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Nutritional status and physical activity of childhood leukemia survivors

Conny Tanjung, Johannes Bondan Lukito, Prima Dyarti Meylani

Abstract

Background Acute lymphoblastic leukemia (ALL), the most common malignancy of childhood, has an overall cure rate of approximately 80%. Long-term survivors of childhood ALL are at increased risk for obesity and physical inactivity that may lead to the development of diabetes, dyslipidemia, metabolic syndrome, as well as cardiovascular diseases, and related mortality in the years following treatment.

Objective To evaluate the physical activity and the propensity for developing obesity longer term in ALL survivors.

Methods This retrospective cohort study included all ALL survivors from Pantai Indah Kapuk (PIK) Hospital. We assessed their physical activity and nutritional status at the first time of ALL diagnosis and at the time of interview.

Results Subjects were 15 ALL survivors aged 7 to 24 years. The median follow up time was 6.4 years (range 3 to 10 years). Only 2 out of 15 survivors were overweight and none were obese. All survivors led a sedentary lifestyle. Most female subjects had increased BMI, though most were not overweight/obese. Steroid therapy in the induction phase did not increase the risk of developing obesity in ALL survivors.

Conclusion Long-term survivors of childhood ALL do not meet physical activity recommendations according to the CDC (*Centers for Disease Control)*. However, steroid therapy do not seem to lead to overweight/obesity in ALL survivors. **[Paediatr Indones. 2014;54:67-72.]**.

Keywords*: acute lymphoblastic leukemia, survivors, obesity, physical inactivity*

The number of survivors of childhood acute lymphoblastic leukemia (ALL) has been steadily increasing with progressive improvements in therapy. This expanding population of survivors mandates better characterization of the long-term complications of treatment to improve our understanding of their future health risks. Recent studies suggest that ALL survivors have an increased prevalence of obesity and physical inactivity and may be at risk of developing diabetes, dyslipidemia, and metabolic syndrome that may contribute to the development of cardiovascular diseases. Thus it is imperative to further study this population.[1-4]

Until now, there has been little data on the nutritional and physical activity status of ALL survivors in Indonesia. We aimed to evaluate the physical activity of ALL survivors, their nutritional status and assess for possible long-term effects of steroid therapy as a potential cause of obesity.

Methods

We conducted a retrospective cohort study in the Pediatric Ward of Pantai Indah Kapuk (PIK) Hospital,

From the Department of Pediatrics, Pantai Indah Kapuk Hospital, Jakarta, Indonesia.

Reprint requests to: dr. Conny Tanjung, Sp.A. RS Pantai Indah Kapuk. Phone +6221.5880.911. Email address: mfconnytanjung@yahoo.com.

Jakarta from April to July 2012 to evaluate the current nutritional status, physical activity and the effect of steroids as a potential cause of obesity on ALL survivors. All patients were treated between 2000 – 2010, according to the ALL '97 Hong Kong (HK ALL 97) Protocol.

Weight in kilograms was measured by electronic scale (*SECA 727*). Height in centimeters was measured with a wall-mounted stadiometer. These two parameters were measured at the time of diagnosis, during treatment, at the end of therapy, and at the time of this study. We used the CDC 2000 growth charts for children over 5-year-old. Nutritional status was determined based on body weight (BW) in relation to body height (BH) and categorized according to the Waterlow criteria for children over 5 years old. For children under 5 years of age, we used the cut-off Z-score from WHO 2006. If the result showed overweight (>+1 SD) or BW/BH >100%, we used the body mass index (BMI) graphs for their age and sex. Body mass index (BMI, kg/m^2), was used as an indicator of obesity according to Centers for Disease Control (CDC) charts. These patients were categorized as overweight when BMI was above 85th - 94th percentile, or obese if BMI ≥95th percentile.[5] For adult patients (age >18 years), the BMI was used to define weight categories as follows: underweight (BMI ≤18.5), normal weight (BMI 18.5 to 24.9), overweight (BMI 25.0 to 29.9), or obese (BMI ≥30).[1]

