Effects of Exercise on Muscle Strength, Fatigue, and Aerobic Capacity in Patients with Multiple Myeloma Bone Disease: Literature Systematic Review

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Efeitos do Exercício na Força Muscular, Fadiga e Capacidade Aeróbica em Pacientes com Doença Óssea do Mieloma Múltiplo: Revisão Sistemática da Literatura

Efectos del Ejercicio sobre la Fuerza Muscular, la Fatiga y la Capacidad Aeróbica en Pacientes con Enfermedad Ósea del Mieloma Múltiple: Revisión Sistemática de la Literatura

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ABSTRACT

Introduction: Multiple myeloma (MM) is an oncohematological cancer, characterized by bone pain and osteolytic lesions or myeloma bone disease (BD), which impacts the quality of life and functionality of these individuals. Although there are reviews on the effectiveness of exercise programs in patients with MM, there are no studies specifically focused on those with BD. **Objective:** To evidence the effects of exercise programs on muscle function, aerobic capacity, and fatigue in patients with BD from MM. **Method:** Systematic review registered in PROSPERO (CRD42024515745) that followed the PRISMA criteria. We searched for randomized controlled trials in the PEDro, MEDLINE/PubMed, Cochrane Library, Scopus, and CINAHL databases, without restrictions on language or publication date. Descriptors and keywords included "multiple myeloma" and "exercise". Methodological quality was assessed using the PEDro scale and the risk of bias by the Risk of Bias 2.0 tool. **Results:** Three randomized controlled trials were included, with 219 participants, 160 of whom presented BD, including individuals of both sexes. The exercise protocols were similar, combining moderate-intensity exercises individualized for each patient. As a result, there was a significant improvement in fatigue and muscle strength. Methodological quality scores ranged from five to seven. **Conclusion:** This review highlights that physical exercise can improve muscle strength and reduce fatigue in patients with MM who have bone lesions.

Key words: Multiple Myeloma/therapy; Exercise Therapy/methods; Fatigue/prevention & control; Rehabilitation; Systematic Review.

RESUMO

Introdução: O mieloma múltiplo (MM) é um câncer onco-hematológico caracterizado pela dor óssea e lesões osteolíticas ou doença óssea (DO) no MM, que impactam na qualidade de vida e funcionalidade desses indivíduos. Embora existam revisões sobre a eficácia de programas de exercício em pacientes com MM, não há estudos com recorte específico para os acometidos com DO. **Objetivo:** Evidenciar os efeitos de programas de exercícios na função muscular, capacidade aeróbica e fadiga em pacientes com DO do MM. **Método:** Revisão sistemática registrada no PROSPERO (CRD42024515745) que seguiu os critérios PRISMA. Buscaram-se ensaios clínicos randomizados nas bases de dados PEDro, MEDLINE/PubMed, *Cochrane Library*, Scopus e CINAHL, sem restrições de idioma ou data de publicação. Descritores e palavras-chave incluíram "mieloma múltiplo" e "exercício". A qualidade metodológica foi avaliada usando a escala PEDro e o risco de viés pela ferramenta *Risk of Bias* 2.0. **Resultados:** Três ensaios clínicos randomizados foram incluídos, com um total de 219 participantes, 160 apresentaram DO, incluindo indivíduos de ambos os sexos. Os protocolos de exercícios eram semelhantes, combinando exercícios de intensidade moderada e individualizados para cada paciente. Como resultado, houve melhora significativa na fadiga e força muscular. As pontuações de qualidade metodológica variaram de cinco a sete. **Conclusão:** Esta revisão evidencia que exercícios físicos podem melhorar a força muscular e reduzir a fadiga em pacientes com MM que possuem lesões ósseas.

Palavras-chave: Mieloma Múltiplo/terapia; Terapia por Exercício/métodos; Fadiga/prevenção & controle; Reabilitação; Revisão Sistemática.

