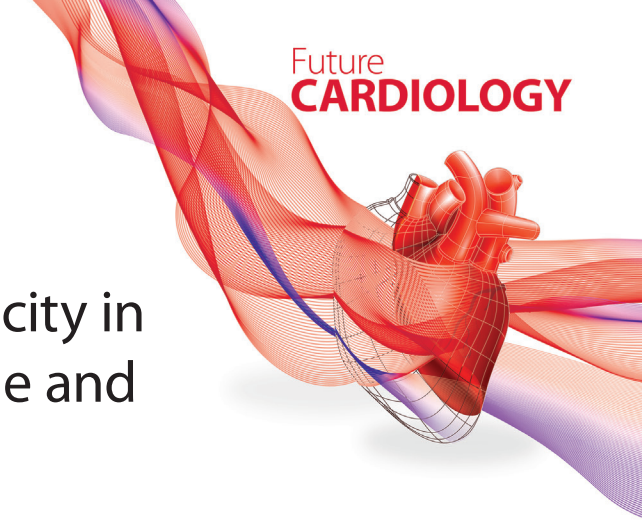
REVIEW
Special Focus Issue: Cardio-oncology



Modulation of cardiovascular toxicity in Hodgkin lymphoma: potential role and mechanisms of aerobic training

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Hodgkin lymphoma (HL) outcomes have improved due to advances in cancer treatment. However, HL survivors remain at increased risk for cardiovascular (CV) morbidity and mortality related to the long-term cardiotoxicity of HL treatment, particularly anthracycline chemotherapy and mediastinal radiotherapy. The role of aerobic training for the prevention of CV disease in the general population has been well established. However the safety and efficacy of aerobic training on CV outcomes has not been well studied in HL survivors. The purpose of this paper is to provide an up-to-date summary of the treatment-related adverse CV effects in HL survivors, review the CV benefits of exercise and review the limited evidence on the potential CV benefit of aerobic training in HL survivors.

KEYWORDS
• aerobic training
• anthracycline
• cardiotoxicity • exercise
• Hodgkin lymphoma
• mediastinal radiotherapy

Hodgkin lymphoma (HL) is now a curable disease with a 5-year survival rate of 86%, and significant survival gains have been achieved through advances of multiagent chemotherapy and radiotherapy [1,2]. The specific treatment regimen for HL varies depending on the presenting stage and other prognostic factors, but anthracycline-based chemotherapy and radiotherapy have emerged as standard components of initial therapy for early stage HL [3]. Given the improved prognosis of HL survivors, the long-term consequences, particularly the cardiovascular (CV) late effects, of HL treatment are becoming an increasingly important aspect of long-term management of HL survivors.

HL survivors are at markedly increased risk of cardiovascular disease (CVD) compared with the general population [4–6]. A robust series of studies indicate an increased risk of myocardial infarction, congestive heart failure and CVD-related mortality in HL survivors [7–9]. Of note, CVD is the leading nonmalignant cause of death among HL survivors, exceeded only by death related to HL or secondary malignancies [8]. The increased risk of CV events in HL survivors persists beyond 25 years from diagnosis, even when the background cardiac event rate in the general population starts to increase [10]. A major challenge in the management of HL patients is to develop strategies that minimize CV-related morbidity and mortality while maintaining the efficacy of anticancer regimens.

Proposed strategies to minimize the CV events related to HL therapy include the use of modern irradiation techniques to reduce cardiac dose, omission of radiotherapy altogether, anthracycline dose reduction, use of liposomal anthracycline preparations and cardioprotective drugs such as iron chelators (e.g., dexrazoxane) [11–14]. There is concern, however, that some of the proposed strategies may diminish the anticancer efficacy of treatment [15,16]. In addition, these strategies have the potential to decrease, but not eliminate, the risk of CV toxicity related to HL treatment exposures.

