SDU

PhD Dissertation

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Early initiated physical exercise in newly diagnosed patients with multiple myeloma

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Rikke Faebo Larsen, October 2019

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SUMMARY

Newly diagnosed patients with multiple myeloma often perceive bone pain and fatigue. They may have experienced fractures or recurrent infections. In Denmark, approximately 440 people are diagnosed with multiple myeloma annually. At the time of diagnosis, bone disease with osteolytic destructions is present in 79% of the patients. Other commonly experienced symptoms are anemia and anxiety. Typically, anti-myeloma treatment will be initiated within few days after diagnosis. Insecurity about precautions in relation to bone disease and the bone pain itself may limit mobilization, and also activities in daily life. This limitation combined with side effects to anti-myeloma treatment can induce physical deterioration. It is well known that exercise has beneficial effects on physical function, also in a preventive perspective, but research in exercise for patients with multiple myeloma is sparse.

The overall aim of the thesis was to investigate a physical exercise intervention in newly diagnosed patients with multiple myeloma, and furthermore examine their level of physical function at the time of diagnosis, in order to add knowledge to the need and effect of exercise at this time point of the patients´ course of treatment.

The thesis was based on the assumption that patients´ level of physical function is lower than expected for their age and may differ from patients with other cancer diagnoses. If true, this would be in favor of the need for physical rehabilitation. Furthermore, it is also based on the assumption that exercise will benefit the patient, if it is initiated early in their treatment course. Therefore, a randomized controlled trial was designed to investigate the effect of exercise in newly diagnosed patients, regardless of age and type of anti-myeloma treatment. Initially, the feasibility and safety of the exercise intervention and test procedures were investigated. Furthermore, a structured assessment of the bone disease was conducted in order to individualize the exercise program, depending on individual restrictions.

In total, 100 patients were included in the randomized controlled trial. The intervention consisted of aerobic exercise, strengthening exercise, stretching, and general physical activity. It comprised eight supervised exercise sessions and home-based exercise for a ten week period. The control group received general information in a leaflet, i.a. about physical activity. Outcomes were measured at baseline and post-intervention, i.e. after 11 weeks. The effect was measured by muscle strength tests (knee extension strength and grip strength by dynamometer, and 30 sec Sit-to-Stand-Test), aerobic capacity (Six-Minute-Walk-Test), physical activity (accelerometers), quality of life (EORTC-QLQ-C30), and pain (Brief Pain Inventory). The primary study outcome was knee extension strength. For the feasibility and safety part, the outcomes were eligibility, acceptance, and attrition to the study, and the attendance, adherence, tolerability, and adverse events to the exercise intervention, and finally completion rates and adverse events to the test procedures.

The study documented that it is possible to recruit patients at the time of diagnosis, regardless of age and type of anti-myeloma treatment. Acceptance rate was 75%, and attrition was 20%. Attendance to the supervised exercise sessions was 92% and adherence was 99%. Adherence to the home-based exercise program was 92%, and to the home-based physical activity it was 94%. Completion rates across the different tests were 82-100%. No serious adverse events occurred. Two non-serious adverse events occurred, but these were not related to exercise.

At the time of diagnosis, the participants had a lower level of physical function in muscle strength of the lower extremities and in aerobic capacity compared to published data from a normal population. However, in general they did not differ from patients with other cancer diagnoses (lymphoma, prostate cancer, and breast cancer).

The effect of the individualized exercise intervention planned according to the individual bone disease did not show any effect when compared to usual care. However, the control group had a decrease in knee extension strength ($p=0.014$), whereas there was an non-significant decrease in the intervention group ($p=0.092$). Both groups had an increase in 30 sec Sit-to-Stand-Test (intervention group, $p=0.004$; control group, $p=0.022$), and in Six-Minute-Walk-Test (intervention group, $p=0.001$; control group, $p<0.001$). Also, global quality of life was better post-intervention than at baseline in both groups (intervention group, $p=0.024$; control group, $p=0.002$). Pain decreased in the control group, both regarding severity ($p<0.001$) and pain interference ($p<0.001$). In the intervention group, it was only the "worst pain" category that decreased.

Conclusions and implications

Patients newly diagnosed with multiple myeloma have a lower functional level compared to the normal population and thus, it may be relevant to initiate physical rehabilitation. A ten week exercise intervention, which was planned according to the individual bone disease, was feasible and safe for the patients. No effect on physical function, physical activity, quality of life, or pain was found between the intervention group and the control group. Reasons for the non-significant effect results may be non-adherence, sub-optimal intensity, contamination in the control group, or the simple fact that exercise is not effective in newly diagnosed patients receiving anti-myeloma treatment. However, changes in physical function within groups from baseline to post-intervention were found. Knee extension strength decreased in the control group, whereas both groups performed better in the functional tests; 30 sec Sit-to-Stand-Test and Six-Minute-Walk-Test. Furthermore, global quality of life increased in both groups. Individualization may be relevant in physical rehabilitation of patients with multiple myeloma, and systematic screening may help identify patients with particular needs. However, the data indicate that exercise at the time of diagnosis is not profitable for the patients with multiple myeloma. The potential value of exercise intervention at a later time point, e.g. after end of primary treatment, should be tested as well as inclusion of the elderly patients with multiple myeloma needs attention.

SAMMENFATNING PÅ DANSK (summary in Danish)

Nydiagnosticerede patienter med myelomatose oplever ofte knoglesmerter og udtalt træthed. De har ofte haft frakturer eller oplevet hyppige infektioner. I Danmark er der cirka 440 mennesker om året, der får konstateret myelomatose. På diagnosetidspunktet har 79% af patienterne knoglesygdom med knogledestruktive forandringer. Andre hyppige symptomer er anæmi og angst. Medicinsk cancerbehandling vil typisk blive igangsat få dage efter diagnosen er stillet. Usikkerhed omkring forholdsregler betinget af knoglesygdommen og knoglesmerterne i sig selv, kan begrænse patientens mobilitet og daglige aktiviteter. En sådan begrænsning kombineret med den medicinske behandling, medførende mulige bivirkninger, kan medvirke til, at patientens fysik forringes. Den gavnlige effekt af træning i forhold til fysisk funktion er velkendt, også i et forebyggelsesperspektiv. Forskning i træning til patienter med myelomatose er dog sparsom.

Afhandlingens overordnede formål var at undersøge en fysisk træningsintervention til nydiagnosticerede patienter med myelomatose, og derudover undersøge det fysiske funktionsniveau på diagnosetidspunktet, for derved at opnå viden omkring behovet for og effekten af træning på dette tidlige tidspunkt i patientens behandlingsforløb.

Afhandlingen var baseret på en antagelse om, at patienternes fysiske funktionsniveau er ringere end, hvad der kan forventes i forhold til alder, samt at funktionsniveauet kan være anderledes end blandt patienter med andre cancerdiagnoser. Hvis antagelsen er rigtig, vil det tale for et behov for fysisk rehabilitering/genoptræning. Derudover var afhandlingen også baseret på en antagelse om, at tidlig iværksat træning vil være gavnlig for patienten.

For at undersøge dette blev et randomiseret kontrolleret studie iværksat med inklusion af flest mulige nydiagnosticerede patienter uafhængig af alder, og valg af medicinsk cancerbehandling. I studiets første del blev gennemførbarheden og sikkerheden af træningsinterventionen og testprocedurerne undersøgt. I studiet foretoges en systematisk vurdering af knoglesygdommen for derved at kunne individualisere træningsprogrammet ud fra de individuelle restriktioner, der måtte være.

Der blev i alt inkluderet 100 patienter til det randomiserede kontrollerede forsøg. Interventionen bestod af aerob træning, styrkende træning, udspænding og generel fysisk aktivitet. Interventionen indeholdt otte superviserede træningssessioner kombineret med hjemmebaseret træning og varede i alt ti uger. Kontrolgruppen modtog en folder med generel information om blandt andet fysisk aktivitet.

Deltagerne blev målt ved diagnosetidspunktet samt efter endt interventionsperiode, dvs. efter 11 uger. Effekten blev målt ved hjælp af muskelstyrketest (knæekstensionsstyrke og gribestyrke målt med dynamometer, samt 30 sekunder rejse-sætte-sig-test), aerob kapacitet (seks-minutters-gang-test), fysisk aktivitet (accellerometer), livskvalitet (EORTC-QLQ-C30) og smerte (Brief Pain Inventory).

I forhold til gennemførbarheden og sikkerheden blev der målt på, hvor mange der reelt kunne indgå, hvor mange der takkede ja, og hvor mange der faldt fra. I forhold til interventionen blev der målt på fremmøde samt om deltagerne udførte interventionen og tolererede den, og ikke mindst om der opstod nogle bivirkninger. Ydermere blev gennemførelsesraten af de forskellige tests undersøgt, samt om der opstod nogle bivirkninger i forbindelse med test procedurerne. Resultaterne viste, at det er muligt at rekruttere patienter ved diagnosetidspunktet, uanset alder og uanset hvilken type medicinsk cancerbehandling patienten skulle modtage. Der var 75%, som takkede ja til at deltage, og der var 20% frafald. Fremmødet til de superviserede træningssessioner var 92%, og 99% af træningssessionerne blev gennemført. I forhold til den hjemmebaserede træning blev 92% af træningssessionerne gennemført, og 94% af de ønskede antal dage med fysisk aktivitet blev gennemført. Gennemførelsesraten for de forskellige tests var 82-100%. Ingen alvorlige bivirkninger opstod. To ikke-alvorlige bivirkninger opstod, men de var ikke relaterede til træning. Deltagerne havde ved diagnosetidspunktet et lavere funktionsniveau i forhold til muskelstyrke i underekstremiteterne og i aerob kapacitet sammenlignet med publicerede data for normalbefolkningen. Generelt var funktionsniveauet for deltagerne ikke forskelligt fra patienter med andre cancerdiagnoser (lymfom, prostata cancer og bryst cancer).
Den individualiserede træningsintervention, som var tilrettelagt ud fra den enkeltes knoglesygdom viste ingen effekt sammenlignet med vanlig behandling. Dog var der et fald i knæekstensionsstyrken ($p=0.014$) i kontrolgruppen, hvorimod der var et ikke-signifikant fald i interventionsgruppen ($p=0.092$). Begge grupper havde en fremgang i 30 sekunder rejse-sætte-sig-test (interventionsgruppe, $p=0.004$; kontrolgruppe, $p=0.022$), samt i seks-minutters-gang-test (interventionsgruppe, $p=0.001$; kontrolgruppe, $p<0.001$). Den globale livskvalitet blev også bedre i begge grupper efter endt intervention (interventionsgruppe, $p=0.024$; kontrolgruppe, $p=0.002$). Smerter blev mindre i kontrolgruppen, både i forhold til sværhedsgrad ($p<0.001$) og smertepåvirkning ($p<0.001$), hvilket var mindre tydeligt i interventionsgruppen, hvor der kun var signifikant reduktion i svær smerte (worst pain).

Konklusion og implikation

Patienter med nydiagnosticeret myelomatose har et lavere funktionsniveau sammenlignet med normalbefolkningen, og på den baggrund kan det være relevant at igangsætte fysisk rehabilitering/genoptræning. En ti ugers træningsintervention planlagt ud fra den enkeltes knoglesygdom var gennemførbar og sikker, men der var ingen effekt på fysisk funktion, fysisk aktivitet, livskvalitet eller smerte sammenlignet med en kontrolgruppe.
Årsager til manglende observeret effekt kan dels være, at deltagerne ikke gennemførte den planlagte hjemmetræning, at intensiteten ikke var den rette, at kontrolgruppen følte sig tilskyndet til øget fysisk aktivitet (kontamination af kontrolgruppen) eller det simple faktum, at nydiagnosticerede patienter, som modtager anti-myelom behandling, ikke profiterer af træning. Dog var der ændringer i henholdsvis

interventionsgruppe og kontrolgruppe fra diagnosetidspunkt til efter endt interventionsperiode. Der var et fald i knæekstensionsstyrken i kontrolgruppen, mens begge grupper præsterede bedre i de funktionelle tests; 30 sekunders rejse-sætte-sig-test og seks-minutters-gang-test. Derudover blev den generelle livskvalitet bedre i begge grupper. Hos patienter med myelomatose kan struktureret screening for påvirket fysisk funktion være relevant og medføre overvejelse af individuel rehabilitering. Vores studie tyder dog ikke på en gevinst af fysisk træning til nydiagnosticerede patienter med myelomatose. Hvorvidt en træningsintervention på et senere tidspunkt, f.eks. efter endt primær behandling, vil være gavnlig, bør undersøges. Desuden er der et behov for inklusion af ældre patienter med myelomatose.

LIST OF PUBLICATIONS

Paper I

Supervised and home-based physical exercise in patients newly diagnosed with multiple myeloma – a randomized controlled feasibility study.

Manuscript accepted for publication in Pilot and Feasibility Studies, October 2019. Not yet published.
(Appendix I)

Paper II

Physical function in patients newly diagnosed with multiple myeloma.

Manuscript submitted.
(Appendix II)

Paper III

Exercise in newly diagnosed patients with multiple myeloma – a randomized controlled trial of effects on physical function, physical activity, pain and quality of life.

Manuscript.
(Appendix III)

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ABBREVIATIONS

A-T1	Activity Time 1 (baseline)
A-T2	Activity Time 2 (day 22)
A-T3	Activity Time 3 (43)
A-T4	Activity Time 4 (post-intervention/week 11)
CG	Control group
HDT-SCT	High Dose chemoTherapy with Stem Cell Support
IG	Intervention group
MM	Multiple Myeloma
SST	30 sec Sit-to-Stand-Test
6MWT	Six-Minute-Walk-Test
T1	Time 1 (baseline)
T2	Time 2 (post-intervention/week 11)

CHAPTER I – INTRODUCTION

This thesis addresses physical function and the perspective of exercise in patients newly diagnosed with multiple myeloma. Physical function is one area out of a broader rehabilitation perspective.

In The World Health Organization report from 2011, WHO defines rehabilitation as:

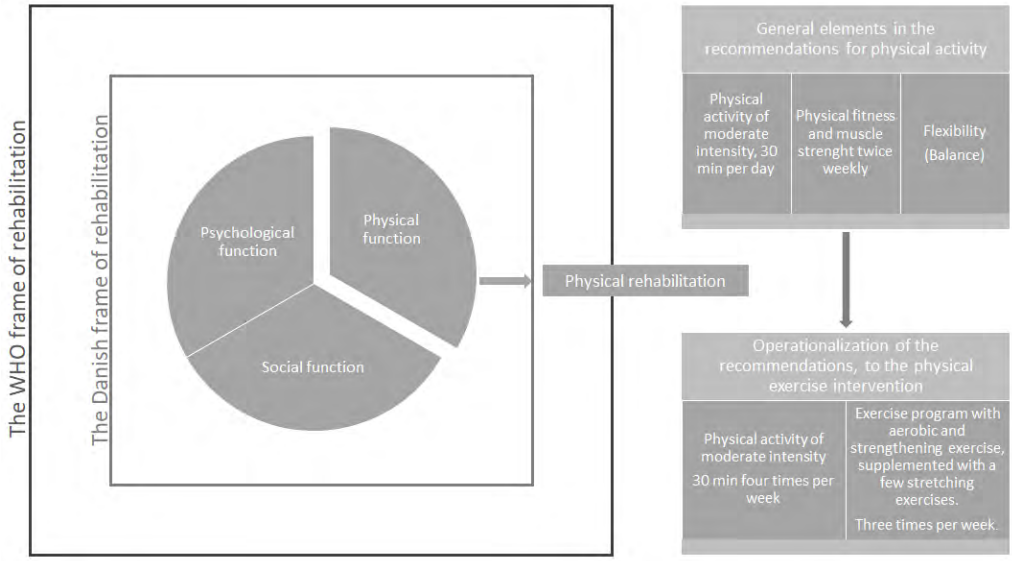
> *"a set of measures that assist individuals who experience, or are likely to experience, disability to achieve and maintain optimal functioning in interaction with their environments"* (1), p.96.

A definition has also been developed in a Danish context (2), and in this work, rehabilitation is more elaborated by talking about four cornerstones; physical, psychological, and social function, and the ability of attaining an independently and meaningful life. Furthermore, the definition points out that rehabilitation must be seen in the perspective of the total life situation, and that it is a collaboration between subject, relatives, and professionals (2).

This thesis takes focuses on *physical function*. Working with physical function is, in this context, considered physical rehabilitation, which is operationalized to an exercise intervention, based on the national recommendations for physical activity. Through physical rehabilitation the patient maintains or achieves some basic physical functions (aerobic capacity and muscle strength), which is important to the ability of independent living, and may indirectly contribute to a meaningful life.

It must be noted that national recommendations have physical activity as the overall term, while the thesis has exercise as the overall term, consisting of daily physical activity and a structured exercise program. Figure 1 illustrates the frame on which this thesis is based.

Figure 1 The frame of the thesis



Nationally and internationally, exercise and physical activity is considered an important factor in many aspects in the area of cancer, from prevention, before, during, and after treatment, and also in relation to survivorship (3–7).

These aspects had special focus in the third national plan for cancer; in Danish named *"Kræftplan III"* (8). It was published in 2010 and was centered on improvement of the treatment courses by focusing on before and after diagnosis, and treatment at the hospitals. In relation to that, three new terms occurred; early detection, rehabilitation, and palliation. This was the onset of a number of implementation initiatives, and especially one implementation initiative was relevant for framing the study on which this thesis is based. Freely adapted from Danish, it says:

Particularly, the Health Regions have a responsibility at the hospitals to identify and examine the rehabilitation needs in patients with cancer, both during the treatment and in connection with discharge from hospital. The Region initiates and conducts targeted rehabilitation, primarily at the hospitals, when there is a need of specialist knowledge, and when rehabilitation requires coordination with the detection of the disease and treatment (9), p.21.

Specific diagnoses were in focus in the former national plan for cancer *("Kræftplan II")* from 2005 (10) with the aim of developing specific programs for the most common cancer diagnoses, and in the following years this was expanded to other cancer diagnoses, including multiple myeloma. The specific package for patients with multiple myeloma has undergone revision, latest in 2016 (11). In the present national plan (11) it states, that because of pain and bone disease, where osteolyses or even fractures (often vertebral) may be present,

the patients are at risk of immobilization (11), p.20-21. Such immobilization may have a negatively effect on physical function.

The plan comprises advice from physiotherapists on movement and transfer techniques, and a systematic focus on identifying rehabilitation needs (11), p.21. This has been implemented in clinical practice, although the role of the physiotherapists differs. Generally, newly diagnosed patients will receive advice concerning physical activity, ergonomic guidance, and transfers. It can be questioned whether this advice is adequate for preventing immobilization and physical deterioration, and furthermore it may be beneficial for the patients with a more structured exercise initiative. As emphasized in the implementation plan for the third national plan for cancer (9), there might be a need of having some initiatives taking place at the hospitals (and not in the municipalities), e.g. if high degree of coordination is required. This would be relevant for patients with multiple myeloma because very often there are many hospital visits starting at diagnosis and the following months.

A particular challenge in multiple myeloma is the associated bone disease. Bone pain, recent fractures and the potential risk of new fractures makes it difficult to prescribe exercise, which needs to be differentiated and individualized. This challenges clinical practice because physical activity guidelines for this group of patients are not that specific (12,13). Furthermore, the disease is rare, and therefore the experience with rehabilitation of patients with multiple myeloma may be limited, especially at the municipal level.

To summarize, the focus of this thesis is physical function and exercise. This focus speaks into a frame based on rehabilitation, and national plans for cancer, but with special focus on physical rehabilitation, and of course in accordance with recommendations for exercise and physical activity in patients with cancer, including patients with multiple myeloma.

CHAPTER II – BACKGROUND

Multiple myeloma

Multiple myeloma is a hematological cancer disease caused by the expansion of clonal plasma cells, primarily in the bone marrow. It is the second most common hematological malignancy (14). Worldwide, the incidence is 4.3 per 100.000 annually (15), and in Denmark, around 440 patients are diagnosed with multiple myeloma each year (16).

The median age at diagnosis is 68-71 years (14,17,18) and the incidence increases with age (14,19,20). Prevalence increases due to the aging population and because overall survival has improved due to better medical treatment (14,18,20–24).

Thus, even if multiple myeloma is incurable, it is treatment sensitive and the introduction of new therapeutics has improved the survival for myeloma patients. Currently, the one-year survival for males and females is 85% and 88%, respectively, and the five-year survival is 55% and 58%, respectively (16,20).

Typically, the patient presents with bone pain, anemia, renal failure, recurrent infections, or in other patients it is detected by chance through abnormal blood or urine tests (21,25).

The bone disease including osteolytic destructions is a hallmark of the disease. The bone disease is caused by an imbalance between osteoclast and osteoblast activity (26). Osteolytic destructions are present in 79% of the patient (21,25,27), and cause bone pain in around two-thirds of the patients (25).

The bone destructions may lead pathological fractures, non-vertebral fractures (26%), as well as vertebral compression fractures (22%) (27). Increased bone resorption may lead to hypercalcemia as well, and at diagnosis this is present in about 20% of the patients (25). Anemia is present in 70-80% of newly diagnosed patients (21,25,27). When diagnosed, about 80% of the patients will have organ damage, defined as bone disease, hypercalcemia, anemia or renal insufficiency, and will be in need of specific anti-myeloma treatment (28).

