Observational Study

Medicine®

OPEN

Effects of medium chain triglycerides on body fat distribution and adipocytokine levels in children with acute lymphoblastic leukemia under chemotherapy

Ru Zhang, MS[a], Jiaqi Chen, MS[b], Haiqing Zheng, MS[c], Yanmei Li, MS[a], Haiying Huang, BS[a], Zhimin Liang, BS[a], Hua Jiang, PhD[a], Jing Sun, MS[d,*]

Abstract

Glucocorticoids used to treat acute lymphoblastic leukemia (ALL) are associated with cytotoxicity and obesity. The aim of the study was to investigate the effects of high-proportion medium chain triglyceride (MCT) on body fat distribution and levels of leptin and adiponectin during chemotherapy of children with ALL.

New-onset ALL children treated at the Guangzhou Women and Children's Medical Center between March 2016 and March 2017 were enrolled. Children were divided into the MCT and control groups. For the MCT group, high-proportion MCT nutrition preparation was added to the diet, while no MCT was added for the control group. The MCT group was further divided into subgroups A and B based on the amount of supplement. Waist circumference, hip circumference, waist-to-hip ratio, bone marrow concentrations of leptin and adiponectin, and leptin-to-adiponectin ratio were measured before and on days 19 and 46 of chemotherapy. Body weight and body mass index (BMI) were measured on admission and discharge.

Waist circumference in the control group increased by day 46 ($P = .047$), but did not change in the MCT group. The BMI of the children in the control group was higher than those in the MCT group on admission ($P = .003$), but not different at discharge. No significant differences in hip circumference, leptin levels, adiponectin levels, and body weight were observed between the 2 groups.

This preliminary study suggests that short-term supplementation of high-proportion MCT nutrition preparation may help reduce the centripetal distribution of adipose induced by the application of glucocorticoids in children with ALL. This will have to be confirmed in future studies.

Abbreviations: ALL = acute lymphoblastic leukemia, BMI = body mass index, Dex = dexamethasone, MCT = medium chain triglyceride, MLLr = MLL gene rearrangement, WBC = white blood cell, WHO = World Health Organization.

Keywords: acute lymphoblastic leukemia, adiponectin, leptin, medium chain triglyceride, obesity

1. Introduction

Acute lymphoblastic leukemia (ALL) is one of the most common childhood malignancies, in which too many immature lymphocytes are released into the circulation. The treatment effectiveness of ALL is generally effective, and the overall survival is approximately 80%.[1] The treatment for ALL includes a combination of chemotherapy drugs over a course of 2 to 3 years.[1–3] Glucocorticoids are among the therapeutic agents used to treat ALL,[4,5] but their use is associated with cytotoxicity and obesity in children.[6,7] Indeed, studies showed high incidence of obesity and increased body mass index (BMI) in ALL survivors.[8–10] Obesity is more pronounced in girls compared with boys and the symptoms for metabolic syndrome (MS) worsen during maintenance therapy for ALL.[11,12] Most child patients are with centripetal obesity, but some of them may return back to normal after withdrawal of glucocorticoids. Nevertheless, higher BMI, fasting insulin, and leptin levels, and lower plasma adiponectin levels may suggest an eventual increase of MS-related morbidity and mortality.[12] Indeed, ALL patients treated with chemotherapy are at an increased risk for cardiovascular diseases.[13,14] Thus, there is a need to address the high rates of obesity and higher BMI in patients with ALL treated with chemotherapy.

Editor: Ahmet Emre Eskazan.

RZ and JC contributed equally to this work.

The Nestle Health Science Project funded this study.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (Ethical approval number: 2017102415).

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

[a] Department of Hematology and Oncology, Guangzhou Women and Children's Medical Center, [b] Department of Pediatrics, Nanfang Hospital, Southern Medical University, [c] Institute of Pediatrics, [d] Department of Clinical Nutrition, Guangzhou Women and Children's Medical Center, Guangzhou, China.

[*] Correspondence: Jing Sun, Department of Clinical Nutrition, Guangzhou Women and Children's Medical Center, Guangzhou 510623, China (e-mail: sunjing1.1@163.com).

Medicine (2019) 98:33(e16811)

Received: 12 November 2018 / Received in final form: 25 June 2019 / Accepted: 22 July 2019

http://dx.doi.org/10.1097/MD.0000000000016811

Medium chain triglycerides (MCT) are easily absorbed in the intestine and are rapidly oxidized to provide energy. Studies in obese mice fed with high-fat diet showed that MCT can lead to reduced body weight and decreased fat deposits when consumed for several months.[15] In addition, MCT lead to reduced food intake and appetite, and loss of subcutaneous adipose tissue in obese men.[16,17] MCT could potentially act as an agent to prevent obesity[18] and to control insulin resistance and the related inflammation.[15,16] The mechanisms of action of MCT are still being studied, but the fast oxidation rate of MCT leads to higher energy expenditure, leading to less lipid deposition. In addition, MCT have a greater satiating effect than long-chain triglycerides, limiting energy intake.[18] In addition, MCT change cells' energetics through mitochondrial biogenesis and by directly inhibiting glutamate receptors.[19] Decanoic acid, which is part of MCT, directly modulated peroxisome proliferator activated receptor (PPARγ), which plays an important role in energy and lipid metabolism.[20] No studies supporting the application of MCT in ALL children undergoing chemotherapy are available to date. Thus, we hypothesized that a high-proportion MCT diet could influence the distribution of body fat and leptin and adiponectin levels during induction chemotherapy for ALL children.

