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Body composition in remission of childhood cancer

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Abstract. Here, we describe the results of a cross-sectional bioimpedance study of body composition in 552 Russian children and adolescents aged 7-17 years in remission of various types of cancer (remission time 0-15 years, median 4 years). A sample of 1500 apparently healthy individuals of the same age interval was used for comparison. Our data show high frequency of malnutrition in total cancer patients group depending on type of cancer. 52.7% of patients were malnourished according to phase angle and percentage fat mass z-score with the range between 42.2% in children with solid tumors located outside CNS and 76.8% in children with CNS tumors. The body mass index failed to identify the proportion of patients with malnutrition and showed diagnostic sensitivity 50.6% for obesity on the basis of high percentage body fat and even much less so for undernutrition – 13.4% as judged by low phase angle. Our results suggest an advantage of using phase angle as the most sensitive bioimpedance indicator for the assessment of metabolic alterations, associated risks, and the effectiveness of rehabilitation strategies in childhood cancer patients.

1. Introduction

An observed dramatic increase in cancer survival rates [1] have lead to the necessity of the prognosis and control of late adverse effects of treatment and quality of life in such patients during the rehabilitation period [2]. In adults, cancer development is not infrequently accompanied with a syndrome of progressive weight loss, or cachexia. Cachexia is more common in people with lung cancer (the most frequent form of malignant tumor in Russia) as well as in pancreatic and gastrointestinal cancers, and, in contrast to semistarvation, is accompanied with a pronounced depletion not only in fat mass, but also in fat-free mass [3]. Unlike this, the body mass in childhood cancer patients follows usually a normal pattern of change at the background of some growth delay, whereas in the structure of cancer morbidity in children, leukemia represents the most prevalent form [4]. Our previous study of a sample of 220 children in remission of acute lymphoblastic leukemia showed significant alterations in body composition parameters in this group relative to the same number of age- and sex-matched healthy controls [5]. Now we aim at the comparison of body composition and nutritional status in children and adolescents in remission of various cancer types, as well as at the identification and ranking of significant bioimpedance variables of patients' state.

2. Subjects and methods

552 children and adolescents (313 males and 239 females aged 7-17 years) after treatment for cancer comprised a patients' group and were assessed cross-sectionally in 2008-2011 at the Russian Field sanatorium (Chekhov area, Moscow region) by the staff members of rehabilitation department of the Federal Centre of Pediatric Hematology, Oncology and Immunology. All patients were in first remission, and none had received any hormone replacement therapy. Remission time ranged from 0 to 15 years. The patients' group was subdivided into five subgroups (denoted A to E) according to diagnosis: 64 were cured of solid (except for brain/CNS) tumors (subgroup A), 86 – of lymphomas and malignant histiocytosis (B), 320 – of acute lymphoblastic leukemia (C), 26 – of non-lymphoblastic leukemia (D), and 56 – of CNS tumors (E). In addition, 1500 apparently healthy children and adolescents (837 males and 663 females) of the same age range were measured representing a control group. The subjects were measured at schools in Moscow, Arkhangelsk, and Arkhangelsk region by the team of trained anthropologists from Moscow University.

Standing height was measured using a stadiometer in cancer patients and the GPM anthropometer in controls, respectively. Weight was measured on a digital scale in both groups. Body mass index (BMI) was calculated as body mass (BM) divided by standing height (Ht) squared.

The whole-body impedance was measured on the right hand side of the body using the bioimpedance meter ABC-01 'Medas' (SRC Medas, Russia) according to a conventional tetrapolar scheme at a frequency 50 kHz. Phase angle (PA) was calculated as $\arctan(X_C/R)\times180°/\pi$, where X_C is the reactance and R the whole-body electric resistance. Fat-free mass (FFM) was assessed using Houtkooper equation [6]: $\text{FFM}=0.61\times(\text{Ht}^2/R)+0.25\times\text{BM}+1.31$, where Ht is measured in cm. Fat mass (FM) was calculated as the difference between BM and FFM, and %FM as (FM/BM)×100. Other body composition variables, such as body cell mass (BCM) and skeletal-muscle mass (SMM), were determined by analogy using appropriate regression formulae provided by the manufacturer. Similarly to BMI, fat mass index (FMi) and fat-free mass index (FFMi) were calculated as FM/Ht^2 and FFM/Ht^2, respectively.

