Body composition in children in remission from acute lymphoblastic leukemia[1–3]

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ABSTRACT

Background: Changes in body composition are commonly reported in pediatric survivors of acute lymphoblastic leukemia (ALL). However, the effect of ALL and of its treatment on body composition in children in remission from ALL has not been fully examined with the use of a reference method.

Objectives: We aimed to determine the body composition and composition of fat-free mass (FFM) in children in remission from ALL. We also aimed to compare the effects that prednisolone and dexamethasone had on the body composition of an ALL survivor population.

Design: This cross-sectional study measured height, weight, body volume, total body water, and bone mineral content in 24 children in remission from ALL and 24 age-matched, healthy control subjects. Body composition and FFM composition were evaluated by using the 4-component model.

Results: The mean body mass index and fat mass index were significantly ($P = 0.05$ for both) higher in the ALL survivors than in age-matched control subjects. The composition of the FFM in the 2 treatment groups was not observed to differ significantly. Examination of the composition of FFM made it evident that children in remission from ALL had both significantly greater hydration ($P = 0.001$) and lower density ($P = 0.0001$) of FFM than did the control children.

Conclusions: Children in remission from ALL may develop excess body fat. To measure body composition accurately in an ALL population, the high hydration and low density of FFM in this population should be taken into consideration. *Am J Clin Nutr* 2006;83:70–4.

KEY WORDS Body composition, acute lymphoblastic leukemia, fat-free mass, 4-component model, dexamethasone, prednisolone

INTRODUCTION

As the number of childhood acute lymphoblastic leukemia (ALL) survivors increases, research focus is shifting to the long-term effects of the disease and its treatment, such as deleterious body-composition changes (1–7). Body-composition changes have important implications for children in remission from ALL, in terms of the quality of life and of their association with increased morbidity and mortality (8). Previous studies focused on the outcome of now-outdated treatment regimens or have used only simple methods to define body-composition changes (2, 3, 6, 7, 9). Consequently, there is a need for a study in which reference body-composition methods are used to ascertain whether body composition is affected in ALL survivors treated under current protocols. Therefore, the primary aim of the current study was to examine body composition in children in remission from ALL.

Most studies of ALL survivors assessed body composition by using body mass index (BMI), skinfold-thickness (ST) measurements, or dual-energy X-ray absorptiometry (DXA), all of which rely on 2-component assumptions. Methods based on the 2-component model rely on the assumption that fat-free mass (FFM) has constant composition in all populations, but FFM composition in children is not the same as that in adults: children's FFM has a lower density because of greater FFM hydration (10). Other factors such as obesity also affect FFM composition (11), and thus 2-component methods are inaccurate in clinical pediatric populations. It is not known how ALL affects FFM composition in pediatric ALL survivors; we are aware of only one published report of a study (12). To improve our understanding of changes in FFM composition after ALL, a second aim of the current study was to ascertain the composition of FFM in children who are in remission from ALL.

Glucocorticoid therapy is standard in ALL treatment regimens. Comparative studies of the efficacy and toxicity of prednisolone and dexamethasone were undertaken, as a result of evidence that dexamethasone may be more effective than prednisolone in preventing relapse, especially in the central nervous system (13–18). Although dexamethasone appears to have benefits in treating ALL, several studies have shown that dexamethasone is more toxic than is prednisolone and that it can cause significantly greater weight gain in ALL patients that can prednisolone treatment (19, 20). Such studies showed that an increase in weight is seen immediately after the start of treatment with

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dexamethasone, but it is not yet clear whether the excess weight persists after treatment. As part of the comparative assessment of dexamethasone and prednisolone, it is important to ascertain the long-term effects that either drug has on body composition. Therefore, the third aim of the current study was to compare the effects of prednisolone and dexamethasone on body composition in an ALL survivor population.

SUBJECTS AND METHODS

Subject population

Twenty-nine subjects aged 6–12 y were recruited for the study. Subjects were in remission from ALL; the average time since ALL diagnosis in the patient group was 4.3 y, and the time since complete of treatment ranged from 1 to 2 y. All subjects had taken part in the ALL 97 Medical Research Council (MRC) trial at Great Ormond Street Hospital for Children (London, United Kingdom), which involved 1800 children from throughout the country. In glucocorticoid treatment in the current study, patients were randomly assigned to received either prednisolone (40 $mg/m^2 \cdot d^{-1}$) or dexamethasone (6.5 $mg/m^2 \cdot d^{-1}$) during induction, intensification, and maintenance therapy. The second study randomization was a comparison of mercaptopurine (75 mg/m^2) and thioguanine (60 mg/m^2) during maintenance therapy only.

