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REVIEW

Is physical fitness decreased in survivors of childhood leukemia? A systematic review

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The aim of this review is to determine whether physical fitness, assessed by peak oxygen uptake (VO_{2peak}) measurement, is reduced in survivors of acute lymphoblastic leukemia (ALL) compared to healthy children. A systematic literature search (up to June 2004) was performed using Medline, Sportdiscus, Cinahl, Embase, Cochrane and PEDro database and reference tracking. The VO_{2peak} ($ml\,kg^{-1}\,min^{-1}$) reached during a maximal exercise test until volitional exhaustion was used as the main outcome for this review. In all, 17 studies were identified in the literature. Data from three studies (102 ALL survivors, age ranging from 7 to 19 years) were pooled in a meta-analysis. Although there was a significant heterogeneity between the included studies ($P=0.0006$), the standardized mean difference (SMD) value of −0.61 ($P=0.07$) indicated that VO_{2peak} tended to be reduced in survivors of childhood ALL compared to healthy control subjects, that is, decrease of $-5.97\,ml\,kg^{-1}\,min^{-1}$ (95% confidence interval (CI): (−12.35, 0.41); $P=0.07$) or −13% (95 % CI: (−27, 0.004)). Physical fitness tends to be reduced in survivors of ALL during childhood, which suggests the need for this population group to engage in regular physical activities with the purpose of increasing their functional capacity. Although more research is needed, this functional improvement might ameliorate the quality of life of ALL survivors as physical and outdoors activities are an essential part of daily routine during childhood.
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Introduction

The peak oxygen uptake (VO_{2peak}) attained during a graded maximal exercise to volitional exhaustion is considered by the World Health Organization as the single best indicator of aerobic physical fitness.[1] This variable, commonly expressed as the volume of oxygen consumed per unit of time relative to body mass ($ml\,kg^{-1}\,min^{-1}$), is also a valid indicator of health status[2] and a powerful predictor of mortality in both healthy and diseased individuals.[3,4] The improvements in exercise capacity and VO_{2peak} brought about by training are related to improved quality of life (QOL), particularly in patients with exercise capacity limited by various disease processes.[5]

In adult cancer patients/survivors, it is not untypical to measure VO_{2peak} levels considerably lower (~50%) than predicted, which reflects the sedentary life habits and poor physical condition of this population group.[6] Poor physical condition self-perpetuated by sedentarism is largely responsible for the disrupting symptoms of fatigue that these individuals experience during normal activities of daily living, with subsequent impairment in QOL.[6] In turn, increases in functional capacity brought about by regular exercise training are reflected by higher VO_{2peak} levels and result in improved OQL, that is, normal activities can be carried out with no fatigue.[7–10]

Less research has focused on the physical capacity and VO_{2peak} of children with cancer or survivors of cancer during childhood. Most studies have been performed on children survivors of acute lymphoblastic leukemia (ALL) and it is unclear whether their VO_{2peak} is significantly decreased compared to healthy controls. For instance, Vizinova *et al*[11]showed no significant difference between ALL survivors and controls, while other authors found significantly decreased VO_{2peak} levels in the former.[12–14] Outdoor physical activities involving cardiorespiratory work of moderate intensity are an essential part of the daily routine of children.[6] Thus, it would be interesting to assess if functional capacity, assessed by VO_{2peak} measurement, is significantly decreased in children survivors of ALL. If this is the case, exercise training prescription is necessary to improve their QOL and more research is warranted in this field.

It was therefore our purpose to determine whether the physical fitness of ALL survivors, assessed with VO_{2peak}, is decreased compared to healthy age-matched children.

Materials and methods

Search strategy

Publications were selected based on a literature search from 1966 until June 2004 using the Medline, Pubmed, Sportdiscus, Cinahl, Embase, Cochrane, and PEDRO database. Search terms 'physical fitness', 'exercise testing', 'exercise', 'exercise capacity', 'exercise tolerance', 'child', 'survivors', 'acute lymphoblastic leukemia', and 'leukemia' were used. References of the selected papers were tracked to find additional publications on this subject.

