

Effects of nonpharmacological interventions on reducing fatigue after hematopoietic stem cell transplantation

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Fatigue is one of the main complaints of patients undergoing allogeneic and autologous hematopoietic stem cell transplantation (HSCT). Since nonpharmacological interventions are cost-effective and causes fewer complications, this study aimed to review the studies performed on the effects of nonpharmacological interventions on fatigue in patients undergoing HSCT during September 2016. MEDLINE, CINAHL, Scientific Information Database, IranMedex, PubMed, ScienceDirect, Scopus, Magiran, and IRANDOC databases were searched using Persian and English keywords. A total of 1217 articles were retrieved, 21 of which were used in this study. Exercise is known as an effective intervention in alleviating physical and mental problems of patients undergoing stem cell transplant. This review-based study showed that nonpharmacological methods such as exercise might be effective in decreasing fatigue in patients undergoing stem cell transplant. There is a multitude of studies on some of the complementary and alternative therapy methods, such as music therapy, yoga, relaxation, and therapeutic massage. These studies demonstrated the positive effects of the aforementioned therapies on reduction of fatigue in patients undergoing stem cell transplantation. All the investigated methods in this study were nonaggressive, safe, and cost-effective and could be used along with common treatments or even as an alternative for pharmacological treatments for the reduction, or elimination of fatigue in patients undergoing stem cell transplantation. Given the advantages of complementary and alternative medicine, conducting further studies on this issue is recommended to reduce fatigue in patients after stem cell transplantation.

Key words: Alternative medicine, bone marrow transplant, complementary medicine, exercise, fatigue, hematopoietic stem cell transplantation, nonpharmacological intervention

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) was used before 1960s to cure patients diagnosed with hematological and metabolic disorders as well as immunodeficiency and autoimmune diseases.^[1] The International Union of Registered Bone Marrow Transplant estimated that more than 50,000 HSCTs (25,000 allogeneic and 30,000 autologous transplants and cord blood) are annually performed worldwide.^[2]

There are three types of HSCT, namely, allogeneic, autologous, and syngeneic. Allogeneic transplant comprises a donor and a receiver that are not immunologically matched. After the allogeneic transplant, the transplanted stem cells or the cells developed from it can react against the host, causing graft-versus-host disease (GVHD).

On the one hand, in case of insufficient immunosuppressive conditioning regimen before the transplant, the immune cells may cause transplant rejection.^[3] Currently, in these kinds of transplants, the donor and receiver are tried

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to be matched in terms of genes such as human leukocyte antigens. Autologous transplant is harvesting and storage of autologous stem cells, and then reinjecting them after receiving high doses of myeloid-derived suppressor cells. Contrary to allogeneic transplant, in autologous transplant, the risk of developing GVHD or transplant rejection does not exist.

On the other hand, autologous transplant lacks the graft versus tumor effect, and autologous stem cell products can become contaminated with tumor cells. Approximately 1% of cases undergoing syngeneic transplant have identical twins. Syngeneic donors are the best sources of stem cell; unlike allogeneic donors, in these cases, the risk of GVHD does not exist.

Contrary to those receiving autologous stem cells, the risk of stem cell contamination by tumor cells does not exist in the patient.^[4]

Although HSCT has good clinical outcomes and increases life expectancy,^[5] cancer patients undergoing stem cell transplant experience high levels of fatigue during their treatment sessions. This problem might be due to high doses of chemotherapy drugs and whole body radiotherapy in the preparation regimen before bone marrow transplant.^[6] In addition, in these patients, the level of physical activity significantly decreases because of prolonged bed rest due to severe aplasia and neutropenia,^[7] which leads to intense and persistent fatigue.^[8,9]

Other factors causing fatigue include immunosuppressive treatment, GVHD, infection, and severe anemia due to bone marrow suppression, pain, sleep disorder, stress, anxiety, and depression.^[10] Approximately 35% of patients experience acute fatigue after receiving bone marrow transplant.^[11] There are disparate reports on the occurrence and prevalence of cancer-related fatigue and its level of improvement in patients receiving bone marrow transplant.^[12] In a study by Bevens *et al.*, the prevalence rate of fatigue was 90% 30 days after HSCT and 81% within 100 days.^[13]

In a study by Hacker and Ferrans, most patients experienced relatively low fatigue 3 days before HSCT and mild to severe fatigue 3 days after HSCT.^[14] In a study by Gielissen *et al.*, 41% of the patients reported severe fatigue 1–5 years after HSCT, and 32% of them experienced fatigue 5–10 years after HSCT.^[6] Nursing Diagnosis Association of North America describes fatigue as weakness and reduced mental and physical capacity.^[15] Based on the description of National Comprehensive Cancer Network, fatigue is a mental unpleasant and resistant sign presented in the form of physical, emotional, and cognitive fatigue, which is caused by cancer or its related treatments.^[16]