We compared the patients's data with reference data being collected by the MRC-Childhood Nutrition Research Centre by using a case-control approach with age- and sex-matched controls. The control subjects were volunteers recruited from schools in and around London.

Written informed consent was obtained from the parents of all children, and oral assent was obtained from all of the children. Ethical approval for the study was granted by Great Ormond Street Hospital for Children National Health Service Trust/Institute of Child Health Research Ethics Committee.

Anthropometry

Height was measured to the nearest 0.1 cm by using a stadiometer (Karrimetre; Castlemead, Ware, United Kingdom), and weight was measured to the nearest 0.01 kg while the subject was dressed in a swimsuit and by using the scales involved in measurements with the BOD POD Body Composition Tracking System (Life Measurement Inc, Concord, CA). BMI was calculated as weight divided by height squared.

Air-displacement plethysmography

Air-displacement plethysmography was used to measure body volume (BV) by using the BOD POD system and by following the manufacturer's instructions. A detailed description of the principles and procedures of air-displacement plethysmography using the BOD POD system are reported elsewhere (21). Before each measurement, the BOD POD system was calibrated at 0 L and with a standard calibration cylinder of 50 L. For the subject measurement, the subject was required to wear a Lycra swimsuit and cap to minimize measurement error. Once the subject was so dressed, his or her weight was measured on the BOD POD scale, which is calibrated daily with a 20-kg weight. For the raw BV measurements, the subject was requested to sit inside the chamber for 50 s. The measurement was completed twice or until the BV measurements were within 150 mL or 0.2% of each other, whichever was the smallest (maximum of 3 attempts). The average of the 2 successful raw BV measurements was used in subsequent calculations. Two complete tests were completed to ensure precision (22). The raw BV given by the BOD POD was adjusted for thoracic gas volume and surface area artifact, which were calculated by using previously described child-specific equations (23).

Deuterium dilution

Total body water (TBW) was measured by using the stable isotope of deuterium in the form of water (^2H_2O). An individual dose was made up for each subject by using the guidelines of 0.05 g deuterium oxide and 2 g water per kg body wt for each dose. Before taking the sample, the subject was asked to provide a saliva sample by wetting a cotton wool swab. The subject then drank the deuterium dose and was asked to provide another saliva sample 4 to 5 h afterward. The results were analyzed by using an isotope ratio–mass spectrometer (Micromass, Crewe, United Kingdom). Deuterium dilution was calculated and corrected for proton exchange as described previously (23). Fluid intake was recorded during the equilibration period and was subtracted from the calculated TBW values.

Dual-energy X-ray absorptiometry

Bone mineral content (BMC) was determined by using DXA (Lunar Prodigy; Lunar Inc, Middletown, WI). The machine was calibrated daily by using standard calibration procedures. For the scan, the subjects were requested to wear light clothing and no metallic objects. A whole-body scan was performed while the subject was in the supine position; the typical scan lasted 10 min. The radiation dose for a whole-body DXA scan is $\approx 0.5\ \mu Sv$.

Four-component model

The 4-component model is considered the reference method of body-composition assessment because it considers FFM composition and divides the body into fat mass (FM) and water, protein, and mineral. The 4-component model combines the measurements of weight, BV, TBW, and BMC to ascertain body composition according to the following equation (24):

$$\text{FM (kg)} = (2.747 \times \text{BV}) - (0.710 \times \text{TBW}) + (1.146 \times \text{BMC}) - (2.053 \times \text{WT}) \quad (1)$$

where WT = weight. FFM was calculated as the difference between weight and FM.

Composition of FFM

The hydration fraction of FFM (H_{FFM}) was calculated as TBW divided by FFM, and the density of FFM (D_{FFM}) was calculated as follows:

$$D_{FFM} = (\text{mass of water} + \text{protein} + \text{mineral}) / (\text{volume of water} + \text{protein} + \text{mineral}) \quad (2)$$

Total mineral mass (TMM) was determined by BMC multiplied by 1.2741 (25), and protein mass (PM) was calculated as the difference between weight and the sum of TBW, FM, and TMM (24).