RESUMEN

Introducción: El mieloma múltiple (MM) es un cáncer oncohematológico caracterizado por dolor óseo y lesiones osteolíticas o enfermedad ósea en mieloma múltiple (EO), que impactan en la calidad de vida y funcionalidad de estos individuos. Aunque existen revisiones sobre la eficacia de programas de ejercicio en pacientes con MM, no hay estudios específicos para aquellos afectados por EO. **Objetivo:** Evidenciar los efectos de programas de ejercicio en la función muscular, capacidad aeróbica y fatiga en pacientes con EO por MM. **Método:** Revisión sistemática registrada en PROSPERO (CRD42024515745) que siguió los criterios PRISMA. Se buscaron ensayos clínicos aleatorizados en las bases de datos PEDro, MEDLINE/PubMed, Cochrane Library, Scopus y CINAHL, sin restricciones de idioma o fecha de publicación. Los descriptores y palabras clave incluyeron "mieloma múltiple" y "ejercicio". La calidad metodológica se evaluó usando la escala PEDro y el riesgo de sesgo con *Risk of Bias* 2.0. **Resultados:** Se incluyeron tres ensayos clínicos aleatorizados, con un total de 219 participantes, 160 presentaban EO, incluyendo individuos de ambos sexos. Los protocolos de ejercicio eran similares, combinando ejercicios de intensidad moderada e individualizados para cada paciente. Como resultado, hubo una mejora significativa en la fatiga y fuerza muscular. Las puntuaciones de calidad metodológica variaron entre cinco y siete. **Conclusión:** Esta revisión evidencia que el ejercicio físico puede mejorar la fuerza muscular y reducir la fatiga en pacientes con mieloma múltiple que presentan lesiones óseas.

Palabras clave: Mieloma Múltiple/terapia; Terapia por Ejercicio/métodos; Fatiga/prevención & control; Rehabilitación; Revisión Sistemática.

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INTRODUCTION

Multiple myeloma (MM) is an incurable neoplasm that originates in plasma cells, responsible for the production and release of monoclonal immunoglobulins or M proteins[1]. Epidemiological data show a higher incidence among men, individuals of African descent, and those aged 60 years and over[2]. Due to the underlying physiopathology of MM and therapeutic interventions, afflicted patients display a clinical spectrum characterized by dysfunction in bone reabsorption, kidney complications, hemoptysis, anemia, fatigue, weight loss, hypercalcemia, and bone fractures[2,3].

Approximately 80% of MM patients manifest clear lytic lesions on skeletal radiographs, while 5% show osteopenia identified by bone densitometry[4]. There are significantly more lytic lesions in the axial skeleton than in the appendicular skeleton. Frequently compromised areas include vertebrae, skull, costal arches, pelvis, and proximal segments of the humerus and femur[5]. These fractures significantly impact the quality of life and are associated with chronic pain and, often, motor deficits.

Among the therapeutic approaches for the disease's bone manifestations, we highlight kinesiotherapy, which can confer significant benefits to the functionality of this group of patients[6]. According to the International Classification of Functioning, Disability and Health (ICF), functionality encompasses all body functions, activities, and participation, involving and correlating factors both intrinsic and extrinsic to the individual[7].

Regarding body functions, a cross-sectional study indicated that the muscle strength and aerobic capacity of patients with MM were below the reference values[8]. Furthermore, Larsen et al.[9] showed that patients recently diagnosed with MM exhibit poorer physical function when compared to normative data and other cancer populations, with that disparity especially attributed to the presence of bone disease (BD), pain, and fractures. These repercussions are more heightened in elderly patients, on whom physical function is intrinsically linked to levels of functionality and independence, encompassing diverse elements of physical fitness, such as endurance, strength, flexibility, balance, and aerobic capacity. Thus, poor physical conditioning can predict functional limitations in activities of daily living and the resulting impact on quality of life[10].

Therefore, the early identification of physical decline and implementation of preventive strategies, such as regularly practicing physical activity, becomes crucial to optimizing disease prognosis and preserving the functionality and quality of life of these individuals. A previous literature review documented the efficacy and applicability of exercise programs in patients with MM[6]; however, no studies have framed the population with BD, and no outcomes related to physical function have been assessed.

