Exercise, concomitant to therapy, has a positive influence on therapy-induced side-effects in patients with haematological malignancies

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Therapiebegleitende Bewegungsinterventionen haben einen positiven Einfluss auf therapie-induzierte Nebenwirkungen bei Patienten mit hämato-onkologischen Erkrankungen

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„put life into their days,
not just days into their life”.

(Nairobi Hospice 1988)

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ABSTRACT

Exercise interventions as a supportive measure in cancer therapy are becoming more and more relevant. With cancer therapy becoming more complex and effective, higher survival rates as well as longer life-spans are being achieved. Consequently, patients' quality of life is becoming increasingly important and the management of therapy-related side-effects therefore essential. An increasing amount of studies are demonstrating, that the previously propagated rest and immobility during cancer therapy is not only counterproductive but that exercise interventions hold enormous potential regarding the management of side-effects in supportive cancer care and should therefore be taken more seriously.

Especially haemato-oncological patients have to cope with many debilitating side-effects due to the disease itself, the long and complex medical therapy as well as the associated immobility. The symptoms cause physiological, psychological and social restraints, leading to acute as well as lasting reductions in patients' quality of life. Poor health and severe side-effects such as chemotherapy-induced peripheral neuropathy (CIPN) are highly relevant, as they can cause dose reductions, disruptions or discontinuation of medical therapy, consequently impacting the clinical outcome.

Although the positive effects of exercise interventions are rather well documented in entities such as breast cancer, the amount of research in haematological patients, especially concomitant to therapy, is still relatively low. For instance only one previous randomized, controlled trial (RCT)[1] has evaluated lymphoma patients. Furthermore, the potential role of exercise regarding CIPN has never been investigated previously, although it is highly prevalent in haemato-oncological patients. Previous studies on patients with neuropathies of similar pathophysiology as CIPN, showed improved parameters after balance exercises, whole body vibration or Tai Chi. This effect has not been investigated in oncological patients.

The primary aim of this work was to improve patients quality of life, therefore investigating whether exercise interventions are feasible for patients with haemato-oncological malignancies, during all phases of therapy and whether it is furthermore possible to reduce immobility and attenuate or possibly even prevent debilitating side-effects such as reduced physical performance, muscle atrophy, loss of balance control, absent reflexes, pain or CIPN.

This has been approached within a cumulative dissertation. Three studies form the main part of this thesis (the full text articles can be found in the appendix), while the introduction aims to give a better insight into the research issue and current state of the art.

In a large randomized, controlled trial (RCT), the effects of exercise (endurance-, strength- and sensorimotor training) on quality of life and therapy-related side-effects were evaluated in lymphoma patients (N=61) undergoing therapy. Patients in the intervention group trained twice a week for 36 weeks, while the control group had no intervention. Intergroup comparisons revealed a significant improvement in quality of life, static and dynamic balance control, aerobic performance level, level of activity as well as CIPN related symptoms, in the intervention group. The exercise intervention, especially sensorimotor training, proved to be a feasible and promising method to support lymphoma patients during therapy.

In order to assess the previous findings appropriately, two reviews were conducted/composed analyzing the various exercise interventions, especially regarding the side-effects of CIPN.

To evaluate the efficacy, safety and feasibility of aerobic exercise interventions for patients with haematological malignancies, a meta-analysis was conducted. RCTs that investigated the effects of aerobic endurance training alone or in combination with resistance training in patients with haematological malignancies, were included. The search identified nine relevant RCTs. Analysis revealed that the above mentioned exercise interventions can improve quality of life, especially physical functioning, depression and fatigue. Currently, there is inconclusive evidence regarding anxiety, physical performance and adverse events.

As the RCT within this work was the first to show beneficial effects of an exercise intervention on symptoms of CIPN and further references are lacking, a systematic review was conducted in order to better understand the effects and underlying mechanisms of various exercise interventions on sensory and motor symptoms of peripheral neuropathy (PNP) in general. The search revealed 18 exercise intervention studies on patients with PNP. Evidence and study quality is highest (11 studies) for diabetic neuropathy (DPN). In addition to the RCT within this work on CIPN, further 6 studies investigated patient groups with neuropathies of heterogeneous origin. Current data suggests that specific exercise interventions are feasible, safe and promising for patients with neuropathies. Analysis

revealed that balance exercises target the relevant symptoms of PNP best in neuropathies with similar pathophysiology as CIPN. Studies focusing exclusively on strength, or a combination of endurance and strength, appear to have a lower impact. For primarily metabolic-induced neuropathies such as DPN, endurance training additionally has the potential to prevent the onset and reduce the progression of PNP.

To summarize, it could be shown that sensorimotor training is a relevant exercise intervention for therapy of haemato-oncological patients. Additionally, effects on sensory as well as motor symptoms of CIPN could be achieved for the first time, opening a promising new field for research and exercise therapy, even enabling preliminary recommendations for the translation into practice. Nevertheless, further studies are necessary to enable researchers to better understand possible structures and underlying mechanisms with the intention to improve supportive care for cancer patients.

DEUTSCHE ZUSAMMENFASSUNG

Die Bewegungstherapie rückt als supportive Maßnahme immer mehr in den Fokus der Behandlung von onkologischen Patienten. Die medizinische Therapie wird zunehmend komplexer und auch effektiver. Dadurch werden nicht nur höhere Überlebensraten erzielt sondern auch eine längere Lebensdauer für Patienten erreicht. Eine Reduktion der Nebenwirkung und damit eine Verbesserung der Lebensqualität, werden daher immer bedeutsamer. Immer mehr Studien belegen, dass die lange Zeit propagierte Ruhe und Schonung kontraproduktiv ist und gezielte körperliche Aktivität im Rahmen der supportiven Therapie ein enormes Potential aufweist.

Insbesondere Patienten mit hämato-onkologischen Erkrankungen müssen häufig eine intensive und langwierige medizinische Behandlung durchlaufen. Neben der Grunderkrankung selbst führen die medizinische Therapie und die damit einhergehende Immobilität zu einer Vielzahl von negativen Auswirkungen. Dadurch wird die physische, psychische und psychosoziale Ebene des Patienten beeinträchtigt, wodurch die Lebensqualität akut jedoch auch nachhaltig sinkt. Ein schlechter Allgemeinzustand sowie schwerwiegende Nebenwirkungen, wie beispielsweise die Chemotherapie-induzierte periphere Polyneuropathie (CIPN), können sogar Dosisreduktionen, Therapieverzögerungen oder gar einen Therapieabbruch zur Folge haben.

Obwohl in anderen Bereichen, wie beispielweise bei Brustkrebs, die positiven Effekte der Bewegungstherapie bereits bekannt sind, ist die Datenlage bei hämato-onkologischen Erkrankungen, insbesondere therapiebegleitend, noch relativ gering. So hat beispielsweise erst eine Studie Lymphompatienten evaluiert[1]. Zudem wurde der Effekt gezielter Bewegungstherapeutischer Maßnahmen auf die Symptome einer CIPN, trotz hoher Prävalenz bei hämato-onkologischen Patienten, noch nie untersucht. Studien an neuropathischen Patienten mit ähnlichem Schädigungsmechanismus wie dem der CIPN, beschrieben eine Verbesserung der relevanten Symptome durch Gleichgewichtstraining, Vibrationstraining oder Tai Chi. Ob dieser Effekt auch bei onkologischen Patienten erzielt werden kann, wurde noch nicht überprüft.

Primäres Ziel dieser Arbeit war es daher, die Lebensqualität von Lymphompatienten in allen Therapiephasen durch gezielte bewegungstherapeutische Maßnahmen zu verbessern. Darüber hinaus soll die Immobilität reduziert, die Leistungsminderung verhindert und

weitere Nebenwirkungen wie beispielsweise Muskelatrophie, Verlust der Gleichgewichtskontrolle, Reflexausfälle, Schmerzen oder Sensibilitätsstörungen gelindert oder gar vermieden werden.

Dies wurde im Rahmen einer kumulativen Dissertation verfolgt. Drei Studien bilden den Hauptteil dieser Arbeit (die Veröffentlichungen befinden sich im Anhang), während die Einleitung des Manuskripts die Problemstellung sowie die aktuelle Forschungslage darstellt.

In einer großen, randomisiert-kontrollierten Studie (RCT), wurden therapiebegleitend die Effekte körperlicher Aktivität bei Lymphompatienten (N=61) evaluiert. Die Patienten der Interventionsgruppe absolvierten über 36 Wochen, zwei Mal pro Woche ein Bewegungsprogramm bestehend aus Ausdauer, Kraft und Sensomotoriktraining. Die Probanden konnten ihre Lebensqualität, die statische und dynamische Gleichgewichtskontrolle, die aerobe Leistungsfähigkeit, das Aktivitätsniveau sowie Symptome der CIPN signifikant verbessern. Die Bewegungsintervention, insbesondere das sensomotorische Training, erwies sich für Lymphompatienten als machbar, sicher und effektiv.

Um Die gewonnenen Erkenntnisse adäquat einordnen zu können, wurden in zwei Übersichtsarbeiten diverse Bewegungsinterventionen, insbesondere hinsichtlich der CIPN, analysiert.

In einer Meta-Analyse wurden daher zunächst die Machbarkeit, die Sicherheit sowie die Wirksamkeit aerober Bewegungsinterventionen für Patienten mit hämato-onkologischen Erkrankungen evaluiert. RCT Studien, die entweder ein reines Ausdauertraining oder eine Kombination aus Ausdauer und Kraft mit hämato-onkologischen Patienten durchgeführt haben, wurden analysiert. Die Recherche ergab neun Studien, die alle Einschlusskriterien erfüllten. Die Analyse zeigte, dass diese Bewegungsinterventionen zu einer Verbesserung der Lebensqualität, der körperlichen Funktionsfähigkeit, des Fatiguesyndroms sowie Depressionen führen können. Die Evidenzlage ist hinsichtlich der Parameter Angst, körperliche Leistungsfähigkeit sowie unerwünschte Ereignisse derzeit noch widersprüchlich.

Da die o.g. RCT-Studie im Rahmen dieser Arbeit erstmalig Effekte auf die CIPN demonstrierte und ein Überblick über effektive Bewegungsinterventionen bei einer

Polyneuropathie, unter besonderer Berücksichtigung der CIPN fehlt, wurden in einem systematischen Review zunächst die Effekte von Bewegungsinterventionen auf Patienten mit peripheren Polyneuropathien unterschiedlicher Genesen analysiert. Die Recherche ergab 18 relevante Studien. Die Evidenz und Qualität ist am höchsten für die diabetische Neuropathie (elf Studien), während, mit Ausnahme der RCT-Studie zur CIPN im Rahmen dieser Arbeit, sechs weitere Studien sehr heterogene Kollektive neuropathischer Patienten untersuchten. Die aktuelle Studienlage zeigt, dass gezielte Bewegungsinterventionen mit neuropathischen Patienten machbar, sicher und vielversprechend sind. Für Neuropathien mit ähnlichem Schädigungsmechanismus wie dem der CIPN, scheint das Gleichgewichtstraining entscheidend zu sein. Studien die Krafttraining oder eine Kombination aus Kraft und Ausdauer untersuchten, konnten keine Effekte auf die relevanten Symptome der PNP nachweisen. Für primär metabolisch-induzierte Neuropathie wie der diabetischen hingegen, ist Ausdauertraining zusätzlich von Bedeutung.

Zusammenfassend zeigen die generierten Erkenntnisse, dass sich Sensomotoriktraining als eine therapeutisch relevante Bewegungsintervention für hämato-onkologische Patienten erweist. Es konnten zudem erstmals positive Effekte auf sensorische und motorische Symptome der CIPN aufgezeigt, Forschungslücken entdeckt sowie wichtige Bewegungsempfehlungen für die Praxis und Therapie definiert werden. Dennoch müssen noch weitere Studien folgen, um zukünftig ein besseres Verständnis für zugrundeliegende Mechanismen zu erhalten und somit die supportive Therapie für Krebspatienten weiter verbessern zu können.

CONTENTS

INTRODUCTION

A haematological malignancy is a tumor of the myeloid or lymphatic cell lines affecting blood, bone marrow or the lymph nodes with possible involvement of other organs. It includes lymphomas, leukemias, myelomas, myelodysplastic syndromes and myeloproliferative diseases. The global age-adjusted incidence rate of haematological malignancies is 40.3 new cases per 100,000 men and women per year. Individual scores are leukaemia (12.6), lymphoma (22.4) and myeloma (5.6) with all their various subcategories[2]}. Depending on the type and stage of the neoplastic disease, the clinical course can be indolent or aggressive. Treatment usually consists of multiple cycles of chemo-, immune- or radiation therapy, haematopoetic stem cell transplantations (HSCT), or a combination thereof. The disease, its treatment and the often long hospital stays required, lead to high immobility, resulting in adverse effects such as physical deconditioning[3,4] apparent as muscle atrophy[5], reduced bone density[6] or loss of balance control[7], anxiety, depression and chronic fatigue syndrome[1] . In consequence, patients' quality of life (QOL) is severely diminished. Additionally, 50% of lymphoma and leukemia patients [8] suffer from chemotherapy-induced peripheral neuropathy (CIPN), a clinically relevant side-effect that induces neuronal damage.

The following section has the aim to provide the background information necessary in order to better understand the research issue and hypothesis of this work. Thus it includes the problems patients and clinicians are confronted with, especially regarding CIPN, the potential of exercise interventions as well as recommendations for the translation into practice, derived from the current state of the art. Finally, the contribution of this work to the research gap will be discussed and future directions derived.

STATE OF THE ART

Possible side-effects patients have to deal with – and the potential of specific exercises to counteract them

Treatment of haematological malignancies consists of multiple cycles of polychemo-, immune- or radiation-therapy, haematopoetic stem cell transplantations (HSCT), or a combination thereof. The disease, its treatment and the extended hospital stays, lead to increased immobility[3]. As bed-rest studies have shown, immobility alone causes a numerable amount of side-effects such as 20-30% muscle atrophy after seven days, reduced oxygen absorption by 21% after nine days, the immune system is weakened, a higher risk for thrombosis and pneumonia, the resting heart rate is raised by 22% after four weeks, total blood volume is decreased by 700ml after four weeks[6,9,1011], balance and coordination are decreased, to name a few. Additionally, cancer treatment consisting of operations, cytostatic- or immunologically active medication and stem cell transplantations, causes further physical deconditioning. Previous studies have shown that exercise holds the potential to counteract many of the debilitating side-effects. For a better overview, these have been put together in the following table (see Table 1):

***Table 1**: An overview of the possible side-effects of cancer therapy on the one hand and the possible effects exercise could have on these symptoms on the other hand*

	Possible side-effects of cancer therapy	Possible effects of exercise
Immobility	• Muscle atrophy: (20-30 % after just 7 days) • Reduction of whole body protein synthesis • Raise of resting heart rate by 22% after 4 weeks • Progressive osteoclasis and degeneration of cartilage • Reduced proprioception and coordination • Reduced lung ventilation which results in a higher risk for pneumonia[11,12] • Secondary diseases induced by immobilty such as diabetes, metabolic syndrom etc. [13,14]	• Reduces or even prevents immobility during all phases of therapy • Maintains and builds up muscle mass • Maintains muscle protein synthesis • Sets sufficient impulse for bone augmentation • Improves proprioception and coordination • Prevents secondary diseases induced by immobility • Reduces risk for pneumonia[15]
Physical performance level	Reduced physical performance-levels due to inactivity, anxiety, depression, Fatigue or therapy induced side-effects.	Can prevent a reduction and improve physical performance status[16-20]
Muscular	• Progressive muscle atrophy due to immobility and therapeutic agents such as Glucocorticoids[21] • Cachexia (syndrome of progressive weight loss, anorexia, and persistent erosion of host body cell mass in response to a malignant growth[22].	• Gain of muscle mass • Improved inter- and intramuscular coordination • Improves neural signals for better agonistic and synergistic muscle action • Could prevent cachexia[22].
Sceletal	• Inhibition of osteoclastogenesis, alteration of **bone** metabolism and negatively impact **bone** homeostasis.	• Sets sufficient impulses to stimulate the osteoblasts and bone metabolism [24] • Can increase supporting muscles and thereforestabilize

	• Hormone sensitive medication causes demineralization[23] • Bone metastasis display an additional danger for bone fractures	bone metastasis [25]
Neural	Neurotoxic agents in chemotherapy can cause neural damage leading to peripheral neuropathy (PNP), reduced sensitivity, reflexes and pain [26]	• Neural adaptions (especially spinal and supraspinal) • Neural adaptation improving the coordination and movement of muscles and joints. • Regeneration of neuro-muscular structures • Improves postural stability [27] [28]
Balance control	Balance control is progressively reduced as the hospitalization period advances	Improves balance control and reflexes [28]
Stability	Higher risk for falls and injuries due to: • Weakness due to muscle atrophy • Loss of sensitivity, numbness or pain (PNP) especially in the soles of the feet • Reduced or lost tendon reflexes (Achillis) • Weak dorsoflexion • Progressive reduction of balance control and coordination	Induces stability, preventing falls and injuries: • Reduced reflex responses • Higher sensitivity for abnormal joint angles • Improvement of muscular control and stabilization of the joints (foot and knee) • Better coping strategies with PNP
Immune system	• Chronic inflammations are held responsible for the etiology of cancer. Additionally, cancer -therapy increases inflammatory reactions. • Hormones, pro- and anti-inflammatory cytokines play an important role for the activity of the immune system. [29]	• Exercise influences oxidative stress level which boosts the enzymatic antioxidative capacity and therefore reduces side-effects (e.g. skeletal protection) • It also induces the release of anti-inflammatory cytokines which regulate the activity of the immune system, also influencing side-effects such as kachexia [29]
Blood values	• Anemia[30] • Cytopenia	• Can improve hemoglobin levels, platelets[31] • Reduces the amount of erythrocyte and thrombocyte concentrates necessary • Less attempts necessary to collect cells for transplant[32]
Clinical outcome	Bad constitution, degrading Karnofsky status or severe side-effect of therapy such as PNP, can influence the therapy regime, dosage of therapeutic agents or even lead to an interruption of therapy.	Higher compliance for therapy and reduced supportive medication can result in better clinical outcome [33,34]
Quality of life	The diagnosis, the disease itself and the associated, debilitating side-effects, can lead to a strong impairment in patients' quality of life.	Higher mobility, better balance control, increasing gait security, less falls and injures, improved self-confidence, more strength, better coping strategies, reduced side-effects or reduces psychological problems, to name a few, contribute to an improvement in patients' quality of life.
Cancer related Fatigue	Multifactorial development of Fatigue, inducing severe tiredness, sluggishness, apathy and demotivation	Improves Fatigue syndrome [35]
Cognitive function	Cognitive impairment, especially regarding short-term memory and concentration [36-38]	Can improve cognitive functions [39-41]
Further psychological parameters **Anxiety** **Depression** **Stress etc.**	The diagnosis, the disease itself and the necessary treatment can cause distress, which becomes apparent in: • Anxiety • Depression • Reduced psychological well-being • stress	Positive influence on • Anxiety • Depression • psychological well-being • stress level [42]

In combination the effects of immobility and therapy can lead into a circulus vitiosus (see Fig.1), seriously influencing patients' physical, psychological and social activities of daily living as well as the clinical outcome and survival of cancer therapy.

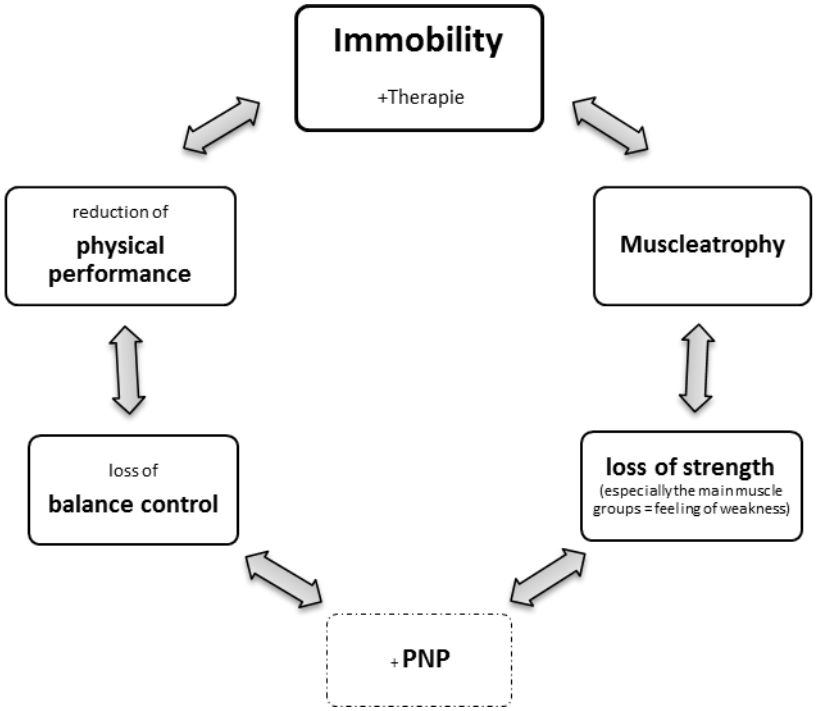

Fig. 1: *The circulus vitiosus of immobility and reduced physical performance (Streckmann 2012[28])*

Chemotherapy-induced peripheral neuropathy (CIPN) – one of the most relevant side-effects

CIPN is a highly prevalent and clinically meaningful side-effect that affects 50%[26,43,44] of Lymphoma and Leukemia Patients. It represents a group of diseases which damage motor, sensory and/ or autonomous peripheral nerves. CIPN can occur as paraneoplastic manifestation, but is much more frequently induced by neurotoxic chemotherapeutic agents[45]. Depending on the agent and its dosage, different nerve fiber modalities are affected: The main agents responsible are platinum-derivates such as Cisplatin, Carboplatin and Oxaliplatin, Vinca-alkaloids (Vincristin, Vinblastin, Vindesin, Vinorelbin) and Taxanes (Doxetacel, Paclitaxel). Additionally, the agents Bortezomib, Thalidomid and Epothilones also lead to neural damage (see Table 2). Motor- and peripheral nerves are especially sensitive towards toxins, causing motor- and sensory dysfunctions such as

painful paresthesia, dysesthesia, burning, pins and needles sensation, reduced or even absent tendon reflexes, altered proprioception, reduced balance control and consequently impaired gait as well as a higher risk of falling[26]. The symptoms not only lead to a reduction in patients' quality of life but CIPN has become a decisive limiting factor for therapy, causing treatment delays, dose reductions or even discontinuation of therapy, which can affect the outcome and compromise survival[26]. Therefore, the occurrence of CIPN presents a diagnostic dilemma as, to date, approved, effective treatment options are lacking[46]. Research has focused on pharmacological therapies aimed to reduce PNP or treat selected side-effects[47-49]. While this has been helpful for neuropathic pain, it does not address the many other sensory and motor side-effects of PNP [47,50-52]. On the contrary, many of these agents have been shown to have additional negative side-effects[26,53]. Though the many positive effects of exercise on the human body are well known, little research has been done to investigate the potentially beneficial effects of specific exercises to counteract the described symptoms of CIPN.

Table 2: *An overview of potentially neurotoxic, therapeutic agents: the neural damage they inflict, their clinical manifestation and the usual onset dose, according to the state of the art. This table does not show all potentially neurotoxic agents in chemotherapy, only the most common according to the data base.*

Therapeutic agent	Neurological damage	Clinical manifestation	Incidence	Onset dose	Author
In general	Damage to small fibers (Aα and C)	Pain symptoms, predominantly sensory symptoms: burning, paroxysmal, stabbing, or electric-shock-like sensation, pins/needles sensation and itching, typically "glove and stocking" distribution. Motor symptoms: reduced/absent reflexes, altered proprioception, which can lead to accidents or falls.			National Health & Medical research council 1999 Stubblefield 2009[26]
Platinum-derivates:	Exert direct damage to the dorsal root ganglion inducing DNA derangement, morphologic changes, and subsequent apoptosis				Tulub 2001[54]
Cisplatin	disrupts axonal microtubule growth that is essential for axonal transport, amplitude reduction of sensory Nerves	decreased vibratory sensation, pins/needles /itching sensation, painful paresthesia or numbness in a stocking-glove distribution, sensory ataxia with gait dysfunction	28%–100% (overall) + paclitaxel: 7%–8%(severe*)	300 mg/m2	Stubblefield 2009[26] Wonders 2010[53]
Carboplatin		Similar to cisplatin but milder Sensory neuropathy	6%–42% (overall)	400mg/m2	Wonders 2010[53]
	Inhibits DNA synthesis and repair due to its ring-structure, which causes the death of neural cell.	Tingling sensation, dysaesthesia, cold-induced painful dysesthesia, reduced	paclitaxel: 4%–9% (severe) 85%–95%	any	

Oxaliplatin	Studies suggest that the acute form of oxaliplatin toxicity may be associated with calcium chelation by oxalate released from the drug, adversely effecting ion channels and synaptic transmission peripheral nerve hyperexcitability, including repetitive motor discharges	or absent Achilles tendon reflex	(overall) FOLFOX: 10%–18% (severe)		Leonard 2005[55] Pietrangeli 2006[56] Benoit 2006[57] Grolleau 2001[58] Andre 2004[59] Gramont 2000[60] Lehky 2004[61] Wilson 2002[62] Krishnan 2005[63]
Vinca-alkaloids Vincristin, Vinblastin, Vindesin, Vinorelbin	Cause axonal damage, disrupt axonal transport via microtubule damage	Symmetrical tingling paresthesia, loss of ankle stretch reflexes, constipation, occasionally weakness, gait dysfunction, wrist or foot drop, progressive quadriparesis, seizures, numbness, tiungling and burning pain in hand and feet	30%–47% (overall)	4–10 mg	Verstappen et al. 2005[64] Macfarlane 1997[65]
Taxane	Axonal damage and disrupts axonal transport (by disruption in tubulin polymerization)			100 bis 200 mg/m²	Forsyth et al. 1997[66]
Docetaxel		Mild to moderate numbness, tingling, autonomic neuropathy and decreased joint position sense		>175mg/m2	
Paclitaxel		Burning stabbing pain of hands and feet, reduced or absent Achilles tendon reflex, weakness of distal muscles		>200mg/m2	Cavaletti 1995[67]
Others:					
Bortezomib	induces neuronal injury via multiple mechanisms such as cytoskeletal change, mitochondrial disturbance and disruption in tubulin polymerization			Unknown	Cavaletti 2007[68] Csizmadia 2008[69] Poruchynsky 2008[70]
Thalidomid	neuronal degeneration			>50mg/m2	Chaudhry 2002[71]
Epothilones	target microtubules			Unknown	Lee et al. 2006[72]

Potential physical activity interventions for haemato-oncological patients – state of the art and exercise recommendations

Aerobic endurance training

Aerobic endurance training can be defined as a type of training with an effective intensity, but simultaneously only inducing such moderate changes to the internal milieu (catecholamines, lactate increase) that training oncological patients are not endangered [73].

State of the art: Aerobic endurance training has become a feasible and effective method to improve the aerobic capacity in oncological patients. Besides the obvious impact on patients' physical performance level, aerobic endurance training has also shown to have a

positive impact on Fatigue and patients' quality of life [1,74]. Regarding haemato-oncological patients, only three RCTs.[1,74 75]have investigated the effect of endurance training alone in haemato-oncological patients while only one of them, the largest RCT by Courneya et al.[1], assessed Lymphoma patients only (see table 3).

