Nutritional status of children with acute lymphoblastic leukemia: a longitudinal study

Laure Delbecque-Boussard, Frederic Gottrand, Simon Ategbo, Brigitte Nelnken, Françoise Mazingue, Philippe Vic, Jean Pierre Farriaux, and Dominique Turck

ABSTRACT To evaluate the nutritional consequences of acute lymphoblastic leukemia and its treatment, 15 children with leukemia were studied. Anthropometric data, fat-free mass by impedance, energy intake, and resting energy expenditure (REE) were determined at diagnosis and on days 22, 36, and 71 of the treatment. Interleukin (IL)-1β, IL-6, interferon-γ, and tumor necrosis factor were also measured. Fifteen healthy control subjects were matched for age and sex. Body weight and height and body composition were comparable at all times of the study, although three children were underweight at diagnosis (weight-for-height < 85% of French standards). Although two different methods were used for dietary recall in the two groups, energy intake expressed as a percentage of normal recommended values for age and sex was lower in patients than in control subjects (104 ± 19%) on day 1 (47 ± 32.1%) and day 22 (58 ± 24%), but was comparable on day 36 (85 ± 71%) and day 71 (85 ± 48%). This low energy intake involved both carbohydrates and fats. Energy and carbohydrate intakes improved significantly during the study in patients. The nonprotein respiratory quotient (RQ) in patients was significantly lower than in control subjects (0.84 ± 0.04) on day 1 (0.79 ± 0.02) but was comparable on day 71. The REE of the patients on day 1 (5057.8 ± 1588.4 kJ/24 h) and day 71 (4844.7 ± 116.1 kJ/24 h) and of the control subjects (4313.8 ± 823.5 kJ/24 h) was not significantly different. Cytokines remained undetectable on days 1, 36, and 71. The results showed that at the time of diagnosis and during this period of chemotherapy there was no evidence of raised RQ. The poor intakes during the first month of chemotherapy were recent as shown by the parents’ questionnaire responses and the absence of consequences in body composition. The transient decrease in RQ seemed to be an adaptive mechanism to the poor carbohydrate intake. No indication of undernutrition in the patients as a group was evident during the first 71 d of treatment although further long-term nutritional assessment is needed. Am J Clin Nutr 1997;65:95–100.

KEY WORDS Children, nutritional status, energy expenditure, leukemia, body composition, dietary recall

INTRODUCTION

Malnutrition is one of the major problems in children with cancer. Severe weight loss and abnormally low concentrations of certain plasma proteins such as albumin and transferrin have been recognized for a long time in patients with cancer, including children (1–3). These changes are caused by inadequate energy and protein intakes, which are caused by side effects associated with chemotherapy and/or the disease itself (4). They may also be due to increased energy expenditure caused by the cachectic side effects of the disease itself, ie, elevated concentrations of tumor necrosis factor (TNF), interleukin 1 (IL-1), IL-6, interferon γ (IFN-γ), the treatments, or infections (5). Moreover, several studies of adult patients have suggested that adequate nutritional support during chemotherapy could prevent weight loss, lead to better tolerance of treatment, and restore cell-mediated immunity, and that good nutritional status may improve survival (6–8).

Most of these studies have only focused on anthropometric data (9, 10) and there are few reports of the energy expenditure of children with cancer (4, 11, 12). The aim of this prospective study was to determine the nutritional status and resting energy expenditure (REE) of children at diagnosis of leukemia and their evolution during the initial 3-mo period of intensive treatment.

SUBJECTS AND METHODS

Patients

Between August 1994 and May 1995, 15 children with newly diagnosed low-risk acute lymphoblastic leukemia (ALL; 13) entered our study (age range: 2.17–11.67 y, x ± SD: 6.2 ± 3.2 y). Exclusion criteria were an age > 18 y, previous chemotherapy (including corticosteroids) or nutritional support, chronic disease that could influence nutritional status, and parental refusal to participate in the study. All children were treated according to the 58881 European Organization for Research and Treatment of Cancer trial (13), as detailed in Figure 1. Fifteen healthy children (age range: 2.17–12.25 y, x ± SD: 6.8 ± 3.1 y) matched for sex and age were used as control subjects.

