Premature Adiposity Rebound in Children Treated for Acute Lymphoblastic Leukemia*

JOHN J. REILLY, ALISON KELLY, PAMALA NESS, AHMAD R. DOROSTY, W. HAMISH B. WALLACE, BRENDA E. S. GIBSON, PAULINE M. EMMETT, AND THE ALSPAC STUDY TEAM

ABSTRACT

The adiposity rebound (AR), when body mass index begins to increase after its nadir in childhood, is a critical period for the regulation of energy balance and adult obesity risk. The aim of the present study was to test whether children treated for acute lymphoblastic leukemia (ALL) experience premature AR. This might, in part, explain their tendency to develop obesity. Timing of AR was assessed by visual inspection of body mass index plots in 68 patients treated for ALL in first remission. This sample comprised all eligible patients treated in Scotland between 1991 and 1998, age 30 months or less at the time of diagnosis. Timing of AR in patients was compared against a cohort of 889 healthy British children studied during the 1990s using the same method. AR occurred significantly earlier in the patients treated for ALL (χ² test, P < 0.001). The AR had occurred in 43% (29 of 68) of the patients and 4% (40 of 889) of the comparison group by age 37 months. At 49 months AR had occurred in 81% (55 of 68) of the patients and 21% (190 of 889) of the comparison group. Treatment of ALL is associated with a significantly advanced AR. This might, in part, explain the extremely high prevalence of obesity in long-term survivors. Clinical management should focus on minimizing excess weight gain during therapy to reduce long-term obesity risk. (J Clin Endocrinol Metab 86: 2775–2778, 2001)

DISEASE-FREE SURVIVAL FROM childhood leukemia has improved significantly over the last 20 yr, to the extent that current emphasis on treatment is the quality of survival and the avoidance of long-term adverse effects of treatment (1). A number of adverse effects have now been described in survivors of acute lymphoblastic leukemia (ALL; Refs. 2 and 3). There is currently considerable concern over the endocrine/metabolic effects: patients who survive ALL are at greatly increased risk of obesity during therapy (4, 5), and after therapy as adult long-term survivors (6–9). They also seem to be at greater risk of other long-term sequelae, including the metabolic syndrome (10). For example, in Scottish children treated for ALL during the 1990s, prevalence of obesity [defined as body mass index (BMI) sd score >2.0] was less than 2% at diagnosis but rose to 16% by 3 yr after diagnosis (4). In English children treated for ALL during the 1970s and 1980s there was a 3-fold excess of obesity (defined as BMI >85th percentile) in long-term survivors compared with a reference population (7). Talvensaari et al. (10) studied a group of long-term survivors of childhood cancer (28 of 50 treated for ALL) and found significant odds ratios (ORs) compared with controls for risk of obesity (relative weight, >120%; OR, 4.5), fasting hyperinsulinemia (>111 pmol/L; OR, 3.0), and reduced high-density lipoprotein cholesterol (<1.07 mmol/L; OR, 7.9). In addition, survivors of childhood cancer were significantly more likely to show clustering of these cardiovascular risk factors (10).

Obesity in ALL develops from a prolonged period of positive energy balance, leading to weight gain in excess of expected rates. This period of positive energy balance begins early in treatment (4, 5) but continues beyond the end of therapy (4, 11, 12). The mechanisms underlying positive energy balance are not entirely clear, but a number of contributors have been definitively identified, notably reduced total energy expenditure secondary to reduced habitual physical activity during (11) and after (12) therapy. One mechanism that might contribute to the long-term problems of obesity in survivors of ALL is early AR. The AR is the period of childhood (typically between 5 and 7 yr; Refs. 13 and 14) when BMI and other indices of adiposity begin to increase after reaching their nadir (14). Early AR is associated with substantially increased risk of adult obesity (13, 14). Although the mechanisms that underlie this process are unknown (13, 15, 16), it is clear that the AR is a critical period for the development of adult obesity (15). Because peak incidence of ALL occurs around the time of the AR and excess weight gain is typical in ALL patients, particularly in the first year of treatment (4, 5), it seemed plausible that patients with ALL would be characterized by premature AR. However, no data on timing of AR are available for patients with ALL. Indeed,
only one published study has attempted to define timing of AR in any disease state (17). The primary aim of the present study was, therefore, to determine the timing of AR in a national cohort of patients treated for ALL in Scotland in the 1990s. A secondary aim was to provide normative data on timing of AR in a large, representative, and contemporary sample of healthy children.

Subjects and Methods

Patients

Patients were considered for study entry if they had been treated on one of two successive Medical Research Council United Kingdom-ALL treatment protocols at Scottish centers, namely UKALL-XI (1990–97) and MRC-97 (1997 to the present). These protocols have been described in detail elsewhere (18) but, in summary, involved use of multiagent chemotherapy to induce remission, followed by two to three intensifications and 100 weeks of maintenance chemotherapy. Maintenance therapy consisted of (UKALL-XI) daily 6 Mercaptopurine, weekly methotrexate, and four weekly cycles of vincristine and prednisolone. Patients treated on MRC-97 were randomly allocated to receive either prednisolone or dexamethasone as part of maintenance therapy.