Deep fatigue can affect various aspects of life through attenuating the ability to perform daily activities. Long-term inactivity and fatigue can result in weakness, lack of tolerance, and decreased muscle strength. Fatigue and lack of energy can lead to reduced concentration, psychosocial adjustment, and life quality.^[17] Methods for curing fatigue in patients undergoing HSCT are divided into pharmacological and nonpharmacological categories. Today, the use of complementary and alternative medicine has increased among the public all throughout the world.^[18] Nonpharmacological methods are often construed as a branch of complementary medicine that the nurses as well as the patients and their family can use to reduce the fatigue caused by disease and its treatment.^[19-21] Most nonpharmacological methods or complementary medicine therapies have little side-effects and risks.^[22] Given the scarcity of data on this issue, this study aimed to review the studies carried out on the effects of nonpharmacological interventions on patients' fatigue after receiving HSCT.

MATERIALS AND METHODS

This study was a narrative review done in 2016. The electronic search was conducted in international (PubMed, MEDLINE, ScienceDirect, Scopus, and SINAHL), and national (IranMedex, Scientific Information Database, IRANDOC, and Magiran) scientific databases during September 2016. The search was conducted using the following keywords: "hematopoietic stem cell transplantation," "bone marrow transplantation," "nonpharmacological intervention," "fatigue," "exercise," "complementary medicine," or "alternative medicine," "music," "touch," or "massage," "herb," "acupuncture," "acupressure," "relaxation," "meditation," and "yoga."

The reference list of all the retrieved articles was hand searched for the related articles. The included studies were Persian- and English-language articles performed on human samples during 1991 – September 2016 and focused on the role of at least one nonpharmacological therapy on patients' fatigue after HSCT. No restriction on age, gender, and culture of the samples was applied. Studies which abstracts related to congresses and conferences, abstracts without full texts were excluded. The process of article selection was performed independently by two researchers, and in case of disagreement, the articles were evaluated by a third researcher [Figure 1].

RESULTS

A total of 1217 articles were retrieved by the initial search of the databases. Afterward, using "and," limiting the search strategy, and increasing its features, the number of articles with related titles reached 282; of the 282 retrieved articles, 28 of them were repeated.

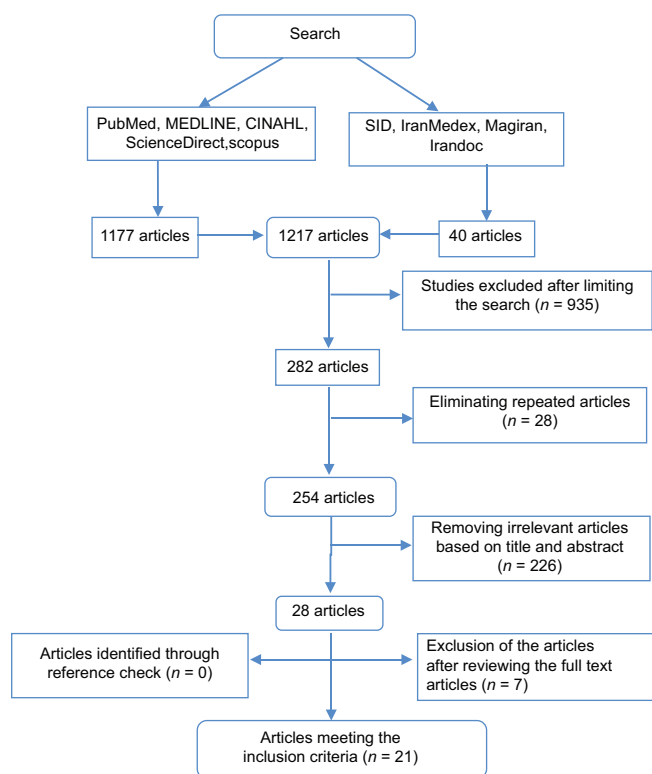


Figure 1: The article inclusion flowchart

The title and abstract of the remaining 254 articles were evaluated, and 226 of them were excluded from the study due to irrelevant objectives. Finally, the full text of the remaining 28 articles was evaluated to assess their quality and check whether they met the inclusion/exclusion criteria; finally, 21 articles were chosen. In addition, no relevant article was found in hand search of the reference list of the articles.