To investigate this hypothesis, we supplemented high-proportion MCT to the enteral nutrition preparation of children with ALL treated with glucocorticoids during remission-induction chemotherapy, and assessed the effects on body fat distribution, body figure, and levels of leptin and adiponectin. In addition, we assessed the body weight and BMI of the children at admission and discharge.

2. Methods

2.1. Study design and patients

This study was a nonrandomized concurrent control trial. Between March 2016 and March 2017, ALL patients who received treatments at the Department of Hematology and Oncology of Guangzhou Women and Children's Medical Center were recruited. The inclusion criteria were: 1 to 10 years of age; newly diagnosed with ALL,[21] and received combination chemotherapy; clear consciousness and the ability to communicate with language, or were accompanied by parent(s); stable disease condition; and patients volunteered to participate, and the parents approved the participation. The exclusion criteria were: acute symptoms (e.g., life-threatening symptoms needing admission to the intensive care unit, such as severe infection/sepsis, acute massive hemorrhage, acute respiratory distress syndrome, acute heart failure, etc.), because of the influence of the drugs given to manage the acute symptoms on metabolism; extreme malnutrition or critical illness; metabolic disorders, such as urea cycle disorder or hyperglycemia; psychiatric disorders or organic encephalopathy; diagnosed or suspected pancreatitis, history of pancreatitis, disorders of the pancreas, or with pancreatic biliary obstruction; required fasting and parenteral nutrition due to the disease condition; or hepatic (aspartate aminotransferase, alanine transaminase, or gamma-glutamyltransferase levels were 5-fold higher than the upper limit of the reference range, according to the Wuhan Conference Classification of liver function), or renal dysfunction (creatinine [Cr] level was 2-fold higher than the baseline level within 48 h). This study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center. All parents of the children signed informed consent forms.

2.2. Nutritional intervention

The children were divided into the MCT and control groups, after agreement with the children and their parents. For each group, professionals who were blind to the grouping provided routine nutrition guidance and education. The 24-hour dietary intake survey was performed daily for 3 consecutive days, then the mean 24-hour intake of carbohydrates, protein, fat, and total energy was calculated, which was then compared with the values for age and sex-matched normal children (i.e., comparing with the energy intake and dietary reference intakes of children recommended in the Dietary Reference Intakes).[22] For the other factors that could impede the nutritional intake of children (such as lack of food variety, too light food to affect appetite, irregular feeding time, eating snacks, and too picky), nutrition guidance was provided to inform the children and parents of the corresponding knowledge and healthy dietary behaviors. If nutrition guiding and education did not improve dietary intake of the children, enteral nutrition preparation was supplemented, and the amount of caloric intake was recorded.

The baseline total caloric intake in the 2 groups were comparable. When the baseline total caloric intake of the children in the MCT group was 25% to 50% lower than the reference level, high-proportion MCT nutrition preparation representing 25% of the reference energy level was supplemented (subgroup A). For the children in whom the baseline total caloric intake was more than 50% lower than the reference level, high-proportion MCT nutrition preparation representing 50% of the reference energy level was supplemented (subgroup B). One spoon of high-proportion MCT preparation was dissolved in 30 mL warm water to obtain a standard solution with a caloric density of 100 kcal/100 mL, in which MCT provided 60% of the total fat. For the patients in the control group, nutrition preparation not containing MCT components was supplemented in the same way as in the MCT group. The compositions of the high-proportion MCT nutrition are described in Supplementary Table 1, http://links.lww.com/MD/D174.

2.3. Remission-induction chemotherapy

For remission-induction chemotherapy, intravenous injection or oral administration of dexamethasone (Dex) (3 mg/m^2, twice per day) was conducted on days 1 to 4. Then prednisone (15 mg/m^2, 3 times per day) was orally administered on days 5 to 28. The dose of prednisone was gradually reduced by half on days 29 to 35 until withdrawal, and then cyclophosphamide, cytarabine, and 6-mercaptopurine were used according to the St. Jude total XV protocol[23] (Supplementary Table 2, http://links.lww.com/MD/D174). The children were discharged after 35 days of remission-induction chemotherapy, and they were rehospitalized for the subsequent chemotherapy after an interval of 2 weeks.

2.4. Data collection

For children of 1 to 3 years of age, Seca416 and Seca376 (Germany, city of branch: Hangzhou, China) were used to measure the length and weight. For children >3 years of age, Seca704 was used to measure the height and weight. The waist and hip circumferences were measured by Seca201. One decimal was used for the results of height, waist circumference, and hip circumference, while 2 decimals were used for the results of weight. The measuring tools were regularly checked to ensure that they were accurate and easy to use, and calibrated before use.

