the study (fig. 4).

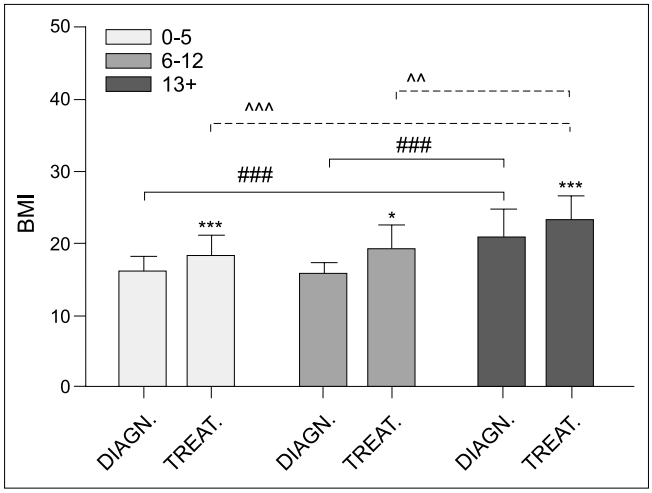

Fig. 4. The values of BMI of children with ALL/NHL in age subgroups with the consideration of the stage of the treatment
Symbols used:
* – comparison between groups: DIAGN. vs TREAT.
# – DIAGN. vs DIAGN. between age groups: 0-5, 6-12, 13+ years
^ – TREAT. vs TREAT. between age groups: 0-5, 6-12, 13+ years
*, #, ^ – p < 0.5, **, ##, ^ ^ – p < 0.01, ***, ###, ^ ^ ^ – p < 0.001

Furthermore, it appears that both the frequency of the physical activity, the eating habits, the quantity and quality of meals have no influence on the level of BMI.

The results of this study show that the presence of complications after anticancer treatment as well as the approach to the physical activity of the medical staff had no effect on the level of BMI.

DISCUSSION

The research so far shows that pediatric patients after anticancer therapy have gained weight regardless of the treatment protocols. After the end of the therapy indicators of physical development of most patients especially BMI normalized with time (6, 11, 12). In our research 65% of the ALL/NHL child survivors had BMI values within normal range. One third of children after ALL/NHL treatment were overweight and obese.

Some of the researchers think that the excess of the body weight during remission sustaining therapy is associated with overfeeding by the parents, decrease of the physical activity and the use of glucocorticosteroids (4, 13-15). After the treatment when the child's normal way of living is restored it's body mass index is normalized with time. Comparison of the mean BMI values of children with ALL/NHL at the moment of the diagnosis with those at the time of the study demonstrated an increase in BMI level for each of the age groups: 0-5 years, 6-12 years and 13+ years.

However, we have not found significant statistical difference in BMI between boys and girls who had undergone chemo and steroid therapy.

Argüelles et al. have demonstrated that children after ALL treatment have a tendency to be overweight (11). However, most of the authors emphasize the need for multiple monitoring for developmental disturbances of patients after ALL therapy in childhood (11). Oeffinger et al. pointed out that too short time of observation does not allow for a complete assessment of the risk of obesity-related disorders in children after anticancer treatment (3). In our study only 10.84% children with the history of ALL/NHL treatment were obese.

A significant relationship was also shown between the age of the onset of the disease and obesity in patients with a history of ALL treatment (1). It was found that the younger the patient was at the moment of ALL diagnosis, the higher was the risk of obesity. In our study, in younger patients at diagnosis the statistically significant highest increase in BMI level was observed after the end of the treatment. After the completion of the treatment in this group of patients the higher percentage of children with obesity was found (15.7%). The statistically significant increase in BMI was observed in each analyzed age group of children with the history of ALL/NHL therapy. The most significant increase in BMI occurred in the oldest group (13+) with the history of anticancer treatment.

There is a steady increase in the number of overweight people in the world (16-18). The decrease in energy expenditure resulting from the lifestyle in combine with unfavorable dietary habits as having snacks between meals or choosing processed products for instance fast foods are the main reasons of such a situation. The analysis of our research has shown however, that there is no correlation between the level of BMI and physical activity levels or dietary habits in sick children. The lack of correlation may be the result of the use of high-calorie diet, as well as the fact of attempting a various forms of physical activity by ALL/NHL child survivors. Preference of lifestyle in families of sick children may be the result of their increased awareness of the effects of the diet and physical activity on quality of life of children after anticancer treatment.

Our study did not reveal any significant differences between the BMI of ALL/NHL child survivors and their healthy siblings. Similar dietary habits, lifestyle and the physical activity levels are supported by parents towards a child patient and his healthy brother or sister. Similar living conditions are an important argument for the recognition of the healthy siblings as an appropriate control group. Van der Sluis et al. also demonstrated no significant differences in BMI of children with ALL who were treated with chemotherapy in comparison to the healthy population (19). In the CCSS study adults who as children were subjected to chemotherapy for ALL also had the levels of BMI comparable with their healthy siblings. The situation was different for patients undergoing radio and chemotherapy. In this group there was a significant increase in BMI of patients in comparison to the group of their siblings (19).

Garmey et al., demonstrated that the treatment with dexamethasone did not result in significant changes in BMI in men and only a small increase in BMI of women (20). In our study, no significant differences in the BMI levels between boys and girls who have undergone ALL/NHL therapy were observed.

CONCLUSIONS

1. The history of ALL/NHL treatment in the childhood had an effect on the body mass index. BMI of the children who have undergone chemo and steroid therapy was significantly higher than the BMI at the moment of ALL/NHL diagnosis.
2. The BMI levels of the patients after anticancer therapy is not significantly different from the levels of the BMI of their healthy siblings.
3. Lifestyle of children who have undergone chemo and steroid therapy had no significant effect on their BMI levels.

Limitations of the study

The absence of contact details and a lack of initial measurement of weight and height recorded in the INFO MEDICA system at the moment of diagnosis excluded 96 patients from the research, which significantly reduced the size of the studied group of patients. Age subgroups analyzes should be interpret carefully because of small number of samples, especially in 13+ age group.

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