Two of the most common symptoms patients experience just before stem cell transplantation are fatigue (67%) and anxiety (53%), followed by pain (49%), and depression (47%) (29). Around one third of the patients experience sleeping disturbances (39%), and difficulties with concentration (31%) (29). Other symptoms that are reported include loss of appetite (27%), nausea (24%), reduced mobility (18%), and diarrhea (16%) (29). Symptoms are interrelated, and a vicious circle may be present (30). Furthermore, symptoms become more prevalent, intense and distressing throughout the course of treatment (31,32), and may persist for up to one year after stem cell transplantation (33). The symptoms are more prevalent and severe among patients with multiple myeloma compared to patients with other hematological diseases, and affect quality of life (34). Furthermore, the elderly part of the patient population is more affected (34).

Multiple myeloma and bone disease

The expansion of abnormal plasma cells in the bone marrow causes changes in the microenvironment and disturbances in the bone remodeling, The malignant plasma cells (myeloma cells) induce hyper-activation of the bone resorbing osteoclasts (35) and inhibition of the bone matrix producing osteoblasts (36). Thus, an abnormal imbalanced situation appears where degraded bone is not replaced by new bone (37), and as this proceeds the characteristic lytic lesions develop and can be visualized on radiographs or computerized tomography (CT) (25).
The lytic destructions may cause pain and are associated with increased fracture risk (27).
Painful bone lesions can be treated with radiation therapy, and orthopedic surgery may be an option to prevent fracture or to treat fracture, e.g. vertebroplasty for treatment of vertebral collapse (38).
To examine the degree of bone destruction, CT or skeletal X-rays are conducted as part of the diagnostic procedure, supplemented by MRI, or PET-CT in some patients (25,39). The bone disease varies in a spectrum from no osteolyses to multiple osteolytic lesions of different sizes and location in the axial skeleton. Pathological fractures in ribs, sternum, long bones and/or vertebrae are common (27).
Less common, but not rare, is spinal cord compression due to compression fractures with posterior displacement of bone fragments or local myeloma tumoral growth.
It is standard of care to treat all myeloma patients with intra-venous bisphosphonates to reduce the risk of progressive bone disease and fractures, unless there is significant renal impairment (40–42).

According to the Danish Multiple Myeloma Study Group (DMSG) guideline from 2017 (12), patients are recommended to stay physically active as much as they can (12), p.99. This may be supported by the use of pain relieving drugs to achieve the goal of being physically active (12), p.99. Static load of the spine should be avoided, and in periods where the disease is active the patient is recommended not to lift more than 3 kg (12), p.99. Dynamic training within the pain threshold is recommended (12), p.99.
However, the recommendations from DMSG are based on expert opinions and not really evidence based.
In 2018, a review of exercise in patients with bone metastases was published showing inconclusive results regarding the effect of exercise on bone disease (43), and recent Consensus Statement from International Multidisciplinary Roundtable on exercise in cancer survivors (44) concluded that there was moderate effect of exercise in relation to bone health.

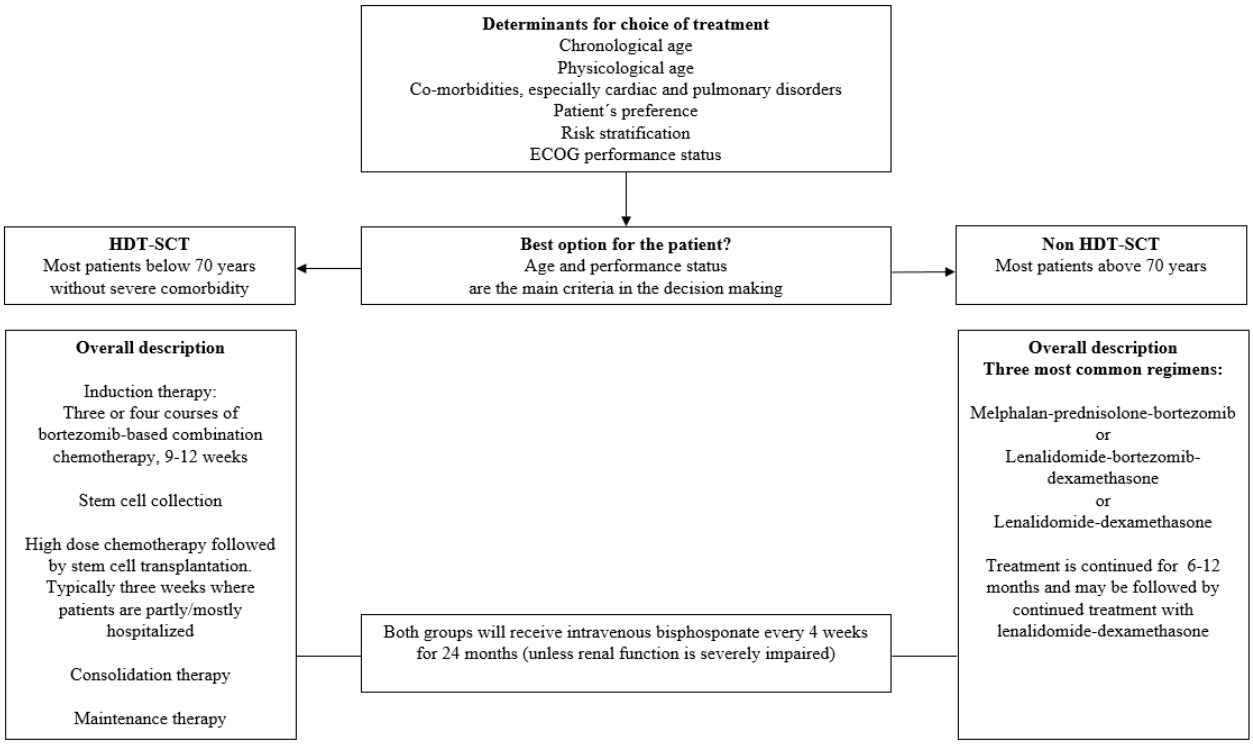
An important message in the review was that there is a need for careful, systematic examination of fracture risk and pain (43), e.g. by Mirels´ score (45) and Brief Pain Inventory (46,47). This, in order to guide prescription and individualization of exercise programs. Attempts to define individualized programs according to the site and degree of the bone metastases have been made (48,49), but further research is

needed. This is of relevance for clinicians, in order to better identify patients who are capable of exercising, and in order to prescribe the most effective and safe exercise.

Medical treatment of multiple myeloma

When a patient is diagnosed with symptomatic multiple myeloma, there are two main treatment options; High Dose chemoTherapy with Stem Cell Transplantation (HDT-SCT) or a less intensive approach (non-HDT-SCT) (12,38). Figure 2 summarizes the typical treatment options (12,38).

Figure 2. Flow chart and overview of the typical treatment options for multiple myeloma.



The choice of treatment depends on age, comorbidity, ECOG performance status, patient´s preference, and general risk (38). Generally, younger, fit patients (<65-70 year) without significant comorbidity are treated with HDT-SCT (11,38).

Though not curative, this treatment has improved survival (23), and some patients experience long term disease free survival (operational cure) (23,50). Elderly patients receive less intensive, yet still effective treatments, which also have improved responses and survival (22).

Consolidation therapy after HDT-SCT has become more common in order to improve treatment response as much as possible, and maintenance therapy is considered in order to prolong the disease free survival and

overall survival (38). The medical treatment of multiple myeloma is increasingly complex. Further details on the medical treatment are however beyond the scope of this thesis.

Exercise and physical activity

Generally, exercise has become an important part of treatment and rehabilitation in patients with cancer, with a growing body of research (44,51), and development of generic evidence-based guidelines for patients in cancer (6,44).

According to the current Danish recommendations for physical activity, patients with cancer are recommended to follow the general recommendations (3,4):

Recommendations for physical activity for adults (18-64 years old)

Be physically active for at least 30 minutes per day. The activity should be of moderate to high intensity and should extend beyond the usual short-term daily activities. If the 30 minutes is divided, each activity should last at least 10 minutes.

Engage in physical activity of high intensity at least twice a week for at least 20 minutes to maintain or improve physical fitness and muscle strength. Activities should include ones that increase bone strength and flexibility.

Physical activity in addition to that recommended will have further health benefits.

Usual short-term daily activities are defined in this context as the activities carried out frequently in daily life that are brief (less than 10 minutes) regardless of intensity.

(3),p.17.

Recommendations for physical activity for older people (65 years old and older)

Be physically active for at least 30 minutes per day. The activity should be of moderate to high intensity and should extend beyond the usual short-term daily activities. If the 30 minutes is divided, each activity should last at least 10 minutes.

Engage in physical activity at least twice a week for at least 20 minutes to maintain or improve physical fitness and muscle and bone strength.

Perform stretching exercises at least twice a week for at least 10 minutes to maintain or improve flexibility. Further, perform regular exercises to maintain or improve balance.

Physical activity in addition to that recommended will have further health benefits.

Exercises that maintain or improve flexibility and ability to balance are intended to maintain the ability to carry out the activities of daily living and to reduce the risk of falling or otherwise sustaining injury in daily life.
People who have a diagnosis for which physical activity is part of treatment should be physically active in a form and quantity that are effective in relation to the diagnosis and consider their mobility.
Usual short-term daily activities are defined in this context as the activities carried out frequently in daily life that are brief (less than 10 minutes) regardless of intensity.

(3), p.18.

The major part of exercise research within cancer has been in patients with breast cancer (52–54), and the most common time point for the intervention has been during or after treatment (52–54). Little is known about the time before treatment (6,51), or at which time point the intervention is best (6).

Exercise has several beneficial effects in cancer patients, such as improvement in overall quality of life and health-related quality of life (52,53,55–57), i.a. comprising patient-reported physical function (52,53) and fatigue (52,54) both during and after cancer treatment. Improvement in muscle strength of upper and lower extremities was found (52), as well as an effect on level of physical activity (52). Objectively measured aerobic capacity has shown mixed results (52,54).

In patients with hematological diseases, most of the research has been conducted in patients with lymphoma or in a mixed group of hematological diseases, and most studies with focus on patients undergoing HDT-SCT with a mixed group of hematological diagnoses (58–60). Overall, the literature points at positive effects, e.g. on aerobic capacity (58), muscle strength (58), fatigue (58–60), and quality of life (overall, and health-related) (58,59), although the effect size differs. Further, results are not always pointing in the same direction on all parameters.

Specific focus on exercise for patients with multiple myeloma seems highly relevant. Firstly, the presence of painful bone disease or even fractures, which may decrease physical function and quality of life makes the group of myeloma patients rather unique compared to other hematological patients (34). Studies have shown that around two-thirds of patients with multiple myeloma do not meet recommendations for physical activity at time of diagnosis (61,62), which can be either their normal status and/or a decrease compared to normal, this is unknown. Secondly, the treatment is a strain, especially the HDT-SCT, and studies have shown that physical activity decreases during treatment (61,62). Finally, multiple myeloma is often diagnosed among the elderly, and age in itself might be a challenge regarding physical function, and the patients might be more vulnerable to the treatment of their disease.

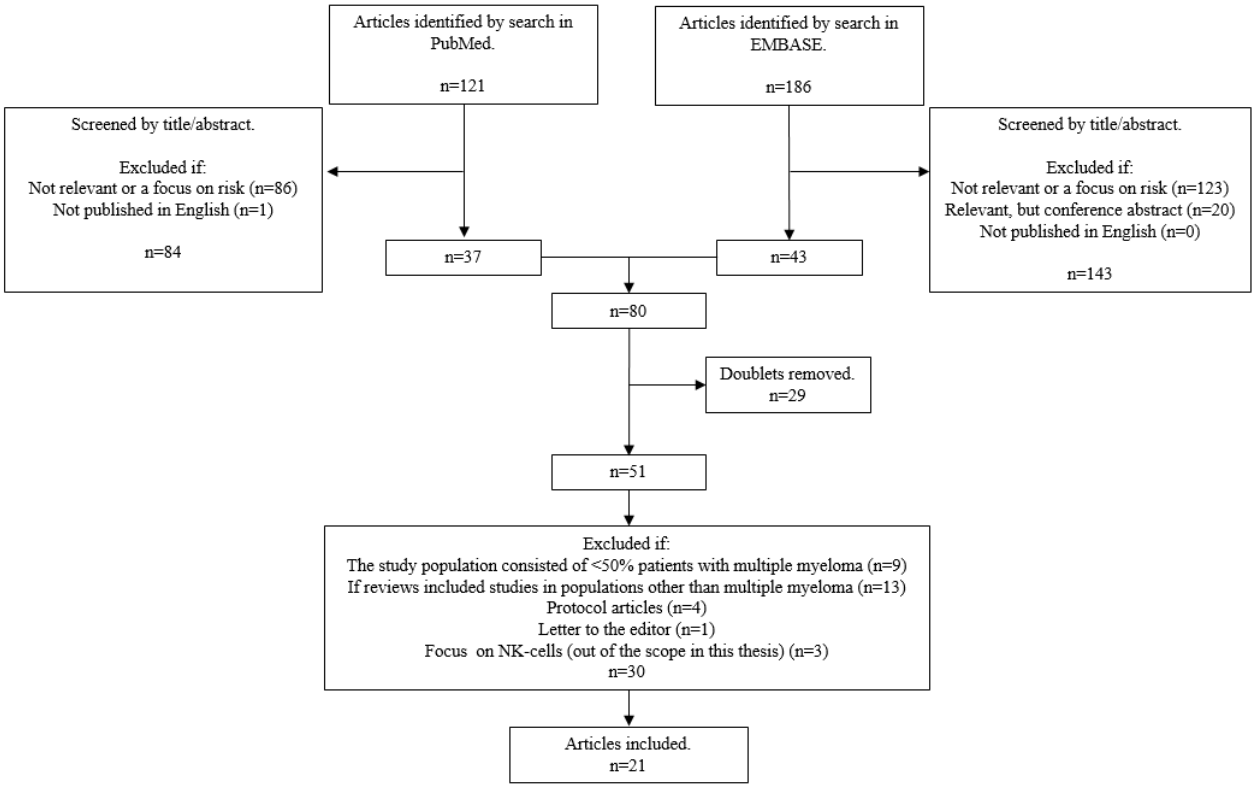
However, it is important to keep in mind, that patients´ level of physical function probably varies a lot at time of diagnosis and that the patients differ regarding presence, type and perception of treatment-related side effects. Disease specific treatments may cause different toxicities; e.g. the commonly used bortezomib as part of induction therapy in myeloma patients is associated with a significant risk of peripheral neuropathy (63). Regardless of variation, e.g. minor side effect versus severe side effect, it can be a challenge to maintain physical function during treatment.

With the generic guidelines of exercise/physical activity in mind, and with the proposed need of more specific guidelines moving away from “one size fits all” (6,13), and with the above mentioned conditions in relation to the disease, it is relevant to specifically present what is known about exercise in patients with multiple myeloma.

Exercise and physical activity in the perspective of multiple myeloma

Research in exercise in patients with multiple myeloma is sparse. In a literature search, 25 September 2019 in the databases, PubMed and EMBASE, 21 relevant studies of exercise and multiple myeloma were found (61,62,64–82). The search strategy is documented in Appendix IV, and the flow chart of the screening process is presented in Figure 3.

Figure 3. Flow chart of the screening process of the literature



The 21 studies covered different designs and aspects of exercise; feasibility and safety, effect, barriers and facilitators, preferences, and recommendations. See Appendix V for a short overview of the 21 included studies, of which two were reviews (64,65). In the following paragraphs, the literature will be presented according to these aspects of exercise.

Feasibility and safety of exercise

To our knowledge, Coleman et al. (66) were the first to investigate feasibility and safety of an exercise intervention specifically in a population of patients with multiple myeloma. Since then, studies of feasibility and safety in other settings have been published (69,80) as well as a single review with feasibility and safety as two of the foci (65).

The exercise intervention was investigated at different time points; during treatment, that is either one/two weeks after diagnosis (80) or after 10 weeks of induction treatment (66) followed by HDT-SCT, or in the stable phase after HDT-SCT (69,70). All studies considered exercise feasible and safe.
In relation to feasibility, it is relevant with supplemental knowledge about the patients´ thoughts about exercising or their perception of the exercise. In a survey of Australian patients with multiple myeloma, patients were asked whether they were likely to attend an exercise program designed for patients with multiple myeloma (62). There was an equal percentage of patients, who would attend/were extremely likely to attend and those who would not attend/were slightly likely to attend (62). Still, other studies have shown that the majority of the patients (65-80%) are willing to participate in exercise studies after completing HDT-SCT (69,70).
Generally, it is relevant to report adverse events, but regarding patients with multiple myeloma, bone disease is a special concern. Overall, the studies excluded patient with risk of fracture (66–69), but one study (69) described the bone evaluation in more details and took e.g. pain into account in their evaluation to categorize the bone disease. No adverse events in relation to bone disease occurred (66–69), but in two studies (67,70) some serious adverse events were reported, e.g. deep vein thrombosis or pneumonia, but none of them were related to exercise.

To summarize, exercise is considered feasible and safe during and after HDT-SCT. Little is known about feasibility and safety of exercise around the time of diagnosis, and it is relevant to apply a more varied view of bone disease through systematic assessment aiming at individualized exercise programs. Moreover, there is a gap regarding patients receiving other treatments than HDT-SCT, which particularly would be in the elderly.

Effects of exercise

Table 1 provides an overview and a short description of the studies evaluating the effect of exercise. In total, eight studies were identified. Out of the eight studies, two of them were pilot studies (66,69), one of them was a randomized controlled trial design (66) and the other was a single-arm study (69) focusing on feasibility and effect. Four of the eight studies were randomized controlled trials (67,68,70,82), two of them based on the same study (the EXIST study) (70,82) taking place after HDT-SCT, and the other two taking place during treatment (67,68). The last two identified studies (out of the eight studies) were reviews (not presented in Table 1, but only in Appendix V (64,65). In both reviews, the studies by Coleman et al. (66–68), and the single-arm study by Groeneveldt et al. (69) were included. The studies published after the reviews were the studies based on the EXIST study (70,82).
In the studies by Coleman (67,68) it was the same intervention in both studies (67,68), and there were many overlaps in the inclusion criteria. Differences were related to treatment regimen and the criteria for

prescription of Erythropoietin (67,68). Unfortunately, the time lines are a bit unclear, but nevertheless, the studies seem alike in many ways (67,68).

To summarize on Table 1 and the two reviews (64–69), the overall conclusions are that exercise is feasible, safe and has potentially beneficial effects, though with the recently studies from 2017 (70) and 2019 (82) in mind, showing no statistically significant effect. Exercise seems beneficial on aerobic capacity, muscle strength, quality of life, fatigue, mood, anxiety and depression, as well as physiological parameters during treatment, but not on response to and recovery from treatment. Beneficial effects are either changes in positive directions or a lesser decline than in the control group. Common characteristics across studies concerning frequency, intensity, type and time (FITT) of the intervention are as follows:

Frequency; two (70,82) or three times (67–69) weekly.

Intensity; moderate intensity (67–69) or moderate to high intensity (70,82).

Type of exercise; aerobic exercise and resistance training (66–70,82) either home-based (66–68) or supervised in combination with home-based (69,70,82).

Time; total duration of interventions was either 12 (70,82), 15 (67,68) or 26 weeks (69), taking place during treatment in the HDT-SCT trajectory (66–68), after HDT-SCT (70,82) or in stable disease (69).

The studies have limitations, e.g. in descriptions (66–68) and designs, including small study populations (59,62). Persoon et al. (70) pointed at contamination in the control group as an explanation of the statistically non-significant results. Furthermore, it was questioned, when the timing to intervene is best (70), also in the perspective of cost-effectiveness (82).

Studies looking at the patients´ perception of effects, showed perceived effect of a psychological character (69,71), (primarily among females) (71), and social benefits (71). Males perceived physical activity as a way to keep busy (71). Furthermore, patients perceived loss in physical performance (strength and stamina) if they interrupted the exercise, but there could be a need of reducing intensity during the exercise period, that is immediately after chemotherapy (72).

Table 1. Overview and a short presentation of the six effect studies (randomized controlled trails or clinical trials) emerged from the literature search in PubMed and EMBASE, sorted by year of publication.

