THE EFFECT OF AEROBIC EXERCISE ON THE FATIGUE LEVEL AMONG ADULT CANCER PATIENTS POST BONE MARROW TRANSPLANT (EVIDENCE BASE PAPER)

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Abstract

Purpose: **The purposes of this evidence base paper are to find the best evidence related to using aerobic exercise to manage post bone marrow transplant fatigue, also to answer the PICO question which has been addressed in this study.**

Methods: **An electronic literature search has been conducted using data bases like CINAHL, Pubmed, and Ovid nursing to find the relevant articles according to specific inclusion criteria; the search process yielded finally twelve articles.**

Results: **This paper found moderate to strong evidence for using aerobic exercise to manage post bone marrow transplant fatigue.**

Implications and recommendations: **Aerobic exercise can be carried out safely, and directly post bone marrow transplant; also adhering to a specific programmed aerobic exercise with the treatment plan will decrease the fatigue level post transplant.**

Key words: **Bone marrow transplant, fatigue, exercise.**

1. Introduction and Background

Fatigue is a multidimensional concept with several modes of expression: physical, emotional and cognitive. Fatigue is associated with the inactivity presentation or lack of motivation (Smets, Garssen, Schuster & Haes, 1993). Fatigue is an exceedingly common often treatable problem in cancer patients that profoundly affects all aspects of quality of life. Patients report fatigue as one of the most important and distressing symptoms related to cancer, also it's one of the most common side effects of chemotherapy (Campos, Hassan, Riechelmann & Giglio, 2011). Insufficient coping with the experience of cancer, fear of disease recurrence, dysfunctional cognition concerning fatigue, dysregulation of sleep and dysregulation of activity are all factors that play a role in fatigue severity. (Gielissen et al., 2007).

Impairment of physical performance and fatigue are common and sometimes serious side effects of cancer treatment. It has been estimated that the problem affects up to 70% of cancer patients during chemotherapy or radiotherapy. One frequently underestimated factor contributing to loss of physical performance in cancer patients is the lack of muscular activity during in-hospital treatment (Lange, Mertelsmann & Keul, 2007).

Bone Marrow Transplant (BMT) can be an extraordinary, life-saving treatment. It has now become the standard treatment for a number of neoplastic and immunological disorders. Post BMT fatigue is common among patients and it has an effect on their quality of life (Appelbaum, 2007). 35% of the BMT patients experienced severe fatigue. The percentage of patients with severe fatigue remained stable during the years after transplantation. Several psychosocial factors, but not medical factors, were associated with fatigue, also with no decrease in fatigue complaints during the first years after Stem Cell Transplant (Gielissen et al., 2007).

The purposes of this evidence base paper are to find the effect of exercise especially aerobic exercise on the fatigue level among adult cancer patients post bone marrow transplant, and to answer the PICO question which represent the following: Population and problem (P): fatigue post bone marrow transplant. Intervention (I): Aerobic exercise.

Comparison (C): Patient daily activities/ other types of exercise with aerobic exercise intervention. **Outcome (O):** Management of fatigue level among post bone marrow transplant patients

2. Methods

An extensive electronic search was conducted to look for articles related to post BMT fatigue management by programmed exercise especially aerobic exercise using data bases and journals. The data bases used were: CINAHL, COCHRANE, Nursing Ovid, and Pubmed. The key words used to find the articles were: exercise, high dose chemotherapy, hematopoietic stem cell transplant, fatigue post BMT, and fatigue induced by chemotherapy, and their alternatives, also a combination of some of these words has been used to find more relevant articles.

The search process yielded many articles but not all of them relevant to the phenomenon of interest, so the articles were reduced to twelve articles after exclusion of duplicated studies, reviewing the titles of some of them, the abstract of others, and the full text for others.

Articles were considered relevant if:

1- They contained information about cancer related fatigue, exercise among cancer patients, exercise for BMT patients, BMT complications, post BMT fatigue, high dose chemotherapy complications management, and the usage of aerobic exercise.

2- Were written in English language.

3- Were quantitative research classified between level I to IV according to a specific leveling system (see appendix).

4- Any type of transplant (Allogenic, Autologous) for malignant disorder.

5- Adult age group (more than 18 years to 65 years).

Although the time frame for the relevant articles should be as the maximum five years, but some articles were used before 2009 to reach the term of data saturation, as there were little current studies related to the topic and that met the inclusion criteria.

