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The benefit of exercise in patients who undergo allogeneic hematopoietic stem cell transplantation

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Abstract

Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is increasingly used in the treatment of hematologic cancers such as leukemias, lymphomas, and myeloma, and for other hematologic disorders such as primary immunodeficiency, aplastic anemia, and myelodysplasia. Allo-HSCT entails a conditioning regimen of frequent high-dose chemotherapy in combination with total body irradiation, followed by infusion of donor-harvested bone marrow or peripheral blood stem cells. As an aggressive and demanding medical therapy that profoundly impacts patient quality of life (QOL), allo-HSCT is associated with numerous treatment-related physical, psychological, and psychosocial side effects. The procedure can result in decreased respiratory and balance function, skeletal muscle strength, and exercise capacity. Thus, as physical exercise has been shown to positively effect physical and psychosocial function and QOL in allo-HSCT patients, it is a recommended intervention for improving essential functions and offsetting lost exercise capacity after the procedure. Furthermore, recent evidence has shown that physical exercise can influence survival rate and mortality in allo-HSCT patients. This review provides an overview of the current research on the effectiveness of physical exercise for allo-HSCT patients.

Introduction

Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is a potentially curative procedure for a variety of hematologic malignancies, such as leukemia, lymphomas, and myeloma¹. Allo-HSCT requires hematopoietic cells from a human leukocyte antigen (HLA)-matched or -mismatched donor, which are given after the patient receives high-dose chemotherapy and total body irradiation. The hematopoietic stem cells (HSC) used in allo-

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Conflicts of Interest

The authors of this review declare no conflict of interest.

HSCT must be sourced from a genetically similar, but not identical, donor². Thus, the donor is often a sister or brother, but is in some cases unrelated.

From 2006–2012, the use of allo-HSCT increased by 57% worldwide³. When initially developed, allo-HSCT was considered a novel approach for protecting patients from the toxic side effects of supralethal doses of radiation and chemotherapy by transplanting hematopoietic stem cells, which have the ability to reconstitute hematopoiesis⁴. The purpose of transplantation can be to restore hematological function in patients with bone marrow failure states, to replace diseased marrow with healthy donor marrow, as a “rescue” to reconstitute hematological function after marrow-ablative chemo radiotherapy, and, most recently, as a means of treating certain genetic and nonmalignant disorders⁵. Hematopoietic stem cells can be sourced from bone marrow, peripheral blood, or umbilical cord blood⁶.

It has been reported that allo-HSCT achieved lower relapse rates and improved survival in patients with hematologic malignancy with recurrent or refractory disease and those at a high risk of resistance or relapse⁷. Allo-HSCT should be preferred to conventional chemotherapy as a post-remission treatment for adults with lymphoblastic lymphoma⁷. However, allo-HSCT is a highly aggressive and demanding medical therapy that profoundly impacts patient quality of life (QOL). Despite the advantages of allo-HSCT for patients with hematologic malignancy, these patients often develop graft-versus-host disease (GVHD), which is commonly observed after allo-HSCT⁸. GVHD causes the donor’s cells to attack not only the underlying malignancy or disorder but also to adversely affect the skin, gastrointestinal tract, and liver⁹, and thus GVHD significantly impacts patients QOL^{10,11}. In addition to possibly developing GVHD, patients who undergo allo-HSCT can experience a range of other side effects (Fig 1). These include mouth sores, nausea and vomiting, diarrhea, decreased physical function, fatigue, anxiety, dry mouth, hair loss, rashes, and breathing problems^{12,13}. GVHD can manifest as acute or chronic. Acute GVHD usually manifests within 100 days following HSCT, while chronic GVHD typically presents after more than 100 days after the transplant¹⁴. Symptoms associated with acute GVHD include skin rash, stomach nausea, diarrhea, and liver problems; in contrast, chronic GVHD symptoms generally include issues with the eyes, lungs, mouth, joints, and muscle function¹⁵. In addition to the side effects mentioned above, patients who undergo allo-HSCT patients have an increased risk of bleeding and infection¹⁶. Allo-HSCT patients have decreased physical function and QOL 6–7 weeks after HSCT compared to that before HSCT^{17,18}. Besides GVHD and infections, reduced physical function, and particularly high levels of fatigue, negatively affect patients’ QOL¹⁹. Allo-HSCT patients may require physical exercise to prevent a decrease in physical function or improve physical function and QOL. The purpose of this review was to provide an overview of the current research on the effectiveness of physical exercise for allo-HSCT patients. We used electronic searches of two databases—PubMed and Scopus up to January 8, 2019 to select studies of the effects of exercise for allo-HSCT patients. This review was then conducted using the following words: “hematopoietic stem cell transplantation”, “HSCT”, “exercise”, and “rehabilitation”.