Selection of publications and types of outcome measures

We first selected all publications that reported one or more of the following outcome variables in ALL survivors: VO_{2peak} (in $ml\,kg^{-1}\,min^{-1}$), maximal heart rate, respiratory exchange ratio (RER), and exercise testing on a treadmill or cycle ergometer. Thereafter, we included in this study only those publications

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reporting: (1) data of survivors of childhood ALL included within the same homogeneous group (ie, excluding survivors of any other type of cancer during childhood) and their corresponding healthy controls, (2) VO_{2peak} values (in $ml\,kg^{-1}\,min^{-1}$) measured during a graded maximal exercise to volitional exhaustion, (3) description of methodology (gas-exchange analysis) for VO_{2peak} measurement, and (4) description of subjects' characteristics (both ALL survivors and controls).

Data were extracted from the publications by two independent reviewers and entered into Review Manager 4.2.3 (Update Software, Oxford, UK).

Statistics

DerSimonian and Laird Random Effects Model were used for analyzing the results on VO_{2peak} because of the significant heterogeneity between the studies. The data were pooled using standardized mean differences (SMDs). SMD is the difference between two means divided by an estimate of the within-group standard deviation, and can be considered as an effect size, for example, negative values for SMD would indicate a lower physical fitness of childhood survivors of ALL compared to healthy controls. The level of statistical significance was set at $P<0.05$.

Results

A total of 17 published studies (two of which were written in the Czech[11] and Polish language[15]) were identified in the literature. Of them, 14 did not meet the criteria described above for inclusion in the meta-analysis (Table 1). The study by Matthys *et al*[13] was excluded because they included in the same group ALL survivors and childhood survivors of several types of cancer other than ALL. The studies from Ostanski *et al*,[15] Black *et al*,[16] Kadota *et al*,[17] Lipshultz *et al*,[18] Pihkala *et al*,[19] Calzolari *et al*[20] Turner-Gomez *et al*,[21] and Zalewska-Szewczyk *et al*[22] were excluded from the meta-analysis, because of missing or incomplete description of the methodology (gas analysis) for VO_{2peak} measurement. The study by Prestor *et al*[23] lacked a clear description of the patients. Johnson *et al*[24] reported only the results of submaximal testing and did not report VO_{2peak} values directly measured during a maximal graded test to exhaustion. Jenney *et al*[25] expressed the results as percent predicted values, and did not report absolute values of VO_{2peak}. Sharkey *et al*[26] did not describe their control subjects, and McKenzie *et al*[29] studied only patients treated for solid tumor cancers.

A total of 102 childhood survivors of ALL and 99 control subjects from three studies were included in this review (Table 2). For the study that reported VO_{2peak} values separately for girls and boys,[14] VO_{2peak} data were also entered separately into the meta-analysis. One study reported values separately for patients with and without normal stress echocardiography.[12] The VO_{2peak} data for this study were also entered separately into the present meta-analysis. All included studies used a calibrated metabolic cart for gas-exchange analysis. Despite variations between studies in exercise mode (subjects pedaling on a cycle ergometer[11] or running/walking on a treadmill[12,14]) and protocols (ie, different rates of workload increases to attain exhaustion) and instrumentation (ie, different commercial models of metabolic carts for gas-exchange measurement), the measurement of VO_{2peak} values was based on the same methodology in all the three included studies. None of the studies included in the meta-analysis specified the number of patients who underwent bone marrow transplantation (BMT). This is to be kept in mind as BMT is associated with reduced VO_{2peak} levels in survivors of childhood ALL.[25]

The results of the meta-analysis are displayed in Table 3. Although there was a significant heterogeneity between the included studies ($P=0.0006$), the SMD value of -0.61 ($P=0.07$) indicated that VO_{2peak} tends to be reduced in survivors of childhood ALL compared to healthy control subjects, that is, decrease of $-5.97\,ml\,kg^{-1}\,min^{-1}$ (95% confidence interval (CI): $(-12.35, 0.41)$) or -13% (95% CI: $(-27, 0.004)$).

