Postgraduate Symposium

Childhood leukaemia: a model of pre-obesity

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The prevalence of obesity in children, as in adults, is increasing dramatically. The extent to which this is due to reduced energy expenditure, increased energy intake, or both, is unclear at present. This in part reflects the limitations of existing models of the pre-obese state. In childhood acute lymphoblastic leukaemia (ALL), patients typically gain weight excessively during and after 2 years of therapy, and are at high risk of becoming obese. Previous studies have failed to identify the cause of obesity in these patients. We have tested the hypothesis that excess weight gain in ALL is due to reduced total energy expenditure (TEE), measured using the doubly-labelled water method, and have identified risk factors for excess weight gain in ALL. Pre-obese children with ALL in the dynamic phase of weight gain are less physically active than their peers, with a reduced TEE of approximately 1·2 (95 % CI 0·2, 2·2) MJ/d. While other factors might contribute to excess weight gain, lifestyle (i.e. reduced habitual physical activity) plays a central role in ALL. Several considerations suggest that ALL might be a useful model of the pre-obese state: lifestyle is critical to development of obesity in ALL; ALL is relatively common; approximately 70 % of patients survive; patients are readily accessible during the 2 years of therapy and beyond.

Obesity: Physical activity: Doubly-labelled water: Energy expenditure

The prevalence of obesity among children and adolescents in the Western world has substantially increased during the past 30 years (Troiano & Flegal, 1998). Obesity is caused by a sustained imbalance between energy intake and energy expenditure, such that intake exceeds expenditure. The dramatic changes in obesity prevalence in adults (Prentice & Jebb, 1995) and children (Troiano & Flegal, 1998) with constant or declining energy intake imply that a lifestyle factor, probably reduced physical activity, is largely responsible for positive energy balance. This conclusion is supported by epidemiological evidence on the consequences of inactivity, particularly television viewing (Gortmaker *et al.* 1996), and the hypothesis that reduced energy expenditure predisposes to obesity is an attractive one (Dietz, 1996). However, studies of the role of reduced energy expenditure in the development of obesity have produced conflicting results (Griffiths & Payne, 1976; Roberts *et al.* 1988; Davies *et al.* 1991; Delany *et al.* 1995; Goran *et al.* 1995), and at present it is not clear whether obesity develops because of an excess in energy intake relative to expenditure, a reduced energy expenditure relative to intake, or a combination of both.

Our failure to understand the pathogenesis of obesity has been the result of two major methodological limitations. First, the difficulty in identifying and studying individuals who will become obese. Obesity is a static physiological state which, although identifiable, is of limited relevance to the development of obesity. Various models of 'pre-obesity' have been studied, including children of obese parents, children from ethnic groups at high risk of obesity, and children with disease states such as Prader-Willi syndrome (Donaldson *et al.* 1994). As models, these groups of children are not ideal, and studies of energy balance have either produced equivocal results (Goran *et al.* 1995; Roberts, 1995) or results which are of limited relevance to childhood obesity. The second major problem has been that the accuracy and precision of the methodology used for the measurement of energy intake and, to a lesser extent, energy

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expenditure has limited our ability to determine the relatively small degrees of energy imbalance which can lead to obesity (Rosenbaum *et al.* 1997). However, with the recent development of the doubly-labelled water technique, it has become possible to measure energy expenditure in free-living subjects with the necessary accuracy and precision to test hypotheses in relation to the causes of positive energy balance and obesity (Schoeller & Fjeld, 1991).

The aims of the present review are to (a) describe recent research, using state-of-the-art techniques for measurement of energy expenditure, on the causes of energy imbalance leading to obesity in children with acute lymphoblastic leukaemia (ALL) and (b) propose ALL as a potentially useful model of pre-obesity.