Physical activity is defined as any movement produced by skeletal muscles that results in energy expenditure, whereas exercise is defined as a regular regimen of physical activity performed for the objective of improving physical fitness [17]. Aerobic training (AT), or a program of structured

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aerobic exercise, is demonstrated to reduce the risk of CVD as well as improve global CV function (peak oxygen consumption, VO_{2peak}). Of relevance, AT may also target many of the mechanisms responsible for treatment-induced CV toxicity in HL survivors (e.g., oxidative stress or endothelial dysfunction) [18,19]. However, the safety and efficacy of AT on CV function and outcomes in patients with HL has received limited attention. Accordingly, the purpose of this paper is to review the CV toxicity of HL therapy, the effect and mechanisms of exercise on CV health in noncancer populations, and the available evidence of AT in HL survivors. We will also discuss research gaps and avenues for future research.

Adverse CV consequences of HL treatment

Increased morbidity and mortality due to CVD in HL survivors have been attributed to the adverse effects of radiotherapy and/or anthracycline-containing chemotherapy regimens which can lead to coronary heart disease (CHD), cardiomyopathy, valvular heart disease, pericardial disease or arrhythmia. In a study of 1261 patients treated for HL with a median follow-up of 17.8 years, the relative risk of CV-related death was 7.6 (95% CI: 2.1–19.4) at 0–5 years but remained elevated at 4.9 (95% CI: 1.6–11.5) at 26–30 years of follow-up compared with the general population (Table 1) [5]. In a cohort of 2528 HL survivors at a median follow-up of 21 years, the cumulative incidence of any CV event (i.e., ischemic heart disease, congestive heart failure or valvular heart disease) more than doubled from approximately 20% at 20 years to >40% at 30 years [20]. The clinical presentation can include symptoms of chest pain, shortness of breath, palpitation or fatigue, and the diagnostic work-up varies depending on the presenting signs and symptoms (Table 2).

• Coronary heart disease

HL survivors treated with mediastinal radiotherapy are at significantly increased risk for premature CHD [21–25]. In a Dutch cohort of 1474 HL survivors treated between 1965 and 1995 (95% of which were treated with radiotherapy to the mediastinum and/or para-aortic lymph nodes), Aleman *et al.* showed an increased risk of myocardial infarction (standardized incidence ratio 3.6, 95% CI: 2.9–4.4) compared with the general population, with a cumulative incidence for myocardial infarction of 12.9% by 30 years after mediastinal radiotherapy exposure [5]. In an analysis by Swerdlow *et al.* of 7033 HL survivors treated with radiotherapy and/or chemotherapy from 1967 to 2000, the risk of death from myocardial infarction was also significantly increased in patients who received total nodal irradiation (standardized mortality ratio [SMR]: 8.9; 95% CI: 5.4–13.8), mantle radiotherapy (SMR: 3.2; 95% CI: 2.3–4.2) or other supradiaphragmatic radiotherapy (SMR: 1.9; 95% CI: 1.2–2.9) compared with the general population [26]. Severe CHD can be asymptomatic in HL survivors [27]. Thus, reliance on clinical history (i.e., symptoms of ischemia) or traditional risk factors for the CV follow-up care of these patients may be unsuitable, and screening for asymptomatic CHD in this high-risk group with stress testing or CT coronary angiography has been proposed [28,29].

• Valvular heart disease

Mediastinal radiotherapy is also associated with an increased risk of valvular heart disease. In a study of 294 asymptomatic HL survivors, valvular disease (particularly aortic regurgitation) was several-fold more common in patients treated with at least 35 Gy of mediastinal radiation compared with the general population [30]. For example, the incidence of moderate to severe aortic regurgitation was 15% in the HL

Table 1. Mortality from cardiovascular disease by follow-up interval in Hodgkin lymphoma survivors, compared with the general population.

Follow-up interval	Relative risk	95% CI
0–5 years	7.6	2.1–19.4
6–10 years	7.0	2.6–15.2
11–15 years	4.5	1.6–9.7
16–20 years	6.8	3.1–12.2
21–25 years	8.3	4.3–14.5
26–30 years	4.9	1.6–11.5
>30 years	2.6	0.1–14.3

Data taken from [8].

Table 2. Adverse cardiovascular effects in Hodgkin lymphoma survivors.