Table 1 Studies excluded from the meta-analysis

Study	*Sample size (survivors/ controls)*	*Subjects' age (years)*	*Disease subgroups*	*Ergometer*	*VO_{2peak} determination*
Matthys *et al*[13]	35/50	10–19	ALL, ANLL, NHL, HL, WT, NB, MB, RS, TC survivors	Cycle ergometer	Direct
Ostanski *et al*[15]	36/28	12–24	ALL	Treadmill	Direct
Black *et al*[16]	56/RV	9–27	ALL, AML	Cycle ergometer	Direct
Kadota *et al*[17]	12/NR	13–27	HL	Cycle ergometer	Direct
Lipschultz *et al*[18]	115/NR	4–32	ALL	Cycle ergometer and treadmill	Direct
Pihkala *et al*[19]	30/38	8–25	ALL, AML, HD, spinal cord glioma, Askin tumor	Cycle ergometer	Direct
Calzolari *et al*[20]	15/RV	9–19	ALL, ANLL	Cycle ergometer	Direct
Turner-Gomes *et al*[21]	12/RV	8–24 years	ALL	Cycle ergometer	Direct
Zalewska *et al*[22]	50/20	5–20 years	ALL, ANLL	Cycle ergometer	Direct
Johnson *et al*[23]	13/15	9–17	Childhood cancer	Cycle ergometer	NR
Prestor *et al*[24]	46/NR	5–23 years	ALL	Cycle ergometer	NR
Jenney *et al*[25]	57/128	6–30	ALL, ANLL	Cycle ergometer	Direct
Sharkey *et al*[26]	10/NR	19 ± 3 years	ALL, Ewings' tumor, RS, NT	Cycle ergometer	Direct
McKenzie *et al*[29]	34/15	8–18	Solid tumor	Cycle ergometer	Direct

RV = reference values; NR = not reported; ALL = acute lymphoblastic leukemia; ANLL = acute nonlymphoblastic leukemia; AML = acute myoblastic leukemia; ANLL = acute nonlymphoblastic leukemia; NHL = non-Hodgkin's lymphoma; HL = Hodgkin's lymphoma; WT = Wilms' tumor; NB = neuroblastoma; MB = medulloblastoma; RS = rhabdomyosarcoma; TC = thyroid carcinoma.

Table 2 Studies included in the meta-analysis

Study	Sample size (survivors/controls)	Disease subgroups	Controls	Subjects' mean (s.d.) age (years)	Physical activity of controls	Anthracycline dose ($mg\,m^2$)	Cranial irradiation	Mean (s.d.) age (years) at diagnosis	Mean (s.d.) length of time (years) after treatment	Ergometer/protocol
Vizinová *et al*[11]	29/29	ALL survivors (13 boys and 16 girls)	Age and sex-matched healthy children	ALL survivors: 12 (3) (range: 8–16); controls: NR	Not engaged in specific physical training	Mean: 224 (s.d. = 39.4)	None	NR	4.8 (2.1)	Cycle ergometer/BW
Hauser *et al*[12]	38/38	ALL survivors (22 boys and 16 girls)	Healthy children matched by age and body surface area	ALL survivors: 6 (2); range: NR; controls: 6 (2)	Normal physical activity of daily life	Mean: 107; range: 32.4–412.5	NR	NR	Mean value: NR (>6 months)	Treadmill/Bruce protocol
Warner *et al*[14]	35/32	ALL survivors (14 boys and 21 girls)	Siblings of ALL survivors	ALL survivors: 13 (3) (boys); 12 (3) (girls) (range: 7–19); controls: 13 (3) (boys); 12 (3) (girls)	NR	Range: 0–330	5 patients 24 Gy, 30 patients <18 Gy	3.2 (1.4)	6.6 (3.3) (>1.5 in all subjects)	Treadmill/Balke protocol

s.d. = standard deviation; NR = not reported; ALL = acute lymphoblastic leukemia; BW = protocol based on body weight.

Discussion

The results of the present systematic review indicate that the VO_{2peak} values (and thus the fitness level) of survivors of childhood ALL tend to be reduced (average of $\sim -6\,ml\,kg^{-1}\,min^{-1}$ or -13%) compared to healthy controls. Besides the decrease in QOL associated with lower VO_{2peak} levels, the aforementioned average decrease in the VO_{2peak} of ALL survivors is of clinical relevance as this variable is a powerful predictor of mortality in both healthy and diseased individuals,[3,4] for example, a $-3.5\,ml\,kg^{-1}\,min^{-1}$ reduction is associated with a 12% decrease in the survival rates of diseased people.[4]

