Physical Activity in Multiple Myeloma: A Review of the Current Literature

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Abstract

One of the major issues patients with multiple myeloma (MM) suffer from is bone instability and the resulting difficulties that come along with it, such as pain and immobility. Few studies have been performed in this patient group to investigate the effects of physical exercise on outcomes such as muscle strength, quality of life, fatigue, and pain. A PubMed search was conducted by entering the search terms "multiple myeloma" and "exercise," and "multiple myeloma" and "physical activity" that yielded 178 and 218 manuscripts, respectively. Limiting the search results to clinical trials left 13 and 14 manuscripts, respectively, and 7 studies (1 retrospective chart review, 1 questionnaire study, and 5 prospective clinical trials). The majority of these studies (5) were published in the past decade. The outcomes of several studies of exercise in MM show that physical exercise is feasible for MM patients. Compared with the control groups, the most active participants show better outcomes, such as improvements in their blood counts and in quality-of-life parameters such as fatigue, pain, sleep, and mood. One trial found that MM patients were in much poorer condition than people in a normative standard group. Some of the reported outcomes of exercise in MM have been promising but need to be substantiated in a broader setting with more diverse participants, for a longer duration, and include more endpoints. Due to the disease-inherent risk of bone-related complications, an individualized, supervised training protocol could be a preferable tool.

Being and staying active as a daily routine can be a significant challenge for patients diagnosed with multiple myeloma (MM). Not only do patients have to deal with the concomitant symptoms of the disease, but they also must face the limiting side effects of treatment. Fatigue, increased muscle tension, and pain, together with other restrictive factors, such as nausea, higher risk of infections, insomnia, and depression, negatively affect quality of daily life.

Physical activity has been shown to be beneficial for many physical functions, such as heart rate, blood pressure, insulin levels, immune function, and bone density. However, despite its potential to improve the

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health and quality of life (QOL) of patients, including those with MM, there are few studies of physical activity interventions in patients with MM. In addition, the results are oftentimes vague, and the trials sometimes lack a procedural approach that could more clearly elucidate the many potential benefits to the patient (Gan et al., 2016).

BACKGROUND

In healthy individuals, the bone-building osteoblasts are in balance with the bone-absorbing osteoclasts. In MM patients, osteoclasts become overactivated, causing bone instability—especially in the spine and long bones—and elevated blood calcium levels, increasing the risk for fractures. For a long time, physical activity was contraindicated in MM patients because of the high risk of bone fractures. This has led to many MM patients having an inactive lifestyle that promotes negative disease- and treatment-related side effects. These include increased fatigue and pain, less mobility, more joint stiffness, less muscle strength, higher sleep disturbances, and depression (Hagstrom et al., 2015). Unfortunately, these side effects can initiate a vicious circle that leads to even more pain, further limiting patients' participation in daily activities.

Studies have shown that resistance training has a positive effect on bone density (Layne & Nelson, 1999). Moreover, higher weight loads combined with fewer repetitions impact the adaptation of bone turnover to more bone health. Understanding the influence of strength training on previously damaged bones in MM patients is one area that needs to be explored more in depth.

Dealing with the consequences of a weakened immune system plays a significant role when managing and treating MM, a complex condition. When the disease is diagnosed for the first time, it oftentimes coincides with a higher susceptibility to infections. Chemotherapy and stem cell transplant, the gold standard in the treatment of MM, cause the immune system to be diminished even further. It can take several years for a patient's immune system to recover from the drastic MM treatment measures. Previous clinical trials and observational studies have suggested that exercise has a positive influence on immune function, including in patients with hematologic disorders (Sitlinger et al., 2020). However, these studies have been limited by small numbers of participating patients, leading to inconclusive results.

Studies of exercise in MM have shown that it can be safe and feasible at different stages of the disease and treatment continuum (Coleman et al., 2003; Larsen et al., 2019). However, many of the results were derived from either literature reviews, surveys patients filled out, or fitness tests as opposed to "hands-on" interventional studies. This is an indicator of how difficult it is to study exercise in MM patients.

