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A precision-based exercise program for patients with multiple myeloma

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Abstract

Objectives: Aim of this study was to retrospectively evaluate an interdisciplinary consultation followed by a precision-based exercise program (PEP) for myeloma patients with stable and unstable bone lesions.

Methods: Data of myeloma patients ($n = 100$) who received a PEP according to an orthopedic evaluation were analyzed. Bone stability was assessed by established scoring systems (Spinal Instability Neoplastic Score [SINS], Mirels' score). All patients with stable and unstable osteolyses received a PEP and $n = 91$ were contacted for a follow-up interview.

Results: In 60% of patients at least one osteolysis of the spine was considered potentially unstable or unstable. Following consultation, the number of patients performing resistance training could be significantly increased (≥2 sessions/week, 55%). Musculoskeletal pain was reported frequently. At the follow-up interview, 75% of patients who performed PEP stated that painful symptoms could be effectively alleviated by exercise. Moreover, only patients who exercised regularly discontinued pain medication. No injuries were reported in association with PEP.

Conclusion: We were able to demonstrate that individualized resistance training is implementable and safe for myeloma patients. By means of a PEP, patients' self-efficacy in managing musculoskeletal pain was enhanced and pain medication could be reduced.

KEYWORDS

bone lesion, bone stability, Mirels' score, multiple myeloma, musculoskeletal pain, precision-based exercise, spinal instability neoplastic score

Novelty Statement

What is the new aspect of your work?

We evaluated an exercise program for myeloma patients, which was tailored to individual clinical conditions and bone lesions. Of note, also patients with unstable osteolyses were included.

What is the central finding of your work?

A individualized resistance training is implementable and safe for myeloma patients. Physical exercise provides a valuable tool for treatment of musculoskeletal pain in multiple myeloma.

What is (or could be) the specific clinical relevance of your work?

Following an orthopedic evaluation, a precision-based exercise program can be recommended for myeloma patients with stable and unstable osteolyses.

1 | INTRODUCTION

Physical exercise is a key element in improving the quality of life and physical function in cancer patients. Several studies have shown that regular exercise might not only improve patients' well-being in general, but also body awareness, coordination, muscle strength, and bone density.[1–4] Furthermore, disease-related or therapy-associated side effects, such as cancer-related fatigue, peripheral neuropathy or cardiotoxicity can be alleviated by physical exercise.[5–13] Even though the benefits of regular exercise have been demonstrated in-depth and patients frequently express interest in structured exercise programs, confidence in recommending physical activity is greatly reduced once bone lesions have occurred.[14] There are only a limited number of studies available on physical exercise in cancer patients with bone metastases in general and even less on patients with unstable bone lesions specifically.[15] Multiple myeloma is a disease characterized by monoclonal expansion of plasma cells in the bone marrow which often causes harmful osteolytic bone lesions in patients. Even though still considered an incurable disease, therapeutic achievements over the last 20 years have immensely increased overall survival and quality of life for myeloma patients.[16–23] Therefore, patients are very interested in pursuing a healthy way of living which also includes regular physical activity. It has been shown that 75% of myeloma patients want to improve their level of physical performance, 59% are interested in advice on physical exercise[24] and 55% would like to follow a structured exercise program.[25] Unfortunately, merely 12%–25% of patients suffering from multiple myeloma are physically active on a regular basis.[24,25] There are a number of reasons that prevent patients from exercising. Among them, uncertainties concerning bone stability, as well as fear of movement and injury are important issues, which concern not only patients themselves, but also oncologic healthcare providers.[24,26] Multiple myeloma is also a highly heterogeneous disease with regards to osseous involvement, which ranges from none to innumerable osteolytic lesions.[20] Therefore, assessment of bone stability and consequently recommendations on physical exercise must be done for each patient individually. There are several well-established classification systems available to evaluate bone stability and risk of fracture in cancer patients (i.e., Mirels' score, Taneichi score, Spinal Instability Neoplastic Score).[27–29] However, it has been previously mentioned that these scoring systems may not be fully applicable to myeloma patients, because several characteristic features of the disease are not included, for example, osteoporosis.[29,30] Additionally, the main objective of these scores is to guide decision-making concerning the need for surgical intervention. So far, there are no clear guidelines available that determine the level of physical exercise that can be safely performed by myeloma patients with stable and unstable bone lesions.