***Table 3**: State of the art – Aerobic endurance interventions on patients with haemato-oncological malignancies.*

Study (only RCT)	*N*	*Entity*	*Exercise program*	*Intensity*	*Duration*	*Frequency*	*Outcome Measures*
Courneya et al. 2009	*122*	*Lymphoma (on and off treatment)*	*Aerobic endurance exercises (supervised)*	*60-75% of peak power output*	*12 weeks*	*3x/week*	*↑ physical function* *↑ QOL* *↑ Fatigue* *↑ happiness* *↑ general health* *↑ cardiovasc fitness* *↑ lean body mass* *↑ less Depression* *↔ anxiety* *No interference with chemo completion rate or treatment response*
Chang et al 2008	*22*	*AML (hospitalized under therapy)*	*Walking exercise program*	60-110 beats/min <30rrt/min 90-160 mmHg systolic 60-100 mmHg diastolic	*3 weeks*	*12min per day*	*↑ walking distance* *↑ fatigue (BFI) intensity and interference* *↓ symptom distress* *↔ anxiety* *↔ depression*
De For et al.2007	*100*	*Leukemia and Lymphoma (during allo-HSCT)*	*walking*	*unspecified*	*Until 100 days post transplant*	*2x/day for 15min during hospitalisation, 1x/day for 30min as outpatients*	*↑ subjective physical and emotional well-being* *↔ Length of hospitalization* *↔ survival* *↔ Karnofsky (smaller decline in TG (-10 TG; -20CG) ↑ in older and less fit -pre HSCT)*

↑ significant improvement, ↓ negative effect, ↔ no significant change detected, TG=training group, CG=control group, QOL=quality of life, HSCT= hematopoetic stem cell transplantations (includes both bone marrow and peripheral blood stem cell transplantations), allo=allogeneic, auto=autologous, AML=acute myeloid leukemia

Courneya et al. evaluated 122 lymphoma survivors both on and off treatment and showed that aerobic endurance training can improve physical function, QOL, fatigue, happiness, depression, aerobic fitness, and body composition. No differences could be detected for the level of anxiety. Additionally, they noted that exercise did not interfere with chemotherapy completion rate or treatment efficacy. Chang et al. found improved walking distance, fatigue intensity and interference as well as symptom distress following a walking program for AML Patients undergoing therapy. The patients participated in a walking regime for 12min every day, over three weeks. No significant differences were found for anxiety or

depression. The third study by De For et al. also investigated the influence of walking, though in Leukemia and Lymphoma patients during HSCT. Inpatients in this study were asked to walk twice a day for 15min, extending walking to 30min per day as outpatients until 100 days post-transplant. In the total study population, they found a smaller (not significant) decline in the walking group (-10) in comparison to the control group (-20). Though, in the subgroup of older and less fit patients prior to transplant, the intergroup comparison was significant. Additionally, patients in the walking group reported better physical and emotional well-being. No differences could be detected regarding the length of hospitalization or survival.

Training recommendation: In Lymphoma and Leukemia patients, training should be individualized as it is codependent on the tumor stage, the phase of therapy they are currently undergoing, possible limiting side-effects such as anemia or cytopenia and even their lifestyle. Therefore the following training recommendations for aerobic endurance training with oncological patients can be derived:

Basic endurance should be trained prior to more intense variations. In the acute phase of therapy, patients should train on a daily basis for 15-30min, at 50-75% max. heart rate. Immobility should be avoided. Weak patients should also train every day, but with a lower intensity and shorter duration. To begin with, interval training should be chosen, starting with 5-10min intervals, slowly increasing the intervals until the continuous method for 20-30min is possible[76,77].

Outpatients undergoing adjuvant therapy, or in rehabilitation, should train regularly 2-3 times per week for 15-45min. In order to ensure a safe but also effective training, the intensity should be 60-80% max. Hf or 50-75% of max. O_2 capacity[17].

Training should always be supervised in the beginning to ensure the correct execution and intensity for patients. Supervision as well as training management is easiest when patients train on a bicycle ergometer or treadmill, until safe to train unsupervised and outdoors again.

In order to prevent overburdening, training should be altered with further training interventions such as resistance training, if combined [78].

Contraindications *for aerobic endurance training:*

- *<10.000 µl thrombocytes*
- *acute bleeding*
- *acute infections (> 38°C fever)*
- *strong nausea and vomiting*
- *within 24h of receiving cardio- or nephrotoxic chemotherapy*

Interruption of aerobic endurance training should occur in the case of:

- *sudden paleness*
- *developing or worsening nausea*
- *vomiting*
- *developing or increasing headache*
- *hyperventilation*[79]

Resistance training

Strength is defined as the ability of the neuro-muscular system, to overcome (concentric), work against (excentric) or hold against (static) resistances with the help of innervation- and metabolic processes[80]. Consequently, resistance training aims to improve strength, inter- and intramuscular coordination as well as neural control, gaining muscle mass.

As leukemia and lymphoma patients have to endure long and intense phases of therapy and accordingly high immobility, patients suffer from muscle atrophy, associated weakness, loss of physical performance, deterioration of bone mass and subsequently a decline in QOL. It may seem obvious that resistance training, which is known to counteract these parameters in the healthy population, is an appropriate measure for cancer patients.

Due to the fact that cancer is a life-threatening disease, the necessary treatment severely straining the body, physicians advised patients to rest and gather their "strength" for the imminent therapy, for years. Additionally, further therapy-induced side-effects such as thrombocytopenia, possibly causing internal bleeding, led to increased anxiety, especially for resistance training. Only slowly, research has been able to prove that resistance training is not only feasible for cancer patients but also very beneficial. Studies in other entities, better investigated, were able to show that cancer patients are able to cope much better with therapy and the accompanying side-effects, if they deteriorate less, lose less muscle mass, feel stronger and their mobility is maintained or even increased.

Therefore, resistance training is important in the support of oncological patients. The main aim is to prevent muscle atrophy during therapy, build it up as soon as possible and help patients to feel strong enough to cope with therapy, maintain their activities of daily living, support them to reintegrate into their social and working life and with that improve their QOL. Additionally, resistance training can offer an adequate impulse to maintain bone mass, especially for patients receiving aromatase inhibitors[81,82] and influence the body composition [17].

Previous studies reported no adverse events and were able to show that resistance training is feasible and safe for cancer patients [83], even in patients with lymphedema[84].

State of the art: Most studies have been performed in breast cancer patients followed by prostate cancer. So far, only two RCTs have performed solely resistance exercises with hemato-oncological patients (see table 4).

Table 4*: State of the art – Interventions on resistance training on haemato-oncological patients*

Study (only RCT)	***N***	***Entity***	***Exercise program***	***Intensity***	***Duration***	***Frequency***	***Outcome Measures***
Hacker 2011	19	Leukemia Lymphoma and further diseases (after allo and auto HSCT)	Strength training	Borg scale 13	6 weeks after discharge	1-2x/week supervised, 1-2x/week advised to move	only time-effects: ↑ physical activity, ↑ muscle strength ↑ health status ↔ QOL ↔ Fatigue
Cunningham 1986	*40*	*Leukemia (receiving HSCT)*	*Resistance training*	*unspecified*	*5weeks*	*3-5/week*	↑ Nitrogen balance ↔Creatinine excretion ↔arm circumference

↑ significant improvement, ↓ negative effect, ↔ no significant change detected, QOL=quality of life, HSCT= hematopoetic stem cell transplantations (includes both bone marrow and peripheral blood stem cell transplantations, allo=allogeneic, auto=autologous

The earliest and largest publication by Cunningham in 1986[85], evaluated blood samples of leukemia patients receiving HSCT after 5 weeks of resistance training 3-5 times per week. They found higher nitrogen balance in the exercise group, but no changes for creatinin excretion and arm circumference. Hacker et al.[86] performed resistance training with Leukemia and Lymphome patients, 1-2 times per week, over 6 weeks. The authors could show improved time-effects only, in physical activity, muscle strength and health status, but no changes in Fatigue and QOl.

Training recommendation: Training should address the main muscle groups and as holistically as possible[17]. Resistance exercises are most effective performed 2-3 times per week with an intensity of 15±1 on the Borg scale or 60-85% of the 1RM and 2-3 sets per exercise with 8-15 repetitions. It is important to ensure recreational breaks in between the exercises in order to avoid fatigue and an accurate, physiological performance. Therefore it should be supervised at the beginning and recurrently in order to prevent muscular dysbalance or injuries.

Contraindications:

- *thrombocytopenia*
  - *<20.000/ µl resistance training not advised*
  - *>20.000/µl moderate exercises possible*
  - *>50.000/µl intensive training possible*
- *osteolysis*
- *haemoglobin <8*
- *acute infection (fever >38°C)*
- *severe nausea*
- *vomiting*
- *direct tension on scared tissue for 4-6 weeks post operation*
- *occurring or worsening somatic symptoms during training*[77]

Combined exercise interventions: Aerobic endurance and resistance training

State of the art: Further 9 RCTs[31,32,87-8957-5919,90-92] on hemato-oncological patients (all undergoing HSCT) chose a combination of endurance and strength training (see table 5).

Table 5*: State of the art – Combined exercise interventions consisting of endurance and resistance exercises in haemato-oncological patients.*

Study (only RCTs)	*N*	*Entity*	*Exercise program*	*Intensity*	*Duration*	*Frequency*	*Outcome Measures*
Wiskeman n 2011	*10 5*	*Leukemia, and Lymphoma (Prior, during and after allo-HSCT)*	*Endurance and resistance training (partly self-administered)*	*"brisk" walking*	*1-4 weeks prior to HSCT, continued through inpatient, 6-8 weeks after discharge*	*During inpatient phase: 2x/week Endurance 20-40min; 3x/week, strength 2x/week*	*↑ Fatigue (MFI)* *↑ physical fitness (6MWT)* *↑ physical functioning and pain (EORTC)* *↑ max strength lower extremeties* *↑ less global stress* *↑ anger/hostility(POMS)* *↓ anxiety higher in TG (HADS)* *↔ pedometer* *↔ coordination*

							↔ *QOL*
Knols 2011	*131*	*Leukemia and Lymphoma (>6months post HSCT)*	*Endurance and strength (outpatient)*	*50-60%, increasing to 70–80% of estimated max. Hf*	*12 weeks*	*2x/week endurance >20min*	↑ *physical performance* ↔ *self-reported physical function* ↔ *body composition* ↔ *walking activity* ↔ *Fatigue* ↔ *QOL*
Baumann 2010	*64*	*Leukemia and Lymphoma (during auto+ allo HSCT)*	*TG: Endurance and ADL/strength (supervised) CG: Mobilisation and gymnastics*	25W /2min, up to Hf 180-age 80% of achieved watt load	*Varied: 6-9days pre HSCT, 43±25 days of hospitalisation*	*Daily 20min ADL 10-20min aerobic endurance*	↑ *Strength* ↑ *Endurance* ↑ *less pneumonias* ↔ *lung function* ↑ *QOL (EORTC) and physical functioning* ↑ *blood values (Plts, Hb)*
Jarden 2009a	*42*	*Leukemia and hematological disorders (during allo-HSCT)*	*multimodal: Endurance and strength , relaxation, and psychoeducational*	*Cycling: low-mod (50-70% max Hf)*	*4-6weeks*	*5 days/week cycling, stretching 3x/week resistance 2x/week progressive relaxation, ongoing psychoeducation*	↑ *Aerobic capacity (VO2max)* ↑ *Muscle strength* ↑ *Functional performance* ↑ *less diarrhea and parenteral nutrition* ↔ *QOL* ↔ *Fatigue* ↔ *Psychological well-being (FACT-An)* ↔ *Anxiety and depression (HADS)* ↔ *Clinical outcome*
Jarden 2009b	*42*	*Leukemia and hematological disorders (during allo-HSCT)*	*Endurance and strength , relaxation, and psychoeducational multimodal*	*Cycling: low-mod (50-70% max Hf)*	*4-6weeks*	*5 days/week cycling, stretching 3x/week resistance 2x/week progressive relaxation Ongoing psychoeducation*	↑ *reduction in symptom intensity :Mucositis, cognitive, gastrointestinal, functional symptoms* ↔ *affective symptom cluster*
Shelton 2009	*61*	*Leukemia and Lymphoma (<6months post HSCT)*	*Aerobic exercises (treadmill, bicycle ergometer versus walking) Resistance (free weight, weight machines versus resistance bands) (self-directed)*	*Aerobic: 60-70% max Hf, 20-30min*	*4 weeks*	*3x/week*	*Supervised: +12% distance 6(MWT), +14% 50-foot walk* *Self-admin: +10% distance 6(MWT)* ↔ *Fatigue (BFI)*
Coleman 2008	*135*	Multiple myeloma (during auto-HSCT)	*Aerobic endurance-walking, resistance with bands , stretching (self-administered)*	*No indication*	*N=120 15weeks N=70 of the 120 +15weeks*	*No indication*	↔ *aerobic capacity (6min walk* ↑ *less thrombocyte and erythrocyte concentrates* ↑ *less attempts to collect cells for transplant*
Mello 2003	*18*	Leukemia and Lymphoma (immediately after allo-HSCT)	active exercise program for upper and lower limb mobility, stretching exercises, and treadmill walking	*70% max Hf*	6 weeks during hospitalization , continued as outpatient	*40min/day (except week-ends)*	↑ *TG: maximal isometric strength for upper and lower extremity muscle groups (shoulder, abductors, flexors, elbow flexors, knee flexors, ankle flexors)* ↑ *CG: knee flexors*
Coleman 2003	*24*	Multiple myeloma (receiving HSCT)	*TG: 1 aerobic component (walking, running, cycling) + resistance*	*Endurance Borg-scale 11-13* *Resistance Borg-scale 15-*	*6 months*	*TG: unspecified* *CG: 20min 3x/week*	↑ *lean muscle mass* ↔ *POMS* ↔ *sleep* ↔ *muscle strength* ↔ *aerobic capacity*

	exercises with resistance bands CG: encouraged to walk (home-based)	*17*	

↑ significant improvement, ↓ negative effect, ↔ no significant change detected, HSCT= hematopoetic stem cell transplantations (includes both bone marrow and peripheral blood stem cell transplantations), allo=allogeneic, auto=autologous, Hf=,heart frequency, POMS= Profile of Mood States, TG=Training group, CG=control group, 6MWT=6-minute walk test, QOL= quality of life

Quality of life: One study by Baumann et al. [79]found significant improvements regarding patients'quality of life. Three studies (Wiskemann 2011, Knols 2011, Jarden 2009a)[90,92,93] could not detect any significant intergroup differences.

Fatigue: Similar results can be found regarding Fatigue. One RCT (Wiskemann 2011)[92] could show an improvement in the exercise group, while three (Knols 2011, Jarden 2009, Shelton 2009)[89,90,93]could not detect any significant changes among the groups.

Physical performance: Regarding patients' physical performance level, many intergreoup differences could be shown. Improved *endurance* parameters were detected by Baumann and Jarden et al., only one study (Coleman 2003) showing no significant differences in the measured parameters. An improvement in *strength* parameters were demonstrated by four studies (Wiskemann 2011, Baumann 2010, Jarden 2009, Mello 2003)[31,88,90,92], while Coleman et al. again found no differences. Two studies (Baumann 2010, Knols 2011)[31,93] also found better *physical fitness* in the exercise group in comparison to the control group. Concerning parameters related to patients' *gait*, two studies (Wiskemann 2011, Shelton 2009) [89,92], found improved walking parameters such as walking distance in the 6-minute walking test (6MWT), while no differences could be detected in the walking activity (Knols 2011) or aerobic capacity (Coleman 2008) with the 6MWT. Only one study included coordination exercises ("one-leg stand and balancing") and found no differences between the groups[92], though it is not apparent how coordination was measured.

Psychological parameters: No significant effect could be found for anxiety, depression or psychological well-being (Jarden 2009a)[90], one study (Wiskemann 2011)[92] even showed a slightly higher anxiety level for the exercise group. With the Profile of Mood States (POMS) questionnaire, anger and hostility improved in one study (Wiskemann2011)[92], while another (Coleman 2003)[87] showed no effects.

Blood parameters: Coleman et al.[32]revealed that less thrombocyte and erythrocyte concentrates were necessary in the exercise group, while Baumann et al.[31]found an increase in platelets and hemoglobin concentration in the blood as well as fewer attempts to collect cells for transplant among the patients in the intervention group.

Further side-effects: Reduced global stress and pain could be shown in the study by Wiskemann et al.[92], Baumann et al. detected less pneumonias though no change in lung function[31] in exercising patients, while Jarden et al.[90] demonstrated less diarrhea and parenteral nutrition necessary. Two studies commented on patients' body composition, one (Coleman 2003)[87] finding improved lean muscle mass whereas another (Knols 2011)[93] found no changes. Jarden et al.[91]additionally detected reduced symptom intensity for mucositis, cognitive, gastrointestinal and functional symptoms.

These studies not only give evidence that endurance as well as resistance training is feasible during all phases of therapy, but also contributes to the improvement of therapy-related side-effects.

Sensorimotor training

Lacking references in hematology and oncology, as this works presents the first implementation of sensorimotor training in oncological patients; the beneficial effects of sensorimotor training will mainly be derived and analyzed from studies on healthy adults and elderly.

State of the art Balance control is a fundamental skill for the successful performance of activities of daily living. Insufficient balance control presents a risk factor for falls and injuries, inducing insecurity and further promoting immobility. The circulus vitiosus is pursued. Balance control is not just something we acquire in the first 7 years of our life, but can still be trained at an old age. As previous studies have shown, sensorimotor training has proven to be an ideal device to train balance control at all ages [27,9495].

Sensorimotor describes a complex system, which is not only reduced to afferent sensory contributions but also includes the efferent mechanisms and reacts to exercise with adaptive processes. The central nervous system integrates sensory information perceived from multiple sources in order to initiate the appropriate motor responses which lead to muscle activation and thus produce the forces necessary to maintain balance.

‘Sensorimotor training can be defined as a training regimen that primarily aims at an improved perception and integration of sensory signals on a spinal and supraspinal level as well as an optimized conversion of the integrative processes in an adequate neuromuscular response or motor action’[96,97] The implementation in practice, involves progressively difficult exercises on a progressively instable surface (see Fig.4). Balancing on various different devices such as balance pads, rocker- or balancing boards for instance induce adaptions in the neuromuscular system which promote neural plasticity in the spinal and supraspinal structures of the central nervous system, on the long run [98,99 100]. Due to this ability, sensorimotor training has also shown to regenerate neuromuscular structures following injuries[27,101-105]. Consequently sensorimotor training has primarily been a training device to rehabilitate (world-class-) athletes after injuries to the ankle or knee. By imitating an unstable surface, the body tries to compensate by stabilizing the joints, enhancing the neuromuscular functions, inducing more supportive muscle mass while generating a high intermuscular coordination between the agonistic and antagonistic muscles in the lower extremities[106]. Later its properties were also implied to prevent injury re-occurrence[107-109]. Former studies demonstrated a reduction of injury incidences by 50% in ball games, when sensorimotor exercises were integrated into the training [110-112], handball[113] volleyball[108,114], soccer[109,115], basketball[109,116]. Previous studies have also revealed that sensorimotor training can influence reflex excitability[117-120]. Most research [106,121-123,117] concerns the Hoffman reflex (H-reflex), demonstrating a down-regulation through balance training. These effects were not only achieved in young healthy adults, but as Granacher and Mynark were able to demonstrate, elderly subjects responded equally to the training. Williams et al.[124] also found an improvement regarding the Achilles tendon reflex, in elderly subject, which suggests that balance training could be beneficial for patients with reduced reflex functions[125]. Furthermore, the ankle angle proprioceptive receptors that react to an abnormal joint angle position and trigger a reflex to maintain balance, also show improved reaction times after sensorimotor training[120] (overview: Horak and Macpherson 1996).

The benefits of sensorimotor training not only lie in the ability to induce neural adaptions and with that influence balance control, but as recent studies have shown, also influence complex motion tasks and functional capacity of the muscles. Strength and jumping abilities were improved[97,126-130117,131], demonstrating reactive forces and a higher maximum

rate of force development [94,128,132,133], maximal voluntary strength [126,134,123]and the vertical jump performance [131,135].

Slowly but surely the benefits of sensorimotor training are being extended to further useful areas of application. In patients who had suffered a stroke or with vestibular dysfunctions for instance, sensorimotor training was able to improve their postural stability [136-139].

For cancer patients, the advantage of sensorimotor training not only lies in the feasibility during all phases of therapy, even in isolation, but also in its above mentioned properties. In comparison to other training interventions, sensorimotor training can be performed at all ages and various performance levels. As Granacher and Gauchard[94,140] could demonstrate, even frail people with a high falling incidence were able to perform and profit from this training. Due to the low intensity but high impact, cancer patients undergoing therapy are able to cope with the exercises and little effort involved. During HSCT and isolation phases for instance, cytopenia and the associated potential risks for the patients are often a limiting factor for many exercise interventions such as strength training. Therefore exercise interventions maintaining patients' physical performance level and mobility throughout this critical period, are scarce. As the training devices used for sensorimotor training meet the requirements of hospital hygiene, thus limiting the risk of infections due to leucopenia, and training involves short interventions of only 20sec. using only bodyweight, diminishing the risk of internal bleeding due to thrombocytopenia, two major risks can be compromised.

50% [8] of the patients have to cope with an additional burden: The loss of sensitivity, pain and reduced or absent tendon reflexes in the foot, due to peripheral neuropathy, cause even more insecurity, instability and consequently immobility. The sole of our foot is crucial for stance stability, balance control and gait[141]. Impairments as found in neurodegenerative diseases such as Morbus Parkinson und Multiple Scleroses[142] but also in PNP[44,143,144 145], show a severe restriction of plantar sensory abilities inducing deficiencies in balance control, the gait pattern and even whole-body coordination.

Furthermore, neuropathic patients may also profit from the effects of SMT on reflex abilities. Patients with sensory neuropathy show longer latency periods[141] and reduced to absent tendon reflexes. Macefield et al.[146] could show that deafferented motoneurons could be activated at a significantly lower frequency, while further studies demonstrated the

beneficial influence of balance training on reflex abilities (see above). Williams for instance achieved a down-training of the Achilles tendon reflex with balance training, a tendon reflex often impaired by PNP. Moreover, elderly, who are also more restricted in modulating reflex responses[27,147] are able to adapt and improve neural control in response to balance training, may indicate that patients with reduced reflex abilities such as cancer patients with PNP could also benefit.

Training recommendations: Training can be performed daily, though it is important to keep in mind that time-related processes take place in response to sensorimotor training. Previous studies have shown that the first phase (0-20sec.) initiates learning or adaptive postural strategies, while durations from 40-60sec. onwards induce fatigue. Therefore durations of 20-40sec. probably induce the highest neuromuscular learning processes and avoid fatigue, while durations above 60sec. are more appropriate if the training intends to train strength [97,117,127,128]. It is therefore also important to allow for a sufficient rest in between the exercises and sets in order to avoid fatigue. The duration of the regeneration break should endure at least as long as the exercise itself (20-40sec.), allowing a 1min to 3min rest between each set and not exceeding 4-6 sets at the most[148,149]. Significant effects could be found after 4-6weeks of training (healthy subjects)[104,108,150] with a frequency of 2-3 times per week [100,123,126,127]. As the neuromuscular system adapts specifically and progressively to the training volume as well as the applied intensity, the exercises should be challenging for the individual participants. Therefore training should be progressive. This can be achieved either via the choice of exercises, following the exercise principals: from easy to complex exercises e.g, from bipedal to monopedal exercises, gradually reducing the supporting surface, making it more and more instable or adding additional perturbations, irritations, tools (e.g. balls, obstacles) or tasks (e.g. cognitive), or by increasing the duration or intensity of the exercises. Previous studies [98,100,117,133]have increased the duration of the exercises from 20 to 40 sec. or the number of sets from 4 to 6 after half of the training sessions[148]

<table>
<tr><td>Instruction</td><td>“Stand as quiet as possible. Avoid falling off the training device”</td></tr>
<tr><td>Initial Position</td><td>- upright position while fixating a given point straight ahead
- one-legged stance (barefoot)
- slightly flexed knee (approx. 30°)
- hands placed on hips/ or hanging down at the side of the body
- the free leg should not touch the supporting leg or the surface</td></tr>
<tr><td>Exercises</td><td>
<table>
<tr><th>content</th><th>duration</th></tr>
<tr><td>minimum duration necessary for effects</td><td>> 4 weeks</td></tr>
<tr><td>frequency</td><td>2-6 x / week</td></tr>
<tr><td>time required in total</td><td>~ 6 – 30 minutes</td></tr>
<tr><td>duration of one exercise</td><td>20 seconds</td></tr>
<tr><td>rest inbetween exercises</td><td>40 seconds</td></tr>
<tr><td>repetitions per exercise</td><td>3</td></tr>
<tr><td>amount of exercise sets</td><td>3-8</td></tr>
<tr><td>rest inbetween exercise sets</td><td>1-3 Minuten</td></tr>
</table>
</td></tr>
<tr><td>Progression</td><td>
<table>
<tr><td></td><td>eyes open</td><td>head turned or looking up</td><td>eyes closed</td><td></td></tr>
<tr><td>stable surface</td><td></td><td></td><td></td><td>no additional tasks</td></tr>
<tr><td></td><td></td><td></td><td></td><td>additional motor OR cognitive task</td></tr>
<tr><td>instable surface</td><td></td><td></td><td></td><td>additional motor AND cognitive task</td></tr>
</table>
</td></tr>
<tr><td>Examples for training devices</td><td>  </td></tr>
</table>

***Fig. 2**: Example of a training regime used in this work and several previous studies[97-100,117,127,128,131,133,151] (modified from Gruber 2007).*

Contraindications: To date, no specific contraindications are known, apart from general contraindications to exercise such as fever, for instance. To ensure patients’ safety, it is crucial though to offer a safety bar or something to hold on to in case of loss of balance and supervise the training, especially in unstable (e.g. neuropathic or isolated) patients.

PHYSICAL ACTIVITIES FOR PATIENTS WITH PNP

Regarding chemotherapy induced peripheral neuropathy the present randomized controlled trial is the first to reveal significant and clinically meaningful results, especially on sensory

symptoms. The component sensorimotor training with its above mentioned properties, distinguishes this paper from others in the field. We therefore presume that this specific type of balance training played a crucial role. Consequently, we wanted to analyze the effects of exercise interventions on various neuropathic patients, in a systematic review in order to determine the direction for future research.

Physical activity in patients with neuropathies of diverse pathophysiology

The largest research field on PNP is based on neuropathic diabetics (eleven Studies). Further six studies on neuropathic patients exist, though with heterogeneous origin. Generally speaking, most exercise interventions target the general performance level of the patient, mainly addressing strength and cardio-respiratory fitness. For neuropathic patients though, the sensory and motor side-effects such as the loss of sensation or pain in hands and feet, reduced or absent reflexes, loss of balance control and impaired gait are far more relevant. Several studies[152,153] have shown an association between PNP and loss of balance as well as changes in gait patterns, subsequently leading to a higher risk of falling and injuries [154,155]. For patients, this presents a severe impact in their quality of life. Specific exercises may have the potential to improve some of the relevant symptoms. In a systematic review we therefore investigated the various exercise interventions and came to the following conclusion:

The analysis of all appropriate Studies showed that for primarily non-metabolic neuropathies such as CIPN, balance exercises seem to target the side-effects most relevant for neuropathic patients best. Though, the type of balance exercises as well as the intensity and frequency is crucial. All studies focusing on balance training solely, and thus performing these exercises 2-3times per week, proved to be beneficial. Studies showing no effect, although containing a balance component, exercised either only once a week, were self-monitored or had integrated only one balance exercise into the training program. Additionally, there are no studies to date, showing an influence of strength training alone or strength and endurance combined, on the relevant side-effects of PNP. Possible interventions to obtain this aim could be e.g. sensorimotor training, Tai Chi and vibration exercises.

For patients with neuropathies of primarily metabolic origin, such as diabetic peripheral neuropathy, endurance exercises will presumably target the onset as well as the progression of PNP best. Additional balance exercises or WBV [156] should be considered[157].

