

Understanding graft-versus-host disease. Preliminary findings regarding the effects of exercise in affected patients

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ABSTRACT

Advances in this century regarding allogeneic hematopoietic stem cell transplantation (allo-HSCT) have led to an expanding population of long-term survivors, many of whom suffer severe side effects, particularly those related to graft-versus-host disease (GVHD), a potentially multi-systemic disorder caused by immunoeffector donor lymphocytes that destroy host tissues. The GVHD, especially in its chronic form (cGVHD), generates considerable morbidity and compromises the physical capacity of patients. We have reviewed the main pathophysiological aspects of the disease as well as the data available on the effects of exercise in GVHD, based on animal and human patient research. Although exercise training as an adjunct therapy to improve health outcomes after allo-HSCT shows promise (particularly, this lifestyle intervention can improve physical fitness and possibly immune function while attenuating fatigue), there is a need for more randomized control trials that focus specifically on GVHD.

INTRODUCTION

Allogeneic hematopoietic stem cell transplant (allo-HSCT) is the only curative option for many patients with leukemia, primary or acquired marrow failure, primary immunodeficiency or inborn genetic diseases (378). Graft-versus-host disease (GVHD) is a frequent complication of allo-HSCT (288), and consists of the destruction of host tissues by donor effector lymphocytes. The incidence of the acute form of GVHD (aGVHD) has been estimated at 10%-80%, with symptoms usually developing 2-3 weeks post allo-HSCT, and 30-70% for chronic GVHD (cGVHD) in allo-HSCT recipients surviving beyond 100 days, with a median onset of 4-6 months following transplant (127) (see below for a definition of aGVHD versus cGVHD). Reasons for the wide variability in the incidence of both of these diseases might include individual differences in a variety of modifiable and nonmodifiable risk

factors. These include type of conditioning regimen and impact of regimen intensity, graft source, degree of human leukocyte antigen (HLA) mismatch, previous donor alloimmunization, use of total body irradiation, GVHD prophylaxis, severity of individual organ sites, female donor-male recipient, parity of female donors, or recipient age (150, 169, 176, 244, 258, 270, 393). Mortality rates of 15-40% have been reported for patients with aGVHD and 30-50% for those with cGVHD (37). Reasons for the usually higher mortality rates found in cGVHD compared with aGVHD likely include a lower magnitude of medical advances in treatment, and the more aggressive, multi-systemic nature of the chronic disease form (151, 225). In addition, GVHD causes severe morbidity, and allo-HSCT survivors with GVHD show impaired physical and social behavior, and undergo a worse physical and psychosocial recovery than survivors without this complication. Quality of life (QoL) is thus severely compromised (119, 196, 218, 367-369).

The first-line option for the treatment of GVHD, steroid therapy, has a failure rate of 30-40% (90). In effect, GVHD refractory from steroids is an unresolved clinical challenge with a high impact on both the survival and QoL of patients (3). It is therefore imperative that researchers pursue other effective therapies for the prevention and treatment of GVHD.

The multi-system benefits of regular exercise have been linked to a lower risk of numerous chronic diseases (see (114) for an in-depth review). There is indeed strong epidemiological evidence that this simple lifestyle intervention leads to lower rates of all-cause mortality, cardiovascular disease, hypertension, stroke, metabolic syndrome, type 2 diabetes, breast cancer, colon cancer, depression, and falls (216). However, the impact exercise may have to prevent GVHD, or to influence the course of the disease in affected patients, is largely unknown. This paper reviews the main features of this life-threatening disease and discusses the rationale and preliminary findings supporting the effects of exercise training in GVHD. To our knowledge, no data are available on the possible association between previous exercise habits, and the risk or severity of GVHD.

Allo-HSCT and GVHD

Allo-HSCT was first introduced to treat patients with end-stage leukemia (381) or aplastic anemia after conventional

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treatment failure, as well as to offset the toxic effects of irradiation and chemotherapy against both of these diseases (377). The process consists of the intravenous transfer of hematopoietic stem cells from a healthy donor to an immunosuppressed recipient, to regenerate normal hematopoiesis in patients in whom it is impaired or non-existent (379). The immunosuppression caused by the transplant conditioning regimen enables the grafting of donor cells, while donor T lymphocytes provide anti-tumor therapy against the host's residual malignant cells (graft-versus-tumor (or leukemia) (GVT) effect) (212). However, several complications may arise during the process. The grafted stem cells may be rejected by the recipient (host-versus-graft (HVG) effect) or, conversely, the donor immune system may act against the recipient (graft-versus-host (GVH) effect). The latter is clinically known as GVHD. Such effects were discovered in studies conducted in the mid-20th century, in which an anti-tumor cell effect of the transplanted graft (GVT effect) was observed after allo-HSCT (23, 24). However, in these studies, transplanted mice later died from a second degenerative, or wasting, disease, which caused diarrhea and weight loss, skin inflammation and liver failure/lesions. This was the first clinical description of aGVHD (25).

In parallel, bone marrow transplants were conducted in patients with malignant tumors with the objective of inducing GVT activity without developing GVHD. This strategy was, however, unsuccessful due to failure of the transplanted hematopoietic stem cells (381) and was soon followed by the technique of total body irradiation plus allogeneic bone marrow cell transplant. This new approach led to the first cure of leukemia by the group of the Nobel prize winner E. Donnall Thomas (380). Early experience was followed by further anecdotal cases, but it was not until the mid 1970s that the first epidemiological data of long-term survival were reported

for patients with acute leukemia subjected to allo-HSCT (377). Since then, allo-HSCT has been widely adopted worldwide (81) following developments made in tools designed to assess donor-recipient synergistic and competitive interactions, the selection of donors according to similarities in the human leukocyte antigen (HLA), anti-microbial therapies, cell transplant conditioning regimens and patient care (26, 137, 148). Allo-HSCT is also currently used as potentially curative treatment for many different diseases (91, 107, 140, 148, 229, 339, 374). Nevertheless, today, almost 50 years after initial studies, the challenge continues to be to maintain the GVT effect while also facilitating the grafting of donor stem cells, thus avoiding graft rejection and the complications of treatment, among which GVHD is the most frequent and life-threatening (199).

Definition and classification of GVHD

GVHD is the outcome of donor immune system cells attacking the recipient's organs (347). Donor T lymphocytes play a major role in the pathophysiology of GVHD (109). After their implant, donor T cells undergo activation upon alloantigen presentation by antigen presenting cells (APCs) and then clonally expand. Donor T cells induce damage to target organs either directly through cytolytic attack, or indirectly through the release of inflammatory mediators. As early as 1966, Billingham identified the necessary conditions for the onset of GVHD (35): (i) the graft should contain immunocompetent cells; (ii) the host should express tissue antigens not present in the donor; and (iii) the host should be incapable of organizing an effective destruction or inactivation response against the transplanted cells. A fourth postulate was added later (324): donor lymphocytes need to reach their target organs in the host.

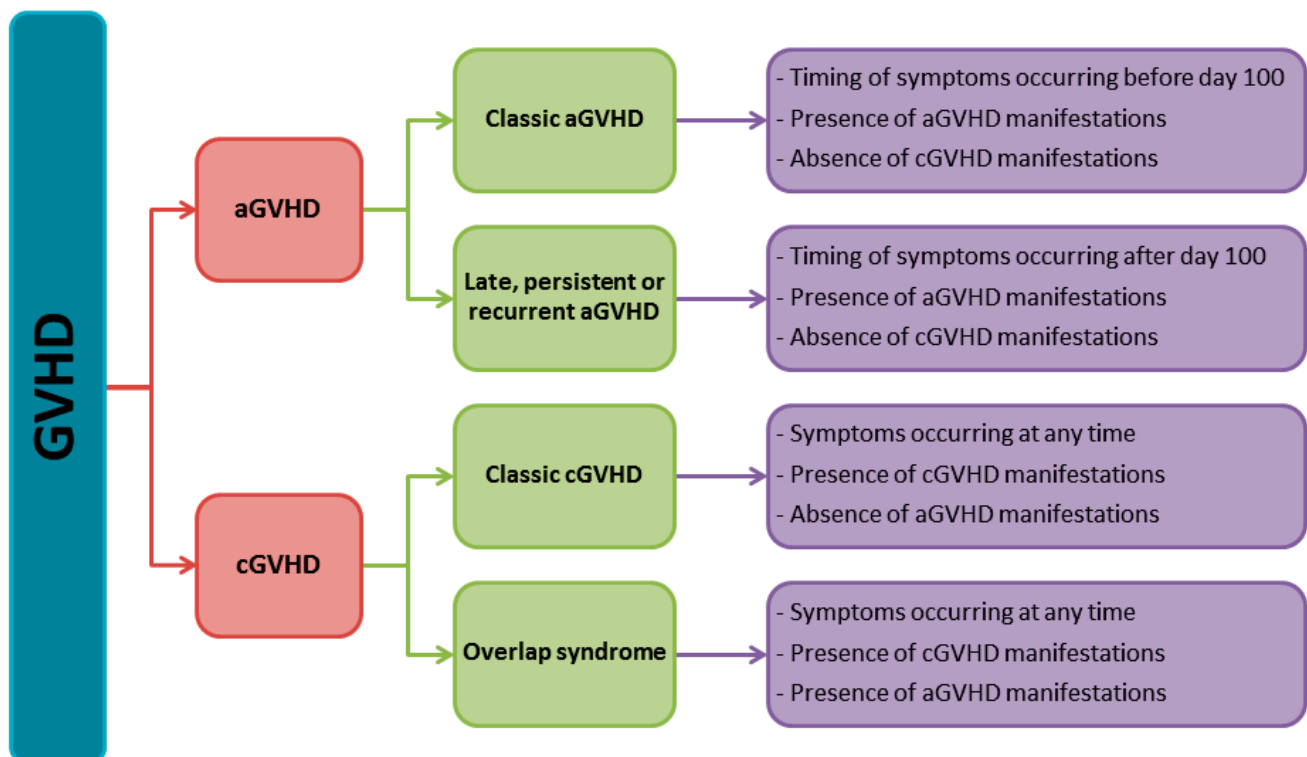


Figure 1. Clinical classification/differentiation of acute (aGVHD) and chronic graft-versus-host disease (cGVHD) according the US National Institutes of Health (NIH) (110).