The protocol was approved by the ethical committee of the University Hospital of Lille, France. Informed written consent

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was obtained from the parents of each child enrolled in the study.

**Methods**

Nutritional assessment was based on dietary history and measurements of weight, height, midarm circumference, and skinfold thicknesses made by the same examiner, and bioelectrical impedance analysis. Each child had an REE measurement by indirect calorimetry. IL-1, IL-6, TNF, and INF-γ were also measured. Nutritional assessment

Weight and height were measured with standard techniques. They were expressed as Z scores, which are the difference between the weight of the child and the mean weight-for-height according to the charts of Sempe et al (14), related to the SD.

Skinfold thicknesses were measured at four sites (triceps, biceps, subscapular, suprailiac) with Harpenden calipers (Eugedia, Chambly, France). The equation of Brook (15) was used to estimate body density. Siri’s equation (16) was used to estimate fat mass. Fat-free mass (FFM) was calculated as the difference between body weight and fat mass. FFM was also determined by bioelectrical impedance analysis (BIA). Body resistance was measured with a tetrapolar bioelectrical impedance analyzer with an alternating current of 800 μA at 50 kHz (model 101; RJL systems, Inc, Detroit). FFM was calculated from body resistance (R) by using the equation of Schaefer et al (17): FFM = 0.65 H²/R + 0.68 age (y) + 0.15, where H is height.

**Energy expenditure**

REE was defined as the minimum energy expenditure for maintaining essential bodily functions under standardized resting conditions, 12 h postprandial, in a thermal-neutral environ-

ment. All measurements were performed between 0730 and 0930 after an overnight fast. REE was determined by indirect calorimetry using an open-circuit ventilated-hood system (Deltatrac II; DATEX, Helsinki). In children whose body weight was < 20 kg, the pediatric mode of the Deltatrac calorimeter, especially designed for this population, was used. Before each test, the calorimeter was calibrated with a reference gas mixture (95% O₂, 5% CO₂). The debit of carbon dioxide expired (VCO₂) and oxygen inspired (VO₂) and the nonprotein respiratory quotient (RQ) were recorded at steady state. REE was calculated from VO₂ and VCO₂ production by using the formula of Weir (18).

After an adaptation period of 15 min under the transparent ventilated canopy system, continuous respiratory exchange measurements were initiated. During the calorimetric measurements, each child rested quietly while watching videotapes or reading. Special care was taken to prevent spontaneous movements that might contribute to increased energy expenditure. The measurements were conducted for a minimum period of 60 min and only steady state values were taken into account for analysis. REE was expressed as kJ/24 h and corrected for differences in FFM.

**Dietary assessment**

Because prospective assessment of dietary intake before diagnosis and admission was impossible for the ALL patients, dietary assessments were therefore retrospective, based on a 24-h dietary recall. For the control subjects, dietary intake was prospectively recorded for 7 d. Children and their families were instructed how to record their food and drink consumption in a notebook provided. Data were analyzed by using a computerized database (BILNUT 3; Nutrisoft, Tours, France), which estimated the energy intake and the proportions of fats, carbohydrates, and proteins according to the French National Institute of Health and Medical Research (INSERM) food table. Energy intakes were expressed in absolute units, corrected in relation to that recommended by the Committee of Nutrition of the French Society for Pediatrics (19).

**Biochemical data**

IL-1β, IL-6, TNF, and IFN-γ were measured by using an enzyme-linked immunosorbent assay method (Genzym, Cambridge, MA). As controls, cytokines from patients without cancer who were hospitalized in other departments of the hospital were measured in the same run. One of the control subjects was an infant with a heat-shock syndrome who died in the intensive care unit.