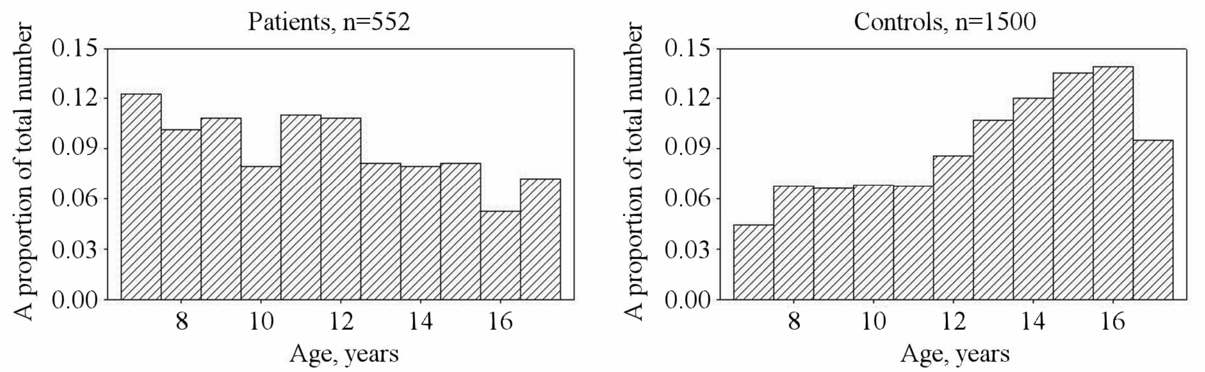

Fig. 1. Distributions of patients and controls according to age

Because of significant difference in age distributions of our patient and control groups (see Fig. 1 and Table 1), the data on healthy controls were first normalized using LMS method, and then the patients' data were expressed as z-scores according to the formula $z=[(y/\mu)^{\nu}-1]/(\sigma\nu)$ if $\nu\neq0$, and $z=\log(y/\nu)/\sigma$ if $\nu=0$, where y is the measured value of a parameter, and μ, σ and ν are, respectively, the mean, dispersion, and asymmetry of the probability distribution function for a subgroup of age-related healthy controls of the same sex. Finally, the data were drawn against the smoothing reference percentile curves representing the control group (for methodology, see [7,8]). For this, a recently developed by the one of authors (*OAS*) software program BIAStatistica [9] was used. The 85th and 95th percentiles for %FM and BMI, as well as the 5th percentiles for phase angle [10,11] and BMI in the control group, were used as a cut-offs to define malnutrition.

Two-sample Mann-Whitney rank test of the equality of two population medians was used. A p value of 0.05 was used to define significance.

3. Results and discussion

Basic anthropometric characteristics of cancer patients are shown in Table 1. Neither body mass, no BMI of total patients' group differ significantly from that of the control group, although in the subgroups B and D the body mass showed significant trends of opposite directions. Body height was moderately but statistically significantly decreased in patients, primarily due to pronounced stunting observed in the subgroup E (see Table 1).

Table 1. Basic anthropometric characteristics of cancer patients, mean (s.d.)

Parameter	Cancer patients (n=552)	Patient subgroups A (n=64)	B (n=86)	C (n=320)	D (n=26)	E (n=56)
Age, yrs	11.4 (3.1)*	11.1 (3.2)^{*bde}	12.6 (3.3)^{ac}	11.0 (3.0)^{*bde}	12.5 (3.3)^{ac}	12.3(2.8)^{ac}
Remission, yrs	4.3 (2.5)	4.6 (2.7)^{be}	3.6 (2.4)^{ac}	4.6 (2.4)^{be}	3.9 (2.0)	3.8 (2.7)^{ac}
BM, z-score	-0.1 (1.2)	-0.2 (1.1)^{d}	-0.3 (1.3)^{*cd}	0.1 (1.2)^{b}	0.3 (1.2)^{*abe}	-0.5 (1.4)^{d}
Ht, z-score	-0.2 (1.2)*	-0.1 (1.0)	-0.3 (1.2)*	-0.1 (1.1)	-0.2 (1.2)	-0.7 (1.4)*
BMI, z-score	0.0 (1.2)	-0.2 (1.2)^{d}	-0.2 (1.3)^{d}	0.1 (1.1)	0.4 (1.3)^{ab}	-0.1 (1.2)

* significant difference compared to healthy controls
$^{a\text{-}e}$ significant difference compared to patient subgroups A-E, respectively

Table 2. Bioimpedance parameters and body composition estimates in cancer patients, mean (s.d.)