Given this gap in the literature, the objective of this review is to assess the effects of exercise programs on muscle function, aerobic capacity, and fatigue in patients diagnosed with MM who have BD.

METHOD

Systematic literature review that followed criteria delineated by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[11] guideline, with protocol recorded in the PROSPERO[12] systematic review state database under record number CRD42024515745. The PICO strategy considered the following: P (patient) = individuals with MM, I (intervention) = exercises, C (comparison) = usual care, O (outcome) = fatigue, peripheral muscle strength, and aerobic capacity.

The study selection included complete randomized controlled clinical trial (RCT) articles, including feasibility studies that investigated the effect of exercise programs for patients with BD due to MM with an emphasis on improving muscle function, aerobic capacity, and fatigue. It is worth mentioning that the population did not need to be composed exclusively of patients with BD. Eligible studies should evaluate functionality outcomes, encompassing parameters such as muscle strength, aerobic capacity, and cancer-related fatigue. Articles that did not highlight the participation of patients with BD or whose samples were not exclusively constituted by individuals with MM were excluded.

To elaborate this study, extensive research was conducted in the Physiotherapy Evidence Database (PEDro)[13], MEDLINE/PubMed, Cochrane Library, Scopus, and CINAHL databases. To ensure a comprehensive search, no restriction was imposed regarding year of publication or language. The search used the descriptors and synonyms "Multiple myeloma" and "Exercise", previously defined by the Medical Subject Headings (MeSH) system, and connected by Boolean operators OR and AND. The full search strategy on the databases is described in Chart 1.

Two independent and blinded reviewers conducted the article selection from February to July 2024. Initially, screening was done by reading titles and abstracts. Later, the included articles were submitted to full reading, which verified if they met the defined eligibility criteria. Reviewers independently extracted data from the published studies using a standard table. This table included aspects related to the study population, type

Chart 1. Full search strategy on databases

Database	Descriptors
PubMed	(((((((((“Multiple Myeloma”[Mesh]) OR (Multiple Myelomas)) OR (Myeloma*, Multiple)) OR (Myelomatosis)) OR (Myelomatoses)) OR (Myeloma-Multiple)) OR (Myeloma Multiple)) OR (Myeloma-Multiples)) AND (((((((“Exercise”[Mesh]) OR (Exercises)) OR (Physical Activity)) OR (Physical Activities)) OR (Physical Exercise*)) OR (Acute Exercise*)) OR (Exercise Training*))) AND ((((Randomized Controlled Trial[Publication Type])) OR (Randomized Controlled Trial*)) OR (Clinical Trial*))
PEDro	“Multiple myeloma” AND “Fitness training” AND “Clinical trial”
Cochrane Library	(Multiple Myeloma) OR (Multiple Myeloma) OR (Myeloma*, Multiple) OR (Myelomatosis) OR (Myelomatoses) OR (Myeloma-Multiple) OR (Myeloma Multiple) OR (Myeloma-Multiples) AND (Exercise) OR (Exercises) OR (Physical Activity) OR (Physical Activities) OR (Physical Exercise) OR (Acute Exercise) OR (Exercise Training) AND (Randomized Controlled Trial) OR (Clinical Trial)
Scopus	“TITLE-ABS-KEY(("Multiple Myeloma" OR "Multiple Myeloma" OR "Myeloma*, Multiple" OR Myelomatosis OR Myelomatoses OR "Myeloma-Multiple" OR "Myeloma Multiple" OR "Myeloma-Multiples") AND (Exercise OR Exercises OR "Physical Activity" OR "Physical Activities" OR "Physical Exercise*" OR "Acute Exercise*" OR "Exercise Training*") AND ("Randomized Controlled Trial" OR "Clinical Trial" OR "Controlled Clinical Trial"))
CINAHL	((MH "Multiple Myeloma" OR "Multiple Myeloma*"" OR "Myeloma*, Multiple" OR Myelomatosis OR Myelomatoses OR "Myeloma-Multiple" OR "Myeloma Multiple" OR "Myeloma-Multiples")) AND ((MH Exercise OR Exercise* OR "Physical Activity" OR "Physical Activities" OR "Physical Exercise*" OR "Acute Exercise*" OR "Exercise Training*")) AND (("Randomized Controlled Trial" OR "Clinical Trial" OR "Controlled Clinical Trial"))

of intervention employed, instruments and devices used to assess the effects on muscle function and aerobic capacity before and after the intervention, as well as the obtained results.