2.1 Study Characteristics

After applying the inclusion criteria on retrieved studies, twelve articles were included in this review. The sample size of these studies ranged from 10 to 293. The studies' classification depended on its design strength as levels according to the leveling system as shown at table (1) in the appendix. The time frame of retrieved articles was between 1997 to 2013. The studies were of mixed types of transplant except one contained only Allogeneic HSCT (Mello, Tanaka & Dully, 2003), also all the studies participants were adult cancer patients. Most of the articles contained different types of exercise like aerobic, strength, and endurance exercise, also some of them were supervised, and others were home based exercises. Table 2 shows more details about the reviewed articles.

3. Findings and Discussion

3.1. Findings From Level I:

All meta- analysis, and systematic literature review is considered as level one; the research process yielded 2 meta analysis and systematic reviews and the evidence was: The newly updated Cochrane Review includes 56 studies, involving a total of 4068 people undergoing cancer treatment. The findings indicate that those with solid tumors benefited from aerobic exercise, such as walking or cycling, both during and after cancer treatment. Other forms of exercise, however, including resistance training, did not significantly reduce fatigue. The evidence suggests that exercise may help reduce cancer-related fatigue and should therefore be considered as one component of a strategy for managing fatigue that may include a range of other interventions and education. Also the review suggested further research is needed to understand how the frequency and duration of exercise, as well as the type of cancer, affects the results, as twenty-eight of the studies were carried out in breast cancer patients (Cramp & Byron, 2012).

Another meta analysis conducted by Brown and his colleagues in 2011 the purpose of which was to evaluate the effect of types of exercise in cancer related fatigue indicated that the resistance exercise interventions of moderate intensity were more effective than low intensity or aerobic exercise.

Author comments: From the previous findings aerobic exercise can be used as a way to decrease cancer and its related treatment fatigue, and it is considered strong evidence to use exercise in general to decrease fatigue level, but the other systematic analysis contradicts the first review and provides other evidence to use other types of exercise which is resistance exercise to decrease fatigue level. But this review has some limitations like the included studies had small sample size, and its results can't be generalized.

3.2. Level II Evidence Findings:

A well designed randomized experimental studies included in the level II evidence according to evidence levels, was the first randomized experimental study conducted in 2011 that demonstrates that there is a potential positive effect of strength training on physical activity, fatigue, and quality of life in people receiving high-dose chemotherapy and HSCT compared with usual activity (Hacker et al., 2011).

The aim of another randomized clinical trial done in 2011 by Villanueva and his colleague was to evaluate the effectiveness of an 8 week multimodal physical therapy program on cancer related fatigue, and the final finding was that the 8 week multimodal exercise has an effect in decreasing cancer related fatigue.

Another randomized experimental trial's purpose was to evaluate the effects of a 12-week outpatient physical exercise program, incorporating aerobic and strength exercises, as compared with a usual care control condition on patients' physical performance and psychosocial well-being, and its final result indicated that the programmed exercise should be considered in the management of HSCT recipients to improve physical performance after discharge from the hospital (Knols et al, 2011). Also the purpose of another one conducted by Jarden and his colleagues in 2009 was to investigate the effect of a 4- to 6-week multimodal program of exercise, relaxation and psycho-education on physical capacity, functional performance and quality of life (QOL) in allogeneic hematopoietic cell transplantation adult recipients, and its final result give evidence of assignment of a multimodal intervention during Allo-HSC T did not cause untoward events, sustained aerobic capacity and muscle strength and reduced loss of functional performance during hospitalization. Also the exercise programs can be carried out safely after HST, as the study investigated the effect of more than one type of exercise such as aerobic exercise 15-30 minutes of cycling five times a week, resistance exercise 15-20 minutes 3 times a week, and dynamic stretch exercise five times a week. 15-20 min. exercises included neck movements, shoulder rotations, hip flexion/extension, standing calf raise, ankle dorsiflexion and plantar flexion and progressive relaxation twice a week, for 20 minutes.

Baumann and his colleauges conducted a randomized controlled trial in 2010 and its purpose was to evaluate the different effects of specific, moderate physical activities on the physical and psychological condition of HSCT patients, and its final result indicated there was a significant difference in the intervention group in regard of strength, endurance, lung function and quality of life. This article providing a technique and duration of aerobic exercise to be carried out by patient pre, during, and post HSCT, as the following: Aerobic exercise: During aplasia twice a day and during chemotherapy and after engraftment once a day 10-20 min cycling at a bicycle ergometer, 80% of the achieved watt load during the modified WHO-test for fatigue.