In 1974, Glucksberg and co-workers classified GVHD as acute or chronic depending on its appearance before or after day 100 after transplant, respectively. However, signs of aGVHD may persist beyond 100 days post allo-HSCT and those of cGVHD may commence before the 100-day time point (397). Since then, there have been many attempts to classify this disease and, today, the accepted system is that created in 2005 by the US National Institutes of Health (NIH), based on the different clinical manifestations of GVHD (63, 110, 248, 335, 349) (see also **Figure 1**):

- 1) aGVHD (lack of findings of cGVHD)
 - a) classic aGVHD, diagnosed before day 100 following allo-HSCT or donor lymphocyte infusion showing characteristics of aGVHD;
 - b) persistent, recurrent or late-acute GVHD, showing characteristic features aGVHD diagnosed after day 100 following allo-HSCT or donor lymphocyte infusion, often after suspending immunosuppressive treatment, lacking characteristics of cGVHD;
- 2) cGVHD
 - a) classic cGVHD, showing symptoms of cGVHD yet lacking symptoms of aGVHD;
 - b) overlap GVHD syndrome, showing characteristics of both aGVHD and cGVHD.

Pathophysiology of aGVHD

The physiopathology of aGVHD is summarized in **Figure 2**. Classically, aGVHD occurs in three phases (156):

Phase I. Transplant conditioning regimen effects and APCs activation

Host tissues may be damaged by the underlying disease and/or infection before HSCT. In addition, the transplant conditioning regimen induces damaged cells to secrete pro-inflammatory cytokines [e.g., tumor necrosis factor (TNF)- α , interleukin (IL)-1, IL-6] (108, 156), endogenous non-infectious molecules known as ‘damage-associated molecular patterns’ (DAMPs) [e.g., adenosine triphosphate (ATP), heat shock proteins or mitochondria, extracellular matrix proteins such as biglycan] (237, 416, 435, 437) and chemokines (77, 413). These molecules serve as “danger signals” and are responsible for the activation of APCs, especially dendritic cells, via toll-like receptors (TLRs) and non-TLRs, enhancing GVHD (61, 156, 435). In the gastrointestinal tract, inflammatory stimuli are translocated to the bloodstream. These signals include microbial products (lipopolysaccharides and unmethylated cytosine-phosphate-guanine) or other “pathogen-associated molecular patterns” (PAMPs), furthering the cytokine cascade (61, 155, 156). Most innate immune cells express pattern recognition receptors (PRRs) and recognize PAMPs through PRRs, such as TLRs and nucleotide-binding oligomerization domain-like receptors. The binding of PAMPs by PRRs on APCs activates the innate immune response, which induces the upregulation of cytokines and MHC class II costimulatory molecules, and promotes dendritic cell migration to the T-cell compartment of lymph nodes so that antigens are presented to other immune cells (77, 81, 92, 155, 156, 237, 430).

Phase II. T lymphocyte activation

Donor T cells are recognized and activated by APCs in secondary lymph nodes (11, 81, 267) and then migrate to their target organs where they can cause tissue damage (73, 241).

II.1. Antigen presentation and T cell activation

In the setting of an HLA-identical donor allo-HSCT, the host’s APCs activate donor T lymphocytes through the presentation of minor histocompatibility antigens (miHAs) by HLA proteins to T cell receptors (14, 20, 38, 108, 139, 211, 226, 342, 348). This is the first activation signal, but costimulatory molecules (second signal) are needed for a full immune response. In an HLA-non-identical allo-HSCT, aGVHD may be induced both by CD4⁺ and CD8⁺ (class II and I major histocompatibility antigen (MHC) coreceptors, respectively) due to the miHAs disparity (108, 424). In mouse models in which donor/recipient genetic differences are controlled for, if the disparity between T lymphocytes and APCs affects class I antigens, cytotoxic/suppressor CD8⁺ lymphocytes are activated. By contrast, if this disparity affects class II antigens, the cells activated are cooperator CD4⁺ T cells (202). When T cells are exposed to antigens in the presence of adjuvants such as lipopolysaccharide, their migration and survival are enhanced (104).

II.2. T lymphocyte proliferation and differentiation

T lymphocyte activation leads to their differentiation into various T cell phenotypes such as effector, memory, regulatory or helper (Th1, Th2, Th17), among other subsets (78, 409). Differentiation into T helper cells is determined by the cytokines present in the environment during the activation process (third signal): (i) interferon (IFN)- γ (228) and IL-12 (165) promote the development of Th1 cells, which express IFN- γ , lymphotoxin, IL-2 and TNF- α (266); (ii) IL-4 and IL-2 promote the development of Th2 cells (164, 215, 338, 366), which express IL-4, IL-5, IL-9, IL-10, IL-13 and TNF- α (266); and (iii) transforming growth factor (TGF)- β and IL-6 promote the Th17 cell phenotype (34, 201, 240, 396) expressing IL-17A, IL-17F, IL-22 (149, 286, 396) or IL-21 (278, 438). Th1 cytokines (IFN- γ , IL-2, TNF- α) have been correlated with aGVHD (103, 106, 311). The balance between Th1/Th2 subsets as well as other subsets such as Th17 and the production of cytokines affects the manifestations of GVHD (432). Although there is some controversy as how Th1/Th2 balance might affect GVHD and various contributions of each of these elements are still under investigation, some explanations have been postulated, as briefly summarized below. aGVHD has been proposed to be mediated by Th1 cells (102), whereas Th2 cells have been reported to suppress aGVHD (208). Yet Th2-biased donor cells deficient in signal transducer and activator of transcription 4 gene (STAT4^{-/-}) can induce lethal GVHD (276). On the other hand, although the absence of Th17 cells can exacerbate aGVHD (433), Th17 cells have been shown to augment GVHD in some circumstances (76, 185), with in vitro-generated Th17 cells mediating lung and skin GVHD (57). Yi et al., (2009) proposed that Th1 cells can down-regulate Th2 and Th17 cells or vice versa (432). Thus, in the absence of IL-17 or IL-4, Th1 differentiation is augmented, and tissue damage in the gut and liver is preferentially exacerbated. In contrast, in the absence of IFN- γ , both Th2 and Th17 differentiation is augmented, and tissue damage in

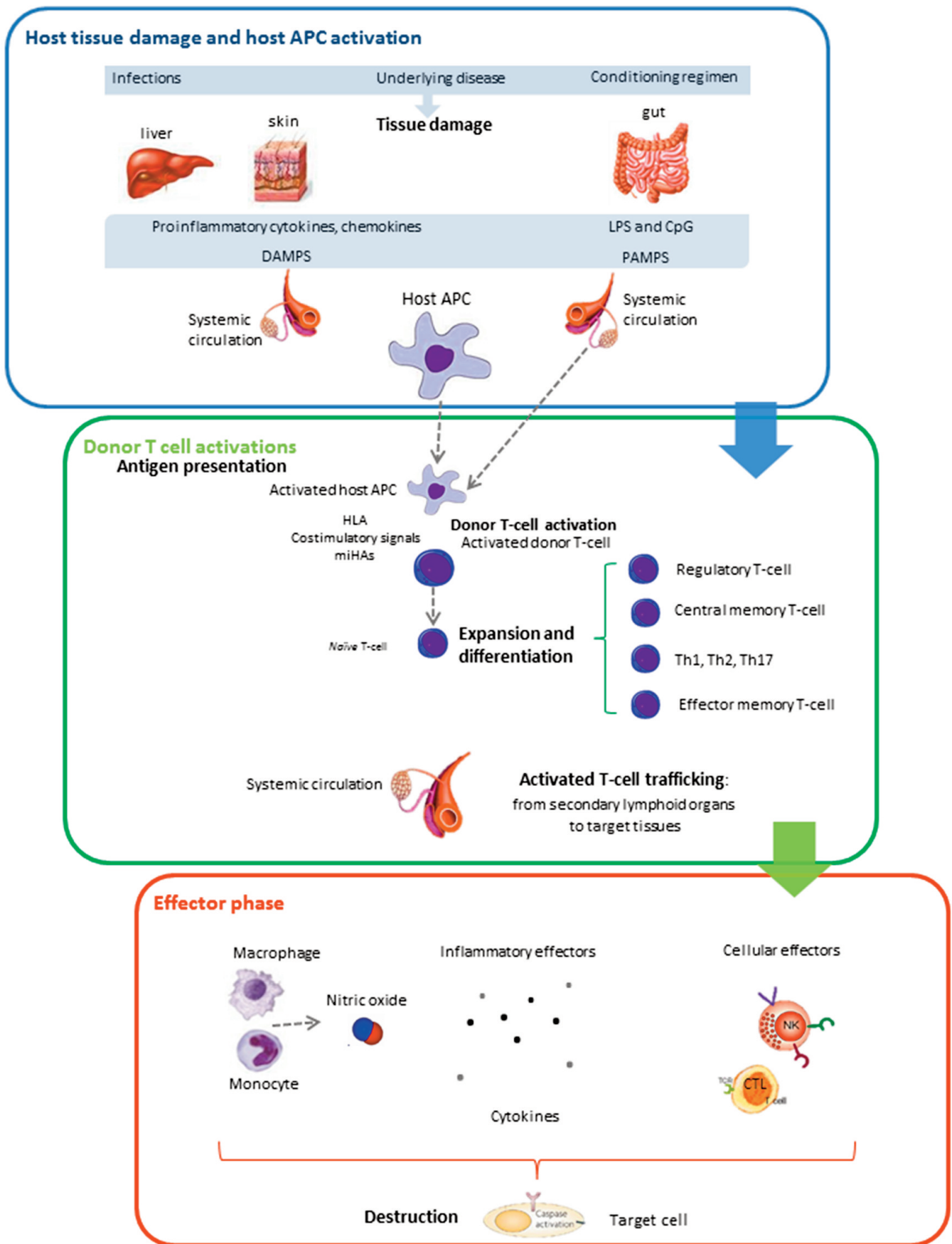


Figure 2. Pathophysiology of acute graft-versus-host disease (aGVHD).