Decreased physical function in allo-HSCT patients

Physical function before allo-HSCT or hospital admission

A previous study reported that 110 allo-HSCT patients had significantly decreased muscle strength, exercise capacity, and QOL compared to sex- and age-matched healthy subjects before HSCT²⁰. Furthermore, 83 of 164 allo-HSCT patients (50.6%) experienced sarcopenia prior to allo-HSCT, and these patients experienced decreased muscular strength and increased fatigue after the procedure compared to patients without sarcopenia²¹. Patients with sarcopenia showed significantly lower scores in physical functioning, bodily pain, and vitality in health-related QOL than those without sarcopenia²¹.

Another report showed that factors significantly associated with reduced leg extension strength after allo-HSCT included pre-procedure leg extension strength, grade of acute GVHD, age, and time interval between pre- and post-evaluation in 88 patients who received allo-HSCT²². Patient leg extension strength and peak VO₂ were significantly reduced after allo-HSCT²². Another study showed that both allogeneic (n = 11) and autologous (n = 11) HSCT patients with lower peak VO₂ had higher symptom burdens and inferior QOL during the early post-HSCT period²³.

The feasibility and preliminary effectiveness of an exercise program for 29 patients before HSCT has also been investigated, and the results showed that patients had a training adherence rate of 69%, and that no adverse events or injuries occurred²⁴. Thus, exercise prior to HSCT appears to be safe and feasible, with favorable preliminary effectiveness²⁴. Therefore, as decreased physical function before allo-HSCT influences physical function after the procedure, research suggests that physical exercise should be recommended to patients prior to undergoing allo-HSCT.

Physical function after allo-HSCT or hospital admission

Allo-HSCT patients receive high-dose chemotherapy, total body irradiation, and hematopoietic cells from an HLA-matched or mismatched donor. These patients are hospitalized in a single-bed isolation room for a period of four to six weeks, as the severely depressed bone marrow function increases the patient's risk of bleeding, infection, and anemia and results in weakness, fatigue, shortness of breath, and insomnia^{16,25}. Additionally, allo-HSCT patients often receive numerous corticosteroid doses to prevent acute GVHD²⁶. The number of these doses was significantly correlated with a decrease in handgrip and knee-extensor strength in 113 allo-HSCT patients²⁶.

The decrease in physical function experienced by patients after allo-HSCT negatively affects activities of daily living (ADL) and QOL (Figure 2). For example, 30 allo-HSCT patients were shown to have significantly decreased balance function when tested using the Timed Up and Go test, as well as decreased center-of-pressure total trajectory length using the body sway test after transplantation²⁷. Balance function is significantly correlated with handgrip and knee-extensor strength²⁷. Another study, which included 23 allogeneic and 21 autologous HSCT patients, showed that patients had significantly worsened results in the two-minute walking test and grip strength after transplantation²⁸. According to that study, these significant differences correspond to decreases in aerobic conditioning before and after

physical stress, declines in functioning and gait performance, reduction of muscle strength and spine flexibility, and diminished functioning in ADLs after HSCT²⁸.

Another report showed that the 6-minute walk test (6MWT) and handgrip strength were significantly decreased six weeks after allo-HSCT compared to two weeks before in 86 allo-HSCT patients²⁹, and that upper extremity muscle mass and trunk muscle mass were significantly decreased after allo-HSCT²⁹. Similarly, another study reported that 64 allo-HSCT patients had significantly decreased handgrip strength and 6MWT scores at the time of discharge from the hospital³⁰.

There are also gender differences in QOL after allo-HSCT. Significant gender and time interactions were observed for handgrip strength and muscle mass in 64 allo-HSCT patients, with a much greater handgrip strength and muscle mass decline in men than in women³⁰. Another study showed that after allo-HSCT women had significantly lower scores for physical function and general health on health-related QOL tests compared with men in 100 patients (66 men, 34 women) who underwent allo-HSCT³¹. Thus, male allo-HSCT patients may tend to have decreased muscle strength, while female allo-HSCT patients tend to have a decreased health-related QOL.