Physical activity in patients with chemotherapy-induced peripheral neuropathy

There are no RCTs and very little research to date that investigated the toxic impact of chemotherapy on the human body and the potential benefits of exercise, to counteract the side-effects.

Previous studies give evidence that PNP induces balance deficits[26,144,145], insecure gait[44] and that the risk of falling increases with each cycle of chemotherapy[158]. Additionally, further investigations revealed that neuropathic pain correlated with an impairment of patients' quality of life. Patients reported that walking was the most affected domain[53].

Steimann[159] and Vogt [160] evaluated the subjective effectiveness of physiotherapy (gait training and balance exercises) and ergotherapy (e.g walking in granulate material), while Steimann also looked at electrotherapy. In both evaluations, patients experienced ergotherapy (walking thorugh granulated material) as well as physiotherapy (stimulation and coordination exercises) as "very helpful". One case-report on a breast cancer patient suffering from painful CIPN showed improved balance following balance training[144].

Within this work (RCT[161]), we were able to demonstrate a positive effect of exercise (endurance, strength and sensorimotor training) on sensory and motor symptoms of CIPN (see Table 6). The systematic review supports the presumption that sensorimotor training was the essential intervention to target the symptoms of CIPN best. Therefore, exercise recommendations are based on types of exercise that can induce neuronal adaptions, such as sensorimotor training or whole body vibration[162].

***Table 6**: Exercise intervention studies for patients with chemotherapy-induced peripheral neuropathy*

Author	N	Type	Entity	Type of exercise	Duration	Frequency	Outcome Measures (sig. intergroup diff.)	LOE	Grade
Streckmann 2013	61 30 IG 31 CG	RCT	lymphoma	Sensorimotor training, endurance and strength	36 weeks	2x/week	↑ QOL ↑peripheral deep sensitivity ↑ higher reduction and total number of CIPN ↑ static, dynamic and perturbed balance control ↑ aerobic performance level ↑ level of activity (outside intervention)	2b	B

Exercise is currently a promising option in supportive therapy which should be taken more seriously, as it may counteract several of the debilitating side-effects, not only improving patients' quality of life, but simultaneously contributing to a better clinical outcome by enabling patients' to receive the optimal therapy regime.

RESEARCH GAP AND HYPOTHESIS

The following table (see table 7) represents the current RCTs in hemato-oncological patients representing the exercise intervention used and the side-effects investigated. The amount of debilitating side-effects patients have to endure, the above mentioned beneficial effects of exercise and the obvious research gap, especially for Lymphoma patients, motivated the present work. We hypothesized that exercise has a positive influence on the therapy-induced side-effects in Lymphoma patients undergoing therapy.

Furthermore, research revealed that CIPN is a highly prevalent and clinically relevant side-effect. I therefore focused on this severe and complex side-effect with the aim to find better supportive measures. Thus the hypothesis arose, that sensorimotor training has the potential to target relevant symptoms of CIPN.

RESULTS (SCIENTIFIC PUBLICATIONS RELEVANT FOR THIS WORK [FULL TEXT IN APPENDIX])

I. Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy – a randomized, controlled trial

F. Streckmann, S. Kneis, J.A. Leifert, F.T. Baumann, M. Kleber, G. Ihorst, L. Herich, V. Grüssinger, A. Gollhofer & H. Bertz, (2014), in Annals of Oncology, 25: 493-499. (IF: 7.4)

Background

Lymphoma patients undergoing therapy must cope with the side effects of the disease itself, therapy and associated immobility. Peripheral neuropathy (PNP), loss of balance control and weakness not only diminishes patients' quality of life (QOL), it can also affect planning and the dosage of therapy. Exercise may enable patients to reverse these declines, improving their performance level and QOL.

Patients and methods

We carried out a randomized, controlled trial, assigning 61 lymphoma patients either to a control group (CG; *N=31*) or to a 36 week intervention (IG; *N=30*), consisting of sensorimotor-, endurance- and strength training twice a week. Primary endpoint was QOL; secondary endpoints included movement coordination, endurance, strength and therapy-induced side effects.

Results

Intergroup comparison revealed improved QOL ($\Delta_{T1\text{-}T0}$ *P=0.03*) and PNP related deep sensitivity in the IG: 87.5% were able to reduce the symptom, compared to 0% in the CG (*P<0.001*). Significant differences in the change of balance control could be found between the groups, with the IG improving while the CG steadily declined (monopedal static $\Delta_{T3\text{-}T0}$ *P=0.03*; dynamic $\Delta_{T3\text{-}T0}$ *P=0.007*; perturbed mono-$\Delta_{T3\text{-}T0}$ *P=0.009* and bipedal $\Delta_{T3\text{-}T0}$ *P=0.006*), failed attempts (monopedal static $\Delta_{T3\text{-}T0}$ *p=0.02*, dynamic $\Delta_{T3\text{-}T0}$ *P< 0.001*and perturbed $\Delta_{T3\text{-}T0}$ *P=0.006*) and improved time to regain balance ($\Delta_{T3\text{-}T0}$ *P=0.04*). Moreover the change in the aerobic performance level ($\Delta_{T3\text{-}T0}$ *P=0.05*) and additional amount of exercise carried out per week [metabolic equivalent (MET); *P=0.02*] differed significantly across groups.

Conclusions

Exercise, especially sensorimotor training, is a feasible and promising method to support cancer patients during therapy. It improves patients QOL, reduces restrictions from side-effects such as PNP and improves patients' balance control, physical performance level and mobility.

German Clinical Trials Register number (DRKS00003894)

Keywords: Exercise, sensorimotor training, lymphoma, peripheral neuropathy, quality of life, side-effects

II. Aerobic physical exercise for adult patients with haematological malignancies – a meta-analysis

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Background

Although people with haematological malignancies have to endure long phases of therapy and immobility which is known to diminish their physical performance level, the advice to rest and avoid intensive exercises is still common practice. This recommendation is partly due to the severe anaemia and thrombocytopenia from which many patients suffer. The inability to perform activities of daily living restricts them, diminishes their quality of life and can influence medical therapy.

Objectives

To evaluate the efficacy, safety and feasibility of aerobic physical exercise for adults suffering from haematological malignancies.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2014, Issue 1) and MEDLINE (1950 to January 2014) as well as conference proceedings for randomised controlled trials (RCTs).

Selection criteria

We included RCTs comparing an aerobic physical exercise intervention, intending to improve the oxygen system, in addition to standard care with standard care only for adults suffering from haematological malignancies. We also included studies that evaluated aerobic exercise in addition to strength training. We excluded studies that investigated the effect of training programmes that were composed of yoga, tai chi chuan, qigong or similar types of exercise. We also excluded studies exploring the influence of strength training without additive aerobic exercise. Additionally, we excluded studies assessing outcomes without any clinical impact.

Data collection and analysis

Two review authors independently screened search results, extracted data and assessed the quality of trials. We used risk ratios (RRs) for adverse events and 100-day survival, standardised mean differences for quality of life (QoL), fatigue, and physical performance, and mean differences for anthropometric measurements.

Main results

Our search strategies identified 1518 potentially relevant references. Of these, we included nine RCTs involving 818 participants. The potential risk of bias in these trials is unclear, due to poor reporting.

The majority of participants suffered from acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), malignant lymphoma and multiple myeloma, and six trials randomised people receiving stem cell transplantation. Mostly, the exercise intervention consisted of various walking intervention programmes with different duration and intensity levels.

Our primary endpoint of overall survival (OS) was not analysed in any of the included trials, but three trials reported deceased participants during the course of the study or during the first 100 days. There is no evidence for a difference between participants exercising and those in the control group (RR 0.93; 95% CI 0.59 to 1.47; P = 0.75; 3 trials, 269 participants, moderate quality of evidence).

Four trials analysed the influence of exercise intervention on quality of life (QoL). Excluding one trial with serious baseline imbalances, physical exercise improves QoL (SMD 0.26; 95% CI 0.03 to 0.49; P = 0.03; 3 trials, 291 participants, low quality of evidence). This positive effect of exercise was also found in the subscales physical functioning (SMD 0.33; 95% CI 0.13 to 0.52; P = 0.0009; 4 trials, 422 participants, moderate quality of evidence) and depression (SMD 0.25; 95% CI -0.00 to 0.50; P = 0.05; 3 trials, 249 participants, low quality of evidence). However, there is no evidence for a difference between additional exercise and standard treatment for the subscale anxiety (SMD -0.18; 95% CI -0.64 to 0.28; P = 0.45; 3 trials, 249 participants, low quality of evidence). Seven trials (692 participants) evaluated fatigue. There is moderate quality of evidence that exercise improves fatigue (SMD 0.24; 95% CI 0.08 to 0.40; P = 0.003).

Eight studies evaluated various aspects of physical performance (e.g. aerobic capacity, cardiovascular fitness), but none of them could be pooled in a meta-analysis. In seven trials there is a tendency or statistically significant effect favouring the exercise group (very low quality of evidence).

Three trials (266 participants) investigated serious adverse events (SAEs) (e.g. bleeding, fever, pneumonia, deep vein thrombosis, and infection), and one trial (122 participants) assessed adverse events (AEs). There is no evidence for a difference between arms in terms of SAEs (RR 1.44; 95% CI 0.96 to 2.18; P = 0.06) or AEs (RR 7.23; 95% CI 0.38 to 137.05; P = 0.19); both findings are based on low quality of evidence.

Authors' conclusions

There is no evidence for differences in mortality between the exercise and control groups. Physical exercise added to standard care can improve quality of life, especially physical functioning, depression and fatigue. Currently, there is inconclusive evidence regarding anxiety, physical performance, serious adverse events and adverse events.

We need further trials with more participants and longer follow-up periods to evaluate the effects of exercise intervention for people suffering from haematological malignancies. Furthermore, we need trials with overall survival as the primary outcome to determine whether the suggested benefits will translate into a survival advantage. To enhance comparability of study data, development and implementation of core sets of measuring devices would be helpful.

III. Exercise intervention studies in patients with peripheral neuropathy – a systematic review

Fiona Streckmann, Eva M. Zopf, Helmar C. Lehmann, Kathrin May, Julia Rizza, Albert Gollhofer, Wilhelm Bloch, Freerk T. Baumann, accepted in Sports Medicine. (IF: 5.2)

Abstract

Introduction

Peripheral neuropathies (PNP) encompass a large group of disorders of heterogeneous origin which can manifest themselves with sensory and / or motor deficits depending on the predominantly affected nerve fiber modality. It represents a highly prevalent disease group which can be associated with significant disability and poor recovery. Exercise has the potential to improve side-effects of PNP. Our objective in this systematic review was to analyze exercise interventions for neuropathic patients in order to evaluate the possible benefits of exercise.

Methods

Three independent reviewers used PubMed, MEDPILOT® (MEDLINE), Cochrane and relevant reference lists to obtain the data. Relevant studies were graded according to the Oxford Levels of Evidence.

Results

18 studies (10 randomized controlled trials and 8 controlled clinical trials) met all inclusion criteria. Three (diabetic) studies were ranked very high quality (1b (A)), nine high quality (4 diabetes, 1 cancer, 4 others) (2b (B)), while six (4 diabetes, 2 others) showed low quality (4/C).

Current data suggests that exercise is a feasible, safe and promising supportive measure for neuropathic patients. This is best documented for patients with diabetic neuropathy (DPN), suggesting that endurance training has the potential to prevent the onset and reduce the progression of DPN. In general balance exercises showed the highest effect on the motor as well as sensory symptoms in all types of PNP.

Conclusion

Overall, balance training appears to be the most effective exercise intervention. Studies focusing exclusively on strength, or a combination of endurance and strength, appear to have a lower impact. For metabolically-induced neuropathies endurance training also plays an important role. Further research with high methodological quality needs to be conducted in order to establish evidence-based clinical recommendations for neuropathic patients.

***Table 7**: State of the art for exercise intervention studies in haemato-oncological patients – the interventions used and the side-effects investigated*

	Interventions						**Side-effects**												
Studies (only RCT)	**Endurance**	**Strength**	**Balance**	**Koordination**	**flexibility, streching**	**other**	**QOL**	**Fatigue**	**Arobic endurance**	**Muscle strength**	**Anxiety & Depession**	**Psychological parameters (POMS)**	**Social parameters**	**GVHD**	**Gait**	**Balance control**	**PNP**	**Blood values**	**Further symptoms/side-effects (mucositis, diarreah, sleep,etc)**
Wiskeman 2011	1	1	0	1	0	0	-	+	+	+	-	+	0	0	0	0	0	0	0
Knols 2011	1	1	0	0	0	0	-	-	+	+	0	0	0	0	0	0	0	0	0
Baumann 2010	1	1	0	1	1	0	+	0	+	+	0	0	0	0	0	0	0	+	0
Jarden 2009 a+b	1	1	0	0	0	1	-	-	+	+	-	-	-	0	0	0	0	0	+
Shelton 2009	1	1	0	0	0	0	0	-	0	0	0	0	0	0	+	0	0	0	0
Coleman 2008	1	1	0	0	1	0	0	0	0	0	0	0	0	0	-	0	0	+	0
Mello 2003	1	1	0	0	1	0	0	0	0	+	0	0	0	0	0	0	0	0	0
Coleman 2003	1	1	0	0	0	0	0	0	-	-	0	-	0	0	0	0	0	0	+
Courneya 2009	1	0	0	0	0	0	+	+	+	0	-	0	0	0	0	0	0	0	+
Chang 2008	1	0	0	0	0	0	0	+	0	0	-	0	0	0	+	0	0	0	-
De For 2007	1	0	0	0	0	0	0	0	-	0	0	0	+	0	0	0	0	0	-
Cunningham 1986	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-	0
Kim 2006	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	-	0
Hacker 2010	0	1	0	0	0	0	-	-	0	+	0	0	0	0	0	0	0	0	0
Amount of sudies	**11**	**10**	**0**	**2**	**3**	**2**	**6**	**7**	**7**	**7**	**4**	**3**	**2**	**0**	**3**	**0**	**0**	**4**	**5**

1= investigated; 0=not investigated; + significant improvement; - no significant difference

Table 8: *Overview of the research on haemato-oncological patients – the interventions used, the side-effects assessed and the contribution of this work to the research gap*

	Interventions						**Side-effects**												
Studies (only RCT)	**Endurance**	**Strength**	**Balance**	**Koordination**	**flexibility, streching**	**other**	**QOL**	**Fatigue**	**Arobic endurance**	**Muscle strength**	**Anxiety & Depession**	**Psychological parameters (POMS)**	**Social parameters**	**GVHD**	**Gait**	**Balance control**	**PNP**	**Blood values**	**Further symptoms/side-effects (mucositis, diarreah, sleep,etc)**
Wiskeman 2011	1	1	0	1	0	0	-	+	+	+	-	+	0	0	0	0	0	0	0
Knols 2011	1	1	0	0	0	0	-	-	+	+	0	0	0	0	0	0	0	0	0
Baumann 2010	1	1	0	1	1	0	+	0	+	+	0	0	0	0	0	0	0	+	0
Jarden 2009 a+b	1	1	0	0	0	1	-	-	+	+	-	-	-	0	0	0	0	0	+
Shelton 2009	1	1	0	0	0	0	0	-	0	0	0	0	0	0	+	0	0	0	0
Coleman 2008	1	1	0	0	1	0	0	0	0	0	0	0	0	0	-	0	0	+	0
Mello 2003	1	1	0	0	1	0	0	0	0	+	0	0	0	0	0	0	0	0	0
Coleman 2003	1	1	0	0	0	0	0	0	-	-	0	-	0	0	0	0	0	0	+
Courneya 2009	1	0	0	0	0	0	+	+	+	0	-	0	0	0	0	0	0	0	+
Chang 2008	1	0	0	0	0	0	0	+	0	0	-	0	0	0	+	0	0	0	-
De For 2007	1	0	0	0	0	0	0	0	-	0	0	0	+	0	0	0	0	0	-
Cunningham 1986	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-	0
Kim 2006	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	-	0
Hacker 2010	0	1	0	0	0	0	-	-	0	+	0	0	0	0	0	0	0	0	0
Amount of sudies	11	10	0	2	3	2	6	7	7	7	4	3	2	0	3	0	0	4	5
STRECKMANN	**1**	**1**	**1**	**0**	**0**	**0**	**+**	**+**	**+**	**0**	**-**	**0**	**+**	**0**	**0**	**+**	**+**	**-**	**+**
Amount of studies	**12**	**11**	**1**	**2**	**3**	**2**	**7**	**8**	**8**	**6**	**5**	**3**	**3**	**0**	**3**	**1**	**1**	**5**	**6**

1= investigated; 0=not investigated; + significant improvement; - no significant difference. In red: the contribution of this work to the research gap

FUTURE DIRECTIONS

As represented in table 8, this work made a substantial contribution to fill the research gap. The newly investigated intervention (Sensorimotor training) proved very promising but most interestingly, beneficial effects were found for crucial side-effects, such as CIPN and balance control that had never been investigated in lymphoma patients and partially even cancer patients, previously. Furthermore this work contributed to create a larger data bank for formerly investigated side-effects (such as QOL, fatigue, physical performance status, anxiety and depression), slowly enabling researchers to understand possible structures and mechanisms behind it with the intention of optimizing future research and most importantly finding ways to improve supportive care for cancer patients. The present findings enhance the possibilities to support cancer patients during therapy.

The analysis of the various exercise interventions and the different effects they can induce, contributed to a better understanding as to which exercises could target specific symptoms such as in CIPN. The novel finding of our RCT and systematic review underline our presumption that the type of exercise as well as the duration, frequency and intensity are also crucial. Symptoms related to neuronal disorders such as in CIPN for instance, will require types of exercise that can induce neuronal adaptions such as sensorimotor- or vibration exercises, while other symptoms such as depression or fatigue may be better addressed with endurance training for instance. Additionally, these have to be conducted appropriately in order to unfold the required potential. Exercise interventions hold far more potential, therefore many more studies will be necessary to allow us to understand the underlying mechanisms and derive a standardized concept for supportive care in cancer therapy. Especially regarding CIPN, the first steps have been taken within in this work to prove feasibility and allow preliminary directions for future research. In order to confirm the presumption that presumably sensorimotor training was responsible for the positive effects regarding the relevant symptoms of CIPN, the exercise intervention has to be singled out and investigated individually. Furthermore, exercise interventions with similar mechanisms as sensorimotor training such as whole body vibration, remain to be investigated. Thus, a pilot study (N=40) was conducted, comparing sensorimotor training alone, to whole body vibration and a control group with no intervention, in patients with a neurologically confirmed CIPN after completion of therapy. Both intervention groups

showed improvements of CIPN related symptoms such as balance control, reflex activity, peripheral deep sensitivity and pain. A larger RCT will have to confirm the results.

Furthermore, our RCT in lymphoma patients showed a lower incidence as well as better progression of CIPN in the intervention group. This led to the assumption, that exercise interventions may also hold potential to prevent the onset of CIPN consequently not only improving cancer patients' quality of life but also enabling them to receive the planned medical therapy which would impact their clinical outcome and overall survival. A large RCT has therefore been started in order to investigate the potentially preventive effects of sensorimotor training or whole body vibration, on the onset and progression of CIPN induced by Oxaliplatin or vinca-alkaloids (DRKS 00006088).

Thus, I believe that this work has enhanced a highly promising and exciting field of research, not only inspiring many more research ideas but most importantly contributing to improve supportive care for cancer patients and raising hope for patients with PNP.

Furthermore, it is essential that novel findings are translated into practice and made available for the patients. Therefore, a close collaboration between the practitioners, patients and researchers is necessary in order to implement these findings. Accordingly, preliminary exercise recommendations have been composed (Streckmann[28,162,163]) and already been implemented in a few hospitals, oncological practices and therapeutic training centers such as the OTT (oncological training site) in Cologne.

The research field "exercise therapy in oncology" is still in its infancy but already very promising. The research gap remains quite large. Evidence is slowly becoming better for some side-effects such as quality of life or fatigue and for selected entities such as breast- or prostate cancer, but remains poor for the many other side-effects and entities such as haematological malignancies. There are still side-effects such as graft versus host disease (GVHD) or gait stability that have not yet been investigated in haematolo-oncological patients at all and many more that require further studies to underline the present findings and to understand the underlying mechanisms in order to optimize supportive care for cancer patients. We need to find out for instance, which exercises, or exercise combinations target which symptoms best, what intensities or which duration is necessary, if the indications vary depending on the type or phase of therapy, or if the findings can be translated among entities or even diseases.

The future challenge lies in the rash development of cancer therapy and the complexity of the associated side-effects. Especially in this research field, more research, better interdisciplinary and international collaborations as well as better education, are necessary to achieve the common goal to improve patients' clinical outcome as well as quality of life.

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LIST OF FIGURES AND TABLES

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APPENDIX

Full text of scientific publications

I. Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy – a randomized, controlled trial

F. Streckmann, S. Kneis, J.A. Leifert, F.T. Baumann, M. Kleber, G. Ihorst, L. Herich, V. Grüssinger, A. Gollhofer & H. Bertz, (2014), in Annals of Oncology, 25: 493-499. (IF: 7.4)

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Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy

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Background: Lymphoma patients undergoing therapy must cope with the side-effects of the disease itself, therapy and associated immobility. Peripheral neuropathy (PNP), loss of balance control and weakness not only diminishes patients' quality of life (QOL), it can also affect planning and the dosage of therapy. Exercise may enable patients to reverse these declines, improving their performance level and QOL.

Patients and methods: We carried out a randomized, controlled trial, assigning 61 lymphoma patients either to a control group (CG; $N = 31$) or to a 36-week intervention (IG; $N = 30$), consisting of sensorimotor-, endurance- and strength training twice a week. Primary end point was QOL; secondary end points included movement coordination, endurance, strength and therapy-induced side-effects.

Results: Intergroup comparison revealed improved QOL- (Δ_{T1-T0}; $P = 0.03$) and PNP-related deep sensitivity in the IG: 87.5% were able to reduce the symptom, compared with 0% in the CG ($P < 0.001$). Significant differences in the change of balance control could be found between the groups, with the IG improving while the CG steadily declined (monopedal static Δ_{T3-T0}; $P = 0.03$; dynamic Δ_{T3-T0}; $P = 0.007$; perturbed mono-Δ_{T3-T0}; $P = 0.009$ and bipedal Δ_{T3-T0}; $P = 0.006$), failed attempts (monopedal static Δ_{T3-T0}; $P = 0.02$, dynamic Δ_{T3-T0}; $P < 0.001$and perturbed Δ_{T3-T0}; $P = 0.006$) and improved time to regain balance (Δ_{T3-T0}; $P = 0.04$). Moreover, the change in the aerobic performance level (Δ_{T3-T0}; $P = 0.05$) and additional amount of exercise carried out per week [metabolic equivalent (MET); $P = 0.02$] differed significantly across groups.

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Conclusions: Exercise, especially sensorimotor training, is a feasible and promising method to support cancer patients during therapy. It improves patients QOL, reduces restrictions from side-effects such as PNP and improves patients' balance control, physical performance level and mobility.

German Clinical Trials Register number: DRKS00003894.

Key words: exercise, sensorimotor training, lymphoma, peripheral neuropathy, quality of life, side-effects

introduction

Treatment of malignant lymphomas consists of multiple cycles of polychemo-, immuno- or radiation-therapy, hematopoetic stem cell transplantation (HSCT) or a combination thereof. The disease, its treatment and the extended hospital stays lead to reduced quality of life (QOL) due to increased immobility, physical deconditioning [1] apparent as muscle atrophy [2], loss of balance control [3], instable gait and enhanced incidence of falls. Additionally, ~50% of lymphoma patients suffer from therapy-induced peripheral neuropathy (PNP), a decisive limiting factor for therapy [4–6]. PNP is a highly prevalent side-effect associated with impaired balance control, an increased risk of falls [7], further increasing immobility. No randomized, controlled trial (RCT) has evaluated the effects of exercise on the side-effects of PNP. Studies in healthy adults e.g. revealed that sensorimotor training (SMT) can induce sensory effects [8], but it has never been studied in cancer patients. In our prospective RCT, we assessed the effects of exercise, especially SMT, in lymphoma patients during therapy. We hypothesized that our exercise program reduces therapy-induced side-effects and improves patients' physical condition, neuromuscular function, balance control and cardiovascular fitness, overall improving QOL.

patients and methods

Our prospective, single-center, two armed, open RCT (ratio 1:1) was approved by the Freiburg University Medical Center institutional review board and ethics commission. All patients gave written informed consent for treatment and prospective data collection in accordance with the Declaration of Helsinki.

patient characteristics

Between May 2008 and July 2011, 365 patients with malignant lymphoma, scheduled for therapy, aged ≥18 years were screened for further inclusion criteria: Karnofsky performance status >60 and an indication for chemotherapy (see S1a).

Every patient passed the institutional lymphoma board, a physical examination, stress electrocardiogram, echocardiography, pulmonary function and blood tests to rule out possible exclusion criteria [instable osteolysis, severe acute infections, severe cardial- and pulmonary impairments (S1b)] or restrictions for physical activity. One hundred eighty-six eligible patients were informed and asked to participate. While 125 declined, 61 signed the written informed consent and were randomized (CONSORT supplementary Figure S1, available at *Annals of Oncology* online). All patients received standard clinical care including physiotherapy. Only the intervention group (IG) carried out the training intervention.

training intervention

The IG trained twice a week, over 36 weeks, supervised by certified sport- or physiotherapists. Training was only interrupted for 24 h after administration of chemotherapy. Protocols were based on previous research [9–12] and designed for all phases of cancer therapy. Each ~1-h session consisted of:

(i) *Aerobic endurance training*: Cardiovascular activation on a bicycle-dynamometer (60%–70% max heart rate), 10- to 30-min walk on a treadmill or bicycle dynamometer (at 70%–80% max heart rate) at the end of the session [10].
(ii) *Sensorimotor training*: Four postural stabilization tasks, progressively increasing task difficulty as well as surface instability, carried out in three sets. Each set was carried out at 20-s intervals, allowing a 20-s rest between each set and 1 min between exercises to avoid fatigue [9].
(iii) *Strength training*: Four resistance exercises carried out for 1 min at maximum force, for inpatients substituted with a Thera-Band™ (Dornburn, Germany) [13].

To ensure patients safety, training was supervised (one-on-one), blood parameters monitored before each training session, blood pressure and heart rate measured before, during and after training (see S1c).

measurements

Primary end point was QOL. Secondary end points were movement coordination, endurance, strength and therapy-induced side-effects.

All participants were evaluated at four time points: prior to chemotherapy (within the first cycle of therapy at the latest) (T0), after 12 (T1), 24 (T2) and 36 (T3) weeks (supplementary Table S1, available at *Annals of Oncology* online), including:

primary end point. *Quality of Life* assessed with the EORTC QLQ-C30 questionnaire [14].

secondary end points.

(i) *PNP*: Peripheral deep sensitivity was evaluated by a tuning fork with a graduating scale from 0 (no sensitivity) to 8 (highest sensitivity). Pathological values are 0–5 for patients <60 years and 0–4 for patients ≥60 years [15, 16]. Measurement was carried out blinded, bilaterally, at the metatarsophalangeal and malleolus medialis, twice. Patients never receiving potentially neurotoxic medication, with a reduction of neurotoxic medication due to PNP, with PNPs of other derivation or due to prior therapy (PD/relapse), were monitored but excluded in the count.
(ii) *Activity level*: Both groups were asked to document any activities (type of exercise, duration in hour/week and frequency) outside the intervention in a training log-book. Activities were subsequently transferred into the metabolic equivalent (MET) [17].
(iii) *Balance control on static surface*: Using a stable force plate (GKS 1000™, IMM Holding GmbH, Germany) with four sensors (100 Hz) recording the center of pressure displacement during bipedal (blind) and monopedal stance (left/ right), during three 20-s intervals.
(iv) *Balance control on dynamic surface*: With foam pad (AIREX™, Sins, Switzerland) adjusted on top of the stable force plate. Again, monopedal (left/right) and bipedal stance (open eyes) were carried out.