Childhood acute lymphoblastic leukaemia

ALL is the most common childhood malignancy, affecting approximately one in 3500 children in the UK each year and has a peak age of occurrence between 2 and 6 years of age (Pui, 1995), at approximately the time of the 'adiposity rebound' (Dietz, 1994). With current chemotherapy regimens long-term survival is expected in approximately 70–75 % of affected children (Burnett & Eden, 1997). Modern treatment protocols involve multi-agent chemotherapy to induce remission, followed by two or three blocks of intensive chemotherapy, and therapy directed at the central nervous system (cranial irradiation (CIrr) for high-risk patients, high-dose intravenous methotrexate or intrathecal methotrexate for low-risk patients). The patients also receive 2 years of 'maintenance' chemotherapy treatment, during which time they are treated as outpatients and live a relatively 'normal' life, attending school and living at home.

As survival rates have improved, it has become apparent that treatment of ALL has a number of long-term sequelae. These 'late effects' of treatment include obesity, the metabolic syndrome (Talevensaari *et al.* 1996), secondary malignancies, disorders of growth and puberty, cardiotoxicity, and educational and psychological dysfunction (Van Der Does-Van Den Berg *et al.* 1995).

Development of obesity in acute lymphoblastic leukaemia

Children treated for ALL are normally well-nourished at diagnosis (Odame *et al.* 1994; Van Dongen-Melman *et al.*

1995), but early studies by Sainsbury *et al.* (1985) and Zee & Chen (1986) confirmed a clinical impression that long-term survivors of childhood ALL tended to be overweight and obese. More recently, Odame *et al.* (1994) were the first to provide evidence of the pattern of excess weight gain in patients with ALL; they showed that excess weight gain occurred from the time of diagnosis and continued well beyond the end of therapy. Obesity does not appear to be a common consequence of other childhood malignancies (Odame *et al.* 1994). Odame *et al.* (1994) also showed that excess weight gain was more pronounced in girls than boys, and suggested that obesity might be a consequence of CIrr-induced hypothalamic dysfunction. Similar conclusions were reached in a study of a different cohort of British patients treated on the same protocol (Warner & Gregory, 1995). More recent evidence suggests that the between-sex difference in obesity risk in ALL is not present in children treated on protocols which do not include CIrr (Reilly *et al.* 1996*a*), and is not present at final height (Didi *et al.* 1995). Within the patient population with ALL, various factors have been proposed as being associated with an even higher risk of obesity (Sainsbury *et al.* 1985; Schell *et al.* 1992), but these have not been confirmed and the strength of their association with obesity is unknown. Identifying these 'risk factors' might provide important insights into the causes of obesity, and might also aid the prevention of the problem.

In a recent study, we examined changes in BMI standard deviation score relative to UK population reference data (Cole *et al.* 1995) up to 6 years after diagnosis in 126 Scottish ALL patients diagnosed between 1990 and 1997. (BMI is a simple proxy for overweight and obesity. In childhood, the BMI must be interpreted relative to a reference population. There is a consensus that this is best achieved by using the standard deviation score, a precise numerical summary of each child's placement relative to the reference population, independent of sex and age, in standard deviation units either above (positive scores) or below (negative scores) the mean of the reference population.) These patients were treated on the Medical Research Council protocol XI (Burnett & Eden, 1997), which did not include CIrr as standard treatment (Ventham *et al.* 1998). There was a significant increase in BMI standard deviation score from diagnosis to 3 years in the fifty-nine ALL patients on whom complete data were available (Table 1). However, the observed rates of excess weight gain were slightly less than those previously described in studies of patients treated with protocols that included CIrr (Odame *et al.* 1994). The results

Table 1. Annual mean changes in BMI standard deviation score from time of diagnosis to 3 years in fifty-nine Scottish patients treated on the Medical Research Council protocol XI (Burnett & Eden, 1997) (Redrawn from Ventham *et al.* 1998)

(Mean values and 95 % CI)

	Change in BMI standard deviation score from time of diagnosis					
	Combined (*n* 59)		Boys (*n* 28)		Girls (*n* 31)	
Period from diagnosis (years)	Mean	95 % CI	Mean	95 % CI	Mean	95 % CI
1	0·66*	0·41, 0·91	0·96*	0·60, 1·33	0·39*	0·10, 0·72
2	0·87*	0·64, 1·10	0·94*	0·60, 1·28	0·81*	0·47, 1·15
3	0·91*	0·69, 1·14	0·97*	0·58, 1·35	0·86*	0·60, 1·13