Nonpharmacological interventions

Physical exercise

Stem cell transplant decreases the level of physical activity due to prolonged bed rest and severe aplasia and neutropenia, causing intense and persistent fatigue in patients.^[7,9] To improve the patient's physical performance after the transplant, exercising, even for a short time, is recommended during pretransplant preparation with chemotherapy drugs.^[23] Physical exercise lowers fatigue and improves cardiovascular performance, cardiac capacity, muscle mass, plasma volume, pulmonary ventilation and perfusion, health condition, and life quality.^[24,25]

Carlson *et al.* conducted a study to evaluate the effect of individual fitness programs on the treatment of severe fatigue after allogeneic HSCT in 12 patients (8 males and 4 females) with mean age of 47.41 years. The participants did cardio exercises in the form of individual resistance training (bicycle ergometer) three times a week for 12 weeks.

The results indicated that individual fitness program could cure fatigue to a large extent ($P < 0.001$).^[26]

A study by Wilson *et al.*, which was conducted on 17 patients, illustrated that doing cardio exercises 3–5 times a week for 12 weeks promoted endurance performance and life quality after stem cell transplant and decreased fatigue ($P < 0.05$).^[7]

Lemercier *et al.* performed a study to evaluate the level of physical activity in adults diagnosed with cancer, who received HSCT. Twelve patients were divided into two groups of intervention ($n = 6$) and control ($n = 6$). The intervention group had 3–45 min exercise sessions once a week for 10 weeks. The results indicated a significant reduction in fatigue scores of the intervention group, compared to the control group, and no change was observed in the scores of depression and anxiety in both groups.^[27]

Wiskemann *et al.* reviewed 29 articles on the effect of exercise interventions on HSCT. The results of that study showed that exercise interventions lowered the severity of side-effects associated with treatment and fatigue.^[7,25,26,28] It also improved physical performance and life quality.^[29]

In a systematic meta-analysis, Persoon *et al.* reviewed eight articles on the impact of exercise on patients with hematologic malignancies undergoing stem cell transplant. The results indicated that exercise could enhance cardiopulmonary fitness and lower extremity muscle strength and reduce fatigue.^[30]

Steinberg *et al.* evaluated the role of physical rehabilitation in patients undergoing stem cell transplant. Their findings demonstrated that one of the key factors in the improvement of life quality and survival of patients undergoing stem cell transplant was supportive care, especially physical medicine and rehabilitation.^[31]

Van Haren *et al.* performed a systematic meta-analysis on 11 articles investigating the effects of exercise on cancer patients undergoing HSCT. The results indicated that exercise during hospitalization improved life quality and reduced fatigue in patients undergoing allogeneic transplant.^[32]

Morishita and Domen evaluated 22 studies on the effects of physical exercise interventions on HSCT. Their findings indicated that exercise interventions reduced treatment complications and improved physical performance in patients. Some of the reviewed articles showed that exercise interventions could diminish fatigue and promote life quality in patients.^[23] However, there was no significant difference between the groups of the study by Knols *et al.*^[17] In a study by Shelton *et al.*, fatigue reduced after 4 weeks,

but the difference was not statistically significant.^[33] In a study by Jarden *et al.*, level of fatigue and mental health changed in the intervention group, but the reduction was not statistically significant.^[34] Several studies demonstrated that aerobic or resistance training could significantly decrease fatigue in patients undergoing HSCT [Table 1].

Complementary and alternative medicine

Nowadays, the use of complementary and alternative medicine is on a growing trend worldwide.^[18] According to the National Center for Complementary and Alternative

Medicine, complementary medicine is used along with common medicine, while alternative medicine is applied instead of common medicine. The reasons for the increasing the use of complementary and alternative medicine include insufficiency of conventional treatments, low communication skills of physicians, and adverse side-effects of therapeutic agents.^[38]

In a study by Barnes *et al.*, 40% of the American citizens had used complementary and alternative medicine in the past 12 months.^[39] In a study by Maftoon *et al.*, the prevalence

Table 1: Studies on the impact of physical exercise on fatigue in patients undergoing stem cell transplantation