Author	Study population	Intervention	Outcome	Results	Comments
Coleman et al. 2003 (66)	N=24 Male, n=14 Mean age in years, male 58.4, female 52.3. During tandem peripheral blood stem cell transplantations, but with intervention starting 10 weeks after induction treatment.	Aerobic exercise for 20 min., at least three times weekly. Strength resistance training. Three times weekly.	Feasibility. Fatigue, mood, sleep, lean body weight, aerobic capacity and muscle strength.	Lean body weight maintained in IG and decreased in CG. The only statistically significant difference. Other results were: Fatigue decreased in IG, no change in CG. Less mood disturbance in both groups. Better night-time sleep in IG, worse in CG. Day-time sleepiness decreased and day-time sleep increased in both groups. Aerobic capacity decreased less in IG than in CG. Muscle strength increased in IG, and decreased in CG.	Pilot study. Small study population, and inclusion did not reach the intended number of 30 patients. Frequency of strength resistance training are not reported.
Coleman et al. 2008 (67)	N=135 Two therapy regimens ("short-term" and "long-term") and thereby two populations are described. Generally, across the two groups, mean age 55 years, equal proportion of gender. Excluded if high risk of fracture. During tandem peripheral blood stem cell.	Strength and resistance training, alternating days with walking days. Daily stretching. Home-based, unsupervised. Moderate intensity. Intervention period of 15 weeks. Both IG and CG: Aerobic walking for 20 min three times weekly.	Number of red blood cell and platelet transfusions. Attempts of stem cell collection. Response to intensive treatment. Time to recovery (defined as number of days before blood cell recovery). Aerobic performance (6MWT).	Statistically significant fewer attempts and days of stem cell collection in IG. No statistically significant differences in response or recovery. Trend toward fewer red blood cell and platelet transfusions in IG. If non-responders to Erythropoietin were removed, the trend became statistically significant. Trend towards less decline in aerobic performance in IG.	RCT. No specific information on how bone assessment was done. Time lines are a little unclear. Frequency of strength resistance training is not clearly specified.
Coleman et al. 2012 (68)	N=187 Male, n=109 Mean age (SD) in years, IG: 56.0 (10.5), CG: 56.4 (9.3). Excluded if high risk of fracture. During tandem peripheral blood stem cell transplantations and Erythropoietin in an attempt to alleviate anemia.	Intervention as described above in Coleman et al., 2008.	Sleep, fatigue, and aerobic performance (6MWT).	Increase in night-time sleep and 6MWT in IG, but not statistically significant between groups. Statistically significant results over time/with more treatment given regarding more fatigue, less sleep at night, and decline in 6MWT in both groups.	RCT. No specific information on how bone assessment was done. Erythropoietin is not used for patients with MM in Denmark. Time lines are a little unclear. Strength training frequency is not clearly specified.

Table 1, continued...

Author	Study population	Intervention	Outcome	Results	Comments
Groeneveldt et al. 2013 (69)	N=45, 37 evaluable. Male, n=26 Median age (range) in years, 61 (46-74) Assessment of fracture risk; significant, moderate or asymptomatic/no. Significant bone disease, n=23 Stable disease and off-treatment/maintenance treatment. Previous HDT-SCT, n=42	Aerobic exercise and resistance training. Three times weekly for six months. Moderate intensity. The first three months one session was supervised. The next three months there was supervision by telephone once monthly.	Feasibility. Quality of life, fatigue, anxiety and depression, body composition, aerobic fitness, grip strength, knee extension strength. Focus groups to gain an understanding of how the exercise intervention impacted patients' lives (not reported here).	The first three months, attendance 87%, adherence 86%. The next three months, attendance 100%, adherence 73%. Statistically significant improvements in quality of life, anxiety and fatigue, and upper and lower limb strength at three months and six months in IG. No statistically significant change in aerobic fitness. Anxiety and depression, and body composition not statistically tested.	Pilot study. No control group. Eight patients dropped out after baseline assessment (20 had significant bone disease, seven has moderate bone disease, and ten had asymptomatic/ no bone disease.
Persoon et al. 2017** (70)	N=109, hereof: MM, n=58 (N)HL, n=51 Male, n=69. Median age (range) in years, 55 (19-67). No information about bone disease. Six to fourteen weeks after HDT-SCT.	Twice weekly for 12 weeks, followed by once weekly for six weeks, includiing five short counselling session. Supervised. Six resistance exercises. Interval training. Moderate to high intensity.	Attendance. Primary: Aerobic capacity, grip strength, 30 sec Sit-to-Stand-Test, fatigue. Secondary: BMI, sum of four skinfolds, max. isometric strength of the quadriceps, quality of life, anxiety and depression, physical activity.	75% attended >80% of the sessions. Improvement in physical fitness, 16-25% in the IG and 12-19% in the CG. General fatigue declined; IG 25 % and CG 12%. Physical fatigue declined; IG 32% and CG 25%. No statistically significant group differences in any of the primary and secondary outcomes, though differences were in a positive direction (except for disease symptoms in the IG).	RCT. Mixed group of patients.
van Dongen et al. 2019** (82)	N=109, hereof: MM, n=58 (N)HL, n=51 Male, n=69. Mean age (SD) in years, 52 (11). No information about bone disease. Six to fourteen weeks after HDT-SCT.	Supervised 18-week high intensity exercise program compared to usual care. As described above in Persoon et al., 2017.	Long-term effectiveness of physical fitness, fatigue, cost-effectiveness.	No statistically significant group differences in physical fitness and fatigue from end of intervention to one year after. Total costs were higher in IG, but not statistically significant.	RCT. Mixed group of patients.

** Based on the same study population. IG; Intervention group. CG; Control group. RCT; Randomized controlled trial. 6MWT; Six-Minute-Walk-Test.MM; Multiple myeloma. HDT-SCT; High Dose Therapy with Stem Cell Transplantation. (N)HL; (Non)Hodgkin Lymphoma.

Barriers, facilitators and compliance

Overall, patients perceived symptoms of multiple myeloma, and side effects of treatment as barriers (71).That is, fatigue (62,71), pain (62,71), other health conditions (62), age-related decline in physical ability (62) and fear of infection (71,73). Attitudes towards exercise were correlated to the intention of exercising (62), that is, whether the patients considered exercise beneficial or harmful. Low self-motivation could be a challenge for the males (71).

Furthermore, the patients perceived lack of knowledge and confidence in the capability to be physically active (62,69,74), and not least fear of injury (62) or bone damage (69) as barriers. The challenge with bone disease is supported by the association between former bone problematics and being non-compliant to exercise (75). Only around 10% of the patients perceived practical issues as barriers, e.g. costs, lack of time, or no one to exercise with (62).

Individual facilitators were believes in beneficial effects of exercise (72) commitment (72,76), also when they were not feeling well (72), taking responsibility for their own situation (72), routines and personal goals (72). External factors as facilitator were good support and encouragement (69,72,76) and treatment with prophylactic Erythropoietin for anemia and fatigue (76).

To summarize, there are both barriers and facilitators to exercise. They can be addressed and acknowledged, but not necessarily solved. Jones et al. (74) have found that perception of capability of exercising and feeling confident in doing it, are correlated, so focus on capability and confidence may help overcome potential barriers.

Exercise preferences

An in-depth explorative qualitative study (73) found that around half of the interviewed patients would have liked a physical activity program during treatment, and the patients who had not received HDT-SCT were more likely to undertake exercise during treatment than those who had received HDT-SCT (73). Opposite, patients also stated that exercise programs should be introduced two to eight months after treatment (73). The point is that timing is important, and patients have different opinions on the timing. There were different points of view on the balance between needed/requested information and overload of information, especially around time of diagnosis (73). Some patients perceived that the present advice is general and not that specified or concrete. More detailed advice is requested, and health professionals with knowledge of and experience with multiple myeloma are preferred (73). The preference of location varied. Some patients preferred hospitals/supervision from experts, and on the other hand, around half of the patients preferred home-based exercise (73). It was possible to achieve a high attendance (86%) within a travel distance of 15 km (longer distance was not explored) (77).

When planning physical activity programs, there were several things that patients found to be important. The program had to be individualized according to preferences, and taking the presence and severity of side effects and also the present level of physical activity into account (73). The patients preferred light to moderate activity (73), and they were not that fond of high-intensity exercise (77). Overall, a combination of aerobic exercise and strengthening exercise was preferred, and walking was a preferred activity (75). Generally, variation is wanted (77), and females had more different types of preferred physical activities than males (71).

Exercise recommendations

Currently, the most specified exercise recommendations to patients with multiple myeloma are given by Gan et al. (65) on the basis of their review.

They highlight that an individualized, structured exercise program is important. In that way, the severity of the disease and the aggressiveness of the treatment the patient receives can be taken into account (65). Periodic supervision of the exercise also plays a significant role for successful exercise (65). The exercise program must include aerobic and strengthening exercise, and if desired other kinds of exercises can be added (65).

Today´s integration of exercise

In Denmark, the majority of physical rehabilitation (73-95%) for outpatients takes place in the municipalities (83). However, it is possible to prescribe specialized physical rehabilitation taking place at the hospitals (84). This could be the case, if it is a complex, comprehensive, rare and/or severe disability of significant importance to the patient´s life (84), or if the physical rehabilitation must be provided by specialized health professionals, or if there is a need of close coordination between physical rehabilitation, diagnosing and outpatient treatment (84).

Data from all cancer types for the period from 2007 to 2016 showed that 13-21% received a physical rehabilitation plan, and that this correspond to one-third of patients who actually said they had a need of a rehabilitation plan. In patients with hematological diseases, physical rehabilitation plans were either prescribed in conjunction with discharge from hospital or if the patient´s physical function was impaired, but prescription was never at time of diagnosis (85).

Summary and study rationale

In summary, exercise in patients with multiple myeloma seem to be beneficial in numerous aspects; physically, psychologically and physiologically. The focus has been on patients undergoing HDT-SCT, and exercise interventions have been conducted during or after HDT-SCT, or when the disease is in stable phase after treatment. There is a lack of knowledge about exercise in patients undergoing other treatment regimens than HDT-SCT, a large group which captures the elderly part of the patient population as well.
Bone disease is a challenge for the patient and for clinical practice, and this is an essential parameter that requires attention when prescribing exercise.

Patients perceive many symptoms limiting their physical function in daily life as well as their quality of life. There is a lack of knowledge of how affected the level of physical function is at time of diagnosis, and whether and to what extent patients with multiple myeloma differ from the normal population, and from other cancer patients. It is relevant to gain that knowledge in a physical function screening perspective. Furthermore, there is a need of trying out an exercise intervention, taking bone disease into account, starting at time of diagnosis, and regardless of treatment regimen, in order to prevent or minimize physical deterioration.

To assess bone disease in a systematic way may contribute with valuable knowledge on how the challenge of bone disease might be overcome and transferred to exercise in a clinical setting.
The timing of the intervention, the effect results up till today, and according to national cancer plans and patient preferences, speak for a set-up with supervised exercise incorporated in the intervention, organized and delivered at the hospitals. Because of the timing and broader focus regarding treatment regimens the feasibility and safety of exercise and testing procedures need to be addressed, and of course the effectiveness.

With these focus points; physical function, and feasibility, safety and effectiveness of exercise, this thesis contributes with knowledge to the field of physical rehabilitation in patients with multiple myeloma.

CHAPTER III – AIM AND OBJECTIVES

The overall aim of this thesis was to investigate a physical exercise intervention in newly diagnosed patients with multiple myeloma, and furthermore examine their level of physical function at the time of diagnosis, in order to add knowledge to the need and effect of exercise at this time point of the patients´ course of treatment.

This overall aim is pursued by three objectives (Paper I-III) which constitutes this thesis.

- To evaluate the feasibility and safety of the exercise intervention and physical test procedures.
  The feasibility study (Paper I).

- To describe age and gender specific physical function among patients newly diagnosed with multiple myeloma and to compare physical function to the normal population and other cancer populations.
  The study of physical function (Paper II).

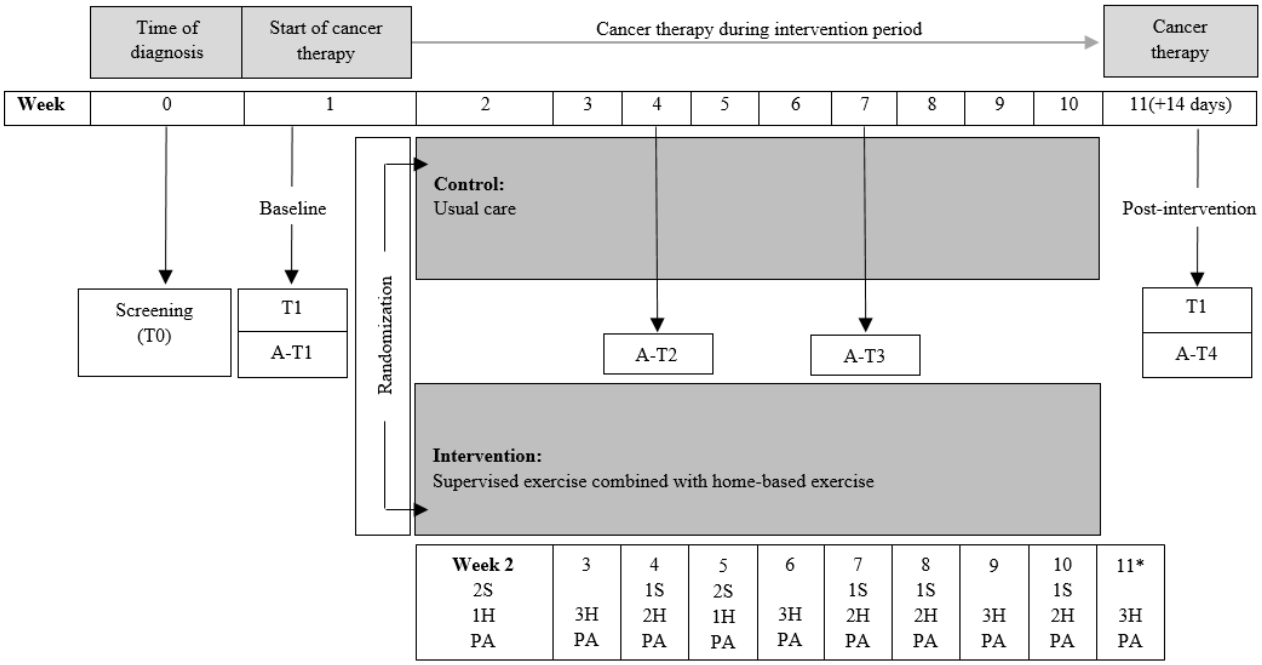
- To study the effect of individualized exercise on physical function, physical activity, quality of life and pain in patients newly diagnosed with multiple myeloma.
  The effect study (Paper III).

CHAPTER IV – METHODS AND MATERIAL

Study design

Overall, the thesis is based on a prospective, single blinded, randomized controlled trial. Patients were screened at time of diagnosis (T0), and inclusion took place after patients had provided their informed consent. This was within a few days after diagnosis. Typically 4 days after diagnosis, participants were tested at baseline (T1), and then randomized. If the participant was randomized to the control group, the participant received usual care. This consisted of an information leaflet, typically received in week 2. If the participant was randomized to the intervention group, the exercise intervention started one week after diagnosis (week 2). The intervention consisted of a combination of supervised exercise and home-based exercise. It lasted for 10 weeks, although the last supervised session was in week 10. The participants were tested post-intervention (T2) in week 11. An overview of the study is illustrated in Figure 4, also presented in Paper I (Figure 1) and Paper III (Figure 1).

Figure 4. Overview of the study and its time line.



T0; Time 0 (time of screening).

T1; Time 1 (physical tests at baseline test).

T2: Time 2 (physical tests post-intervention).

A-T1; Activity-Time 1 (accelerometer measures at baseline).

A-T2; Activity-Time 2 (accelerometer measures at week 4).

A-T1; Activity-Time 3 (accelerometer measures at week 7).

A-T4; Activity-Time 4 (accelerometer measures post-intervention).

1S and 2S; Supervised exercise session one or two times weekly, respectively.

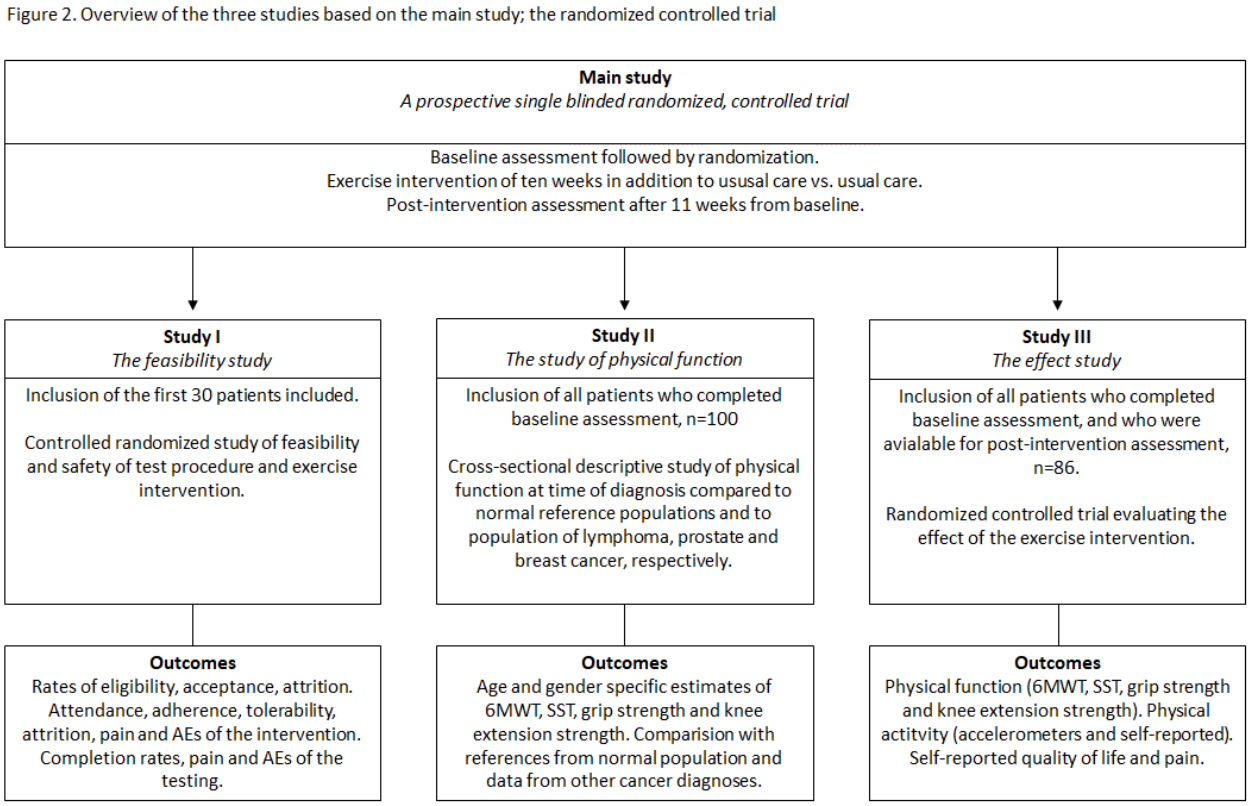
H1, H2 and H3; Home-based exercise session one, two or three times weekly, respectively.

PA; Physical activity taking place the remaining four days, where exercise sessions are not conducted.

**The test procedure can, but will not necessarily be performed in week 11. This means that in some cases, the participant will not perform a full week of exercise in week 11 before performing the post intervention test.*

The main study with the randomized controlled trial design formed the basis of three separate studies, *The feasibility study*, *The study of physical function*, and *The effect study*. Each study refers to a separate paper or manuscript. Figure 5 provides an overview of the three studies, including the appertaining outcomes.

Figure 5. Overview of the three studies, including the appertaining outcomes. All based on the main study.



Data in the randomized controlled trial (the main study) were collected in the period from June 2015 to April 2019.

For Study I, data from the first 43 patients screened were included, of which 30 included patients gave their informed consent. The inclusion of the 30 patients took around one year.

For Study II data from all included patients, who had gone through the baseline measurements, were included (N=100). The inclusion of all 100 patients took 43 months.

Study III counted the total study population who had completed baseline assessment and the post intervention assessment (N=86). This lasted for a period of 46 months.

The method for collecting data in the three studies was the same, but different outcomes and data from different time points were used.

Study procedures

Recruitment of participants

Patients from Zealand University Hospital and Odense University Hospital, who were newly diagnosed with multiple myeloma, were screened for eligibility on the basis of inclusion and exclusion criteria, at their first appointment with the hematologist at time of diagnosis.

The inclusion criteria were:

- Adult patients >18 years newly diagnosed with multiple myeloma requiring treatment.
- The patient had to be be able to speak and understand Danish and be able to give his/her informed consent.

The exclusion criteria were:

- Patients with spinal cord compression.
- Unstable vertebral fracture (SINS score >12) (86).
- Untreated cardiac failure and untreated cardiac arrhythmia
- Severe chronic cardiac failure (NYHA 3-4).
- Other severe comorbidity that would not allow physical training, e.g. neurological or uncompensated liver failure.
- Psychological or psychiatric disorder that would not allow compliance in physical training.

If eligible, the patient was briefly informed by the physician about the project, and was given the written participation information. Within two to three days (typically it was before the next consultation) the investigator called the patient and provided further information, and addressed any questions the patient may have regarding the project. Before start of chemotherapy, the patient gave their written informed consent.
If not eligible, or if the patient did not want to participate, a registration of the patient and some basic information were obtained, if the patient gave his/her informed consent to this procedure.

Handling the bone disease

Before testing and in order to individualize the specific exercises, a systematic assessment of the bone disease was conducted by the hematologist (Appendix VI). The assessment was developed on the basis of Mirels´ scoring system (45). Originally, Mirels´ score was developed to assess whether a metastatic lesion in a long bone is at risk of pathologic fracture, looking at site, pain, type, and size of lesion (45). This mindset was translated into an assessment, which generally assessed two parameters of the specific bone site; size and pain. If one of the following criteria was fulfilled, it led to exercise restriction in the specific area.