To assess the quality of articles, the 11-criterion PEDro[13] scale was applied. Among the evaluated criteria, the scale assessed whether the eligibility criteria were described, how the allocation of subjects was conducted, whether there was blinding of subjects, and how the data analysis was done. Each criterion corresponds to one point; however, criterion 1 is not considered in the score as it assesses the study's external validity, so the maximum points these studies could score would be 10[13]. Thus, studies that scored between 8 and 10 were considered of excellent quality; between 6 and 7, of good quality; those with scores between 4 and 5, of reasonable quality; and those with scores below 4 were considered low quality[14].

The risk of bias assessment was conducted independently by two reviewers who used the Revised Cochrane Risk of Bias 2.0 (RoB 2.0)[15] tool, provided by Cochrane Collaboration, as a reference. To assess the possible risk of biases, RoB 2.0 analyzes the following aspects of an RCT: bias in the randomization process, deviations from the planned intervention, bias due to absent data, bias in measuring outcomes, and bias in reporting results[16]. Each domain is classified as low risk of bias, with some concerns, or high risk of bias. The study's final evaluation is determined by the worst classification obtained in any domain; therefore, if a single domain is considered high risk, the entire study will be classified that way.

RESULTS

Of the 526 articles identified through database searches, 153 were excluded as duplicates. After analyzing titles and abstracts, 11 articles were considered eligible for full-text review. A manual search of reference lists was also conducted in parallel, leading to the inclusion of one more study. Finally, only three studies met the defined inclusion criteria, as described in Figure 1.

Ultimately, the selected studies comprised a total sample of 219 participants, from both sexes, with most patients presenting MM BD (n=160; 73%). The participants' age group ranged from 35 to 86 years, with the male sex predominating. In both categories, there was a significantly greater prevalence of patients with BD in comparison to those without this clinical condition[17-19]. However, participants were in different cancer stages. One of the studies was conducted with recently diagnosed people[18], the second with patients submitted to stem-cell transplant[19], and the last one with survivors who completed treatment at least six months before[17].

The exercise program was not compared to any other intervention; thus, the control group followed usual care[17,19] or additionally received health education[18].

The articles included (Table 1) used the following instruments to assess the outcomes of interest for this study: the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)[17,19] questionnaire to assess fatigue; manual dynamometer[17-19], for hand grip strength; 10 maximum repetitions test (10MR)[17], sit-to-stand test (STST)[18,19] and dynamometer[18], for muscle strength of lower limbs; estimated peak oxygen uptake (VO2peak)[17], and 6-minute walk test (6WT)[18,19], for aerobic capacity.

Peripheral muscle strength significantly improved in two studies after the intervention period[17,19], although in the Larsen et al.[18] RCT, the control group significantly outperformed the intervention (exercise) group in the STST at different moments of the assessment. There was no improvement in hand grip strength in any of the included articles[17-19]. Only two RCTs assessed fatigue, one of them showed significant improvement[19], while the other's exercise program had minimal effect[17]. Finally, the findings diverged about the post-intervention aerobic capacity, presenting a statistically significant increase in one of the studies[18] and a median increment of the distance traveled when 6WT was assessed[17], but no statistically significant difference in the study that assessed VO2peak[17].

Regarding methodological quality, two of the selected studies presented good quality, and one was deemed reasonable according to the PEDro scale, varying from 5 to 7 points (Table 2).F1

Regarding the risk of bias, the overall analysis raised some concerns for two studies, while one study was rated as having a high risk of bias (Figure 2). The most frequently compromised domains were deviations from the proposed intervention, measurement of outcomes, and selection of the reported result. For instance, the feasibility study by McCourt et al.[19] required adjustments to the research protocol due to the COVID-19 pandemic, including modifications to the assessment methods.