Researcher(s)	Title	Type of study	Type of transplant	Sample characteristics	Type of intervention (exercise type)	Results	Conclusion
Bargi <i>et al.</i> (2016) ^[11]	Inspiratory muscle training in allogeneic hematopoietic stem cell transplantation recipients	Two-group intervention	Allogeneic	n=38 (20 IG, 18 CG) with a mean age of 36.6±12.61 years	Inspiratory muscle training for 6 weeks	Statistically significant difference in fatigue scores were observed in both groups after exercise of the inspiratory muscles (P<0.05)	Inspiratory muscle training intervention was safe and effective in improving respiratory muscle strength, exercise capacity, breathing, and reducing depression and fatigue
Chamorro-Viña <i>et al.</i> (2012) ^[35]	Exercise in pediatric autologous stem cell transplant patients	Two-group intervention	Autologous	24 samples (age range: 5–18 years)	Aerobic exercise, resistance training, and flexibility exercise five times a week during hospital stay and three times a week for 60 minutes after discharged for 10 weeks	Exercise reduced fatigue and improved the immune system serum cytokine level, natural killer cells, nutrition, quality of life, and physical activity	Exercise reduced fatigue and improved the quality of life
Wiskemann <i>et al.</i> ^[28]	Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation	Two-group intervention	Allogeneic	n=105, (52 IG, 53 CG) completed the program n=80 (40 IG, 40 CG), with a mean age of 38.8 years	Three sessions of exercise once a week, two sessions of resistance training once a week before admission and after discharge, five sessions of exercise once a week, and two sessions of resistance training during hospital stay	The exercise group showed significant improvement in fatigue scores (15% improvement in the exercise group versus 28% deterioration in the control group) (P<0.1–0.3)	Exercise reduced fatigue and stress and enhanced physical performance and quality of life

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Researcher (s)	Title	Type of study	Type of transplant	Sample characteristics	Type of intervention (exercise type)	Results	Conclusion
Hacker <i>et al.</i> ^[25]	Strength training following hematopoietic stem cell transplantation	Two-group intervention	Allogeneic autologous	$n=19$ (9 IG, 10 CG), with mean age of 46.26 ± 16.23 years	Exercise and strength training intervention to strengthen the abdominal muscles, the muscles of the upper and lower extremities with a combination of elastic band resistance training 1–2 times a week for 5–6 weeks	The level of fatigue was significantly different in the two groups ($P<0.01$)	Resistance training had a positive effect on fatigue, quality of life, and physical activity of patients receiving high-doses of chemotherapy and hematopoietic stem cell transplant
Baumann <i>et al.</i> ^[36]	Physical activity for patients undergoing an allogeneic hematopoietic stem cell transplantation	Two-group intervention	Allogeneic	$n=47$, completed program $n=33$ (17 IG, 16 CG), with mean age of 42.11 ± 12.91 years	Exercise group: aerobic exercise with daily activities twice a day Control group: standard clinical physiotherapy program once a day	There was a significant difference between the groups in terms of fatigue (lower in the exercise group) ($P=0.046$)	Exercise had a positive effect on physical function and quality of life in patients undergoing allogeneic hematopoietic stem cell transplantation
Jarden <i>et al.</i> ^[34]	Effect of a multimodal intervention on physical capacity, functional performance, and quality of life in adult patients undergoing allogeneic stem cell transplant	Two-group intervention	Allogeneic	$n=42$ (21 IG, 21 CG), completed program $n=34$ (17 IG, 17 CG), completed follow-up (3 months) $n=30$ (17 IG, 13 CG), completed follow-up (6 months) $n=29$ (16 IG, 13 CG), with mean age of 39.1 ± 12.2 years	Aerobic exercise and resistance training	Changes in quality of life, fatigue, and mental health; the intervention group was observed, but the difference was not statistically significant (3 months after the intervention, $P=0.302$ and 6 months after the intervention, $P=0.097$)	Exercise in patients undergoing stem cell transplantation did not have adverse effects, but it enhanced aerobic capacity, muscle strength, and the level of performance
Shelton <i>et al.</i> ^[33]	A randomized control trial of a supervised versus self-directed exercise program for allogeneic stem cell transplant patients.	Two-group intervention	Allogeneic	$n=61$ (30 supervised and 31 self-directed), completed program $n=53$ (26 supervised, 27 self-directed), with mean age of 46.29 ± 12.42 years	Aerobics and resistance training three times a week for 4 weeks	Fatigue level decreased in both groups after 4 weeks, but it was not statistically significant. Mean fatigue score in the group under supervision was 4.43 ± 2.41 and in the self-performed group was 3.83 ± 2.71	Self-directed and supervised exercise was effective in reducing fatigue in patients undergoing hematopoietic stem cell transplantation

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Table 1: Contd...

