METABOLIC RISK IN LONG-TERM SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Survivors of childhood acute lymphoblastic leukemia (ALL) are at increased risk of metabolic dysfunction as a long-term side effect of cancer treatment. They have higher rates of adiposity, dyslipidemia, arterial hypertension and insulin resistance and are therefore more likely to suffer from cardiovascular diseases (CVD). Unhealthy behavior may further exacerbate morbidity.

The **AIM** of this study is to evaluate the modifiable factors of metabolic risk in survivors of childhood acute lymphoblastic leukemia (ALL) treated in a single Bulgarian pediatric hematology center.

PATIENTS AND METHODS:

- 47 patients in long-term remission

- mean age 20,6 ± 6,2 y (9 y – 32 y) (M:F 53,2%:46,8%)
- 19 survivors < 18 years (40,4%), 28 survivors ≥ 18 years (59,6%)
- treatment between 1990 – 2012 according to 2 ALL protocols: Dana Farber Cancer Institute Consortium (DFCI) protocol 87-01 and BFM protocols: BFM 1998, BFM 2002
- ≥ 5 years after completion of therapy, FU period: mean 11,4 ± 4,4 y (5 y - 25 y)

- 35 age- and sex-matched healthy controls

ALL survivors' initial disease characteristics, treatment exposure and follow-up period are summarized in Table 1.

	ALL survivors (n=47)
Age at Dg (months)	83 ± 54.5
Risk group	
high risk n (%)	16 (34)
standard risk n (%)	31 (66)
Cranial radiotherapy	
no n (%)	12 (25.5)
yes n (%)	35 (74.5)
Treatment protocol	
DFCI n (%)	19 (40.4)
BFM n (%)	28 (59.6)
Follow-up period	
5 – 10 y n (%)	20 (42.5)
10 – 15 y n (%)	15 (31.9)
> 15 y n (%)	12 (25.5)

Table 1. Disease characteristics and treatment exposure in ALL survivors

Clinical assessment:
Weight, Height, BMI, WC, blood pressure, pulse rate
Biochemistry: fasting Cholesterol, HDL-C, LDL-C, TG and BGL
Body composition evaluation (Dual-Energy X-ray Absorptiometry, Lunar Prodigy): Fat mass, Fat mass Index (FMI), % Fat, Android % Fat, Gynoid % Fat, A/G ratio

Questionnaires and interview:
Traditional cardiovascular risk factors (treatment for diabetes, arterial hypertension, hyperlipidemia, current smoking and sedentary lifestyle habits)
Physical activity (PA): PA adequate to WHO healthy PA recommendations; modified Godin Leisure-Time Activity Questionnaire

The metabolic syndrome (MS) was measured according to the International Diabetes Federation consensus.
Dyslipidemia was determined by presenting at least one of three factors: high LDL-C (≥ 3,36 mmol/l, high TG (≥ 1,7 mmol/l) and/or low HDL-C (< 1,03/1,29 mmol/l in children and men, and in women, respectively).

RESULTS:

The BMI, the SDS_{BMI}, the WC and the A/G ratio were higher in younger ALL survivors and in adult male survivors than among matched controls. Female survivors and female controls ≥18 y had n.s. difference (Table 2).

Survivors, especially children and male survivors, had significantly higher body fat mass than healthy controls (Figures 1 and 2). 57% of the adult female survivors had normal weight obesity (as defined by the BMI and the DEXA indices). Survivors treated with high doses of cranial radiotherapy (CRT)(≥ 20Gy) had significantly higher Fat mass (p=0,03), % FM (p=0,01), FMI (p=0,04), Android % Fat (0,02), Gynoid % Fat (p=0,02), and higher A/G ratio, BMI, SDS_{BMI} and WC (n.s.), than patients treated with lower doses or no CRT.