All measurements were conducted by 2 trained nurses according to the Standard Methods for Somatometry issued by the World Health Organization (WHO) in 2008.[24]

For the bone marrow examination, the routine time points for bone marrow aspiration in clinical practices (days 0, 19, and 46) were selected to obtain the specimen. The children were in lateral position, and the bone marrow aspiration was performed from the posterior superior iliac spine. After obtaining 0.5 to 1 mL of bone marrow fluid, centrifugation was performed to obtain the supernatant, which was stored at −80°C.[25] Attending physicians, uniformly trained with rich experience of bone marrow aspiration, performed the bone marrow aspirations.

The RayBio Human Leptin enzyme linked immunosorbent assay (ELISA) kit (RayBiotech, Inc, GA) and the RayBio Human Acrp30 ELISA kit (RayBiotech, Inc) were used to measure the concentrations of leptin and adiponectin, according to the manufacturer's instructions. The specimens were diluted 3000 times before measuring the concentrations of adiponectin.

2.5. Classification of risks

The risk classification was performed according to the CCCG-ALL-2015 protocol, which was modified based on the St. Jude total XV protocol[23] and after considerations specific to the Chinese population.[26] The essential conditions for the low risk were (children with B-ALL were required to meet at least 1 of the following conditions): age ≥365 days but ≤10 years, and white blood cell (WBC) $\leq 50 \times 10^9$/L; chromosome number ≥50, or DNA index ≥1.16; and TEL-AML1 fusion genotype. The ones with 1 or more of the following conditions were excluded: central nervous system leukemia-3 and/or testicular leukemia; t (1; 19) or t (9; 22) gene, MLL gene rearrangement (MLLr), chromosome number <44, or intrachromosomal amplification of chromosome 21 (iAPM21); or minimal residual disease (MRD) ≥1% on day 19.

Children with intermediate risk were required to meet at least 1 of the following conditions: Philadelphia chromosome-positive ALL (Ph+ALL); T-ALL; MLLr-ALL children ≥6 months of age or WBC $<300 \times 10^9$/L; chromosome number <44; and other ALL children not meeting the conditions of low or high risk.

Children with high risk were required to meet at least 1 of the following conditions: children with remission-induction chemotherapy failure (MRD ≥1% on day 46, or immature cells ≥5% for the children without MRD labeling); and MLLr-ALL children <6 months of age and WBC $\geq 300 \times 10^9$/L.

2.6. Primary and secondary outcomes

Leptin and adiponectin concentrations in the bone marrow were measured at days 1 to 4, 19 ± 2, and 46 ± 2. The leptin-to-adiponectin ratio (LAR) was calculated. The waist and hip circumferences were measured. The waist-to-hip ratio (WHR) was calculated. The height and weight of the children were measured before chemotherapy and after 46 ± 2 days. The BMI was calculated. The primary outcome was the change of waist circumference. The secondary outcomes included the changes of hip circumference, WHR, weight, BMI, leptin concentration, adiponectin concentration, and LAR.

2.7. Statistical analysis

All data were analyzed using SPSS 22.0 software (IBM, NY). Continuous data were tested for normal distribution using the Kolmogorov–Smirnov test. Continuous variables with normal distribution are presented as means ± standard division, and were tested using the independent-sample *t* test (intergroup comparisons) or using repeated measure analysis of variance and the Student-Newman-Keuls post hoc test (intergroup comparisons in time). Frequencies (percentage) were used to present the categorical variables, and the Chi-squared test was used for the intergroup comparisons. When the results showed statistically significant difference between the MCT and control groups, the differences between the MCT subgroups A and B were further evaluated. $P < .05$ was considered statistically significant.

3. Results

3.1. Recruitment and baseline characteristics

In this study, 105 children with B-ALL were recruited. Five children were excluded according to the eligibility criteria, including 1 child due to severe allergy to milk proteins, 2 due to severe disease conditions needing intensive care, and 2 due to history of pancreatitis. Another 10 children were withdrawn during the study, including 3 picky eaters who ate too less, 3 who changed to parenteral nutrition for refusing oral diet due to severe oral ulcers, 2 who had variable blood glucose levels, and 2 who changed to other medical nutrition due to intestinal infection or diarrhea. Finally, 90 children were included in the analysis, among whom 60 were in the MCT group (including subgroups A and B) and 30 were in the control group (Fig. 1). Baseline characteristics including age, sex, gestational age, birth weight, and risk classification were not significantly different between the MCT and control groups ($P > .05$) (Table 1). The caloric intake of the patients is presented in Supplementary Table 3, http://links.lww.com/MD/D174. The baseline total caloric intake, nutrition preparation caloric intake, and mean caloric intake through the 46-day chemotherapy were not significantly different between the 2 groups ($P > .05$).