Researcher (s)	Title	Type of study	Type of transplant	Sample characteristics	Type of intervention (exercise type)	Results	Conclusion
Knols <i>et al.</i> ^[17]	Effects of an outpatient physical exercise program on hematopoietic stem cell transplantation recipients	Two-group intervention	Allogeneic	<i>n</i> =131 (64 IG, 67 CG), completed program <i>n</i> =114, completed follow-up (3 months) <i>n</i> =105, with mean age of 46.7±12.8 years	Aerobic exercise and resistance training twice a week for 12 weeks	The fatigue scores were not significantly different between the two groups (<i>P</i> =0.056)	Exercise was effective in the improvement of physical function after hospital discharge
Dimeo <i>et al.</i> ^[37]	Aerobic exercise in the rehabilitation of cancer patients after high-dose chemotherapy and autologous peripheral stem cell transplantation	Two-group intervention	Autologous	<i>n</i> =32 (16 IG, 16 CG) with mean age of 40.5±10 years	Aerobic exercise for 6 weeks	Physical function and hemoglobin concentration level at discharge were similar in both groups, but the level of physical performance and concentration of hemoglobin 7 weeks after discharge was significantly higher in the exercise group (<i>P</i> <0.05). No patient reported fatigue in the exercise group, and only four patients in the control group reported fatigue	Aerobic exercise improved physical function in patients with cancer undergoing transplant. In addition, to reducing fatigue, increasing physical activity in this group of patients should be considered rather than resting

CG = Control group; IG = Intervention group

of using complementary and alternative medicine in Iran was reported to be 42%.^[40] Although there is ample evidence on the positive effects of complementary and alternative medicine on cancer treatment, there is a paucity of studies on the impact of complementary and alternative medicine on stem cell transplantation.^[38]

In a clinical trial, Kim and Kim divided 35 patients undergoing HSCT into two groups of intervention (*n* = 18) and control (*n* = 17). Respiratory relaxation training was performed in 30-min sessions once a day for 6 weeks in the intervention group, and the control group received no intervention. The results showed that the mean scores of fatigue subscales including cognitive/mood, behavioral/severity, emotional, and sexual were significantly different in the two groups after the intervention (*P* = 0.02, *P* = 0.01, *P* = 0.04, and *P* = 0.001, respectively).^[41]

Diorio *et al.* evaluated the effects of yoga on 11 children aged 7–18 years undergoing HSCT. Yoga was done three times a week for 3 weeks. The mean fatigue score was 55.6 ± 15.5

on day 21 of the intervention. The results of the study illustrated that yoga has positive effects on hospitalized children undergoing HSCT.^[42]

Cassileth *et al.* investigated the impact of music therapy on behavioral disorders of patients undergoing HSCT. The results exhibited that the mean scores of some variables such as anxiety, depression, fatigue, and mood disorders were significantly different (*P* = 0.065, *P* = 0.065, *P* = 0.03, and *P* = 0.01, respectively). Music therapy is a nonaggressive and inexpensive intervention, which can reduce mood disorders in hospitalized patients undergoing transplant.^[43]

Ahles *et al.* examined the effect of massage therapy on patients undergoing autologous bone marrow transplant. In their study, 34 patients were randomly divided into two groups of intervention (*n* = 16) and control (*n* = 18). The patients in the massage therapy group received 20-min sessions of massage three times a week until hospital discharge. The mean duration of hospital stay was 3 weeks. The mean scores of some variables such as distress, nausea, fatigue, and anxiety were significantly different after the

intervention ($P = 0.02$, $P = 0.01$, $P = 0.06$, and $P = 0.0001$, respectively).^[44]

CONCLUSION

Physical exercise is known as an effective intervention in alleviating physical and mental problems of patients undergoing stem cell transplant. This review-based study showed that nonpharmacological methods such as exercise might be effective in lowering fatigue in patients undergoing stem cell transplant. Although there is a scarcity of studies on complementary and alternative medicine, the existing evidence clearly suggests that these methods can be applied to reduce fatigue in patients.

Recommendations

Given the advantages of complementary and alternative medicine and high prevalence of fatigue in patients after transplant and that pharmaceutical methods impose great economic losses and adverse side-effects, promoting awareness of patients regarding nonpharmaceutical methods can effectively reduce fatigue and enhance quality of life.

Future studies on this issue are recommended to develop and carry out research projects on the nonpharmaceutical interventions on patients undergoing hematopoietic stem cell transplant and raise awareness of physicians, nurses, and patients regarding the use of nonpharmaceutical interventions. Furthermore, traditional and nonpharmaceutical methods as effective and safe interventions should be considered in planning theoretical and practical lessons.

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Conflicts of interest

There are no conflicts of interest.

AUTHORS' CONTRIBUTION

HJ contributed to conducting the research project, preparing and editing the manuscript, and approving the final version

of the manuscript. YJ prepared and edited the manuscript. SH helped with collecting data, preparing and editing the manuscript, and approving the final version of the manuscript.

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