The cumulative sway path of all sets was averaged to minimize any learning effects. Measurements were regarded as failed attempts whenever patients needed support to maintain balance.

(i) *Balance control following mechanical perturbation*: On the Posturomed™ (Pullenreuth, Germany), an oscillating, 2D platform, allowing translational movements in the transversal plane, a perturbation impulse was applied by releasing the platform attached to a magnet (2.5 cm away) unexpectedly. Tasks were carried out in five sets at 10-s intervals.

Analysis included cumulative sway paths, peak-to-peak amplitudes, the time needed to regain balance control and the number of failed attempts, leading to average values from all five attempts (S1d).

(i) *Incremental step test to determine lactic threshold*: Simultaneously to a stress ECG, starting at 25 watts, increasing by 25 watts every 3 min. We evaluated lactate levels, heart frequency, watts, maximum performance levels [maximum power (watts), in relation to bodyweight: p max/kg] and the individual anaerobic threshold (IAS).
(ii) *Side-effects monitored*: Subjective Global Assessment questionnaire (SGA) [18] was used to monitor the nutritional status. Further, 22 clinical signs were queried via a checklist as well as the level of anxiety and depression (Hospital Anxiety and Depression Scale) and cognitive impairment (Fragebogen Erlebter Defizite der Aufmerksamkeit), at each time point (S1d).

sample size

In order to demonstrate a intergroup difference for the primary end point QOL with a power of 80% at a two-sided level of $\alpha = 5\%$, assuming a relevant difference of 10 points and a standard deviation of 24 points, 92 patients per group are necessary. In order to account for dropouts and for the application of nonparametric tests, it was planned to randomize a total of 240 patients, assuming that 60–120 patients could be enrolled per year.

Owing to low recruitment, an unscheduled interim analysis was carried out after 3 years with 61 patients randomized. The primary end point did not reveal significant group differences; however, the physiological secondary end points showed highly relevant and significant results. With the ongoing recruitment velocity, it seemed unrealistic to achieve the planned sample size within the course of the study. At this point, we considered physiological parameters much more relevant to evaluate the intervention than QOL; hence, the study was stopped early.

randomization

Randomization was carried out by an independent randomization office (WiSP GmbH, Langenfeld, Germany).

statistical analysis

For continuous outcomes, changes from baseline to T1, T2 and T3 were computed. Intergroup differences were analyzed using Wilcoxon's two-sample test. For parameters of particular interest, the test was used for additional intragroup comparisons. Categorical variables were analyzed using Fisher's exact test. The incidence of PNP was computed at each time point. The average of these values is reported.

The amount of missing data was distributed relatively fair between groups (see Consort). Intention to treat strategies for substituting missing values aim to reach conservative results. However, especially for the physiological parameters, we did not want to underestimate the effect size; hence, missing data due to patient's dropout were excluded from the analysis. In the balance tasks, missing values resulting from failed attempts were replaced by values sufficiently high to be recognized as extreme (maximum or minimum).

All results presented refer to the intention to treat analysis analysis and intergroup comparison unless specified otherwise. Following previous research, exercise should be carried out at least twice a week [9]. An additional per protocol analysis excludes patients participating only once a week (25% adherence).

Level of significance was set to $P < 0.05$, two-sided. No alpha adjustment was made. Analyses were carried out using SAS, version 9.2 and SPSS statistics 21.

results

Overall 61 patients were randomly assigned to the IG ($N = 30$) or CG ($N = 31$) (Table 1 and supplementary Table S2, available at *Annals of Oncology* online). Patient characteristics at baseline (Table 2) and during the study regarding therapy revealed no significant intergroup differences (Table 3). Average compliance for all time points and all interventions was 65% (highest for SMT, lowest for strength, highest in stationary phases, lowest after completion of therapy).

primary end point

QOL. A significant intergroup difference ($\Delta_{T1-T0;}P = 0.03$) could be detected for health-related QOL within the first 12 weeks, though not after 36 weeks. Additionally, constipation ($\Delta_{T2-T0;}P = 0.03$), diarrhea ($\Delta_{T2-T0;}P = 0.04$), emotional function ($\Delta_{T3-T2;}P = 0.007$) and financial problems ($\Delta_{T3-T2;}P = 0.04$) differed between the groups at various time-points. The IG (intragroup) significantly improved their QOL ($\Delta_{T3-T0;}P = 0.03$) (supplementary Figure S2, available at *Annals of Oncology* online), constipation ($\Delta_{T3-T0;}P = 0.05$), diarrhea ($\Delta_{T3-T0;}P = 0.02$) and a tendency regarding pain ($\Delta_{T3-T0;}P = 0.06$), while the CG showed no changes.

secondary end points

(i) *PNP: Peripheral deep sensitivity*: The average incidence was lower in the IG (12%) than in the CG (27%) ($\Delta_{T3-T0;}P = 0.07$). Additionally, the symptom diminished in 87.5% of the IG, while no patient (0%) in CG showed reduced PNP, once developed ($P < 0.001$). At T3, the total number of patients suffering from reduced peripheral deep sensitivity was significantly lower in the IG ($P = 0.002$) (supplementary Figure S3A and B, available at *Annals of Oncology* online). There were no significant intergroup differences concerning neurotoxic medication and therapy. PNP was symmetrical in all but two patients at T2, thus counting the neuropathic value.
(ii) *Activity level*: (MET hour/week) Activity levels not only differed significantly among the groups due to the intervention but also outside the intervention ($\Delta_{T3-T0;}P = 0.03$). The IG increased their activity level by 2.5MET/week (median), while the CG deteriorated (supplementary Figure S4, available at *Annals of Oncology* online).
(iii) Balance control on static surface:

a) *Cumulative sway paths*: In the monopedal stance, the IG reduced sway paths by an average of 18%, while the CG declined ($\Delta_{T3-T0;}P = 0.04$) (supplementary Figure S5A, available at *Annals of Oncology* online). Neither the static bipedal blind task nor the baseline comparison differed significantly.

b) *Failed attempts*: (supplementary Figure S5B, available at *Annals of Oncology* online). In the monopedal task, we found significant intergroup differences at all time-

Table 1. Results

			IG	CG
Sample size	T0	*N*	28	28
	T1	*N*	28	28
	T2	*N*	27	28
	T3	*N*	26	25
Outcome	Δ Time point	*P* value (intergroup)	IG	CG
			Mean/median (range), *P* value (intragroup)	Mean/median (range), *P* value (intragroup)
EORTC-QLQ-C-30				
Quality of life	T1–T0	0.028	9.1/8.3 (−25 to 58)	−6.15/0 (−50 to 17)
	T3–T0	0.113	12/16.6 (−67 to 67)	−1/0 (−66 to 42)
			P = 0.033	*P* = 0.920
Emotional function	T3–T2	0.007	10/8.4 (−17 to 42)	−4.16/0 (−42 to 50)
Pain	T3–T0	0.396	−16/−8.3 (−100 to 67)	−8/0 (−83 to 33)
			P = 0.063	*P* = 0.449
Constipation	T3–T0	0.537	−19/0 (−100 to 33)	−11.1/0 (−67 to 33)
			P = 0.047	*P* = 0.117
Diarrhea	T2–T0	0.039	18.3/0 (−100 to 100)	−5.8/0 (−100 to 100)
	T3–T2	0.058	−19/0 (−100 to 0)	0/0 (−67 to 67)
			P = 0.016	*P* = 1.000
Financial problems	T3–T2	0.045	−4.8/0 (−33 to 67)	4.2/0 (0 to 33)
PNP			No. (%)	No. (%)
Incidence (total)	T3–T0	0.398	8 (30)	12 (44)
Decline	T3–T0	<0.001	7 (88)	0 (0)
SMT sway			Median (range[a])	Median (range[a])
Static left	T3–T0	0.035	−17.75 (−82 to 23)	0.88 (−108 to 31)
Dynamic left	T3–T0	0.007	−14.80 (−134 to 6)	0 (−88 to 24)
Dynamic right	T3–T0	0.045	−22.35 (−167 to 5)	0 (−43 to 9)
SMT failed attempts			No. (%)	No. (%)
Static left	T3	0.024	01 (4)	09 (36)
Static right	T3	0.075	02 (8)	08 (32)
Dynamic left	T3	0.014	04 (15)	14 (56)
Dynamic right	T3	<0.001	03 (11)	16 (64)
PM sway			Median (range[a])	Median (range[a])
Med/lat bipedal	T3–T0	0.006	−14.5 (−42 to 9)	10.3 (−13 to 13)
Ant/post bipedal	T3–T0	0.049	−21.2 (−38 to 5)	−9.8 (−73 to 23)
Monopedal	T3–T0	0.009	−60.3 (−81 to 26)	0 (−61 to 69)
PM failed attempts			No. (%)	No. (%)
Monopedal	T3	0.002	1 (4)	11 (44)
Time (*t*)			Median (range[a])	Median (range[a])
Med/lat bipedal	T3–T0	0.045	−0.26 (−11 to 25)	0.2 (−3 to 13)
Ant/post bipedal	T3–T0	0.007	−0.26 (−9 to 8)	0.27 (−5 to 16)
MET			Median (range)	Median (range)
Outside intervention	T3–T0	0.026	2.5 (−57 to 33)	0 (−57 to 30)
Incremental step test			Mean/median (range)	Mean/median (range)
Lactate peak	T2–T0	0.222	−1.3/−1.23 (−6 to 2.7)	−0.6/−0.5 (−8 to 2.9)
			P = 0.029	*P* = 0.735
p max/kg	T3–T0	0.229	0.12/0.14 (−0.6 to 0.7)	0.04/0.03 (−0.5 to 0.4)
			P = 0.050	*P* = 0.480
Side-effects			Mean/median (range)	Mean/median (range)
	T3–T0	0.226	−2.1/−1 (−16 to 6)	−0.4/−1 (−6 to 5)
			P = 0.043	*P* = 0.514

[a]range of the patients with valid attempts.

No., number; PNP, peripheral neuropathy; SMT, sensorimotor training; Med, medial; Lat, lateral; p max/kg, performance level; MET, metabolic equivilant.

Table 2. Patients' characteristics at baseline

	IG ($N = 28$)	CG ($N = 28$)
Average age, years, (range)	44 (20–67)	48 (19–73)
Gender, *n* (%)		
Male/female	20 (71)/8 (29)	22 (79)/6(21)
BMI mean (range), kg/m^2	24 (19–30)	26 (19–32)
Diagnosis, *n* (%)		
Hodgkin's disease	7 (25)	5 (18)
B-NHL	13 (46)	13 (46)
T-NHL	3 (11)	3 (11)
Multiple myeloma	5 (18)	8 (29)
N ID*/relapse/PD	21/5/2	23/4/1
Stage		
Ann Arbor classification, *n*		
Stage (I, II, III, IV)	22 (3/5/4/10)	17 (2/5/3/7)
ISS	4	8
Not available	2	3
Therapy received at baseline (T0), *n* (%)		
Begin first cycle of therapy	20 (71)	18 (64)
Immunotherapy	10 (36)	8 (29)
Radiation	0	1 (4)
PNP status at T0 – before intervention ($N = 28$)		
Patients receiving neurotoxic drugs	20 (71)	17 (61)
In first cycle of therapy		
Patients with PNP	5 (25)	4 (24)

No., number; BMI, body mass index; CIPN, chemotherapy induced peripheral neuropathy; ID, Initial Disease; PD, Progressive Disease; ISS, International Staging System for Multiple Myeloma; PNP/CIPN, peripheral neuropathy.

points (right: T1: $P = 0.009$; T2: $P = 0.001$/left: T1: $P = 0.003$; T2: $P = 0.002$; T3: $P = 0.02$) though groups showed no difference at baseline. The IG achieved all tasks (100%), while the CG worsened progressively to only 60% succeeding. The bipedal tasks revealed no significant differences.

(iv) *Balance control on dynamic surface*:

a) *Cumulative sway paths*: In the monopedal tasks the IG reduced their sway paths by median −14.8 cm (35.65%), the CG showing no changes (Δ_{T3-T0};$P = 0.007$ (supplementary Figure S5C, available at *Annals of Oncology* online)).

b) *Failed attempts*: (supplementary Figure S5D, available at *Annals of Oncology* online). Significant intergroup differences were measured in the right (T3: $P < 0.001$) and left monopedal stance (T3: $P = 0.01$), with no differences in bipedal tasks.

(v) Balance control following mechanical perturbation:

a) *Cumulative sway paths*: The IG significantly reduced sway paths in the bipedal (−14 cm/30%) as well as monopedal tasks (−60 cm/52.6%) in relation to baseline, while the CG increased sway paths at all time-points (medial–lateral: Δ_{T3-T0};$P = 0.006$/antero-posterior: Δ_{T3-T0};$P = 0.05$/monopedal: Δ_{T3-T0}; $P = 0.009$).

b) *Failed attempts*: The monopedal perturbed task also revealed significant differences (Δ_{T3-T0};$P = 0.002$) at all measuring points. The IG fulfilled all tasks (100%). The CG progressively declined (to only 40% succeeding) throughout the study. No significant differences were detected in the bipedal tasks.

c) *Time necessary to regain balance* (bringing the oscillating force plate to a halt): The IG improved time by 0.32 s, while the CG gained 0.29 s compared with baseline (Δ_{T3-T0}; $P = 0.007$).

(vi) *Incremental step test to determine lactic threshold*: The IG (intragroup) presented a reduction in maximum lactate (Δ_{T2-T0}; $P = 0.03$) simultaneously raising their performance level (Δ_{T3-T0}; $P = 0.05$). No intergroup changes were shown for T3–T0, IAS or IAS in relation to bodyweight.

(vii) *Amount of side-effects* was reduced in the IG in relation to baseline (Δ_{T3-T0}; $P = 0.043$).

In the per protocol analysis, results were equal or better.

discussion

Consistent with our hypothesis, patients benefited from our specific exercise program throughout all phases of therapy and were able to improve their QOL.

No study has addressed the distinct impact in QOL due to PNP and loss of balance control. Only one study has assessed exercise in lymphoma patients [10]. The toxic components of chemotherapy can cause functional and structural damage to nerve fibers. The axonal damage caused leads to reduced nerve-conduction velocity and excitability [6]. In consequence, patients experience reduced sensitivity, pain, increased loss of balance control and risk of falling [19]. This further diminishes QOL and causes treatment delays, dose reductions or discontinuation of therapy, affecting outcome and survival [5]. Management remains challenging, as treatment strategies to limit or prevent PNP are insufficient [20]. Balance training has shown beneficial effects e.g. in diabetics with PNP [21]. We found exercise, especially SMT, not only improved balance control, but seemingly also influences the incidence and recovery of PNP. The underlying mechanisms must still be elucidated. One possibility could lie in the regenerative effect of SMT on nerve fibers [22]. A further possibility is attributed to the nervous system's plasticity: (i) an increase in the density of receptors, (ii) activating deafferented neurons [23] by increasing the metabolism, (iii) lowering the threshold for excitability [24] or (iv) inducing supraspinal learning effects [22]. Twelve-week intervals leave room for regeneration and possible functional adaptions of the peripheral nerves. Short-term effects should also be considered in future studies.

Exercise further contributes to QOL and can counteract additional risk factors. Studies in healthy adults have revealed that SMT can lead to functional adaptations of the neuromuscular system [8] regenerate neuromuscular structures, reduce reflex excitability, improve balance and diminish the prevalence of falls [22]. In line with these findings, in the perturbed monopedal stance, simulating stumbling, 54% of the CG patients were unable to maintain balance once therapy started and would have fallen, while the IG remained stable at all times. These

Table 3. Therapies and PNP development

	IG ($N = 28$)	CG ($N = 28$)
Therapy total		
Radiation, no. (%)	9 (32)	4 (14)
Immunotherapy, no. (%)	16 (57)	13 (46)
High-dose chemotherapy, no. (%)	16 (57)	14 (50)
Stem cell transplantation, total	18 (60)	13 (42)
Allogeneic/autologous, no. (%)	2/(7)	1/9 (3/29)
2 × autologous, no. (%)	2 (7)	2 (6)
Autologous plus allogeneic	0	1 (3)
Therapy received at various time points		
T1: therapy received in first 12 weeks	$N = 28$	$N = 28$
Chemotherapy, no. (%)	28 (100)	28 (100)
High-dosage chemotherapy, no. (%)	3 (11)	5 (18)
HSCT, no. (%)	0	0
Immunotherapy, no. (%)	13 (46)	11 (39)
Radiation, no. (%)	0	1 (4)
T2: therapy between weeks 12 and 24	$N = 27$	$N = 28$
Chemotherapy, no. (%)	10 (37)	12 (42)
High-dosage chemotherapy, no. (%)	9 (33)	7 (25)
HSCT, no. (%)	9 (33)	7 (25)
Immunotherapy, no. (%)	3 (11)	8 (29)
Radiation, no. (%)	6 (22)	1 (4)
Maintenance therapy/in CR, no. (%)	3 (11)/10 (37)	4 (14)/1 (4)
T3: therapy between weeks 24 and 36	$N = 26$	$N = 25$
Chemotherapy, no. (%)	0	1 (4)
High-dosage chemotherapy, no. (%)	2 (8)	4 (16)
HSCT, no. (%)	5 (19)	6 (24)
Immunotherapy, no. (%)	2 (8)	4 (16)
Radiation, no. (%)	0	0
Maintenance therapy/in CR, no. (%)	6 (23)/17 (65)	5 (20)/16 (64)
Peripheral deep sensitivity (PNP)		
Patients receiving neurotoxic drugs T0–T3	$N = 27$	$N = 27$
Total incidence of PNP (T0–T3), no. (%)	8 (29)	12 (45)
Reduction of PNP (T0–T3), no. (%)	7 (87.5)	0 (0)
Patients with PNP at T3, no. (%)	1 (4)	12 (49)

no., number; HSCT, hematopoietic stem cell transplantation; CR, complete remission.

positive effects are selectively associated with SMT and cannot be achieved with endurance or strength training alone [25].

The impact for our patients is reflected in the significant correlation with their QOL and an increase in physical activity (MET). Previous arguments let us conclude that possibly balance training, improving balance control, peripheral deep sensitivity and gait, contributes to an increased mobility (2.5MET/week-intervention excluded). With diagnosis, the CG carried out no exercise between the first two time-points and still only 3.5MET/week after completion of therapy. Underlying mechanisms remain to be investigated. Correlations ($r = -0.40$) (S2b) between endurance parameters and fatigue suggest that endurance training can affect fatigue.

Strength of our trial includes being the first RCT addressing balance control and PNP in cancer patients. It covers all phases of therapy, entails low-intensity exercises showing a large impact, no adverse events and its effects on outcomes are statistically and clinically meaningful; it also provides a comprehensive assessment of important outcomes with validated measures.

Yet, there are potential limitations: low recruitment and compliance due to the long duration, large catchment area and the single-center design. Interestingly, recruitment was similarly low in the comparable RCT on exercise in lymphoma patients (1306 screened/474 eligible/122 assessed) [10]. Sample-size suggests underpowerment but the highly significant physiological parameters were considered more relevant for patients' outcome; hence, the study was stopped early.

Furthermore, the study design was challenging, as there were no comparable references in hematology or oncology. Tasks had to be feasible for patients exhibiting very different performance levels, phases of therapy and age (range 19–75 years). This resulted in additional failed attempts rather than high sway paths. Furthermore, the time points had to target as many

parameters as possible but simultaneously keep the burden low for patients. Resistance exercises had to be substituted with a Thera-Band™ for inpatients. This complicated data acquisition and revealed no viable results. Regarding physical activity, patients were only asked to report on additional exercises, not taking daily physical activities into account. In future, a questionnaire assessing physical activity could be useful.

In line with the gender-distribution of the disease, more men than women were recruited. As they are distributed evenly in both groups, bias should be small but cannot be excluded.

In summary, we provide evidence that exercise improves balance control and reduces side-effects of PNP, acknowledging these as substantial factors for QOL. Together with physical functioning, they are decisive factors for patients to receive their planned therapy regime, optimizing cancer control. Exercise, especially SMT, should therefore be implemented in the standard clinical care of cancer patients. Additional research on the impact of these findings for primary prevention, rehabilitation and further tumor entities is necessary.

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disclosure

The authors have declared no conflicts of interest. Results have partially been presented on the following conferences: oral presentations: ECSS conference (Bruges, Belgium 2012) Young Investigator Award; DGHO conference (Heidelberg/Mannheim, Germany 2009, Stuttgart, Germany 2012); DGSP conference (Frankfurt, Germany 2011). Poster presentations: DGSP conference (Berlin, Germany 2012) 1st Prize Poster Award; DGHO conference (Basel. Switzerland 2011); ECSS conference (Oslo, Norway 2009) Young Investigator Award.

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II. Aerobic physical exercise for adult patients with haematological malignancies – a meta-analysis

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Aerobic physical exercise for adult patients with haematological malignancies (Review)

Bergenthal N, Will A, Streckmann F, Wolkewitz KD, Monsef I, Engert A, Elter T, Skoetz N

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[Intervention Review]

Aerobic physical exercise for adult patients with haematological malignancies

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ABSTRACT

Background

Although people with haematological malignancies have to endure long phases of therapy and immobility which is known to diminish their physical performance level, the advice to rest and avoid intensive exercises is still common practice. This recommendation is partly due to the severe anaemia and thrombocytopenia from which many patients suffer. The inability to perform activities of daily living restricts them, diminishes their quality of life and can influence medical therapy.

Objectives

To evaluate the efficacy, safety and feasibility of aerobic physical exercise for adults suffering from haematological malignancies.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2014, Issue 1) and MEDLINE (1950 to January 2014) as well as conference proceedings for randomised controlled trials (RCTs).

Selection criteria

We included RCTs comparing an aerobic physical exercise intervention, intending to improve the oxygen system, in addition to standard care with standard care only for adults suffering from haematological malignancies. We also included studies that evaluated aerobic exercise in addition to strength training. We excluded studies that investigated the effect of training programmes that were composed of yoga, tai chi chuan, qigong or similar types of exercise. We also excluded studies exploring the influence of strength training without additive aerobic exercise. Additionally, we excluded studies assessing outcomes without any clinical impact.

Data collection and analysis

Two review authors independently screened search results, extracted data and assessed the quality of trials. We used risk ratios (RRs) for adverse events and 100-day survival, standardised mean differences for quality of life (QoL), fatigue, and physical performance, and mean differences for anthropometric measurements.

Main results

Our search strategies identified 1518 potentially relevant references. Of these, we included nine RCTs involving 818 participants. The potential risk of bias in these trials is unclear, due to poor reporting.

The majority of participants suffered from acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), malignant lymphoma and multiple myeloma, and six trials randomised people receiving stem cell transplantation. Mostly, the exercise intervention consisted of various walking intervention programmes with different duration and intensity levels.

Our primary endpoint of overall survival (OS) was not analysed in any of the included trials, but three trials reported deceased participants during the course of the study or during the first 100 days. There is no evidence for a difference between participants exercising and those in the control group (RR 0.93; 95% CI 0.59 to 1.47; P = 0.75; 3 trials, 269 participants, moderate quality of evidence).

Four trials analysed the influence of exercise intervention on quality of life (QoL). Excluding one trial with serious baseline imbalances, physical exercise improves QoL (SMD 0.26; 95% CI 0.03 to 0.49; P = 0.03; 3 trials, 291 participants, low quality of evidence). This positive effect of exercise was also found in the subscales physical functioning (SMD 0.33; 95% CI 0.13 to 0.52; P = 0.0009; 4 trials, 422 participants, moderate quality of evidence) and depression (SMD 0.25; 95% CI -0.00 to 0.50; P = 0.05; 3 trials, 249 participants, low quality of evidence). However, there is no evidence for a difference between additional exercise and standard treatment for the subscale anxiety (SMD -0.18; 95% CI -0.64 to 0.28; P = 0.45; 3 trials, 249 participants, low quality of evidence). Seven trials (692 participants) evaluated fatigue. There is moderate quality of evidence that exercise improves fatigue (SMD 0.24; 95% CI 0.08 to 0.40; P = 0.003).

Eight studies evaluated various aspects of physical performance (e.g. aerobic capacity, cardiovascular fitness), but none of them could be pooled in a meta-analysis. In seven trials there is a tendency or statistically significant effect favouring the exercise group (very low quality of evidence).

Three trials (266 participants) investigated serious adverse events (SAEs) (e.g. bleeding, fever, pneumonia, deep vein thrombosis, and infection), and one trial (122 participants) assessed adverse events (AEs). There is no evidence for a difference between arms in terms of SAEs (RR 1.44; 95% CI 0.96 to 2.18; P = 0.06) or AEs (RR 7.23; 95% CI 0.38 to 137.05; P = 0.19); both findings are based on low quality of evidence.

Authors' conclusions

There is no evidence for differences in mortality between the exercise and control groups. Physical exercise added to standard care can improve quality of life, especially physical functioning, depression and fatigue. Currently, there is inconclusive evidence regarding anxiety, physical performance, serious adverse events and adverse events.

We need further trials with more participants and longer follow-up periods to evaluate the effects of exercise intervention for people suffering from haematological malignancies. Furthermore, we need trials with overall survival as the primary outcome to determine whether the suggested benefits will translate into a survival advantage. To enhance comparability of study data, development and implementation of core sets of measuring devices would be helpful.

PLAIN LANGUAGE SUMMARY

The role of aerobic physical exercise for adults with haematological malignancies

Review question

We reviewed the existing evidence regarding the effect of aerobic physical exercise plus standard care compared to standard care alone in adults with haematological malignancies. We found nine randomised controlled trials.

Background

A haematological malignancy is a tumour of the myeloid or lymphatic cell lines. Lymphomas, leukaemias, myelomas, myelodysplastic syndromes and myeloproliferative diseases are all haematological malignancies. These diseases account for nearly 10% of new cancer diagnoses in the United States and are characterised by highly variable and divergent clinical courses and prognoses. Various treatments are available for people with haematological malignancies, from a watch-and-wait approach to single- or multi-agent chemotherapy,

radiotherapy, immunotherapy and autologous or allogeneic stem cell transplantation. Additionally, best supportive care is provided to make people more comfortable and to prevent, control or treat complications and side effects. Although people with haematological malignancies have to endure long phases of therapy and immobility which reduces their physical performance level, the advice to rest and avoid intensive exercises is still common practice. This recommendation is partly linked to the reduced number of red cells and platelets from which many patients suffer. The inability to perform activities of daily living restricts them, diminishes their quality of life and may influence medical therapy.

Study characteristics

We searched several databases of medical literature and included nine randomised controlled trials covering 818 people that compared a physical exercise intervention, intending to improve the oxygen system, plus standard care to standard care alone. The majority of people suffered from acute leukaemia, multiple myeloma or lymphoma. In five trials participants received their own stem cells or stem cell transplantation from a donor. The aerobic exercise interventions consisted of various walking programmes of different durations and intensity. The evidence is up-to-date as of January 2014.

Key results

None of the included trials looked at overall survival, although three trials reported how many participants died during the study period or during the first 100 days. There is no evidence for differences in this outcome between the exercise group and the control group.

Four trials measured quality of life (QoL). We dropped one trial from this analysis, due to differences between the groups at baseline. The remaining three trials showed QoL improvements for the exercise arm. Four trials evaluated physical functioning, depression and anxiety, and we combined them in meta-analysis. There is a benefit for the exercise group for physical functioning and depression, but no clear evidence of a difference between exercise and control for anxiety. Seven trials evaluated fatigue, with an advantage for those exercising.

Eight studies assessed the physical performance level (e.g. aerobic capacity, cardiovascular fitness) and in seven of these trials we found a tendency or a statistically significant improvement in the exercise arm.

Three trials measured serious adverse events, and one trial reported adverse events (side effects), but the results of these trials are inconclusive.