DISCUSSION

Physical exercise interventions have been studied to improve physical function and quality of life in patients with BD secondary to MM, demonstrating beneficial effects in muscle strength and mobility[20]. This review demonstrated that exercise programs can be effective in improving the physical function of these patients, particularly by enhancing lower limb muscle strength and promoting benefits against fatigue. The included studies compared exercise programs with usual care and guidance for the practice of physical activity in the control group and combined aerobic resistance and/or functional exercises supervised individually or at home[17-19].

The exercise programs were consistent with the physical activity recommendations for this population with moderate intensity for two or three non-consecutive

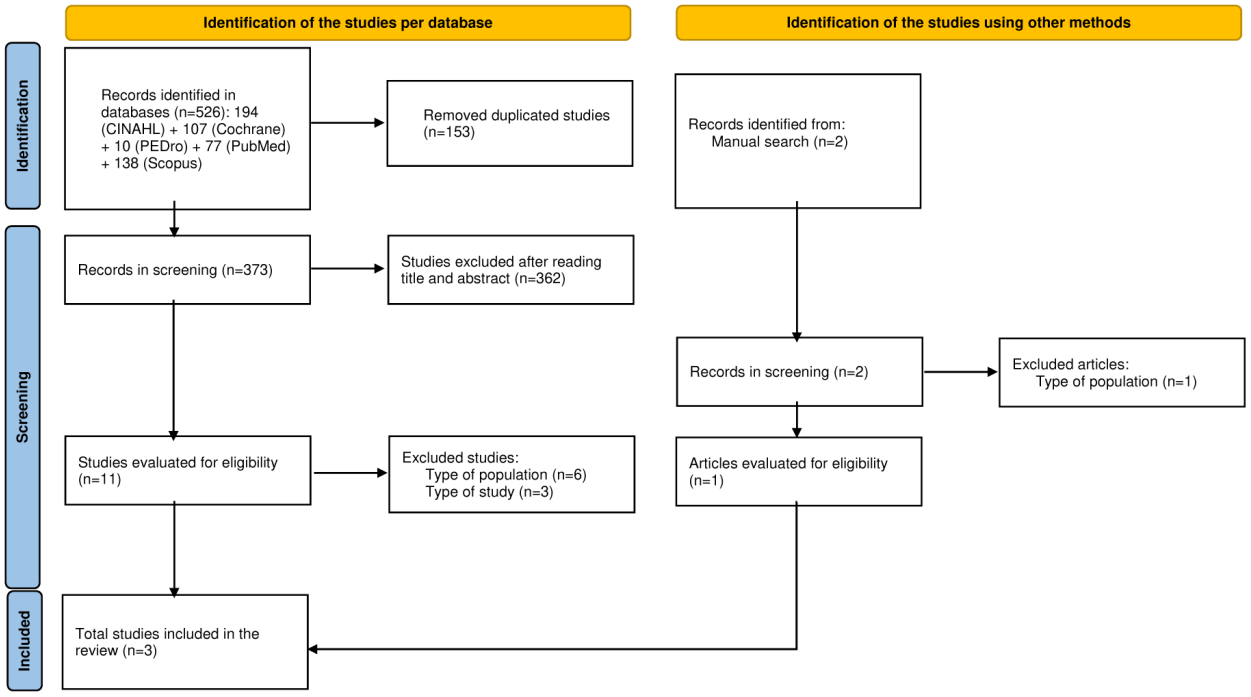

Figure 1. Flowchart of the article search and selection process
Source: Adapted from PRISMA, 2020[11].