**Experimental design**

**ALL patients.** At 0800, after an overnight fast, weight, height, midarm circumference, skinfold thicknesses, body resistance, and plasma interleukins were measured. The dietary assessment was done after the respiratory-exchange measurements. Blood was drawn for the measurements of biochemical data. These investigations were made at the time of diagnosis and repeated on day 71 after the consolidation treatment. On day 22 (in the middle of the induction period) and on day 36 (at the end of the induction treatment) skinfold thicknesses, weight, height, midarm circumference, and body resistance
were measured again. An additional measurement of interleukins was performed on day 36.

Control subjects. During the day before the indirect calorimetry test the control subjects were on an unrestricted diet and no attempt was made to influence their usual diet. On the day of the test the children arrived by car at the pediatric department at 0900, having fasted from midnight the day before, and having recorded their food and drink consumption for the past week in a notebook. Height, weight, and skinfold thicknesses were measured. They laid down on a hospital bed and rested for 15 min. After an additional adaptation period of 15 min under the ventilated canopy system, continuous respiratory exchange measurements were initiated for 1 h. Body resistance was then measured.

Data analysis

Results are expressed as means ± SDs. Paired Student's t tests were used to compare the ALL patients with their matched control subjects. The Wilcoxon test was used to compare data of patients at diagnosis (day 1) and at the end of the consolidation period (day 71). The F test was used to compare data of ALL patients during the 71 d (variance analysis). An analysis of variance (ANOVA) test was used for the dietary changes over time within patients. A P value < 0.05 was considered significant. SAS (SAS Institute, Inc, Cary, NC) was used for statistical analyses.

RESULTS

Anthropometry

Physical characteristics of the children on day 1 are reported in Table 1. The mean values for body size and composition of the patients were similar to those of the control subjects on the day of diagnosis. However, when the range of values for the patients' weight-for-height was considered (63.6–113%), three patients appeared to be in the malnourished range. Two patients were < 85% (83.9% and 82.6%) and one patient was < 80% (63.6%) of French standards for weight-for-height. The results were similar on days 22, 36, and 71 (Table 2).

There was no difference for FFM whether it was estimated with skinfold thicknesses or with BIA. FFM obtained by anthropometry correlated well with FFM by BIA (Figure 2).

Energy intakes

Energy intakes and the proportional intakes of carbohydrate, protein, and fat of the children are reported in Table 3. Reduced energy intake was seen in patients on day 1 compared with control subjects. This difference persisted at day 22 but disappeared by days 36 and 71. Nine of the 15 patients were consuming < 80% of the French recommended daily allowance (RDA) on day 1 (19). On day 71, only five patients had intakes that were < 80% of the French RDA and four of them had intakes > 100%. The low energy intakes included both carbohydrates (days 1 and 22) and fats (days 1, 22, and 36). All patients had protein intakes that were above the French RDA and significantly lower than those of the control subjects on day 1. There was a significant variation in energy and carbohydrate intakes from day 1 to day 71 concerning carbohydrates (Table 3). Inversely, there was no significant variation in fat and protein intakes (Table 3).

Energy expenditure

REEs and the RQs are reported in Table 4. The mean REE, whether expressed as kJ/24 h or kJ·kg FFM⁻¹·24 h⁻¹ was not significantly different between the two groups. However, the RQ of the ALL patients on day 1 was significantly lower than that of control subjects. This difference between the two groups disappeared at day 71.

Biochemical data

Cytokines remained undetectable in the serum on days 1, 36, and 71. An error in the dosage or dilution was eliminated because the infant with the heat-shock syndrome had very high concentrations of all the cytokines in his serum.

DISCUSSION

To our knowledge, this study is the first that included longitudinal nutritional assessment with simultaneous anthropometry, BIA, dietary evaluation, and REE measurements in children with leukemia. Few studies measured anthropometric data in leukemic children. Tamminga et al (10) reported a study of 53 children with ALL. At diagnosis, weight, height, weight-for-height, and midarm circumference were normal in all patients. Three months later, the weight gain was excessive, whereas growth velocity tended to decrease. A few children

### Table 1

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<th>Physical and anthropometric characteristics of the children at the time of diagnosis (day 1)</th>
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<tr>
<td>Age (y)</td>
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<td>Weight-for-height Z score</td>
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<tr>
<td>Height-for-age Z score</td>
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<tr>
<td>Midupper arm circumference (cm)</td>
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<td>Fat-free mass for anthropometry (kg)</td>
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<tr>
<td>Fat-free mass for bioelectrical impedance analysis (kg)</td>
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1 x ± SD. ALL, acute lymphoblastic leukemia. There were no significant differences between groups.