Cardiovascular effect	Clinical presentation	Diagnostic tests
Coronary heart disease	Chest pain, shortness of breath	ECG, exercise or pharmacologic stress testing, CT coronary angiogram
Cardiomyopathy	Systolic and diastolic dysfunction; symptoms of heart failure (e.g., shortness of breath, peripheral edema)	2D echocardiography, cardiac MRI
Valvular heart disease	Heart murmur, symptoms of heart failure (e.g., shortness of breath, peripheral edema)	2D echocardiography
Pericardial disease	Pericardial friction rub, chest pain, hypotension	ECG, 2D echocardiography
Arrhythmia	Palpitations, lightheadedness, dizziness, syncope	ECG, Holter monitor
Cancer-related fatigue	Diminished energy, generalized weakness, decreased motivation, emotional tiredness, insomnia	Physical activity assessment, quality of life questionnaire

survivor group compared with 0.15% in the general population. In a study by Adams *et al.*, 48 HL survivors treated with mediastinal radiation (median 40 Gy) were assessed at a median of 14.3 years after diagnosis [31]. Although no patient was symptomatic at the time of testing, CV abnormalities were common including 42% with significant valvular defects, 75% with conduction abnormality or arrhythmia on resting ECG, and 30% with significantly reduced VO_{2max} (<20 ml/kg/m^2). The dose response relationship of valvular heart disease and radiation dose to the heart valves was confirmed in a recent case–control study by Cutter *et al* [32]. Of note, this relationship was nonlinear, with little or no increase in the risk of valvular heart disease for radiation <30 Gy and progressively increased risk with radiation >30 Gy.

• Heart failure

Anthracyclines, an important component of treatment for HL as well as many other cancer types such as leukemia, sarcoma and breast cancer, can cause irreversible damage to the heart. First described in the 1970s, anthracycline cardiotoxicity is dose dependent and results in myocyte damage that can be diagnosed pathologically using endomyocardial biopsy [33,34]. The clinical manifestations of anthracycline cardiotoxicity, including cardiomyopathy, heart failure and conduction defects, rarely present acutely (within 1 week of treatment) and more commonly occur late (≥1 year) after treatment. Notably, the combination treatment of anthracyclines and radiotherapy has been shown to produce additive cardiotoxic effects in HL patients. Tsai *et al.* reported echocardiographic measurements in a group of HL survivors treated successfully with mediastinal radiotherapy with (n = 27) or without (n = 20) anthracycline treatment [35]. Global longitudinal strain measured by speckle tracking echocardiography was reduced in patients receiving mediastinal radiotherapy with anthracycline compared with without anthracyclines (-16.1 ± 1.9% vs -17.5 ± 1.7%; $p < 0.05$), and both groups were reduced compared with healthy controls (-20.4 ± 1.7%). Other studies have demonstrated an increased risk of cardiac hospitalization, congestive heart failure and valvular disease with combination anthracycline and mediastinal radiotherapy compared with radiotherapy alone [5,36].

• Fatigue

Fatigue, a hallmark of cancer therapy-related toxicity, may in part be a manifestation of the CV effects associated with HL treatment. Fatigue is defined by persistent exhaustion and a decreased capacity for physical and mental work and is encountered in many patients throughout the cancer survivorship continuum (i.e., before, during and after cancer therapy) [37]. Fatigue is especially common in HL patients, even among patients in remission and treatment-free for several years [38]. Hjermstad *et al.* performed a cross-sectional study of 476 HL survivors (median age 46 years, median follow-up time 195 months) and reported that 30% of the study participants reported symptoms consistent with chronic fatigue compared with 11% of the

general population [39]. The underlying mechanism of fatigue is multifactorial and is influenced by a number of different medical, psychosocial and behavioral factors. Treatment with radiotherapy and multiagent chemotherapy is known to cause direct insults to the CV system resulting in muscle weakness, CHD, left ventricular systolic dysfunction or pulmonary fibrosis [21,40,41]. These direct insults in combination with indirect lifestyle perturbations (e.g., physical inactivity, weight gain) can cause marked impairments in global CV function (VO_{2peak}). We contend that treatment-induced impairments in VO_{2peak} may have an underlying basis in the development or persistence of fatigue [42].

Alarmingly, cancer patients may avoid physical activity or exercise to improve feelings of fatigue. However, avoidance of exercise results in further impairments of VO_{2peak} and leads to a self-perpetuating cycle of fatigue, increased avoidance of physical activity and further deconditioning [43]. Physical inactivity can persist beyond the cancer treatment phase into survivorship, as less than one-third of lymphoma survivors (HL and NHL) meet the current public health guidelines for physical activity defined by the American College of Sports Medicine [44,45].