The mean change in BMI standard deviation score from the time of diagnosis was significant (paired *t* test): *$P < 0.05$.

also showed that the prevalence of obesity (defined as BMI standard deviation score > 2·0) steadily increased in the patients from 1·7 % at diagnosis to 15·3 % at 3 years after diagnosis (six to seven times the expected rate). This study also identified a number of risk factors which predisposed the patients to excess weight gain, including a low BMI standard deviation score at diagnosis, younger age at diagnosis, and gender. Despite reaching statistical significance ($P < 0.05$), the strength of these associations does not permit targeting of those patients at high risk of obesity, and all patients with ALL should be considered at risk.

The excess weight gain observed in children treated for ALL persists, and 40–50 % of young adult survivors are obese (Schell et al. 1992; Didi et al. 1995), with an unusually high proportion overweight (Zee & Chen, 1986). In addition, there is evidence that the survivors of ALL are fatter than might be implied by the degree of increase in relative weight which they show (Armburst et al. 1994; Talevensaari et al. 1996). In summary, children treated for ALL gain weight from the time of diagnosis at rates in excess of those from predicted, the process of weight gain continues well beyond the end of treatment, and an unusually high proportion of survivors are overweight and obese.

Causes of excess weight gain in acute lymphoblastic leukaemia

Energy intake

There is currently no evidence of unusually high energy intake in patients treated for ALL (Bond et al. 1992; Delbecque-Boussard et al. 1997; Reilly et al. 1998). While testing hypotheses in relation to energy intake is limited by flaws in the methodology, these studies do not support the hypothesis that hyperphagia, induced by hypothalamic insult or corticosteroid effects (Tataranni et al. 1996), is an important contributor to obesity in ALL. The evidence that excess weight gain also occurs in children treated on more modern protocols which do not employ CIrr (Van Dongen-Melman et al. 1995; Reilly et al. 1996a), and the evidence that the process can persist well beyond the end of therapy, is consistent with this conclusion.

Resting energy expenditure and diet-induced thermogenesis

A number of studies have concluded that resting energy expenditure (REE) is not abnormal in patients treated for ALL (Bond et al. 1992; Vaisman et al. 1993; Delbecque-Boussard et al. 1997), even in children studied during the dynamic phase of excess weight gain (Reilly et al. 1996a). Vaisman et al. (1993) also showed that diet-induced thermogenesis is normal in ALL patients, although Stallings et al. (1989) provided some preliminary evidence for inhibition of fat oxidation during certain stages of treatment for ALL.

Total energy expenditure and physical activity

Identifying the causes of energy imbalance in chronic disease requires an approach which involves measurement

of all components of energy balance (Reilly et al. 1997a). Two recent studies have shown that measurement of total energy expenditure (TEE), rather than just REE (which can be uninformative or misleading) is an essential component of this approach (Macallan et al. 1995; Motil et al. 1998). Before the work described here was carried out, there was no information on TEE in patients treated for ALL. However, there was some evidence that survivors of ALL may be less physically fit than their peers (Calzolari et al. 1985; Matthys et al. 1993; Jenney et al. 1995; Warner et al. 1997). It has been suggested that reduced aerobic capacity and impaired exercise tolerance might be secondary to cardiotoxicity of treatment, particularly on the older treatment protocols (Jenney et al. 1995), but the extent to which this can impair habitual physical activity on more modern protocols is unknown. One small study of engagement in habitual activity of patients with ALL by heart-rate monitoring showed reduced activity in patients with normal cardiac function compared with healthy controls (Reilly et al. 1997b).