Table 1. Detailing of the studies selected for the systematic review on exercise programs for patients with bone disease related to multiple myeloma

Author/Year	Population	Assessment method	Intervention	Results
Koutoukidis et al. (2020)[17]	83 participants CG: 42 [29 (69%) with bone disease] IG: 41 [29 (71%) with bone disease]	FACIT-F, VO2peak estimated on the ergonomic bike, 10MR test, and manual dynamometer	6 months **CG**: usual care **IG**: aerobic exercises (50-75% of max HR) + endured and customized functional exercises	The IG presented little effect on fatigue at 3 or 6 months. The IG VO2peak increased in 3 months, but with no statistical significance ($p=0.08$). The LLs MS presented significant improvement between groups, with an 8.4 kg increase (CI 95%: 0.5-16.3) in favor of IG at 3 months and 10.8 kg (CI 95%: 1.2-20.5) at 6 months. However, there was no difference among the hand grip strength groups After 12 months, the means of the results measurements in each experimental group were consistent with those recorded at 3 and 6 months, especially LLs MS
Larsen et al. (2024)[18]	86 participants CG: 42 [29 (69%) with bone disease] IG: 44 [35 (80%) with bone disease]	Dynamometer, 6WT and 30s STST	10 weeks **CG**: usual care + health education (guidance on physical activity and ergonomic instructions for lifting and transferring) **IG**: Exercise program 3x/week (resistance training, 3x12-15 reps + aerobic training, 20 min, 14-16 RPE) and physical activity 4x/week (~30 min, 12-13 RPE) Time marks: baseline (T1), post-intervention (T2), after 6 months (T3), and after 12 months (T4)	Knee stretch strength decreased in the first 6 months for both groups. From T3 to T4, strength returned in both groups, but remained significantly lower than in T1 Grip strength decreased significantly in both groups in 6 months, and in IG, also after 12 months The 30s STST presented a statistically significant increase in both groups (except IG after 6 months). Increase of 1.6 repetitions in IG ($p=0.009$) and almost two repetitions in CG ($p=0.003$) post-intervention. In T4, the number of repetitions increased 2.1 ($p<0.001$) in IG and 3.5 ($p<0.001$) in CG In 6WT, there was a statistically significant increase of about 42 m in both groups from T1 to T2. Generally, both groups continue to have little increases over time
McCourt et al. (2023)[19]	50 participants CG: 27 [20 (74%) with bone disease] IG: [18 (78%) with bone disease]	FACIT-F, 6WT, manual dynamometer, and STST	11 months **CG**: Usual care + physiotherapy or occupational therapy during admission to ASCT **IG**: Behavior change + aerobic exercises (3x/week; 60–80% HRR, initial duration 15 min, increasing 5 min/week) + functional exercises (3x/week; intensity, progression, and personalized adaptation to bone disease) Temporal marks: in-person supervised exercises (Phase 1), telecommunication-supervised (Phase 2), and with no supervision (Phase 3)	In phase 3, only IG presented an important significant difference for fatigue (+5.7, CI 95%: 0.1, 11.2) and greater improvements in the 6WT distance median were observed in phase 3 and throughout the study period. There were no significant changes in hand grip strength. The 1-min STST indicated intragroup improvements for IG comparing all phases

Captions: 10MR: 10 maximum repetitions; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; Max HR: maximum heart rate; HRR: heart rate reserve; MS: muscle strength; CG: control group; IG: intervention group; CI: confidence interval; LLs: lower limbs; rep: repetition; RPE: rate of perceived exertion; ASCT: autologous stem cell transplant; 6WT: 6-minute walk test; STST: sit-to-stand test; VO2peak: peak oxygen uptake.

Table 2. PEDro scale methodological quality assessment of the articles that applied exercise programs to patients with bone disease related to multiple myeloma

Author/year	1*	2	3	4	5	6	7	8	9	10	11	Total
Koutoukidis et al. (2020)[17]	Yes	X	X	X				X	X	X	X	7/10
Larsen et al. (2024)[18]	Yes	X		X				X	X	X	X	6/10
McCourt et al. (2023)[19]	Yes	X		X				X		X	X	5/10

Note: 1. Eligibility criteria were specified; 2. Random allocation of subjects; 3. Concealed allocation of subjects; 4. Groups were similar at baseline; 5. Blind subjects; 6. Blind therapists; 7. Blind evaluators; 8. Measured 85% of results; 9. Intention of treatment; 10. Comparison between groups; 11. Precision and Variability. *Disregarded criteria in the final score.