The mechanisms implicated in the pathophysiology aGVHD are summarized below. Phase I: infections, the disease itself and the conditioning regimen damage host tissues (mostly liver, skin and intestinal mucosa). Phase II: activation of donor T cells against host antigens and subsequent clonal T-cell expansion. Phase III: release of inflammatory cytokines leading to further host tissue damage (104).

Symbol: \dashrightarrow , danger signals. Abbreviations: APC, antigen-presenting cells; CpG, unmethylated cytosine-phosphate-guanine; CTL, cytotoxic T lymphocytes; DAMPS, damage-associated molecular patterns; HLA, human leukocyte antigen; LPS, lipopolysaccharide; NK, natural killer; PAMPS, pathogen-associated molecular patterns; Th1, T cell helper 1; Th2, T cell helper 2; Th17, T cell helper 17; NK, natural killer.

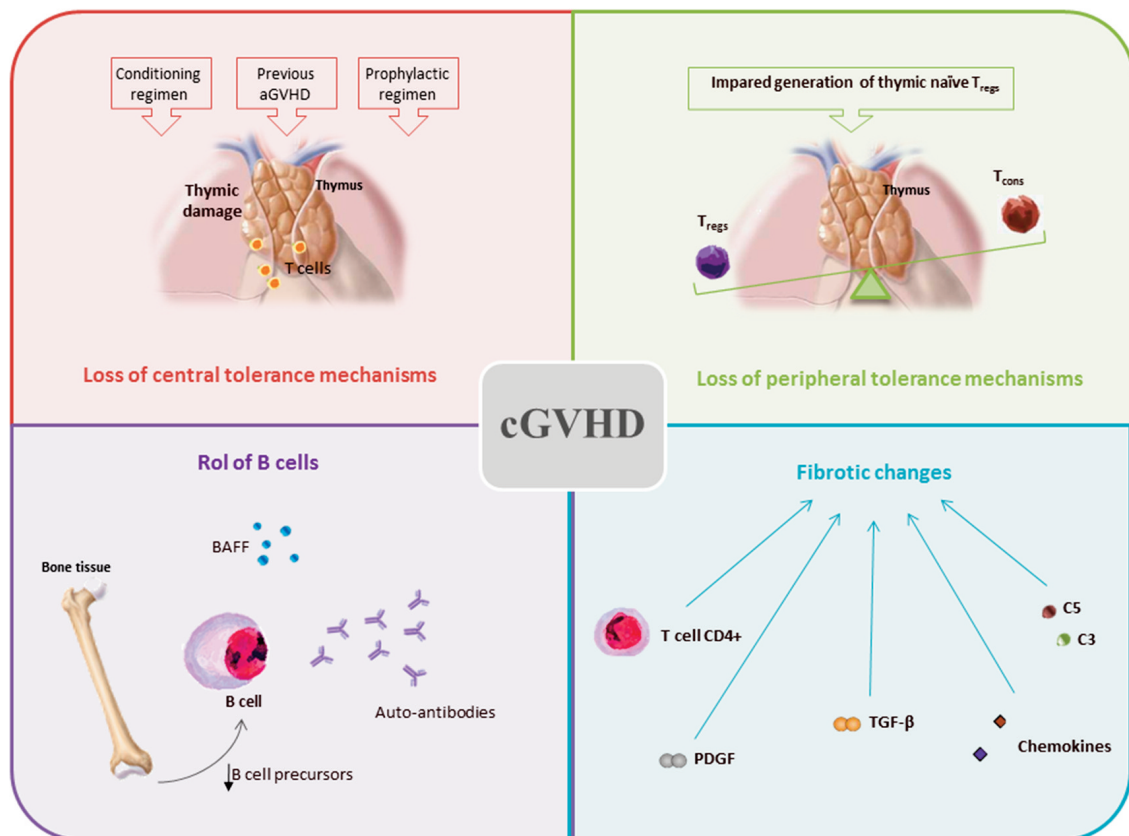


Figure 3. Pathophysiology of chronic graft-versus-host disease (cGVHD).

The mechanisms implicated in the pathophysiology cGVHD are summarized below. First, thymic damage alters the central tolerance mechanisms during immune reconstitution, producing cGVHD. Further, the thymus production of naive regulatory T cells (T_{regs}) is impaired, also causing cGVHD as well as loss of peripheral tolerance. As for the implication of B cells, patients with cGVHD have high levels of B cell activating factor (BAFF), a high prevalence of auto-reactive antibodies, poor recovery of B cell levels, and prolonged immunodeficiency. Finally, fibrotic changes also occur due to several factors such as complement factor 3 and 5, chemokines, CD4+ T lymphocytes, transforming growth factor (TGF)- β 1 and deregulation of platelet-derived growth factor (PDGF).

Abbreviations: BAFF, B-cell activating factor; C3, complement component 3; C5, complement component 5; T_{cons} , conventional T cells; TGF- β , transforming growth factor beta; Tregs, regulatory T cells; PDGF, platelet-derived growth factor.

lung and skin is exacerbated (432). Absence of both IFN- γ and IL-17 leads to further augmentation of Th2 differentiation and exacerbated lung damage (idiopathic pneumonia) (432). Lack of both Th1 and Th2 cells further augments Th17 differentiation and exacerbates skin damage. Therefore, the balance among Th1, Th2 and Th17 effector subsets plays an important role in regulating T-cell immune response and, neutralizing either Th1, Th2 or Th17 cytokines may lead to biased Th1, Th2 or Th17 differentiation and thus can cause organ-specific tissue damage (432).

II.3. T cell trafficking

Activated T cells migrate to secondary lymph organs and target tissues through a combination of chemokine-receptor, selectin-ligand and integrin-ligand interactions (73, 96, 267, 268, 285, 324, 394, 405, 414, 426, 427). For example, chemokine ligand 2 (CXCL2)-5, CCL9, CCL11, CCL17 and CCL27 are overexpressed in the liver, spleen, skin and lungs during aGVHD (427, 428). T cells with chemokine receptors (CCR)3 and CCR5 cause aGVHD in the gut and liver (95, 268, 426).

Phase III. Cellular and inflammatory effects

GVHD culminates with cytotoxic effects mediated by different processes:

III.1. Cellular effectors

The main cellular effectors of aGVHD are cytotoxic T lymphocytes and natural killer (NK) cells (182, 391). The effector lysis mechanisms employed by cytotoxic T lymphocytes are the pathways FAS/FASL, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and perforin/granzyme B (42, 45, 46, 182, 329, 331, 391, 413, 429, 439), though other pathways may exist (81).

III.2. Inflammatory effectors

Cell damage is aggravated by inflammatory mediators including IFN- γ , TNF- α (45, 156, 300) and IL-1 (2). Microbial products filtered by the gut mucosa trigger the production of cytokines (156, 171).

III.3. Other factors

Nitric oxide produced by monocytes/macrophages impairs the cell proliferation needed for damaged epithelial tissues to heal (206, 273).

Pathophysiology of cGVHD

The pathophysiology of cGVHD is summarized in **Figure 3**. Chronic GVHD was first described as a disease mediated by Th2 lymphocytes (307, 372), although this idea is not fully supported because it may be caused by Th1 cytokines (22, 111, 279, 314, 438). While several studies have revealed the

important role played by the Th1/Th2 balance (44, 167, 272, 276, 306, 340, 413), others suggest different cytokine profiles depending on the disease stage (320). Th17 cells (84, 230, 277) and auto-antibodies (436) can also cause cGVHD, though the spectrum of Th17 cells varies according to whether the cells are classic or alternative Th17 cells (4, 86, 130, 223, 297). To some extent, the pathophysiology of cGVHD resembles that of an autoimmune disease in which auto- and allo-reactive T and B lymphocytes intervene (107). However, it differs from the pathophysiology of aGVHD (384) and several theories for its development exist.