Quality of the evidence

The quality of the included evidence is moderate for deaths, physical functioning, and fatigue, low for overall quality of life, depression, anxiety, adverse events and serious adverse events, and very low for physical performance. The main limitations were that participants, physicians and outcome assessors were not blinded, and the low number of participants in the included studies, which meant that we could not exclude the possibility that the intervention had little or no effect.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Physical exercise versus no physical exercise for adults with haematological malignancies

Patient or population: Adults with haematological malignancies
Settings:
Intervention: Physical exercise versus no physical exercise

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control group without exercise	Physical exercise				
Overall survival not reported **Mortality**	**224 per 1000**	**208 per 1000** (132 to 329)	**RR 0.93** (0.59 to 1.47)	269 (3 studies)	⊕⊕⊕○ **moderate** [1]	Overall survival not reported, number of participants deceased during study or first 100 days
Quality of Life Scale from: 0 to 1 with 1 indicating best outcome		The mean QoL in the intervention group was **0.26 standard deviations higher (better)** (0.03 to 0.49 higher)	**SMD 0.26** (0.03 to 0.49)	291 (3 studies)	⊕⊕○○ **low** [1,2]	
Physical functioning/ QoL Scale from: 0 to 1 with 1 indicating best outcome		The mean physical functioning/QoL in the intervention groups was **0.33 standard deviations higher (better)** (0.13 to 0.52 higher)	**SMD 0.33** (0.13 to 0.52)	422 (4 studies)	⊕⊕⊕○ **moderate** [2]	

Depression/QoL Scale from: 0 to 1 with 1 indicating best outcome		The mean depression/qol in the intervention groups was **0.25 standard deviations higher (better)** (0 to 0.5 higher)	**SMD 0.25** (0 to 0.5)	249 (3 studies)	⊕⊕○○ **low** [1,2]	
Anxiety/QoL Scale from: 0 to 1 with 1 indicating best outcome		The mean anxiety/qol in the intervention groups was **0.18 standard deviations lower (worse)** (0.64 lower to 0.28 higher)	**SMD -0.18** (-0.64 to 0.28)	249 (3 studies)	⊕⊕○○ **low** [1,2]	
Fatigue Scale from: 0 to 1 with 1 indicating best outcome		The mean fatigue in the intervention groups was **0.24 standard deviations higher (better)** (0.08 to 0.40 higher)	**SMD 0.24** (0.08 to 0.40)	692 (7 studies)	⊕⊕⊕○ **moderate** [2]	
Physical performance	see comment	see comment	see comment	see comment	see comment	Due to various outcome definitions and measuring instruments no meta-analysis possible
Serious adverse events	**169 per 1000**	**244 per 1000** (162 to 369)	**RR 1.44** (0.96 to 2.18)	266 (3 studies)	⊕⊕○○ **low**[1,3]	
Adverse events	**10 per 1000**	**72 per 1000** (4 to 1000)	**RR 7.23** (0.38 to 137.5)	122 (1 study)	⊕⊕○○ **low**[4]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Small number of participants and events, wide confidence interval
[2] Outcome assessor (participant) not blinded in participant-reported outcome (QoL questionnaires)
[3] Baseline imbalances, especially usage of erythropoietin and thalidomide unknown in both intervention arms
[4] Very small number of participants and events, very wide confidence interval

BACKGROUND

Description of the condition

A haematological malignancy is a tumour of the myeloid or lymphatic cell lines affecting blood, bone marrow or the lymph nodes with possible involvement of other organs. Lymphomas, leukaemias, myelomas, myelodysplastic syndromes and myeloproliferative diseases are all haematological malignancies and account for nearly 10% of new cancer diagnoses in the United States (Howlader 2012). The global age-adjusted incidence rate of haematological malignancies is 40.3 new cases per 100,000 men and women per year. Individual scores are leukaemia (12.6), lymphoma (22.4) and myeloma (5.6) with all their various subcategories (Altekruse 2009).

Depending on the type and stage of the neoplastic disease, the clinical course can be indolent or aggressive with different patterns of treatment behaviour and treatment response. Various treatment options are available for people with haematological malignancies, extending from watch-and-wait approaches to single- or multi-agent chemotherapy, radiotherapy, immunotherapy and autologous or allogeneic stem cell transplantation. Additionally, best supportive care is provided to make them more comfortable and to prevent, control or treat complications and side effects (Cullen 2001).

Generally, the prevailing advice for patients is to rest and avoid intensive exercise, without taking note of the detrimental consequences of omitting physical exercise. This advice is mainly based on the properties of cytopenia from which most patients suffer. A low performance status due to severe anaemia and thrombocytopenia can potentially lead to haemorrhages, while the reduced immune status due to leukopenia increases the risk for infections (Tosetto 2009).

Description of the intervention

One important challenge in treating people with haematological cancer is physical deconditioning. It is highly prevalent in this population and is the result of various circumstances such as the oncologist's advice to rest, cardiotoxic, neurotoxic or pulmo-toxic anti-cancer therapy, anaemia, thrombocytopenia or cachexia. Exercise has been introduced to improve physical functioning and to increase the ability to cope with activities of daily living. Some evidence suggests that physical exercise, especially aerobic exercise that aims to improve the oxygen system, increases cardiorespiratory fitness, muscle strength and physical well-being in people with haematological cancer (Coleman 2012; Courneya 2009; Moyer-Mileur 2009; Thorsen 2005).

People undergoing intensive chemotherapy suffer from unintended effects of the therapy such as inflammation due to long-lasting immunosuppression and leukopenia. Apart from this, the inability to perform normal physical activity is a decisive limiting factor in the treatment of people with haematological malignancies. For them this implies detrimental effects on their quality of life, as several studies have shown (Broers 2000; Fife 2000; McQuellon 1998; Zittoun 1999). Nevertheless, physical exercise programmes still occupy a minor role in the treatment concepts of haematological malignancies. Furthermore, we lack reliable data from randomised controlled trials about risk factors, feasibility and outcomes of exercise in people with haematological malignancies, particularly with regard to overall survival.

The first study of therapeutic exercise in the follow-up treatment of people suffering from breast cancer explicitly showed a positive physical and psychological effect (Schule 1983). Owing to the positive impact of this and further studies, exercise therapy has become a part of oncological treatment concepts (Dimeo 1996; Mock 1994; Peters 1994). The former opinion that exercise as part of health-orientated therapy, concomitant with or immediately after medical therapy, could be harmful and should not be started before complete remission is achieved, has proved to be incorrect (Andrykowski 1989; Dimeo 1996).

Another essential burden for people with cancer is cancer-related fatigue. It is defined as debilitating symptoms of physical, emotional and cognitive tiredness or exhaustion related to cancer or cancer treatment (NCCN 2014). Cancer-related fatigue is very common during or after treatment and is reported by 60% to 90% of people with cancer (Wagner 2004). In recent meta-analyses physical exercise has resulted in some reduction of cancer-related fatigue in people with solid tumours (Cramp 2012; Velthuis 2010).

Aside from this recent development, the extent of physical exercise for people suffering from blood cancers remains unclear. Previous studies suggest that aerobic exercise can be safely carried out immediately after high-dose chemotherapy and can partially prevent loss of physical performance (Dimeo 1996; Dimeo 1997). Data from Dimeo 1997 suggest that exercise mediates better maximal physical performance at discharge and shorter durations of neutropenia, thrombopenia and hospitalisation.

How the intervention might work

There is some evidence for a protective role of physical activity for cancer, in particular colon, breast (postmenopausal) and endometrial cancers (Parent 2010). A 20% to 40% reduced risk of several cancer types is reported in the current literature (Parent 2010). The precise/further underlying mechanisms for physical activity in reducing cancer risk remain to be elucidated. Several biological mechanisms have been suggested, which could equally apply to many cancer entities (Friedenreich 2001). These include a decrease in obesity and central adiposity, hormone level and growth factor modulation, modification of carcinogen activation and improvement in immune function (Li 2010a). Li 2010b reported immunomodulation due to physical activity as an increase of hu-

man natural killer activity and enhanced expression of intracellular anti-cancer proteins in lymphocytes.

Why it is important to do this review

This is the first systematic review taking into account the evidence from randomised comparisons on the impact of physical exercise in adults with haematological malignancies. One question is whether physical exercise in addition to standard care is beneficial in terms of overall survival, fatigue and quality of life compared to standard care alone. Further questions elucidate the role of physical exercise in terms of physical strength, well-being and adverse effects.
To attempt to obtain conclusive evidence on the impact of physical exercise, we have performed a systematic review and meta-analysis. A summary of all results will help us to choose the best available physical exercise approach and to draw conclusions about safety and effectiveness.

OBJECTIVES

To evaluate the efficacy, safety and feasibility of aerobic physical exercise for adults suffering from haematological malignancies.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised controlled trials (RCTs) for inclusion. We include both full-text and abstract publications.

Types of participants

We include trials on adults (18 years and over) with confirmed diagnoses of haematological malignancies. We did not apply gender or ethnicity restrictions. We considered all subtypes and stages of haematological malignancies, including newly-diagnosed patients and those with relapsed or drug-resistant disease. If trials had consisted of mixed populations with different conditions or types of cancer, we would have used data only from the haematological malignancy subgroups. If subgroup data for these participants had not been provided (after contacting the authors of the trial), we would have excluded the trial if fewer than 80% of participants had haematological malignancies.

Types of interventions

The main intervention was aerobic physical exercise in addition to standard care, compared to standard care alone. We only included studies that evaluated the response of the participant to aerobic exercise, intending to improve the oxygen system. Accordingly, we included studies that chose exercise interventions such as moderate cycling, walking, Nordic walking, running, swimming and other related forms of sport. These kinds of sports are easy to regulate with regards to load control. We also included studies that analysed further physical exercise programmes, such as moderate strength training in addition to the aerobic exercise programme. We did not include training programmes that were composed of yoga, tai chi chuan, qigong and similar types of exercise. We also excluded studies solely exploring the influence of strength training. Additionally, we excluded studies assessing outcomes without any clinical impact.

Types of outcome measures

We included only trials which reported at least one of the outcomes published in the protocol and mentioned below to analyse only trials that reported patient-relevant outcomes. See Differences between protocol and review.

Primary outcomes

We predefined overall survival (OS) as the primary efficacy outcome.

Secondary outcomes

We analysed the following outcomes as secondary outcomes:

- Quality of life;
- Fatigue;
- Physical performance (e.g. aerobic capacity, cardiovascular fitness);
- Anthropometric measurements (e.g. weight, body mass index);
- Adverse events.

Search methods for identification of studies

Electronic searches

We adapted the search strategies as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We applied no language restriction, to reduce the language bias. There were no restrictions by date or by publication status (e.g. abstract, conference proceedings, unpublished data, dissertations, etc).
We searched the following databases and sources:

- Databases of medical literature:

- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2014, Issue 1) (for search strategy, see Appendix 1);
- MEDLINE (1950 to January 28, 2014) (for search strategy, see Appendix 2).

- Conference proceedings of annual meetings (1990 to 2013) of the following societies for abstracts if not included in CENTRAL:
  - American Society of Hematology (ASH) (2011 to 2013);
  - American Society of Clinical Oncology (ASCO) (2011 to 2013);
  - European Hematology Association (2011 to 2013).
- Databases of ongoing trials:
  - meta-register of controlled trials: www.controlled-trials.com/mrct/.

Searching other resources

- Handsearching of references:
  - We checked references of all identified trials and relevant review articles for further literature.

Data collection and analysis

Selection of studies

Two review authors (NB, NS) independently screened the results of the searches for eligibility in this review by reading the abstracts. In case of disagreement, we obtained the full-text publication. If we could reach no consensus, we asked a third review author (FS) to resolve the disagreement.

Data extraction and management

Two review authors (NB, NS) independently extracted the data according to the guidelines proposed by The Cochrane Collaboration (Higgins 2011b). We used a standardised data extraction form containing the following items.

- General information: author, title, source, publication date, country, language, duplicate publications.
- Quality assessment: sequence generation, allocation concealment, blinding (participants, personnel, outcome assessors), incomplete outcome data, selective outcome reporting, other potential sources of bias.
- Study characteristics: trial design, aims, setting and dates, source of participants, inclusion and exclusion criteria, comparability of groups, subgroup analysis, statistical methods, power calculations, treatment cross-overs, compliance with assigned treatment, length of follow-up, time point of randomisation.
- Participant characteristics: underlying disease, stage of disease, histological subtype, additional diagnoses; age, gender, ethnicity; number of participants recruited, allocated, evaluated; participants lost to follow-up; type of treatment (multi-agent chemotherapy, intensity of regimen, number of cycles), additional radiotherapy, type and dosage of monoclonal antibodies, bone marrow transplantation.
- Interventions: type, duration and intensity of physical exercise; standard care; duration of follow-up.
- Outcomes: overall survival, aerobic capacity, cardiovascular fitness, anthropometric measurements, quality of life, fatigue, adverse events.

Assessment of risk of bias in included studies

To assess the quality and risk of bias, we used a questionnaire (validity assessment form) containing the items as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a):

- Sequence generation;
- Allocation concealment;
- Blinding (participants, personnel, outcome assessors);
- Incomplete outcome data;
- Selective outcome reporting;
- Other potential sources of bias.

Measures of treatment effect

We calculated continuous outcomes as mean differences or standardised mean differences (SMDs) with 95% confidence intervals (CIs) for each trial. For binary outcomes, we calculated risk ratios (RRs) with 95% CIs.

Dealing with missing data

As suggested in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c), there were many potential sources of missing data which we had to take into account, at a study level, outcome level, and summary data level. Firstly, it was important to distinguish between 'missing at random' and 'not missing at random'. We did not identify any missing data, see Differences between protocol and review.

Assessment of heterogeneity

In meta-analyses with two or more trials we assessed heterogeneity of treatment effects between trials by using a Chi² test with a significance level at $P < 0.1$. We used the I^2 statistic to quantify possible heterogeneity ($I^2 > 30\%$ moderate heterogeneity, $I^2 > 75\%$ considerable heterogeneity) (Higgins 2003; Higgins 2011a). We would have explored potential causes of heterogeneity by sensitivity and subgroup analysis.

Assessment of reporting biases

Not possible, due to lack of data, see Differences between protocol and review

Data synthesis

Data from the included studies were sufficiently similar to be pooled in meta-analyses. We performed analyses according to the recommendations of The Cochrane Collaboration (Deeks 2011), using the Cochrane statistical package Review Manager 5 (RevMan 2012) for analysis. To account for clinical heterogeneity, we pooled data using the random-effects model.

Subgroup analysis and investigation of heterogeneity

We considered the following characteristics for subgroup analyses, but data were too sparse to perform subgroup analyses

- Age;
- Entity, therapy of underlying disease;
- Type, duration, intensity of physical exercise.

Sensitivity analysis

We analysed quality components, excluding studies at high risk of bias.

We considered analysing full-text publications versus abstract publications, but all the included trials were reported as full texts.

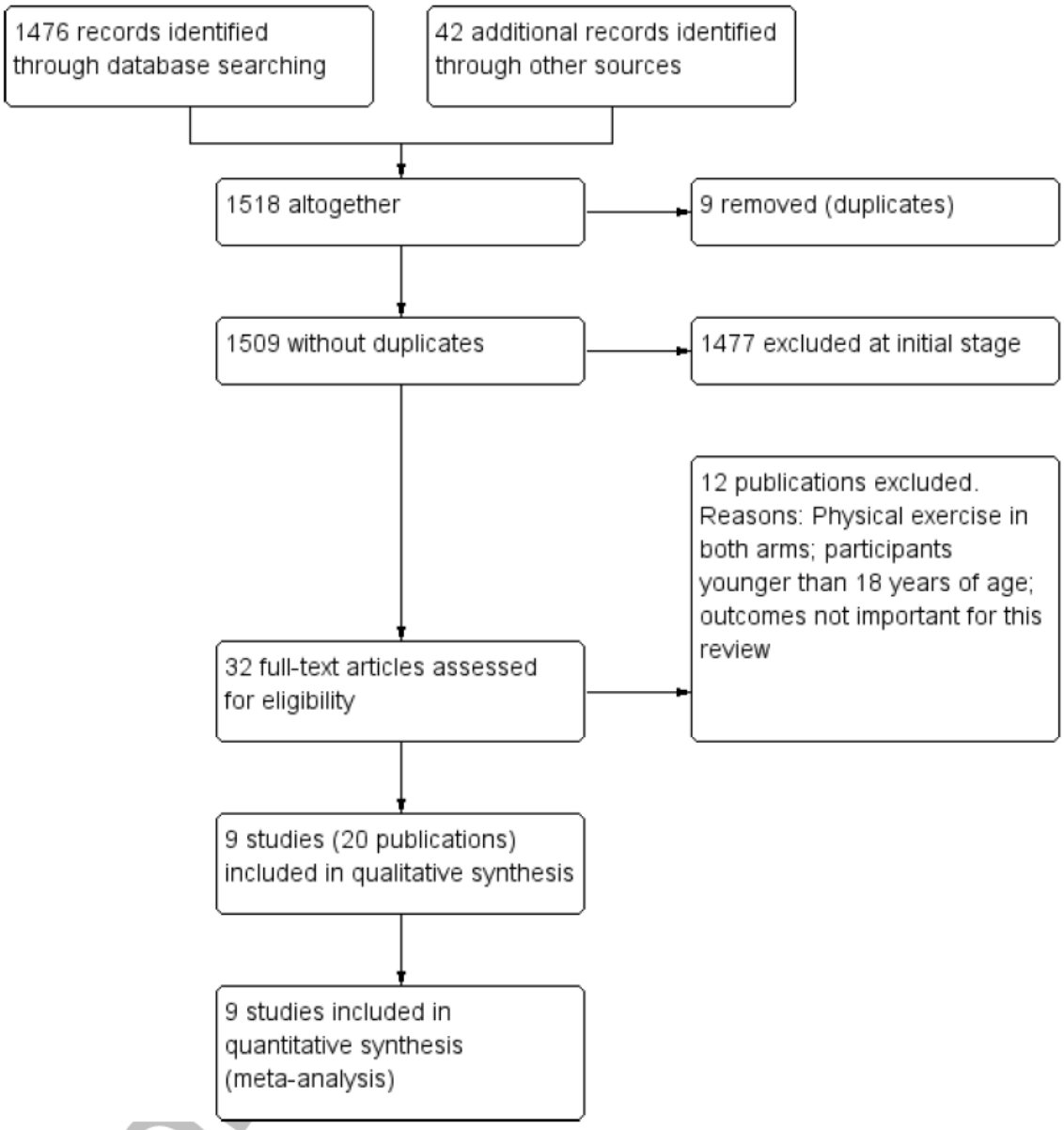
RESULTS

Description of studies

Results of the search

We identified 1518 potentially relevant references through database searches and handsearching. From these, we discarded nine duplicate publications. We excluded 1477 publications at the initial stage of screening because they did not fulfil our predefined inclusion criteria. We retrieved the remaining 32 publications as full-text or abstract publications for detailed evaluation. Of these 32 publications, we excluded 12. At the end of the screening procedure, nine included studies (20 publications) remained. The overall number of references screened, identified, selected, excluded and included is documented according to the PRISMA flow diagram (Figure 1).

Figure 1. Flow diagram.



Included studies

Nine trials in 20 publications, including a total of 818 participants (range 24 to 187), fulfilled the inclusion criteria (Baumann 2010; Chang 2008; Coleman 2003; Coleman 2012; Courneya 2009; DeFor 2007; Knols 2011; Streckmann 2014; Wiskemann 2011). We summarise the features of the included trials in the Characteristics of included studies table.

Three trials reported no periods for trial recruitment. The earliest trial started recruitment in 2002 (Baumann 2010) until 2004, and the latest trials stopped in 2011 (Streckmann 2014). All trials were published as full-text publications.

Design

All nine included trials were two-armed randomised controlled trials (RCTs).

Sample sizes

The two smallest trials (Chang 2008; Coleman 2003) randomised 24 participants and the largest trial 187 participants (Coleman 2012). Three trials provided sample size calculation (Coleman 2012; Knols 2011; Streckmann 2014). However, Coleman 2012 provided different calculations in various publications and Streckmann 2014 was stopped early due to slow recruitment.

Location

Three trials were conducted in the USA (Coleman 2003; Coleman 2012; DeFor 2007); one trial was conducted in Canada (Courneya 2009), one in Taiwan (Chang 2008), one in Switzerland (Knols 2011) and three in Germany (Baumann 2010; Streckmann 2014; Wiskemann 2011).

Participants

A total of 818 men and women with haematological malignancies were randomly allocated either to a physical exercise group plus standard care or to a standard care alone group. The type of underlying haematological malignancy differed between studies. One study only explored people with acute myeloid leukaemia (Chang 2008). In two studies all evaluated participants suffered from multiple myeloma (Coleman 2003; Coleman 2012). Two studies randomised participants with lymphomas (Courneya 2009; Streckmann 2014). In the trials by Baumann 2010, DeFor 2007, Knols 2011 and Wiskemann 2011, participants suffered from various haematological diseases (mainly acute myeloid leukaemia or acute lymphatic leukaemia).

In six trials participants received stem cell transplantation (Baumann 2010; Coleman 2003; Coleman 2012; DeFor 2007; Knols 2011; Wiskemann 2011). In two trials participants received autologous blood stem cell transplantation (Coleman 2003; Coleman 2012) and in another two trials participants received allogeneic stem cell transplantation (DeFor 2007; Wiskemann 2011). In two trials participants received either autologous or allogeneic transplantation, depending on the underlying disease and donor availability (Baumann 2010; Knols 2011).

Interventions

In all included trials, physical exercise was performed in addition to standard care and compared to standard care alone. The intensity and the extend of the physical exercise intervention differed between the studies.

Baumann 2010: Participants in the exercise arm were offered endurance training on a bicycle ergometer, for 10 to 20 minutes twice a day. Moreover, they participated twice a day in training activities for daily living to maintain mobility. Mostly, this training consisted of walking, stepping and stretching. The exercise programme started six days before transplantation, for five days a week, and lasted until one day before hospital discharge. People in the control group attended a low-intensity programme of active and passive mobilisation, starting one day after transplantation until hospital discharge.

Chang 2008: The exercise intervention consisted of a three-week walking programme of 12 minutes walking for five days a week. The control group did not perform any physical exercise programme. All participants in both arms received chemotherapy with cytarabine and idarubicin.

Coleman 2003: Exercise consisted of an aerobic component (usually walking, but depending on the fitness and preferences of the participant, perhaps running or cycling) and strength resistance training (using exercise stretch bands). This programme was home-based. The exercise programme started three months before and ended three month after stem cell transplantation. The control group received best-practice usual care in terms of activity and rest provided by their physician.

Coleman 2012: Participants in the exercise group received individualised exercise and a set of exercise stretch bands with varying resistance. Strength resistance training was included to strengthen muscles so participants could improve the aerobic component of the exercise programme. People in the control group were advised to remain as active as possible and to try to walk 20 minutes a day. Duration of this short-term study was 15 weeks. The first 70 participants who were eligible for long-term participation (i.e. response to erythropoietin) continued in the study for an additional 15 weeks. Participants in both groups (exercise and control) re-

ceived chemotherapy with an intensive treatment protocol (called Total Therapy II) and stem cell transplantation. Fifty per cent of all participants were randomised to receive additionally thalidomide (400 mg daily) during induction, after transplantation consolidation, and maintenance therapy. Furthermore, 76% (N = 102 participants) received erythropoietin.

Courneya 2009: The exercise programme consisted of bicycle ergometer training three times a week for 12 weeks. Intensity began at 60% of the peak power output and was increased by 5% each week to 75% by the fourth week. Duration began at 15 to 20 minutes for the first four weeks and increased by five minutes a week to 40 to 45 minutes in the ninth week. Additionally participants in the physical exercise group performed one session a week of interval training. Participants in the control group were asked not to increase exercise above baseline. In both groups, some participants received chemotherapy. These participants may have started treatment before enrolment, but needed to have at least eight weeks of planned treatment remaining. Some participants had already received chemotherapy and some were off treatment.

DeFor 2007: Participants in the exercise group were asked to walk for at least 15 minutes twice a day on a treadmill that was placed in their hospital room. After discharge, participants in the exercise group were asked to walk once a day for at least 30 minutes. Participants were told to walk at a comfortable speed and to discontinue the workout if they felt any discomfort or dizziness or if the medical staff advised them to do so. This regimen continued until 100 days posttransplant. Participants in the control group were not asked to perform any formal exercise, and were not provided with a treadmill unless the participant or staff requested it. In both arms, there was a subset of participants receiving nonmyeloablative conditioning and a subset receiving myeloablative conditioning before allogeneic stem cell transplantation. The authors reported that the activity level prior to transplantation did not differ between the two arms (P = 0.45), but that more participants in the intervention arm (93%) exercised during hospital stay compared to the control arm (58%; P = 0.01).

Knols 2011: Participants were randomised to a 12-week outpatient programme of physical exercise, consisting of supervised aerobic and strength exercises, or to a usual care group without any advice for physical exercise. The physical exercise was performed twice weekly in a physiotherapy practice or fitness centre. Participants started with ten minutes ergometer cycling or walking treadmill, followed by progressive resistance training.

Streckmann 2014: Participants in the exercise arm attended an aerobic endurance training programme, consisting of cardiovascular activation on a bicycle dynamometer and 10 to 30 minutes walk on a treadmill or bicycle ergometer at the end of the training. Participants were also offered sensorimotor training, progressively increasing in task difficulty, and a strength training of four resistance exercises carried out for one minute. Participants in the control group received physiotherapy.

Wiskemann 2011: Participants started the exercise intervention on an outpatient basis before allogeneic haematopoietic stem cell transplantation (in general one to four weeks before admission to the hospital), proceeded during the inpatient period and continued the intervention until six to eight weeks after discharge from the hospital. The outpatient intervention was continued as a self-directed activity at home, whereas the inpatient period was partly supervised twice a week and adapted to the conditions of an isolation unit. The intervention consisted of three endurance training sessions (up to five during hospitalisation) and two resistance training sessions a week. Endurance training in the outpatient setting was recommended as rapid walking for 20 to 40 minutes. In the inpatient setting the participants performed bicycling and treadmill walking instead of the walking intervention. Additionally, participants performed strength training with and without stretch bands. Participants in the control group were told that moderate physical activity is favourable during the treatment process, without further advice. During the inpatient period, physiotherapy was offered up to three sessions a week (average duration of one session: 30 minutes). For this period, the control group had the same access to stationary bicycles and treadmills as the intervention group (not reported, how many participants exercised). All participants received allogeneic stem cell transplantation.

Outcomes

Primary outcome measure

Overall survival was not reported in any study; however, one study assessed 100-day mortality (DeFor 2007). Baumann 2010 and Wiskemann 2011 reported the number of participants who died during hospital stay; all deaths occurred as a transplant-related complication.

Secondary outcome measures

Four studies reported quality of life (Baumann 2010; Courneya 2009; Streckmann 2014; Wiskemann 2011). Seven studies mentioned fatigue (Baumann 2010; Chang 2008; Coleman 2012; Courneya 2009; Knols 2011; Streckmann 2014; Wiskemann 2011). Eight trials assessed physical performance data (Baumann 2010; Chang 2008; Coleman 2003; Coleman 2012; Courneya 2009; Knols 2011; Streckmann 2014; Wiskemann 2011). Anthropometric measurements were captured by two studies (Courneya 2009; Knols 2011). Four trials reported serious adverse events or adverse events (Chang 2008; Coleman 2012; Courneya 2009; Streckmann 2014). Some studies explored further outcomes that are irrelevant for this systematic review but could be partly relevant for clinical practice. Baumann 2010 reported lung function, Chang 2008 explored the time to recovery after transplantation, DeFor 2007 investigated physical and emotional well-being at discharge and 100 days posttransplant, and Streckmann

2014 reported movement co-ordination and balance control (see Characteristics of included studies).