Because of the complexity of the disease, we initiated an interdisciplinary consultation for myeloma patients at the Heidelberg Myeloma Center in cooperation with the Working Group Exercise Oncology, National Center for Tumor Diseases (NCT), Heidelberg University. Following an orthopedic evaluation of bone stability and physical performance, a precision-based exercise program (PEP) was established for each patient according to individual clinical conditions. Aim of this study was to retrospectively evaluate patients' characteristics, as well as to assess the implementability and safety of a PEP for myeloma patients with stable and unstable bone lesions.

2 | PATIENTS AND METHODS

Data of multiple myeloma patients ($n = 100$) who received a PEP according to an orthopedic evaluation of bone stability and individual physical performance were analyzed retrospectively. The study was approved by the local ethics committee (No. S-075/2023). Patients presented at the Multiple Myeloma outpatient department between July 2021 and January 2023 for joint consultation by an orthopedic specialist and an exercise therapist. Prior to recommending physical activity, 87% of patients received a current whole-body CT-scan (≤3 months) which was evaluated according to established stability scores (Mirels' Score for upper and lower extremities and Spinal Instability Neoplastic Score [SINS]). The SINS was chosen to evaluate spinal lesions because it uses a comprehensive set of factors to aid in the assessment of instability including: global spinal location of tumor, spinal alignment, pain, bone lesion quality, vertebral body collapse, and posterior involvement.[29] Only patients in stable remission and with no osseous involvement did not receive current CT-scan imaging ($n = 13$). Based on detailed instructions concerning stable and/or unstable bone lesions, as well as evaluation of individual physical performance, a PEP was designed, which included body awareness, stretching, coordination, and resistance training at patient-individualized levels. An exercise therapist performed an introductory session under orthopedic supervision. Subsequently, PEP was performed home-based supported by an exercise therapy mobile app

(Physiotec, Quebec, Canada) or under 1:1 supervision led by a local physical therapist. Additionally, patients were advised to perform moderate aerobic training for 150 min per week and two to three sessions of resistance training per week (according to guidelines by the American College of Sports Medicine).

One main focus of PEP was on strengthening of core and lower extremity muscles, because significant weakening could be observed, particularly following high-dose therapy and autologous stem cell transplantation. Even though each PEP was highly individualized, the following exercises were most frequently recommended, also for patients with potentially unstable and unstable osteolyses (see Supporting information S1). An orthopedic follow-up assessment at the outpatient department was recommended after 3–4 months. If sufficient strengthening of core muscles could be observed, more demanding exercises, such as rotation of the spine were included in PEP.

Patients were contacted for a follow-up interview by telephone ($n = 91$) a median of 9 months (range: 2–18, interquartile range [IQR] 5–11) after initial consultation. Nine patients could not be reached despite several attempts.

Data were summarized by descriptive statistics and differences between groups were calculated by Fisher's exact test respectively, using Graph Pad Prism 9 software (Graph pad software, Boston, MA). Significance level was determined as $p < .05$.

3 | RESULTS

3.1 | Clinical data

Clinical data of patients included in this study are listed in Table 1. Patients' median age was 61.5 years. 62 patients were male and 38 were female. All patients received treatment for multiple myeloma. The majority of patients ($n = 53$) asked for consultation on physical exercise after successfully undergoing autologous stem cell transplantation and starting maintenance therapy.

TABLE 1 Clinical data of myeloma patients who received a precision-based exercise program according to orthopedic evaluation of bone stability and individual physical performance.

Patients' clinical data	$n = 100$
Age (years)	Median 61.5 Range: 27–83 IQR 56–69
Gender	
Male	62
Female	38
Multiple myeloma type	
IgA kappa	18
IgA lambda	6
IgG kappa	38
IgG lambda	14
IgM lambda	2
Light chain kappa	17
Light chain lambda	5
Time since initial diagnosis (months)	Median 25.5 Range: 2–159 IQR: 33
Current treatment	
Consolidation/maintenance therapy following HDT with ASCT	53
Relapsed myeloma	23
Mobilization/HDT with ASCT	9
Induction therapy	7
Continuous therapy, not eligible for HDT with ASCT	6
None	2
Response assessment	
≥VGPR	76
PR, MR, SD	10
PD	6
Not available	8

Abbreviations: ASCT, autologous stem cell transplantation; HDT, high dose therapy; MR, minimal response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