Central tolerance failure. The thymus damage caused by the conditioning regimen, aGVHD or the prophylaxis regimen

lead to dysregulation of the patient's central tolerance mechanisms during immune reconstitution following cell transplant, giving rise to cGVHD (356). During the early recovery stage, mature T cells obtained from the donor and expanded in a thymus-independent manner are responsible for the development of the disease. During late recovery, T cells generated *de novo* from the donor's hematopoietic stem cells through the host's thymus gland will condition the pathophysiology of cGVHD (160, 203). Although the T cells produced in this way should not attack tissues expressing autoantigens, impaired immunological tolerance to these autoantigens leads to the autoimmune characteristics of cGVHD (325). Although the CD4⁺ T cells generated *de novo* from the donor stem cells seem to

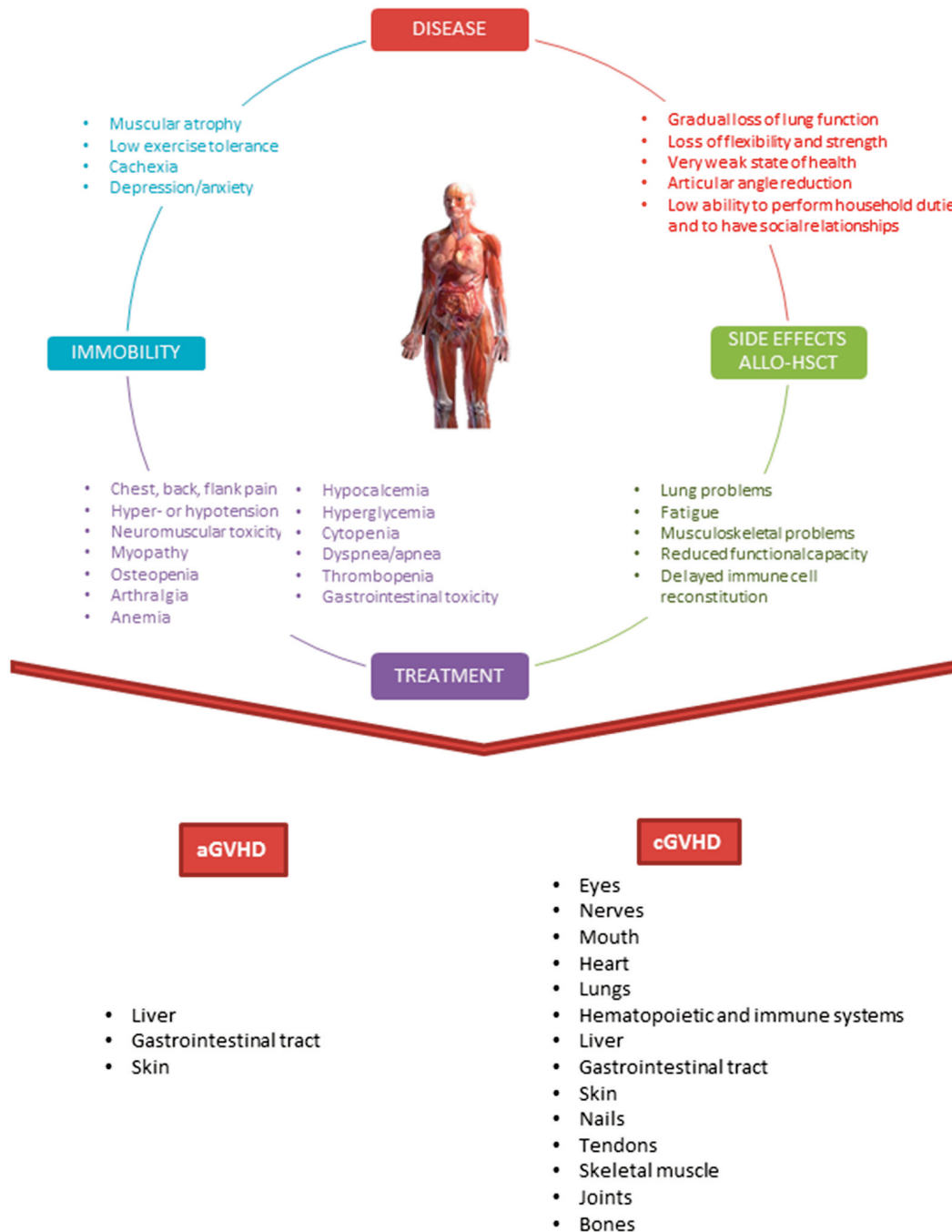


Figure 4. Main clinical features of acute (aGVHD) and chronic graft-versus-host disease (cGVHD). Abbreviation: allo-HSCT, allogeneic hematopoietic stem cell transplant. Patients with GVHD are affected at the multi-system level, which leads to a debilitated physical condition with a subsequent decrease in the ability to cope with activities of daily living. Patients' health status and physical condition further deteriorate in the mid and long-term by the pharmacological treatment they receive, which induces muscle toxicity (i.e., due to high doses of immunosuppressant drugs). The muscle tissue also deteriorates as a result of bed rest, resulting in muscle atrophy and eventually in cachexia. All together, these phenomena severely impair the patients' well-being and quality of life.

mediate conversion from aGVHD to cGVHD (97), the latter is also produced without being preceded by aGVHD. However, the host's thymus is not needed to induce cGVHD, because autoreactive quiescent T and B cells in transplants from non-autoimmune donors may also be activated and expanded to cause cGVHD (436).

Regulatory T cells (T_{regs}) and cGVHD. T_{regs} are a T-cell subset marked by a $CD4^+ CD25^{hi} Foxp3^+$ phenotype. Its deterioration has been associated with peripheral tolerance loss, autoimmunity and with cGVHD (48, 76, 436, 440). During the lymphopenia period, thymus production of naïve T_{regs} is impaired and the T_{regs} generated show a memory phenotype (374). Initially T_{regs} undergo greater proliferation than conventional T cells (T_{cons}), but this expansion is offset by their greater susceptibility to apoptosis (252). This determines that in patients who show chronic $CD4^+$ cell reduction, the balance T_{regs}/T_{cons} is disrupted, and this has been linked to a high incidence of extensive cGVHD and peripheral tolerance loss (252).

B lymphocytes and cGVHD. The role of B lymphocytes in cGVHD has been identified in mice (336) and humans (55, 72, 180, 189, 190, 195, 308, 309, 403, 434), and several authors have described the factors that affect B cell subsets in the development of this disease (101, 259, 289, 352, 382, 436, 441). Patients with cGVHD show high levels of B cell activating factor (BAFF) (43, 59, 121, 327, 328) such that the BAFF/B cell ratio is elevated (210, 328). Several factors have been correlated with the presence and severity of cGVHD: a high prevalence of autoreactive antibodies (19, 27, 43, 75, 93, 105, 121, 142, 186, 192, 249, 260, 264, 289, 304, 317, 350, 365, 373, 398, 410), the relationship among genotypes of the Fc receptor-like 3 gene (*FCRL3*) (345) (335) and an increased number of B cells strongly expressing TLR-9 (344). Moreover, these patients show poor recovery of B cell numbers and prolonged immunodeficiency (9, 62, 101, 360, 361). However, a return to homeostasis is essential (261) and B cell precursor depletion can be a predictor of cGVHD development. In addition, elevated numbers of these cells in the bone marrow or an increase in naïve B and transition cells in blood can predict the success of allo-HSCT (101, 225, 328). Finally, depleted naïve B and transition cell compartments enhance the autoreactivity of B cells with antigenic experience in these patients (16, 172, 328).

Fibrotic changes. Various soluble factors play a role in the course of cGVHD. Complement factor 3 is deposited at the dermal-epidermal interface in patients with cGVHD (386), and complement factor 5 has been identified as a quantitative trait that modifies liver fibrosis (157). Chemokines have been attributed a role in the pathogenesis of systemic sclerosis as potent chemoattractants of leukocytes and collaborators of pro-fibrotic cytokines (18, 275, 438). $CD4^+$ T lymphocytes produce fibrotic lesions in the skin, liver, exocrine glands and thymus (1, 8, 88, 94, 126, 371, 389, 425). Elevated plasma levels of transforming growth factor (TGF)- β 1 have been correlated with the development of hepatic and pulmonary fibrosis (12, 21, 269). In addition, skin fibrosis and the overregulation of TGF- β 1 and mRNA for collagen have been observed in human and murine models of scleroderma (175). In the mouse, TGF- β has been related to sclerodermal skin changes (82, 254), and in humans, elevated levels of this growth factor have been detected in patients with cGVHD (227). TGF- β

plays a role in the generation and maintenance of peripheral T_{regs} and in improving their suppressive actions (321). Finally, the dysregulation of platelet-derived growth factor (PDGF) signaling has been related to atherosclerosis, pulmonary hypertension and fibrosis. Anti-PDGF receptor antibodies recognize the native PDGF receptor inducing tyrosine phosphorylation, the build-up of reactive oxygen species, the expression of collagen type I genes and conversion of the myofibroblast phenotype in normal human primary fibroblasts, which leads to sclerosis (27). These antibodies have been detected in patients with scleroderma (27) and in all patients with extensive cGVHD (365).

CLINICAL FEATURES

GVHD features a heterogeneous pattern of clinical presentation (see **Figure 4** for a schema). The three main target organs of aGVHD are the skin, gastrointestinal tract and liver (85, 105, 107, 122, 134, 156, 245, 255, 274, 353, 354, 400) though the thymus (60, 207, 312, 411) and lungs (81); eyes and kidneys (362) may also be affected. In contrast, the clinical manifestations of cGVHD resemble those observed in autoimmune diseases (141, 277). Although considered to be a multi-organ disorder, initial signs of disease appear in the oral mucosa before affecting other organs such as the skin, nails, eyes, muscles, lungs, tendons, gut, liver, joints, nerves, serosal surfaces, heart and immune system (79, 100, 110, 129, 141, 143, 153, 154, 204, 280, 307, 349, 350, 395).

Pharmacological treatment

All allogeneic transplant patients receive prophylaxis against GVHD. The commonly used regimens for prevention of aGVHD consist of a combination of a calcineurin inhibitor, either cyclosporine-A (CsA) or tacrolimus, and an anti-metabolite (359). However, these interventions that prevent aGVHD are not effective in preventing cGVHD. Strategies using anti-thymocyte globulins for *in-vivo* T-cell depletion show promise but no benefit on survival (112). Despite prophylaxis, many patients suffer from acute or cGVHD.