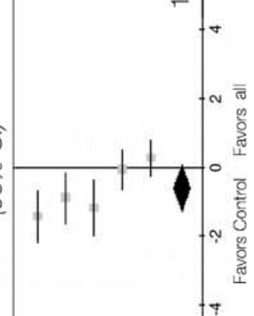
There existed some heterogeneity between studies, mainly attributable to the study of Vizinova *et al.*[11] These authors did not find significant differences between ALL survivors and control subjects. It must be, however, noticed that ALL survivors were encouraged to be physically active, whereas the children of the control group followed a sedentary lifestyle. The second factor that contributed to the heterogeneity between studies arises from the inclusion of ALL survivors with normal stress echocardiography in one of the studies.[12] Indeed, Hauser *et al*[12] found no significant differences in exercise capacity between ALL survivors with normal stress echocardiography results and healthy control children. This finding suggests that impaired cardiac function is responsible, at least partly, for the reduced functional capacity of ALL survivors, as discussed below. On the other hand, the wide CI we obtained (impairment -13%, 95% CI: (-27, 0.004)) indicates a considerable variation in the physical fitness levels of ALL patients after successful treatment. This might be due to differences in treatment and response to treatment in leukemia patients. For instance, Sharkey *et al*[26] found normal exercise capacity in patients receiving minimal doses of anthracycline and no irradiation.

In humans, decreases in VO_{2peak} are largely attributable to impaired cardiac function as VO_{2peak} mainly reflects (and is largely limited by) maximal O_2 supply to muscles (ie, maximal cardiac pump capacity) rather than maximal rate of O_2 utilization by muscle mitochondria.[27,28] Anticancer therapy may affect central cardiac dynamics and thus blood supply to body tissues, particularly exercising muscles. Anthracyclines can induce myocardial damage (eg, doxorubicin-induced cardiomyopathy) with subsequent decreases in cardiac output.[29,30] Sedentary habits (especially bed rest) induce cardiac atrophy and further reduce stroke volume and thus cardiac output in young adults[31] and children.[32] Since sedentary ALL survivors with reduced VO_{2peak} are able to reach normal values of maximal heart rate during exercise,[13,14] impaired stroke volume is largely responsible for their reduced cardiac output and thus decreased VO_{2peak} (as cardiac output is the product of heart rate by stroke volume). Anticancer therapy can also alter the exercise capacity of ALL survivors due to its deleterious effects on lung function. Craniospinal irradiation, cyclophosphamide or lung infections during or subsequent to treatment for leukemia (eg, bacterial, or due to respiratory syncytial virus, candida, pneumocystis or cytomegalovirus) can reduce total lung capacity.[25] Lung function impairment in ALL survivors is reflected by the occurrence of arterial desaturation (oxygen saturation values $<90\%$) during exercise.[13]

Besides insufficient pumping of oxygenated blood to working muscles, several phenomena at the peripheral (muscle tissue) level might severely limit the maximal capacity of muscle fibers to consume oxygen and further decrease the VO_{2peak} of ALL survivors. Muscle atrophy is a common problem in this population group due to the catabolic effects of several

Table 3 Forrest plot with the comparison of VO_{2peak} values of ALL patients with controls

Study or subcategory	*N*	*All patients (mean (s.d.))*	*N*	*Healthy controls; mean (s.d.)*	*SMD (random) (95% CI)*	*Weight (%)*	*SMD (random) (95% CI)*
Warner (female)	21	30.50 (6.10)	14	41.30(9.20)		19.07	−1.41 (−2.17, −0.65)
Warner (male)	14	39.90 (3.50)	18	47.60(8.40)		19.39	−0.89 (−1.63, −0.15)
Hauser (abnorm. str)	10	35.40 (11.60)	19	50.20(12.60)		18.19	−1.17 (−2.00, −0.34)
Hauser (norm. stress)	28	49.50 (10.90)	19	50.20(12.60)		21.29	−0.06 (−0.64, 0.52)
Vizinova	29	37.40 (7.80)	29	35.60(4.30)		22.06	0.27 (−0.24, 0.79)
Total (95% CI)	102		99			100.00	−0.61 (−1.27, 0.061)