3.2 | Bone stability

A current (≤3 months) whole-body CT-scan was conducted in 87% of patients before recommending physical exercise. In 20% of patients, new findings could be detected compared with the previous CT-scan, also in absence of clinical symptoms. These were either new myeloma-related bone lesions (progressive disease) or new skeletal-related events, such as spinal compression fractures or progression of a previously diagnosed compression fracture. None of the newly detected skeletal-related events required surgical intervention; however, these changes were taken into consideration for PEP planning and further treatment. One patient received radiation therapy of a new osteolytic lesion. 75% of patients showed multiple osteolytic lesions (≥7) on CT-scan and according to Spinal Instability Neoplastic Score (SINS) 60% of patients had at least one bone lesion of the spine, which was classified as potentially unstable or unstable (Figure 1). Stability of upper and lower extremities was evaluated by Mirels' score. As expected, the upper and lower extremities were considerably less affected than the axial skeleton. In seven patients there was a fracture risk of 15% of the femur (Mirels score 8) and in one patient of the humerus. Two patients showed a high fracture risk (Mirels score ≥9) of either humerus or femur.

3.3 | Physical exercise behavior

At initial consultation, patients were asked whether they were already physically active. 90% of patients stated that they already performed

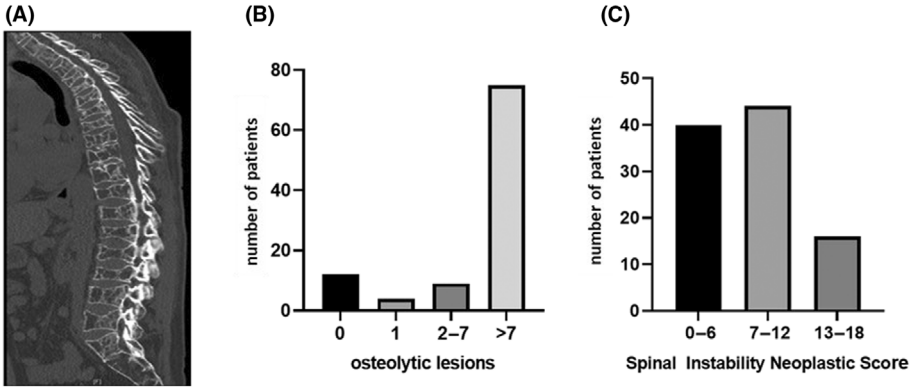

FIGURE 1 (A) examplary sagittal CT-scan image of a myeloma patient who received consultation on bone stability and PEP at the outpatient clinic. The image shows severe bone degradation of the spine, multiple vertebral fractures and osteolyses, as well as deformity of the spine. (B) Number of osteolytic lesions based on current whole body CT-scan (≤3 months). (C) Bone lesions of the spine were evaluated according to the Spinal Instability Neoplastic Score (SINS). Criteria of instability: Total score: 0–6 stable spine, 7–12 potentially unstable spine, and 13–18 unstable spine. In case of total score ≥7, surgical intervention should be considered.

some kind of aerobic training (mostly walking or cycling). However, only few patients (24%) pursued resistance training, primarily due to uncertainties concerning bone stability (Figure 2). At the follow-up interview, particularly with regards to resistance training, there was a significant increase in patients who performed PEP on a regular basis (≥2x/week, 55%) and 1×/week or intermittently (24%; $p < .0001$ as calculated by Fisher's exact test). Concerning aerobic training, the total number of patients that were active (≥150 min/week and <150 min/week) was unchanged. Patients who did not exercise at all indicated recurring infections ($n = 7$), a lack of motivation ($n = 4$) and persistent fear of movement/injury ($n = 2$) as main reasons. Importantly, no injuries occurred in association with PEP.

3.4 | Musculoskeletal pain

At initial presentation, 75% of patients reported to be suffering from musculoskeletal pain, at least occasionally. Pain intensity was mostly specified as mild or moderate (31% mild, 36% moderate, and 8% severe; Figure 3). However, only in 20% of patients pain could be directly attributed to the localization of myeloma-associated osteolyses. In most cases, symptoms resulted from muscle disorders, spinal deformity, and also degenerative changes of the spine. Overall, 25% of patients required pain medication regularly at initial consultation (Table 2). Of note, there was no significant difference in time that had elapsed since initial diagnosis between patients requiring pain medication or not.

At the follow-up interview, 79% of patients who did not exercise and 65% of patients that performed PEP reported to be suffering from at least occasional musculoskeletal pain. However, 75% of patients who performed PEP stated that painful symptoms could be effectively alleviated by exercise. These results were also reflected by the intake of pain medication. Patients who exercised stopped taking pain medication regularly (21% at initial consultation vs. 10% at follow-up interview; Table 2), whereas none of the patients who did not exercise were able to discontinue medication.