Parameter, z-score	Cancer patients (n=552)	Patient subgroups A (n=64)	B (n=86)	C (n=320)	D (n=26)	E (n=56)
R	0.6 (1.2)*	0.5 (1.2)^{e}	0.7 (1.1)^{ce}	0.4 (1.2)^{be}	0.5 (1.1)^{e}	1.3 (1.3)^{**abcd}
X_C	-0.5 (1.2)*	-0.4 (1.0)^{c}	-0.4 (1.2)^{c}	-0.7 (1.1)^{abe}	-0.4 (1.2)	-0.2 (1.1)^{**c}
PA	-1.3 (1.3)*	-1.1 (1.3)^{ce}	-1.2 (1.2)	-1.3 (1.2)^{a}	-1.1 (1.3)	-1.8 (1.2)^{**a}
FM	0.3 (1.1)*	0.0 (1.2)^{**cde}	0.2 (1.1)^{d}	0.4 (1.0)^{a}	0.8 (1.0)^{**ab}	0.4 (1.0)^{a}
%FM	0.5 (1.1)*	0.1 (1.2)^{**de}	0.4 (1.1)^{de}	0.5 (1.0)^{e}	1.0 (1.0)^{ab}	0.9 (1.0)^{**abc}
FMi	0.4 (1.0)*	0.0 (1.2)^{**cde}	0.2 (1.1)^{de}	0.4 (1.0)^{a}	0.8 (1.1)^{ab}	0.6 (1.0)^{ab}
FFM	-0.3 (1.3)*	-0.3 (1.0)^{a}	-0.5 (1.2)^{ce}	-0.2 (1.2)^{be}	-0.1 (1.2)^{e}	-1.1 (1.6)^{**abcd}
FFMi	-0.4 (1.2)*	-0.4 (1.2)	-0.6 (1.1)^{c}	-0.2 (1.2)^{be}	-0.1 (1.4)^{e}	-0.9 (1.3)^{**acd}
SMM	-0.4 (1.2)*	-0.3 (0.9)^{e}	-0.6 (1.1)^{ce}	-0.3 (1.2)^{be}	-0.4 (1.1)^{e}	-1.2 (1.6)^{**abcd}
%SMM	-0.2 (1.1)*	0.0 (1.1)^{e}	-0.2 (1.1)^{e}	-0.2 (1.0)^{e}	-0.6 (1.4)	-0.7 (1.3)^{**abc}
BCM	-0.7 (1.3)*	-0.6 (1.2)^{e}	-0.9 (1.2)^{ce}	-0.6 (1.3)^{be}	-0.5 (1.1)^{e}	-1.5 (1.6)^{**abcd}
TBW	-0.3 (1.3)*	-0.3 (1.0)^{e}	-0.5 (1.2)^{ce}	-0.2 (1.1)^{be}	-0.1 (1.2)^{e}	-1.1 (1.6)^{**abcd}
ECF	-0.7 (0.7)*	-0.7 (0.6)^{e}	-0.9(0.7)^{**d}	-0.7 (0.7)^{e}	-0.7 (0.5)^{b}	-1.1 (0.8)^{**ac}

* significant difference compared to healthy controls
** significant difference compared to total patients group
$^{a\text{-}e}$ significant difference compared to patient subgroups A-E, respectively

In contrast to anthropometric data, all the parameters of bioimpedance and body composition differed significantly in the two groups (see Table 2). Importantly, the most pronounced changes occurred in the values of phase angle which is directly measurable and, hence, is independent of any assumptions accompanying BIA predictions of body composition. As opposed to Table 1, the parameters present in Table 2 showed unidirectional trends and changed only in amplitude. The subgroup E had the largest, and the subgroup A the least, extent of the parameters change (and, hence, metabolic alterations) compared to healthy controls. In the subgroups A and E, the mean values of 10 out of 13 variables presented in Table 2 were significantly different.

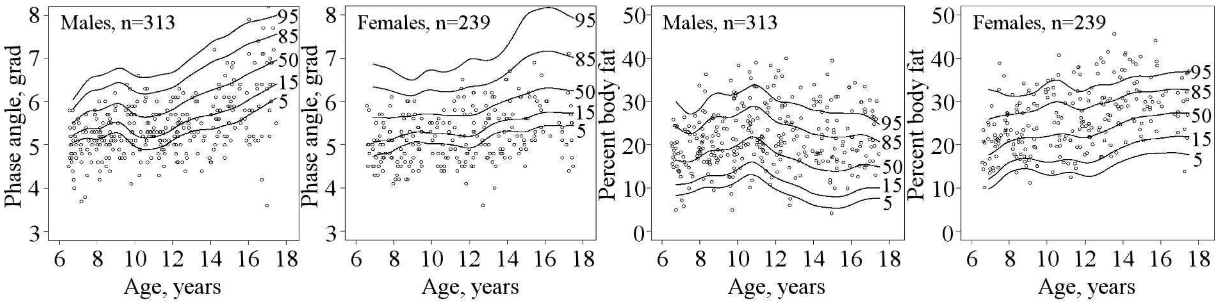

Fig. 2. Scatter plots of phase angle and percentage body fat across age in cancer patients. The smoothing reference percentile curves representing the control group are shown as continuous lines