Physical activity was assessed by asking, "During the past month, did you participate in any physical activities or exercises such as running, calisthenics, golf, gardening, bicycling, swimming, wheelchair basketball, or walking for exercise?" Participants were then asked a series of six questions to quantify the amount of time (number of days per week and number of minutes per day) spent in moderate or vigorous physical activity during a usual week. Vigorous activities were defined as any activity causing a large increase in breathing or heart rate. Examples provided by the surveyors included running, aerobics, wheelchair basketball, and heavy yard work. Moderate activities were defined as any activity causing small increases in breathing or heart rate, including brisk walking, bicycling, vacuuming, gardening, and manual wheelchair operation. Participants were considered to "not meet CDC recommendations" if they did not report moderate-intensity physical activities for at least 30 min, ≥5 days in a week or vigorous-intensity physical activity for ≥20 minutes per occasion ≥3 days per week.[4]

Results

There were 42 children admitted to PIK Hospital with a diagnosis of acute lymphoblastic leukemia (ALL). Of these, 20 children did not receive further therapy because of parent refusal (15 patients) or failure to achieve remission (5 patients). One patient died one year after completing the regimen. The final study sample consisted of 21 ALL survivors, but six ALL subjects were excluded because of incomplete data. The remaining subjects consisted of 7 females and 8 males. The median age at diagnosis was 6.7 years (range 2 to 15 years) and the median age at the time of interview was 13.1 years (range 7 to 24 years). The median time from diagnosis to last assessment was 6.4 years (range 3 to 10 years).

These subjects started induction chemotherapy comprised of vincristine, ara C, leunase, daunorubicin, cyclophosphamide, and high-dose of intrathecal methotrexate (MTX). All patients received intravenous high-dose MTX (5 g/m^2), prednisolone (60 mg/m^2/day for 28 days) in the induction phase 1 and dexamethasone (10 mg/m^2/day for 21 days) in the re-induction phase. None of the subjects received cranial irradiation. In the maintenance phase, subjects received mercaptopurine, methotrexate, and dexamethasone orally.

Subjects' nutritional status at the time of diagnosis and at the time of study are summarized in **Table 1.** At diagnosis, five patients were underweight, two patients were obese and three were overweight. At the time of this study, this proportion changed. At the last assessment almost all survivors had good nutritional status, none were obese, and only 2/15 patients fulfilled the criteria for overweight.

None of the ALL survivors met the CDC recommendations for physical activity, as no patients regularly exercised 5 times per week or engaged in vigorous activity 3 times per week. The age at cancer diagnosis did not modify outcomes. Subjects spent more than two hours in front of the television, playing games or surfing the internet. Only 5 survivors engaged in regular exercise for 30 minutes one or two times per week (**Table 2**).

Figure 1. shows about the differences of BMI in the boys and the girls survivors that were evaluated at the first time of ALL diagnosis and the last interview. The figure also shows the increasing trend of BMI among the girls, that linked to the fat composition in the body.

have been proposed for this effect, including cranial radiotherapy, growth hormone insufficiency, use of corticosteroids and reduced energy expenditure.[6-9]

This single-institution study provides longitudinal follow-up observations of weight and height. We

Table 1. Subjects' nutritional status

		Nutritional status at study time			
	Number of patients	Under weight	Normal	Over weight	Obese
Age at study time, years					
≥18	2	1	1	-	-
10 - 14	8	-	8	-	-
5 – 9	5	-	3	2	-
Gender					
Female	7	-	6	1	-
Male	8	1	6	1	-
Nutritional status at diagnosis					
Underweight	5	-	5	-	-
Normal	5	1	3	1	-
Overweight	3	-	3	-	-
Obese	2	-	1	1	-

Table 2. Subjects' physical activity (according to CDC recommendation criteria)

		Physical activity study time		
	Number of patients	Moderate physical activity (> 30 min for ≥ 5 days a week)	Vigorous physical activity (> 30 min for ≥ 3 days a week)	Sedentary lifestyle (watching TV/ computer for ≥ 2 hours)
Age at study time , years				
≥18	2	-	-	2
10–14	8	-	-	8
5–9	5	-	-	5
Gender				
Female	7	-	-	7
Male	8	-	-	8
Nutritional status at assessment				
Underweight	5	-	-	5
Normal weight	5	-	-	5
Overweight	3	-	-	3
Obese	2	-	-	2