Conflict of interest

One study was supported by the Lance Armstrong Foundation (Courneya 2009), and one study by AMGEN (Streckmann 2014).

Excluded studies

In total, we excluded 12 studies. Four studies included participants younger than 18 years (Hartman 2009; Marchese 2004; Moyer-Mileur 2009; Tanir 2013). We excluded one study because exercise was offered in both arms (Shelton 2009). In one trial, a multimodal intervention was offered, including a structured exercise programme, progressive relaxation, and psycho-education (Jarden 2009). We excluded three studies because they did not assess clinically relevant outcomes and had no outcome predefined in our protocol (Cunningham 1986; Kim 2006; Mello 2003). Cunningham 1986 and Mello 2003 investigated the influence of resistance training on muscle strength or muscle protein status. Moreover, Cunningham 1986 did not evaluate endurance training. Kim 2006 investigated the effect of physical exercises on lymphocyte and T-cell subsets. We excluded one study because of the involvement of participants suffering from non-haematological cancers, such as breast cancer, testicular cancer or gynaecological cancer (Thorsen 2005).

We excluded two studies because the applied exercise interventions did not correspond to our inclusion criteria (Cohen 2004; Hacker 2011). Cohen 2004 explored the influence of a Tibetan yoga intervention on psychological adjustment and sleep quality. Hacker 2011 explored the effect of strength training on physical activity, muscle strength, health status perception, and quality of life (Hacker 2011).

Risk of bias in included studies

Overall, the risks of bias were unclear. For detailed information see the 'Risk of bias' tables of included trials and Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

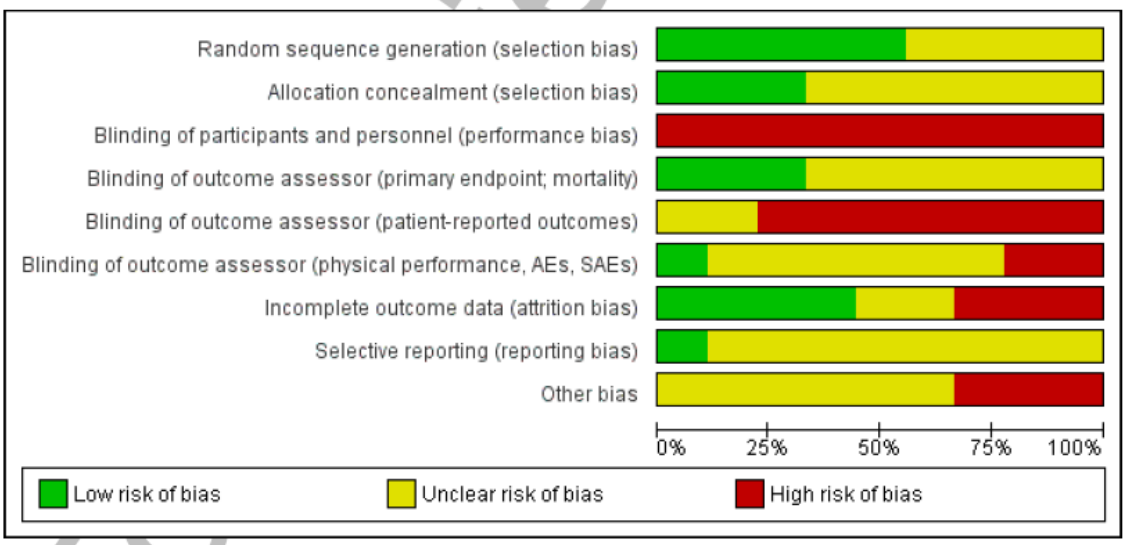
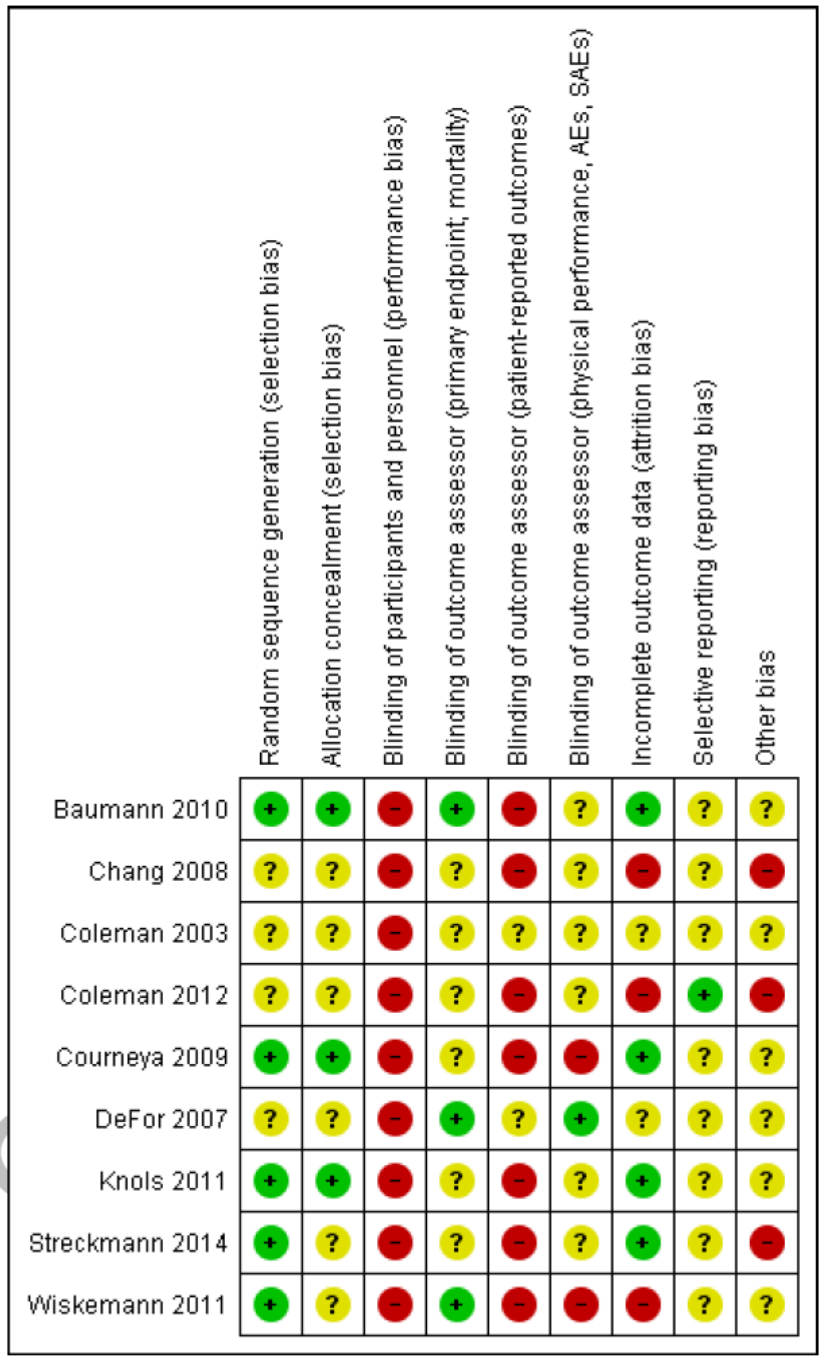


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

In only three studies, we rated the random sequence generation and the allocation concealment as adequate (Baumann 2010; Courneya 2009; Knols 2011), thus we judged the potential risk of bias as 'low'; no information was available for the six other studies. Because of this, the potential risk of bias remained 'unclear'.

Blinding

Performance bias

When exploring the influence of physical exercise intervention on people suffering from haemological malignancies, it is not feasible to blind participants or physicians. Consequently, in all nine studies we judged the potential risk of bias for blinding of participants and physicians as 'high'.

Detection bias

As the outcome of mortality is not influenced by the outcome assessor, we judged risk of bias for outcome assessor blinding for those trials that assessed this outcome as low (Baumann 2010; DeFor 2007; Wiskemann 2011).

Seven studies measured participant-reported outcomes for quality of life or fatigue. As it is not feasible to blind the intervention exercise, the participants were aware of the assigned intervention when they filled out the questionnaires. We therefore judged the risk of bias for outcome assessor blinding for those trials that assessed participant-reported outcomes as high (Baumann 2010; Chang 2008; Coleman 2012; Courneya 2009; Knols 2011; Streckmann 2014; Wiskemann 2011).

Six studies did not report whether the outcome assessors for physical performance or adverse events were blinded, so we judged their risk of bias as 'unclear' (Baumann 2010; Chang 2008; Coleman 2003; Coleman 2012; Knols 2011; Streckmann 2014). In two studies we judged the assessor bias at 'high' risk (Courneya 2009; Wiskemann 2011). In Courneya 2009 the outcome assessors were not always blinded to group assignment, but they were trained in standardising testing procedures. In Wiskemann 2011 the assessors were not blinded to randomisation. In one study, the assessor was unaware of the randomised assignment (DeFor 2007), and we therefore judged the risk of bias as 'low'.

Incomplete outcome data

For two studies, we judged the risk of attrition bias as 'unclear' as they did not report whether all randomised participants were analysed (Coleman 2003; DeFor 2007). In three studies not all the randomised participants were considered in the outcome analysis. Consequently, we judged the risk of attrition bias as 'high' (Chang 2008; Coleman 2012; Wiskemann 2011). In four studies we could not detect any risk of attrition bias, with all randomised participants analysed in the arm to which they were assigned, so we judged the risk of attrition bias as 'low' for these studies (Baumann 2010; Courneya 2009; Knols 2011; Streckmann 2014).

Selective reporting

For eight of the nine included studies, there is no protocol available at www.controlled-trials.com/mrct/, so we were not able to judge the potential risk of reporting bias (Baumann 2010; Chang 2008; Coleman 2003; Courneya 2009; DeFor 2007; Knols 2011; Streckmann 2014; Wiskemann 2011), and we therefore rated the potential risk of reporting bias as 'unclear'. For one study, a protocol is registered (Coleman 2012). All planned outcomes are reported. According to this, we judged the potential for reporting bias as 'low'.

Other potential sources of bias

In one study the distribution of gender is unbalanced in the exercise and in the control group. In consequence of this distribution, we judged the potential risk of bias as 'high'; however, the unequal distribution could be due to the small number of participants randomised (Chang 2008).

One study was finalised before the last six participants were enrolled (Coleman 2003). This premature termination was due to time and funding constraints. There is no indication that the premature stopping could have been due to other reasons. On the basis of this abandonment, we judged the potential risk of bias as 'unclear'.

In Coleman 2012 50% of participants received thalidomide. It is was neither reported whether the thalidomide administration was equally distributed between both arms, nor were subgroup analyses provided for participants receiving or not receiving thalidomide. We therefore judged the potential risk of bias as 'high'. Moreover, in an abstract publication of the trial, Coleman 2012 reported that all participants (in both the exercise and control group) received erythropoietin. In the study description published as full text the authors reported that erythropoietin was administered to only 102 of 135 study participants, meaning that some participants did not receive erythropoietin therapy. We therefore judged the potential risk of bias as 'high'.

Streckmann 2014: Due to a slow recruitment rate, the trial was stopped early. The authors planned to randomise 240 people, but randomised only 61 participants. They argued that physiological parameters are more important than the primary outcome (quality

of life (QoL)). We therefore judge the potential risk of bias as 'high'. Moreover, there is a serious baseline imbalance for the outcome QoL, favouring the control group. We therefore excluded this trial for the outcome QoL in a sensitivity analysis.

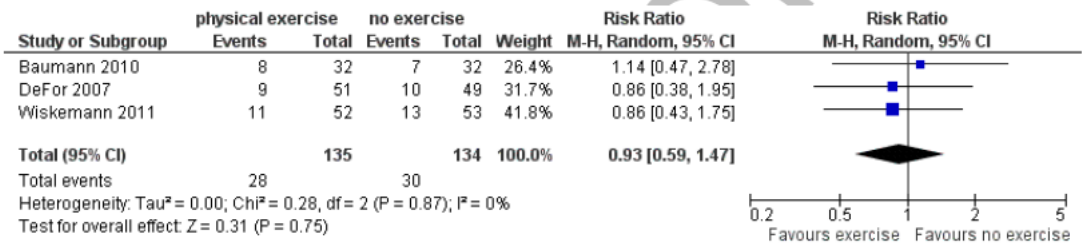
Effects of interventions

See: **Summary of findings for the main comparison** Physical exercise versus no physical exercise for adults with haematological malignancies

Overall survival (OS)

None of the trials explored our primary outcome, overall survival, but three trials (N = 269) reported the number of deceased participants (Baumann 2010; DeFor 2007; Wiskemann 2011). We found no statistically significant difference between exercise and control arms (risk ratio (RR) 0.93; 95% confidence interval (CI) 0.59 to 1.47; P = 0.75; Analysis 1.1). There are no suggestions of heterogeneity (I^2 = 0%) (see Figure 4).

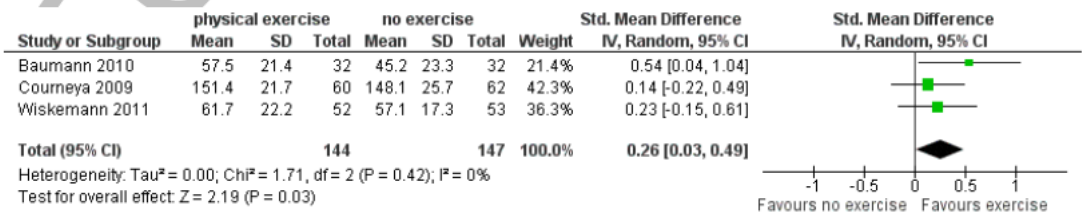
Figure 4. Forest plot of comparison: 1 Physical exercise versus no physical exercise, outcome: 1.1 Mortality.



Quality of life (QoL)

Four studies measured the outcome quality of life. However, one trial reported a serious baseline imbalance favouring the control arm (Streckmann 2014), and we thereforeexcluded this trial in a sensitivity analysis. We found a statistically significant advantage for participants in the exercise arm (standardised mean difference (SMD) 0.26; 95% CI 0.03 to 0.49; P = 0.03; 291 participants; Analysis 1.3), without indications for heterogeneity (I^2 = 0%) (see Figure 5). There are no indications of subgroup differences between participants receiving stem cell transplantation or chemotherapy only (Analysis 1.4).

Figure 5. Forest plot of comparison: 1 Physical exercise versus no physical exercise, outcome: 1.3 QoL sensitivity analysis.



Subscale physical functioning

Four trials with 422 participants evaluated physical functioning. This outcome is statistically significantly improved in the exercise arm (SMD 0.33; 95% CI 0.13 to 0.52; P = 0.0009; Analysis 1.5).

Subscale depression

The pooled result of three trials (N = 249) for depression shows a statistically significant benefit for the exercise arm (SMD 0.25; 95% CI -0.00 to 0.50; P = 0.05; Analysis 1.6).

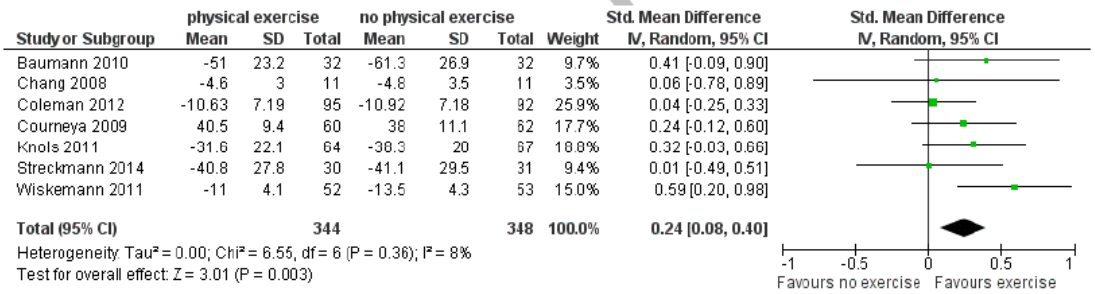
Subscale anxiety

There is moderate heterogeneity for the analysis of anxiety (I^2 = 64%), but no evidence for differences between the additional exercise arm and the standard treatment arm (SMD -0.18; 95% CI -0.64 to 0.28; P = 0.45; 3 trials, 249 participants; Analysis 1.7).

Fatigue

Seven studies (N = 692) assessed fatigue and found a statistically significant advantage for those participants exercising (SMD 0.24; 95% CI 0.08 to 0.40; P = 0.003; Analysis 1.8), with minimal heterogeneity (I^2 = 8%) (see Figure 6). The test for interaction between the subgroups stem cell transplantation versus no stem transplantation revealed no statistically significant differences (Analysis 1.9).

Figure 6. Forest plot of comparison: 1 Physical exercise versus no physical exercise, outcome: 1.8 Fatigue.



Physical performance (e.g. aerobic capacity, cardiovascular fitness)

Eight studies evaluated physical performance (Baumann 2010; Chang 2008; Coleman 2003; Coleman 2012; Courneya 2009; Knols 2011; Streckmann 2014; Wiskemann 2011). However, all studies used different concepts, measuring instruments and outcome definitions, and we therefore have not pooled the data.

Baumann 2010 reported statistically significant differences in the inter-group comparison for repeated measurements for endurance (P = 0.004), endurance time (P = 0.004) and relative endurance (P = 0.031) between the exercise and the control group, favouring the exercise arm. There were no statistically significant intra-group changes in the exercise arm between admission and discharge, but there were significant changes between these data in the control group. Endurance between these two time points decreased from 86.5 Watt (W) to 60 W (P = 0.001) and endurance time reduced from 5.4 minutes to 3.3 minutes (P < 0.001) in the control group.

Chang 2008 assessed physical performance by a 12-minute walking test. In this test, participants were encouraged to walk at a speed to reach their specific heart rate, predefined by the study protocol. At baseline there were no statistically significant differences between the two study arms.The authors reported a statistically significant decrease in 12-minute walking distance for the control group (estimate -119.1 metre (m); 95% CI -207.1 to -31.0 m; P = 0.008). On the other hand, the 12-minute walking distance for participants in the exercise programme increased over time.

Coleman 2003 investigated the outcomes strength changes and treadmill minutes. Strength changes were tested by four strength tests using Keiser pneumatic equipment. Treadmill minutes, in detail the measurement of aerobic exercise capacity, were measured by a modified Balke protocol. Comparison between exercise and control groups did not achieve statistical significance, either for strength change or for treadmill minutes. The authors provided no further data.

In Coleman 2012 all participants performed a six-minutes walking test before and after intervention. The mean values for the walking

test showed a tendency for improved performance in the short-term exercise group, but not in the short-term control group. Aerobic capacity, measured by the six-minute walking test, decreased over time in both arms, but less so in the exercise group. No further precise data were published for this outcome.

Courneya 2009 measured VO_2 peak power output, VO_2 peak (ml/kg/min) and ventilatory threshold (l/min). In all three measures, the exercise group was statistically significantly superior to the control group.

Knols 2011 reported statistically significantly improved six-minute walking test results (P = 0.011), increased walking speed (P = 0.000) and improved knee extension for the exercise arm compared to the standard care arm from baseline to follow-up examination three months after programme completion. The authors found no difference for grip strength between the two arms (P = 0.624).

Streckmann 2014 reported that the aerobic performance level increased statistically significantly in the exercise group over time compared to the control group with deteriorating activity levels (P = 0.03). This is true for balance control, with improving balance control in the exercise arm and reducing control in the standard arm (dynamic control P = 0.007; static control P = 0.02).

In the trial by Wiskemann 2011 participants in the exercise group achieved statistically significantly more meters in the six-minute walking test six to eight weeks after discharge; no more detailed data were published.

Anthropometric measurements

Two studies (N = 253) provided data for anthropometric measurements and body composition (Courneya 2009; Knols 2011). There was no statistically significant difference between the groups for body weight (mean difference (MD) 0.30 kg; 95% CI -4.08 kg to 4.68 kg; P = 0.89; Analysis 1.10) and lean body mass (MD 1.34 kg; 95% CI -1.34 kg to 4.02 kg; P = 0.33; Analysis 1.11).

Adverse events

Three studies (N = 266) reported serious adverse events (SAEs) (Chang 2008; Coleman 2012; Courneya 2009) and were pooled in one analysis. There is a statistically non-significant disadvantage for participants in the exercise group (RR 1.44; 95% CI 0.96 to 2.18; P = 0.06; I^2 = 0%; Analysis 1.12), without heterogeneity.

Chang 2008 reported that one participant in each arm (8%) dropped out of the study due to a SAE. The participant in the exercise group experienced severe bleeding, and the participant in the control group a severe infection.

In the trial by Coleman 2012 the most common SAEs were fever, hyponatraemia, pneumonia, hyperglycaemia, deep vein thrombosis, infection and neutropenia. In the short-term groups, 15 out of 23 participants (65%) experienced one or more SAEs, while the corresponding rate in the control group was 8 out of 28 participants (28%).

Regarding the long-term study group, 15 out of 35 participants (43%) in the exercise group experienced at least one SAE and 14 out of 34 (41%) in the control group. As the authors reported variations in cancer treatment between both study arms (whether erythropoietin or thalidomide, or both were administered or not) the reasons for the differences between study arms remain unclear.

Courneya 2009 reported that no SAE occurred in either arm, but three (5%) adverse events (back, hip and knee pain) related to the exercise programme. One participant with knee pain withdrew from the exercise programme, and the other two participants proceeded with a modified exercise programme. In the control group (N = 62) no adverse events were reported (RR 7.23; 95% CI 0.38 to 137.05; P = 0.19).

Streckmann 2014 (61 participants) reported that the number of cancer-related side effects was statistically significantly reduced in the exercise group by 2.1 compared to baseline (P = 0.043). In the control group, the side effects were reduced by only 0.4 (P = 0.514).

DISCUSSION

Summary of main results

In this review we evaluated the efficacy, safety and feasibility of aerobic physical exercise for adults with haematological malignancies and included nine randomised controlled trials (RCTs). The results are as follows:

- Instead of overall survival, 100-day survival was measured in one trial and mortality during hospital stay in two other trials. For this outcome (269 participants) we could not detect any statistically significant difference between the exercise and control arms.
- Quality of life was measured in four studies. Excluding one trial with serious baseline imbalances, there is low quality evidence that physical exercise improves quality of life (291 participants). This positive effect is found for the subscales physical functioning (422 participants) and depression (249 participants). There is no evidence for an effect on anxiety (249 participants).
- Seven trials evaluated fatigue (692 participants). There is moderate quality evidence that exercise improves fatigue.
- Eight studies evaluated physical performance, but used different concepts, measuring instruments and outcomes, so that we did not pool the data. Seven trials reported a tendency or statistically significant benefits for the exercise arm.
- Two trials reported anthropometric measurements (253 participants), without evidence for differences in body weight and lean body mass.

- Serious adverse events were evaluated in three trials (266 participants). There is no evidence for a difference between the arms.
- One trial (61 participants) reported adverse events, without evidence for a difference between the arms.

Overall completeness and applicability of evidence

The results of this meta-analysis should be interpreted considering the following aspects:

- The nine included studies, comprising 818 participants, may not be adequately powered to detect small differences, especially in outcomes with few events.
- We identified three further trials which meet our inclusion criteria, but did not report the predefined outcomes of our review, as they reported laboratory values or muscular strength only. However, in total, they analysed only 83 participants, so we did not expect any important impact of these trials on overall results.
- Data appear deficient, in particular for overall survival. We note a lack of study data, which requires further research.
- The exercise programme (type, duration and follow-up), supportive care and medical treatment differed between trials and thus could influence the outcomes.

Quality of the evidence

Overall, we judged the potential risk of bias of the nine included trials as unclear. All the included trials were reported as randomised and as open-label studies. In six of the nine included studies the scientific quality of allocation concealment remained unclear. The open-label design and unclear allocation concealment could lead to selection, performance or detection biases. In the included studies, blinding of participants as well as blinding of physicians in the context of physical exercise was impossible. Consequently, we judged the risk of performance bias as high for all studies. As the outcome mortality is not influenced by the outcome assessor, we judged risk of detection bias for this outcome as low. As it is not feasible to blind the intervention exercise, we judged the risk of detection bias for participant-reported outcomes as high. For the other reported outcomes, most studies did not report whether outcome assessors were blinded, and we therefore judged risk of detection bias for these outcomes as unclear. For three trials we judged the potential risk of attrition bias as high, because not all participants randomised were analysed.

We judged the quality of the evidence body as low to moderate for most outcomes, because of an open-label design and a small number of events, leading to wide confidence intervals and imprecision of the results. For the outcomes adverse events and serious adverse events, we judged the quality of the evidence body as low, due to imprecision. Moreover, one small trial with baseline imbalances was included, decreasing the quality of evidence for the outcome serious adverse events. It is unclear how many participants in the intervention and control arms received thalidomide or erythropoietin, or both; both are agents with a high potential for serious adverse events.

Potential biases in the review process

We tried to avoid bias by doing all relevant processes in duplicate. We are not aware of any obvious flaws in our review process. With sensitive search strategies and handsearching of conference proceedings we tried to avoid retrieval bias.

As the number of included studies is too low to perform tests for publication bias, we cannot be sure that we obtained all relevant studies. Moreover, as this type of intervention, aerobic physical exercise, is usually evaluated in investigator-initiated trials, there is no manufacturer or company available to ask for missing data. Additionally, for an intervention like physical exercise there might be less need to be registered in advance in clinical trials registries, as this applies more cogently to randomised controlled trials of pharmaceutical interventions. Moreover, we excluded three trials that did not report any of the predefined outcomes of this review. However, as the three feasibility studies analysed only 83 participants, the impact of these trials on our overall results seems likely to be small. All these points could have introduced publication bias.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first comprehensive systematic review based on RCTs evaluating the efficacy, safety and feasibility of aerobic exercise for adults suffering from haematological malignancies.

Liu 2009 included ten studies, three randomised and seven non-randomised, which assessed the influence of physical exercise in children and adults with haematological malignancies. We included one of these RCTs in our review (Coleman 2003), as one was without patient-relevant data (Mello 2003) and the other trial included children (Marchese 2004). The results of Liu et al. are quite similar to the results of our review. The authors found a low to moderate methodological quality and a clear variation of exercise type, frequency, duration and intensity in the ten trials. They concluded that physical exercise is feasible in people suffering from haematological malignancies.

Another review investigated the effect of exercise in adults and children who survived haematological malignancies (Wolin 2010). A total of thirteen studies (eight randomised, five non-randomised) were in adult patients were included. Of those RCTs five trials were included in our review (Chang 2008; Coleman 2003; Coleman

2012; Courneya 2009; DeFor 2007), as two did not report patient-relevant data (Kim 2006; Mello 2003; Shelton 2009). The authors reported strong evidence for a benefit of physical exercise on body composition and weak evidence for improved cardiorespiratory fi tness, fatigue, muscle strength, physical functioning and quality of life. In addition to the adult trials, the authors analysed twelve trials (two RCTs, 10 non-randomised trials) in children. They found strong evidence for improvement of cardiorespiratory fi tness and muscle strength. For both adults and children, the authors reported no exercise-related adverse events. In contrast to this review, we found very low quality evidence for increased serious adverse events in adults in the exercise arm.