4 | DISCUSSION

Multiple myeloma is a disease which is in most patients associated with severe loss of bone substance and structure resulting in reduced stability of the skeletal system.[20] Through recent therapeutic advances patients affected by this disease live longer and acquire a higher physical performance level.[18] Patients also frequently express the wish to increase their fitness level and to actively contribute to a favorable course of the disease by staying as healthy as possible.[24,25] However, myeloma patients often exhibit multiple unstable bone lesions,[31] predominantly of the axial skeleton, which raises the question whether regular exercise, resistance training in particular, is at all possible. Even though there is an abundance of literature available on oncologic exercise therapy, expertise concerning patients with bone metastases is limited.[1,2,5] So far, only very few randomized-controlled trials or controlled trials have addressed this question in myeloma patients.[32–37]

Since multiple myeloma is a complex and heterogenous disease, evaluation of bone stability and recommendations on physical exercise require an interdisciplinary setting. Established scoring systems alone might not capture the full extent of bone changes in myeloma patients.[29,30] Specifically, the following aspects are not considered in scoring systems, but commonly occur in myeloma patients and should therefore be taken into account before recommending physical activity.

4.1 | Osteoporosis

It has been well-established in literature that osteoporosis increases fracture-risk in affected patients.[38,39] Kang et al.[40] recently examined physiological loading in three different motion patterns in osteoporotic and normal spines using finite element modeling. They were able to show increased stress in osteoporotic vertebrae and particularly also in the nucleus pulposus, which—aside from an increased fracture-