Discussion

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood, accounting for approximately 25% of all childhood cancers.[6] Since the 1960s, the ALL cure rate in children has improved dramatically, from less than 30% to a current estimated 5-year overall survival of 80-86%. Reports on long-term childhood ALL survivors have claimed that obesity is a common finding.[7,8] Several explanations

observed that children who were younger at diagnosis did not have greater likelihood of becoming overweight at the interview assessment (a median time of 6.4 years after diagnosis). In contrast, Razzouk *et al.*[1] found a correlation of younger age to the likelihood of becoming obese. Patients who were underweight at the time of diagnosis had the largest increase in BMI, as would have been expected with improvement in their nutritional status after achieving complete remission of their leukemia.[1]

Based on BW/BH assessments, we found that no survivors fulfilled the criteria for obesity. Furthermore, only two survivors were overweight. Similarly, Jarfelt *et al.* found no obese survivors in their study, but in their study 12/35 patients were overweight.[7] Although we found that almost all survivors had good nutritional status, changes in BMI were evident in our study population **(Figure 1).** The BMI is a potential clinical marker for metabolic abnormalities. Interpretation of BMI in childhood and adolescents is not as straightforward as in adults because of progressive changes with growth. Increased total fat mass with or without increased BMI has been described after recovery from malignancy.[7] Our results were contrary to the findings of Nysom *et al.* who found a high BMI at the follow up of Danish children and young adults at a median time of 10 years after diagnosis.[10] Other studies have reported on the changes of body fat composition after completion of therapy. The amount of fat, fat-free mass, and fat distribution are more important risk factors for predicting cardiovascular diseases and non-insulin dependent diabetes mellitus (NIDDM).[11]

Unlike our male subjects, almost all females had increased BMI, similar to the findings of Murphy *et al.* who showed a tendency of increased fat mass in female subjects.[3] Warner *et al.* also found that only female survivors tended to be obese,[12] and Odame *et al.* reported that female ALL survivors had significantly higher BMI standard deviation scores than did other patients who had been treated with chemotherapy.[13] It is unclear how gender affects the body composition of children in remission from ALL.

Some reports have shown a correlation between obesity and corticosteroid treatment applied during the induction of remission. One theory is that during glucocorticoid treatment, ALL patients have increased energy intake and reduced energy expenditure while