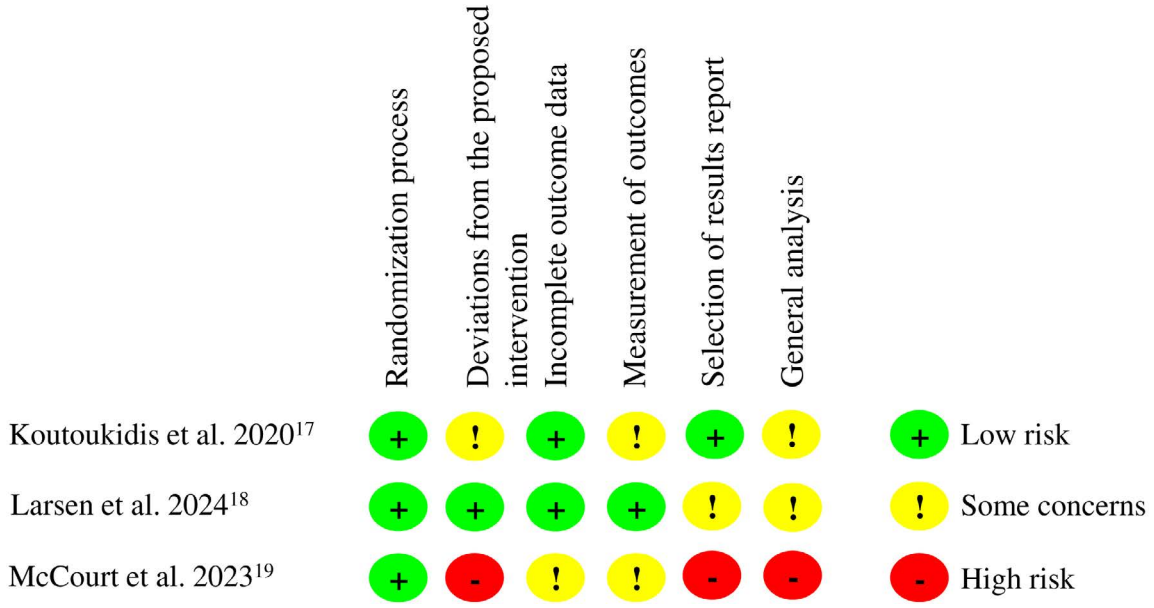

Figure 2. *Risk of Bias* 2.0 risk of bias assessment per domain

days per week[21]. Despite the training prescription being individualized to each participant, load progression and aerobic exercises were also similar, considering the 10MR test results and estimated maximum heart rate. Finally, the exercise frequency in the studies was comparable among the studies, starting with three times a week in the first three months and increasing to four times a week in the following period[17-19].

None of the included studies found a significant between-group difference in hand grip strength[17-19] and, additionally, Larsen et al.[18] observed a significant decline in this measure among recently diagnosed patients after 6 and 12 post-intervention compared to baseline. However, the intervention period of this study was the shortest (10 weeks) compared to the others, and had no improvements in lower limb muscle strength, which decreased after six months[9]. On the other hand, Koutokidis et al.[17] implemented a six-month exercise protocol, which presented significant improvement in leg muscle strength in the first three months, in the second trimester of intervention, and after 12 months, indicating the benefits of exercise in the long term. A single-arm pilot trial with treated MM survivors, in which half the sample presented severe BD, also reported significant improvement in upper and lower limb strength after a six-month combined exercise program[22].

The STST is also a functional measurement for strength in the lower limbs. In two RCTs, patients demonstrated improved performance from baseline, but the between-group difference was not statistically significant[18,19]. However, another study with patients diagnosed with leukemia that underwent a multimodal program, including combined exercises and nutritional support, showed significant improvement, in favor of

the intervention group, for this same outcome[23]. Thus, the positive effect on muscle strength becomes evident, and, given the context of a senior population, immediate strengthening in the long term is essential, both for maintaining functionality, preventing falls, and reducing mortality and morbidity for this group.

The aerobic capacity of patients with BD is significantly reduced in comparison to the general population and can be attributed to several factors associated with MM, including bone destruction, pain, anemia, and fatigue, which negatively affect physical function[18]. In the studies included in this review, aerobic capacity was assessed by 6WT[18,19] and VO2peak[17].