Patients were considered for inclusion if they remained in continuous complete remission and had been treated in Scottish centers. They were excluded if they had relapsed, had received testicular irradiation, GH therapy, or had other conditions relevant to energy balance or growth (e.g. Down’s syndrome). Of 126 patients treated in Scotland on protocol UKALL-XI, 95 met these criteria. Of the 55 patients treated in Scotland on protocol MRC-97 (January 1997 to the present; data collection in April 2000), 41 met these criteria. Two additional entry criteria were applied in order that timing of AR could be identified with confidence. First, only those children diagnosed before the AR occurred were included (before the age of 30 months, Ref. 16). Second, only those children with data on heights and weights for at least 2 yr after diagnosis were included (that is a minimum of five measurements of BMI). After applying these additional criteria, the total sample size was 68, 41 from UKALL-XI and 27 from MRC-97.

Differences in the degree of excess weight gain shown by patients on the two protocols seemed unlikely on the basis of evidence in the literature (6, 19). However, we formally tested for differences in degree of excess weight gain between the two groups of patients using a two-sample t test, and for differences in timing of AR using a χ² test.

Determination of timing of AR in patients and comparison group

In the patients treated for ALL, BMI was calculated as weight (kg)/height² (m²) from measurements of height and weight made routinely for determination of drug dosage. These measurements were made by the nursing staff. We provided staff training (from an auxologist), checked and calibrated stadiometers and scales, and emphasized the importance of the measurements to the nursing staff in an effort to minimize measurement error. As an additional precaution, we used BMI measures at diagnosis and only every 6 months (22–26 weeks) thereafter for all eligible patients. Timing of AR was determined using the standard approach based on visual inspection, as described previously (14, 16). In brief, this involved using a plot of BMI against age for each individual to identify an upward trend (rebound) in BMI after its nadir (14, 16). To confirm that the rebound had occurred, we also specified that all measures of BMI after the nadir had to show an increase, and that this increase had to exceed 0.1 kg/m². BMI was also expressed as a z score relative to contemporary United Kingdom reference data (20) using software provided by the Child Growth Foundation (London, UK).

Comparison group

To assess whether the timing of AR in the patients with ALL was typical of contemporary British children a comparison group was required. It was essential that this comparison group was studied around the same time because there is evidence of a secular trend to earlier AR (20, 21). It was also essential that the same method of defining AR was used for both groups. We used exactly the same method to define timing of AR, described above, and our comparison group consisted of a cohort of 889 children from the Bristol area born in 1991 and 1992 who experienced AR in the mid to late 1990s (16). This cohort, the so-called “Children in Focus” subgroup of the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC), has been studied prospectively since birth and is broadly representative of the United Kingdom in terms of socioeconomic status (22). Summary anthropometric measurements from the cohort in early childhood were not significantly different from United Kingdom anthropometric reference data (22, 23). Measurements of BMI on the Children in Focus cohort were made at 4, 8, 12, 18, 24, 31, 37, 43, 49, and 61 months, as described previously (16, 22, 23). Measurements of height and weight were made by 5 highly trained researchers with calibrated equipment. The quality control procedures and results (e.g. interobserver differences) are available from the authors (Children In Focus: Development and Progress, 3rd edition, University of Bristol, 1997). In brief, all researchers followed the same measurement protocol, and their measurements of height and weight were formally compared against an experienced anthropometrist in a subsample of 10–20 children at each of the following ages: 4, 12, 25, and 49 months. Agreement with the anthropometrist after training was excellent in almost all cases, and where this was not the case further training was provided. Errors in data transcription were minimized by double entry/checking when data were put onto the Children in Focus database.

The timing of AR in a recent representative sample of healthy children has not been described in the literature: previous studies have published data on children who experienced AR in the 1960s to 1970s, before the recent secular trend (13, 14). We have previously described the characteristics associated with extremely early AR in healthy British children (16) but have not provided normative data on timing of AR. In the present study, we set out to describe the timing of AR in healthy British children and to use these data as a basis of comparison for the data on timing of AR obtained from the patients treated for ALL.

Statistical analyses and power

The primary aim of the analysis was to test for differences in timing of AR between patients with ALL and the healthy comparison group. We formally tested for such differences by using a χ² test on the distribution of AR between the two groups. The timing of AR in each group was described using simple plots of BMI and age as described above.

The power of the present study was difficult to determine at the outset because it was dependent on the magnitude of any difference between ALL patients and the comparison group. However, it was felt that power might be adequate with the sample size available to us given the dramatic difference in rates of weight gain between ALL patients and controls described in previous studies (4, 5, 11, 19).

Results

Characteristics of patients

Our sample of 68 patients consisted of 35 boys and 33 girls. The mean age at diagnosis was 2.6 yr (sd, 0.3). Only three of the patients were from ethnic minority groups. The mean BMI at diagnosis was 16.3 (sd, 1.4), and the mean BMI at AR 15.8 (sd, 1.1).