Long bones (femoral or humeral bone)

- Moderate or functional pain ***with*** osteolysis/destruction/fracture.
- Osteloysis size > 2/3 of bone width or cortical thinning, ***regardless*** of pain or not.
- Osteolysis, size 1/3 – 2/3 of bone width ***with*** pain, but ***regardless*** of degree of pain.
- Fracture, ***regardless*** of pain or not.

Pelvis

- Osteolysis > 2 cm in the top of acetabulum **OR** >1/3 in the rami.
- Fracture.

Spine (thoracic/lumbar) or costae

- Recent compression/fracture **OR** compression/fracture of unknown age ***with*** pain.

The exact exercise restriction for a given site was translated into clinical practice by using the exercise principles described by Galvão et al. in 2011 (48). Initially, Galvâo et al. assessed these principles in patients with prostate cancer with bone metastases (48), and recently, in two large, randomized controlled trials in patients with prostate cancer, and breast cancer with bone metastases (49,87).
The principles regarding resistance training and flexibility were followed, but opposite to Galvão et al. (48) and supported by Mirels (45), weight bearing exercises were allowed, although modified. That is, high load, e.g. running, was not allowed if there was restriction in any site (except for humeral bones), but walking was allowed.

So in this thesis, restriction for exercise was based on an assessment of the bones, and afterwards restrictions were translated into practice by exercise principles for bone metastases (Figure 6). Right and left side of the long bones were separated in the assessment, as well as in the following exercise prescription.

Figure 6. The matrix of how exercise restrictions were handled in connection with prescription of exercise. Inspired by Galvão et al. (48)*, p.5*

Site of bone assessment where restriction is needed (yes)	**Exercise mode** + = allowed and (+) = partly allowed (see comment)			
	Resistance exercise			**Flexibility**
	Upper extr.	*Lower extr.*	*Trunk*	*Static*
Femoral bone[a]	+	(+)	+	+
Pelvis[a]	+	(+)	+	+
Thoracic spine and/or costae[b]	(+)	+		(+)
Lumbar spine[c]	+	+		(+)
Humeral bone[d]	(+)	+	+	+

[a]*Exercises for lower extremities must be without flexion/extension of the hip.*
[b]*Resistance exercises must be without flexion/extension/abduction/adduction of the shoulder. Flexibility exercises must be without flexion/extension/rotation of the spine.*
[c] *Flexibility exercises must be without flexion/extension/rotation of the spine.*
[d]*Maximum load of 2 kg*

Randomization

Patients were randomized 1:1 to an intervention group (IG) or control group (CG). Stratified block randomization was used. The stratification was according to treatment (planned HDT-SCT versus (vs.) non-intensive treatment), WHO performance status (PS 0-1 vs. PS≥2), and study site. The randomization procedure was conducted after the baseline assessment by a study coordinator, who was not part of the study group.

Test procedure and intervention

Training of physiotherapists

All physiotherapists, who were involved in the RCT, underwent structured training. First, an introduction was given, and then practical training sessions started.
Physiotherapists who performed the testing procedures, tested each other, and the principal investigator. Afterwards they tested a minimum of two participants, under supervision.
Physiotherapist who performed the exercise part followed the principal investigator for one or two exercise sessions with participants. Afterwards, they were supervised for one or two sessions with participants, before conducting the exercise sessions themselves. There were follow-up sessions within the hospitals and across the two hospitals, when needed.

Assessments in the randomized controlled trial

The physical outcome assessment took place in a room at the departments of physiotherapy, arranged for the testing procedure. The outcomes were measured at baseline and post-intervention (Figure 4).
Testers were blinded for allocation of the randomization. However, it was not possible for all participants to not tell, whether or not they had received the exercise intervention, even though they were reminded prior to testing not to tell the assessor.

The following description of the tests is presented in the order, that they were performed in the total test procedure. Before starting tests of physical outcomes, participants were asked about basic demographics, and physical exercise, physical activity, and sedentary behavior on a weekly basis (88). Furthermore, they filled in the quality of life questionnaire (EORTC-QLQ-C30) (89) and the pain questionnaire (Brief Pain Inventory) (46,47,90). After testing the knee extension strength, the accelerometer (ActivPal Micro) was attached to the patient´s left thigh (one third of the distance from hip to knee) (91,92). The accelerometer was programmed to start the measurement at midnight, and then measure in the following five days (93,94).

The static knee extension strength (primary outcome) was measured by a “handheld” dynamometer (Lafayette Manual Muscle Tester) (95–98). It was perpendicularly fixated to a bench by a strap. The participant was placed sitting on the bench with hip and knee flexion of 90°, and arms resting on the side. The tester marked the lateral epicondyle proximal on tibia, and the top of the lateral malleolus (Illustration A). This, in order to measure the distance from the two marks to be used in the later analysis.

Illustration A

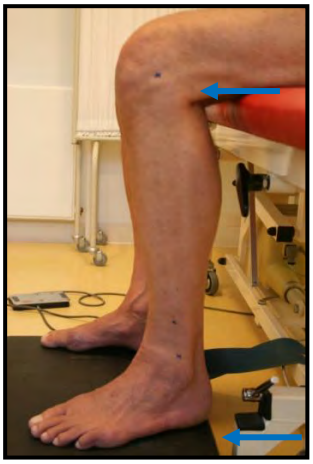


Illustration B

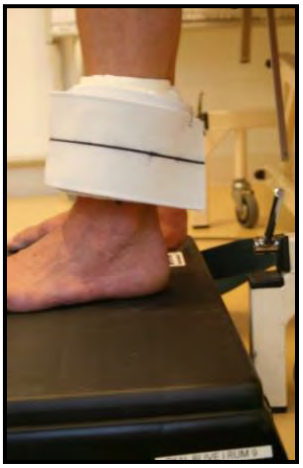


Illustration C

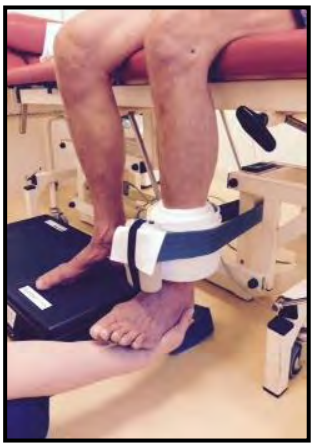
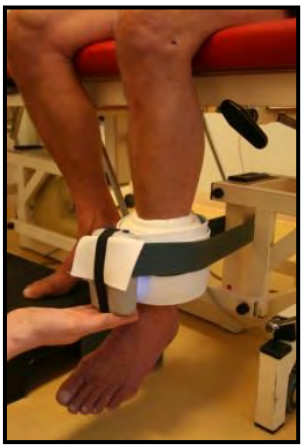


Illustration D



A piece of firm rubber foam was tightly fitted to the lower leg by a tight elastic band, so the lower border of the rubber foam was level with the mark at the lateral malleolus (Illustration B).

Then the strap with the dynamometer was placed around the participant´s lower leg. The lower border of the dynamometer was placed five centimeters from the top of the lateral malleolus, corresponding to the black line in Illustration B.

The tester gave the same instruction to the participant prior to every testing while the participant´s foot was held by the tester in a resting position (Illustration C). When the participant performed the test, the tester

removed their hand to the lower border of the dynamometer to secure the position of the dynamometer (Illustration D). After the five seconds of strength performance, the tester held the foot again until the next try. The leg, which was not tested, rested on a stool. The participant had three tries with 60 seconds of rest between each try. All three scores of each leg were registered, and in the later analysis the highest score across right and left side was used.

The grip strength was measured by a handheld dynamometer (Saehan model DHD-1 (SH1001)). The position was with the elbow flush to the side of the body, shoulder and elbow in a vertical line, elbow flexion of 90°, and the wrist in a neutral position (Illustration E), according to national standards (99), based on the standards from American Society of Hand Therapists (100).

Illustration E

(99), p.23

Right and left hand were tested, and the participant had three tries of each hand with 30 seconds rest between each try. All three scores of each hand were registered, and in the later analysis the highest score across right and left side was used.

The 30 sec Sit-to-Stand-Test was performed in accordance with guidelines (101–103). The same chair was used at both sessions, although different chairs across the two hospitals. Both chairs followed the guidelines regarding height of the seat. The chairs had arm rests in case the participants needed them. If that was the case it was registered that there was a modification to the test, and in the analysis, the number of raises were coded as eight.

The Six-Minute-Walk-Test was performed in accordance with guidelines (104,105). It took place in a corridor, where 20 meters were measured out and marked. At one of the hospitals it could happen that people would pass by, but they knew testing was going on, and thus, did not disturb by talking, or walking in the middle of the corridor.

Intervention

The exercise intervention took place in a room located where the other physiotherapists (testers) normally did not come by. This to increase the chance to maintain the blinding of the testers.

The exercise equipment was exactly the same at the two hospitals, i.e. the same ergometer bike, free weights, and weights which could be attached to the lower extremities.

The exercise session with the structured program was performed as described in Table 2. This table is also presented in Paper I (Table 1).

Table 2. Exercise intervention; mode, intensity, duration, and progression.

Mode	Intensity	Duration per session	Progression
Exercise program, three times per week			
Warm up	10-11 RPE[a]	5 min	-
Aerobic exercise[b]	12-13 RPE	20 min	↑ intensity to 14-16 RPE
Strengthening exercise *Five exercises for the lower extremities*[c] *Three exercises for the upper extremities*[d] *One exercise for truncus*[e]	Three sets of 12-15 reps	30-45 min	↑ weight to three sets of 10-12 reps
Stretching *Three muscle groups of the lower extremities*[f]	30 sec static	5 min	-
Physical activity, four times per week			
Preference of the participant	12-13 RPE	30 min. at least for 10 continuous min	14-16 RPE A possibility, but not standard

[a]*RPE, Rate of Perceived Exertion; Reps, repetitions.*
[b]*Aerobic exercise: If not possible to do aerobic exercise for 20 min on the stationary bike during the supervised session, the progression is an increase in total time (up to 20 min).*
[c]*Knee extension in sitting position, knee flexion in standing position, hip extension in prone position, toe raising in standing position, knee bent OR raise from chair.*
[d]*Arm lift in frontal plane OR circulation of shoulders in standing position, elbow extension in supine position and elbow flexion in standing or sitting position.*
[e]*Static in supine position with knees bent OR supine position with knees bent and lift of foot with press from the opposite hand.*
[f]*Femoral muscles (standing position), hamstring muscles (standing or sitting position), calf muscles (standing in front of wall).*

The exercise program was compiled in an online exercise database (Exorlive) and encompassed pictures, written instructions and information about the individual intensity. The participant received a printed version of the exercise program. The variation of exercises can be seen in Appendix VII. Furthermore, the participants kept a diary to document the adherence to the home-based exercise program and the physical

activity, see Appendix VIII. Furthermore, it was used as a planning tool for the patients between the supervised exercise sessions.

Statistical methods

All test results from the physical outcomes and patient reported questionnaires were registered on paper. Afterwards the results were entered into a database (REDCap) provided by OPEN (Open Patient data Explorative Network, Odense University Hospital, Odense, Denmark). Data from medical records were extracted, and entered to the database as well.
The statistical analyses were conducted in the statistical program, STATA 15.1 with help from a statistician.

Power calculation for the RCT

For the estimation of the required number of included participants, a power calculation was conducted.
The following parameters were included:

- Significance level, $\alpha = 0.05$.
  This corresponds to five per cent probability of a type I error.
  That is, rejects a true null hypothesis.
- Power of 80%, $\beta = 0.20$.
  This corresponds to 20% probability of a type II error.
  That is to reject an alternative hypothesis, even though the null hypothesis is false.
- Minimum clinical difference of mean (SD) 7 kg (13.1) (69).
  This corresponds to 69 N (128.5) in the knee extension strength (increase of 23%).
- A one-way estimation was done.

The power calculation estimated that the number of participants needed was 44 participants in each group (intervention and control). Taking a drop-out rate of 15% into account, 102 participants needed to be included.

Study I – The feasibility study

Descriptive statistics were conducted using simple report data from the REDCap project database. The analysis was based on intention to treat. Outcomes of interest in order to investigate feasibility and safety were rates of eligibility, acceptance, attrition, attendance and adherence. Furthermore, completion rates of physical tests, pain, and adverse events were also recorded. Further details are available in Paper I.

Study II – The study of physical function

The physical outcome measures; Six-Minute-Walk-Test, 30 sec Sit-to-Stand-Test, grip strength and knee extension strength were stratified by gender and age groups. Data were compared by z-test (after standardization to mean=0 and SD=1) to reference values from normative populations and furthermore, to published data from patients with malignant lymphoma, prostate cancer and breast cancer, respectively. Moreover, outcome measures were presented as box plots stratified by bone involvement, and fractures, and the standardized measurements were compared. Further details are available in Paper II.

Study III – The effect study

Outcomes were compared between groups by two-sample t-test for individual time points and by mixed effects linear regression models, including the patient as random intercept, for longitudinal comparisons. Relative changes were compared between groups by Wilcoxon rank sum test. Normality assumptions were ascertained by quantile plots. Further details are available in Paper III.

Ethical considerations

The study adhered to the laws and regulations in Denmark, and the Declaration of Helsinki II. The study was approved by the Ethical Scientific Committee in Region Zealand (SJ-422), registered 11 December 2014 and by the Danish Data Protection Agency (REG-122-2014), registered 30 December 2014. The study was registered at ClinicalTrials.gov. ID NCT02439112, registered May 7, 2015.
Written informed consent was obtained from all participants included in the study. Participants who did not wish to participate, or did not fulfill the inclusion criteria gave their written informed consent to be registered in the study.

CHAPTER V – RESULTS

In this section the three studies are presented one by one. For each study, the overall aim and key results are presented. Further details to be found in each paper (Paper I, Paper II, and Paper III).

Study I – The feasibility study

The aim was to evaluate the feasibility and safety of the exercise intervention and the physical test procedures (Paper I).

The median age of the participants (n=30) was 69 years (range 38-90), 75% were men. Around two-thirds (67%) had bone disease, and half of them were assessed to have restrictions regarding tests or exercise. Patients with restrictions were not equally distributed between intervention group (36%) and control group (83%).

As summarized in Table 3 the main findings were that the exercise intervention and test procedures were feasible and safe. Patients were interested in participation to the study and adhered to the intervention, which proved to be safe for the patient.
Furthermore, the patients were able to perform all tests, which is reflected in the test completion rates. Regarding the primary outcome (knee extension strength), the majority (over 80%) were able to perform the testing in both right and left side.
There were two non-serious adverse events; one patient perceived pain and one patient perceived dizziness. Both patients had to discontinue the exercises session.

Table 3. Overall findings from the feasibility study (Paper I)

Feasibility	**Per cent**	**Comment**
Eligibility rate	82 %	40 out of 49 participants
Acceptance rate	75 %	30 out of 40 participants
Attrition rate	20 %	6 out of 30 participants
Completion rates of the physical tests	82-100 %	
Completion rate of the intervention	86 %	12 out of 14 participants
Attendance rate to all supervised exercise sessions	92 %	11 out of 12 participants
Adherence rate to supervised exercise sessions	99%	95 out of 96 sessions
Adherence to home-based exercises program	89 %	203 out of 228 sessions
Adherence to home-based physical activity	94 %	405 out of 432 sessions
Diary registration, all weeks	87 %	10 out of 12 participants
Diary registration, some weeks	13 %	2 out of 12 participants
Safety	**Numbers**	**Comment**
Adverse events during test procedure	0	
Adverse events during exercise	2	Non-serious, leading to discontinuation of the session. No further consequences.

Study II – The study of physical function

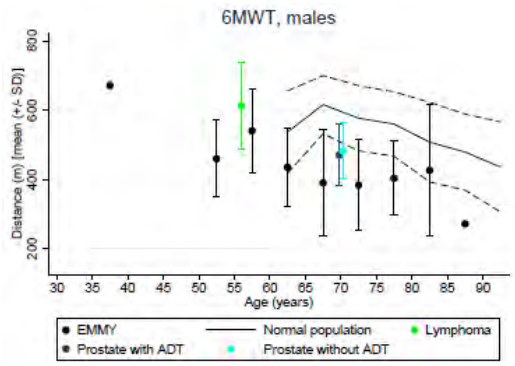
The aim of this study was to describe age and gender specific physical function among patients newly diagnosed with multiple myeloma and to compare physical function to the normal population and other cancer populations (Paper II).

The mean age (SD) of the participants (n=100) was 67.7 (10.3) years The age group with the highest representation was 70-79 years (35%), followed by the age group 60-69 years (28%).
Around three quarters (73 %) of the participants had bone disease, and around half of those (56%) had bone disease to an extent, which caused restrictions to tests and/or exercise. One-third (33%) of the participants had fractures (n=33), and the most common were vertebral fractures (73%) resulting in pain; 17 % had mild pain, 33 % had moderate pain, and 29 % had functional pain.

Patients with multiple myeloma had poorer physical function than the normal population, regarding Six-Minute-Walk-Test ($p<0.0001$), 30 sec Sit-to-Stand-Test ($p<0.0001$), and knee extension strength (total group) ($p<0.0005$) (Figure 7a-d). Grip strength was statistically significantly better ($p<0.0001$) in the patients with multiple myeloma than in the normal population (Figure 8a-d). Figures are presented in Paper II as well (Figure 1a-d, and 2a-d).
The performance in the 30 sec Sit-to-Stand-Test was modified by the presence of bone involvement and fractures, grip strength was modified by the presence of fractures, and the performance in Six-Minute-Walk-Test was marginally modified by the presence of vertebral fracture. The knee extension strength was not modified, by bone involvement, fractures or vertebral fractures.
Compared to patients with lymphoma, patients with multiple myeloma had lower aerobic capacity and performed better in lower extremity strength. No differences were found compared to patients with prostate cancer and breast cancer, except for grip strength, where patients with multiple myeloma performed better than the breast cancer group.

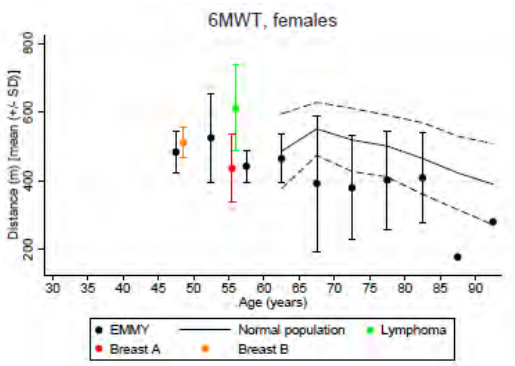
Figure 7a-d. Age group and gender specific Six-Minute-Walk-Test (6MWT) and 30 sec Sit-to-Stand-Test (SST from the multiple myeloma study population (EMMY), and from other cancer diagnoses.

a.



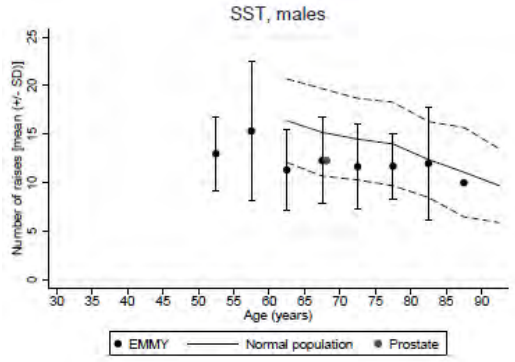
Normal (106). *Lymphoma* (107). *Prostate (+/- ADT)* (108).

b.



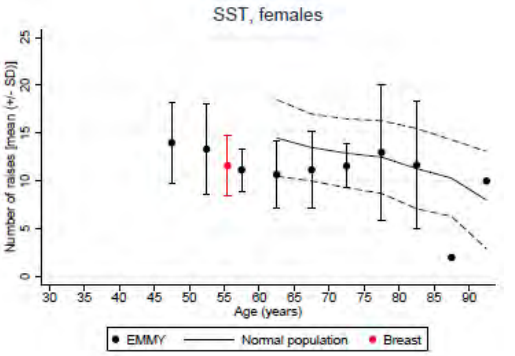
Normal (106). *Lymphoma* (107). *Breast A* (109). *Breast B* (110).

c.



Normal (106). *Prostate* (111).

d.

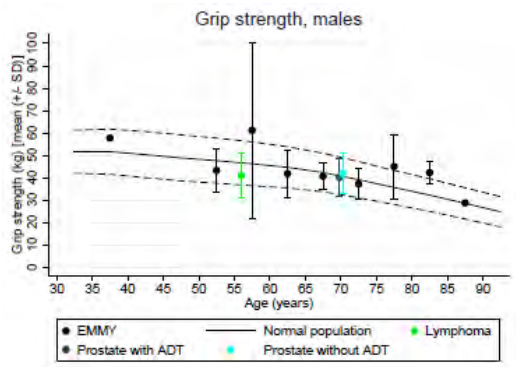


Normal (106). *Breast* (109).

Data are illustrated by means and SD-bars (within the five year intervals) and reference values from the normal populations are illustrated by curves (full line indicates mean and dotted lines are +/- SD).