METHODS

A literature search in PubMed in January 2021 using the search terms "exercise" and "multiple myeloma" provided 178 manuscripts; a search of the terms "physical activity" and "multiple myeloma" resulted in 218 articles. The majority of these manuscripts were published in the past decade. Limiting the search results to clinical trials left 13 and 14 manuscripts, respectively. These studies, published between 2003 and 2020, present the outcomes of only seven studies of myeloma patients performing physical exercise. In only five of these studies did patients actually exercise as part of an intervention. The two other reports are descriptive analyses of previously collected data.

Results of Clinical Trials

A prospective study conducted by Coleman and colleagues (2003) showed that physical exercise (e.g., aerobic or strength training which is planned, structured, and repetitive, in contrast to physical activity, which is any movement that one does; American College of Sports Medicine, 2021) is not only feasible for myeloma patients preparing for an autologous stem cell transplant (ASCT) but also resulted in better outcomes, including improved fatigue, mood, and better sleep, compared with the control group in a 26-week study. The number of participants was small, however, with only 24 patients in the combined intervention and control groups.

A study by Coon and Coleman (2004) randomized 12 men and 9 women with MM to an exercise intervention and interviewed them regarding their perceived exercise habits and physical activity. The authors found that the patients' hope was that being physically active would improve their myeloma outcomes.

A trial conducted by Coleman and colleagues (2008) enrolled 120 MM patients undergoing ASCT. The results of this trial suggested that patients who were more physically active during treatment had higher levels of red blood cells and therefore required fewer transfusions than the patients in the control group (Coleman et al., 2008).

In a more recent randomized study, 58 myeloma patients who were part of a larger group of hematologic cancer patients (n = 121) participated in a supervised exercise program after they underwent an ASCT (Persoon et al., 2017). The results of this 18-week study suggested that the supervised exercise program resulted in no benefits in any of the examined endpoints (e.g., cardiovascular fitness, muscle strength, and fatigue). More results from the same trial were later analyzed, which concluded that investing monetarily in the fitness program for this patient group did not result in less costly treatment afterwards (van Dongen et al., 2019).

The largest study of physical exercise and MM to date had 187 participants (Coleman et al., 2012). Over 15 weeks, newly diagnosed myeloma patients (NDMM) were randomized to perform a home-based individualized exercise program (HBIEP) or into the control group, which was given best practice recommendations of 20 minutes of walking three times a week. All participants' sleep (measured by ActiGraph), fatigue (several questionnaires), and performance in a 6-minute walk test were measured at three different timepoints, regardless of the cohort. Compared with the control group, the patients in the intervention group had better sleep, less fatigue, and better performance.

The most recent study is a cross-sectional descriptive analysis (Larsen et al., 2020). A total of 100 patients with NDMM took part in this evaluation. Compared with a normative standard of exercise performance, the MM patients were in much poorer condition. The participants underwent four physical function tests to measure their fitness: a 6-minute walk test, grip strength assessment, sit-to-stand test, and knee-extension strength test. There were no differences in the physical function tests between the intervention and control groups. The intervention and control groups both performed similarly to cancer patients in other studies.

Published Guidelines

A literature search of supporting guidelines for MM patients and exercise resulted in six articles. Of these, two reported that it would be preferable to have guidelines, and three suggested general strategies and procedures. Only one article, published by the Canadian Physical Therapy Association, provided practical recommendations developed by physical therapists in conjunction with myeloma patients (Jeevanantham et al., 2021). The guidelines provide 30 action statements for the safe and optimized application of physical exercise and management of the specific challenges that this patient group faces.

TAKEAWAYS FROM THE LITERATURE

The literature review showed that there have been only a small number of studies of physical activity in patients with MM. Some recent studies are ongoing with results still pending. Others are limited by a relatively low number of enrolled participants, leading to results and recommendations that are either too vague or not generalizable. Additionally, the durations of many reported interventions were rather short, limiting their ability to effect a significant change in the endpoints of interest.

Some of the reported outcomes have been promising but need to be substantiated in a broader setting, with more participants, a more diverse patient population, for a longer duration, and with more QOL endpoints. For example, performing physical activity regularly over a longer period of time has been shown to improve QOL in several areas, such as a decrease in fatigue, better mood, and better sleep (Layne & Nelson, 1999). Therefore, more studies are needed to explore these potential benefits of physical activity in MM patients and to detail the various barriers and challenges this patient group faces.