Fatigue is another common side effect of allo-HSCT. One study showed that fatigue significantly increased and physical activity decreased following high-dose chemotherapy and HSCT in 7 allogeneic and 10 autologous HSCT patients; as a result, patients experienced diminished physical, emotional, role, and cognitive functioning³². Additionally, the symptoms that patients experienced, such as fatigue, pain, nausea and vomiting, sleep disturbances, appetite loss, and diarrhea, increased during the acute post-transplant period³².

The proportion of daily activities performed at an intensity >3.0 metabolic equivalents (METs) has been shown to increase significantly after allo-HSCT in 30 patients³³. Daily activity time performed at an intensity of 1.6–2.9 METs significantly correlated only with knee strength³³. The total number of daily steps and the proportion of activity performed at 1.6–2.9 METs and >3.0 METs were positively correlated with the 6MWT. Additionally, physical functioning and general health subscales in health-related QOL were found to be positively correlated with daily activities performed at >3.0 METs³³. For allo-HSCT patients, it may be important to assess physical activity prior to the procedure, and to increase levels and intensity of physical activity to prevent reduced physical function thereafter.

There is recent evidence that allo-HSCT patients have decreased muscle oxygen consumption and decreased blood flow to skeletal muscles after transplantation. Furthermore, there may be a relationship between fatigue and decreased muscle oxygen consumption in patients after allo-HSCT in 25 male patients³⁴. Similarly, muscle oxygen hemoglobin saturation was also found to be significantly lower in 18 patients after allo-HSCT, both during and after exercise, which directly affects exercise capacity³⁵; however, no difference has been found in total hemoglobin before and after allo-HSCT. As with the effects of decreased muscle oxygen hemoglobin saturation, a decrease in skeletal muscle oxygenation was also associated with a reduction in exercise capacity in 18 allo-HSCT

patients³⁵. In one study, changes in hemoglobin parameters in the tibialis anterior muscle in 16 patients before allo-HSCT were found to be different from those in 21 age-matched healthy controls; in the healthy control group, there was a correlation between muscle strength and hemoglobin dynamics, but this correlation was not observed in patients before allo-HSCT³⁶.

In an investigation of patient physical function and QOL before allo-HSCT in 30 patients undergoing allo-HSCT, at hospital discharge, and one year after transplantation, handgrip strength and 6MWT scores were significantly lower at time of discharge than at pre-transplantation³⁷. However, both returned to pre-HSCT levels within one year after HSCT. Similarly, QOL scores also returned to pre-HSCT levels within one year after HSCT³⁷.

QOL and physical function have also been compared between 126 patients allo-HSCT patients (HID group, n = 100; other donor group, n = 26) who received HSC from an HLA-matched sibling, a matched unrelated donor, or an unrelated umbilical cord blood donor¹⁸. After the procedure, the haploidentical donor group showed significantly greater improvements in the general health subscale and Mental Component Summary of QOL than the other donor groups. However, the haploidentical donor group actually showed significantly greater decline in handgrip strength and knee extensor muscle strength after HSCT when compared to the other donor groups¹⁸. From these results, the donor type may affect QOL and physical function in allo-HSCT recipients.

One study investigated the relationship between GVHD and physical function in 40 allo-HSCT patients³⁸, and found that allo-HSCT patients had a 6% loss of muscle strength one month after the transplantation, whereas patients with acute GVHD had a 12% loss of muscle strength in the same timeframe³⁸. In summary, allo-HSCT patients frequently experience decreased muscle strength, exercise capacity, and QOL after transplantation, and there are differences between men and women. Compounding factors of impaired physical function included increased fatigue, lower muscle mass, decreased physical activity, decreased skeletal muscle oxygenation, donor type, and GVHD.

Physical exercise improves physical function for allo-HSCT patients

A systematic review and meta-analysis of 11 randomized controlled trials (RCTs), which included patients undergoing either allogeneic or autologous HSCT (n = 734), showed that physical exercise that includes aerobic exercise, resistance training, and relaxing stretching exercises may have positive effects on the physiological, psychological, and psychosocial health of allo-HSCT patients³⁹. Physical exercise during hospitalization has been shown to lead to higher QOL and lower fatigue in allo-HSCT patients at the time of discharge from the hospital³⁹. This study suggested significant positive effects on QOL, fatigue, psychological well-being and distress, and physical functioning³⁹. Another systematic review that included 8 studies of allo-HSCT patients (n = 472) showed that physical exercise had a statistically significant, moderately favorable effect on cardiorespiratory fitness, lower extremity muscle strength, and fatigue⁴⁰. Small but significant positive effects were found for upper extremity muscle strength, overall QOL, and physical, emotional and cognitive functioning in patients with both allogeneic and autologous HSCT⁴⁰. One RCT that