### Table 2

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<th>Changes in body composition of acute lymphoblastic leukemia patients during 71 days of treatment</th>
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<td>Midupper arm circumference (cm)</td>
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<td>Fat-free mass by anthropometry (kg)</td>
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<td>Fat-free mass by bioelectrical impedance analysis (kg)</td>
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1 x ± SD; n = 15.
develop obesity, which can last for 5 y after the end of the treatment. Viana et al (8) studied 128 Brazilian children with ALL at diagnosis. The prevalence of malnutrition was high (21.2% of the patients had a weight-for-age Z score < −2 and 17.4% had a height-for-age Z score < −2) but was not different from the actual prevalence of malnutrition in the Brazilian population, which is higher than in more developed countries. Donaldson et al (7) studied the weight-for-height of 244 children with cancer but found no significant difference between the patients and the control subjects. Other authors (9, 20) reported that children with cancer were mostly malnourished at diagnosis. They only studied the weight, height, weight-for-height, midarm circumference, and triceps skinfold thickness. They did not distinguish between children who had ALL or solid tumors.

Some methodologic bias can be ruled out concerning the negative result of this study. Lack of sensitivity of anthropometric measurements could be considered to explain the absence of differences in nutritional status between leukemic children and control subjects. However, accuracy of these data was improved by the fact that all the measurements were done by the same investigator (LDB). Moreover, BIA, which is known to have a high sensitivity, was also used to evaluate the nutritional status of the children and showed a good correlation with the anthropometric data (Figure 2).

The negative results could also be related to the small number of subjects used in our study. We therefore calculated the sample size before the beginning of the study to show a difference of weight-for-height of ≥10% and a difference of REE of ≥1200 kJ/d, which were considered to be differences of biological importance. Our sample size of 15 was greater than required for an α of 0.05 and a β of 0.1.

Three children had poor nutritional status at diagnosis (weight-for-height: 63.6%, 83.9%, and 82.6% of the French standard). It was probably constitutional because there was no decrease in their growth velocity and/or weight gain during the years preceeding the ALL diagnosis. These data could be related to their parents’ weight and height being below average. One of the three children was a single child, but the siblings of the two others had similar anthropometric measurements. None of the three children belonged to a low economic class and we could not find any risk factor for undernutrition. Moreover, their energy intakes were not significantly different from those of the other children.

Parents of leukemic children often express concern that their child may not be eating adequately to satisfy their body’s requirements for energy and nutrients. Anorexia seems to be prevalent in cancer patients, and children who receive treatments for long periods are more likely to have diminished energy intakes. Olive et al (21) consider anorexia to be the

![FIGURE 2. Correlation between fat-free mass obtained by anthropometry and bioelectrical impedance analysis.](https://academic.oup.com/ajcn/article-abstract/65/1/95/4655414/21)

### Table 3

Energy and nutrient intakes of acute lymphoblastic leukemia (ALL) patients and control subjects

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>ALL patients (24-h recall)</th>
<th>Control subject (7-d record)</th>
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<tr>
<td></td>
<td>Day 1</td>
<td>Day 22</td>
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<tr>
<td>Energy (% of French recommended daily allowance)</td>
<td>47.2 ± 32.1^a^</td>
<td>58.3 ± 24.0^b^</td>
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<tr>
<td>Fat (g · kg⁻¹ · d⁻¹)</td>
<td>1.8 ± 1.7^a^</td>
<td>2.0 ± 1.0^b^</td>
</tr>
<tr>
<td>Carbohydrate (g · kg⁻¹ · d⁻¹)</td>
<td>4.2 ± 3.3^a^</td>
<td>6.1 ± 3.7^b^</td>
</tr>
<tr>
<td>Protein (g · kg⁻¹ · d⁻¹)</td>
<td>1.7 ± 1.4^a^</td>
<td>2.9 ± 1.2</td>
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^a^ ± SD; n = 15 in each group.