Rates of excess weight gain, and differences between patient groups

Rates of excess weight gain, expressed as changes in BMI sd score, did not differ significantly between patients treated on UKALL-XI and MRC-97. A mean change in BMI sd score to 2 yr after diagnosis for patients was +0.87 (sd, 1.30) for UKALL-XI and +0.65 (sd, 1.40) for MRC-97. There was no significant difference in the distribution of timing of AR between the patients treated on protocol UKALL-XI and those treated on MRC-97 (χ² test, P > 0.05). We also found no significant difference in the timing of AR between boys and
girls in patient and comparison groups ($\chi^2$ tests, $P > 0.05$). In the absence of significant differences between the protocols and the literature evidence that such a difference would be unexpected (6, 19), patient data from both protocols were combined for the subsequent analyses.

Timing of AR in the comparison group

Figure 1 describes timing of AR for the comparison group ($n = 889$). The AR had occurred by age 3 yr (37 months) in only 4.5% of children (40 of 889). This increased to 21.2% (190 of 889) by 49 months.

Timing of AR in the patients treated for ALL

Figure 1 describes timing of AR for the 68 patients with ALL. The AR had occurred by age 3 yr (37 months) in 29 of 68 patients (42.6%) and in 55 of 68 patients (80.9%) by age 4 yr (49 months). Differences in timing of AR between patients with ALL and the comparison group were highly significant ($\chi^2$ test, $\chi^2 = 10.2; P < 0.001$).

Discussion

Obesity, and its sequelae, are well established adverse consequences of ALL, its treatment, and/or the behavioral responses to ALL therapy (4–9, 11, 12). The present study demonstrated that children with ALL experience AR much earlier than their healthy peers. Because early AR is an important risk factor for adult obesity (13–15), this might, in part, explain the high prevalence of obesity in adult survivors of ALL. It is important to note that the influence of the AR on later obesity risk is a function of its timing and is independent of the BMI or degree of underweight/overweight when AR occurs (13). The present study suggests that the degree of positive energy balance characteristic of treatment for ALL is sufficient to produce early AR and that this should be a concern even for children with ALL who are not overweight or obese. Because the present study used a design that compared cases with controls, causal relations cannot be established definitively, but the association of ALL therapy and early AR was strong (Fig. 1). It should also be noted that our comparisons between patients and healthy children were restricted to BMI. More sophisticated measures, of body composition and/or fat distribution, might have revealed more subtle differences between the two groups (9, 24).

In the present study, the patients and comparison group were contemporary, but from different areas of the United Kingdom. The ALSPAC cohort was broadly representative of the United Kingdom (22, 23) in terms of socioeconomic status and anthropometry in early life. However, the secular trend to increasing fatness in British children has been slightly more marked in Scotland than the United Kingdom (25). It is, therefore, possible that there might be slight differences in timing of AR between Scottish and English children, but there are currently no data with which to address this question. In our view, the marked differences in timing of rebound observed between patients and the comparison group suggest that there is a real and clinically important difference in timing of AR associated with ALL treatment. Because normative data on the timing of AR are so difficult to obtain, the present study might also be useful as reference data for identifying unusually early or late AR in other disorders.

Whereas the mechanisms by which early AR sets later obesity risk are unknown (13, 16), it is clear that the AR is a critical period for the regulation of energy balance (15). Children with ALL have an early and predictable AR and so might represent a useful model for future studies of the mechanisms underlying the influence of timing of AR on regulation of energy balance (26). The mechanisms by which positive energy balance occurs in ALL are now reasonably clear. The principal difference in the components of energy balance between patients with ALL and controls is that the patients expend substantially less energy than controls (11, 12), largely due to reduced habitual physical activity both during (11) and after (12) therapy. Other mechanisms, such as steroid effects on appetite, or effects of treatment directed at the central nervous system on appetite regulation, might also contribute (27). However, evidence as to the magnitude of these effects is inconclusive for children treated on modern protocols (26).

In summary, the AR occurs much earlier in patients with ALL than in healthy children. Indeed, for most of the patients in the present study, plots of BMI against age suggested that the AR occurred within the first year of treatment for ALL. The occurrence of AR by age 4 is extremely unusual (13–16) and known to be associated with long-term obesity risk, but was the norm in our patients. Timing of ALL is an important independent risk factor for adult obesity (13–15), and the minimization of late effects of ALL therapy is now the focus of a great deal of attention. We, therefore, suggest that excess weight gain during therapy for ALL should be viewed with concern. Attempts to prevent the problem of early AR in these patients are indicated in the interests of prevention of later obesity. These efforts might take the form of encouraging a more active lifestyle (11, 12).

Acknowledgments

We thank all of the parents and children who took part in the study and the ALSPAC Study Team, which consists of interviewers, technicians, clerical workers, scientists, volunteers, and managers. We also thank Dr. Marie Francoise Rolland-Cachera for help and advice on the methodology for defining timing of the AR. Dr. Jan Love of the Rob-
ertson Centre for Biostatistics (Glasgow, Scotland) provided statistical advice, and the Child Growth Foundation (London, UK) provided the growth monitoring equipment. We thank Diane Henderson and Drs. Julianne Duff, Paula Shaw, and Derek King for assistance in collection of data on the patients with ALL; and Dr. Angela Thomas for allowing her patients to be included in the study.

References