We have recently measured all components of energy balance in twenty patients from Scotland who had been treated on the Medical Research Council protocol XI and compared them with twenty controls pair-matched for age, sex, fat-free mass, season and socio-economic status (Reilly et al. 1998). All the patients who participated in the study were in positive energy balance and had shown excess weight gain, but were not obese, and all were well at the time of the study, attending school and living as outpatients. TEE was measured using doubly-labelled water, REE by indirect calorimetry, energy expended on activity calculated as TEE–REE, energy intake by 3 d household-measures record and body composition by bioelectrical impedance using a prediction equation validated for Scottish children (Reilly et al. 1996b). The physical activity level was calculated as TEE : REE. We found that TEE was significantly higher in controls than patients ($P < 0.01$; Fig. 1), with a mean paired difference of 44 (95 % CI +20, +67) kJ/kg per d. The difference in TEE was largely due to a mean paired difference in energy expended on activity of 27 (95 % CI +3, +50) kJ/kg per d with a smaller mean paired difference in resting metabolic rate of 16 (95 % CI +2, +6) kJ/kg per d ($P < 0.05$). Mean physical activity level was 1·6 (SD 0·2) in the patients and 1·8 (SD 0·3) in the controls. Within the patients treated for ALL, lower levels of energy expended on activity were associated with a higher rate of excess weight gain (r −0·67, $P < 0.01$) over a 6-month follow-up period after the initial measurements. The application of the doubly-labelled water method has shown therefore that children treated for ALL are predisposed to excess weight gain, and ultimately obesity, by reduced TEE secondary to reduced habitual physical activity.

This work has revealed the importance of lifestyle to the development of obesity in ALL, and implies that the process is not an inevitable consequence of treatment (e.g. CIrr) and is not pathological in nature.

Conclusions

As noted previously, the epidemiological evidence suggests that reduced habitual physical activity can predispose to
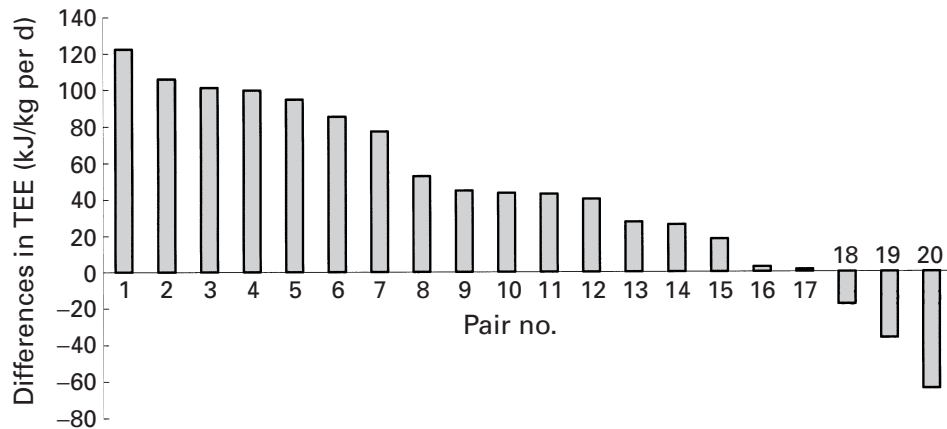
Fig. 1. Paired differences in total energy expenditure (TEE; kJ/kg body mass per d) between twenty controls closely-matched with patients who had been treated on the Medical Research Council protocol XI (Burnett & Eden, 1997) (Redrawn from Reilly *et al.* 1998.)

obesity, but there have been few well-established experimental models of this process. Childhood ALL might represent a useful model of the 'pre-obese' state, since it is the consequence of a lifestyle change, occurs predictably (Odame *et al.* 1994; Van Dongen-Melman *et al.* 1995), and is relatively common, with approximately 650 new cases per year in the UK (Eden *et al.* 1994). As a model, ALL also has a number of practical advantages, notably the extent to which patients are both accessible and relatively well for much of the period of treatment and beyond. An improved understanding of the process of obesity development in ALL, and the prevention of obesity in ALL, could provide valuable clues to the mechanisms which cause dysregulation of energy balance in childhood, and the means by which paediatric obesity might be prevented.

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