Impairment of VO_{2peak} has been observed before, during, and after treatment in patients with HL. A cross-sectional study by Page *et al.* assessed VO_{2peak} prior to beginning treatment and observed a significantly decreased VO_{2peak} among patients with advanced stages (IIB–IV) of disease (VO_{2peak} 21.4 ± 1.2 ml/kg/min, 65 ± 4% predicted) [46]. An association between fatigue and VO_{2peak} was also proposed in a prospective longitudinal study by Vermaete *et al.* In this study, 17 NHL and 12 HL patients underwent serial assessments of physical activity (METs per day) with a portable accelerometer, VO_{2peak} with a maximal cycle ergometer test, and fatigue using a self-reported questionnaire before, during and after cancer treatment [47]. Compared to baseline, VO_{2peak} decreased by 17% during treatment (2.42 l/min vs 2.01 l/min; $p < 0.01$) and patient reported measures of fatigue increased both during and after treatment.

Radiation-induced injury to the autonomic nervous system has recently been proposed as another treatment-related effect that contributes to fatigue and impaired exercise capacity, as measured by maximal METs achieved during an exercise treadmill test. In a retrospective study of 263 HL survivors, signs of autonomic dysfunction (e.g., elevated resting heart rate and abnormal heart rate recovery) increased with radiation dose and were associated with reduced exercise capacity [48]. Abnormal heart rate recovery was also associated with increased all-cause mortality (age-adjusted HR: 4.6; 95% CI: 1.62–13.02), suggesting the contribution of autonomic dysfunction to adverse outcomes observed in HL survivors treated with radiotherapy.

CV benefits of exercise in adults without cancer

Exercise has long been associated with dramatic reductions in the primary and secondary risk of CVD. Research in this field dates back to 1953 in a study by Morris *et al.*, which showed that men with physically demanding jobs had a lower risk of CHD compared with their sedentary counterparts [49]. Since that time, additional studies have confirmed that higher levels of exercise are associated with substantial reduced risk of CHD, stroke, hypertension, dyslipidemia, diabetes and metabolic syndrome [50–54].

The protective importance of regular exercise on the primary and secondary incidence of CHD has been assessed in multiple studies. In the Harvard Alumni Health Study, 12,516 men were prospectively followed to examine the association of the quantity and intensity of physical activity with risk of CHD [55]. Men that reported more than 4200 kJ/week (equivalent to brisk walking, recreational cycling or swimming, home repair or yard work for 30 min/day) had a reduction in CHD risk by approximately 20% compared with inactive men (<2100 kJ/week). No additional CHD risk reduction was observed with higher reported levels of physical activity. A separate analysis from the same cohort showed an inverse relationship between the perceived intensity of physical activity and risk of CHD [56]. The relative risk of CHD among men who perceived the intensity of their exercise as 'moderate,' 'somewhat strong' and 'strong' using the Borg scale was 0.86, 0.69 and 0.72, respectively, when compared with 'weak' exercise. A meta-analysis by Sattelmair *et al.* provided data on the dose-response relationship between physical activity and CHD risk from nine primary prevention studies of over 250,000 men and women [57]. After follow-up ranging from 3.2 to 16 years, individuals meeting the US physical activity recommendations of 150 min per week of moderate intensity exercise had

a 14% lower CHD risk (RR: 0.86; 95% CI: 0.77–0.96), with further reduction of CHD risk in participants engaged in 300 min per week of moderate intensity exercise (RR: 0.80; 95% CI: 0.74–0.88).

Subsequent studies have utilized symptom-limited exercise treadmill protocols to assess peak exercise capacity to provide a more objective assessment of exercise behavior. Exercise capacity is expressed in units of metabolic equivalents (MET), which is equal to the amount of oxygen per kilogram of body weight expended during rest (i.e., 3.5 ml O_2/kg/min). Myers *et al.* performed a study of 6213 men (mean age 59 ± 11 years) referred for exercise treadmill testing for clinical reasons. After 6.2 years of follow-up, peak MET was the strongest predictor of death among both subjects with a normal exercise test (HR 0.84 per 1 MET increment, 95% CI: 0.79–0.89; $p < 0.001$), those with CVD (i.e., CHD, myocardial infarction, coronary bypass surgery, congestive heart failure or peripheral vascular disease), as well as subjects with an abnormal exercise test (HR 0.91 per 1 MET increment, 95% CI: 0.88–0.94; $p < 0.001$) [58].