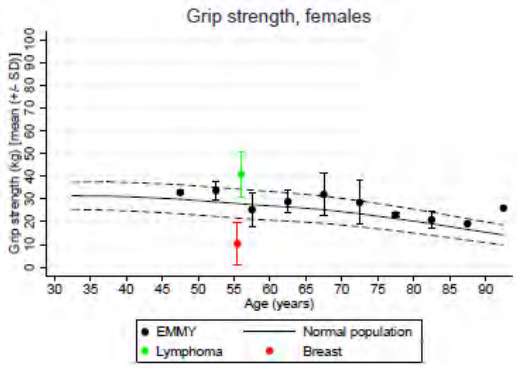
Figure 8a-d. Age group and gender specific grip and knee extension strength from the multiple myeloma study population (EMMY), and from other cancer diagnoses.

a.



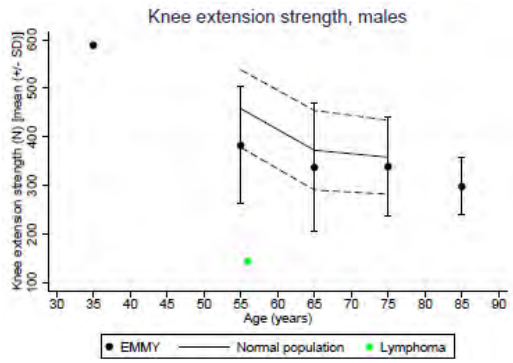
Normal (112). *Lymphoma* (107). *Prostate (+/-ADT)* (108).

b.



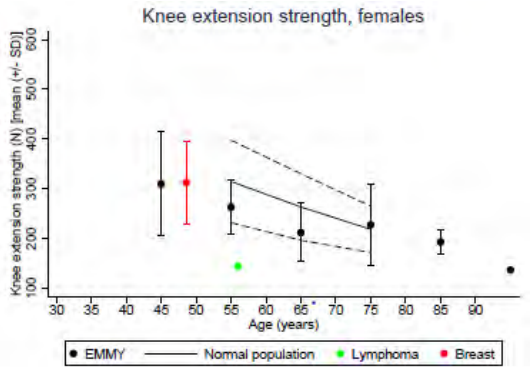
Normal (112). *Lymphoma* (107). *Breast* (109).

c.



Normal (113). *Lymphoma* (107)

d.



Normal (113). *Lymphoma* (107). *Breast* (110).

Data are illustrated by means and SD-bars (within the five years intervals for grip strength and ten year intervals for knee extension strength) and reference values from the normal population are illustrated by curves (full line indicates mean and dotted lines indicate +/- SD).

Study III – The effect study

The aim was to study the effect of individualized exercise on physical function, physical activity, quality of life and pain in patients newly diagnosed with multiple myeloma (Paper III).
Out of the 100 included participants, we included those with physical test data from baseline and post-intervention (n=86).
In the study population, 53% were males. The mean age (SD) of the participants was 67.3(10.3) years. The majority (74%) had bone disease, and out of these, involvement of the spine was the most common. HDT-SCT was planned for 57% of the patients.

The key findings concerning physical measures are presented in Table 4, and the self-reported measures of quality of life and pain are presented in Table 5. Both tables are presented in Paper III as well (Table 2 and Table 4).

Overall, no statistically significant differences between the IG and the CG were found across all physical outcome measures. We found a decline in knee extension strength and grip strength from baseline to post-intervention in both groups, but it was only in the control group, the decline of knee extension strength reached statistical significance (p=0.014). The 30 sec Sit-to-Stand-test and Six-Minute-Walk-Test showed a significant increase within the two groups.
We found a positive and clinically important improvement in global quality of life in both groups (114). Pain was significantly reduced in the control group. In the intervention group the reduction was less evident, since it was only the reduction in “worse pain” that was statistically significant.
The levels of physical activity based on accelerometer measurements did not differ between groups (Figure 9). Figure 9 is presented in Paper III as well (Figure 4).

Table 4. Measures of physical function at baseline (T1) and post-intervention (T2) according to intervention group (IG) and control group (CG) as well as within group differences, and between groups differences with corresponding p-values and relative changes (RC) from baseline to post-intervention.

	IG (TP1) n=44	**IG (TP2) n=44**	**Within IG**	**CG (TP1) n=42**	**CG (TP2) n=42**	**Within CG**	**Between groups**	**P-value for RC between groups**
Knee extension strength (Newton)								
Mean (SD)	304.2 (117.5)	282.6 (113.6)		295.4 (113.08)	270.8 (103.88)			
Mean diff.(p-value)			-19.6 (0.092)			-26.9 (0.014)	-7.3 (0.648)	
RC (mean% (SD))			-0.06 (0.30)			-0.05 (0.24)		0.799
Knee extension strength (Nm/kg body weight)								
Mean (SD)	4.2 (1.54)	4.0 (1.66)		4.03 (1.41)	3.55 (1.35)			
Mean diff.(p-value)			-0.20 (0.210)			-0.34 (0.024)		
RC (mean% (SD))			-0.05 (0.30)			-0.04 (0.25)	-0.14 (0.528)	0.906
Grip strength (kilogram)								
Mean (SD)	36.1 (13.29)	34.0 (11.11)		38.6 (18.0)	37.2 (20.96)			
Mean diff. (p-value)			-2.1 (0.083)			-1.3 (0.48)	0.8 (0.742)	
RC (mean% (SD))			-0.03 (0.30)			-0.03 (0.17)		0.205
30 sec Sit-to-Stand-Test (number of raises)								
Mean (SD)	12.5 (4.5)	14.1 (5.3)		11.0 (3.89)	12.5 (4.85)			
Mean diff.(p-value)			1.9 (0.004)			1.5 (0.022)	-0.4 (0.707)	
RC (mean% (SD))			0.22 (0.52)			0.24 (0.49)		0.949
6 Min-Walk-Test (meter)								
Mean (SD)	435.5 (134.7)	476.7 (114.9)		409.5 (147.16)	451.6 (119.89)			
Mean diff. (p-value)			44.1 (0.001)			42.1 (<0.001)	-2.2 (0.900)	
RC (mean% (SD))			0.26 (0.63)			0.39 (1.65)		0.902

Missing values: Nine for knee extension strengths (N), twenty for knee extension strengths (Nm/kg), one for grip strength, twelve for 30 sec Sit-to-Stand-Test, and one for Six-Minute-Walk-Test. Difference between the two knee extension strength measures is caused by missing weights.

Table 5. Measures of quality of life and pain at baseline (T1) and post-intervention (T2) according to intervention group (IG) and control group (CG) as well as within groups differences, and between groups differences with corresponding p-values and relative changes (RC) from baseline to post-intervention.

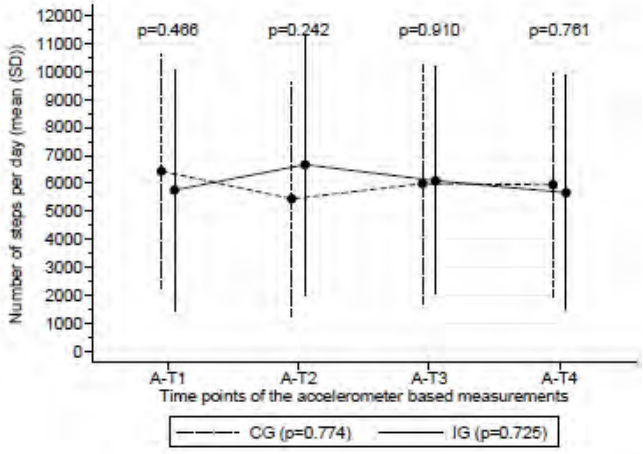
	IG (T1) n=44	IG (T2) n=44	Within IG	CG (T1) N=42	CG (T2) N=42	Within CG	Between groups	Missing
QUALITY OF LIFE								
EORTC-QLQ-C30								4
Global QoL								
Mean (SD)	54.7 (25.3)	65.3 (21.3)	10.9 (0.024)	54.7 (23.94)	65.5 (18.1)	10.9 (0.002)	-0.4 (0.941)	
Median (range)	58.3 (0-91.7)	66.7 (16.7-100)		58.3 (0-100)	66.7 (33.3-100)			
IQ range	33.3-75.0	50.0-83.3		33.3-66.7	50.0-83.3			
RC (mean%)			0.43 (1.09)			0.36 (0.65)	0.764	
Functional domains								
Physical functioning								1
Mean (SD)	73.7 (25.6)	79.5 (19.0)		70.1 (20.3)	74.6 (19.3)			
Mean diff. (p-value)			5.8 (0.016)			4.52 (0.116)	-1.3 (0.726)	
Role functioning								1
Mean (SD)	57.1 (33.1)	64.3 (30.7)		51.1 (36.73)	61.6 (32.44)			
Mean diff. (p-value)			7.1 (0.106)			10.5 (0.050)	3.3 (0.632)	
Emotional functioning								3
Mean (SD)	6.9 (17.1)	84.72 (18.9)		71.7 (19.7)	83.5 (16.5)			
Mean diff. (p-value)			8.5 (<0.001)			11.7 (<0.001)	3.3 (0.380)	
Cognitive functioning								3
Mean (SD)	87.9 (19.6)	88.9 (18.3)		83.7 (20.80)	86.8 (16.08)			
Mean diff. (p-value)			2.1 (0.492)			2.8 (0.207)	0.5 (0.890)	
Social functioning								3
Mean (SD)	82.5 (24.7)	82.5 (22.4)		78.0 (26.4)	80.6 (21.5)			
Mean diff. (p-value)			2.2 (0.426)			2.5 (0.495)	0.6 (0.890)	
Symptoms domains								
Fatigue								1
Mean (SD)	38.4 (29.3)	39.8 (24.1)		44.2 (27.2)	36.7 (23.6)			
Mean diff. (p-value)			1.5 (0.702)			-7.5 (0.076)	-9.0 (0.116)	
Nausea and vomiting								1
Mean (SD)	11.5 (16.7)	8.3 (15.7)		6.1 (12.0)	8.5 (13.8)			
Mean diff. (p-value)			-3.2 (0.260)			2.4 (0.262)	5.6 (0.113)	
Pain								1
Mean (SD)	37.3 (33.5)	19.4 (22.4)		47.7 (32.9)	24.0 (23.9)			
Mean diff. (p-value)			-17.9 (<0.001)			-23.8 (<0.001)	-6.0 (0.371)	
Dyspnoea								2
Mean (SD)	23.6 (28.13)	26.3 (31.70)		23.5 (25.50)	19.4 (27.44)			
Mean diff. (p-value)			2.9 (0.574)			-3.8 (0.415)	-6.6 (0.338)	
Insomnia								2
Mean (SD)	23.0 (28.0)	33.3 (27.6)		33.3 (34.5)	22.2 (29.1)			
Mean diff. (p-value)			10.3 (0.028)			-10.7 (0.071)	-21.0 (0.006)	
Appetite loss								2
Mean (SD)	15.08 (24.6)	15.08 (28.7)		27.1 (31.1)	13.2 (26.4)			
Mean diff. (p-value)			0.00 (1.000)			-14.3 (0.004)	-14.4 (0.028)	
Constipation								2
Mean (SD)	23.0 (30.8)	23.8 (30.0)		23.3 (32.2)	17.1 (26.6)			
Mean diff. (p-value)			0.8 (0.847)			-6.7 (0.128)	-7.5 (0.212)	
Diarrhea								4
Mean (SD)	8.3 (16.5)	8.9 (18.3)		9.1 (16.7)	14.7 (23.4)			
Mean diff. (p-value)			0.7 (0.833)			5.6 (0.180)	5.0 (0.354)	
Financial difficulties								4
Mean (SD)	4.2 (11.2)	4.0 (13.2)		5.4 (19.2)	9.3 (18.3)			
Mean diff. (p-value)			-0.1 (0.956)			3.9 (0.048)	4.0 (0.159)	
BRIEF PAIN INVENTORY								
Pain severity rate[a]			Mean diff (p)			Mean diff (p)	Mean diff (p)	
Worst	3.7 (2.9)	2.7 (2.5)	-1.0 (0.040)	4.6 (3.4)	2.8 (2.7)	-1.8 (0.001)	-0.8 (0.292)	2
Least	1.3 (1.3)	1.4 (1.5)	0.1 (0.801)	1.7 (2.1)	0.9 (1.2)	-0.8 (0.015)	-0.9 (0.045)	6
Average	2.6 (2.3)	2.2 (2.1)	-0.5 (0.314)	3.1 (2.6)	2.0 (2.1)	-1.2 (0.004)	-0.7 (0.261)	3
Now	1.8 (2.00)	1.5 (2.0)	-0.3 (0.376)	2.7 (3.0)	0.9 (1.6)	-1.8 (<0.001)	-1.5 (0.013)	5
Composite score	2.4 (1.9)	2.0 (1.9)	-0.5 (0.221)	3.0 (2.45)	1.7 (1.5)	-1.4 (<0.001)	-1.0 (0.067)	2
Pain interference[b]	2.5 (2.5)	2.2 (2.5)	-0.3 (0.468)	2.8 (2.4)	1.7 (1.9)	-1.1 (<0.001)	-0.8 (0.162)	2

EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

[a]*Pain severity is rated by four items: Worst within the last 24 hours, least within the last 24 hours, average generally, and now. The composite score is the mean of the four pain items.*

[b]*Pain interference covers seven items of daily activities: General activity, walking, work, mood, enjoyment of life, relations with others, and sleep. The pain interference mean score is the mean score of the seven items.*

Figure 9. Measures of physical activity (steps per day) at baseline (T1/A-T1), week 4 (A-T2), week 7 (A-T3), and week 11 (T2/A-T4) according to the intervention group and the control group. P-values are reported between groups (intervention group (IG) and control group (CG)) and within groups across all four time points.



CHAPTER VI – DISCUSSION

This thesis provides results derived from the main study; the randomized controlled trial investigating the effect of early initiated physical exercise in newly diagnosed patients with multiple myeloma. Within the study population, feasibility and safety of intervention as well as test procedures were evaluated based on the first 30 included patients (Paper I). Age and gender specific physical function at the time of diagnosis of all included patients were compared to the normal population, as well as compared with other cancer populations in a cross-sectional design across published studies (Paper II). The randomized controlled study evaluated the effect of the exercise intervention with pre- and post-intervention measurements (Paper III). Results of the three studies are discussed in papers; I, II, and III, respectively.
In the following, overall methodological considerations including strengths and limitations are discussed, as well as the external validity of the findings. Furthermore, considerations regarding the outcomes measurements are discussed, and perspectives of findings are elaborated.

Methodological considerations

The design

The intervention in this study can be considered a complex intervention in several aspects (115).
It had interacting components (115), i.e. pain related to bone disease, which may have affected the ability to exercise. Another example could be pros and cons for the combination of structured supervised and home-based exercise versus the information given to the control group with a higher degree of freedom to decide when and how to exercise, i.e. depending on variation in pain or side effects. Furthermore, the way the exercise program was individualized according to the bone disease assessment means that this replication of the exact intervention was impossible. However, it was well documented how the bone disease assessment was translated into the exercise prescription matrix (Figure 6). So despite the efforts to minimize bias and addressing reliability, which must be seen as a strength for the study, these aspects also become a limitation.

On the other hand, the systematic assessment of bone disease is also a strength for the study. This contributed to the representative study population, rendering inclusion of patients with various degrees of bone disease / bone destructions possible. Furthermore, the aim was to be able to prescribe exercise safely by combining the two approaches to bone disease, that is, the principles from Mirels´ score system (45) and the exercise principles developed by Galvão et al. (48,49). Mirels´ score classifies the risk of fracture with the purpose of recommending prophylactic fixation or radiotherapy and medical treatment (45), but in this thesis, a more site specific output was wanted, aiming at taking the bone disease into account in a differentiated way (43). The chosen approach was relatively pragmatic, without any extra costs except for the

time of performing the systematic bone assessment, and it was easy for the physiotherapist to translate into clinical practice.

The way the intervention was organized seemed successful, because of the high attendance and low attrition (Paper I). One of the important things in this success is probably the effort of coordinating the test procedure and the supervised exercise sessions with other visits at the hospital. This is in keeping with the intentions of *Kræftplan III* (8,9), as well as organizational models for physical rehabilitation in the Danish Health Care system (84) To summarize, these state that targeted rehabilitation must primarily be delivered by specialists at the hospitals, if a high degree of coordination is required.

The study took place at two sites, and although, much effort was put into standardizing the study procedures, standardization will always be a challenge, and differences cannot be avoided (115). An example of this is how the usual care was delivered. At one of the sites, the information leaflet was delivered by a physiotherapist leaving time for questions, while at the other site, the leaflet was handed out by a nurse, where an actual review of the leaflet was not part of the usual procedure.

The above mentioned components are related to the intervention. Components related to testing were also a challenge. The physiotherapists´ experience with the patient group varied, and the cadence of testing, which depended on continuity in testing also varied. Cadence and continuity are related to the size of teams and variation in inclusion rate. Controlling for experience was accomplished through careful instructions, practical sessions and supervision, whereas control for the continuity was not possible.
To compensate for definite and potential differences between the two investigational sites we stratified the randomization according to site, which strengthens our findings.

The design of the main study; the randomized controlled trial has definite strengths. The blinded randomization procedure worked well in order to equal the two groups based on the choice of stratification. Stratification was used in order to avoid confounding, and the block randomization were used in order to obtain the random selection of intervention and control, respectively. However, double blinding cannot be achieved in an intervention study like this. Besides the potential risk of having patients unveiling their allocation to the assessor, the behavior in the control group may bias the results if these patients are changing exercise behavior towards more exercise, just because they are participating in the study, and thereby might get motivated.

External validity

The screening based on broad inclusion criteria aimed to include patients who were representative of clinical practice. This, in combination with high acceptance to study participation (Paper I) contributed to a study population reflecting the real population of newly diagnosed patients with multiple myeloma, in respect of

age, bone disease, and planned treatment (Paper I; II and III). This speaks for successful minimization of selection bias, and thus heightens the external validity

On the other hand, the total inclusion period was long, which could speak for some degree of selection bias. Possible reasons could be that patients, who are very affected by their disease are left out (without screening), and/or that hospitalized patients were not screened, because of a need of acute care, and naturally, focus of inclusion into an exercise study changed (Paper III).

The set-up of the intervention can strengthen the external validity, as well as limit it. The strength is that the exercise program can easily be conducted at home, although the use of elastic bands instead of weights would be preferable in relation to practical issues for the patients, as well as costs. The limitation is, that the outcomes to some degree reflect the intervention. A more relevant outcome for the patients could have been quality of life.

Although, ambulatory physiotherapy differs between the two sites, the intervention has the potential to be implemented, with the limitation that some organizational adjustments may be required. E.g. open exercise sessions may have more potential in an organizational perspective than individual sessions, and in an implementation phase there is work to be done in relation to assessing the bone disease. Based on the results in Paper II, working with systematic screening of the need of physical rehabilitation will also require attention on how this should be to organized

Outcome measurement considerations

Physical outcomes

Special attention must be paid to the primary outcome; knee extension strength. It is associated with, predictive of, and important for physical function, e.g. mobility, physical function limitation, physical independence, and activities of daily living (116,117). First of all, hand-held dynamometry was found to be reliable in terms of intra and inter-tester reliability (95). Satisfactory validity was found as well, in terms of concurrent validity in comparisons to isokinetic dynamometry (95,118), but also functional measures, such as 30 sec Sit-to-Stand-Test, gait, and stair ascent (118). However, the reliability of the knee extension strength measurement was not tested, which is a critical point, although the method and the validity were supported by the literature (95,101,118). Other physiotherapists and research teams at two other university hospitals were also consulted regarding their experience of using this measure, both the exact method of conducting the strength testing in hematological patients, and more generally, experiences with use of dynamometer in research protocols.

In this study, a belt stabilized the “hand-held”-dynamometer, whereby the belt made it possible to measure the strength without limitation by the tester´s strength (118). Otherwise, this would result in bias and decreased validity (118). It could have been useful with fixation of the patients (96), but this method was not

available. The minimal important difference varies in the literature (119). Thus, it can be a challenge in the interpretation of the results and implications for clinical practice. This, and because of lack of reference values from populations similar to the population in this study, may have the consequence that the power analysis is either underestimated or overestimated. The power calculation was based on available data from an original study (69), where knee extension strength was one of the outcomes.
In the light of these limitations, it can be questioned whether another, more simple measure of lower body strength with better described psychometric properties should have been the primary outcome instead of the knee extension strength. Sit-to-Stand-Test could have been a possibility, and this would have been a more functional test, but it also has its limitations. For example it has not been tested in adults under the age of 60 years (116), and it cannot be rejected that there might be a ceiling effect in younger participants. Knee extension strength showed to be the only outcome (Paper II), which was not modified by bone disease, fractures, or vertebral fractures, and in that light a relevant choice of primary outcome.

Six-Minute-Walk-Test is a valid measure in cancer patients (120,121), and was considered appropriate for the majority of the participants in the study (Paper I). It is a functional measure of aerobic capacity, although not a maximal test of aerobic capacity. The Cardio Pulmonary Exercise Test could be a more precise alternative, which has been used in cancer patients (70,122–124). When the study was initiated the equipment for performing the Cardio Pulmonary Exercise Test was not available. Furthermore, it can be questioned, whether all participants would have been able to safely perform such a maximal test at time of diagnosis, e.g. bone disease might be a challenge, and according to Scott et al. (124), more research of reliability is needed before it can be used before, during and after cancer treatment. The Cardio Pulmonary Exercise Test has been investigated in patients with multiple myeloma, but only patients with stable disease after end of treatment (125).