SUGGESTIONS FOR PROSPECTIVE EXERCISE INTERVENTIONS

There is a real, significant risk of fractures in MM patients, and any effort to realize the benefits of physical activity in improving disease- and treatment-related side effects must be balanced with adequate control of the risks. Therefore, to develop a safe and effective workout program for myeloma patients, many targets can and should be considered, including bone

lesions, spine instabilities and cord compression, hypercalcemia (which can lead to cardiac arrhythmia and renal failure), pain, low blood counts, and other contraindications (Keilani et al., 2019).

To investigate whether patients can adhere to a supervised program and to understand the reasons for not wanting to participate (e.g., some patients may worry about the effects of the program), a pilot study should use a longer intervention of more than 3 months. Due to the disease-inherent risk of bone-related complications, an individualized, supervised training protocol would be preferred. To have a positive impact on both bone disease and fatigue, a combined protocol of strength and cardiovascular aerobic training should be offered. Frequent assessments of adverse events and potential beneficial effects can provide guidance for the adjustment of interventions and endpoints, as previous definitive data are rather sparse.

For safety reasons, at our center, we present the patient's most recent imaging at an interdisciplinary conference to assess stability and give recommendations on which exercises are allowed and which should be avoided. We take additional risk-reducing steps by requiring an in-person assessment by an orthopedic surgeon or neurosurgeon and/or a physical therapist before the start of an intervention.

The COVID-19 pandemic made in-person training sessions more challenging but revealed opportunities for developing remote interventions using live and recorded streaming and fitness tracker technology. Many patients already use fitness trackers to document their daily activities. If authorized by the patient, access to the data on these devices can provide further insight into the effects of an exercise intervention on the activities of daily living beyond the assessments performed at a research institution. When setting up these protocols, it is essential to adhere to HIPAA privacy and data security standards.

Lastly, exercises that are used in clinical trials with MM patients need to be easy to perform correctly and should provide a variety of ways to adjust the performance to make them both flexible and more challenging over time.

Potential Endpoints for Exercise Interventions

Areas of interest in myeloma research that could be addressed with an exercise intervention are MM bone disease, fatigue, and treatment side effects such as peripheral neuropathy, sleep, and other markers of QOL. The International Myeloma Working Group has also provided guidelines on how to assess frailty in patients with MM (Palumbo et al., 2015).

Suggested Exclusion and Inclusion Criteria

To be eligible for exercise studies, patients with MM should (1) be older than 18 years, (2) have an Eastern Cooperative Oncology Group Performance Status of 0 to 1, (3) show no signs of comorbidities, myeloma symptoms, or treatment side effects that are considered by the treating physician to exclude them from physical activity, (4) be able to understand and adhere to the training procedures, and (5) sign a specific informed consent form. Exclusion criteria would be (1) symptomatic pathological fractures and spine instabilities, (2) other acute bone instability, (3) comorbidities that would cause danger to the patient, and (4) unwillingness or inability to follow study requirements.

PRELIMINARY EXPERIENCE

The results of a study at our center (NCT03793907), "Feasibility of Strength Training and Impact on Pain and Quality of Life in Patients with Multiple Myeloma," are pending as follow-up is ongoing. The primary endpoint of this study is to investigate if participating in a 6-month intervention is feasible. Adherence to either cohort is the secondary endpoint. In addition, comparison of lab parameters, physical activity level, pain, polyneuropathy, fatigue, and psycho-oncologic parameters during and after intervention will be measured.

Thus far, it has been feasible to offer a supervised individualized exercise program to myeloma patients at different stages of their disease. Some patients are currently undergoing treatment, some are in remission and are not receiving any medications for MM, and others are enrolled during maintenance therapy. Many patients initially feared that they could not adhere to a longer-term (more than 3 months) intervention, but to date, only two patients have withdrawn from the study due to lack of time. Table 1 lists anecdotal reports on the positive effects the participants have experienced during their time on the study.

Therefore, the preliminary results of this trial have suggested that participation in a supervised

training protocol can improve patients' QOL in immediate and tangible ways. Challenges noted by patients have been adherence to regular workout sessions (especially in patients with active disease), long travel time to the institution, and monetary constraints.

