Obesity and Metabolic Syndrome in Adolescent Survivors of Standard Risk Childhood Acute Lymphoblastic Leukemia in Saudi Arabia

Fahad Aldhafiri, MSc,[1] Abdullah Al-Nasser, MB, ChB,[2] Abdulaziz Al-Sugair, MB, ChB A,[2] Hanan Al-Mutairi, RD,[2] David Young, PhD,[3] and John J Reilly, PhD[1,4]*

Background. This study estimated prevalence of unhealthy weight status and metabolic syndrome (MS) amongst Saudi survivors of standard risk ALL. ***Procedure.*** We recruited 56 survivors, mean age 13.4 years (SD 4.1), a mean of 9.1 years (SD 4.1) post-diagnosis. The BMI for age was used to define weight status relative to national (Saudi) and international (Cole et al., Cole-IOTF, WHO, and CDC) reference data. We measured body composition by dual-energy X-ray absorptiometry (DXA), waist circumference, blood pressure, lipid profile (HDL-C, Triglycerides), fasting glucose and insulin. ***Results.*** According to international definitions based on BMI for age, around half of the sample had unhealthy weight status. All of the approaches based on BMI for age underestimated over-fatness, present in 27/51 (53%) of the sample according to DXA. Prevalence of MS was 7.1% (3/42 of those over 9-years old) and 5.4% (3/56) by applying the International Diabetes Federation (IDF) definition and National Cholesterol Education Program Third Adult Treatment panel Guidelines (NCEP III), respectively. However, MS by the NCEP III definition was present in 19% of the overweight and obese survivors and 7.1% of the sample had at least two of the components of MS. ***Conclusion.*** Unhealthy body weight and over-fatness may be common amongst adolescent Saudi survivors of standard risk ALL, though overweight and obesity may be no more common than in the general Saudi adolescent population. Defining weight status using BMI underestimates overfatness. Ideally, body composition and cardiometabolic risk factors should be monitored at late effects clinics. Pediatr Blood Cancer 2012;59: 133–137.

Key words: acute lymphoblastic leukemia; late effects; metabolic syndrome; obesity

INTRODUCTION

Underweight, overweight, and obesity in childhood and adolescence have adverse consequences for health [1–4]. Obesity during and after treatment of ALL may be very common, even in patients treated on modern protocols, which do not involve cranial radiotherapy [5]. Metabolic syndrome (MS) may also be more common than might be expected in survivors of ALL [6,7]. A particular concern for obesity in ALL is the possibility that it might be associated with increased risk of relapse [8]. Underweight is also present in patients with ALL [9,10], and it may also increase risk of relapse [10,11].

Several major problems exist in the literature on weight status and MS in ALL: most studies have taken place during therapy, with limited evidence on survivors of ALL [12–15]; almost no evidence has been published outside the western world [6]; published studies have generally used older definitions of underweight, overweight, obesity, and MS-few have used recent international consensus definitions of unhealthy weight status and MS.

The primary aim of the present study was therefore to examine the prevalence of unhealthy weight status and MS in a relatively homogenous group of survivors-in first remission from standard risk ALL-in Saudi Arabia. A secondary aim was to examine whether BMI for age-based estimates of overweight and obesity agreed with measures of over-fatness from dual-energy X ray absorptiometry (DXA).

METHODS

Study Participants

The present study recruited standard risk patients with ALL in first remission, and who had been treated at King Faisal Specialist Hospital and Research Centre on treatment Protocol Cancer Study Group (CCG) 1891 and 1881, during the period 1994–2009. Standard risk ALL was defined as: age >1 and <10 years, initial white blood cell count $<50 \times 10^9$/L, DNA index $\geq$1.16 or $\leq$1.60, lack of adverse cytogenetics/molecular genetic studies (t(9;22)/ BCR-ABL; t(1;19)/ E2A-PBX1; t (4; 11)/AF4–MLL) and negative for central nervous system or testicular involvement. Patients were potentially eligible if they had been treated on CCG 1891 and 1881 and were in first remission (n = 77). This treatment protocol did not involve cranial radiotherapy. Patients were ineligible if they had relapsed (n = 3), were pregnant (n = 2), had pre-existing type 1 diabetes (before diagnosis of ALL) (n = 1) or had a longbone fracture in plaster (n = 2), leaving 69 potentially eligible survivors. The rationale for the exclusions was to leave a sample to which abnormalities in weight status or body composition might be attributable to ALL or its treatment. All 69 eligible survivors were invited to participate, but 56 (81%) agreed to take part in the present study. The sample of 56 patients was similar to the sample of 69 eligible for age at diagnosis, and for sex distribution, though the small number of those who did not consent precluded statistical analysis.