In 2006 a randomized controlled trial done by Carlson and his colleges, and consist of 12 participants indicated very large improvements in fatigue level over the course of an individualized aerobic exercise program in post-HSCT patients who were suffering from high levels of fatigue for which no morphological, biochemical, hormonal or psychological correlate could be identified.

A final level II evidence trial was conducted in 1997 by Diemo and his colleagues and the title of their study was "Effects of Aerobic Exercise on the Physical Performance and Incidence of Treatment-Related Complications After High-Dose Chemotherapy", and the result indicated the fatigue level among patients post high dose of chemotherapy decreased significantly after an aerobic exercise program, even though the study was conducted in 1997 its result provided a significant improvement in fatigue level, also the safety of aerobic exercise program among patients.

3.3 Level III Evidence:

Evidence obtained from well designed non-randomized controlled trials OR from well designed cohort or case-control analytical studies, preferably multicenter or conducted at different times. There was no study found according to this level of criteria.

3.4. Level IV Evidence:

The retrieved evidence included two descriptive studies and one prospective study, and the results were as following : In 2012 Tonosaki conducted a descriptive study the purpose of which was to analyze the effects of leg muscle strength and fatigue on step-count as a measure of physical activity for people staying at home after hematopoietic stem cell transplantation (HSCT) and the results indicated the effect of HST on physical activity as Mean step-count at home was most strongly affected by ankle plantar flexion strength/kg, and increasing ankle plantar flexion strength/kg was shown to promote recovery of normal physical activities. Another descriptive study showed the importance of exercise to reduce cancer related fatigue, but the specific exercise type wasn't mentioned, and physiotherapists' management of cancer related fatigue includes recommending and using exercise and teaching energy conservation techniques. Another recommendation can be concluded from this study when comparing the strength exercise with the aerobic exercise; the aerobic exercise is easier than strength exercise. That means the aerobic exercise should be feasible more than strength, and we can conclude that the aerobic exercise program is feasible among patients post HSCT (Donnelly et al, 2009). Also another literature review emphasised these recommendations by suggestion as there is significant benefits from the exercise interventions reported for physical performance, quality of life and fatigue status of the patient, like faster recurrence of immune cells or reduced severity of therapy-related side effects can be estimated. Also ithas been proposed that exercise be used as a non-pharmacologic adjuvant therapy to combat the physiological and psychological symptoms of HCST (Wiskemann & Huber, 2008).

The last evidence was a prospective study conducted in 2011 by Hackers and his colleagues that indicated the strength-training intervention refined from an unsupervised, home-based program to a combination supervised and unsupervised program with weekly clinic

visits, were very acceptable, although some started out at a very low intensity.

Summary and Conclusion

The previous evidence of the literature review aimed to find the effect of exercise in general and aerobic exercise, especially on the fatigue induced by cancer treatment among adult cancer patients post bone marrow transplant.

The analyzed literature provided a moderate to strong evidence of using aerobic exercise to decrease the post bone marrow transplant fatigue, and also recommended to adhere to aerobic exercise such as walking, or bicycling as part of the treatment plan.

The previous findings are compatible with the recent guidelines for exercise prescription for cancer survivors from the American College of Sports Medicine (2010) which report no contraindication for starting an exercise program in patients undergoing either autologous or allogeneic HSCT however, issues regarding the ideal time for starting a program safely and effectively, type of program, frequency, intensity and duration is not confirmed, especially in relation to the HSCT treatment trajectory. Also it is proved that aerobic exercise for adults post HSCT can be practiced safely and it has a lot of benefits like improvement of physical fitness, muscular strength, flexibility, bone health, sleep, depression, anxiety, and quality of life. The specific period of training was 75 minutes weekly for vigorous exercise, and 150 minutes for moderate intensity aerobic exercise.

Finally many types of exercise can be practiced by cancer patients like aerobic, strength, and endurance exercise, but most of the literature regarded using aerobic exercise to reduce cancer related fatigue especially among bone marrow transplant patients.

Still there is debate on the specific details about aerobic exercise like duration and weekly frequency, but the conclusion about this debate may be as the current recommendation as the patients should be exercised three to five times weekly with moderate aerobic exercise intensity, the type of aerobic exercise may be walking on a treadmill, or ergo-motor bicycling. Also another recommendation is to adherence to aerobic exercise with treatment conditioning is an advantage to control fatigue post HSCT. Aerobic exercise can be carried out safely, and immediate post bone marrow transplant, 3-5 times weekly, such as walking or bicycling on an ergometer bicycle.