Patient involvement in research has increased in recent years. Patients are involved in different aspects of the research process, e.g. study protocols and funding. It could have been interesting to ask the patients about their opinion of primary outcome.

Patient reported outcome measures

We included validated questionnaires, the cancer generic EORTC-QLQ-C30 (ref) and the Brief Pain Inventory (ref), to get important information on the patient perception of quality of life and pain.
When studying newly diagnosed patients with multiple myeloma who starts anti-myeloma treatment, improved quality of life is expected (126), so in that perspective the results of clinical relevant improvement in global quality of life in both groups are not surprising. An alternative or additional approach to investigate quality of life could have been by qualitative methods. This could have been more relevant considering the time period of the exercise intervention in the study. However, generally seen the EORTC-QLQ-C30 is a relevant and commonly used instrument. The advantage is that it maintains a variety of domains, e.g.

physical function, pain, and side effects, which can give important information compared to instruments solely covering global quality of life.

The Brief Pain Inventory was added to outcomes of interest, because pain is a very common disease-related symptom caused by the bone disease, and bone disease is a hallmark in multiple myeloma. Brief Pain Inventory added information about pain severity. Interestingly, the control group perceived less pain and less interference, while there were no significant changes in the intervention group, except for the "worst pain" category. Thus, pain seemed to be more present in the intervention group, and could have been partly caused by exercise intervention. Conversely, pain could have caused non-adherence to home-based exercise, as suggested by the diary registration.

The different results in the two groups were not reflected in the symptom domain, *pain* in the EORTC-QLQ-C30, since both groups perceived significantly less pain from baseline to post-intervention. On the other hand, the functional domain, *physical functioning* only changed in the control group, in a positive direction. Thus, either exercise might have an effect on this domain, or the change can be due to other things, i.a. start of anti-myeloma treatment (126).

Measurements of physical activity

During the intervention period the accelerometers became instable because of software issues. The consequence was incomplete measurements. In the analysis, this was resolved by using three days of registration instead of the planned five days. Regardless of these problems, the most optimal registration period, would have been minimum four days, including one weekend day in order to cover variation over a full week (93,94). It could have strengthened the results if treatment-related side effects were registered along with the measurements, which would have made it possible to interpret the results in a more comprehensive way. The accelerometers may have some shortcomings regarding the validity, since counting steps depends on gait speed and stride length (91), and in the study, correction was not made for this. Furthermore, it would have been interesting to incorporate some of the other measures (time sitting/lying, standing, and walking) collected by the accelerometers, if focus is on the importance of avoiding inactivity and the potential benefits of enhancing activity of shorter duration of bouts (< ten minutes) (127).
The low adherence to home-based exercise (Paper III) could indicate that the intervention was too comprehensive or complex. This, combined with knowledge of characteristics of patients with multiple myeloma, such as painful bone disease, which may limit daily activities, speaks for physical activity of shorter bouts as relevant focus in this group of patients.

Another self-reported measure of the level of physical training and physical activity with fixed categories (88), such as the modernized Saltin-Grimby Physical Activity Level Scale (128) would have enhanced the validity of the self-reported level of physical exercise and physical activity (88,129).

Perspectives on findings

Feasibility

The main finding in the feasibility study was that the exercise intervention and physical test procedure were feasible and safe. This same conclusion was made in other studies in patients with multiple myeloma as well, but earlier studies did not investigate exercise at the time of diagnosis, nor in elderly patients, or in patients undergoing other treatment regimens than HDT-SCT (66–70,80). Overall, the feasibility and safety of the supervised exercise sessions were reproduced in the full scale effect study, but the home-based exercise and physical activity did not reach the same level of adherence in the effect study (Paper III).

Because of the incomplete diary registration it is unknown whether the lower adherence actually is non-adherence to exercise or it is due to forgotten diary registration. The diary registration had two purposes; to be a motivational planning tool for the patient, and to document adherence. The diary was not adequately tested, and when it was put into practice, it became clear that many participants needed help to fill out the diary. Alternatives such as regular telephone calls could have been useful in gaining knowledge about adherence to the home-based exercise. Because of incomplete diary registrations it cannot be ruled out that low adherence may be a reason for the non-significant effect results (Paper III).

Finally, the non-adherence could also be related to a perception of the intervention being too comprehensive. A qualitative approach, i.e. by interviews could have shed light on the patients´ perception and experience with the intervention.

Timing and differentiation

It is relevant to reflect on the timing in the study. First of all, the inclusion periods were long both for the feasibility part and for the full study. Several things may explain this, such as severe complications at the time of diagnosis, need of acute treatment, immobilization due to bone pain or fracture, or a question of forgetting to screen for eligibility (Paper I and Paper III). Bottom line is that intervention at this critical time point of newly diagnosed disease is a challenge. Despite the different points of view on the balance between needed and requested information (73), this thesis demonstrates, that patients are willing to participate at this time point, reflected by the high acceptance rates (Paper I and Paper III). This is supported by the Danish report of physical rehabilitation plans (85), stating that more patients would like a physical rehabilitation plan than the actual number of plans prescribed.

Timing in relation to perform exercise can be discussed, not least because of the non-significant findings on effect (Paper III). According to the results in the control group, timing might be right, because they increase their level of physical activity and physical function, even though they do not receive a structured exercise intervention. This speaks for a motivated group of patients, also around the time of diagnosis, or it may be due to an increased focus on exercise due to participation, which may lead to contamination.

On the other hand, the increased perceived pain from baseline to post-intervention in the intervention group must be observed. The increased pain could be caused by exercise, and furthermore this could lead to non-adherence, and on that basis, non-significant results. The difficulties of determining the right dose and intensity, reflected by the need of both progression and regression of exercises, can in all probability be based on a pain problem. So, in this perspective, there might be an important message of how physical rehabilitation must be organized, namely, a huge need of individualization of physical rehabilitation, which can be underpinned by national cancer plans (8) as well as the statutory instrument of physical rehabilitation (84).

Naturally, a conclusion may also be that exercise at the time of diagnosis is ineffective, and maybe it should be initiated later in the disease course or after end of treatment (64,65) and tested in that context. Although, exercise studies at these other time points show inconclusive results of effectiveness, research in this area is still sparse (64,65,70,82), and needs more attention.

Another issue is whether the inclusion criteria to this study have been too broad, because of the endeavor of attaining a representative study population. More differentiation in accordance with patients´ needs, e.g. in proportion to physical function, but also a differentiation on disease specific symptoms or treatment related side effects, such as fatigue, severe bone disease, or neuropathy could be an alternative approach. According to the recent Consensus Statement from International Multidisciplinary Roundtable on exercise in cancer survivors, this approach is needed (44). In this perspective, case studies with interventions based on best available evidence could be an interesting design in such an explorative work, as well as designing studies with these specific approaches, such as the study in patients with bone metastases (130).

Screening of physical function

If differentiated physical rehabilitation in a structured setup is the way forward, it is relevant to gain knowledge of the value of screening. The results in the cross-sectional study showed that generally, the physical function concerning muscle strength in the lower extremities and the aerobic capacity, though highly variable, were decreased compared to a normal healthy population (Paper II). However, it should be noted that results were influenced by the bone disease and fractures, which in itself may speak for differentiated physical rehabilitation.

It would be relevant to explore how health professionals work with screening of rehabilitation needs in general, and how they act on it, and what kind of physical rehabilitation offers exist to accommodate these needs. This area has been investigated in earlier studies, and there is definitely a potential in working with health professionals´ knowledge of and insight into the benefits of exercise in patients with cancer (131,132), and recently, a guide to the screening process has been published (133).

Exercise in patients with bone disease

The assessment of bone disease guided the intervention (Paper I and Paper III). The assessment and the translation into practice were based on earlier work by Mirels (45) and Galvão et al. (48), respectively. This was a ”safe” approach, which was considered natural, since no other studies have investigated exercise in a population like in this study. However, studies of other types of cancer patients with bone disease have been conducted with other approaches. Uth et al. (134,135) investigated football training in patients with prostate cancer. Among the men who participated in the football training, two men had a fibula fracture during football training (134). This football intervention is in contrast to the exercise matrix by Galvão et al. (48). Generally, patients with multiple myeloma are recommended to avoid “contact sports”, e.g. football, handball etc. because of the risk of fractures, but it can be questioned whether the intervention tried out in this thesis was too safe and restrictive, leading to the non-significant results.

Research on this intensity balance for patients with bone disease, and careful assessment of adherence, could be interesting work in the future.

CHAPTER VII – CONCLUSIONS AND CLINICAL IMPLICATIONS

Patients newly diagnosed with multiple myeloma have a lower functional level compared to the healthy, normal population, and in that light, a need for physical rehabilitation. Other aspects speaking in favor of physical rehabilitation are the disease-related symptoms and complications, e.g. pain and bone disease, the treatment-related side effects, e.g. neuropathy, and the fact that physical function may decline during treatment. There is no doubt that individualization in the physical rehabilitation is needed.

Patients are motivated for exercising, and they adhere to supervised exercise starting one week after diagnosis. The exercise intervention, which was planned according to an assessment of the individual bone disease, was feasible and safe for the patient, but no effect was found in the comparison to patients who received usual care, which is i.a. information on transfer techniques and recommendations on being physically active.

The muscle strength of the lower extremities decreased in the control group, whereas performance in the more functional tests; 30 sec Sit-to-Stand-Test and Six-Minute-Walk-Test, increased in both groups. Furthermore, global quality of life increased in both groups, whereas pain only decreased in the control group. The question is whether the lack of significant effect of the intervention is due to either non-adherence or sub-optimal intensity in the exercise group, due to contamination in the control group, or simply because intervention is not effective at the given time point.

An important message for clinical practice is that there is a need of physical rehabilitation, and that exercise is safe. Patients with multiple myeloma do not seem to differ from patients with other cancer diagnoses, but individualization is probably key in physical rehabilitation of patients with multiple myeloma, where follow-up is needed in order to make adjustments. The timing of exercise is not clear, and there may be a need of differentiated approaches, depending on e.g. physical function, side effects, and bone disease. Systematic and structured screening may help identifying needs and the optimal timing for the individual patient.

CHAPTER VIII – FUTURE RESEARCH

This research included elderly patients undergoing other treatments than High Dose Therapy with Stem Cell Transplantation. The elderly patients with multiple myeloma are definitely an un-investigated group, and there might be a great potential in screening and in preventing physical deterioration into this group of patients, as well as interventions after end of treatment to this group would be relevant to investigate.

In patients with multiple myeloma another simpler approach to physical activity may have more potential, both in the short and long term. A focus of activity bouts of shorter duration may be more realistic to adhere to, and it would be cost-effective, and relatively easy to implement. However, there would probably be an advantage in addressing motivational factors and how to change physical activity behavior.

It would be of great interest to initiate research based on symptoms and side effects, and not necessarily the specific diagnoses. This knowledge would benefit the health professionals in clinical practice, and not at least the individual patient experiencing specific symptoms or side effects.

Dissemination of the research results to clinicians is relevant, and potentially this could put focus on e.g. screening of the physical function, and how to handle bone disease in relation to exercise. The alternative approach to physical activity, as mentioned above, would also be a relevant inter-disciplinary focus. Such dissemination could take its starting point in relevant networking, workshops and courses, including at the pre-graduate level. Such dissemination can give rise to new research questions, in a valuable cooperation between health professionals.

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APPENDICES

Appendix I – Paper I

Title

Supervised and home-based physical exercise in patients newly diagnosed with multiple myeloma – a randomized controlled feasibility study

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Abstract

Background: The study evaluated the feasibility and safety of the exercise intervention and physical test procedures of our ongoing randomized controlled trial, examining the effect of physical exercise in newly diagnosed patients with multiple myeloma.

Methods: Patients are randomized 1:1 to a control group (usual care) or an intervention group (usual care and exercise) by block randomization with stratification of planned treatment, WHO performance status and study site. The exercise intervention consists of eight supervised exercise sessions combined with home-based exercise over a 10-week period. Bone disease is systematically evaluated to determine limitations regarding physical testing and/or exercise. Feasibility outcome measures were study eligibility, acceptance and attrition, and furthermore attendance, adherence, tolerability, and safety to the exercise intervention. Additionally, test completion, pain, and adverse events during the physical test procedures were evaluated. Outcome assessors were blinded to allocation.

Results: Of 49 patients screened, 30 were included. Median age was 69 years, range 38-90, 77% were males and 67% had bone disease. Study eligibility was 82%, acceptance 75% and attrition 20%. Attendance at supervised exercise sessions was 92%, and adherence to supervised exercise sessions and home based exercise sessions was 99% and 89%, respectively. No serious adverse events attributed to exercise or physical tests were reported. All patients completed the physical tests, except for two patients, where physical test procedures were modified due to bone disease.

Discussion: The exercise intervention and physical test procedures were feasible and safe in patients with multiple myeloma, even in older patients with multiple myeloma and in patients with myeloma bone disease.

Trial registration: ClinicalTrials.gov. ID NCT02439112. Registered May 7, 2015, https://clinicaltrials.gov/

Keywords

Physical exercise. Multiple Myeloma. Bone disease. Feasibility. Safety.

Background

Physical exercise in patients with hematological cancer has been shown to be feasible and safe, and yielding benefits for aerobic capacity, muscle strength, quality of life (QoL), psychosocial wellbeing, treatment-related symptoms, fatigue, and body composition, before, during, and after stem cell transplantation [1–4] . However, exercise research in hematological malignancy is rather sparse [5,6], having been carried out in specific hematological diagnoses such as acute leukemia [1]. Few exercise studies have been conducted in patients with multiple myeloma (MM), recently reviewed by Gan et al. [7].

MM is a plasma cell cancer in the bone marrow that primarily affects older adults. The incidence and prevalence have increased as the aging population continues to grow, and survival has improved due to advancements in medical treatments [8–11]. In Europe, the incidence of MM is 5.72 per 100,000, and the median age at diagnosis is 68 years [9]. At the time of diagnosis, most patients have symptomatic disease that requires treatment.

Younger, fit patients (<65-70 year) are treated with bortezomib-based induction treatment followed by high dose chemotherapy with stem cell support (HDT-SCT) [12]. Older patients or patients with comorbid conditions receive less intensive, yet still effective treatments that include the proteasome inhibitor bortezomib and/or the immunomodulatory agent lenalidomide [13–15]. Bone disease with osteopenia, pathological fractures, and typically “punched out” lytic lesions are hallmarks of the disease and are present in approximately 80% of the patients at the time of diagnosis and even more during the course of the disease [16]. The bone disease is caused by myeloma-induced increased bone degradation by osteoclasts and inhibited formation of new bone matrix by osteoblasts [17]. Painful bone lesions may be treated with radiation therapy, and all patients receive intravenous bisphosphonates to reduce the risk of progressive bone disease, pain, and fractures [18,19]. Anemia is present in 70-80% of the patients [16,20]. Patients with MM experience more symptoms and more severe symptoms than patients with other hematological diseases, negatively affecting QoL [21]. Due to the frequent and potentially serious bone involvement, and because MM is a cancer in the older population, the potential role of exercise needs to be investigated separately in patients with MM.

Three randomized controlled trials [22–24] and one single arm pilot study [25] investigating the effect of exercise in patients with MM have been conducted and summarized in the review by Gan et al. [7]. The exercise interventions comprised stretching, aerobic exercise and strength resistance exercises (22–25), lasted between 18 and 26 weeks, and started either approximately 10 weeks after start of induction [22–24] or after HDT-SCT [25]. The studies found exercise to be feasible and safe, whereas efficacy data showed mixed results. However, studies that intervene at the time of diagnosis and start of active anti-myeloma therapy are lacking, as are studies that include older patients who comprise the majority of patients newly diagnosed with MM. Thus, the effectiveness of participation in exercise programs remains unclear for patients with MM.

Gan et al.'s exercise recommendations for patients with MM suggest that exercise should be individually adjusted, taking the severity of the disease and the aggressiveness of the treatment into consideration to prevent or minimize physical deterioration [7].

In 2015, we initiated a randomized controlled trial (RCT) to investigate the efficacy of early initiated, individualized physical exercise intervention, combining supervised exercise sessions and home based exercise sessions and physical activity in patients newly diagnosed with MM. The RCT is still ongoing. The aim of the current study is to evaluate the feasibility and safety of the exercise intervention and physical test procedures. Feasibility of participation is evaluated by eligibility, acceptance and attrition to the study. Feasibility and safety of the exercise intervention are evaluated by attendance, adherence, tolerability, attrition and adverse events (AEs). Feasibility and safety of the test procedure were evaluated by completion, registration of pain, and AEs. We have used the CONSORT 2010 statement: extension to randomized pilot and feasibility trials [26].

Methods

Study design, patient recruitment and procedures

The RCT is a two-center study, with blinded outcome assessors, carried out at the departments of hematology at Zealand University Hospital, Roskilde, and Odense University Hospital in Denmark. A total of 102 patients will be included for efficacy evaluation in the RCT. The primary objective of the RCT is muscle strength of the knee extensor muscles measured by dynamometer [27], and secondary objectives are physical measures (30 second Sit-to-Stand Test, grip strength, Six-Minute-Walk-Test), level of physical activity (by accelerometers), QoL (EORTC-QOLQ-C30 and EORTC-QLQ-MY20), pain (Brief Pain Inventory, short version), and bone disease (DEXA-scans and markers of bone metabolism markers). Outcomes are assessed after 11 weeks, 6 months and 12 months.

Patients are consecutively screened for eligibility at the time of diagnosis by the hematologists at each site, based on inclusion and exclusion criteria. Patients >18 years newly diagnosed with MM planned for HDT-SCT or less intensive treatment regimens are eligible. The patient must speak and understand Danish. Exclusion criteria are spinal cord compression, unstable vertebral fracture (SINS score >12) [28], untreated cardiac failure or untreated cardiac arrhythmia, severe chronic cardiac failure (NYHA 3-4), other severe comorbidity that would not permit physical exercise, and psychological or psychiatric disorders. Informed consent are obtained from all individual participants included in the study.

The hematologist performs a systematic assessment of the impact of bone disease to determine restrictions regarding the physical tests or exercise. This assessment is based on radiographs or computed tomography of the skeleton, and captured site, size of osteolytic lesions, and if applicable, time since fracture, moreover the degree of pain. Bone

destructions are assessed using the principles of the Mirel´s scoring system [29]. Restrictions of not performing the static knee extensor strength and 30 second Sit-to-Stand Test are given if a fracture is detected in the femoral bone, if the osteolysis has a size of over two-third/involving compacta, or if the size is between one-third to two-third accompanied by any kind of pain, or finally if there is femoral bone destruction with moderate or functional pain. Restriction to test of knee extensor strength is only for the affected side. The same assessment is applied for exercise restrictions, and the humeral bones are assessed in the same way. Furthermore, pelvis, costae, thoracic and lumbar spine are assessed. Pelvis restriction is given if there is fracture or osteolysis (>2 cm of the acetabulum or two-third of rami). New fractures (less than six weeks) of the costae or vertebral bodies will result in restrictions, or a former fracture accompanied by any kind of pain will also lead to restriction. Exercise restrictions followed the resistance and flexibility principles by Galvão et al. [30], which generally means that patients do not use weights in the strengthening exercises for the involved site and movements are restricted at the involved site, e.g. rotation of the spine.

Patients are tested at baseline within one week after start of active anti-myeloma treatment. Assessment is conducted by physiotherapists, who have received a structured introduction to the test procedure. Hereafter patients are randomized 1:1 to an intervention group (IG) or control group (CG). Block randomization and stratification according to treatment (planned HDT-SCT versus (vs.) non-intensive treatment), WHO performance status (PS 0-1 vs. PS≥2) [31], and study site are performed. The randomization procedure follows a random allocation list, which is made prior study commencement. The randomization is conducted by a project nurse who is not part of the study group, and the randomization list are only available to the project nurse, and thus outcome assessors are blinded to allocation.

This feasibility study evaluated the first 30 included patients in the period from 22 June 2015 to 30 June 2016. This is considered as an adequate sample size because of the nature and aim of this feasibility study [32].

Control group

The CG receives usual care, which consists of written information on the importance of being physically active, suggestions on how to remain physically active, and ergonomic guidance on how to lift and perform transfers properly from a lying to sitting position. Written information is given to the patient, by a study physiotherapist or a nurse, during the second week after start of treatment. Usual care could (if needed) also include a physician ordered rehabilitation plan, prescribing exercise for the patient in the municipality, see Figure 1.

Intervention group

In addition to usual care, the patient is instructed to do the exercise program 3 times/week and to be independently physically active for 30 minutes per day, the other 4 days of the week. The exercise intervention is designed to meet the

Danish recommendations for persons >65 years and for patients with cancer including being physically active 30 minutes a day for at least 10 continuous minutes at moderate intensity [33,34]. Further, at least two times a week, the activity must be of high intensity and include strengthening exercises and stretching [33,34]. The Danish recommendations are in accordance with international guidelines [35–37].