Expression of body-composition data

Traditionally, body-composition data have been expressed in the following way: FM is divided by weight and expressed as percentage FM (%FM), whereas FFM is not adjusted for body size. Such an approach is unsatisfactory, for 2 reasons. First, it is statistically inappropriate to express FM as a proportion of weight, because weight contains FM (26). Second, it is inappropriate not to adjust both FM and FFM for variability in body size (27), especially when evaluating the effect of a disease such as ALL, which is associated with reduced height. Therefore, we used an approach proposed by Van Itallie et al (28) for use in adults and subsequently shown to be appropriate for children (29), in which both FM and FFM are adjusted for height. The FFM index (FFMI = FFM/height^2) and the FM index (FMI = FM/height^2) are independent of each other, and both are adjusted for body stature.

Statistical analysis

Values are given as means ± SD. We calculated SD scores for BMI by using the method described by Cole et al (30) and those for height by using the method of Freeman et al (31). Children with ALL and the matched control subjects were compared with paired *t* tests, whereas the 2 treatment groups were compared with independent-sample *t* tests. Significance was set at $P < 0.05$. We used SPSS for WINDOWS statistical software (version 13.0; SPSS Inc, Chicago, IL) for all analyses.

RESULTS

The final study sample consisted of 24 children with ALL, 13 females and 11 males between the ages of 6.2 and 12.8 y. Five ALL subjects were excluded because of incomplete data. The characteristics of the children with ALL and the control subjects are given in **Table 1**. The control subjects did not differ from 1990 UK reference data in terms of height SD scores, but they had significantly ($P < 0.05$) greater BMI SD scores. The 2 groups of children did not differ significantly in age, weight, or height.

There was no significant difference in BV ($P = 0.13$), TBW ($P = 0.43$), BMC ($P = 0.63$), FFM ($P = 0.76$), or FFMI ($P = 0.41$) between the 2 groups of children. The %FM ($P = 0.08$) and FM ($P = 0.08$) tended to be higher in the ALL group, although, when FM was adjusted for height, the FMI was significantly different between the 2 groups ($P = 0.05$).

Examination of the composition of FFM showed that children with ALL had a significantly ($P = 0.001$) higher H_{FFM} than did the control subjects. The D_{FFM} was significantly ($P = 0.0001$) lower in the children with ALL than in the control subjects. The difference between the groups for TMM ($P = 0.63$), PM ($P = 0.11$), and PM ratio ($P = 0.37$) was not significant.

When the subjects were randomly assigned to treatment groups, 15 subjects (7 females) were treated with prednisolone and 9 subjects (6 females) were treated with dexamethasone. Characteristics of the 2 groups are shown in **Table 2**. The groups did not differ in age, weight, height, or BMI. When body-composition components were examined by independent-sample *t* test, there was no difference in the amount of FM ($P = 0.70$), FMI ($P = 0.55$), FFM ($P = 0.59$), or FFMI ($P = 0.23$). The dexamethasone group had a 6% higher mean %FM than did the prednisolone group, but this difference was not significant ($P = 0.18$). There was no observable difference in the composition of the FFM between the 2 treatment groups after adjustment for age and sex.

TABLE 1
Characteristics of body composition in subjects with acute lymphoblastic leukemia (ALL) and control subjects[1]

	ALL group ($n = 24$)	Control group ($n = 24$)
Age (y)	9.6 ± 1.8	9.6 ± 2.0
Weight (kg)	36.90 ± 14.70	32.95 ± 7.20
Height		
(cm)	134.7 ± 0.12	135.9 ± 0.11
SD scores	−0.20 ± 0.86	0.08 ± 0.93
BMI		
(kg/m^2)	19.7 ± 5.1[2]	17.6 ± 1.7
SD scores	0.95 ± 1.29	0.42 ± 0.78
Body volume (L)	36.2 ± 15.2	31.8 ± 7.1
Total body water (L)	19.3 ± 4.7	18.6 ± 3.5
BMC (kg)	1.15 ± 0.35	1.17 ± 0.28
Fat mass (kg)	11.8 ± 9.5	8.2 ± 3.3
FMI (kg/m^2)	6.2 ± 4.1[2]	4.3 ± 1.4
Fat-free mass (kg)	25.1 ± 6.3	24.8 ± 4.7
FFMI (kg/m^2)	13.6 ± 1.6	13.3 ± 1.0
Percentage fat (%)	28.9 ± 11.1	24.2 ± 5.7
H_{FFM} (%)	76.8 ± 1.8[3]	75.0 ± 1.5
D_{FFM} (kg/L)	1.085 ± 0.006[4]	1.092 ± 0.006
Total mineral mass (kg)	1.46 ± 0.44	1.50 ± 0.36
Protein mass (kg)	4.4 ± 1.3	4.7 ± 1.0
Protein:mineral	3.0 ± 0.5	3.2 ± 0.4