Ethics committee approval was provided by the Research Advisory Council (RAC) at King Faisal Specialist Hospital and Research Centre on 26 October 2009. Study participants provided informed written consent to their participation.

[1]College of Medical, Veterinary, and Life Sciences, University of Glasgow, Royal Hospital for Sick Children, Glasgow, Scotland, UK; [2]King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; [3]Department of Mathematics and Statistics, University of Strathclyde, Glasgow, Scotland, UK; [4]Physical Activity for Health Research Group, School of Psychological Sciences and Health, University of Strathclyde, Glasgow, Scotland, UK

Conflict of interest: nothing to report.

*Correspondence to: John J Reilly, PhD, College of Medical, Veterinary, and Life Sciences, University of Glasgow, Royal Hospital for Sick Children, 1st Floor QMH Tower Block, Glasgow G3 8SJ, Scotland, UK E-mail: john.j.reilly@strath.ac.uk

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Anthropometric Data

Height and weight were measured to 0.1 cm and 0.1 kg, respectively, using a Scale-Tronix 5002 stand on scale while patients removed shoes and outdoor clothes. The BMI was calculated and expressed as an age and sex specific z-score or centile.

Classification of Weight Status

In the present study, we used the most modern, recommended definitions of body weight status based on BMI for age. Saudi BMI reference data are available [16] in the form of centile charts for boys and girls and so these were used in the present study. Various international BMI for age reference data are also available, the most widely used probably those provided by WHO [17] and the US Centers for Disease Control and Prevention (CDC) [18], so both of these were also used in the present study. BMI z-scores were calculated from WHO 2007 reference data using WHO Anthro version 3.2.2, January 2011 software [19]. BMI z-scores were calculated relative to US CDC reference data [18]. When using Saudi, WHO, and US CDC BMI for age reference data obesity was defined conventionally, as ≥95th centile, overweight as 85th to 94th centile, and underweight as <5th percentile [18,20,21].

In recent years, the Cole-International Obesity Task Force (IOTF) BMI [22] based definitions of pediatric overweight and obesity have become popular [23]: these facilitate international comparisons of obesity prevalence and use age and sex specific cut-offs for absolute BMI. We therefore also defined overweight and obesity in participants in the present study using the Cole-IOTF approach. More recently, Cole et al. [24] proposed an international definition of pediatric underweight based on BMI for age and so we used this to define underweight [24].

Body Composition Measures

A recent systematic review [23] concluded that the BMI for age is a helpful simple proxy for excessive body fatness. However, the BMI may not be as informative as measurement of body composition in pediatrics in general, including studies of survivors of childhood cancer [25,26]. In addition, body composition is recommended by the International Diabetes Federation (IDF) as a useful research measure, which is relevant to defining MS [27]. In the present study, we therefore measured body composition (% body fat) in participants by DXA as recommended by Warner et al. [25] using DXA Lunar Prodigy software version 9.15.

Levels of total body fat % which are excessive (because of associations with adverse cardiometabolic risk profiles) have been established by previous studies as: >25% fat for males and >30% for females age 5–18 years, >25% and >32% in males and females aged over 18 years [28] and so these definitions were applied in the present study.

Metabolic Syndrome: Definitions and Measurements

We defined the presence or absence of the MS in all participants using two modern and widely accepted definitions: the IDF approach [29] and the approach of The National Cholesterol Education Program Third Adult Treatment Panel guidelines (NCEP III) modified by Cook et al. [30].