Corticosteroids (prednisone/6-methylprednisolone) are the standard-of-care first-line treatment for both acute (158, 236, 245, 258, 393, 412) and chronic forms of GVHD (110, 153, 364, 398, 421). The treatment protocol for each patient varies in terms of the dose, regimen and length of therapy. First-line treatment produces a response in fewer than 50% of patients with aGVHD and in 40–50% of patients with cGVHD depending on initial disease severity (127). This has meant that research efforts have been directed towards developing additional therapies combining corticosteroids with other agents (see **Table 1** for more detailed information). However, trials performed to date have shown no benefits when other agents are added to corticosteroids (355). Moreover, steroids have numerous side effects (e.g., osteoporosis, osteonecrosis, diabetes mellitus, hypertension, and can be detrimental in a growing child), which compromise the QoL of patients (5, 120, 127, 219, 337). There is no standard second-line treatment for aGVHD or cGVHD. Numerous therapeutic agents have been assessed to treat aGVHD and cGVHD (see **Table 1** for more details) but no single treatment has proven better

Table 1: Summary of pharmacological therapies against acute (aGVHD) and chronic graft-versus-host disease (cGVHD)

		aGVHD	Refs.		
First line therapies	Standard of care	Corticosteroids (prednisone/6-methylprednisolone)	(158, 236, 245, 258, 392, 393, 412)		
		Etanercept	(6, 41, 224, 388)		
	Methylprednisolone combined with either	Mycophenolate mofetil (MMF)	(7, 28, 193)		
		Denileukin	(7, 343)		
		Pentostatin	(7, 40)		
		Infliximab	(67)		
		Antibodies against IL-2R	(54, 222)		
		Horse anti-thymocyte globulin (ATG)	(40, 70)		
		Mesenchymal stem cells (MSC)	(187)		
		ATG	(15, 191, 233-235, 246, 319, 392)		
Second-line therapies	Alone	Alefacept	(383)		
		Alemtuzumab (Campath)	(136, 250, 333, 334)		
		Beclomethasone	(162)		
		IL2 receptor antagonists such as daclizumab	(10, 217, 291, 302, 418)		
		Inolimomab	(32, 71, 125, 301)		
		Denileukin diftitox	(161, 343)		
		Basiliximab	(123, 251, 332, 407)		
		Antitumour necrosis factor antibodies such as infliximab	(67, 69, 290)		
		Etanercept	(7, 51, 67)		
		ECP	(64, 144, 293, 326, 390)		
Combinations		MMF	(124, 144, 146, 193, 205, 257, 293, 298)		
		Sirolimus	(33, 163)		
		Pentostatin	(40, 299)		
		MSC	(99, 152, 187, 213, 214, 271, 292, 313, 401, 402, 404)		
		Horse ATG + etanercept with or without MMF	(188)		
		Daclizumab, infliximab and horse ATG	(357)		
		Daclizumab + etanercept	(422)		
		Daclizumab + infliximab	(305)		
				cGVHD	Refs.
		First line therapies	Corticosteroids alone or combined with:	Calcineurine inhibitors	(17, 198, 363, 364)
Thalidomide	(17, 197)				
Sirolimus	(46, 58, 308)				
MMF	(50, 231, 247)				
Pentostatin	(40, 135)				
Rituximab	(72, 403, 434)				
Hydroxychloroquine	(133)				
Methotrexate (MTX)	(133)				
Extracorporeal photophoresis (ECP)	(66, 117, 118, 147, 184)				
Second-line therapies	Alone			Azathioprine	(98)
		Alemtuzumab	(322)		
		Alefacept	(341)		
		Etanercept	(51)		
		Infliximab	(351)		
		Oral beclomethasone	(162)		
		Hydroxychloroquine	(133)		
		Thalidomide	(47, 209, 287, 318, 399)		
		Clofazimine	(221, 323)		
		Cyclophosphamide	(303)		
Combinations:		Steroid pulse	(5)		
		Sirolimus	(69, 180, 181)		
		ECP	(13, 36, 39, 53, 66, 80, 83, 117, 118, 128, 138, 145, 147, 183, 184, 257, 284, 294-296, 316, 326, 330, 337, 390)		
		Imatinib	(238, 239, 265, 282, 283, 358)		
		MMF	(28, 29, 50, 52, 124, 193, 205, 220, 231, 263)		
		Rituximab	(55, 56, 72, 190, 195, 262, 281, 308, 309, 346, 370, 375, 403, 434)		
		mTOR inhibitor	(178, 310)		
		MSC	(415)		
		Thoracoabdominal irradiation	(49)		
		Pentostatin	(173, 174, 299)		
Retinoids (Am80, etretinate/isotretinoin)	(242, 277)				
Calcineurin inhibitors	(58, 387)				
MTX	(87, 132, 166, 168, 179)				
Prednisone + MMF + sirolimus or ECP	(50, 68, 117, 147, 180, 231)				
Isotretinoin + PUVA	(131)				
Pulse cyclophosphamide + MMF + steroids	(253)				
Infliximab + daclizumab	(315)				

than others. All are associated with high failure rates and cause severe toxic effects (127, 243, 244). The evaluation of therapeutic options is complicated by the heterogeneous nature of the patient group (in terms of organ involvement, age, conditioning regimens, GVHD prophylaxis), the lack of a clear definition of corticosteroid-refractory disease, availabili-

ty of therapies, financial considerations, inconsistent treatment end points, preferences and experience of treating physicians, and secondary effects of treatment. The outcome of refractory aGVHD is poor, including a high morbidity and mortality figures approaching 80% (90, 392). Response rates to agents against cGVHD range from 20% to 70% (420).

Non-pharmacological treatment: rationale for exercise interventions

Clearly there is an urgent clinical requirement to optimize current therapies and develop novel treatments for GVHD based on the patient's individual needs. The heterogeneous nature of its manifestations calls for a multidisciplinary approach to patient management including input from physiotherapists, microbiologists, occupational therapists, dieticians, pharmacists and psychologists. There is strong epidemiological evidence that regular physical exercise (e.g., brisk walking, jogging) leads to a lower risk of all-cause mortality, cardiovascular disease, hypertension, stroke, metabolic syndrome, type 2 diabetes, breast cancer, colon cancer, depression and falls (216). Exercise has therapeutic benefits on many systems in the body because working skeletal muscles produce numerous secreted factors ('myokines') with potential drug-like effects such as IL-6 (an anti-inflammatory cytokine when released during exertion), secreted protein acidic and rich in cysteine (SPARC) or calprotectin (with potential anti-tumorigenic effects) (see Fiuza-Luces et al. for an extensive review (114)). Exercise also stimulates the release of stem cells with a strong regenerative potential from their source of origin (e.g., bone marrow) to the bloodstream (114). Moreover, the beneficial effects of moderate-intensity exercise on immune function, at least in non-immunocompromised individuals, have been well established (406). Because regular physical exercise has positive effects on the chain of interactive events that occur from the time of central nervous system stimulation to skeletal muscle contraction, it increases a person's ability to cope with activities of daily living, and improves cardiorespiratory capacity (commonly expressed as peak oxygen uptake, VO_{2peak}) in virtually all population groups (232). Finally, exercise is a lifestyle intervention that is also recommended for all patient groups, including children and adult recipients of HSCT (423). Thus, it is of medical interest to assess the effects of exercise in GVHD.

Exercise interventions in GVHD (I): Murine model studies

The present authors sought to determine the effects of a moderate-intensity exercise (treadmill running) program on GVHD in mouse models of aGVHD (115) and cGVHD (113, 115, 116). No other data are available on exercise and murine models of GVHD. In one of our studies (115), we addressed the effects of exercise (treadmill running) in the absence of CsA or any immunosuppressive treatment in a murine model of aGVHD and one of cGVHD. In the setting of aGVHD, mice subjected to 12 weeks of training showed an improved functional capacity and clinical course of disease relative to controls. At the muscle level, these mice featured higher citrate synthase activity (a classic indicator of mitochondrial oxidative capacity), although no effects were detected on the phospho-p70 S6 kinase/p70 S6 kinase ratio (an indicator of muscle anabolic state). However, both experimental animals and controls showed a similar response throughout the study in terms of rates of survival, immune cell recovery, systemic inflammation and target organ (skin, liver, intestine) damage. In the cGVHD model, the exercise group showed less worsening of physical capacity, accompanied by increases in citrate synthase activity. In addition, immune recovery was unmodified, such that no

detrimental effects were produced on the GVT effect or on infections provoked by the immunocompromised state of the mice. These benefits did not appear to be linked to a possible anti-inflammatory effect of exercise, though reduced IL-6 levels were recorded in the exercise intervention group. However, the exercise intervention failed to affect variables such as survival, disease progression or target organ histological findings.

In another of our studies (116), we reported our analysis of the effects of exercise added to the standard immunosuppressive therapy used for this disease (CsA) in the same murine model of cGVHD. Mice in the intervention group showed significantly higher survival rates, a reduced resting heart rate (an indicator of cardiovascular fitness), and an improved disease course compared to control animals. Further, the exercise program led to lower TNF- α and IL-4 levels, reflecting a weaker inflammatory state. Immune reconstitution was improved, with expanded B lymphocytes and CD4 T lymphocyte compartments. At the muscle tissue level, citrate synthase, respiratory chain complex activities and the phospho-p70 S6 kinase/p70 S6 kinase ratio failed to show an improvement with exercise training, probably due to the detrimental muscle effects of CsA. Finally, similar histological observations were made in the disease's target organs in mice surviving the study period.

In another study (113), we examined the role of autophagy as a possible mechanism for cardiac adaptations produced in response to exercise in mice with cGVHD that survived until the end of the study described above (116). Autophagy is an intracellular quality control mechanism of degradation and recycling of damaged macromolecules and organelles that is currently gaining attention because of its potential involvement in longevity and defense against chronic diseases. After 12 weeks of training, levels of several markers of autophagy (autophagy related gene 12 (Atg12), microtubule-associated protein 1 light chain 3 alpha (LC3B), unc-51-like kinase 1 phosphorylated at serine 555 (phospho-ULK1 S555) and sequestosome 1 (SQSTM1/p62), were elevated, as were the activities of the antioxidant enzymes catalase and glutathione reductase relative to those recorded in control mice. These benefits of exercise were observed in the absence of modifications to the proteins involved in mitochondrial dynamics and heart muscle contraction, and thus failed to affect cardiac structure and function. No significant differences were detected in control and experimental animals in terms of electron transport chain complexes or citrate synthase activity.