Velthuis 2010 meta-analysed the effects of physical exercise on cancer-related fatigue during cancer treatment. All included studies compared physical exercise with standard care. No restrictions on inclusion in this meta-analysis were made in regard to participants' age, tumour type, tumour stage and type of cancer treatment. The authors included 18 studies, of which 12 evaluated the effects of exercise during breast cancer treatment, three during treatment of prostate cancer and three during treatment of haematological malignancies (Chang 2008; Coleman 2003; Courneya 2009). These three trials are also included in this Cochrane review. Several types of physical exercise were performed, including aerobic exercise, strength training, flexibility exercises or combinations of these exercise types. Only short-term effects of physical exercise were assessed, as only one study evaluated long-term effects (six months). A subgroup analysis of three high-quality trials in women with breast cancer revealed a significant reduction in cancer-related fatigue, with favourable results in the aerobic groups. Moreover, supervised aerobic exercise prescriptions seemed to be more effective in decreasing cancer-related fatigue compared to the home-based version (no significant reductions in cancer-related fatigue). In contrast to these results, one further subgroup evaluation of supervised and home-based aerobic and resistance exercise programmes in men suffering from prostate cancer revealed no significant decrease in cancer-related fatigue in the exercise group. In contrast with our results, the authors could not detect a beneficial effect of exercise on the outcome of fatigue in the two trials in people with haematological malignancies.

AUTHORS' CONCLUSIONS

Implications for practice

Currently, there is moderate to very low quality evidence available for the benefits and harms of aerobic physical exercise in adults with haematological malignancies. Aerobic physical exercise in addition to standard care improves quality of life, physical functioning, depression and fatigue. There is currently no evidence for differences in deaths during the study or within the first 100 days between people exercising and the control group. There is inconclusive evidence regarding anxiety, physical performance, serious adverse events and adverse events.

Implications for research

To establish the most effective type and intensity of physical exercise, further trials with more participants and longer follow-up periods are needed. We also need trials with overall survival as the primary outcome, to determine whether the suggested benefits will translate into a survival advantage. To enhance comparability of study data, we require the development and implementation of core sets of measuring devices.

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* *Indicates the major publication for the study*

III. Exercise intervention studies in patients with peripheral neuropathy – a systematic review

Fiona Streckmann, Eva M. Zopf, Helmar C. Lehmann, Kathrin May, Julia Rizza, Albert Gollhofer, Wilhelm Bloch, Freerk T. Baumann, accepted in Sports Medicine. (IF: 5.2)

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Exercise intervention studies in patients with peripheral neuropathy - a systematic review

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Exercise intervention studies in patients with peripheral neuropathy – a systematic review

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ABSTRACT

Introduction

Peripheral neuropathies (PNP) encompass a large group of disorders of heterogeneous origin which can manifest themselves with sensory and / or motor deficits depending on the predominantly affected nerve fiber modality. It represents a highly prevalent disease group which can be associated with significant disability and poor recovery. Exercise has the potential to improve side-effects of PNP. Our objective in this systematic review was to analyze exercise interventions for neuropathic patients in order to evaluate the possible benefits of exercise.

Methods

Three independent reviewers used PubMed, MEDPILOT® (MEDLINE), Cochrane and relevant reference lists to obtain the data. Relevant studies were graded according to the Oxford Levels of Evidence.

Results

18 studies (10 randomized controlled trials and 8 controlled clinical trials) met all inclusion criteria. Three (diabetic) studies were ranked very high quality (1b (A)), nine high quality (4 diabetes, 1 cancer, 4 others) (2b (B)), while six (4 diabetes, 2 others) showed low quality (4/C).

Current data suggests that exercise is a feasible, safe and promising supportive measure for neuropathic patients. This is best documented for patients with diabetic neuropathy (DPN), suggesting that endurance training has the potential to prevent the onset and reduce the progression of DPN. In general balance exercises showed the highest effect on the motor as well as sensory symptoms in all types of PNP.

Conclusion

Overall, balance training appears to be the most effective exercise intervention. Studies focusing exclusively on strength, or a combination of endurance and strength, appear to have a lower impact. For metabolically-induced neuropathies endurance training also plays an important role. Further research with high methodological quality needs to be conducted in order to establish evidence-based clinical recommendations for neuropathic patients.

1. BACKGROUND

Peripheral neuropathy (PNP) represents a group of diseases which affect motor, sensory and/ or autonomous peripheral nerves. PNP can be subdivided by its etiology or by pathological features such as predominantly affected fiber modality. They can be further classified on the basis of primarily myelin or axonal damage resulting in demyelinating or axonal PNP. Furthermore, PNP is a highly prevalent disease: worldwide, about 168 million people are affected[1]. At the age of 55 years, around 5-8 percent of all people suffer from symptomatic peripheral neuropathy, whereas in the age group above 65 years, almost one third are estimated to have sensory symptoms attributed to peripheral neuropathy[1, 2]. Common symptoms include pain, altered sensation (numbness, burning, tingling, etc.), reduced or absent reflexes, muscle weakness, reduced balance control, insecure gait and higher risk of falling[3, 4]. All of those symptoms can affect activities of daily living and subsequently reduce patient's quality of life[5].

PNP can develop genetically or be acquired. About one third is caused by diabetes, another third results from a variety of factors such as medication (e.g. chemotherapeutic agents), genetics, autoimmune disorders, infections, nutritional deficiencies, and metabolic imbalance, whereas the rest is termed idiopathic (cause unknown)[6]. PNP does not only have a severe impact on the activities of daily living, reducing patients' quality of life, but for some patients it can even influence their survival[6, 7].

For patients with diabetic peripheral neuropathy (DPN), who represent the largest group (50% of all diabetic; 110 million people)[8], small and large nerve fibers are damaged to different degrees, causing foot ulcers and non-traumatic foot amputation[9].

In cancer patients, PNP is the most common[10] neurological and clinically relevant side-effect. Peripheral neuropathy can occur as paraneoplastic manifestation, but much more frequently PNP is induced by neurotoxic chemotherapeutic agents (platinum-derivates, vinca-alkaloids and taxanes, as well as bortezomib, thalidomide and epothilones)[11, 6, 12, 13]. Not only do patients have to deal with the debilitating side-effects these drugs induce, but chemotherapy-induced peripheral neuropathy (CIPN) has become a decisive limiting factor for therapy, causing treatment delays, dose reductions or even discontinuation of therapy, which can affect the outcome and compromise survival[6]. Therefore, the occurrence of PNP presents a diagnostic dilemma because up to now approved and effective treatment options are lacking[6, 13].

Even though PNP causes so many symptoms that may even lead to life-threatening consequences, little research has been done to investigate the potentially beneficial effects of specific exercises to counteract the described symptoms. Research has focused on pharmacological therapies aimed to reduce PNP or treat selected side-effects[14, 10, 15].While this has been helpful for neuropathic pain, it does not address the many other sensory

and motor side-effects of PNP [12, 16, 17, 14]. To the contrary, many of these agents have been shown to have additional negative side-effects[13].

Previous studies have shown that exercise can attenuate motor deficits induced by PNP. Apart from the obvious effect of strength training preventing muscle loss, it also improves inter- and intramuscular coordination as well as neural control, contributing to improved stability and gait[18, 19]. Endurance training improves cardio-vascular fitness, but also has an influence on metabolic factors such as glycemic control, insulin sensitivity, lipid abnormalities and hypertension[20, 21] and therefore may also be able to improve related neuromuscular parameters [22].

Alternative interventions such as sensorimotor training (SMT), whole-body vibration (WBV) or Tai Chi for instance, have not received much attention so far but have considerable potential as they not only target motor components but simultaneously address small and large sensory nerve fibers[23-25].

Studies in healthy adults for instance, have revealed that SMT can induce supraspinal reorganization[26], regeneration of neuromuscular structures after injuries[27], reduction in reflex excitability[28] and diminish the prevalence of injuries[29] leading to improved proprioception[26], balance control, causing fewer falls[30] and increasing mobility. Similar effects have been shown with WBV. Kawanabe et al.[24] and Bogaerts et al.[31] for instance, showed that elderly people improve their gait after vibration exercises. Rittweger et al. [32] and Kirchner et al.[33], found WBV to have a positive impact on pain reduction, while further studies showed an effect on deconditioned skeletal muscle[34], improved isometric strength[35, 36, 32], postural sway[37] and reduced fall frequency[31]. Tai Chi, a traditional Chinese martial art, improves balance[38], gait, reducing the risk of falling[39], inducing muscle strength[38], stabilization of the joints, flexibility[40], stamina and coordination[41-45].

Nevertheless, the translation of those results to patients with neuropathic conditions is scarce. To date, treatment is predominantly symptom-orientated with little consensus regarding the benefits of the various exercises. Consequently, patients are uninformed as to how much exercise is advisable or if they should exercise at all during acute neuropathy.

Only in the last three years has the potential of exercise as a measure of supportive therapy gained more attention, for the first time enabling a systematic review based on sufficient evidence to derive preliminary recommendations.

This systematic review has the aim to analyze all exercise interventions performed with neuropathic patients in order to critically review the exercises chosen and the influence they may have on the motor and sensory side-effects of PNP. The intention is to improve future research and generate recommendations as to which exercises

may be beneficial for which side-effects of PNP, in order to better support neuropathic patients as well as the therapists guiding them, and improve their quality of life.

2. METHODS

2.1 Literature search

Three reviewers (F.S., K.M., and J.R.) independently searched the literature (April 2013-December 2013) with PubMed, MEDPILOT® (MEDLINE), and the Cochrane Database in order to find exercise intervention studies for patients with peripheral neuropathy. Additionally, relevant reference lists were hand-searched. We used the terms *peripheral neuropathy, PNP, CIPN, chemotherapy induced peripheral neuropathy, diabetic neuropathy* and combined these by AND with the terms: *physical activity, physical exercise, physical fitness, exercise, exercise program, exercise intervention, moving therapy, sports therapy, sport, endurance, aerobic training, resistance training, strength training, strength, balance, balance training, balance exercise, coordination, coordination exercises, gait, postural stability, postural control, and proprioception.* The German equivalents of all terms were also searched for.

To be included in the review, studies had to have examined the effect of an exercise intervention in patients with PNP, independent of the derivation. Animal studies, expert opinions without critical appraisal or studies with less than ten patients, no control group or combining exercise and nutrition, therapeutic footwear, medication for PNP etc, therefore not enabling a clear interpretation of the results, were excluded. Reviews were excluded from analysis, yet analyzed for additional, possibly relevant literature. Full-text articles of the studies meeting the inclusion criteria were then critically reviewed and graded according to the Oxford levels of evidence (see Table 1) by two authors (F.S. and F.B.) and in case of doubt by a third (E.Z.), leading to grades of recommendation. This evaluation system by the Oxford Center for Evidence Based Medicine (OCEBM) was ranked most effective in a comparison by Atkins in 2004[46] and has been used for reviews in similar context [47-50]. The evaluation is based on the study design, quality of the study and its results, creating ten gradations of quality, which are then translated into four grades of recommendation (A=1a,1b; B=2a, 2b,3a, 3b; C=4a,4b; D=5a,5b) (see Table 1). Only high quality studies (Level 1(A) and Level 2(B)) were considered to derive recommendations. Studies were abstracted for the tables to include the amount of study participants (N), type of exercise, duration, and frequency for which the exercise was performed, as well as the main outcome measures. Results given are based on intergroup comparison unless stated otherwise.

Table 1: Oxford levels of evidence and corresponding grades of recommendation

Level	Content	Grade of recommendation
1a	Systematic reviews with homogeneity of randomized controlled trials	A
1b	Individual randomized controlled trials (with narrow confidence interval)	
2a	Systematic reviews with homogeneity of cohort studies	B
2b	Individual cohort study (including low quality randomized controlled trials)	
3a	Systematic review with homogeneity of case-control studies	
3b	Individual case-control study	
4	Case-series (and poor quality cohort and case-control studies)	C
5	Expert opinion without explicit critical appraisal	D

This table represents an overview of the standardized Oxford levels of evidence. The entire table can be obtained from the Centre for Evidence Based Medicine[51]

3. RESULTS

We screened 8701 search results in PubMed as well as 959 in MEDPILOT® (MEDLINE and Cochrane) and 177 in relevant reference lists. After careful reviewing, the total number of studies meeting inclusion criteria for this review is 18 studies: Ten randomized controlled trials (RCT) and eight controlled clinical trials (CCT) (see Fig. 1) evaluated the effects of an exercise intervention on the side-effects of PNP, assessing a total of 841 patients.

Eleven studies assessed patients with diabetes induced neuropathies, one study chemotherapy-induced peripheral neuropathy (CIPN), while six studies dealt with PNP of other derivation such as liver-transplanted familial amyloid polyneuropathy (FAP), sensory neuron disease, hereditary sensorimotor neuropathy(HMSN)(Charcot Marie Tooth disease1+2), chronic acquired PNP, toxic neuropathy or antimyelin-associated glycoprotein. No Studies were found for any other causes of PNP such as HIV or alcohol (see Table 2).

Critical grading of the 18 studies revealed twelve high quality (Level 1 and 2) studies (7 diabetic PNP, 1 CIPN, 4other) and six of poor quality (Level 4) (4 diabetic PNP, 2others) (see Table 3)

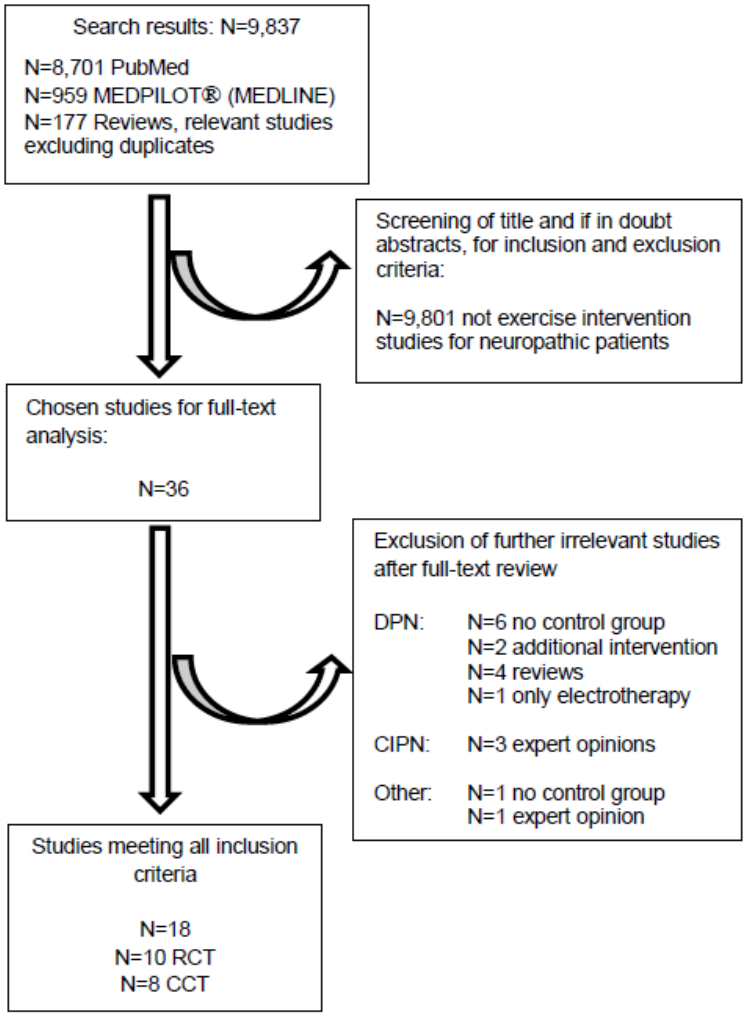

Fig. 1: Procedure of literature search and selection of studies for the systematic review

DPN=diabetic peripheral neuropathy; CIPN=chemotherapy-induced peripheral neuropathy; RCT=randomized controlled trial; CCT=clinical controlled trial

Table 2: Numbers of studies and reported effects of exercise interventions on different types of neuropathy

Type of neuropathy	Studies showing beneficial effects of exercise	Studies showing no beneficial effects of exercise	Studies that did not report on differences between groups*
Diabetic	9 [4, 52-54, 25, 55-57, 22]	1[58]	1[59]
CIPN	1 [60]	0	0
HMSN	0	1 [61]	0
Liver transplanted FAP	1 [62]	0	0
Inflammatory peripheral neuropathy after GBS or stable CIDP	1 [63]	0	0

Mixed aetiologies	1 [64]	2 [65, 66]	0
HIV, alcohol, chronic kidney disease, amyloidosis, lyme disease, diphtheria, etc.	0	0	0

*not included in percentage of beneficial studies; CIPN=chemotherapy.induced peripheral Neuropathy; HMSN= hereditary motor and sensory neuropathy; FAP= familial amyloid polyneuropathy; GBS= Guillain-Barré Syndrome; CIDP= chronic inflammatory demyelinating Polyradiculoneuropathy; HIV= human immunodeficiency virus

Table 3: Quality of studies on exercise interventions for neuropathic patients based on Oxford levels of evidence

Grade of recommendation	LOE	Cancer	Diabetes	Others
A	1b	0	3	0
B	2b	1	4	4
C	4	0	4	2
D	5	Excluded	Excluded	Excluded
Total N=18		1	11	6

LOE=levels of evidence

3.1 Diabetic peripheral neuropathy

Table 4: Exercise interventions for patients with diabetic neuropathy

Reference	N	Study design	Study population	Type of exercise	Duration	Frequency	Outcome measures (significant intergroup differences)	LOE	Grade of recommendation
Dixit et al. 2014 [52]	87 40 IG 47 CG	RCT	Diabetics	Endurance on treadmill at 40-60% HRR	8 weeks	3-6x/week 150-360min	↑ Distal peroneal nerve conduction velocity ↑ Sural sensory nerve conduction velocity ↑ MDNS ↔ latency, duration and amplitude	2b	B
Lee et al. 2013 [4]	55 19 WBV+BE 18 BE 18 CG	RCT (two interventions, one control)	Diabetics	WBV + balance exercises or balance exercises solely	6 weeks	Balance exercises: 2x/week for 60min WBV: 3x/week for 3min at 15-30Hz; 1-3mm	WBV comp to BE and CG: ↑ Postural sway ↑ BBS ↑ TUG ↑ Five-times-sit-to-stand ↑ HbA_{1c} WBV and BE comp to CG: ↑ FRT ↑ One leg stance	2b	B
Mueller et al. 2013 [53]	29 15 WB 14 NWB	RCT (two exercise groups)	Diabetics	Balance, flexibility, strengthening, and aerobic exercise conducted sitting or lying (NWB) or standing and walking (WB)	12 weeks	3x/week	WB group: ↑ 6MW ↑ average daily step counts NWB group: ↑ HbA_{1c}	1b	A
Akbari et al. 2012 [54]	20 10 IG 10 CG	CCT (age-matched)	Diabetics	Balance: Biodex stability and rocker and wobble-board	10 sessions	1-2x/ session	↑ Stability indices (open and closed eyes)	4	C
Ahn, Song 2012 [25]	39 20 IG 19 CG	CCT (nonequivalent CG)	Diabetics	Tai Chi	12 weeks	2x/week for 1h	↑ Balance ↑ quality of life ↑ total neuropathic symptom score ↑ glucose control	4	C
Song et al. 2011 [55]	38 19 IG 19 CG	RCT	Diabetics	Balance exercise program	8weeks	2x/week for 32min	↑ Balance and trunk proprioception: decreased sway paths ↑ unipedal stance ↑ dynamic balance ↑ fkt reach test, ↑ timed up and go ↑ 10m walk	2b	B

							↑ less trunk repositioning errors		
Allet et al. 2010 [56]	71 35 IG 36 CG	RCT	Diabetics	Balance and gait exercises with function-orientated strengthening	12 weeks	2x/week	↑ Gait speed ↑ dynamic balance (walk over beam and balance index), Biodex sway index ↑ performance-oriented mobility ↑ degree of concern about falling ↑ hip flexion mobility ↑ hip and ankle plantar flexor strength	2b	B
Kruse et al. 2010 [58]	79 41 IG 38 CG	RCT	Diabetics	Leg strengthening, balance exercises and graduated, self-monitored walking program	3 months supervised 12 months home-based	1x/week 8 instructive session	↔ Between the groups for strength, balance, participant-reported falls	1b	A
Hung et al. 2009 [57]	60 28 IG diabetics 32 CG healthy	CCT (age matched)	Diabetics	Tai Chi Chuan	12 weeks	3x/week	↑ Fasting blood glucose levels ↑ nerve conduction velocities ↑ motor nerve conduction velocities ↔ amplitudes	4	C
Balducci et al. 2006 [22]	78 31 IG 47 CG	RCT (preventive)	Diabetics	Endurance (long-term) brisk walking on a treadmill (50-85% heart rate reserve)	4 years	4x1h/week	Exercise group: ↑ less development of PNP ↑ vibration perception threshold ↑ nerve conduction velocity (peroneal and sural)	1b	A
Richardson et al. 2001 [59]	20 10 IG 10 CG	CCT (first ten placed in IG, following in CG)	Diabetics	IG: balance exercises CG: seated exercises: neck flexion and rotation, strengthening exercises of upper extremities, low frequency	3 weeks	Daily	Only intragroup results given ↑ 3 clinical measures of balance ↔ ABC Scale ↔ motor response amplitudes (tibial, sural, peroneal)	4	C

Legend: LOE=Levels of Evidence; RCT=randomized controlled trial; HRR=heart rate reserve; CCT = clinical controlled trial; IG= intervention group; PNP=peripheral neuropathy; CG= control group; MDNS=Michigan Diabetic Neuropathy Score; WBV=whole body vibration; HbA_{1c}=glycosylated hemoglobin; BE=Balance exercise group; BBS=Berg Balance Scale; TUG=Timed up and go test; FRT=Functional reach test; Hb = haemoglobin; fkt = function; WB=weight-bearing; NWB=non-weight-bearing; 6MW= 6min walk test; fkt=functional; ↑improvement, ↔ no change.

Eleven studies (7 RCT and 4 CCT), assessing 576 diabetic adults, were evaluated regarding the side-effects of PNP. Three studies were graded 1b (A), four 2b (B) and four 4 (C) (see Table 4).

Five studies (Lee et al.[4], Akbari et al.[54], Song et al.[55], Allet et al.[56], Richardson et al.[59]) assessed the influence of balance training on the side-effects of PNP, showing a significant impact on balance control. Two studies (Song et al.[55], Allet et al.[56]) also showed improved gait-parameters, while Lee et al.[4] compared two interventions: WBV and a combination of WBV with balance exercises, to a control group. Further two studies (Ahn, Song[25], Hung et al.[57]) chose Tai Chi as intervention and showed improved motor, sensory and metabolic symptoms of PNP. Kruse et al.[58] and Mueller et al.[53] chose a combination of endurance, balance and strengthening exercises. Both groups performed progressive balance-, flexibility-, strengthening- and aerobic exercises, though one group conducted the exercises standing or walking (weight-bearing group (WB N=15)), while the other group (non-weight-bearing group (NWB N=14)) was sitting or lying. Positive effects on motor

performance could only be detected if exercises were performed standing or walking. Kruse et al.[58] instructed patients in leg strengthening- and balance exercises as well as a graduated, self-monitored walking program for 8 sessions and then monitored patients while they continued home-based for 12 months. No significant intergroup differences were found.

The only existing preventive study was conducted by Balducci et al.[22], evaluating 78 diabetics over four years of endurance training (brisk walking on a treadmill at 50-85% heart rate reserve). Intergroup comparison with the CG revealed significant sensory improvements.

No adverse events were reported by Dixit et al.[52], Ahn, Song[25], Kruse et al.[58] and Balducci et al.[22]. Mueller[53] reported that one patient sustained a calf strain during treadmill walking, but was able to continue to exercise with lower intensity. Allet[56] declared two patients to develop pain in their Achilles tendon, making it necessary to slow down the progression for 'toe walking' and 'one leg stance' exercises. The remaining five studies (Lee et al.[4], Akbari et al.[54], Song et al.[55], Hung et al.[57] and Richardson et al.[59]) did not indicate adverse events.

3.2 Chemotherapy-induced peripheral neuropathy

Table 5: Exercise intervention studies for patients with chemotherapy-induced peripheral neuropathy

Reference	N	Study design	Study population	Type of exercise	Duration	Frequency	Outcome measures (significant intergroup differences)	LOE	Grade of recommendation
Streckmann et al. 2014 [60]	61 30 IG 31 CG	RCT	CIPN-lymphoma	Sensorimotor training, endurance and strength	36 weeks	2x/week	↑ QOL ↑peripheral deep sensitivity ↑ higher reduction and total number of CIPN ↑ static, dynamic and perturbed balance control ↑ aerobic performance level ↑ level of activity (outside intervention)	2b	B

LOE=Levels of Evidence, QOL=Quality of Life, RCT=randomized controlled trial, CIPN=chemotherapy induced peripheral neuropathy, IG=intervention group, CG=control group, ↑improvement.

So far, only one RCT, graded 2b (see Table 5), has assessed the effects of exercise intervention in patients suffering from CIPN. Streckmann et al.[60] was the first to show beneficial effects of exercise (sensorimotor-, endurance- and resistance training) on motor as well as sensory side effects of CIPN in cancer patients (lymphoma). The amount of patients with reduced deep sensitivity could be diminished significantly in the IG by 87.5%, while no changes (0%) were observed in the CG. Furthermore, patient's quality of life as well as their level of activity were also improved significantly. No adverse events occurred.

3.3 Neuropathy of other derivation

Table 6: Exercise intervention studies for patients with heterogeneous causes of neuropathy

Reference	N	Study design	Study population	Type of exercise	Duration	Frequency	Outcome measures (significant intergroup difference)	LOE	Grade of recommendation
Tomás et al. 2013 [62]	39 23 IG (8 supervised/ 15 home-based) 16 CG	CCT	Liver-trans-planted FAP	Aerobic (treadmill, bicycle, rowing)<15 RPE, Resistance training with Thera-Band, FlexBar and stability trainer	24 weeks	3x/week for 1h	↑ Body-composition ↑ walking capacity	4	C
Nardone et al. 2010 [64]	33 19 IG: PNP 14 CG: vestibular disorder	CCT (crossover: both groups received exercise, only in other order)	Ménière, sensory neuron disease, Ramsey-Hunt, Charcot Marie Tooth, diabetes, nutritional, entrapment neuropathy, tomaculous nephropathy, antimyelin-associated glycoprotein	Powered platform and Cawthorne-Cooksey (vestibular disorder) and Frenkel (PNP) balance exercises	10 sessions	2 sessions daily/ 30min	↑ Improved balance – regardless of order	2b	B
Graham et al. 2007 [63]	26 16 IG PNP 10 CG healthy	CCT (both exercised)	Inflammatory peripheral neuropathy after GBS or stable CIDP	Unsupervised, community based strengthening, aerobic andfunctional exercise	12 weeks (36 sessions)	3x/week for 1h	↑ Knee extensors ↑ total work load after exercise Significant baseline difference: ↑ ODSS scores ↑ physical functioning (SF-36) ↑ fatigue	2b	B
Matjacic , Zupan 2006 [61]	16 8 IG 8 CG	RCT (both groups received exercise)	HMSN	Both groups: passivestretching, muscle strengthening dynamic balance training differed: CG: managed by physiotherapist IG: performed on balance trainer	12 days	6 days/ 1day rest/ 6 days for 40min	↔ Intergroup results intragroup: ↑ Berg Balance Scale ↑ TUG ↑ 10-m walk test	2b	B
Ruhland et al. 1997 [65]	28 14 IG 14 CG	CCT (only partially randomized)	Chronic acquired peripheral neuropathy, HMSN, toxic neuropathy	Home-exercise: strengthening with Thera-Band, stretching, aerobic conditioning	6 weeks	Advised daily	↔ Intergroup results intragroup results: ↑ average muscle score	4	C
Lindeman et al. 1995 [66]	58 29 IG 29 CG	RCT (matched according to muscle strength and stair-climbing performance and then randomized into IG or CG)	30 MYD 28 HMSN	Strength – training	24 weeks	3x/week	↔ In MYD group ↔ timed motor performance ↑ knee torques in HMSN group	2b	B

Legend: IG= intervention group; RCT=randomized controlled trial; CCT = clinical controlled trial ; CG= control group; TUG=timed-up and go test; FAP= familial amyloid polyneuropathy; RPE= received perception of exertion; PNP = peripheral neuropathy, GBS =Guillain-Barré Syndrome; CIDP= chronic inflammatory demyelinating Polyradiculoneuropathy; ODSS= overall disability sum score; SF-36= short form health survey; MYD=myotonic dystrophy; HMSN=hereditary motor and sensory neuropathy, ↑improvement, ↔ no change.