MS in 10–15 years was defined by the IDF as having central obesity assessed by Waist circumference (WC) ≥90th centile plus two or more of the following criteria: triglycerides ≥150 mg/dl; HDL-cholesterol < 40 mg/dl blood pressure ≥130/85 mm Hg; fasting glucose ≥100 mg/dl. For those age ≥16 years, MS was defined by the IDF as having central obesity assessed by WC ≥94 cm for men and WC ≥80 cm for women plus two or more of the following criteria: triglycerides ≥150 mg/dl; HDL-cholesterol < 40 mg/dl in males and <50 mg/dl for females; Blood pressure ≥130/85 mm Hg; fasting glucose ≥100 mg/dl.

The NCEP III approach to defining MS for those aged 10–19 years requires at least three of the following five criteria: (i) central obesity, WC ≥90th centile; (ii) triglycerides ≥110 mg/dl; (iii) HDL-cholesterol ≤40 mg/dl; (iv) blood pressure ≥90th centile; (v) fasting glucose ≥ 110 mg/dl. For those ≥19 years three criteria are required from the following: (i) central obesity assessed by WC ≥102 cm for men and WC ≥88 cm for women; (ii) triglycerides ≥150 mg/dl; (iii) HDL-cholesterol ≤ 40 mg/dl for men and HDL-cholesterol ≤50 mg/dl for women; (iv) blood pressure ≥130/85 mm Hg; (v) fasting glucose ≥110 mg/dl.

In order to apply these two approaches to defining the MS a single trained observer measured abdominal obesity by WC at 4 cm above the umbilicus [31], blood pressure, triglycerides, fasting glucose. We interpreted these in the age and sex specific ways recommended by the IDF [29] and by the NCEP [30]. In addition, we calculated the prevalence of 1 and 2 components of the MS by both definitions.

Statistical Analysis, Power, and Sample Size

Power of the present study was fixed by the size of the cohort of patients available to us, who had been treated on protocol CCG 1891. The sample size was similar to or larger than many previous studies of weight status in ALL [6,32–34].

Means and standard deviations are presented in the results unless otherwise stated. Normality of data was tested by using formal Normality tests. A *P*-value of < 0.05 was considered as significant. Minitab 15.1.30.0 software was used for all statistical analyses except for the weighted kappa analysis, which used Medcalc software version 11.5.0.0. Differences between groups were tested for statistical significance by using two sample *t*-tests. Two proportion tests were applied to test the significance of differences between two proportions.

The weighted Kappa statistic (k) with 95% CI was used to assess the degree of agreement between the different approaches to defining underweight, healthy weight, overweight, obesity, and overfatness. We also used the weighted kappa analysis as a preliminary test of agreement between the two definitions of pediatric MS. The k statistics were interpreted as recommended by Landis and Koch [35]: "slight agreement" 0.0–0.20; "fair agreement" 0.21–0.40; "moderate agreement" 0.41–0.60; "substantial agreement" 0.61–0.80; "almost perfect agreement" 0.81–1.00.

RESULTS

Characteristics of Study Participants

The sample of 56 consented to all measures, though five did not attend for DXA measurements. Mean (SD) time from diagnosis was 9.1 (4.1) years, and mean time from end of therapy was 6.2 (3.9) years. Characteristics of study participants are shown in Table I.

Weight Status of the Sample

Weight status of the sample is illustrated in Table II. Approximately half of the sample was of unhealthy weight status (underweight, overweight, obese) by most of the approaches used to define weight status, though prevalence of unhealthy weight status varied by the approach taken. In particular, the prevalence of overweight and obesity was lower when using the local Saudi BMI reference data (prevalence 21.4%; 12/56 participants) than when using the alternative definitions (prevalence of combined overweight and obesity varied between 28.6% and 32.1% for the other definitions). Underweight was present in the sample, with prevalence varying differing slightly between the different definitions, as illustrated in Table II.