Appendices

Table 1: Levels of Evidence Ratings

Level 1	Evidence obtained from systematic review of relevant randomized controlled trials (with meta-analysis where possible).
Level 2	Evidence obtained from one or more well designed randomized controlled trials.
Level 3	Evidence obtained from well designed non-randomized controlled trials OR from well designed cohort or case-control analytical studies, preferably multicenter or conducted at different times.
Level 4	The opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

Articles Summary Table

Title & Author	Year	Design & Purpose	Sample Size	Results
Exercise for the management of cancer-related fatigue in adults (Cramp & Byron)	2012	Systematic meta analysis-Cochrane review Evaluate the effect of exercise on cancer-related fatigue both during and after cancer treatment	56 studies	Aerobic exercise can be regarded as beneficial for individuals with cancer-related fatigue during and post-cancer therapy, specifically those with solid tumours. Further research is required to determine the optimal type, intensity and timing of an exercise intervention.

Title & Author	Year	Design & Purpose	Sample Size	Results
Efficacy of Exercise Interventions in Modulating Cancer-Related Fatigue among Adult Cancer Survivors: A Meta-Analysis. Brown et al,	2011	Meta analysis. The purpose of this meta-analysis was to explore the efficacy of exercise as a non-pharmacologic intervention to reduce cancer-related fatigue (CRF) among adult cancer survivors.	44 studies	Exercise reduced cancer related fatigue especially in programs that involved moderate-intensity, resistance exercise among older cancer survivors.
Strength Training Following Hematopoietic Stem Cell Transplantation Hacker E et al	2012	Randomized experimental study. To test the effects of strength training compared with usual activity on physical activity, muscle strength, fatigue, health status perceptions, and quality of life following HSCT.	19 patients	Study demonstrates the potential positive effects of strength training on physical activity, fatigue, and quality of life in people receiving high-dose chemotherapy and HSCT. Comment: Another type of exercise which is the strength exercise can reduce the fatigue effect post HSCT.
A multimodal exercise program and multimedia support reduce cancer-related fatigue in breast cancer survivors: A randomized controlled clinical trial. (Villanueva et al, 2011)	2011	Randomized clinical trial To evaluate the effectiveness of an 8 week multimodal physical therapy program on cancer related fatigue		8 week multimodal exercise has an effect in decreasing cancer related fatigue
Effects of an outpatient physical exercise program on hematopoietic stem-cell transplantation recipients: a randomized clinical trial (Knols et al, 2011)	2011	to evaluate the effects of a 12-week outpatient physical exercise program, incorporating aerobic and strength exercises,as compared with a usual care control condition on patients' physical performance and psychosocial well-being.		Programmed exercise should be considered in the management of HSCT recipients to improve physical performance after discharge from the hospital.

Title & Author	Year	Design & Purpose	Sample Size	Results
A randomized trial on the effect of a multimodal intervention on physical capacity, functional performance and quality of life in adult patients undergoing allogeneic SCT Jarden M et al.,	2009	Randomized controlled trial To investigate the effect of a 4- to 6-week multimodal program of exercise, relaxation and psycho-education on physical capacity, functional performance and quality of life (QOL) in allogeneic hematopoietic cell transplantation adult recipients.	42	Assignment of a multimodal intervention during Allo-HSC T did not cause untoward events, sustained aerobic capacity and muscle strength and reduced loss of functional performance during hospitalization. **Comment:** The exercise programs can be carried out safely after HST, as the study investigated the effect of more than one type of exercise such as aerobic exercise 15-30 minutes of cycling five times a week, resistance exercise 15-20 minutes 3 times a week, and dynamic stretch exercise: Five times a week, 15–20 min. Exercises included neck movements, shoulder rotations, hip flexion/ extension, standing calf raise, ankle dorsiflexion and plantar flexion Progressive relaxation: Twice a week, 20 min. Patients alternated between muscle tensing (5 s) and muscle relaxation (30 s) for each muscle group
A controlled randomized study examining the effects of exercise therapy on patients undergoing haematopoietic stem cell transplantation Baumann, F., Kraut, L., Schul, K., Bloch, W., & Fauser, A	2010	Controlled randomized study. To evaluate the different effects of specific, moderate physical activities on the physical and psychological condition of HSCT patients	64	Significant differences in the intervention group regarding strength, endurance, lung function and quality of life. Comment: This article provides a technique and duration of aerobic exercise to be carried out by patient pre, during, and post HSCT, as the following: Aerobic exercise: During aplasia twice a day and during chemotherapy and after engraftment once a day 10–20 min cycling at a bicycle ergometer, 80% of the achieved watt load during the modified WHO-test for fatigue.
Individualized exercise program for the treatment of severe fatigue in patients after allogeneic hematopoietic stem-cell transplant: a pilot study Carlson LE, Smith D, Russell J, Fibich C & Whittaker T	2006	Randomized experimental study. This pilot study investigated whether patients with no clinical or psychological abnormalities but severe fatigue would respond to an individually adapted aerobic exercise program.	12 patients	The study found very large improvements in fatigue over the course of an individualized aerobic exercise program in post-HSCT patients who were suffering from high levels of fatigue for which no morphological, biochemical, hormonal or psychological correlate could be identified. Comments: As this a pilot study and has a small sample side, its result can't be generalized, but may give us a hint for the importance of aerobic exercise program.
Effects of Aerobic Exercise on the Physical Performance and Incidence of Treatment-Related Complications After High-Dose Chemotherapy Dimeo F., Fetscher S., Lange W., Mertelsmann R., & Keul J.	1997	Randomized experimental study. To investigate if the impairment of physical performance post BMT can be partially prevented.	33 patients	Aerobic exercise can be safely carried out immediately after high-dose chemotherapy and can partially prevent loss of physical performance. Comment: Event the study conducted in 1997, but its result is significant as the fatigue level among patients decreased significantly after aerobic exercise program.