The prevalence of dyslipidemia was higher among survivors (Figure 3), and multiple abnormalities were more frequent in male than in female survivors. Similarly, the prevalence of MS components and their clustering was higher among ALL survivors than among controls (Figure 4).

The rate of modifiable factors of metabolic risk in survivors < 18 y is presented on Figure 5.

ALL survivors, especially children and females, were engaged in weekly sport activities twice less frequently than controls (2,2±2,6 vs 4,0±3,4, p=0,005). Fewer of them practiced sports on a regular basis (12% vs 44%, p=0,01) and complied with recommendations for healthy PA (44% vs 69%, p=0,03).

	participants < 18 years		p value	participants ≥ 18 years		p value
	survivors	**controls**		**survivors**	**controls**	
Weight (kg)	63.3 ± 14.2	51.6 ± 18.0	0.06	72.9 ± 22.9	66.8 ± 13.9	0.23
Height (cm)	162.5 ± 11.5	161.7 ± 16	0.88	167.0 ± 9.5	172.2 ± 8.7	0.04
BMI (kg/m^2)	23.8 ± 4.6	19.0 ± 3.7	0.008	25.7 ± 6.0	22.3 ± 3.4	0.02
SDS_{BMI}	1.02 ± 0.78	-0.23 ± 0.9	<0.0001	0.32 ± 1.1	-0.34 ± 0.7	0.01
WC (cm)	79.9 ± 10.4	65.9 ± 9.0	0.001	84.8 ± 16.8	78.0 ± 11	0.09
Android/Gynoid % Fat ratio	0.96 ± 0.1	0.69 ± 0.2	<0.0001	0.93 ± 0.22	0.86 ± 0.2	0.24

Table 2. Anthropometric characteristics of participants

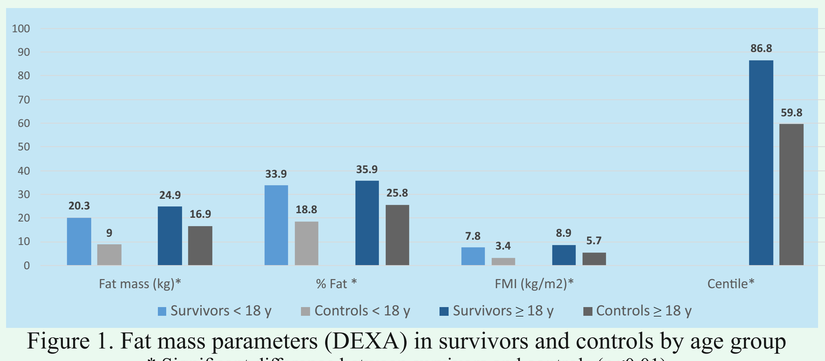

Figure 1. Fat mass parameters (DEXA) in survivors and controls by age group
* Significant difference between survivors and controls (p<0,01)

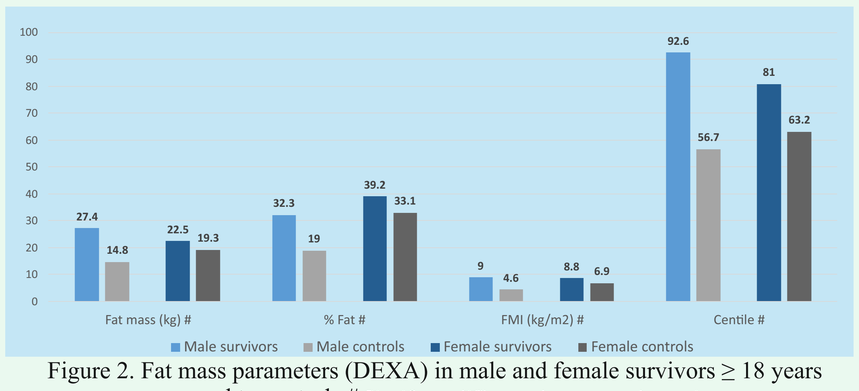

Figure 2. Fat mass parameters (DEXA) in male and female survivors ≥ 18 years compared to controls # Significant difference between male survivors and male controls (p<0,01)