3.2. Waist circumference, hip circumference, WHR, and bone marrow concentrations of adipocytokines

The waist circumference of the children in the MCT and control groups was not significantly different before and on day 19 of chemotherapy, but the difference was significant on day 46 of chemotherapy ($P = .027$). The waist circumference of the children increased in the control group and MCT subgroup A, but decreased in the MCT subgroup B on day 46 of chemotherapy, compared with baseline (Tables 2 and 3). The hip circumference and WHR were not significantly different either between the MCT and control groups or within the same groups during chemotherapy (Table 4).

The level of leptin in both groups was significantly increased on day 19 of chemotherapy. The leptin concentration in the control group was decreased but maintained at a high level on day 46 of chemotherapy, while the leptin concentration in the MCT group was significantly decreased on day 46. The adiponectin concentration in the control group was significantly increased on day 19 of chemotherapy, and then was significantly decreased on day 46 ($P = .027$). The adiponectin concentration in the MCT group was slightly increased on day 19 of chemotherapy, and was slightly decreased on day 46, but with no significant difference. The LAR did not significantly change after chemotherapy compared with baseline. In addition, the adipocytokine concen-

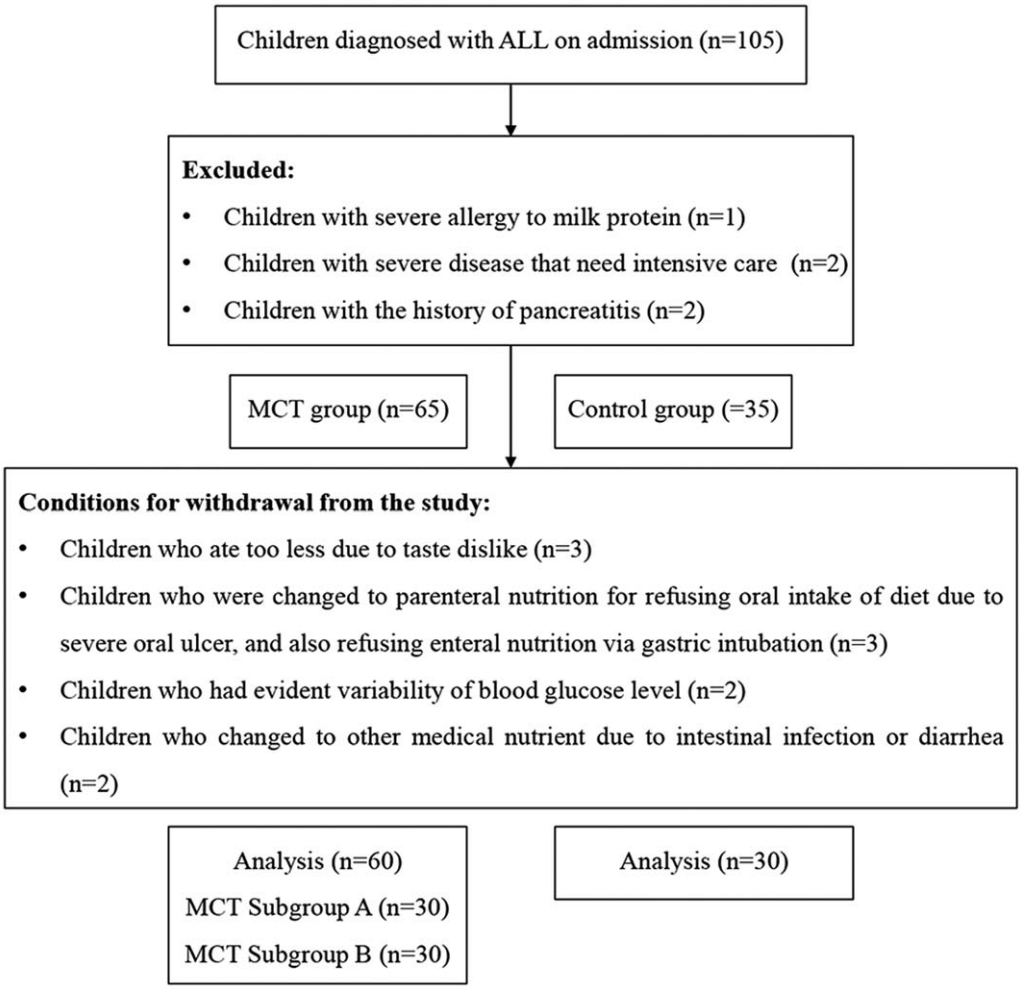

Figure 1. Flowchart. ALL = acute lymphoblastic leukemia; MCT = medium chain triglyceride.

trations and LAR were not significantly different between the MCT and control groups (Table 5).

3.3. Weight and BMI

The body weight of the children was not significantly different between the MCT and control groups during hospitalization ($P = .171$ at admission, and $P = .116$ at discharge). In contrast, BMI was significantly different between the 2 groups at admission ($P = .003$), but was not at discharge ($P = .981$). The BMI was not significantly different between subgroups A and B at admission ($13.80 \pm 0.77\,kg/m^2$ vs. $12.60 \pm 0.54\,kg/m^2$, $P = .069$). The BMI in the control group decreased from $17.13 \pm 2.09\,kg/m^2$ at admission to $15.05 \pm 2.97\,kg/m^2$ at discharge, but this difference was not statistically significant ($P = .905$). The BMI in the MCT group was increased slightly at discharge, compared with baseline, but this difference was not significant ($P = .855$) (Table 6).