The patient receives careful instruction regarding the exercise intervention and a booklet with a description of the exercises. Instructions are carried out by a study physiotherapist who received careful and structured introduction to the exercise intervention. The exercise program is conducted three times weekly, and it fluctuates between being conducted under supervision or unsupervised at home. Furthermore, the patient is expected to be physically active, the remaining four days, see Table 1. In total, there are eight supervised exercise sessions during the 10-week intervention period, starting one week after diagnosis, see Figure 1. The interval between the supervised exercise sessions vary, because the sessions are planned according to the patients' treatment plan to minimize the number of visits to the hospital. The patient receives an exercise diary to document adherence to the intervention, and the study physiotherapist uses the diary as a pedagogical and motivational planning tool. Each supervised exercise session lasts for 1 hour +15 min and consists of warm-up, aerobic exercise, strengthening exercises and static stretching exercises, see Table 1.

Outcome measures

Data were collected at four time points; T0: time of diagnosis (screening for eligibility), T1: baseline (pre-intervention), Ti: during intervention (week 1-10) and T2: post-intervention (week 11-13), see Figure 1.

Outcomes measures were:

1. Feasibility of participation at T0: eligibility, acceptance and attrition rates were registered as well as reasons for non-eligibility and decline.
2. Demographic and medical data at T1: age, gender, PS, plan of treatment, and bone disease.
3. Feasibility and safety of the intervention at Ti: attendance, adherence, tolerability, attrition, and AEs. The reason for, and number of time of dropouts were registered. Attendance, adherence, tolerability and safety of the supervised exercise sessions were obtained by intervention logs, and documented by the study physiotherapist. Adherence to home-based exercise sessions was documented in an exercise diary. Safety, i.e. AEs, during and between supervised exercise sessions were recorded by observation (during sessions) and questioning patients at each of the supervised sessions. Further, patients documented AEs in their exercise diary.

3. Feasibility and safety of physical tests at T1 and T2 and of accelerometer measurements at A-T1, A-T2, A-T3, and A-T4. Strength of lower extremities was measured by two tests; Static knee extension strength test by dynamometer [23,38,39] and 30 second Sit-to-Stand-Test [39,40]. Upper body strength was measured by grip strength, using a hand-held dynamometer [27,39]. Submaximal aerobic capacity was measured by Six-Minute-Walk-Test [23,41,42]. Feasibility was measured by completion rates, and safety by recording of pain, if any. Other AEs were recorded by the study physiotherapist.

Statistical analysis

Descriptive statistics were conducted using simple report data from the project database in REDCap provided by Open Patient data Explorative Network (OPEN), Odense University Hospital, Odense, Denmark. The analysis was based on intention to treat. Rates of eligibility, acceptance, attrition, attendance, and adherence are presented in numbers and percentages, as well as completion rates of physical tests. Furthermore, the number of patients perceiving pain or AEs were recorded. Medical and demographic data were collected and presented for all included patients and for each group separately (IG and CG).

Results

Demographics and medical characteristics

Baseline characteristics of the participants are summarized in Table 2. Median age was 69 years (range 38-90), 46% of the patients were above 70 years and 75% were men. Sixty-seven percent had bone disease, and half of them were assessed to have restrictions for tests or exercise. The two groups (IG vs. CG) were comparable in age, gender, PS and planned treatment.Bone disease in the intervention group was higher than in the control group, but not in whether the bone disease led to any restrictions regarding tests or exercise.

Feasibility and safety

Eligibility, acceptance and attrition

Of 49 patients screened at T0, 40 met the inclusion criteria (82% eligibility). Reasons for non-eligibility were comorbidity (n=3), spinal cord compression (n=2), bilateral involvement of the femoral bone (n=3), and immobility because of pain (n=1). Of the 40 eligible patients, 30 accepted participation (75% acceptance rate) and ten patients declined (25%). Reasons for decline were lack of energy (n=4), not interested in exercise (n=2), and unknown (n=4). Of the 30 patients included, six participants dropped out after inclusion (20 % attrition); from IG, five out of 17 participants (29%) and from CG, one out of 13 participants (7%). From IG, two dropped out prior to baseline test (T1) (lack of

energy (n=1), sudden impairment (n=1)), and furthermore there was a randomization failure in these two cases, since they were randomized before T1. One dropped out prior to start of exercise intervention (the patient had the possibility of receiving anti-myeloma treatment closer to home). Two dropped out during the intervention period (due to stroke (n=1), and due to experiencing exercise as being too strenuous (n=1)). Dropouts took place before the fourth and the eighth sessions, respectively. From CG, one participant dropped out because of lack of energy to participate in the study, see Figure 2.

Attendance at supervised exercise sessions

In total, 12 participants out of 14 participants (86%) who started intervention completed the full intervention, and 11 out 12 participants (92%) attended all supervised sessions. The one participant who did not attend all sessions, participated in seven out of eight sessions, and the one session was cancelled by the participant for private reasons, see Table 3.

Adherence, tolerability and safety

Adherence rate of the supervised exercise sessions was 99%. Two patients discontinued one supervised session each, due to non-serious AEs; symptoms of pain (n=1) and dizziness (n=1), see Table 3. None of the AEs were found to be related to testing or exercise. Importantly, no patients experienced pathological fractures during testing or exercise. Adherence to home-based exercise sessions was 89%, and 94% out of the recommended number of days with physical activity were completed. Eighty-three percent of the participants had complete diary registration.

All physical tests were tolerated and safe. All participants, except one, were able to complete the knee extensor strength test (primary outcome), at least in one leg. We lack information about the reason for the missed knee extensor strength test in the one participant.

At T1 and T3, 82% and 88%, respectively, completed the knee extensor strength test in both legs. Test completion of the secondary outcomes was 100%, except for two participants, who did not complete the 30 sec SST, see Table 4. The completeness of data from accelerometers was 92-96%. We had apparatus failure (n=2) at A-T4 and in one case at A-T3 we were not able to detect the reason for incomplete data. Missing data at A-T1 were unknown, and at A-TP2 the participant did not wear the accelerometer. There was no AEs, e.g. skin irritation.

Discussion

This study examined the feasibility and safety of an early initiated, individualized physical exercise intervention, combining supervised exercise sessions and home-based exercise sessions in combination with physical activity in

patients newly diagnosed with MM. Our main finding was that the exercise intervention and physical test procedures were feasible and safe.

We succeeded to include a broad group of patients, including older patients planned for less intensive treatment than HDT-SCT. In only one former study in patients with MM in stable phase, and either off treatment or on maintenance therapy [25], patients were included regardless of whether they had undergone a HDT-SCT or other chemotherapeutic treatments. However, only 8% had not undergone HDT-SCT, compared to 40% in our study. The median age was 61 years, range 46-74 years, compared to 69 years, range 38-90 years in our study. The median age of 69 years indicates that concerning age our cohort is representative for the general MM population.

The eligibility and acceptance rates in our study are in accordance with results from other studies [25,43], even though our study started recruitment at an earlier stage and with inclusion of older patients. This indicates that participants found exercise relevant at time of diagnosis, as well as during the recovery phase (6-14 weeks after first line HDT-SCT) [43] and in the stable plateau phase [25].

Forty-nine patients were screened for participation in the study during the first year. This was fewer than expected according to the Danish MM Registry, which about 75 patients with newly diagnosed MM should have been diagnosed at the two departments within one year [44]. Thus, approximately one third of the newly diagnosed patients with MM were not assessed for eligibility. There are several possible explanations for this; some of the most likely are disease presentation with severe complications (including severe infections), need of hemo-dialysis, and severe immobilization due to bone pain. Another reason is that some hematologists simply forgot to screen and offer participation to some patients. Probably, the included patients are skewed according to the severity of disease and have fewer complications at diagnosis than the general MM population. Twenty-five percent of the eligible patients declined to participate. Time of diagnosis is a sensitive time for the patient with a large information burden, and some patients are anxious and have difficulty coping with their situation. We included fewer female patients than expected, which is not a finding supported by the literature [45].

The attrition rate in IG (29%) is within, but in the high end of, the range that has been observed in other studies (4%-29%) [22,23,25,43]. The attrition rate in the CG (7%) is lower than in other studies, where attrition rates ranged from 15% to 30% [22,23,43]. The four-times higher attrition rate in IG than in CG can partly be explained by randomization failure. By following a stricter randomization procedure, we expect more equal attrition rates in the larger RCT, although the intervention itself might play a role. Thus, exercise intervention at time of diagnosis is feasible for most, but not all patients with MM. However, it is noteworthy that the attendance and the adherence were relatively high. In total, 24 out of 30 included patients (80%) were available for analysis, which is informative for us regarding dropouts in the RCT.

The studies with the lowest overall attrition (regardless of group assignment) [25,43] took place either in the recovery phase or stable plateau phase. Nevertheless, attrition during active anti-myeloma treatment can be expected to be higher. The overall attrition in our study (20%) is within the range of other studies conducted during treatment (11%-42%) [22–24,43].

Our attendance rate to supervised exercise sessions was higher than rates in other studies with supervised sessions [25,43]. Our more favorable attendance rate may be because we strive to plan the sessions on the same days as the medical visits at the hospital, contrary to e.g. exercise in a physiotherapy practice [43].

Adherence to supervised exercise sessions was 99%. Discontinuation was a minor issue, and no serious AEs related to physical exercise or testing were registered. Adherence to home-based exercise sessions was 89%, which is in accordance with the adherence of 86% in another study with a mixed intervention (supervised and home based) [25]. Importantly, we observed no pathological fractures, even though we intervene at a very early stage. The same safety findings were reported in other studies of exercise in patients with MM [23–25].

The completion rates of the physical tests were high, not least of the primary outcome (knee extensor strength), where we succeeded to test both legs in most participants. Our careful assessment of bone status resulted in successful inclusion of patients with bone disease in the lower extremities, as long as there was no restriction in one of the legs. Thus, we allow inclusion of patients with bone disease and even patients with assessed increased risk of fracture. Instead of excluding these patients, we differentiate testing and exercising according to bone disease and pain, and therefore we were able to carry out tests and exercise in a safe manner. In general, other studies excluded patients with risk of fracture [22–24], and only one study specifically defined this risk [25]. Our bone assessment might explain the higher rate of test completion than seen in an earlier study, where 76% completed the isometric strength measurement at the initial assessment, 1-2 weeks after diagnosis [46].

All studies, except Groeneveldt et al. [25], were designed by adapting the program individually at baseline [22–25,43] and with adjustments during the intervention period, based on the patients´ exercise logs [22–25] or by brief, individual counseling to enhance compliance and motivation [43]. Only Groeneveldt et al. [25] had supervised exercise as part of the intervention, which is important in order to make adjustments and to enhance compliance [7,47]. We consider the combined exercise intervention (supervised and homebased) a strength for our study.

The effects of exercise on physical parameters, QoL, and fatigue have been conflicting across earlier studies in patients with MM. Suboptimal compliance, timing of the intervention or non-optimal intensity are reasons discussed by authors to be possible explanations for the non-significant results [22–24,43]. Thus, so far, the effectiveness of physical exercise in patients with MM is unclear, which highlights the importance of our ongoing randomized trial.

In conclusion, early initiated, individualized physical exercise in patients with multiple myeloma is feasible and safe, even in older patients and in patients with bone involvement. We succeeded in including an age representative cohort of newly diagnosed patients and in including patients with clinical bone disease. Our ongoing randomized study will hopefully contribute importantly to answer the question if early initiated physical exercise in patients with multiple myeloma is effective on physical function, quality of life, pain and bone disease.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study is approved by the Ethical Scientific Committee in Region Zealand (SJ-422), registered 11 December 2014 and by the Danish Data Protection Agency (REG-122-2014), registered 30 December 2014. Informed consent are obtained from all individual participants included in the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors´ contribution

RFL designed the work, did the analysis and interpretation of data and drafted the work, and made changes after revision. MJ designed the work, contributed to analysis and interpretation of data, and revised the manuscript. LRM designed the work contributed to analysis and interpretation of data, and revised the manuscript. UCF designed the work and revised the manuscript. NA designed the work, contributed to interpretation of data, and revised the manuscript.

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List of abbreviations

AEs	Adverse Events
CG	Control Group
HDT-SCT	High Dose Therapy with Stem Cell Support
IG	Intervention Group
MM	Multiple Myeloma
PS	Performance Status
QoL	Quality of Life
RCT	Randomized Controlled Trial

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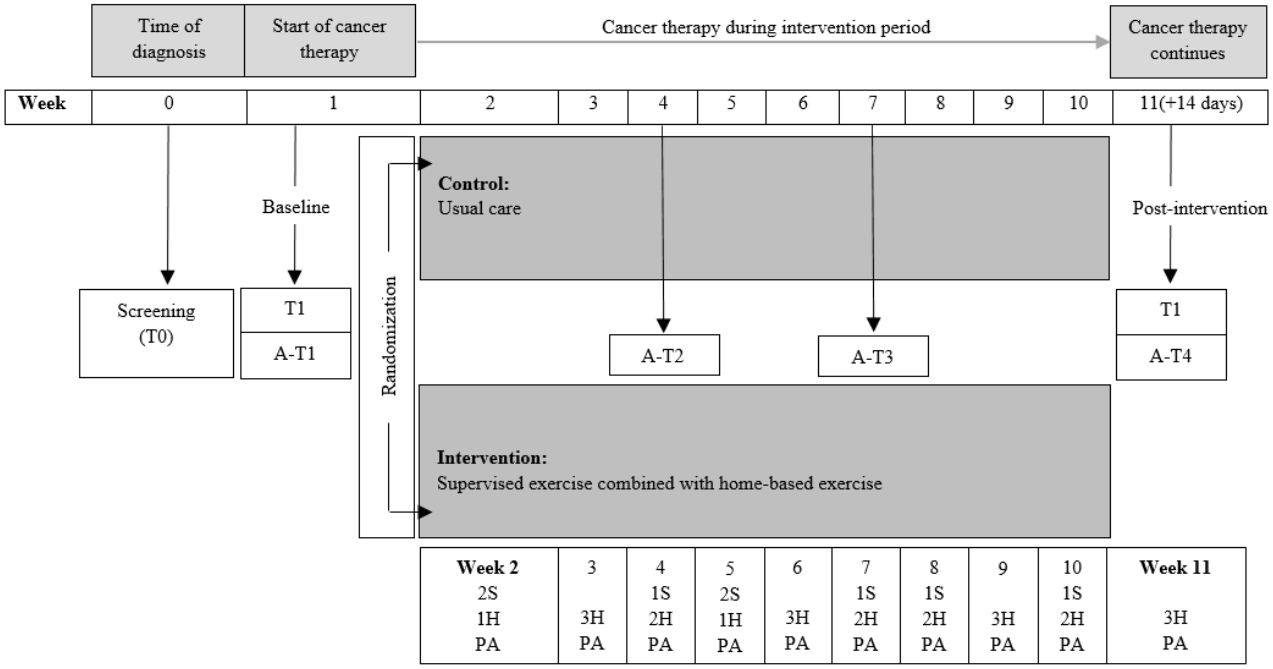
Table 1 Exercise intervention; mode, intensity, duration, and progression

Mode	Intensity	Duration per session	Progression
Exercise program 3 times/week			
Warm up	10-11 RPE	5 min	-
Aerobic exercise[a]	12-13 RPE	20 min	↑ intensity to 14-16 RPE[b]
Strengthening exercise Five exercises for the lower extremities[c] Three exercises for the upper extremities[d] One exercise for truncus[e]	3 sets of 12-15 reps	30-45 min	↑ weight to 3 sets of 10-12 reps
Stretching Three muscle groups of the lower extremities[f]	30 sec static	5 min	-
Physical activity 4 times/week Preference of the patient	12-13 RPE	30 min. at least for 10 continuous min	14-16 RPE (is a possibility, but not a standard)

[a]*Aerobic exercise: If not possible to do aerobic exercise for 20 min on the stationary bike during the supervised session, the progression is an increase in total time (up to 20 min).*
[b]*RPE, Rate of Perceived Exertion; Reps, repetitions.*
[c]*Knee extension in sitting position, knee flexion in standing position, hip extension in prone position, toe raising in standing position, knee bent OR raise from chair.*
[d]*Arm lift in frontal plane OR circulation of shoulders in standing position, elbow extension in supine position and elbow flexion in standing or sitting position.*
[e]*Static in supine with knees bent OR supine position with knee bent and lift of foot with press from opposite hand.*
[f]*Femoral muscles (standing position), hamstring muscles (standing or sitting position), calf muscles (standing in front of wall).*

Figure 1: Overview of the randomized controlled feasibility study including intervention and physical measurements.



T0; Time 0 corresponding to time of screening.

T1; Time 1 corresponding to physical tests at baseline test.

T2: Time 2 corresponding to physical tests post-intervention.

A-T1; Activity-Time 1 corresponding to accelerometer measures at baseline.

A-T2; Activity-Time 2 corresponding to accelerometer measures at week 4.

A-T1; Activity-Time 3 corresponding to accelerometer measures at week 7.

A-T4; Activity-Time 4 corresponding to accelerometer measures post-intervention.

1S and 2S; Supervised exercise session one or two times weekly, respectively.

H1, H2 and H3; Home-based exercise session one, two or three times weekly, respectively.

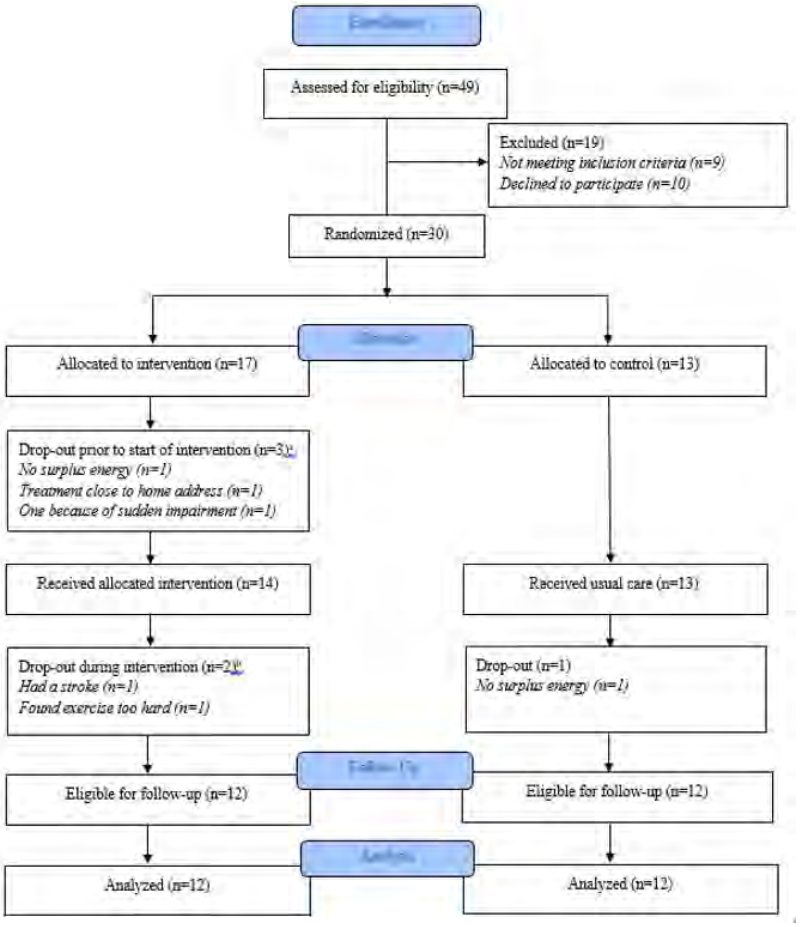
PA; Physical activity taking place the remaining four days, where exercise session are not conducted.

Table 2 Patient characteristics

Patient characteristics	**Total N = 30**	**IG n =17**	**CG n = 13**
Age (years)			
Mean (SD)	68 (12.2)	69 (9.7)	67 (15.3)
Median (range)	69 (38-90)	68 (48-82)	70 (38-90)
Age groups, years (n (%))			
≤ 49	3 (10)	1 (6)	2 (15)
50-59	4 (13)	2 (12)	2 (15)
60-69	9 (30)	7 (41)	2 (15)
70-79	10 (33)	5 (29)	5 (38)
80-89	3 (10)	2 (12)	1 (8)
≥ 90	1 (3)	0 (0)	1 (8)
Gender (n (%))			
Male	23 (77)	14 (82)	9 (69)
Female	7 (23)	3 (18)	4 (31)
WHO performance status (n (%))			
0-1	25 (83)	13 (77)	12 (93)
≥ 2	5 (17)	4 (24)	1 (8)
Planned treatment (n (%))			
HDT-SCT[a]	18 (60)	10 (59)	8 (62)
Not HDT-SCT	12 (40)	7 (41)	5 (38)
Bone disease, in general (n (%))			
No	10 (33)	3 (18)	7 (54)
Yes	20 (67)	14 (82)	6 (46)
Bone disease with restriction for tests or exercise, n=20 (n (%))			
No	10 (50)	9 (64)	1 (17)
Yes	10 (50)	5 (36)	5 (83)

[a]*HDT-SCT, High Dose Therapy with Stem Cell Transplantation.*

Figure 2 Flowchart based on the CONSORT 2010 Flow Diagram (26).