Exercise interventions in GVHD (II): Human studies

Patients experience considerable levels of physical and psychological distress before, during and after allo-HSCT. In addition to GVHD, muscle atrophy, decrements in physical performance, cachexia, pneumonia, psychological impairments and mortality are more pronounced in the allogeneic compared to the autologous transplant setting (159, 200, 408, 431). Physical exercise has recently been purported to ameliorate some of these treatment-related side effects and enhance the rehabilitation process in allo-HSCT patients (419). Despite this, however, no research effort to date has characterized the effects of exercise in patients with GVHD. Existing exercise training interventions have targeted patients undergoing allo-HSCT, among whom patients with GVHD have sometimes been included (**Table 2 see next side**). Among the

beneficial effects of exercise reported in these studies were positive effects on QoL (30, 177, 419), improvements in endurance/aerobic capacity (30, 31, 74, 177, 419), muscular strength (30, 31, 74, 177, 256, 419), functional capacity (30, 177), and perceptions of fatigue, physical emotional and social well-being (419). Exercise training has also been shown to reduce perceived pain scores and subdue anxiety, depression and aggressive or hostile behavior (419). Although the patient cohorts and experimental designs employed in these studies were very heterogeneous, both aerobic and resistance based exercise appeared to positively influence various outcomes in allo-HSCT inpatients, as well as outpatients.

The vast majority of studies that have examined the effects of exercise after allo-HSCT have involved inpatient cohorts (**Table 2 see next side**). In a small retrospective study of allo-HSCT patients that received myeloablative conditioning regimens (i.e., chemotherapy, irradiation), an inverse correlation was found between the level of physical activity performed during hospitalization (number of steps taken daily by the patient) and time to discharge (170). This relationship was observed regardless of whether or not the patient experienced GVHD, infections or cytomegalovirus reactivation. Interestingly, however, physical activity did not impact the length of hospitalization in patients receiving non-myeloablative conditioning regimens.

Exercise training studies involving allo-HSCT outpatients are relatively uncommon. A home-based aerobic exercise training intervention was administered to cancer survivors (at least 6-months post allo-HSCT), although only ~31% of these patients received an allo-transplant (417). Patients performed 20-40 minutes of activity at 40-60% of predicted heart rate reserve 3 to 5 times per week for 12 weeks. Although lacking a control group, scores on aerobic fitness, fatigue severity and physical well-being improved after exercise training, with no adverse events being reported. Another study involving allo-HSCT outpatients (385) enrolled 10 patients with severe cGVHD and *bronchiolitis obliterans* syndrome, which is the most common and serious pulmonary complication of cGVHD (63, 65). The 8-week pulmonary rehabilitation program, which involved both strength and aerobic based exercise session ~3 times per week, improved 6-minute walk distance, exercise tolerance, subjective symptoms of dyspnea and QoL scores (385). To our knowledge this is the only study conducted to date in which all participants had some form of GVHD (385).

The diverse nature of the exercise training studies involving allo-HSCT patients makes it difficult to draw any firm conclusions pertaining to how physical exercise may benefit a patient with GVHD. Although no study reported an adverse event as a direct result of testing or exercising, safety issues or the feasibility of performing exercise training interventions in patients with GVHD were not clearly confirmed in most of these studies. Combining these studies is challenging due to study limitations and the disparate nature of the patient cohorts and experimental designs. These include small sample sizes, a wide range of different outcomes and measurements, varying types of interventions, different starting and end points, the duration, frequency and intensity of the different exercise components, different proportions and severity of GVHD patients, the presence or absence of a control group, or varying standard care regimes used in controls, among others.

Although exercise training shows promise, there is a critical need for more randomized clinical trials to determine if exercise is capable of ameliorating the detrimental effects of both acute and cGVHD in humans. Although exercise has been shown to have profound immunologic effects and GVHD is primarily an immunoreactive disorder, it is surprising that very few studies have focused on the effects of exercise on immunological outcomes in the allogeneic transplant setting. In one randomized control trial involving allogeneic bone marrow transplant patients, a series of bed exercises (performed 30 minutes daily for 6-weeks) increased total lymphocyte counts by 40.9 cells/ μ l compared to a decrease of 640.7 cells/ μ l in the non-exercising control group (194), without affecting the composition of CD4⁺ and CD8⁺ T-cell subsets. As immune reconstitution is a major determinant of prognosis and progression-free survival after allo-HSCT (89, 376), further randomized control trials exploring the effects of exercise training on immune reconstitution against viruses and tumors in patients with both acute and cGVHD would be illuminating.

CONCLUSION

Since exercise training as an adjunct therapy to improve health outcomes after allo-HSCT shows promise, there is a critical need for more randomized control trials that focus specifically on GVHD. While outcome measures such as hospitalization time, exercise tolerance, physical functioning and emotional and social well-being are all important, there is also a need to explore potential mechanisms underpinning the beneficial effects of exercise. For instance, it remains to be seen in human models of GVHD if exercise training can alter cytokine profiles and regulatory T-cell function, improve immune reconstitution to viruses and tumors, or dampen the activity of alloreactive T-cells.

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Table 2: Summary of exercise interventions in graft-versus-host disease (GVHD)

REFERENCE	DESIGN	PATIENTS				INTERVENTION	CONTROL		OUTCOME VARIABLES	MAIN RESULTS
		Intervention group	Control group	Intervention group	Control group		Passive mobilization	active		
Baumann, Kraut et al., 2010 (30)	Pilot RCT with inpatients	Sample size (N)	32	32	<p>Aerobic training (cycle ergometer) Total duration: from day -6 until 1 day before the hospital discharge Frequency: daily during aplasia (2 sessions/day) and 5 sessions/week after engraftment. Time/session: 10-20 min. Intensity: 80% of peak wattage in WHO-test.</p> <p>ADL-training (walking, stepping and stretching) Total duration: during conditioning, not during aplasia, and after engraftment. Frequency: 5 sessions/week Time/session: 20 min Intensity: "slightly strenuous" to "strenuous" (Borg scale).</p>	<p>Passive mobilization (gymnastics, stretching, massages) Total duration: from day +1 until 1 day before the scheduled discharge from hospital. Frequency: 5 sessions/week. Time/session: 20 min. Intensity: "not strenuous" (Borg scale).</p>	<p>Endurance performance peak wattage in modified WHO test.</p> <p>Muscle strength (isometric test in knee extensor muscles)</p> <p>QoL</p> <p>EORTC QLQ-C30 questionnaire</p> <p>Hematological variables leucocytes, platelets, hemoglobin and neutrophil engraftment</p> <p>Lung function IVC and FVC</p>	<p>Endurance performance (peak watts, test time) remained nearly constant in the intervention group but decreased in controls ($p=0.004$). The <i>relative endurance</i> ($\text{watts}\cdot\text{kg}^{-1}$) increased in the former but decreased in the controls ($p=0.031$). The muscle strength performance decline was greater in the controls (-24%) than in the intervention group (-10%) during hospitalization. At the time of discharge, the intervention group showed 13% higher strength compared to the controls ($p=0.002$). At the time of discharge, the intervention group rated higher their global QoL ($p=0.037$) and physical functioning ($p=0.039$) compared to the controls. The hematological variables declined in both groups but there was no difference between them. The lung function values did not change during the study period in either group.</p>		
		Age (years; mean±SD)	44.9±12.4	44.1±14.2						
		Sex (N; male/female)	21/11	14/18						
		HSCT (N)								
		Autologous	9	9						
		Related allogeneic	5	11						
		Unrelated allogeneic	18	12						
		Conditioning regimen (N)								
		TBI-based	17	14						
		Not TBI-based	6	9						
Full intensity	18	15								
Reduced intensity	5	8								
Patients with GVHD (N, %)	13 (41%)	9 (28%)								
Baumann, Zopf et al., 2011 (31)	RCT with inpatients (included some patients from the study by those Baumann et al., 2010)	Sample size (N)	24 → 17*	23 → 16*	<p>Aerobic training (cycle ergometer) Total duration: from day -6 until 1 day before the hospital discharge Frequency: daily during aplasia (2 sessions/day), 5 sessions/week during chemotherapy and 1 session/day after engraftment. Time/session: 10-20 min Intensity: 80% of peak wattage in WHO-test.</p> <p>ADL-training (walking, stepping, coordination, strength and stretching) Total duration: during conditioning, not during aplasia, and after engraftment. Frequency: 1 session/day Time/session: 20-30 min Intensity: "slightly strenuous" to "strenuous" (Borg scale).</p>	<p>Passive mobilization (gymnastics, massages, coordination training). Total duration: from +1 day until 1 day before hospital discharge. Frequency: 5 days/week Duration: 20 min Intensity: "not strenuous" in Borg scale.</p>	<p>Same as above + anthropometric assessments (weight, height and BMI).</p> <p>There were no other significant differences between groups.</p>			
		Age (years; mean±SD)	41.4±11.8	42.8±14.0						
		Sex (N; male/female)	11/6	5/11						
		HSCT (N)								
		Related allogeneic	4	6						
		Unrelated allogeneic	13	10						
		Patients with GVHD (N, %)	13 (76%)	9 (56%)						