Review: all; Comparison: VO_{2peak}.
Test for heterogeneity: $\chi^2 = 19.59$, df = 4 ($P = 0.0006$), $I^2 = 79.6\%$.
Test for overall effect: $Z = 1.79$ ($P = 0.07$).
N = number of subjects; mean (s.d.) = mean and s.d. of the VO_{2peak} (in ml kg^{-1} min^{-1}); SMD = standardized mean difference; weight (%) = the contribution of the study to the overall result; favors control = controls have a higher VO_{2peak} compared to survivors of childhood ALL; favors treatment = survivors of childhood ALL patients have a higher VO_{2peak} compared to controls. Forrest plot with the SMD and error bars (95% CI) indicates the result of each individual study. The black diamond indicates the overall effect of all included studies. I^2 is measuring the extent of inconsistency among results.

chemotherapeutic agents as vincristine or corticosteroids.[14,33] Muscle atrophy implies a smaller muscle mass to consume oxygen during exercise. In addition, the metabolic function of muscle fibers can be altered. Impaired aerobic metabolism (due to decreased mitochondrial volume and/or mitochondrial myopathy) or reduced capillarization can occur after immunosuppressive therapy.[34] Muscle atrophy and altered muscle function are further aggravated by sedentary habits due to the catabolic effects that sedentarism and prolonged bed rest induce on skeletal muscle tissue.[6] As a result, muscle atrophy and early fatigue during low-to-moderate physical tasks become self-perpetuating conditions.[6] Although more research is needed, some data suggest that the total daily energy expenditure of ALL survivors is indeed reduced compared to healthy children, leading to further deconditioning. Particularly, female patients show a greater impairment after treatment with anthracyclines, which results in further deterioration of functional capacity and increased body fat compared to males.[13,14,16] For instance, Matthys *et al* estimated the physical activity of ALL survivors with a questionnaire. Sport leisure time was lower in girl survivors of cancer (the majority, but not all, of which was ALL) than in their corresponding controls. Their VO_{2peak} levels were also lower (-8 ml kg^{-1} min^{-1}).[13] Warner *et al*[35] measured total daily energy expenditure (TDEE) and physical activity levels (= TDEE/basal metabolic rate) in long-term survivors of ALL and compared them with results from survivors of other malignancies and healthy sibling control subjects. The median TDEE was reduced in the ALL group (150 kJ kg day^{-1}) compared with other malignancies and controls (207 and 185 kJ kg day^{-1}, respectively). In turn, this reduction was accounted for mainly by a relative decrease in their levels of physical activity. Total energy expenditure and physical activity were in turn correlated with percentage body fat, indicating that obesity in survivors of ALL may, in part, be explained by a decrease in their TDEE as a consequence of their low physical activity levels. The detrimental effects of sedentarism are aggravated by the fact that diseased children may underestimate their own potential for performing physical tasks due to low self-esteem or overprotection by their parents.[13] Only physical training can break the ‘vicious circle’ of sedentary habits and subsequent exercise intolerance.[6]

Finally, it must be kept in mind that glucocortocoid therapy can increase adiposity and body mass in children receiving treatment for ALL.[36] As VO_{2peak} is expressed relative to body mass (ml kg^{-1} min^{-1}), the decreased VO_{2peak} levels of ALL survivors might be partly attributable to the aforementioned side effects of glucocorticoid treatment. Nevertheless, the difference in VO_{2peak} levels between the ALL survivors and controls included in our meta-analysis cannot be fully explained by differences in body mass, as the mean values of this variable were very similar in both groups of subjects studied by Vizinova *et al*[11] (ALL survivors: 46.2 kg; controls: 45.1 kg) and Warner *et al*[14] (boys survivors of LLA: 50.9 kg; controls: 51.0 kg), except for the girls included in the report by Warner *et al*[14] (ALL survivors: 49.0 kg; controls: 45.5 kg). Although Hauser *et al*[12] did not report body mass, they stated that their controls and ALL survivors were ‘matched for age and body surface area’.

Conclusions and perspectives

The physical fitness (as reflected by VO_{2peak} levels) of ALL survivors tends to be reduced compared to healthy children. Impaired physical fitness leads to early fatigue during physical activities and can severely deteriorate the QOL of ALL survivors,

which suggests the need for these children to engage in regular physical activities. Exercise physiologists could assist oncologists in prescribing exercise programs for attenuating cancer-related fatigue and help improve the physical fitness and QOL of children surviving cancer.[6] Furthermore, there are scientific indications that exercise training improves the function of several anti-cancer immune system components,[37] and can attenuate tumor development.[38]

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