3.4. Adverse events

One child in the MCT subgroup B suffered from mild vomiting. After fasting for 1 meal without medication, the vomiting stopped without any subsequent occurrence.

4. Discussion

High-dose glucocorticoids are needed during remission-induction chemotherapy of children with ALL, but glucocorticoids affect the body fat distribution and lead to moon face and centripetal obesity in children. We showed that the use of MCT for 46 days postchemotherapy reduced the waist circumference compared to the control groups, suggesting that MCT could inhibit the adipose tissue centripetal distribution induced by the treatments with glucocorticoids.

The mechanisms of action of MCT are still being studied, but the fast oxidation rate of MCT leads to higher energy expenditure through activation of PPARγ,[20] leading to less lipid deposition. Both animal and human trials suggest a greater satiating effect of MCT compared with long-chain triglycerides (LCT), limiting energy intake.[18] In addition, MCT change cells' energetics through mitochondrial biogenesis and by directly inhibiting glutamate receptors.[19] Modulation of the gut microbiota would also be involved.[27] A number of studies show the effects of MCT on central obesity.[28,29] Nevertheless, the effect of MCT on adiposity in individuals receiving chemotherapy or glucocorticoids is mostly unknown. Additional studies are necessary to examine these effects.

Table 1

Baseline characteristics of the children.

Variable	Control group (n = 30)	MCT group (n = 60)	P
Age (years)	5.26 ± 3.01	4.68 ± 2.93	.614
Sex			.669
Male	15 (50)	33 (55)	
Female	15 (50)	27 (45)	
Gestational age (weeks)	38.00 ± 1.41	39.33 ± 1.57	.219
Birth weight (kg)	3.37 ± 0.72	3.36 ± 0.52	.990
Fever	26 (87)	53 (88)	.820
Anemia	27 (90)	51 (85)	.511
Hemorrhage	17 (57)	32 (53)	.765
Risk classification			.656
Low risk	21 (70)	47 (78)	
Intermediate or high risk	9 (30)	13 (22)	

Data are expressed as mean ± standard deviation or n (%).
MCT = medium chain triglyceride.

Table 2

Waist circumference (cm) change in the control and medium chain triglyceride groups during the chemotherapy.

Group	Baseline	D19 of chemotherapy	D46 of chemotherapy	P
Control group (n = 30)	54.85 ± 10.01	54.83 ± 8.46	61.40 ± 9.79*	.036
MCT group (n = 60)	49.33 ± 6.12	48.88 ± 5.80	50.50 ± 6.55	.801
P	.127	.096	.027	

Data are expressed as mean ± standard deviation.
MCT = medium chain triglyceride.
* $P < .05$, vs. baseline.

Waist circumference and WHR are the most intuitive indicators of body shape, and can be easily measured and calculated. These 2 indicators, in combination with weight and BMI, are generally used to comprehensively assess the body shape, physical development, and adiposity. The BMI of the children was significantly higher in the control group than in the MCT group at admission. BMI reduced in the control group during treatment, but did not change significantly in the MCT group, thus the BMI in the 2 groups was not significantly different on discharge. These findings suggest that intervention with MCT could help reducing body weight loss induced by chemotherapy.

The follow-ups in this study were all conducted on the time points routinely scheduled for the bone marrow examinations, which are also the critical time points for assessing the effectiveness of chemotherapy. The specimens were obtained during routine bone marrow aspiration, and no other time points could be used in this study, in order to reduce the pain in the children. In this study, the bone marrow concentrations of leptin and adiponectin both fluctuated (both significantly increased and then decreased later) during treatments with glucocorticoids in the control and MCT groups. The elevation and decrease of adiponectin levels in the control group are obvious, but they showed relatively stable levels in the MCT group. Although there is no difference between the 2 groups at each time point, it suggests that the levels of adipokines are more stable in the MCT group than in the control group, near the baseline levels, suggesting that MCT has a stabilizing effect on the fluctuation of adipokines caused by chemotherapy. It is true that it is only a hypothesis that needs confirmation.

Both leptin and adiponectin are factors secreted by adipocytes and are associated with the inflammatory reactions of vascular endothelial cells. Barbosa-Cortés et al[25] followed 26 ALL children that had completed chemotherapy for 4 years, and found that 42% and 29% of them had low high-density lipoprotein-cholesterol levels and centripetal obesity. In addition, such metabolic changes were associated with the increase in leptin and LAR. Such high leptin levels may last till adulthood, and are associated with increased body fats. Therefore, despite the fact that these people had normal weight and BMI,[30] they were at higher risk for cardiovascular diseases. In another study in 159 ALL survivors, the patients were followed for 36.8 months, and the rate of overweight/obesity was 26%. Although the leptin and insulin levels were not significantly different from the nonobese group, the serum levels of adiponectin were significantly lower in the obese group.[31] Warris et al[32] observed 44 ALL children aged between 3 and 16 years, and found that the intake of energy, total protein, saturated fats, carbohydrates, and electrolytes

Table 3

Waist circumference (cm) in the medium chain triglyceride subgroups during the chemotherapy.