<p>Chamorro-Viña et al., 2010 (74)</p> <p>Controlled (but not randomized) trial with inpatients</p>	<p>Sample size (N)</p> <p>7</p>	<p>Intervention group</p> <p>8±3</p>	<p>Control group</p> <p>13</p>	<p>Aerobic + resistance training</p> <p>Total duration: from the beginning of the conditioning phase to the end of the neutropenic phase.</p> <p>Frequency: 5 sessions/week (3 aerobic sessions and 2 aerobic + resistance sessions).</p> <p>Time/session: ~50 min</p> <p>Aerobic training (cycle ergometer):</p> <p>Time/session: 25-30 min</p> <p>Intensity: 50%-70% of age-predicted maximum heart rate.</p> <p>Resistance training (arm curl, elbow extension, bench press, leg extension, half squat, abdominals, supine bridge, and rowing)</p> <p>1 set of 12-15 repetitions per exercise</p> <p>Intensity: their own body weight, <i>therabands</i> with resistance gradually increasing over the program and barbells</p>	<p>'Historical' control group from hospital records not performing any type of exercise</p>	<p>Anthropometric assessments</p> <p>body mass, BMI and estimated fat-free mass.</p> <p>Immune cell recovery</p> <p>blood counts of leukocytes, monocytes, and lymphocytes and main lymphocyte subpopulations (T lymphocytes, natural killer cells, NK T, CD4+ and CD8+ and dendritic cells.</p>	<p>The intervention resulted in decreased resting heart rate ($p=0.034$) and increased muscle strength, as reported by gradually increasing loads (in <i>therabands</i> and barbells) as training progressed ($p=0.018$).</p> <p>The intervention group showed increased weight ($p<0.001$), BMI ($p<0.001$), body fat ($p=0.006$), and fat-free mass ($p=0.021$), as opposed to controls.</p> <p>There was a significant training effect for dendritic cells, ($p=0.045$ for the interaction effect group x time) which became non-significant after adjustment for multiple comparisons.</p>
	<p>Age (years; mean±SD)</p> <p>8±3</p> <p>Sex (N: male/female)</p> <p>5/2</p> <p>HSCCT (N)</p> <p>4</p> <p>Related Allogeneic</p> <p>3</p> <p>Unrelated Allogeneic</p> <p>4</p> <p>Conditioning</p> <p>Nonmyeloablative</p> <p>7</p> <p>Patients with GVHD (N, %)</p> <p>2 (29%)</p>	<p>Intervention group A</p> <p>13</p> <p>43.0 (20-55)</p> <p>7/6</p> <p>n.a.</p> <p>12</p> <p>1</p> <p>6</p> <p>7</p> <p>5 (38%)</p>	<p>Intervention group B</p> <p>13</p> <p>54.0 (27-62)</p> <p>5/8</p>	<p>Physical activity level (daily steps)</p> <p>Duration of hospitalization</p> <p>Daily steps versus duration of hospitalization</p>	<p>No significant differences (1,710.4 steps/day (range=301.8 – 3,444.7) in group A and 2,093.0 steps/day (range = 571.6 – 3,251.6) in group B ($p=0.90$).</p> <p>Hospitalization was longer in group A than in group B ($p=0.0001$).</p> <p>The correlation coefficients between mean daily steps and duration of hospitalization were -0.71 ($p=0.0071$) in group A and 0.09 ($p=0.77$) in group B. Increased physical activity levels through early rehabilitation prevented deconditioning and shortened the duration of hospitalization after allogeneic-HSCT among the patients of group A.</p>		
<p>Chamorro-Viña et al., 2010 (74)</p>	<p>Sample size (N)</p> <p>7</p>	<p>Intervention group</p> <p>8±3</p>	<p>Control group</p> <p>13</p>	<p>Aerobic + resistance training</p> <p>Total duration: from the beginning of the conditioning phase to the end of the neutropenic phase.</p> <p>Frequency: 5 sessions/week (3 aerobic sessions and 2 aerobic + resistance sessions).</p> <p>Time/session: ~50 min</p> <p>Aerobic training (cycle ergometer):</p> <p>Time/session: 25-30 min</p> <p>Intensity: 50%-70% of age-predicted maximum heart rate.</p> <p>Resistance training (arm curl, elbow extension, bench press, leg extension, half squat, abdominals, supine bridge, and rowing)</p> <p>1 set of 12-15 repetitions per exercise</p> <p>Intensity: their own body weight, <i>therabands</i> with resistance gradually increasing over the program and barbells</p> <p>Stretching (exercises for shoulder, elbow, hip, knee, and ankle joints),</p> <p>aerobic training (cycle ergometer) and resistance training (exercises for upper/lower limbs and abdominal muscles)</p> <p>Total duration: from the neutrophil engraftment to the last day of hospitalization.</p> <p>Frequency: 5 sessions/week.</p> <p>Time/session: 20-40 min</p> <p>Aerobic training intensity: 60% of age-predicted maximum heart rate</p>	<p>'Historical' control group from hospital records not performing any type of exercise</p>	<p>Anthropometric assessments</p> <p>body mass, BMI and estimated fat-free mass.</p> <p>Immune cell recovery</p> <p>blood counts of leukocytes, monocytes, and lymphocytes and main lymphocyte subpopulations (T lymphocytes, natural killer cells, NK T, CD4+ and CD8+ and dendritic cells.</p>	<p>The intervention resulted in decreased resting heart rate ($p=0.034$) and increased muscle strength, as reported by gradually increasing loads (in <i>therabands</i> and barbells) as training progressed ($p=0.018$).</p> <p>The intervention group showed increased weight ($p<0.001$), BMI ($p<0.001$), body fat ($p=0.006$), and fat-free mass ($p=0.021$), as opposed to controls.</p> <p>There was a significant training effect for dendritic cells, ($p=0.045$ for the interaction effect group x time) which became non-significant after adjustment for multiple comparisons.</p>
<p>Inoue et al., 2010 (170)</p> <p>Non-controlled trial with inpatients</p>	<p>Sample size (N)</p> <p>13</p> <p>Age (years; mean (range))</p> <p>43.0 (20-55)</p> <p>Sex (N: male/female)</p> <p>7/6</p> <p>HSCCT (N)</p> <p>n.a.</p> <p>12</p> <p>1</p> <p>6</p> <p>7</p> <p>Patients with GVHD (N, %)</p> <p>5 (38%)</p>	<p>Intervention group A</p> <p>13</p> <p>43.0 (20-55)</p> <p>7/6</p> <p>n.a.</p> <p>12</p> <p>1</p> <p>6</p> <p>7</p> <p>5 (38%)</p>	<p>Intervention group B</p> <p>13</p> <p>54.0 (27-62)</p> <p>5/8</p>	<p>Physical activity level (daily steps)</p> <p>Duration of hospitalization</p> <p>Daily steps versus duration of hospitalization</p>	<p>No significant differences (1,710.4 steps/day (range=301.8 – 3,444.7) in group A and 2,093.0 steps/day (range = 571.6 – 3,251.6) in group B ($p=0.90$).</p> <p>Hospitalization was longer in group A than in group B ($p=0.0001$).</p> <p>The correlation coefficients between mean daily steps and duration of hospitalization were -0.71 ($p=0.0071$) in group A and 0.09 ($p=0.77$) in group B. Increased physical activity levels through early rehabilitation prevented deconditioning and shortened the duration of hospitalization after allogeneic-HSCT among the patients of group A.</p>		

<p>Jarden, Baadsgaard et al., 2009 (177)</p> <p>Prospective RCT with inpatients</p>	<p>Sample size (N)</p> <p>Intervention group: 21 Control group: 21</p>		<p>Usual care</p>	<p>Physical functioning Karnofsky performance scores. VO₂max (Astrand-Rhyming cycle test). Muscle strength Functional performance (2-min chair climb test). QoL: EORTC QLQ-C30 Psychological well-being and distress Hospital Anxiety and Depression Scale (HADS) Fatigue Functional Assessment of Cancer therapy-Anemia scale FACT-An scale Adherence to the intervention "monitoring logbook" Several clinical outcomes</p>	<p>There was a significant effect in favor of the control group at post-testing for: VO₂max (p=0.0001), chest press (p=0.0001), leg extension (p=0.0003), isometric right elbow flexors' strength (p=0.0009), isometric right knee extensors' strength (p=0.0001) and the stair test (p=0.0008). The intervention group reported having less diarrhea, over the time than the controls (p=0.014) and received parental nutrition for fewer days than the controls (p=0.019). There was no significant effect on QoL, fatigue, psychological well-being or physical activity levels, but there were longitudinal trends that favored the intervention group. Though not significant, there was a 19% decrease in the occurrence of aGVHD in the intervention group.</p>
	<p>Age (years; mean±SD)</p> <p>Intervention group: 40.9±13.3 Control group: 37.4±11.1</p> <p>Sex (N; male/female)</p> <p>Intervention group: 13/8 Control group: 13/8</p> <p>HSCT (N)</p> <p>Intervention group: 11 Control group: 12</p> <p>Related Allogeneic Unrelated Allogeneic</p> <p>Conditioning agents (N)</p> <p>Intervention group: 2 Control group: 3</p> <p>CY/ATG CY/BU CY/TBI Et/TBI CY/ATG/TBI</p> <p>TBI (N)</p> <p>Intervention group: 8 Control group: 3</p> <p>No Yes</p> <p>Patients with GVHD (N, %)</p> <p>Intervention group: 5 (24%) Control group: 9 (43%)</p>				
<p>Kim and Kim 2006 (194)</p> <p>RCT with inpatients</p>	<p>Sample size (N)</p> <p>Intervention group: 18 Control group: 17</p>		<p>Usual care and multimodal intervention (aerobic and resistance exercises, relaxation and psycho-education) Total duration: from the first day of admission (day -7) until the day of discharge. Frequency: 5 sessions/week. Time/session: 1 hour±10 min. Aerobic training (cycle ergometer) Frequency: 5 days/week. Time/session: 15-30 min Intensity: 50-75% of age-predicted maximum heart rate and 10-13 in the Borg scale. Resistance training (free hand and ankle weights, biceps curl, shoulder press, triceps extension, chest press, flyers, squat, hip flexion, knee extension, and leg curl and extension) Frequency: 3 days/week Time/session: 15-20 min 1-2 sets of 10-12 reps (intensity: 10-13 in the Borg scale). Relaxation (5 sec of muscle tensing and 30 sec of muscle relaxation) Frequency: 2 days/week. Time/session: 20 min. Intensity: 6-9 in the Borg scale.</p>	<p>Physical functioning Karnofsky performance scores. VO₂max (Astrand-Rhyming cycle test). Muscle strength Functional performance (2-min chair climb test). QoL: EORTC QLQ-C30 Psychological well-being and distress Hospital Anxiety and Depression Scale (HADS) Fatigue Functional Assessment of Cancer therapy-Anemia scale FACT-An scale Adherence to the intervention "monitoring logbook" Several clinical outcomes</p>	<p>There was a significant effect in favor of the control group at post-testing for: VO₂max (p=0.0001), chest press (p=0.0001), leg extension (p=0.0003), isometric right elbow flexors' strength (p=0.0009), isometric right knee extensors' strength (p=0.0001) and the stair test (p=0.0008). The intervention group reported having less diarrhea, over the time than the controls (p=0.014) and received parental nutrition for fewer days than the controls (p=0.019). There was no significant effect on QoL, fatigue, psychological well-being or physical activity levels, but there were longitudinal trends that favored the intervention group. Though not significant, there was a 19% decrease in the occurrence of aGVHD in the intervention group.</p>
	<p>Age (years; mean±SD)</p> <p>Intervention group: 32.9±7.0 Control group: 34.3±7.8</p> <p>Sex (N; male/female)</p> <p>Intervention group: 8/10 Control group: 9/8</p> <p>HSCT/BMT (N)</p> <p>Intervention group: 0 Control group: 0</p> <p>Autologous Allogeneic (BM) Allogeneic (BM + PBSC)</p> <p>Diagnosis (N)</p> <p>Intervention group: 10 Control group: 8</p> <p>AML ALL SAA</p> <p>Patients with GVHD (N, %)</p> <p>Intervention group: Not reported Control group: Not reported</p>				