The following six studies (2 RCT and 4 CCT), investigated 204 adults with neuropathies due to various causes. Grading revealed four 2b (B) studies and two were ranked a 4 (C) (see Table 6).

Apart from two studies that focused on liver-transplanted FAP (Tomás et al.[62]) and HMSN (Matjacic, Zupan[61]) all other studies evaluated a heterogeneous collective.

Only three studies were able to achieve improvements through the exercise regime chosen. Tomás et al.[62] and Nardone et al.[64] were able to improve balance and gait parameters while Graham et al.[63] showed improved knee extensors and total work load. Tomás et al[62]chose a combination of endurance-, resistance- and balance exercises. Intergroup differences in favor of the exercising groups were shown for their walking capacity. Nardone et al.[64] compared neuropathic patients to patients with vestibular disorder. Both groups performed ten sessions of balance exercises on a powered platform, as well as Cawthorne-Cooksey and Frenkel exercises. Due to a crossover-design, both groups received the same exercises, only in a different order. Regardless of the treatment order, both groups were able to improve their balance.

The other three studies (Matjacic, Zupan[61], Ruhland et al.[65] and Lindeman et al.[66]) did not detect any significant intergroup results. The earliest study by Lindemann et al.[66] in 1995, investigated the effects of strength training. Ruhland et al. in 1997[65] also assessed the effects of strength training but combined it with endurance and stretching exercises. Patients were advised to train daily for six weeks (home-based). Matjacic, Zupan[61]combined strength training with passive stretching and dynamic balance exercises. Both groups performed the same exercises. They solely differed in the dynamic balance training: The CG was managed by a physiotherapist, while the IG performed the exercises on a balance trainer.

Graham et al.[63] did not report any adverse events. All other authors (Tomás et al.[62], Nardone et al.[64], Matjacic, Zupan[61], Ruhland et al.[65] and Lindeman et al.[66]) did not indicate adverse events.

4. DISCUSSION

Though PNP is a highly prevalent and debilitating disease, affecting 168 million people worldwide[1], predominantly expert opinions and poor quality studies have dominated the research field, hinting at the potentials of exercise interventions for patients suffering from PNP. Only in the last three years, more and more high-quality studies are confirming this presumption. Consequently, previous evidence has been insufficient to generate a systematic review until now. The only other existing review from 2010 [52] merely found one study that met the inclusion criteria.

Summarizing, one can say that the evidence for exercise interventions in neuropathic patients has improved though study quality is diverse. Overall the quality of the 18 included studies is 2b. Evidence is best in patients

with diabetes and neuropathy, revealing most RCTs and therefore the highest quality in the field of neuropathic patients. With only one study on CIPN to date, results are promising but evidence is low. This also applies to the studies on the many other causes of PNP. Diseases such as HMSN or FAP for instance, are also only represented in one study, while the many other causes of PNP are either merely represented with very few individuals in a heterogeneous patient group or not at all (see Table 2).

The current data suggests that exercise is feasible, safe and beneficial (see Table 2) for patients with PNP: Overall, exercise-compliance was good and only two studies, both in diabetic patients, reported mild adverse events (Mueller et al.[53], Allet et al.[56]), due to which patients had to modify their training schedule temporarily on account of pain in the Achilles tendon or the calf.

Currently there is little evidence for a beneficial effect of supportive therapies such as vitamin E or high-dose vitamin B[67], electrolyte infusions (Ca/Mg) or electrotherapy in patients with PNP. Even neuroprotective treatments such as amifostine, nerve growth factors or corticosteroids, are not well evaluated or failed to demonstrate beneficial effects in clinical trials[13, 68, 69]. Specific treatment for nerve damage is currently not available[70] and the efficacy of available pharmaceutical interventions is limited. In DPN for instance, 90% of patients require two or more medications and despite high prescription compliance, only 27% respond to those pharmaceutical treatments[71-73]. There is no consensus regarding the treatment of PNP. To the contrary, most medication exerts additional side-effects [10][74]. Oncological patients with CIPN for instance were asked to report on the effect of supportive measures during rehabilitation. Patients reported that walking through granulated material as well as balance and gait exercises were most effective[75]. Therefore, exercise is currently a promising option in supportive therapy which should be taken more seriously.

In general, the patient cohorts were quite heterogeneous with regard to symptoms and underlying cause. Therefore future intervention studies should consider this shortcoming in study design. Groups should at least consist of patients with similar symptoms, not mixing diverse mechanisms or patients with symptoms only in the hands or face for instance, with patients experiencing numbness in their feet, as most assessments performed are consequently biased.

Most studies reported on side-effects caused by dysfunction of motor nerve fibers. All studies showing an additional impact on the sensory symptom balance control chose balance exercises as intervention method, revealing improved parameters of balance control such as decreased sway paths, improved unipedal stance, less failed attempts and trunk repositioning errors, faster reaction time, better performance orientated mobility, improved static and dynamic balance and a reduced concern about falling[60, 54],[55],[56],[64, 4]. Apart from

specific gait training, balance-exercises were also able to improve gait parameters such as gait speed, walking distance in the six- and ten meter walk, and improved timed up and go. Lee et al.[4] showed additive effects of balance training, when combined with WBV. Two studies by Ahn, Song[25] and Hung et al.[57] suggest that Tai Chi also targets balance control, due to the high demand on balance control during the monopedal stances and weight shifting movements.

A combination of strength and endurance training, not including any balance indices, was performed in two CCT studies (Graham et al.[63], Tomás et al.[62]). They revealed improvements on the knee extensors and total work load as well as the walking capacity. Lindemann et al.[66] detected significant improvements for knee torques in the HMSN group. These three studies only achieved improvements regarding muscle atrophy in general though not for specific PNP related symptoms.

Interestingly, studies assessing either a combination of strength and endurance training, or strength training alone, (Kruse et al.[58] (RCT), Matjacic, Zupan[61] (RCT) and Ruhland et al.[65] (CCT)) did not detect any significant intergroup differences.

Only three RCTs (Dixit et al.[52], Streckmann et al.[60] , Balducci et al.[22]) demonstrated improvement on small and large sensory nerve fiber function. A combination of endurance, strength and SMT revealed improved peripheral deep sensitivity in cancer patients (lymphoma) (Streckmann et al.[60]).

Balducci et al.[22] found that long-term, supervised endurance training was able to prevent the onset of PNP in diabetics, while Dixit et al.[52] achieved positive effects with moderate-intensity (40-60% heart rate reserve) aerobic exercise on the progression of DPN.

The underlying mechanisms for the beneficial effects of exercise on PNP have not yet been fully understood. Explanations may include positive modulation of regenerative mechanisms such as altered expression of growth factors, induction of remyelination or accelerating axonal regeneration[76, 77]. Recently it has been demonstrated that treadmill exercise has the potential to improve the regeneration of transected nerves by altered expression of neurotrophic growth factors such as NGF[78].

However, we will presumably have to address two different mechanisms of PNP in order to target the symptoms best: When analyzing the current data, it is noticeable that studies showing effects of endurance exercises on sensory symptoms of PNP target DPN, which is metabolically-induced, whereas the other types of PNP better respond to balance training. Exercise recommendations will probably have to differ whether we desire to primarily target metabolically-induced PNP such as DPN, or whether we have to target nerve cells damaged by toxins directly, as in CIPN.

In metabolically-induced PNP, exercise, especially endurance training, can induce glycemic control and reduce the body weight. DPN for instance is attributed, amongst other mechanisms, to prolonged hyperglycemia, causing up to fourfold higher neuronal glucose levels[79] and additionally initiating an accumulation of sorbitol. Glucose and sorbitol in such concentrations disturb the homeostasis and cause neuronal damage[52]. Additionally, sorbitol requires a higher amount of antioxidants in order to detoxify, thereby contributing to enhanced oxidative stress, which leads to neuronal cell damage. Previous studies have shown that aerobic exercise has the potential to reduce the glucose level, therefore modulating the polyol-sorbitol pathway and increasing antioxidative capacity, consequently preventing and restoring neuronal damage [52, 80]. Recent studies have also revealed that neurons can alternatively use lactate as a substitute for glucose and therefore reduce the level of neuronal glucose and oxidative stress[81]. Endurance exercises, inducing a steady state of lactate and additionally removing surplus glucose, may therefore enhance the use of this alternative metabolic pathway and contribute to the regulation of the glucose level. Consequently the intensity and duration will also play a substantial role as a certain lactate level (presumably $\geq$ 2mmol/l, in order to create the required gradient as the brain holds a lactate state of 1,9mmol/l[82]) will have to be sustained. Therefore, the type of endurance exercise is probably secondary to the intensity necessary for each individual to obtain an effective lactate state. Furthermore, exercise also increases the blood flow through distal muscle groups, increasing oxygenation to the peripheral tissue.

Dixit et al.[52] even detected an influence of endurance exercise on the amount of OHA and insulin necessary. Further studies comparing this observation to exercise interventions would be highly desirable.

Whereas for non-metabolically induced PNP, specific balance training such as SMT or whole body vibration will probably play a more crucial role as they have the potential to induce neural adaptions[26]. The underlying mechanisms must also still be elucidated. Though, one possibility could lie in the regenerative effect of SMT on nerve fibers [Taube 2008]. A further possibility is attributed to the nervous system's plasticity: (i) an increase in the density of receptors, (ii) activating deafferented neurons [Gollhofer 2003] by increasing the metabolism, (iii) lowering the threshold for excitability [Sjostrom 2008] or (iv) inducing supraspinal learning effects [Taube 2008].

Especially regarding the small and large sensory nerve fibers, the intensity, frequency and choice of exercises seem to be crucial. Presumably, not every type of balance training will be able to induce sensory changes.

As previous studies on SMT in healthy adults have shown, neural stimulation is only achieved if exercises are performed within a range of 20-40sec., not exceeding five exercises and allowing for sufficient regeneration time between the exercises in order to prevent neural fatigue[23, 26].

The indication 'balance training' is very diverse and can include many different variations, targeting different effects. For this reason studies should specify on the balance training performed and indicate the frequency and duration in order to enable comparison and generate better recommendations in the future.
All studies applied the intervention at least twice a week (2-3x/week balance; 4-6x/week endurance) for at least 6 weeks (6-36 weeks balance; 8weeks - 4years endurance).

This review also has limitations: Although the studies were ranked by three independent reviewers in order to minimize subjectivity, a selection bias cannot be ruled out completely. It must also be considered that ranking according to the criteria of the Oxford Levels of Evidence-Based Medicine was hampered due to lack of access to the raw data in the papers. Many studies lacked confidence intervals and indications regarding adverse events. Consequently, studies were difficult to interpret and rank and may therefore be under- or overrated. However, those limitations are well-known and apply at different degrees for other evaluation strategies as well [83, 84].

To date, special recommendations regarding exercise interventions for neuropathic patients are scarce. Solely for DPN the American Diabetes Association (ADA) and the American College of Sports Medicine (ACSM) have released a statement [70] recommending patients to do 150min/week of moderate-intensity exercise, or to refrain to non-weight bearing activities such as swimming, bicycling or arm exercises in case of foot injuries. Other than that, internet sites, as well as ADA personnel, advise patients with diabetes and PNP to "be careful when exercising" as "some physical activities are not safe for people with neuropathy"[85]. Possible risks are mentioned such as an increased risk of skin breakdown and infection as well as Charcot joint destruction, due to reduced sensitivity in the extremities[70]. Current studies however reveal that mild adverse events only occurred in 2 out of 18 studies. Furthermore, patients exercising do not seem at higher risk for skin-breakdown or foot ulceration, neither have weight-bearing exercises induced a higher risk than non-weight bearing activities. Additionally, the efficacy of non-weight bearing activities is low[53].
The large heterogeneity of the existing studies makes it difficult to define evidence-based recommendations, for peripheral neuropathy in general but also for the various subgroups. In order to give precise training guidelines including duration, frequency and intensity, more studies will be necessary. It is challenging to compare the various exercise programs of the individual studies, as data is insufficient for the subgroups and a general comparison may be biased due to the potentially diverse underlying mechanisms of PNP that could alter the response to exercise. Furthermore, the studies differ in terms of the interventions, duration, frequency, supervision, in-and exclusion criteria and outcome measures, which could also influence the effects. Since most

neuropathies are characterized by a chronic disease course, exercise interventions at different time points during the disease course may impact their potential treatment benefit. Nevertheless, we will try to present some prevailing directions and therefore generate preliminary recommendations that will have to be confirmed by further studies.

Table 7: Preliminary recommendations for patients with neuropathy based on the measured effects of current studies

Neuropathy	Symptoms	Interventions	Effects of exercise on sensory function	Effects of exercise on motor function	Other effects of exercise	Duration	Frequency, Intensity	Reference
Chemotherapy-induced peripheral neuropathy (platinderivates, vinca-alkaloids, taxanes, bortezomib, thalidomid, epothilones)	decreased sensation pins/needles/itching sensation painful paresthesia or numbness cold-induced dysesthesia reduced or absent reflexes (Achilles and patellar) loss of balance control gait instability more falls and injuries weakness	sensorimotor training	improved peripheral deep sensitivity and balance control (static, dynamic and perturbed)		QOL higher level of activity	36 weeks, 2x/week	3-5 Exercises: 20-40 sec. ≥ 40sec. rest between each repetition ≥ 1 min rest between each exercise	Streckmann et al. [60]
		endurance		aerobic performance level	QOL higher level of activity	36 weeks, 2x/week	10-30min (60-70% max hf)	Streckmann et al. [60]
		strength			QOL higher level of activity	36 weeks, 2x/week	4 exercises 1min max force	Streckmann et al. [60]
Diabetic neuropathy	Hypoesthesia, pin sensation, pain, reduced or absent reflexes (Achilles and patellar) loss of balance control autonomic dysfunction	balance	improved balance	gait	n.a.	8 weeks 2x/week	30min	Song et al. [55]
		endurance	preventive: less development PNP better vibration perception threshold improved nerve conduction velocity progressive: nerve conduction velocity distal and sural sensory MDNS	n.a.	n.a.	preventive: 4 years 4x/week progressive: 8 weeks/ 3-6x/weeks 150-300min	preventive: 60min (brisk walking at 50-85% heart rate reserve) progressive: on treadmill (40-60% heart rate reserve)	Balducci et al. [22] Dixit et al. [52]
		combination (balance + strength) (balance + strength + endurance)	improved balance n.a.	gait orientated mobility gait	reduced concern about falling n.a.	12 weeks 2x/week		Allet et al. [56] Mueller et al. [53]
		WBV + balance exercises	postural sway BBS	TUG Five-times-sit-to-stand	HbA_{1C}	3x WBV +2x balance	WBV: 3min; 15-30Hz balance: 60min	Lee et al. [4]
Neuropathy of other causes		balance	improved balance	n.a.	n.a.	10 sessions	30min	Nardone et al. [64]
Charcot-Marie-Tooth (hereditary mutation of axonal and / or myelin proteins) FAP (extracellular deposition of insoluble amyloidal fibers, mostly synthesized within the liver [62])	Motor and sensory symptoms (depending on the subtype), no pain, chronic progressive Autonomic dysfunction, pain, hypoaesthesia, paresis					2 daily	Powered platform and Cawthorne Cooksey or Frenkel exercises	
		strength	n.a.	knee torques (only in HSMN group)	n.a.	24 weeks 3x/week		Lindeman et al. [66]
		combination balance + strength	no effect	no effect	no effect	12 days		Matjacic et al. [61]
		combination strength + endurance	n.a.	knee extensors total work load	n.a.	12 weeks 3x/week	60min unsupervised	Graham et al. [63]

QOL=quality of life; max hf=maximum heart rate; PNP=peripheral neuropathy; n.a.=not assessed; FAP=familial amyloid polyneuropathy; HSMN=hereditary motor and sensory neuropathy, MDNS=Michigan

According to the current evidence (see Table 7), balance exercises seem to have the highest effect on the crucial side-effects of PNP, especially in primarily non-metabolic neuropathic disorders. Therefore balance exercises should be included in exercise interventions and supportive care for PNP patients. Possible interventions to obtain this aim could be e.g. sensorimotor training, Tai Chi and vibration exercises, as these target the same mechanisms. Additionally, the exercises within the type of balance training will also have to be chosen carefully according to the aim.

For patients with neuropathies of primarily metabolic origin, endurance exercises will presumably target the onset as well as the progression of DPN best. This is likely to also apply to other metabolically-induced neuropathies. Additional balance exercises or WBV [4] should be considered.

In accordance with other reviews on exercise interventions for various causes[47], better results were achieved if training was supervised rather than home-based or community-based[63],[58]. It also seems that exercises need to be repeated at least twice a week, preferably for 12 weeks or longer, as studies with very short interventions (12days to 6 weeks) and less frequency (once a week) [58, 61, 65] fail to produce significant intergroup effects. Of course it depends on the intervention and aim. SMT for instance, is known to impact balance control after just four weeks in healthy older adults[30]. Further studies will have to evaluate the individual types of exercises and determine whether combinations of exercises such as endurance and SMT for instance, could have additive effects as well as the intensity and duration necessary to achieve the highest effect for this specific patient cohort. Furthermore, the potential of exercise in the various phases of the disease (preventive, acute and rehabilitation) needs to be evaluated.

Scientists should preferably choose a control group that has the same disease but does not participate in the exercise intervention. If it is desired to offer an intervention to the control group, the intervention should not target the outcome measurements, as intergroup results will be too weak and biased[61].

The recommendations generated are based on rather low evidence and very heterogeneous studies and can thus only present a preliminary direction. Therefore many more studies will be necessary to develop comprehensive clinical exercise recommendations. Nevertheless, exercise is currently an effective supportive measure for neuropathic patients and a good alternative to pharmaceutical approaches. Therefore, the translation of the present knowledge into practice should be initiated. The various societies responsible ought to contribute to the education and instruction of therapists and physicians, in order to guarantee the best possible support for patients. Interdisciplinary collaborations are essential in the strive towards a standardization of exercise in supportive therapy.

5. CONCLUSION

Exercise is feasible, safe and effective for neuropathic patients. Balance training has the potential to improve sensory and motor symptoms in PNP, while in PNP of metabolic etiology, endurance training can prevent the onset and delay the progression of PNP. Exercise is therefore a supportive therapy for neuropathic patients which should be taken more seriously.

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Declaration of originality – Eigenständigkeitserklärung

„Ich erkläre hiermit, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe der Quelle gekennzeichnet. Insbesondere habe ich hierfür nicht die entgeltliche Hilfe von Vermittlungsbeziehungsweise Beratungsdiensten (Promotionsberater oder anderer Personen) in Anspruch genommen. Niemand hat von mir unmittelbar oder mittelbar geldwerte Leistungen für Arbeiten erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen.

Die Arbeit wurde bisher weder im In- noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.“

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Datum Unterschrift

Curriculum Vitae

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Education and Qualifications

Since 01/2012	**Research Associate at the German Sport University Cologne** Institute of Cardiovascular Research and Sport Research group: "physical activity and cancer"
09/2011- 08/2012	**Secondary school teacher at Kepler-Gymnasium, Freiburg i. Br.** Subjects: Biology, Physical Education, Natural Science Technology.
08/2011	**Seminar in Didactics and Teacher-Training (Gymnasium) Freiburg i.Br. / Droste-Hülshoff Gymnasium Freiburg i.Br.** Student teacher for secondary-school teaching. Subjects: Biology, Sports, English
Since 06/2008	**Albert-Ludwigs-University, Freiburg i.Br.** Institute for Sport und Sport science. PhD: *Exercise interventions for patients with haematological malignancies*
10/2002 - 11/2008	**Albert-Ludwigs-University, Freiburg i.Br.** Student for secondary school teaching. Biology and Sports science (Main subjects), English (Additional subject)
03/2007 - 07/2007	Thesis for the State exam in Sports science Title: *The Effect of a defined sports program on the physical, psychological and psychosocial aspects of oncology patients*.

Awards

10/2012	**1st Place, Poster Award** Deutsche Gesellschaft für Sportmedizin und Prävention, Berlin
07/2012	**Young Investigator Award, oral presentations 2012** (equal 5th) European College of Sport Science, Brügge, Belgium
06/2009	**Young Investigator Award, poster presentations 2009** (equal 5th) European College of Sport Science, Oslo, Norway
03/2009	**Best Poster Award** for the poster presentation: *Effects of a defined Sports Program – Concomitant to Chemotherapy – on Patients with Malignant Lymphoma* Scientific Advisory Board der Bio-Thera Stiftung
11/2008	**Award of the Institute of Sport and Sport Science (Gerschler-Preis)** Albert-Ludwigs-Universität, Freiburg i.Br. For outstanding academic achievements in studies of Sport Science

Publications

2014 ***Fiona Streckmann,*** *Eva M. Zopf, Helmar C. Lehmann, Kathrin May, Julia Rizza, Albert Gollhofer, Wilhelm Bloch, Freerk T. Baumann, Exercise intervention studies in patients with peripheral neuropathy – a systematic review, accepted in Sports Medicine (IF: 5.2)*

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2014 Friederike Scharhag-Rosenberger[1*] , Tim Becker[2*], **Fiona Streckmann[3*],** Katharina Schmidt[4*] (geteilte Erstautorenschaft), et al., Wissenschaftliche Studien zu körperlichem Training bei onkologischen Patienten: Empfehlungen zu den Erhebungsmethoden, accepted in Deutsche Zeitschrift für Sportmedizin.

2014 Beulertz J, Bloch W, Prokop A, Rustler V, Fitzen C, Herich L, **Streckmann F**, Baumann F.T, Limitations in ankle dorsiflexion range of motion and gait as side-effects of childhood cancer. A controlled, cross-sectional study, submitted in Physical & Occupational Therapy in Pediatrics.

02/2014 ***F.Streckmann,*** *S. Kneis, J.A. Leifert, F.T. Baumann, M. Kleber, G. Ihorst, L. Herich, V. Grüssinger, A. Gollhofer, H. Bertz, Exercise improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy, Annals of Oncology, 35: 493-499. (IF: 7.4)*

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01/2012 **F.Streckmann,** Sensomotorik, in „Sport und körperliche Aktivität in der Onkologie“, Baumann F, Bloch W, Jäger E. (Hrsg.), Springer Verlag, S.145-151.

Invited presentations

03/2014 **F.Streckmann,** Bewegung, Sport und Krebs – Aktueller Wissensstand, 31. Deutscher Krebskongress, Berlin

09/2013 **F. Streckmann**, Workshop Sensomotorik Training
Deutsche Gesellschaft für Sportmedizin und Prävention, Frankfurt

10/2012 **F.Streckmann**, Kneis S, Leifert JA, Kleber M, Gollhofer A, Bertz H. Therapiebegleitendes Sensomotorik-Training beeinflusst Gleichgewichtskontrolle und PNP bei Lymphompatienten.
Deutsche Gesellschaft für Sportmedizin und Prävention, Berlin.

Chair

03/2014 **F.Streckmann,** M. Reuß-Borst, Session: ASORS Bewegungstherapie in der onkologischen Rehabilitationsklinik, 31. Deutscher Krebskongress, Berlin

Academic Lectures

03/2014 **F. Streckmann**, Sportärzte Fortbildung des Sportärztebunds Nordrhein e.V., Theorie und Praxis, Körperliche Aktivität und Tumorerkrankungen, DSHS Köln.

02/2014 **F.Streckmann**, T.Elter, Ärztefortbildung, Eschweiler, Aachen

05/2013 **F. Streckmann**, J. Beulertz, F.Baumann, Fortbildung „Sporttherapie in der Onkologie“ für den Deutschen Verband für Gesundheitssport und Sporttherapie (DVGS), Bad Rappenau

10/2012 **F. Streckmann**, J.Wiskemann, Fortbildung „Sporttherapie in der Onkologie“ für den Deutschen Verband für Gesundheitssport und Sporttherapie (DVGS), an der Universität Freiburg

03/2010 **F. Streckmann,**
Körperliche Aktivität und Sport bei Krebserkrankungen; Was ist möglich? Fortbildung für Pflege- und Sozialdienste, Unterstützende Maßnahmen

Conference presentations

09/2013 **F.Streckmann**, W.Bloch, F.T. Baumann
Bedeutung körperlicher Aktivität für onkologische Patienten mit Polyneuropathie, Deutsche Gesellschaft für Sportmedizin und Prävention, Frankfurt

11/2012 **F.Streckmann**, Kneis S, Leifert JA, Kleber M, Gollhofer A, Bertz H.
Sensomotoriktraining hat einen positiven Einfluss auf die Gleichgewichtskontrolle und PNP von Patienten mit malignem Lyphom, Jahrestagung der Deutschen Gesellschaft für Hämatologie und Onkologie, Stuttgart.

10/2012 **F.Streckmann**, Kneis S, Leifert JA, Kleber M, Gollhofer A, Bertz H.
Therapiebegleitendes Sportprogramm hat positive Effekte auf Lymphompatienten,, Deutsche Gesellschaft für Sportmedizin und Prävention, Berlin.

07/2012 **F.Streckmann**, Leifert JA, Kleber M, Kneis S, Bertz H, Gollhofer A.
Sensorimotor training influences balance control and PNP in Lymphoma patients undergoing therapy, ECSS, Brügge, Belgien.

05/2012 **F.Streckmann**, Leifert JA, Kleber M, Kneis S, Gollhofer A, Bertz H.
Lymphoma Patients Benefit from Exercise Concomitant to Therapy, Internationales Symposium „Sport und körperliche Aktivität in der Onkologie – Neues aus Wissenschaft und Versorgung“, DSHS Köln.

10/ 2011 **F.Streckmann**, Kleber M, Gollhofer A, Kneis S, Bertz H, Leifert JA
Sensorimotor Training has a Positive Influence on Patients with Malignant Lymphoma Receiving Chemotherapy, Jahrestagung der Deutschen Gesellschaft für Hämatologie und Onkologie, Basel, Schweiz.

10/2011 **F.Streckmann**, Leifert JA, Kleber M, Kneis S, Gollhofer A, Bertz H.
DER POSITIVE EINFLUSS VON THERAPIEBEGLEITENDEM SENSOMOTORIK TRAINING AUF PATIENTEN MIT MALIGNEM LYMPHOM, Sportärzte Kongress, Frankfurt.

10/2009 **F. Streckmann**, Kleber M, Gollhofer A, Mertelsmann R, Bertz H, LeifertJA.
THE POSITIVE INFLUENCE OF SENSORIMOTOR TRAINING ON PATIENTS WITH MALIGNANT LYMPHOMA RECEIVING CHEMOTHERAPY, Jahrestagung der Deutschen Gesellschaft für Hämatologie und Onkologie, Mannheim.

06/2009 **F. Streckmann,** Leifert JA, Mertelsmann R, Kleber M, Bertz H, Gollhofer A. EFFECTS OF SENSORIMOTOR TRAINING ON PATIENTS WITH MALIGNANT LYMPHOMA, European Journal of Sport Science, ECSS, OSLO, Norway.

05/2009 **F. Streckmann,** R. Mertelsmann, M. Kleber, H. Bertz and J.A. Leifert The effect of a defined in-hospital sports program on the physical, psychological and sociological aspects of patients suffering from cancer compared to patients suffering from obesity**, ACSM, Seattle, abstract published in** Medicine & Science in Sports & Exercise. 41(5):40.

05/2009 **F. Streckmann,** R. Mertelsmann, M. Kleber, H. Bertz and J.A. Leifert A matched-pair prospective study on the effect of a defined in-hospital sports program on cognitive functions in patients suffering from cancer, **ACSM, Seattle, abstract published in** Medicine & Science in Sports & Exercise: May 2009 - Volume 41 - Issue 5 - pp 295-296