^a,b^ Significantly different from control subjects: ^a^ P ≤ 0.001, ^a^ P = 0.01, ^b^ P < 0.05.

^a,b,c^ Significantly different from day 1 (ANOVA): ^a^ P = 0.01, ^b^ P = 0.003.
major cause of malnutrition in cancer patients. However, there is very little published information on energy intake for these children. Bond et al (11) studied energy intake during maintenance chemotherapy; the mean value of the treated group (85% of the French RDA) was not significantly different from that of the control group (87%). To the best of our knowledge, there is no study concerning energy intake during induction treatment.

In our study, comparisons of the food intake data were obtained by two different methods (7-d records and 24-h recalls) in the two different groups, and therefore should be interpreted very cautiously. Although 7-d records are more accurate for individuals, it was impossible to collect 7-d records in leukemic patients, particularly at the time of diagnosis. However, we used a repeated-measures ANOVA to identify dietary changes over time within the patient group.

A poor energy intake at diagnosis and during the first month of treatment was observed (47.2 ± 32.1% of the French RDA for ALL patients compared with 104.1 ± 18.7% of the French RDA for control subjects) and involved intake of both carbohydrates and fats. Corticotherapy (from day 1 to day 36) did not increase energy intake. Anorexia was recent as shown by the parents' questionnaire and the normality of the anthropometric and body composition data. The low energy and carbohydrate intakes observed at diagnosis in ALL patients improved significantly during treatment whereas there was no difference for fat and protein intakes over time.

Five patients had energy intakes < 80% of the French RDA on day 71. The oral intakes of this group also did not increase during corticotherapy. There was no correlation between energy intake and the fat mass of these patients, suggesting that the low energy intake was recent and transient.

Mauer et al (4) reported measuring the REE in seven children aged 9–16 y with newly diagnosed ALL. REE was measured by indirect calorimetry for a 5-min period at diagnosis and again 7 d after the treatment began. There was no difference between the patients and the control subjects, but it is important to note the potential errors associated with such a brief period of measurement because the steady state may not be reached. Bond et al (11) studied the REE of 16 children with a diagnosis of ALL during maintenance chemotherapy. Greater attention was paid to technical details and REE was measured by indirect calorimetry for 30 min after a stable energy expenditure was achieved. The mean REE value of the patients, whether expressed as kJ/d or kJ/kg FFM, was not significantly different from that of control subjects.

In our study there was no significant difference in REE between the ALL patients and the control subjects at diagnosis and after 71 d of treatment. However, the RQ of patients at diagnosis was lower than that of control subjects, but was similar on day 71. Because we measured the nonprotein RQ, and because the ratio of carbohydrates to fats increased by a factor of 2.5 between days 1 and 36 (as shown in Table 3), this difference was probably related to the poor carbohydrate intake. The RQ of patients normalized when energy intake increased to normal values, strongly suggesting that the decrease of RQ was an adaptive mechanism.

Undetectable concentrations of cytokines could be noteworthy. However, a methodologic error can be ruled out because we found very high concentrations of cytokines in the child with the heat-shock syndrome in the same run that we made the dilutions of cytokines for the children with leukemia. We therefore think that low-risk ALL is not a hypercatabolic disease, which is consistent with the absence of a raised REE and the nutritional status we found in our patients.

In conclusion, this study showed that neither body composition nor REE changed significantly in ALL patients at the time of diagnosis or during the first 3 mo of treatment. A recent reduction of energy (i.e., carbohydrate) intake was noted during the first month of the treatment but normalized on follow-up. Long-term follow-up is needed to detect and prevent obesity, which has been reported recently in leukemic children (22–24).

REFERENCES