Fig. 2 shows scatter plots of PA and %FM in cancer patients across age against the reference percentile curves for our healthy controls. It can be seen that a significant proportion of male and female patients have PA values below the 5th percentile of the reference group thus reflecting a pronounced undernutrition state. Similarly, a considerable number of patients had %FM values above the 85th and 95th percentiles regarding them as having overweight or obesity. The data on prevalence of malnutrition in the two groups according to various diagnostic criteria are summarized in Table 3.

Table 3. Prevalence of malnutrition in patients and controls (%) according to various diagnostic criteria

Malnutrition sign	Control group (n=1500)	Patients' group (n=552)	Patient subgroups				
			A (n=64)	B (n=86)	C (n=320)	D (n=26)	E (n=56)
Overweight by %FM ($1.04<Z_{\%FM}<1.65$)	11.3	16.5	12.5	12.8	16.9	23.1	21.4
Overweight by BMI ($1.04<Z_{BMI}<1.65$)	9.8	10.6	7.8	5.8	12.8	7.7	10.7
Obesity by %FM ($Z_{\%FM}>1.65$)	5	15.4	10.9	12.8	13.8	26.9	28.6
Obesity by BMI ($Z_{BMI}>1.65$)	5.4	7.8	6.3	7.0	7.2	23.1	7.1
Normal weight obesity ($Z_{BMI}<1.04$; $Z_{\%FM}>1.65$)	0.3	4.2	1.6	3.5	3.1	3.8	14.3
Undernutrition by PA ($Z_{PA}<-1.65$)	5.1	43.5	34.4	36.0	44.4	38.5	62.5
Undernutrition by BMI ($Z_{BMI}<-1.65$)	4.7	8.2	10.9	11.6	6.6	3.8	10.7

Overweight and obesity judged from %FM occurred in 31.9% of cancer patients, twice as much as compared to healthy controls (16.3%). In spite of significant correlation between BMI and %FM in patients ($r=0.73$, $p<0.05$), the body mass index failed to detect this marked distinction between the study groups (see Table 3) and showed low diagnostic specificity for obesity (i.e. the ability to correctly identify those with the disease) at the level of 50.6% compared to bioelectric impedance analysis. This is due to the fact that an increase in body fat in patients was accompanied by a proportional decrease in fat-free mass so that BMI values were not affected significantly even in individuals with high percentage fat mass content (see Table 2). The prevalence of normal weight obesity was uncommonly sizeable, reaching a maximum of 14.3% in the subgroup E. Like the usual obesity, normal weight obesity is associated with an increased risk of metabolic syndrome and cardiovascular pathology [12].

On the basis of phase angle, reflecting a proportion of metabolically active body cell mass in fat-free mass [13], 43.5% of patients were considered malnourished (see Table 3). This number is close to the result of Murphy et al [14] who reported a proportion of malnourished of 45% among children being treated for cancer and blood-related disorders based on BCM estimates using total body potassium counting. From this, one can speculate that malnutrition, if tolerated, can persist for years after treatment of cancer thus representing a matter of concern. On the basis of BMI, only 8.2% of cancer patients were defined as undernourished (see Table 3). The sensitivity of BMI for undernutrition was only 13.4% as judged by low phase angle.

Based on meeting at least one of the following two malnutrition criteria, namely high percentage fat and low phase angle, 52.7% of subjects in the total patient group were considered malnourished with the range between 42.2% (subgroup A) and 76.8% (subgroup E of patients with CNS tumors). Because of known association of malnutrition with the reduced tolerance to chemotherapy, increased susceptibility to infections and unfavorable outcomes [15,16], it is practical to use bioimpedance analysis, as a safe, rapid, inexpensive and portable method, for monitoring of nutritional state in pediatric oncology patients. A schedule for such an assessment containing a prescription of monthly body composition screening for nutritional state and alterations with a subsequent adaptation of substrate intake according to current requirements was proposed recently in [17].

Taken together, our data show significant level of malnutrition in children and adolescents in remission of cancer depending on the type of malignancy. The results suggest an advantage of using phase angle as the most sensitive bioimpedance indicator for the assessment of metabolic alterations, associated risks, and effectiveness of rehabilitation strategies in childhood cancer patients. For adverse late effects prophylaxis, additional tracking and control of %FM could also be useful.

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