[1] All values are $\bar{x}$ ± SD. BMC, bone mineral content; FMI, fat mass index; FFMI, fat-free mass index; H_{FFM}, hydration fraction of fat-free mass; D_{FFM}, density of fat-free mass.
[2–4] Significantly different from controls (paired *t* test): [2]$P < 0.05$, [3]$P < 0.001$, [4]$P < 0.0001$.

DISCUSSION

The first aim of this study was to examine body composition of children in remission from ALL by using a 4-component reference technique. Our study showed that, an average of 4 y after being diagnosed with ALL, children trend toward having excess body fat and have a marked increase in BMI, BMI SD scores, FM, %FM, and FMI. There was no evidence that ALL survivors had low FFM or that TBW or BMC had been affected by the disease or treatment.

When each sex was examined separately, only females with ALL had a tendency for decreased height and increased FM: they had an FM ≈60% greater than that of control subjects but an almost identical FFM. Some studies support our finding of sex differences in response to ALL. A study by Warner et al (7) looked at ALL survivors and found that only female survivors tended to be obese, and Odame et al (32) reported that female ALL survivors had significantly higher BMI SD scores than did other patients who had been treated with chemotherapy. However, studies by Van Dongen-Melman et al (33) and Davies et al (34) found no difference in results between males and females. It is unclear why there may be sex differences in the body composition of children in remission from ALL.

To the best of our knowledge, no other studies have measured body composition in ALL survivors by using the 4-component model. However, several reports described body-composition measurements obtained by using DXA. Fourteen children with ALL who were treated under the same protocol as was used in the

TABLE 2
Characteristics of body composition in treatment groups[1]

	Prednisolone group (n = 15)	Dexamethasone group (n = 9)
Age (y)	9.4 ± 2.0	9.8 ± 1.5
Weight (kg)	36.85 ± 16.95	36.95 ± 10.80
Height		
(cm)	134.6 ± 12.9	134.7 ± 11.1
SD score	−0.10 ± 0.82	−0.37 ± 0.95
BMI		
(kg/m^2)	19.7 ± 5.9	19.9 ± 3.7
SD score	0.90 ± 1.33	1.02 ± 1.32
Body volume (L)	36.1 ± 17.6	36.5 ± 11.1
Total body water (L)	19.7 ± 5.0	18.5 ± 4.4
BMC (kg)	1.17 ± 0.38	1.11 ± 0.30
Fat mass (kg)	11.2 ± 11.0	12.8 ± 6.7
FMI (kg/m^2)	5.8 ± 4.6	6.8 ± 3.3
Fat-free mass (kg)	25.6 ± 6.8	24.2 ± 5.8
FFMI (kg/m^2)	13.9 ± 1.6	13.1 ± 1.6
Percentage fat (%)	26.5 ± 11.1	32.8 ± 10.5
H_{FFM} (%)	76.9 ± 2.0	76.7 ± 1.4
D_{FFM} (kg/L)	1.085 ± 0.007	1.086 ± 0.005
Total mineral mass (kg)	1.49 ± 0.49	1.41 ± 0.39
Protein mass (kg)	4.5 ± 1.4	4.2 ± 1.2
Protein:mineral	3.0 ± 0.6	3.1 ± 0.6

[1] All values are $\bar{x}$ ± SD. BMC, bone mineral content; FMI, fat mass index; FFMI, fat-free mass index; H_{FFM}, hydration fraction of fat-free mass; D_{FFM}, density of fat-free mass. Groups were compared by independent t tests. There were no significant differences between the treatment groups.

current study were studied from diagnosis by Davies et al (35), and those investigators found a significant increase in %FM 24 mo after treatment. Also with the use of DXA, Halton et al (36) studied the change in body composition in children treated for ALL and found significant changes, with %FM increasing from 22% at diagnosis to 28% at completion of therapy. Not all studies, however, support the finding of body-composition changes in ALL survivors. In a study by Van der Sluis et al (37), body composition was examined by using DXA in ALL patients 1 y after cessation of treatment. The study showed that, although FFM was decreased and FM was increased during treatment, by 1 y after treatment, there was no evidence of an effect of ALL on the subjects' body composition.