Group	Baseline	D19 of chemotherapy	D46 of chemotherapy	P
MCT subgroup A (n = 30)	50.15 ± 6.42	49.45 ± 6.17	52.29 ± 6.36	.657
MCT subgroup B (n = 30)	45.25 ± 1.06	46.00 ± 2.83	44.25 ± 5.35	.736
P	.051	.469	.015	

Data are expressed as mean ± standard deviation.
MCT = medium chain triglyceride.

Table 4

Changes of hip circumference and waist to hip ratio in the control and medium chain triglyceride groups during the chemotherapy.

Group	Baseline	D19 of chemotherapy	D46 of chemotherapy	P
Hip circumference (cm)				
Control group (n = 30)	58.10 ± 9.66	57.00 ± 8.97	66.00 ± 14.47	.852
MCT group (n = 60)	52.33 ± 7.82	51.23 ± 7.27	53.24 ± 8.18	.200
P	.147	.169	.054	
WHR				
Control group (n = 30)	0.94 ± 0.05	0.96 ± 0.05	0.94 ± 0.08	.374
MCT group (n = 60)	0.97 ± 0.09	0.99 ± 0.09	0.95 ± 0.07	.789
P	.423	.694	.758	

Data are expressed as mean ± standard deviation.
MCT = medium chain triglyceride, WHR = waist-to-hip ratio.

Table 5

Changes of the adipocytokines in the control and medium chain triglyceride groups during the chemotherapy.

Group	Baseline	D19 of chemotherapy	D46 of chemotherapy	*P*
Leptin (pg/mL)				
Control group (n = 30)	63.22 ± 55.96	200.84 ± 129.90*	126.64 ± 120.20*	.001
MCT group (n = 60)	69.18 ± 68.67	193.49 ± 106.75*	111.40 ± 115.88†	.002
P	.830	.883	.765	
Adiponectin (pg/mL)				
Control group (n = 30)	686.96 ± 322.12	1698.50 ± 1105.14*	835.17 ± 509.48†	.027
MCT group (n = 60)	1259.61 ± 2050.42	1430.48 ± 978.10	1050.91 ± 872.74	.497
P	.419	.548	.511	
LAR				
Control group (n = 30)	0.10 ± 0.12	0.17 ± 0.22	0.17 ± 0.22	.513
MCT group (n = 60)	0.10 ± 0.15	0.16 ± 0.10	0.15 ± 0.20	.287
P	.954	.898	.815	

Data are expressed as mean ± standard deviation.
LAR = leptin-to-adiponectin ratio, MCT = medium chain triglyceride.
* $P < .05$, vs. baseline.
† $P < .05$, vs. D19 of chemotherapy.

during the 4 days of treatment with Dex was significantly higher than the age and sex-matched normal children. In addition to the changes in feeding behavior, glucocorticoids could also evidently reduce the sense of satiation. In addition, leptin and adiponectin levels also significantly increased during Dex treatment. These results were similar to the findings in this study, which underscore the importance of nutritional intervention and dietary education during treatment.

Leptin is a hormone encoded by Ob gene and plays a pivotal role in fat accumulation, appetite regulation, and energy metabolism. It is present in the blood circulation, and its concentration is equivalent to body fat volume and is closely associated with the energy balance. Leptin resistance means that the body is insensitive or nonresponsive to leptin, and even if the level of leptin is elevated, its effective biological effects cannot be achieved, thereby resulting in metabolic disorder in the body, which is characterized by enormous appetite, reduced energy consumption, obesity, and other symptoms. Hyperleptinemia and leptin resistance are present in most obese people.[33,34] Nevertheless, it is true that high leptin levels could be a compensatory mechanism for leptin resistance. This will have to be examined in future studies.

Both malnutrition and obesity are common nutritional issues in ALL children. A pervious meta-analysis showed that overweight/obesity could be found in 29% to 69% of the ALL survival children after treatment,[8] and overweight/obesity could be an independent prognostic factor for ALL children.[35] Comparing with ALL children with normal weight, the obese ones are at higher risk of tumor recurrence, as adipose tissues could provide energy for the proliferating tumor cells. In addition, high insulin levels promote cancer cell growth.[36] In addition, adipose tissues could also affect the pharmacokinetics of chemotherapy drugs and induce resistance to drugs such as vincristine and nilotinib.[37]

In this study, compared with baseline, the leptin levels of the control group were increased on day 46. The leptin levels of the MCT group were increased on day 19 vs. baseline, but came back to the baseline levels on day 46. Regarding the adiponectin levels, the results on days 19 and 46 were similar to baseline in the MCT group, but the adiponectin levels of the control group were increased on day 19 vs. baseline. Based on these statistical results, it could be hypothesized that MCT may have a stabilizing effect on the fluctuation of adipokines caused by chemotherapy. Because of the small sample size and short follow-up, this will have to be tested in a future study.