In the 18 months since the study began, we enrolled a total of 32 patients in either a strength training or walking cohort. Only one patient experienced a serious adverse event, but it was not related to the study.

FUTURE PLANS AND CONSIDERATIONS

Our ongoing study suggests that physical activity is feasible for myeloma patients. In order to expand this intervention to more patients in different stages of disease, it is necessary to consider multiple means of delivering the intervention, including remote options. This will be done in a new prospective trial (https://clinicaltrials.gov/ct2/show/NCT05312255), "Improving Host Factors in Patients With Monoclonal Gammopathies." In this study, after they have received a thorough assessment upfront, patients work out two times a week for half a year in their homes. They will be equipped individually with dumbbells, resistance bands, and a fitness tracker. Patients get prompts to increase their weekly step count to the recommended 300 minutes per week. A personal trainer, who is also an experienced myeloma nurse, supervises the particular workouts consisting of different individualized sessions of resistance training. The study team also includes a physical therapist, a hematologist, a neurosurgeon, and research personnel. Participants are identified by the treating advanced practice providers (APP) and physicians. One question is whether it is possible to give patients an individualized exercise plan to perform at home. There are several factors to consider in order to design an effective remote intervention. One requirement is that patients have a customized strategy suitable to their strengths and weaknesses. Additionally, the intervention should include a self-guided, automated questionnaire to assess restrictions and limitations in order to identify the proper movements for each patient.

A well-designed remote, home-based intervention will also need to consider what tools would be helpful or necessary to perform the exercises.

Table 1. Participant Reports on Positive Effect of the Study

- "I can now open a juice bottle again."
- "I don't feel as tired after treatment."
- "I have less back pain."
- "It is much easier getting into my car and not having to drag my leg into it."
- "My neuropathy has improved."
- "I feel stronger in my legs and can stand up from a chair more easily."
- "I can reach the top shelf in the kitchen, because I can stand on my toes again without pain or balance issues."
- "I can take longer walks with my dog, and I can even pick up the droppings more easily."
- "I have fewer muscle cramps at night."

The COVID-19 pandemic caused many events to go online and be performed in a remote setting. Some personal trainers offer training sessions live via virtual platforms or as recorded videos. Using these technologies, a much broader group of patients could be reached, as transportation, starting times, parking, and other barriers would not be relevant in a remote scenario. Along with a fitness tracker, a smartphone with off-the-shelf or customized apps would complement the intervention.

While there are many positive aspects to participating remotely, there is also a downside. In a home-based intervention, patients would not be immediately supervised, and if accidents happened during their workout, help might be far away. Furthermore, the remote setting would allow "cheating" more easily, with negative effects on outcomes and a higher risk of accidents, as no one would be present to help the patient complete an exercise with proper form. Many people report that it is not easy to adhere to a program if they are alone at home. It helps them to have it marked on their calendars or scheduled in their timetables. This gives the right amount of pressure to stick to the intervention schedule. In addition, the benefits of meeting others, exchanging ideas, and having some fun is not to be underestimated.

SUMMARY

Physical exercise in MM patients has been proven to be feasible and can be done at any stage of treatment. Data indicate that it should be performed in a supervised, individualized setting. Potential endpoints of respective studies should be QOL, influence on immune function, and bone disease. Physical exercise, when it is safe to do so, has

many benefits for each patient regardless of their state of disease. Especially when considering that patients live longer with better treatment, the impact on improved performance of daily routines is desirable. To enhance the range of motion and strengthen the bones and joints, supervised, individualized cardiovascular exercise in combination with body weight or free weight training can be implemented safely for almost every patient.

The present literature review shows that patients can be physically active not only in times of remission but also when newly diagnosed, preparing for a stem cell transplant or cellular therapy, and later on in a more advanced setting. This requires a thorough assessment upfront to provide a highly secure environment to ensure no adverse events occur.

It is recommended to do at least two workout sessions per week to not only get good results, but also to maintain them. When performing exercise in a research setting, we recommend having at least 6 months of physical activity due to better expected outcomes. Moreover, having a supervised setting is favorable to home-based due to better documentation. To have reliable results, not only questionnaires but also measurable variables such as blood parameters or using a fitness tracker provides more accurate information.

Disclosure

The authors have no conflicts of interest to disclose.

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