It is not fully understood why ALL survivors gain excess FM. One theory is that, during glucocorticoid treatment, ALL patients have an increased energy intake (38, 39) and reduced energy expenditure on habitual physical activity (40, 41) and that this effect continues after treatment ceases. Other theories are that glucocorticoid treatment causes increased adiposity by suppressing growth hormone secretion (42) or that it causes resistance to leptin (35). No studies using the current treatment regimens have been conclusive, and further research in this area is warranted for a full understanding of what can be done to prevent obesity's becoming a long-term side effect of ALL.

The second aim of this study was to ascertain FFM composition in children in remission from ALL. Our results show significantly greater hydration and significantly less density of FFM in pediatric survivors of ALL than in healthy control subjects. The composition of FFM is known to vary with age, sex, and nutritional status. Our study shows that FFM composition is also affected by ALL or the associated treatment regimens (or both).

Our findings of greater FFM hydration conflict with the previous findings of Warner et al (12), who found that the hydration of FFM was significantly lower in ALL survivors (71.3%) than in control subjects (73.8%). The reason for this difference is not clear, but it may be due to the earlier study's use of DXA to measure FFM. We are not aware of any other studies that have examined FFM composition in ALL survivors, but a recent study by Haroun et al (11) examined the composition of FFM in obese children. They found that obese children had greater hydration and lesser density of FFM, which is similar to our findings in children with ALL. The elevated fatness in ALL survivors, similar to that in obese patients, may therefore be one reason for greater FFM hydration in children with ALL.

Altered FFM composition in this population has implications for the use of body-composition methods that are based on the 2-component model and that rely on the assumption that FFM composition is constant in all pediatric subjects. The use of body-composition methods that rely on the 2-component model may result in misleading findings in this population. Application of normative FFM constants to ALL survivors will lead to the overestimation of FFM and the underestimation of FM. We suggest that studies using 2-component–based methods in an ALL population should be interpreted with caution and that the greater hydration and lesser density need to be taken into account in assessments of body composition in children in remission from ALL.

Dexamethasone and prednisolone are 2 glucocorticoids that can be used to treat ALL. Previous research showed that the use of dexamethasone, with its greater potency, causes more significant short-term body-composition effects than does that of prednisolone. Ahmed et al (43) reported that dexamethasone was 18 times as potent as prednisolone in suppressing short-term growth and in increasing body weight, and Groot-Loonen et al (19) showed that dexamethasone-treated patients gained significantly more weight than did patients treated with an equivalent dose of prednisolone. Wallace et al (20) found that, after adjustment for differences in dose, dexamethasone is more potent than is prednisolone in increasing leptin, an indicator of %FM.

We found that, in our small sample of ALL survivors, body composition and FFM composition did not differ significantly between those treated with dexamethasone and those treated with prednisolone. Children treated with dexamethasone did, however, trend toward a higher %FM, although this difference was not statistically significant (32.8% and 26.5%, respectively). Our sample size had the power to detect a difference of 1.33 SD units in any variable between the 2 treatment groups, and thus the lack of significant differences between the results of the 2 treatments in our study may be due to our small subject numbers. Our findings suggest that further studies are needed to examine the longer-term body-composition effects of dexamethasone in a larger cohort in order to ascertain whether increased %FM is a true long-term side effect of dexamethasone.

With the use of a 4-component reference model, our study shows for the first time that children in remission from ALL have a significantly greater amount of FM and significantly greater hydration and less density of the FFM than does a healthy reference population. These findings have clinical significance for the management of FM gain in ALL survivors, as well as practical significance for appropriate measurement of body composition in this clinical population.

The study was conceived of and designed by JCKW, AJM, and DKW in collaboration with PSWD and MSF. The original randomized trial of treatment was conducted by DKW. AJM coordinated the study and recruited subjects. AJM and JEW were responsible for data collection and modeled the body-composition data. AJM conducted the statistical analyses with JCKW and PSWD. AJM wrote the first draft of the manuscript. All authors contributed to subsequent revisions of the manuscript. None of the authors had a personal or financial conflict of interest.

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