Agreement Between Different Approaches to Defining Weight Status

Agreement between the different definitions based on BMI for age, using weighted Kappa (k) statistics, was "moderate-substantial" between use of the Saudi reference data and definitions versus those from the US CDC (k = 0.70) and WHO (k = 0.67). There was poorer agreement between the Saudi approach and the Cole et al. [24] and Cole-IOTF [22] approaches to defining weight status (k = 0.47).

Body Composition of the Sample

According to DXA estimates of body fatness, more than half of the sample (52.9%, 27 out of 51 survivors) had over-fatness. Mean (SD) body fat % by using DXA was 24.7% (SD 10.6) for males and 37.6% (SD 8.8) for females ($P < 0.001$).

When the ability of the various anthropometric approaches (with reference data from Saudi Arabia, the US CDC, the WHO and the Cole-IOTF approach) to defining overweight and obesity based on BMI for age was compared against the measures of overfatness by DXA (Table III), agreement was only fair [35].

Metabolic Syndrome

Prevalence of MS was 7.1% (3/42 survivors aged ≥10 years) by the IDF definition [29] and 5.4% (3 out of 56) by the NCEP approach [30]. Of the three survivors defined as having MS by the IDF definition, two survivors were also defined as having MS using the NCEP definition. The weighted kappa statistic for agreement between the two methods was 0.65, indicating "substantial agreement", but with a wide confidence interval (95% CI: 0.19–1.00). In those survivors who were overweight or obese (BMI at or above the 85th centile relative to CDC reference data) prevalence of MS was much higher (19% by the NCEP III criteria).

Prevalence of 1 MS component was 35.7% (15/42) using the IDF criteria, and 37.5% (21/56) using the NCEP III criteria. Prevalence of 2 MS components was 11.9% (5 /42) using the IDF criteria and 7.1% (4/56) using the NCEPIII criteria.

DISCUSSION

In the present study, around half of the adolescent survivors of standard risk ALL had unhealthy weight status (underweight, overweight, or obesity) by applying the international approaches based on BMI, an average of 6 years after completion of chemotherapy. Prevalence of excessive body fatness measured by DXA was very high, and much higher than the BMI for age-based definitions of overweight and obesity suggested. It is likely that

TABLE I. Characteristics of Study Participants Mean (SD)

	Males	Females	Total sample
	(n = 34)	(n = 22)	(n = 56)
Age (years)	13.0 (4.6)	14.0 (3.1)	13.4 (4.1)
Height (m)	1.49 (0.20)	1.51 (0.11)	1.50 (0.17)
Weight (kg)	42.0 (16.9)	49.3 (18.4)	46.7 (17.5)
Time from diagnosis (years)	9.1 (4.5)	9.1 (3.2)	9.1 (3.2)
Time since completion of therapy (years)	5.9 (4.5)	6.7 (3.1)	6.2 (3.9)
CDC[a] BMI-z score	−0.17 (1.6)	0.16 (1.3)	−0.04 (1.48)
WHO[b] BMI-z score	0.14 (2.0)	0.31 (1.5)	0.21 (1.77)
% body fat by DXA[c]	24.7 (10.6)	37.6 (8.8)	29.2 (11.7)

[a]CDC, US Centers for Disease Control and Prevention. [b]WHO, World Health Organisation. [c]DXA, dual-energy X-ray absorptiometry.

TABLE II. Prevalence of Obesity, Overweight, and Underweight by Four Methods

Reference approaches	Obesity (n), %	Overweight (n) %	Underweight (n), %
Saudi reference data [16]	(4) 7.1	(8) 14.3	(5) 8.9
Cole et al. and Cole-IOTF[a]; [22,24]	(5) 8.9	(13) 23.2	(12) 21.4
CDC[b] [18]	(6) 10.7	(10) 17.9	(10) 17.9
WHO[c] [17]	(6) 10.7	(12) 21.4	(7) 12.5

[a]Cole-IOTF, Cole-International Obesity Task Force. [b]CDC, US Centers for Disease Control and Prevention. [c]WHO, World Health Organisation.