investigated the effects of aerobic exercise in 64 allo- and auto-HSCT patients showed that a physical exercise regimen that combined aerobic endurance training on a bicycle ergometer and ADL training showed significant positive effects in the training group in terms of strength, endurance, lung function, and QOL compared to the control group⁴¹. Similarly, a moderate exercise program was shown to increase endurance performance, muscular strength, fatigue levels, and emotional states without posing additional risks to 47 allo-HSCT patients⁴². Another RCT of allo-HSCT patients (n = 100) showed that regular, light-intensity exercise, including walking or biking, can lead to significantly better physical performance during the recovery period and a better perceived physical and emotional state⁴³.

Combined multimodal physical exercise has also been shown to have a significant effect on VO₂max and muscle strength, as measured by chest press, leg extension, right elbow flexor, right knee extensor, and functional performance (stair test) in 42 patients who underwent allo-HSCT⁴⁴. Furthermore, the physical exercise group showed significantly better results for the severity of post-procedure diarrhea and fewer days of total parenteral nutrition⁴⁴. Similarly, a four- to six-week structured physical exercise program has been shown to significantly improve treatment-related symptoms in 42 allo-HSCT patients⁴⁵. Another study investigated the effectiveness of endurance and resistance training sessions on physical function in 105 allo-HSCT patients in a home-based setting before hospital admission, during inpatient treatment, and during a six- to eight-week period after discharge; the physical exercise group showed significant improvement in fatigue scores, physical fitness, physical functioning, and overall QOL⁴⁶.

The effectiveness of an outpatient physical exercise program for allo-HSCT patients has also been evaluated⁴⁷. All patients were randomly assigned to a supervised PE program (n = 64) or a usual care control group (n = 67). A 12-week outpatient program that included both aerobic and strength exercises showed that physical performance improved in allo-HSCT patients after the intervention⁴⁷. However, body composition, physical activity levels in daily life, fatigue, and QOL did not show improvement⁴⁷. Another study, which was not a RCT, investigated the effectiveness of physical exercise without a control group, and showed that 12 patients who followed a 12-week individualized mild aerobic exercise program had significant improvements in fatigue after allo-HSCT⁴⁸. A six-week physical exercise program with active exercise, muscle stretching, and treadmill walking resulted in significantly higher muscle strength in 9 allo-HSCT patients compared to 9 allo-HSCT patients in a control group⁴⁹.

Pulmonary exercise can also be beneficial for allo-HSCT patients, improving their pulmonary function and exercise capacity. In one program, inspiratory muscle training to improve early transplantation-related outcomes consisted of 40 % maximal inspiratory pressure⁵⁰. As a result, the distance covered during an incremental shuttle walking test, 6MWT scores, respiratory muscle strength, and depression showed significant improvement in the treatment group (n = 20) compared to controls (n = 18)⁵⁰. Among 11 allo-HSCT patients with bronchiolitis obliterans syndrome, those who received pulmonary rehabilitation had significantly improved 6MWT and physical functioning scores after rehabilitation compared to before⁵¹.

In summary, physical exercise appears to offer several beneficial effects for allo-HSCT patients, including positive impacts on physical and emotional recovery following transplant therapy and possible acceleration of patients' return to health and function after the procedure⁴³. Even light aerobic exercise has been shown to have a beneficial effect on physical and emotional recovery. Thus, allo-HSCT patients should perform physical exercise to maintain physical function before admission, during hospitalization, and after discharge. Physical exercise should include resistance training and aerobic exercise, relaxation stretching, and pulmonary exercise, and should be tailored to the patient's condition. A physiotherapist, exercise trainer, and hospital staff should prevent bleeding during exercise in patients with a low platelet count (Fig 3). Further high-quality research is needed to determine optimal physical exercise interventions for allo-HSCT patients.