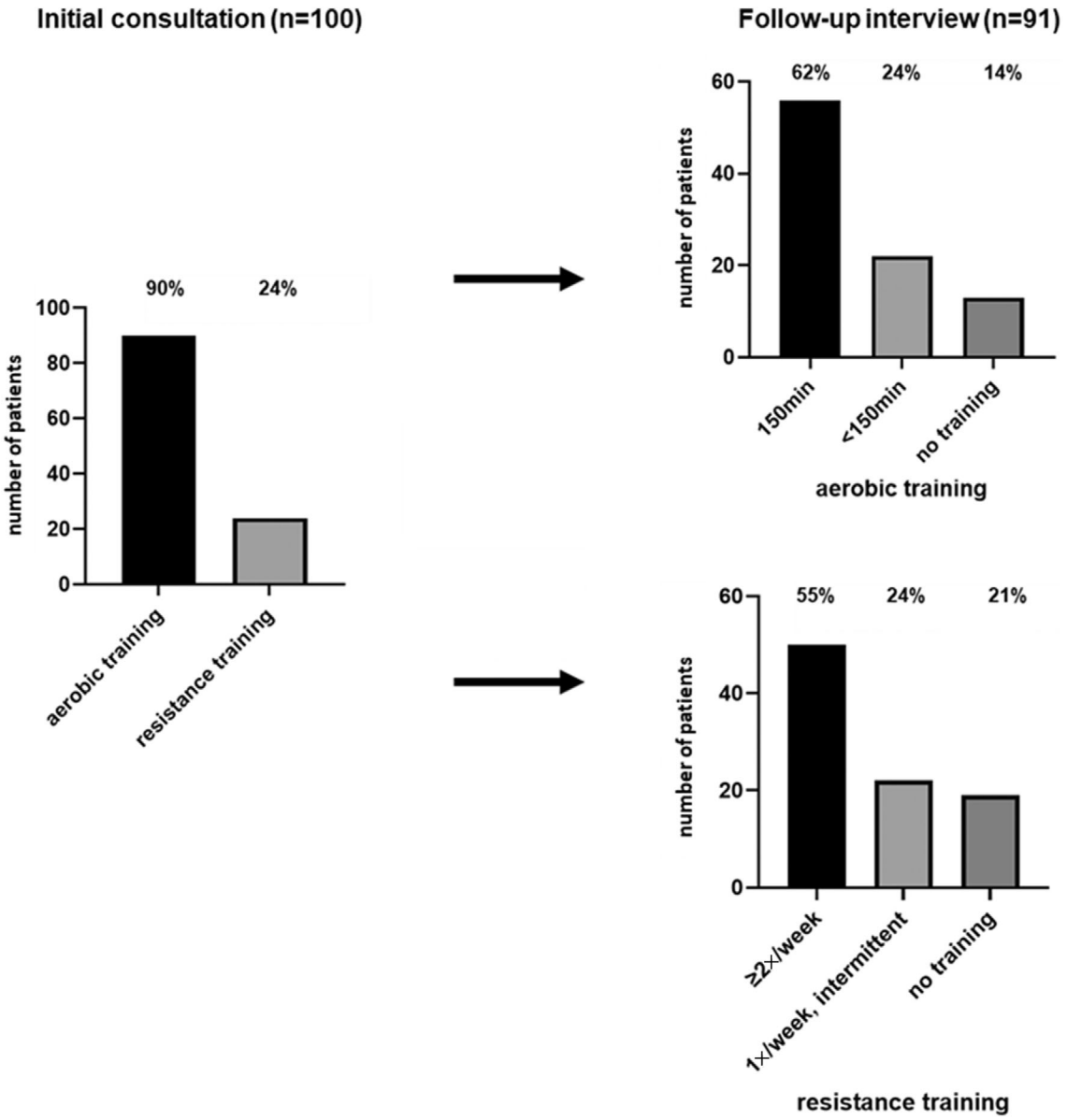

FIGURE 2 At initial consultation, most patients pursued aerobic training (90%), but frequently expressed uncertainties whether resistance training was at all possible. Following consultation on bone stability and physical exercise they were contacted for a follow-up interview ($n = 91$) a median of 9 months (range: 2–16, IQR 5–11) later. The total number of patients pursuing aerobic training (≥150 min/week and <150 min/week) remained unchanged. Significantly more patients performed tailored resistance training (≥2×/week, 55%) and 1×/week or intermittently (24%). Differences between groups were calculated by Fisher's exact test and significance level was determined as $p < .05$.

risk—might also contribute to discogenic pain and degeneration in these patients.

4.2 | Diffuse osteolytic infiltration

Even if each single osteolysis does not meet instability criteria according to scoring systems such as Taneichi score, SINS, or Mirel's score, it is unclear whether bone stability might be affected to a similar degree due to numerous osteolytic lesions. Current engineering-based technologies, such as computed tomography-based structural rigidity analysis and finite element analysis approaches are noninvasive and might predict fracture-risk more reliably in the future.[41]

4.3 | Multiple vertebral fractures

Compression fractures of the spine are particularly common in myeloma patients and might result in kyphotic deformity, which alters biomechanics and increases stress on other spine levels. Consequently, occurrence of one osteoporotic compression fracture has

been shown to increase the risk of additional compression fractures, particularly of the next adjacent vertebrae.[42,43] Myeloma patients frequently suffer from multiple compression fractures along with severe osteolytic lesions distributed over the entire spine, which alters biomechanics and hence load distribution not merely on a specific level of the spine, but might affect overall stability.

4.4 | Stage of the disease and response assessment

Patients in the early disease and treatment stages frequently suffer from new skeletal-related events with no signs of stabilizing bone remodeling (i.e., sclerosis). It has been shown that osteosclerosis can be observed as early as 12 weeks after initiation of treatment and the incidence is higher in patients with a remission status ≥very good partial response, meaning that the tumor load has been successfully reduced to >90%.[44] Higher disease-activity and lack of osteosclerosis should therefore be taken into account for evaluation of bone stability and hence recommendations on physical activity.

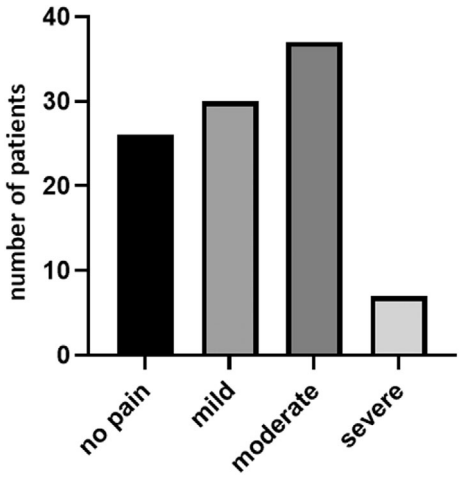

FIGURE 3 Musculoskeletal pain was reported by 75% of patients at initial consultation (31% mild, 36% moderate, and 8% severe).