TABLE III. Extent of Agreement (Weighted Kappa Statistic With 95%CI) Between Different BMI-Based Approaches for Defining Overweight and Obesity Compared to Over-Fatness Defined as Excessive[a] Body Fat % From Dual-Energy X-ray Absorptiometry

Comparisons	Weighted kappa	95% Confidence interval	Level of agreement [35]
DXA vs. Saudi reference data [16]	0.24	0.08–0.39	Fair
DXA vs. CDC[b] reference data [18]	0.34	0.16–0.51	Fair
DXA vs. Cole-IOTF[c] approach [22,24]	0.22	0.03–0.41	Fair
DXA vs. WHO[d] reference data [17]	0.39	0.21–0.57	Fair

[a]Excessive defined as: >25% fat for males and >30% for females age 5–18 years, >25% and >32% in males and females age over 18 years. [b]CDC, US Centers for Disease Control and Prevention. [c]Cole-IOTF, Cole-International Obesity Task Force. [d]WHO, World Health Organisation.

BMI-based approaches to defining overweight and obesity will underestimate the scale of the problem in survivors of ALL.

The optimal population reference data (for BMI for age or for body fatness) on which to base estimates of unhealthy body weight is unclear, though one common view is that such reference data should have been collected prior to the obesity epidemic. Data collected prior to the obesity epidemic might represent ''standards''. More recently collected data might describe norms characterised by a higher prevalence of unhealthy weight status [36].

While prevalence of underweight, overfatness, overweight, and obesity seemed high in the present study, comparison with recent Saudi population data is necessary to establish if this as an ALL-specific problem or if it simply reflects the nutritional status of contemporary Saudi adolescents. El Mouzan et al. [20] provide a healthy population-based comparison group for the present study. This survey of 19,317 Saudi children and adolescents, which defined overweight and obesity as BMI for age >85th and > 95th centiles, respectively relative to Saudi reference data for BMI for age [16], found that 34.4% of the children and adolescents were overweight or obese (combined). The prevalence of BMI for age defined overweight and obesity in the adolescent survivors of ALL in the present study (combined 28.5%) was actually lower than in the general population in Saudi Arabia, suggesting that overweight and obesity observed is probably not an ALL specific problem. Further research on the causes of obesity in ALL and the general population in Saudi Arabia would be desirable. We are not aware of any etiological studies of adolescent obesity in Saudi Arabia-studies to date have focused on describing the rapid recent increases in obesity prevalence [20,21].

While MS was not common in the present study, prevalence of 1 and 2 components of MS were higher. We are not aware of any comparable studies of prevalence of MS for the general adolescent population in Saudi Arabia, and so further research would be required to establish whether or not the prevalence estimates observed in the present sample were high or low.

Relatively few other studies have focused on medium term survivors of ALL and we have been unable to find any reports of weight status, body composition, or MS (with modern definitions) in survivors of ALL treated on modern protocols outside western countries [12,34].Warner et al. [25] found that the BMI for age provided a poor indicator of excess adiposity in patients with childhood cancer and other chronic diseases, consistent with the findings of the present study.

The present study was limited by small sample size, but the sample recruited was similar to or larger than a number of previous studies in this area [6,32–34] and was fairly homogenous, in that all participants were survivors of standard risk childhood ALL on the same treatment protocol. Another limitation was the short time between end of the therapy and the present study. Longer-term follow-up studies would be useful, and the high prevalence of both overfatness and unhealthy body weight status observed in the present study indicates that longer-term follow-up studies of survivors of ALL outside the Western world are indicated. While contemporary Saudi data were available on prevalence of overweight and obesity using the BMI for age, no Saudi data were available for body fatness measured by DXA and so a population comparison group was not available for body fatness.

CONCLUSIONS

Unhealthy body weight status and unhealthy body composition appear to be quite common among the medium-term survivors of standard-risk ALL in Saudi Arabia, though overweight and obesity may be no more common than in the general population. Use of BMI for age-based definitions of overweight and obesity will underestimate the prevalence of overfatness, and so body composition measurement should be considered. Future care of long-term survivors of ALL should include assessment of weight status, should consider body composition measurement rather than just measures of BMI, and should consider cardiometabolic health.

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