In corroboration, Kokkinos *et al.* studied 18,102 male veterans that completed an exercise treadmill test with no evidence of ischemia between 1986 and 2011 [59]. In comparison with a reference value of 7.0 METs, mortality risk increased for patients in the least-fit (>2 METs below the reference value, HR: 1.51; 95% CI: 1.37–1.66) and low-fit (2 METs below threshold the reference value, HR: 1.21; 95% CI: 1.12–1.3) categories but decreased for the moderate-fit (2 METs above reference, HR: 0.71; 95% CI: 0.65–0.78), fit (2–4 METs above reference value, HR: 0.63; 95% CI: 0.56–0.78) and high-fit (>4 METs above reference value, HR: 0.49; 95% CI: 0.41–0.58) categories. This study established age-specific exercise thresholds and mortality risks associated with each level of fitness. Importantly, this study suggests the potential for significant health benefits associated with increasing levels of physical activity.

An association between physical activity or exercise and reduced risk of CVD has also been observed in women [60–62]. For example, the Nurse's Health Study included 72,488 women (40 to 65 years) found a strong inverse association between physical activity and risk of nonfatal or fatal myocardial infarction, suggestive of a 30–40% risk reduction with regular vigorous exercise (≥6 MET-h/week) [63]. In the St. James Women Take Heart Project, 5721 asymptomatic women age 35 years or older (mean age 52 ± 11 years) that underwent a symptom-limited exercise treadmill test were studied [64]. In this cohort, exercise capacity was an independent predictor of all-cause death, with a 17% decrease in mortality risk for every 1 MET increase in exercise capacity. In the Lipid Research Clinics Prevalence Study, the prognostic value of exercise capacity was studied in 2994 asymptomatic women aged 30 to 80 years [62]. With 20 years of follow-up after exercise testing, lower exercise capacity was independently associated with increased all-cause and CV mortality, with an age-adjusted hazard ratio for CV death of 1.20 (95% CI: 1.18–1.3; $p < 0.001$) for every 1 MET decrease in exercise capacity.

CV benefits of exercise in adults without cancer: mechanisms of action

Exercise and physical activity are protective against CVD in part via the modulation of traditional CV risk factors:

- Lipid profile: exercise leads to improvement in lipid profiles, including lower triglycerides [65], higher high density lipoprotein cholesterol [66] and decreased low-density lipoprotein cholesterol [67,68].
- Blood pressure: a meta-analysis of randomized controlled trials (RCTs) on the effects of AT on blood pressure in normotensive and hypertensive patients was performed by Cornelissen *et al.*, and showed a net overall reduction in systolic and diastolic blood pressure by 3.0 mm Hg and 2.4 mm Hg, respectively [69]. This change was more pronounced in hypertensive study groups, with a reduction of systolic and diastolic blood pressure of 6.9 mm Hg and 4.9 mm Hg, respectively.
- Glycemic control: in a systematic review of 10 prospective cohort studies, moderate intensity physical activity was associated with a lower risk of Type 2 diabetes (RR: 0.69; 95% CI: 0.58–0.83) [70]. In adults with Type 2 diabetes, a meta-analysis of controlled clinical trials on the effect of AT on glycemic control showed a lower hemoglobin A1c in exercise groups versus control groups (7.65 vs 8.31%; $p < 0.001$) [71].
- Inflammation: an inverse relationship between exercise and inflammatory markers such as

C-reactive protein has previously been observed [72,73]. This is of significance given that inflammation plays an important role in the pathogenesis of atherosclerosis [74,75]. One of the proposed mechanisms of the anti-inflammatory effect of exercise is through increased expression of peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α), which has been shown to suppress ROS production [76]. Upregulation of other key antioxidative enzymes such as glutathione peroxidase, catalase and manganese superoxide dismutase may also play a role in the anti-inflammatory effect of exercise [77].