Regarding 6WT, although improvement was observed in the intervention group, the difference was not statistically significant, with greater distance improvements during the rehabilitation phase and after 11 months[18,19]. These findings are in line with two other RCTs by Alibhai et al.[24] and Coleman et al.[25], in which onco-hematological patients from the exercise group showed improvement in 6WT, but with no significant difference when compared to the control group. In contrast, the studies by Jarden et al.[23] and Knols et al.[26] investigated the effects of a 12-week multimodal exercise program in patients with hematological neoplasms, reported a significant improvement in 6WT performance.

One of the RCTs analyzed the estimated VO2peak to assess aerobic capacity, which presented apparent improvement with no statistical significance at three months (p=0.08), an effect that was not maintained at six months (p=0.27)[17]. Similarly, a study that also applied a combined exercise program in patients with MM did not find significant differences in VO2peak after three months and six months of intervention[22]. Thus, the effect of exercise on aerobic capacity was inconclusive, considering the use of different measurements and the divergent results across studies.

Using the FACIT-F questionnaire, McCourt et al.[19] observed significant improvement in fatigue in the intervention group compared to the control group, while the second study found little effect on this variable in an exploratory analysis of a subsample with clinical fatigue at baseline[17]. The study by Groeneveldt et al.[22], which also used combined exercises as intervention in patients with MM and BD, found significant improvements in fatigue after three months and six months of intervention using the same assessment instrument. These results contradict the findings of two RCTs, in which patients with MM reported a worsening of fatigue, a finding the authors attributed to the increasing number of myeloablative treatments[25,27].

However, the findings of this review are in line with the results of a meta-analysis that reported significant improvement in fatigue through aerobic exercise in patients with hematological neoplasms[28]. Cancer-related fatigue is a subjective and multifactorial symptom, influenced by factors such as lifestyle and treatment phase, which can also justify divergence between some of the studies' findings. Moreover, through baseline correlation analysis, Koutoukidis et al.[17] observed that participants who reported greater fatigue had a lower VO2peak (p<0.001) and leg strength (p=0.017), indicating a negative correlation between fatigue level and physical function in this population.

The limitations found in this study included the sample size[19], variable follow-up time[15-17], and high participant withdrawal rate[17-19]. Additionally, one study noted that the COVID-19 pandemic necessitated adaptations to the intervention protocol and assessments[9].

The findings from this review are useful to help the therapeutic planning of patients with MM and bone lesions, aiming to improve muscle function and aerobic capacity, and consequently, their quality of life. Considering that MM survivors often suffer from persistent deformities, chronic pain, and reduced mobility due to bone destruction, physical activity is hypothesized to improve mobility and functional capacity, in addition to reducing the risk of falls and improving bone health[21,29]. Therefore, exercise programs should be recommended from the time of diagnosis, as they represent a safe and evidence-based non-pharmacological intervention.

The present study had the following limitations: scarcity of clinical trials addressing this specific population, quality of the studies, and impossibility of conducting meta-analysis, given that the assessment instruments of the included studies were heterogeneous, so the study presents only a qualitative analysis of the outcomes. Therefore, further robust clinical trials are needed to assess the effects of exercise on the evaluated outcomes and others, such as balance and coordination, to strengthen the evidence base.

CONCLUSION

This systematic review highlights the benefits of exercise programs in improving lower limb muscle function and potential benefits related to fatigue in patients with MM-related bone lesions. The findings regarding their effect on aerobic capacity are inconclusive.

CONTRIBUTIONS

Tayla Teixeira Lima has substantially contributed to the study design, planning, data acquisition, analysis, and interpretation, as well as the wording. Cássio Magalhães da Silva e Silva has substantially contributed to the study planning, data interpretation, and wording.

Camila Reinbold Rezende has contributed to the study design, planning, and wording. Anita Gabriele de Jesus Damasceno has contributed to data acquisition, analysis, interpretation, and wording. All the authors approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

All the contents associated with the article are included in the manuscript.

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