Feasibility of physical exercise for allo-HSCT patients

Despite the health-related challenges that patients face after receiving allo-HSCT, they tend to have a relatively high adherence rate to physical exercise. One study showed that the adherence rate to a physical exercise plan of five sessions weekly during the inpatient period was 64% in myeloablative conditioning, 54% in reduced-intensity conditioning, and 63% in nonmyeloablative conditioning in 113 allo-HSCT patients⁵². Another study reported a 90% average adherence rate to a supervised multimodal exercise program performed five times per week for four to six weeks during the inpatient period after allo-HSCT in 42 allo-HSCT patients⁴⁴; similarly, 12 elderly allo-HSCT patients in a different study showed an 85% adherence rate⁵³. However, in a different cohort of 59 HSCT patients, the overall adherence rate to a four-week outpatient progressive physical exercise after allo-HSCT was 61%⁵⁴. Another study showed that the adherence rate to physical exercise for the total expected training days was 74% in 227 allo-HSCT patients¹⁶.

Using Borg scale in physical exercise

Borg scale is a frequently used quantitative measure of perceived exertion during physical exercise in rehabilitation and particularly exercise testing⁵⁵. A previous study used the Borg scale on the intensity of the ADL training which was meant to match the patient's subjective feeling of "slightly strenuous" to "strenuous" (Borg scale)⁴¹. Another research study also used the Borg scale on target scores 12–14 for endurance and 14–16 for resistance exercises in allo-HSCT patients. Another study investigated the relationship between the Borg scale and intensity of resistance training and an exercise tolerance test in 28 allo-HSCT patients⁵⁶. Borg ratings increased with increasing load intensity during knee extension resistance training, both before and after HSCT⁵⁶. Furthermore, Borg ratings was found to be associated with heart rate and load intensity during exercise tolerance test in patients both before and after HSCT⁵⁶. The Borg scale could be useful to determine the intensity of physical exercise in patients who have undergone allo-HSCT.

The relationship between physical function and survival rate and mortality

In a previous RCT of allo-HSCT patients, the physical exercise group (n = 50) had a significantly lower total mortality rate than the control group (n = 53), suggesting that

physical exercise after allo-HCT improves survival after discharge in this patient group⁵⁷. Another report showed that patients presenting with a pre-HSCT 6MWT of <400 m who experienced a decline in 6MWT post-HSCT had the highest risk of non-relapse mortality in 407 allo-HSCT patients⁵⁸. The same study found that pre-transplant 6MWT is a significant univariate predictor of clinical outcomes in hematological patients beyond age but not beyond that of performance status⁵⁸. Similarly, a different study reported that patients with pre-HSCT peak VO₂ <16 mL/kg/min had a higher risk of mortality post-HSCT and more hospitalized days before day 100 in both allogeneic (n = 11) and autologous (n = 11) HSCT patients²³. Furthermore, peak VO₂ pre- HSCT is feasible and might predict symptom severity, QOL, and mortality²³.

Conclusions

Allo-HSCT patients require physical exercise to prevent a decrease in physical function or improve physical function. Future studies are required for allo-HSCT patients. For example, causes and strategies for prevention of decreases in physical function after HSCT have not been clarified. The use of corticosteroids and decreases in physical activity post-HSCT seem to be related to decreases in physical function. However, other factors may influence decreases in the physical function of allo-HSCT patients. These patients experience nausea, loss of appetite, and GVHD, and tend to experience a decline in nutritional status and weight, which leads to muscle loss and loss of physical vitality. Therefore, future studies on the effects of nutritional therapy combined with physical exercise for allo-HSCT patients are needed. Moreover, as exercise capacity may be related to mortality in allo-HSCT patients, it is possible that muscle strength and physical activity could have a relationship with mortality in these patients. Future studies should investigate these possible relationships. Finally, future long-term follow-up studies focusing on the long-term physical function and overall QOL are needed. The survival rates of allo-HSCT patients have been improving, with many allo-HSCT patients living longer than those in the past. Thus, the maintenance of physical function, and its relationship to physical exercise, should be investigated in long-term survivors of allo-HSCT in addition to inpatient populations.

The current review suggests that physical exercise is beneficial for the physiological, psychological, and psychosocial health of allo-HSCT patients. Thus, clinicians should encourage patients to perform physical exercise before, during, and after transplantation, and physical exercise should be integrated into the conditioning and recovery plans for all allo-HSCT patients.

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Figure 1.

Physical function associated with treatment-related side effects after allo-HSCT

Figure 2.
Decrease in physical function, disability, and QOL in patients with allo-HSCT after treatment

Figure 3.
Physical exercise before admission, during hospitalization, and after discharge