- Obesity: in a meta-analysis of RCTs, exercise alone as a single treatment was shown to induce a modest reduction in weight in overweight and obese populations compared with no treatment (weighted mean difference = -1.6 kg, 95% CI: -1.64 to -1.56) [78].

The protective effects of exercise on the CV system extend beyond modulation of traditional CV risk factors [79]. Direct cardiac effects of exercise include protection against myocardial damage related to ischemia/reperfusion injury [77], reverse remodeling leading to reductions in LV end diastolic diameter and modest improvements of ejection fraction in patients with congestive heart failure [80,81], and improved diastolic function [82]. Vascular effects of exercise include improvement of endothelium-mediated vasodilatation [83,84] and increased nitric oxide production [85]. Exercise may also improve parameters of the autonomic nervous system including improvement in baroreflex function [86] and improved heart rate variability [87].

Consistent with this growing body of evidence on the CV effects of exercise, practice guidelines by the American Heart Association and the Department of Health and Human Services recommend 40 min sessions of moderate to vigorous intensity exercise at least 3 days per week or at least 150 min a week of moderate intensity exercise, respectively [88,89].

Exercise trials in adults with HL: current evidence

There is a growing body of evidence to support the safety and efficacy of exercise among cancer survivors for a variety of cancer and noncancer related outcomes [90,91]. Studies in survivors of breast and prostate cancer have demonstrated that structured AT interventions are associated with improvements in strength, body composition, quality of life, global CV function (VO_{2peak}) and psychosocial outcomes such as depression and anxiety [91–99]. However, data on the potential CV benefit of exercise in HL survivors are limited.

In a report from the Childhood Cancer Survivor Study, Jones *et al.* recently investigated the association between self-reported exercise and risk of CV events in 1187 adult survivors of childhood HL [100]. The severity of CV events was graded as severe (grade 3), life threatening (grade 4) or fatal (grade 5), based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (v4.03). After a median follow-up of 11.9 years, the cumulative incidence of any major (grade 3 to 5) CV event (i.e., CHD, heart failure, arrhythmia and valve abnormalities) was 12.2% at 10 years for survivors reporting 0 MET hours/week of activity compared with 5.2% for those reporting ≥ 9 MET hours/week. The ability to confirm a causal relationship between exercise and CV outcomes is also limited given the retrospective study design. However, this was the first study to show an inverse relationship between exercise and CV outcomes in a population of cancer survivors known to be at increased risk due to prior cardiotoxic treatment exposures.

Three studies investigated the effects of AT interventions on HL patients — two randomized controlled trials and one uncontrolled pilot study (Table 3). In the first published study, Oldervoll *et al.* assessed the feasibility and preliminary efficacy of a home exercise program in 9 HL survivors with chronic fatigue [101]. The outcome measures were fatigue and physical functioning as assessed by self-report questionnaire and VO_{2peak} measured by cardiopulmonary exercise testing. In comparison to 15 nonfatigued HL survivors matched for age and gender, a baseline cardiopulmonary exercise testing showed no significant difference in VO_{2peak} (32.7 ml/kg/min vs 34.0 ml/kg/min). The exercise program consisted of 3 weekly sessions of 40–60 min at an intensity of 65–80% of target heart rate for 20 weeks. VO_{2peak} increased from 33.9 ml/kg/min at baseline to 36.0 ml/kg/min ($p = 0.04$). Self-reported measures of physical functioning ($p = 0.04$) and fatigue ($p = 0.001$) also improved significantly with exercise.

In the Health Exercise for Lymphoma Patients trial, Courneya *et al.* examined the impact of a 12 week supervised AT program on physical

Table 3. Summary of studies investigating the effects of exercise interventions in Hodgkin lymphoma survivors.