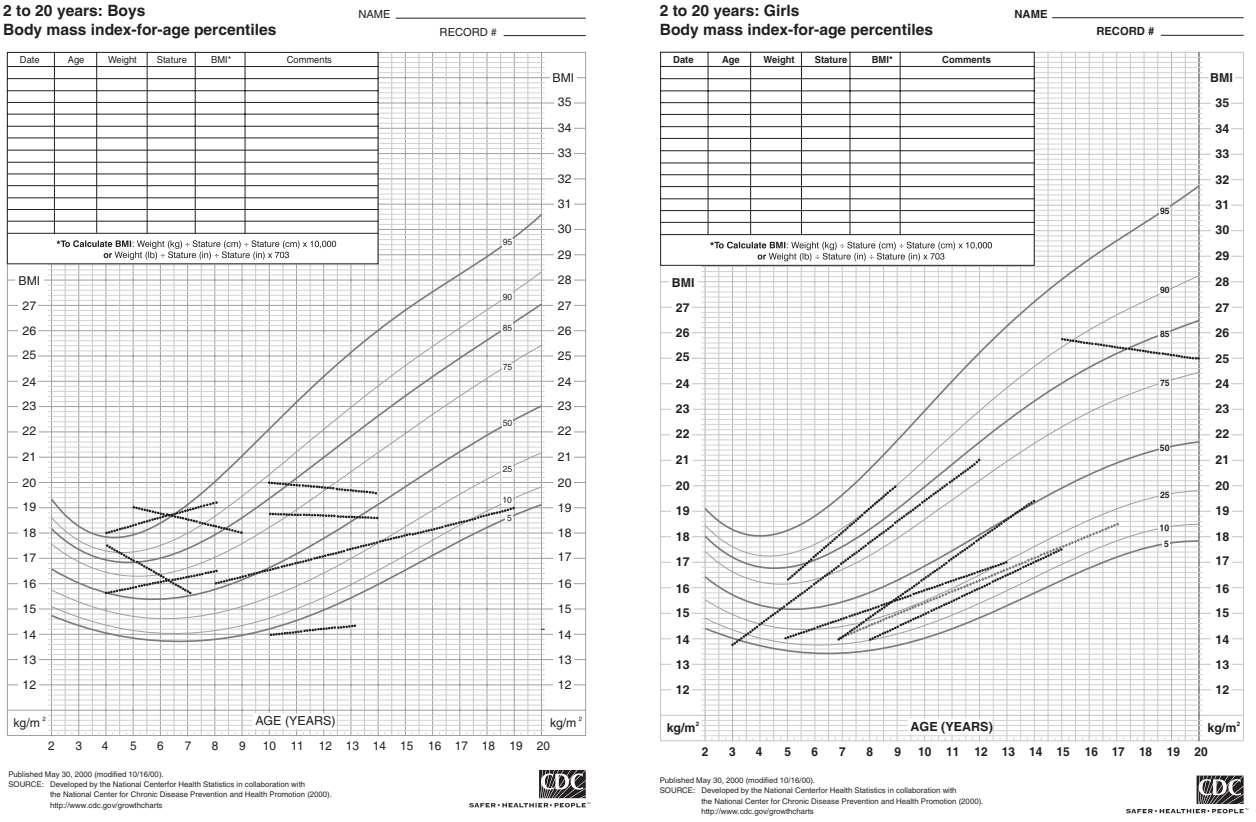

Figure 1. The BMI changes in ALL survivors (the BMI differences measured at the ALL diagnosis and at the time of interview)

continuing on their baseline physical activity and that this effect continues after treatment ceases. Other theories are that glucocorticoid treatment causes increased adiposity by suppressing growth hormone secretion or that it causes resistance to leptin. Dexamethasone and prednisolone are two glucocorticoids usually used in ALL treatment. Ahmed *et al.* reported that dexamethasone was 18 times as potent as prednisolone in suppressing short-term growth and in increasing body weight.[14] After adjustment for differences in dose, dexamethasone was more potent than prednisolone in increasing leptin, an indicator of percentage of fat mass.[15] Unfortunately we did not observe this correlation in our study, as a longer follow up time would be required in order to track subjects' final height. Our findings suggest that further studies are needed to examine the longer term effects of glucocorticoids on body composition in a larger cohort for a longer time of observation.

Cranial irradiation, especially at doses of 20 Gray or higher, has been reported to be a significant predictor of risk for overweight/obesity in previous investigations of childhood ALL, especially in females treated before 5 years of age.[2] Since none of our subjects underwent cranial radiation, it may be one reason why none of our subjects was obese.

Although we had a relatively small number of patients, this study has several strengths. First, all patients were treated at a single institution, using the same treatment protocol, with a duration of follow up of 3 - 10 years (mean 6.4 years) permitting us to determine changes in BMI over time. Second, all height and weight values used in the BMI determinations were measured during routine clinic visits.

The second aim of this study was to evaluate the physical activity in our ALL survivors. In the general population, regular moderate intensity physical activity has been shown to be protective against osteoporosis, hypertension, non–insulin dependent diabetes mellitus, and cardiovascular diseases. However, in 2001, only 45.4% of the ALL patients were reported meeting the CDC recommendation of ≥ 30 min of moderate intensity physical activity for ≥ 5 days per week or ≥ 20 minutes of vigorous intensity activity for ≥ 3 days per week. Given that ALL survivors are at higher risk than the general population for several modifiable health problems, the importance of participating in regular physical activity is even greater for this group.[17-19]

The study of Florin *et al.* shows that ALL survivors were more likely to not meet CDC recommendations for physical activity [odds ratio (OR) 1.44; 95% CI 1.32 to 1.57] and more likely to be inactive (OR 1.74; 95% CI 1.56 to 1.94) compared to the general population.[4] A systematic review shows that the physical fitness (as reflected by peak oxygen uptake/VO_2 peak levels) of ALL survivors tend to be reduced compared to healthy children. Impaired physical fitness leads to early fatigue dur ing physical activities and can severely diminish the quality of life of ALL survivors, which suggests the need for these children to engage in regular physical activities. Furthermore, there are scientific indications that exercise training improves the function of several anti-cancer immune system components and can attenuate tumor development.[16]

In conclusion, we find no obesity in the childhood ALL survivors in our institution. Steroid therapy in the intensification phase seems to not increase the risk of obesity in ALL survivors. However, all survivors are physically inactive. This level of inactivity likely increases their risk of cardiovascular diseases, osteoporosis, and metabolic syndrome. Further studies of longer duration are needed to assess the factors contributing to these findings.

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