Mello, Tanaka and Dullea, 2003 (256)	Controlled (but not randomized) trial with inpatients	Sample size (N)	Intervention group	Control group	Active exercises, muscle stretching and a walking-based program on a treadmill Total duration: exercise initiated during the inpatient period after bone marrow engraftment and concluded in the outpatient facility (over 6 weeks). Frequency: 5 days/week. Time/session: 40 min. Intensity 70% of age-predicted maximum heart rate.	No exercise program. Usual care.	Muscle performance Maximum isometric contraction (assessed with a dynamometer) in upper and lower limb muscles.	1 st assessment (prior to HSCT). No difference between groups for all muscle groups, except for the dominant elbow flexors ($p=0.042$) and the dominant hip abductors ($p=0.035$), with higher values in the controls. 2 nd assessment (post-HSCT). Both groups had similarly decreased values. 3 rd assessment (6 weeks after exercise training or normal life). The intervention group showed a trend towards higher values than the control group for all muscle groups tested, with a significant difference for non-dominant hip flexors ($p=0.011$).
		Age (years; range)	27.9 (18-39)	n.a. → 9**				
		Sex (N; male/female)	5/4	3/6				
		HSCT (N)	n.a.	n.a.				
		Related and unrelated allogeneic						
		Conditioning agents (N)	8	8				
		BU + melphalan	1	1				
		BU + CY	6 (67%)	7 (78%)				
		Patients with GVHD (N, %)						
Tran et al., 2012 (385)	Not controlled trial with outpatients	No (N)	Intervention group		Pulmonary rehabilitation program (breathing techniques), and strength (free weights and weight machines; upper and lower body exercises) and aerobic training (recumbent bike, treadmill or step machine and upper body bike). Total duration: exercise intervention initiated during the outpatient period (8-12 weeks). Frequency: ~3 days/week. Time/session: ~65 min. Intensity: individualized and gradually increasing throughout the intervention.	Spirometry/pulmonary function tests. 6 minute walk tests. QoL: SF-36 survey.	All patients with pre-HSCT pulmonary function tests had a drop of at least 10% in FEV1 after HSCT, and most had a drop >25%. There was no significant change in spirometry when comparing pre and post rehabilitation values ($p=0.446$ for FEV1, and $p=0.822$ for FVC). Patients who completed the pulmonary rehabilitation improved their 6 minute walk distance ($p=0.005$) an average of 307 feet post-rehabilitation. There was a significant improvement in the physical functioning score by a mean of 14.4 points ($p=0.029$).	
		Age (average)	48					
		Sex (N; male/female)	6					
		HSCT (N)	5					
		Related Allogeneic						
		Unrelated Allogeneic						
		Conditioning agents (N)	3					
		Cytoxan + TBI	4					
		Fludarabine + busulfan + ATG	2					
		Fludarabine + busulfan	1					
Busulfan + cytoxan	1							
Busulfan + CY	10 (100%)							
Patients with GVHD (N, %)								
Wilson et al., 2005 (417)	Pilot controlled with outpatients	Sample size (N)	Intervention group		Home-based aerobic training (walking, swimming, cycling, exercise tapes) Total duration: 12-weeks Frequency: at least 3 times weekly Time/session: 20 continuous minutes in training zone Intensity: 40%-60% of age-predicted heart rate reserve	No control group but training diaries were monitored weekly by telephone contact. Nine of 13 subjects reported completing 273 (84%) of the 324 exercise sessions assigned at the prescribed intensity and duration	Aerobic fitness (defined as the oxygen uptake at the ventilatory threshold) was poor at baseline but increased >15% after the intervention Fatigue levels at baseline were modest; symptom severity scores but not fatigue symptom duration or interference scores, improved significantly ($p<0.05$) after the intervention. At baseline, reported levels of physical functioning and physical role functioning were substantially lower (>0.5 SD) than those reported for the normal US population. Statistically significant improvements in the SF-36 Physical Functioning and Physical Role Functioning subscales were observed after the intervention.	
		Age (years; mean±SD)	48.9±10.4					
		Sex (N; male/female)	6/11					
		HSCT/BMT (N)	13					
		Autologous	4					
		Allogeneic	16.9±8.3					
		Time since transplant (months; mean±SD)	Not Reported, although 3 of the 4 allogeneic-BMT patients were using cyclosporine and corticosteroids, presumably for GVHD.					

Wiskeman et al, 2011 (419)	RCT with in- and outpatients	Intervention group		Control group		Self-administered outpatient intervention and partly supervised inpatient intervention (aerobic and resistance program) Total duration: from 1-4 weeks before admission to 6-8 weeks after discharge from the hospital.	Outpatient setting: daily steps Inpatient setting: possibility to have physiotherapy (30 min/session) or to use stationary cycles and treadmills.	Fatigue MFI and POMS QoL EORTC QLQ-C30 questionnaire. Psychological well-being HADS. Distress National Comprehensive Cancer Network Distress Thermometer. Physical capacity Endurance performance: 6-minute walk test. Hand-grip test. Physical activity levels Number of steps.	The intervention group had less fatigue at 6-8 weeks after discharge from the hospital than the controls in MFI scales general fatigue ($p=0.009$), physical fatigue ($p=0.01$) and in the POMS scale ($p=0.004$). EORTC physical functioning was higher in the intervention group than in the controls ($p=0.03$) at the end of the intervention ($p=0.007$). HADS anxiety, and global distress was higher ($p = 0.01$) at the end of the intervention and lower ($p=0.05$) at discharge from the hospital, respectively, in the intervention group than in the controls. Endurance capacity post-intervention ($p=0.02$) and strength of the lower extremities from baseline to discharge ($p=0.03$) improved in the intervention group but not in the controls. Physical capacity was inversely correlated with general fatigue ($p=0.01-0.02$).
		No (N)	Age (years; mean (range))	Sex (N; male/female)	HSCT (N) HLA-identical (related) HLA-matched/unrelated HLA-mismatched/unrelated				
		52	47.6 (18-70)	32/21	53	50 (20-71)	39/13		
		13			15				
		26			30				
		13			8				
	Intensity of Conditioning regimens Myeloblastic Reduced intensity TBI	11 41 18			13 40 18				
	Patients with GVHD (N, %)	21 (40%)			18 (34%)				
									No differences were found in pedometer steps and coordination tasks.

*The data and analyses were focused on the final N (i.e., final number of participants completing the study).

** Same as above + initial N per group not provided (initial total N=32)

Abbreviations: ADL, activities of daily living; aGVHD, acute graft versus host disease; ALL: acute lymphocytic leukemia; AML: acute myeloid leukemia; ATG, anti-thymocyte globulin; BMI, body mass index; BMT, bone marrow transplant; BU, busulphan; cGVHD, chronic graft versus host disease; CY, cyclophosphamide; EORTC, European Organization for Research and Treatment of Cancer; Et, etopofos; FACT-An, Functional Assessment of Cancer Therapy-Anemia; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; GCSF: granulocyte colony stimulating factor; GVHD, graft versus host disease; HADS, Hospital Anxiety and Depression Scale; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplant; IVC: inspiratory vital capacity; QoL, quality of life; MFI: Multidimensional Fatigue Inventory; n.a., not available; NK, natural killer; PBSC: peripheral blood stem cell; POMS: Profile of Mood States; RCT, randomized controlled trial; SAA: severe aplastic anemia; SF-36, Short Form-36; TBI, total body irradiation; VC, vital capacity; VO₂max, maximal oxygen uptake.

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