Study (year)	Patient population	Exercise intervention	Outcome	Ref.
Courneya *et al.* (2007)	Hodgkin lymphoma (n = 22), non-Hodgkin lymphoma (n = 100)	Supervised aerobic exercise training, 15–45 min/day at 60–75% peak power output; 3 day/week × 12 weeks	↑ physical functioning, ↑ quality of life, ↑ VO_{2peak}, ↓ lean body mass	[92]
Courneya *et al.* (2015)	Hodgkin lymphoma (n = 22), non-Hodgkin lymphoma (n = 100)	Supervised aerobic exercise training, 15–45 min/day at 60–75% peak power output; 3 day/week × 12 weeks	In exploratory analysis after 61 months of follow-up, ↓ in progression-free survival	[102]
Oldervoll *et al.* (2003)	Hodgkin lymphoma (n = 12)	Home based exercise regimen; 40–60 min/day at 65–80% target heart rate; 3 day/week × 20 weeks	↑ VO_{2peak}, ↑ physical functioning, ↓ fatigue	[101]
Streckmann *et al.* (2014)	Hodgkin lymphoma (n = 12), non-Hodgkin lymphoma (n = 32), multiple myeloma (n = 13)	Supervised aerobic exercise training, 15–45 min/day at 60–75% peak power output; 3 day/week × 12 weeks	↑ quality of life, ↑ physical activity level	[103]

functioning (assessed using the Trial Outcome Index-Anemia) and quality of life in a randomized controlled trial of 122 lymphoma patients (22 with HL, 100 with NHL) [44]. The AT program consisted of 3 cycle ergometer sessions per week, with progressive increases in intensity and duration over the 12 week period. Results indicated that the AT group had significant improvements in physical functioning, quality of life, fatigue, happiness, and depression. Upon completion of the exercise intervention, AT was also associated with an improvement in VO_{2peak} (+5.2 ml/kg/min, 95% CI: 4.0–6.4; $p < 0.001$) and lean body mass (+0.8 kg; 95% CI: 0.2–1.4; $p = 0.10$) from baseline compared with the usual care group. No serious adverse events were reported, and AT did not interfere with chemotherapy completion in 54 of 122 patients undergoing active treatment. Importantly, this study showed that changes in physical and functional aspects of quality of life were mediated by VO_{2peak}, suggesting that exercise-induced improvements in global CV function (i.e. VO_{2peak}) are required for subsequent improvements in psychosocial outcomes. In a secondary, unplanned analysis, Courneya *et al.* found that after a median follow-up of 61 months, the adjusted progression-free survival for patients in the AT group (including controls that crossed over to the AT group) was 68.5% compared with 59% for the control group without exercise [102]. Although this data suggest that AT may be associated with improved progression-free survival, additional studies are needed to further investigate the effect of exercise on cancer-related outcomes.

In the final study, Streckmann *et al.* conducted a RCT to determine the effects of exercise on quality of life and therapy-related side effects in 61 lymphoma patients (12 with HL) [103]. Participants in the exercise arm attended 1-h training sessions twice weekly, consisting of walking or cycling at 70–80% max heart rate, strength training with resistance exercises and postural stabilization tasks for sensorimotor training over 36 weeks. Exercise led to improvements in quality of life and balance control and an increase in physical activity level by 2.5 MET/week. No adverse events were reported.

Overall, the findings of the three studies suggest that AT is safe in HL survivors and may be an effective strategy for improving quality of life, cardiorespiratory fitness and cancer related fatigue. Generalizability of these findings to HL survivors is limited given the heterogeneity of the study population in two of the studies that included patients with multiple cancer types.

Modulation of CV toxicity with exercise in HL: potential mechanisms

Many of the beneficial effects of exercise discussed previously may counteract the perturbations caused by HL treatment. Radiation causes a number of adverse effects including endothelial dysfunction [104], lipid and inflammatory cell infiltration [105] and fibrosis [21,106]. As previously described, exercise is an effective treatment for traditional CV risk factors of CHD. Exercise has also been shown to restore endothelial function and improve coronary flow reserve [19,107]. In a study by Hambrecht *et al.*, the effect of AT on endothelial function was studied in 19 patients with underlying CHD. Ten patients were randomly assigned to an AT group consisting of six 10-min sessions per day of exercise on a bicycle ergometer at 80% target heart rate. Compared to control, AT led to improvement

in endothelium-dependent vasodilatation in both epicardial coronary arteries and resistance vessels among patients with coronary atherosclerosis [83].