Table 6

Changes of weight and body mass index in the control and medium chain triglyceride groups on admission and discharge.

Group	Admission	Discharge	*P*
Weight (kg)			
Control group (n = 30)	23.99 ± 16.41	23.38 ± 14.13	.934
MCT group (n = 60)	16.27 ± 8.11	15.86 ± 6.33	.892
P	.171	.116	
BMI (kg/m^2)			
Control group (n = 30)	17.13 ± 2.09	15.05 ± 2.97	.905
MCT group (n = 60)	14.07 ± 0.81	14.36 ± 1.34	.855
P	.003	.981	

Data are expressed as mean ± standard deviation.
BMI = body mass index, MCT = medium chain triglyceride.

5. Limitations

There are some limitations in this study. It was a preliminary study without randomization. The grouping was based on the communication between physicians and parents. Only 1 dose in a given subgroup of subjects and the 2 groups studied were based on the children's metabolic status, preventing an observation of a potential dose–effect relationship. Treatment duration was only 46 days and no follow-up was done after treatment. We did not observe the long-term effects of the nutritional intervention by MCT on bone marrow levels of leptin and adiponectin. We still could not rule out the potential effects of MCT on such adipocytokines, as well as body fats, blood lipid, and insulin. The patients received L-asparaginase, which is known to affect the glycemic and insulin metabolism, but all children in both groups received the same chemotherapy regimen. Further studies are needed to investigate the long-term effects of MCT nutrition preparation on the body fat distribution and adipocytokine levels in ALL children.

6. Conclusions

This preliminary study suggests that short-term MCT supplementation may help reduce the centripetal distribution of adipose tissue or the waist circumference in ALL children postchemotherapy. It may be hypothesized that MCT also has a stabilizing effect on the fluctuation of leptin and adiponectin in ALL children, but this will have to be tested. The long-term effects of this treatment still need to be investigated. Clinicians should pay attention on the nutrition status and long-term quality of life of ALL children, monitor the nutrition status and related index, correct unhealthy dietary behaviors promptly, and reduce the side effects of glucocorticoid treatments.

Acknowledgments

Thanks to the help from the physicians and nurses from the Department of Hematology and Oncology, as well as the staffs from the Central Laboratory of the Guangzhou Women and Children's Medical Center.

Author contributions

Conceptualization: Ru Zhang.
Data curation: Yanmei Li, Haiying Huang, Jing Sun.
Formal analysis: Ru Zhang, Jiaqi Chen.
Investigation: Haiqing Zheng.
Methodology: Ru Zhang, Zhimin Liang.
Project administration: Jiaqi Chen, Hua Jiang, Jing Sun.
Resources: Yanmei Li.
Software: Jiaqi Chen, Haiqing Zheng, Haiying Huang.
Supervision: Zhimin Liang, Jing Sun.
Validation: Jiaqi Chen, Yanmei Li, Haiying Huang.
Visualization: Jing Sun.
Writing – original draft: Ru Zhang, Jing Sun.
Writing – review & editing: Ru Zhang.