4.5 | Individual physical fitness

Aside from evaluation of whole-body CT-scans and disease activity, clinical evaluation of muscle strength and individual physical fitness is a key element to determine fracture risk. Alajlouni et al.[45] demonstrated that measurement of muscle strength and physical performance further improves prediction of osteoporotic fracture risk compared with established scoring tools alone. Similar findings have been described for breast cancer patients.[46]

We established an interdisciplinary consultation at the Multiple Myeloma center of Heidelberg University Hospital. Patients received in depth information on bone stability by an orthopedic specialist and were advised on everyday activities and physical exercise. Following a clinical examination and evaluation of performance level, a PEP was generated by an exercise therapist. We were able to show that a PEP could be established for all myeloma patients with stable and unstable bone lesions. Most patients presented at the outpatient department after completing high dose chemotherapy and stem cell transplantation or during maintenance therapy. Thus, in the majority of patients (80%) no new bone lesions were observed. For patients in earlier stages of the disease and/or with new skeletal-related events on current CT-scan, as well as for patients with a persistently high disease activity (≥partial response) and no signs of osteosclerosis, PEP was reduced accordingly. Importantly, no exercise-associated injuries were reported by patients. Therefore, PEP can be safely performed by myeloma patients with stable and also unstable bone lesions. Overall, patients that presented at the outpatient department were highly motivated to be physically active. After consultation on bone stability and introduction to PEP, the number of patients pursuing regular resistance training could be significantly increased. The majority of patients also reported of musculoskeletal pain, which could not be linked to myeloma-associated bone lesions exclusively, but also to muscular weakening (mainly of core and leg muscles), spine deformity and/or to degenerative changes of the musculoskeletal system. Therefore, it is of particular importance that patients receive recommendations on conservative orthopedic treatment options which can be safely performed, even in the context of myeloma-associated bone changes. At the follow-up interview, occasional musculoskeletal pain

TABLE 2 Number of patients requiring pain medication regularly.

Analgesics	Overall number of patients who required pain medication regularly at initial consultation	Number of patients who required pain medication and performed PEP	
		At initial consultation	At follow-up interview
WHO 1 non-narcotics	12	6	1
WHO 2 weak opioid	1	1	2
WHO 3 strong opioid	17	13	4
Neuropathic pain	12	9	3

Note: Analgesics are depicted according to the WHO 3-Step Pain Ladder (non-narcotics, weak opioid, and strong opioid) Also, ananlgesics for neuropathic pain are included. Several patients required a combination of different analgesics.
Abbreviation: PEP, precision-based exercise program.

was continuously reported, but most patients were aware that they could positively influence these symptoms by performing PEP, which is essential for patients' self-efficacy and for reducing fear of pain/injury due to movement. In line with this observation, patients performing PEP were also more likely to discontinue pain medication.

However, the following limitations of this study should be addressed. We evaluated data of a nonrandomized, single arm intervention retrospectively at a single center. All of these factors are prone to various biases and other or contributing beneficial effects cannot be excluded. A conclusive long-term assessment of risk for fracture, other skeletal events and exercise adherence of myeloma patients is not yet possible, because up to now, we performed only one follow-up interview after a rather short amount of time since initial consultation. However, patients are continuously monitored at our institution and we intend to evaluate long-term results of an interdisciplinary consultation followed by PEP in due time. In order to minimize interfering factors, we are currently conducting a randomized-controlled trial on an exercise intervention for newly diagnosed multiple myeloma patients, which also includes long-term follow-up assessment.

5 | CONCLUSION

Due to widely varying physical function levels and the high incidence of unstable bone lesions in multiple myeloma patients, it is instrumental that exercise programs are tailored to individual clinical conditions, which requires an interdisciplinary setting. We were able to demonstrate that a precision-based exercise intervention is implementable and safe, also for patients with unstable bone lesions. However, exercises should only be performed after an orthopedic evaluation or ideally an interdisciplinary consultation by an orthopedic specialist and an exercise therapist together. By means of regular exercise intervention, patients' self-efficacy in managing musculoskeletal pain was enhanced and pain medication could be reduced. Prediction of fracture risk and hence recommendations on physical exercise in myeloma patients might be improved by new engineering- and computational-based analyses in combination with clinical information on disease activity and physical performance.

AUTHOR CONTRIBUTIONS

Ulrike Dapunt, Pauline Ehret, Joachim Wiskemann, Marc-Steffen Raab, and Hartmut Goldschmidt conceived and designed the study. Ulrike Dapunt, Pauline Ehret, Jean-Luc Paratte, Rea Maria Kuehl, and Marc-Steffen Raab acquired the data. Ulrike Dapunt and Hartmut Goldschmidt analyzed the data. Ulrike Dapunt wrote the article. Joachim Wiskemann, Dirk Jäger, Carsten Müller-Tidow, Marc-Steffen Raab, and Hartmut Goldschmidt contributed to the draft. All authors have given final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All files with original data are available upon request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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