Oxidative injury to cardiomyocytes has been proposed as a central mechanism of anthracycline-mediated cardiotoxicity, thereby leading to impairments in left ventricular systolic and diastolic function [97]. Several studies have demonstrated that exercise reduces levels of ROS after anthracycline exposure by enhancing cellular antioxidant capacity [19,108–110]. More recent data have identified Top2β as a key mediator in the development of anthracycline-induced mitochondrial dysfunction and ROS formation [111]. Top2β is required for activation of apoptotic pathways in response to anthracycline-induced damage and alteration in gene expression involved in mitochondrial function and oxidative phosphorylation pathways [112]. Anthracycline therapy in the presence of Top2β also reduces the level of PGC-1α, which is critical for mitochondrial biogenesis [112]. The effect of exercise on Top2β and PGC-1α requires further investigation.

Conclusion

Treatment for HL has led to important survival gains but is associated with increased risk of CVD. Efforts to prevent and treat late CV effects in HL survivors are increasingly important to reduce CV-related morbidity and mortality. Although far more work is required, exercise may be a safe intervention and holds promise for improving global CV health and mitigating HL treatment-related symptoms in HL survivors.

Future perspective

Our recommendations for future research in this field are outlined in detail here. Current evidence for exercise in HL survivors is limited. Additional studies in adult HL survivors are needed to firmly establish an association between exercise and CV risk, which will complement the novel findings of Jones *et al.* from the Childhood Cancer Survivor Study. Once established, this along with the observed increased risk of CVD in HL survivors will provide a strong rationale for additional studies to investigate the efficacy of AT to reduce

EXECUTIVE SUMMARY

Adverse cardiovascular consequences of Hodgkin lymphoma treatment

- Increased cardiovascular (CV) morbidity and mortality in Hodgkin lymphoma (HL) survivors has been attributed to the cardiotoxic effects of anthracycline chemotherapy and mediastinal radiation exposure, leading to an increased risk of coronary heart disease, left ventricular systolic dysfunction, valvular heart disease and conduction abnormalities.
- Fatigue, a hallmark of toxicity in HL survivors, is manifest by persistent exhaustion and a decreased capacity for physical and mental work. Treatment-related impairments in global CV function (i.e., VO_{2peak}) likely contribute to the development and/or persistence of fatigue.

CV benefits of exercise in adults without cancer

- Exercise has long been recognized to be closely linked with improvements in many CV-related health outcomes including coronary heart disease, CV mortality and all-cause mortality.
- The benefits of exercise on other traditional CV risk factors such as lipid profile, blood pressure, glycemic control, inflammation and obesity have been well established. Exercise is also associated with direct effects on the cardiac, vascular and autonomic nervous system.

Exercise trials in adults with HL: current evidence

- A study from the Childhood Cancer Survivors Study provides the first report of an inverse relationship between exercise exposure and CV events in a Hodgkin lymphoma population.
- A limited number of exercise intervention studies in HL survivors have shown an improvement in VO_{2peak} and patient reported outcomes of fatigue, quality of life and physical functioning.

Modulation of CV toxicity with exercise in HL: potential mechanisms

- Potential mechanisms for the cardioprotective effect of exercise in HL survivors include a reduction in traditional CV risk factors, decreased inflammation and improvement of endothelial function.

the CV toxicity of HL treatment. Studies of the optimal timing of exercise interventions will be especially important given the potential latency period between HL treatment and adverse CV events. Investigations on the safety and optimal dose/intensity of exercise will also be required in this population, given the risk of occult obstructive CHD.

Future efforts will also be focused on elucidating the underlying mechanism of cardioprotective effects from exercise. The potential effects of exercise on Top2β and PGC-1α represent two promising areas of additional research. Noninvasive measures such as brachial artery flow mediated dilation could be used to further elucidate the effects of an exercise intervention on endothelial function. These efforts may lead to the discovery of predictive biomarkers for the risk of CV toxicity or response to exercise. Additional research is needed to inform the optimal cardiac screening strategy (e.g., timing and frequency of testing, or best modality of testing) for cancer survivors and identify high-risk patients, which may in turn allow for the selection of patients most likely to benefit from an exercise intervention [113].

We envision future work not only to demonstrate the CV benefit of exercise, but also to explore the effect of exercise on cancer-related outcomes. The Health Exercise for Lymphoma Patients trial by Courneya *et al.* was the first known study to provide data on exercise and survival outcomes in lymphoma patients [102]. The potential benefit of exercise on progression free survival warrants the collection of data on physical activity and exercise in prospective studies to adequately address this question.

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