Title & Author	Year	Design & Purpose	Sample Size	Results
Experience of severe fatigue in long-term survivors of stem cell transplant. Gielissen M et al.,	2007	Descriptive study To investigate the prevalence of fatigue after completion of stem cell transplantation.	98 patients	35% of the patients experienced severe fatigue. The percentage of patients with severe fatigue remained stable during the years after transplantation. Several psychosocial factors, but no medical factors, were associated with fatigue, no decrease in fatigue complaints during the first years after SCT. Comment: This article gave us the significance of the initiated study, as the fatigue is a very important complaint among cancer patients post HST.
The long-term effects after hematopoietic stem cell transplant on leg muscle strength, physical inactivity and fatigue Tonosaki A	2012	Descriptive longitudinal. To analyze the effects of leg muscle strength and fatigue on step-count as a measure of physical activity for people staying at home after hematopoietic stem cell transplantation (HSCT).	19	Mean step-count at home was most strongly affected by ankle plantar flexion strength/kg, and increasing ankle plantar flexion strength/kg was shown to promote recovery of normal physical activities. Comment: The effect of HST on physical activity had been shown in this study.
Physiotherapy management of cancer-related fatigue: A survey of UK current practice. Donnelly, C., Lowe-Strong, A., Rankin, J.,Campbell, A., Allen, J., & Gracey J.	2009	Descriptive Study. To establish physiotherapy management of cancer-related fatigue (CRF), in particular, to determine physiotherapy exercise management of CRF.	223	Physiotherapists' management of CRF includes recommending and using exercise and teaching energy conservation techniques. Comment: Another general importance of exercise to reduce cancer related fatigue revealed in this study, but the specific exercise type wasn't mentioned.
Exercise in patients receiving hematopoietic stem cell transplantation: lessons learned and results from a feasibility study Hacker, E., Larson, J., & Peace, D	2011	Prospective study To test the feasibility and acceptability of a strength-training intervention in patients receiving hematopoietic stem cell transplantation (HSCT).	10	The strength-training intervention refined from an unsupervised, home-based program to a combination supervised and unsupervised program with weekly clinic visits, and the patients reported that the exercises were very acceptable, although some started out at a very low intensity. Comment: When comparing the strength exercise with the aerobic exercise, the aerobic exercise is easier than strength exercise, that means the aerobic exercise should be feasible more than strength, and we can conclude that the aerobic exercise program is feasible among patients post HSCT.
Physical exercise as adjuvant therapy for patients undergoing hematopoietic stem cell transplantation. Wiskemann J & Huber G	2008	Literature Review	15 Study	Significant benefits from the exercise interventions have been predominantly reported for physical performance, quality of life and fatigue status of the patients. Several other benefits like a faster recurrence of immune cells or reduced severity of therapy-related side effects can be estimated. **Comment:** This study's results revealed the importance of exercise post BMT, and there is no significant decrease in physical capacity at the point of hospital discharge or during the inpatient period.

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