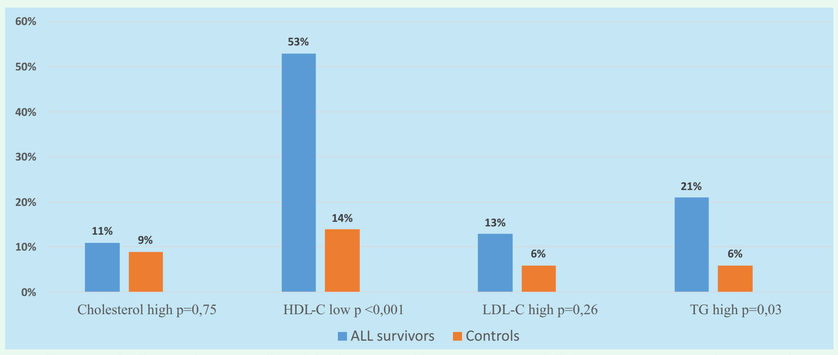

Figure 3. Prevalence of lipid abnormalities among ALL survivors and controls

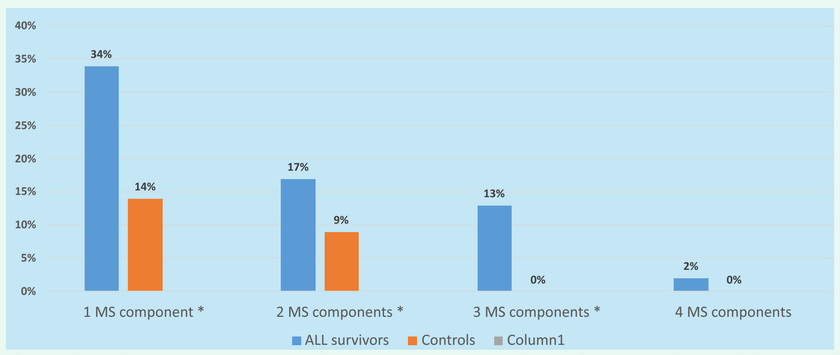

Figure 4. MS components clustering among ALL survivors in comparison with controls
* Significant difference between ALL survivors and controls (p<0,05)

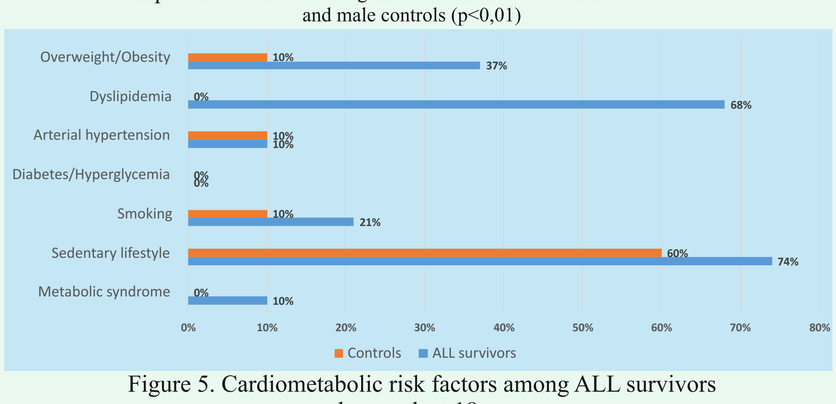

Figure 5. Cardiometabolic risk factors among ALL survivors and controls < 18 years

Conclusions:

At a relatively young age survivors of childhood ALL develop an unfavorable metabolic profile and increased clustering of traditional CVD risk factors.

Continuous monitoring, early identification and aggressive management of modifiable risk factors would reduce the overall metabolic burden.

Physical activity is an important tool for the prevention of premature metabolic complications in this high-risk group.

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