References

[1] Cooper SL, Brown PA. Treatment of pediatric acute lymphoblastic leukemia. Pediatr Clin North Am 2015;62:61–73.
[2] Locatelli F, Schrappe M, Bernardo ME, et al. How I treat relapsed childhood acute lymphoblastic leukemia. Blood 2012;120:2807–16.
[3] Rp. Yvette C T, BS P. Advances in the treatment of pediatric acute lymphoblastic leukemia. 2018
[4] Ronghe M, Burke GA, Lowis SP, et al. Remission induction therapy for childhood acute lymphoblastic leukaemia: clinical and cellular pharmacology of vincristine, corticosteroids, L-asparaginase and anthracyclines. Cancer Treat Rev 2001;27:327–37.
[5] Inaba H, Pui CH. Glucocorticoid use in acute lymphoblastic leukaemia. Lancet Oncol 2010;11:1096–106.
[6] Reilly JJ, Brougham M, Montgomery C, et al. Effect of glucocorticoid therapy on energy intake in children treated for acute lymphoblastic leukemia. J Clin Endocrinol Metab 2001;86:3742–5.
[7] Belgaumi AF, Al-Bakrah M, Al-Mahr M, et al. Dexamethasone-associated toxicity during induction chemotherapy for childhood acute lymphoblastic leukemia is augmented by concurrent use of daunomycin. Cancer 2003;97:2898–903.
[8] Zhang FF, Kelly MJ, Saltzman E, et al. Obesity in pediatric ALL survivors: a meta-analysis. Pediatrics 2014;133:e704–15.
[9] Iughetti L, Bruzzi P, Predieri B, et al. Obesity in patients with acute lymphoblastic leukemia in childhood. Ital J Pediatr 2012;38:4.
[10] Garmey EG, Liu Q, Sklar CA, et al. Longitudinal changes in obesity and body mass index among adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2008;26:4639–45.
[11] Odame I, Reilly JJ, Gibson BE, et al. Patterns of obesity in boys and girls after treatment for acute lymphoblastic leukaemia. Arch Dis Child 1994;71:147–9.
[12] Esbenshade AJ, Simmons JH, Koyama T, et al. Obesity and insulin resistance in pediatric acute lymphoblastic leukemia worsens during maintenance therapy. Pediatr Blood Cancer 2013;60:1287–91.
[13] Geenen MM, Bakker PJ, Kremer LC, et al. Increased prevalence of risk factors for cardiovascular disease in long-term survivors of acute lymphoblastic leukemia and Wilms tumor treated with radiotherapy. Pediatr Blood Cancer 2010;55:690–7.
[14] Werner RA, Rudelius M, Thurner A, et al. Cardiac manifestation of acute lymphoblastic leukemia. Clin Nucl Med 2016;41:570–1.
[15] Geng S, Zhu W, Xie C, et al. Medium-chain triglyceride ameliorates insulin resistance and inflammation in high fat diet-induced obese mice. Eur J Nutr 2016;55:931–40.
[16] St-Onge MP, Mayrsohn B, O'Keeffe M, et al. Impact of medium and long chain triglycerides consumption on appetite and food intake in overweight men. Eur J Clin Nutr 2014;68:1134–40.
[17] St-Onge MP, Jones PJ. Greater rise in fat oxidation with medium-chain triglyceride consumption relative to long-chain triglyceride is associated with lower initial body weight and greater loss of subcutaneous adipose tissue. Int J Obes Relat Metab Disord 2003;27:1565–71.
[18] St-Onge MP, Jones PJ. Physiological effects of medium-chain triglycerides: potential agents in the prevention of obesity. J Nutr 2002;132:329–32.
[19] Augustin K, Khabbush A, Williams S, et al. Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders. Lancet Neurol 2018;17:84–93.
[20] Malapaka RR, Khoo S, Zhang J, et al. Identification and mechanism of 10-carbon fatty acid as modulating ligand of peroxisome proliferator-activated receptors. J Biol Chem 2012;287:183–95.
[21] Pui CH, Evans WE. Acute lymphoblastic leukemia. N Engl J Med 1998;339:605–15.
[22] The Dietary Reference Intakes. National Academy of Sciences. 2002
[23] Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med 2009;360:2730–41.
[24] iv. Training Course on Child Growth Assessment
[25] Barbosa-Cortes L, Lopez-Alarcon M, Mejia-Arangure JM, et al. Adipokines, insulin resistance, and adiposity as a predictors of metabolic syndrome in child survivors of lymphoma and acute lymphoblastic leukemia of a developing country. BMC Cancer 2017;17:125.
[26] Wang YF, Zhang G, Jiang YM, et al. Relationship between immune differentiation antigen and minimal residual disease in childhood B-ALL. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2018;26:1301–8.
[27] Rial SA, Karelis AD, Bergeron KF, et al. Gut microbiota and metabolic health: the potential beneficial effects of a medium chain triglyceride diet in obese individuals. Nutrients 2016;8:
[28] St-Onge MP, Bosarge A. Weight-loss diet that includes consumption of medium-chain triacylglycerol oil leads to a greater rate of weight and fat mass loss than does olive oil. Am J Clin Nutr 2008;87:621–6.
[29] Mumme K, Stonehouse W. Effects of medium-chain triglycerides on weight loss and body composition: a meta-analysis of randomized controlled trials. J Acad Nutr Diet 2015;115:249–63.
[30] Jahnukainen K, Heikkinen R, Henriksson M, et al. Increased body adiposity and serum leptin concentrations in very long-term adult male survivors of childhood acute lymphoblastic leukemia. Horm Res Paediatr 2015;84:108–15.
[31] Srivastava R, Batra A, Tyagi A, et al. Adiponectin correlates with obesity: a study of 159 childhood acute leukemia survivors from India. Indian J Cancer 2015;52:195–7.
[32] Warris LT, van den Akker EL, Bierings MB, et al. Eating behavior during dexamethasone treatment in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 2017;64:
[33] Kelesidis T, Kelesidis I, Chou S, et al. Narrative review: the role of leptin in human physiology: emerging clinical applications. Ann Intern Med 2010;152:93–100.
[34] Park HK, Ahima RS. Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. Metabolism 2015;64:24–34.
[35] Gelelete CB, Pereira SH, Azevedo AM, et al. Overweight as a prognostic factor in children with acute lymphoblastic leukemia. Obesity (Silver Spring) 2011;19:1908–11.
[36] Vigneri R, Goldfine ID, Frittitta L. Insulin, insulin receptors, and cancer. J Endocrinol Invest 2016;39:1365–76.
[37] Sheng X, Mittelman SD, Frittitta L. The role of adipose tissue and obesity in causing treatment resistance of acute lymphoblastic leukemia. Front Pediatr 2014;2:53.