[a]*One patient was tested at baseline (T1). Two patients dropped out before performing the baseline test, which is considered as a randomization failure.*

[b]*One patient dropped out before session 4 and one before session 8.*

Table 3 Adherence to the intervention and the individual components of intervention, and adverse events.

	IG n = 12*	Comments
Adherence to supervised exercise session		
Patients who completed (n (%))	11 (92%)	One participant cancelled one session because of condition.
Sessions completed (n (%))[a]	95 (99%)	
Adjustments of the exercise program		
Progression of exercise program (n (%))	4 (33%)	
Regression of exercise program (n (%))	1 (8%)	
No progression or regression (n (%))	0 (0%)	
Both progression and regression (n (%))	7 (58%)	
Adherence to home-based exercise sessions (n (%))[b]	203 (89%)	
Adherence to physical activity[c]	405 (94%)	
Diary registration (n (%))		
All weeks	10 (83%)	
Some weeks	2 (17%)	
No weeks	0 (-)	
Adverse events (n)	2	Dizziness (n=1), symptoms of pain (n=1). All non-serious adverse events.
Consequences of the adverse events		
None	0	
Discontinuation of the supervised exercise session (n)	2	

**Data is based on participants who completed the intervention for the whole intervention period (n=12)*
[a]*Out of 96 possible sessions (eight sessions for each participant).*
[b]*Out of 228 recommended sessions based on a period of nine weeks.*
[c]*Out of 432 recommended sessions based on a period of nine weeks.*

Table 4 Patients who performed the physical tests and worn accelerometers at the investigated times.

Physical tests	**T1[*] n=28**	**T2[#]n=24**	**A-T1[*] n=28**	**A-T2 n=24**	**A-T3 n=24**	**A-T4[#] n=24**
Knee extensor strength test (n (%))						
Both legs tested	23(82)	21 (88)				
Only one leg tested because of bone restriction	2 (7)	2 (8)				
Only one leg tested because of patient inability	0 (-)	1 (4)				
Only one leg tested without explanation	2 (7)	0 (-)				
Not done	1 (4)	0				
Pain during test[a]	4 (14)	5 (21)				
Adverse events	0	0				
Grip strength test (n (%))						
Patients who performed the test	28 (100)	24 (100)				
Not done	0 (-)	0 (-)				
Pain during test[b]	5 (18)	3 (13)				
Adverse events	0	0				
30 second Sit-to-Stand Test (n (%))						
Patients who performed the test	26 (93)	24 (100)				
Not done	2 (7)	0 (-)				
Pain during test[c]	5 (19)	1 (4)				
Adverse events	0	0				
Six-Minute-Walk-Test (n (%))						
Patients who performed the test	28 (100)	24 (100)				
Not done	0 (-)	0 (-)				
Pain during test[d]	8 (29)	5 (21)				
Adverse events	0	0				
Accelerometers (n (%))						
Worn, complete data			27 (96)	23 (96)	23	22
Worn, incomplete data			0 (-)	0 (-)	(96)	(92)
Not worn/missing			1 (4)	1 (4)	1 (4)	2 (8)
Adverse events			0 (-)	0 (-)	0 (-)	0 (-)

[*]T1 and A-T1 correspond to the same time point (baseline)

[#]T2 and A-T4 correspond to the same time point (post-intervention)

[a]Pain during test of knee extensor strength test

At T1; related to equipment (n=2), knee pain (n=1), undescribed (n=1)S

At T3; related to equipment (n=2), back pain (n=1), minor leg pain (n=1), missing (n=1)

[b]Pain during test of grip strength

At T1; sternum (n=1), clavicular (n=2), breast muscle (n=1), sternum and costae (n=1)

At T3; fingers (n=1), costae (n=1), known pain (n=1)

[c]Pain during 30 second Sit-to-Stand Test

At T1; knee pain (n=1), back pain (n=2), scapula and sternum (n=1), thorax (n=1)

At T3; back pain (n=1)

[d]Pain during Six-Minute-Walk-Test

At T1; thorax (n=1), sternum (n=1), scapula and sternum and right hip (n=1), thorax and dyspnea (n=1), toe (n=1), missing (n=2)

At T3; hip muscle pain (n=1), reaction from thigh (n=1), back pain (n=1), Achilles tendon (n=1), lower extremity (n=1)

Appendix II – Paper II

Physical function in patients newly diagnosed with multiple myeloma

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Keywords

Multiple myeloma; bone disease; physical function; reference values; cross sectional

Abstract

Background: Multiple myeloma is a cancer in the bone marrow causing bone destruction. Patients experience various symptoms related to the disease and/or treatment, such as pain and fatigue, leading to poorer quality of life. The symptom burden might affect physical function and physical activity levels, posing a risk of physical deterioration. The aim was to investigate whether physical function in newly diagnosed patients with multiple myeloma differs from the reference values of the normal population and other cancer patients.

Methods: The study is a cross sectional descriptive analysis of a prospective cohort of 100 patients newly diagnosed with multiple myeloma. Four physical function tests were carried out; Six-Minute-Walk-Test, Sit-to-Stand-Test, grip strength and knee extension strength. Age and gender specific results of physical function from the multiple myeloma population were compared to normative data and to data from other cancer populations.

Results: Of the 100 patients included, 73% had bone disease and 55% received pain relieving medicine. Mean age was 67.7 years (SD 10.3). Patients with multiple myeloma had significantly poorer physical function compared to normative data, both regarding aerobic capacity and muscle strength, although not grip strength. No differences in physical function were found between patients with multiple myeloma and other cancer populations.

Conclusions: Physical function in newly diagnosed patients with multiple myeloma is lower than in the normal population. Exercise intervention studies are warranted to explore the value of physical exercise on physical function.

ClinicalTrials.gov, ID NCT02439112, registered 28 April 2015.

https://register.clinicaltrials.gov/prs/app/template/Home.vm?uid=U0002O53&ts=25&sid=S0005HR9&cx=-8hthut

Background

Multiple myeloma (MM) is a plasma cell cancer in the bone marrow that primarily affects older adults. In Europe the incidence of MM is 5.72 per 100,000, and the median age at diagnosis is 68 years [1,2]. A hallmark of MM is the associated bone disease, which includes bone destructions, vertebral collapses and other pathological bone fractures, and hypercalcemia. Bone involvement is seen in about 79% of newly diagnosed patients with MM [3]. In addition, anemia is common, presenting in approximately 73% of patients with MM [3]. Patients newly diagnosed with MM report low quality of life and reduced physical function, and pain and fatigue are dominant symptoms [4–7]. Moreover, patients with MM experience a greater symptom burden and more severe symptoms than patients with other malignant haematological diseases, negatively affecting their quality of life, especially, role, physical, and social function [8].

Physical fitness, including endurance, strength, flexibility, and balance, is associated with physical function, physical functional limitation and physical independence [9,10]. Physical indicators, such as low level of physical activity, lower extremity function, and low grip strength can predict disabilities related to activities of daily living, e.g. walking, transferring, bathing or dressing [11]. Mobility limitations 30 days after discharge among older medical patients can be predicted by measurements of handgrip strength, gait speed, modified chair stand test and the Cumulated Ambulation Score, where chair stand test (Sit-to-Stand-Test) and gait speed are the strongest predictors [12]. Thus, both aerobic capacity and strength are important for physical function in daily life, not least in the older population, since physical fitness is associated with age [9,10].

Though not being the only determining factor, physical function contributes significantly to the performance status of a patient, exemplified when the Eastern Cooperative Oncology Group

(ECOG) performance status of a patient is assessed. In patients with MM, affected ECOG performance status, particularly performance status 3-4, is a major predictor of an adverse prognosis [13,14].

In spite of the bone destructive nature of MM and well described low patient-reported physical function levels, we have not been able to identify studies that report the objective physical function among newly diagnosed patients with MM. By testing physical function, patients at risk could be identified, and interventions to prevent physical deterioration or improve physical function could be initiated. Maintaining or improving physical function is fundamental for the patients to carry out usual activities and in maintaining their quality of life [15,16]. In patients with MM physical training has been shown to be safe and feasible [17,18].

We hypothesised, that patients with MM have poorer physical function than the normal population and patients with other cancer diagnoses. The aim of this study was to describe age and gender specific physical function among patients newly diagnosed with multiple myeloma and to compare physical function to the normal population and other cancer populations.

Methods

This is a cross sectional, descriptive analysis of a cohort of 100 patients with newly diagnosed MM. The patients were prospectively and consecutively included at two departments of haematology at two University Hospitals in Denmark from 22 June, 2015 to 18 January, 2019 as part of a randomised, controlled trial (ClinicalTrials.gov., ID NCT02439112) investigating the effect of a ten week exercise intervention. Included were patients ≥18 years of age newly diagnosed with treatment demanding MM (High Dose Therapy with Stem Cell Transplantation (HDT-SCT) or less intensive treatment), and who were able to speak and understand Danish. Exclusion criteria were spinal cord compression, unstable vertebral fracture (Spinal Instability

Neoplastic Score >12) [19], untreated cardiac failure or untreated cardiac arrhythmia, severe chronic cardiac failure (NYHA 3-4), other severe comorbidity that according to treating physician would not permit physical exercise, and psychological or psychiatric disorders. Written informed consent are obtained from all individual participants included in the study.

Data collection

Prior to start of the treatment in an outpatient setting, all eligible patients were tested with the following physical function measurements: Six-Minute-Walk-Test (6MWT) [20] as a functional measure of aerobic capacity, Sit-to-Stand-Test (SST) [21] as a functional measure of lower body strength, grip strength [22,23] as a measure of upper body strength and a direct measure of isometric knee extension strength [23,24]. Prior to testing, the haematologist performed a systematic assessment of the impact of the radiologically assessed bone disease to determine restrictions regarding the physical tests (and exercise as well, to be used in the randomised controlled trial). In relation to testing, our focus was on the femoral bone. The assessment captured size of osteolytic lesions, fractures, and if applicable, estimated the time of fractures, and the haematologist assessed the degree of pain. Based on Mirel´s scoring system [25], this combined information of location, fractures/size of lesions and pain were used to assess whether the fractures and/or bone destructions should restrict certain tests. That was the case if an osteolytic lesion in the femoral bone involved between one third and up to two thirds of the diameter and caused pain, *or* if an osteolytic lesion involved more than two thirds of the diameter or involved the cortical bone (cortical thinning), even without associated pain. In these cases we only tested the unaffected side and omitted SST.

The physical function data (6MWT, SST, grip strength and knee extension strength) used in the current analysis are data from the baseline measures in the randomised controlled trial

(ClinicalTrials.gov, ID NCT02439112), conducted by a project team of trained physiotherapists. Patient demographic and medical characteristics were collected from the patients' medical records.

We included normative data of physical function outcomes from different healthy populations [26–28] and published data from other cancer disease populations; malignant lymphoma before starting chemotherapy and without bone metastasis or elevated risk of fracture [29], prostate cancer after surgery or radiotherapy [30,31] and breast cancer post-treatment [32,33]. These cancers were chosen to compare MM data to other haematological cancers, both malignant lymphoma without bone destructions, and solid cancers where bone destructions are common. In the following our study population is called the EMMY population (Exercise in Multiple MYeloma).

Statistical analyses

Characteristics of the cohort are reported as counts and proportions and stratified by gender. The physical outcome measures 6MWT, SST, grip strength and knee extension strength are reported as mean and standard deviation (SD) and stratified by gender and age groups. Data are compared by z-test (after standardisation to mean=0 and SD=1) to reference values from normative populations and furthermore, to published data from patients with malignant lymphoma, prostate cancer and breast cancer, respectively. Moreover, we present outcome measures as box plots stratified by bone involvement and fractures and compare the standardised measurements by Wilcoxon rank sum test.

Results

In the randomised, controlled trial, 158 patients were screened for eligibility. Out of the 158 patients, 33 were excluded because they did not meet the inclusion criteria, and 24 declined to participate. One patient accepted, but withdrew and did not give consent to use data. Thereby, the study cohort consisted of 100 participants. Demographic and medical characteristics are presented in Table 1.

Mean age (SD) was 67.7 (10.3) years, median (range) was 69 (38-90) years. The age group with the highest representation was 70-79 years (35%), followed by the age group 60-69 years (28%). The major part of the patients (85%) had an ECOG performance status of 0-1, and 17% were using walking aids. Over half were retired (56%), and 14% were on sick leave. Bone disease was present in 73% of the participants, and 56% of those were assessed to have bone disease, which caused restrictions to tests and/or exercise. Thirty-three per cent had fractures (n=33). Hereof most common were vertebral fractures (73%) resulting in mild pain (17%), moderate pain (33%), and functional pain (29%). Nine per cent had non-vertebral fractures with associated pain that followed the same patterns as the vertebral fractures. In total, 55% used pain relieving medications (31% non-opioid drugs (mild), 11% opioid drugs but less or maximum equivalent to 20 mg morphine per day (moderate), and 13% opioid drugs equivalent to more than 20 mg morphine per day (strong)).

Patients who did not meet the inclusion criteria (n=33), or fulfilled the inclusion criteria but did not wish to participate (n=24) had a similar mean age as the included patients (68.4 years (SD 9.4) and 70.1 years (SD 7.8), respectively), and gender was similar as well (58% and 54% were males, respectively). Around two thirds (67%) and one third (38%) of the participants, respectively, were screened during hospitalisation. The major part, 94% and 79% respectively, had bone disease, which is slightly more than patients in the study cohort.

The physical function measurement data are presented in Figure 1a-d and 2a-d, and the specific estimates (mean (SD)) for the four outcome measures are presented in Table 2. Box plots for the four physical measures according to bone disease, fracture and vertebral fracture are presented in Figure 3.

Six-Minute-Walk-Test (6MWT)

All mean scores, regardless of gender, were lower than for the normal population [26] and furthermore, all mean scores were below the lower SD-reference line for the normal population (Figure 1a and 1b). The difference between EMMY and the reference population was statistically significant ($p<0.0001$, z-score -1.24). The 6MWT measurement was neither modified by the presence of vertebral fracture ($p=0.054$), bone disease ($p=0.717$) nor fracture ($p=0.713$) (Figure 3). Compared to lymphoma cancer (mixed genders) aged 55-59 years [29], the EMMY population had a shorter walking distance with a mean difference of 73 meters and 171 meters for males and females, respectively (Figure 1a and 1b). Males with prostate cancer aged 70-74 years [30] achieved a longer walking distance than the EMMY population (Figure 1a). Females with breast cancer aged 55-60 years [32] had a shorter walking distance than females from the EMMY population (Figures 1b, Breast B), but younger females with breast cancer (approximately 47 years) [33] had almost the same walking distance as females from the EMMY population (Figure 1b, Breast A).

Sit-to-Stand-Test (SST)

Compared to the normal population [26], males between 60 and 80 years (Figure 1c) and females between 60 and 75 years (Figure 1d) had a lower number of mean raises. The total EMMY population (males and females) had statistically significantly lower mean raises than the

reference group (p<0.0001, z-score -0.55), and number of mean raises was modified by the presence of bone involvement (p=0.035) or fracture (p=0.043), but not by vertebral fracture (p=0.056) (Figure 3). Comparing SST scores for males from the EMMY population to males with prostate cancer within the age group 65-70 years [31] or to females with breast cancer [32] the number of raises was almost identical.

Grip strength

Grip strength (mean (SD)) in the total group was statistically significantly higher than in the normal population [27] (Figure 2a and 2b) (p<0.00001, z-score 0.48) and modified by the presence of fracture (p=0.032) or vertebral fracture (p=0.006), but not bone involvement (p=0.224) (Figure 3). Compared to the population with lymphoma (mixed group of gender), the females from the EMMY population scored lower than the population with lymphoma cancer, while males had almost the same grip strength [29]. Though, this must be with reservations of comparing a mixed group of gender with females and males, respectively. For males with prostate cancer [30] there was no difference in mean grip strength compared to the EMMY population. Females with breast cancer [32] had a lower grip strength than the EMMY population.

Knee extension strength

Within the different age groups, the EMMY population (both genders) generally had lower strength compared to the normal population [28]. For the total group this difference was statistically significant (p=0.0005, z-score -0.39) and not modified by the presence of bone involvement (p=0.235), fracture (p=0.826) or vertebral fracture (p=0.565) (Figure 3). The lymphoma population [29] had much lower strength than the EMMY population. Females with

breast cancer [33] and the patients from the EMMY population had almost the same strength in the age span 40-50 years.

Discussion

The aim of this study was to describe age and gender specific physical function among patients newly diagnosed with multiple myeloma and to compare physical function to healthy populations and other cancer populations.

We found that the EMMY population had poorer physical function than the normal population, though unexpectedly, grip strength was found to be better in patients with MM. The presence of bone involvement and fractures modified SST and grip strength (fractures only) and the presence of vertebral fracture marginally modified the 6MWT. In the three cancer comparison groups, we found the patients with lymphoma to have better aerobic capacity, but lower strength in the lower extremities, whereas we did not observe differences compared to the prostate cancer and breast cancer groups, except grip strength, which was better in patients with MM.

Generally, the EMMY population did not follow a clear age-decline pattern. A possible explanation could be that the younger patients (from around 60 years up to 70 years) with MM are more vulnerable to the disease, resulting in affected physical function, than those under the age of 60 and over 70 years, regardless of gender. However, we need to take the number of patients in the EMMY population in each age span into consideration, which means that the uncertainty becomes wider in the younger and older ages. Most patients (63%) were within the ages of 60-79 years. Another explanation could be the confounding factors (bone involvement, fracture or vertebral fracture), which are not related to age.

Knee extension strength in patients with lymphoma [29] was below the knee extension strength in patients with MM, and accordingly, the grip strength in patients with breast cancer [32] was

below the grip strength in patients with MM. According to the authors, the poor knee extension strength might be explained by the disease itself, weight loss as part of B-symptoms, including enhanced protein catabolism, and upregulated tumor necrosis factor stimulating muscle wasting and causing contractile dysfunction [29]. However, it should be added that another study of a mixed group of patients with lymphoma and MM [34] (mean age of 55 years, range 19-67) did not find poorer muscle strength in lower extremities measured by SST [34] compared to the EMMY population.

The poorer grip strength among patients with breast cancer is an expected finding because of disease location and treatment side effects. Further, a study showed that reduced grip strength was not restricted to the affected side [35]. A hypothesis could be that patients with breast cancer generally protect their upper extremities and thus, are losing grip strength. This is underpinned by the comparable results of knee extension strength and SST, respectively between the EMMY population and the breast cancer population. Thus, there does not seem to be a general muscle strength problem among patients with breast cancer.

Patients with lymphoma performed better in the 6MWT compared to patients with MM. In the study by Persoon et al. [34] investigating health-related physical fitness after HDT-SCT, they included patients with MM and patients with lymphoma. Unfortunately, they did not present physical outcome results for the two diagnoses separately, which could either have supported or rejected our interpretation of strength as a challenge for patients with lymphoma and aerobic capacity as a challenge for patients with MM.

Validity

The Danish test procedure for 6MWT (used in our study) [36] is in accordance with the American Thoracic Society test procedure [20], but Rikli et al. [26] deviated from that

procedure regarding instruction to the patient. In the ATS test procedure patients are encouraged to walk as far as possible and are told that they will experience exertion [20], while Rikli et al. [26] told them to walk the best they could, but to avoid pushing themselves to overexertion or beyond what they thought would be safe for them.

Potentially, this could have the consequence that the reference values could be higher, if Rikli et al. [26] had followed the ATS procedure. Thus, the 6MWT difference between the patients with MM compared to reference values may be underestimated. Overall, the test position in the knee extension strength measure does not differ from the one used in the EMMY population. There is a difference regarding grip strength (using sitting or standing position) in the review [27], but the authors conclude that the different positions do not affect grip strength. We assume, that SST is very standardised, and thus does not differ between studies.

Methods considerations, strengths and limitations

In the field of MM and physical function, the size of our cohort is quite large. We covered all age groups, included patients with or without bone disease, and only excluded the most bone morbid patients who were not able to perform tests or where it was not found safe to test them. Thus, our study reflects the patient representation in the ordinary clinic and thus, heighten the external validity. The associations between physical function and bone disease or fracture, indicate that these subgroups need special attention in a physical function perspective.

It is a strength that we have age specific data from normal samples, but regarding age-specific comparisons, when divided into age groups we are hampered by a rather small number of participants, especially in the lower and upper age groups.

There are some shortcomings in the comparisons, since we were unable to cover the total age span of the EMMY population in the comparisons with the normal population as well as comparisons with other cancer disease populations. We do not have data from citizens under the age of 60 years for 6MWT and SST, and under the age of 55 years for the knee extension strength. However, we assume that the association between age and physical performance will follow the same pattern for the younger age groups (<60 years) [37], at least, according to the literature, for the walking distance [38,39] and grip strength [37]. Furthermore, we did not have data on all the needed physical outcomes in the cancer disease populations. Finally, we need to address that the EMMY data are at time of diagnosis, which is different from the time points in the other cancer population studies, except for the lymphoma population.
The differences in time points, and settings as well could influence the external validity.

Implications for practice and future perspectives

Generally, our results indicate, that patients with MM have lower physical function at time of diagnosis and that this particularly is the case for patients with bone involvement. After start of anti-myeloma treatment, physical function may worsen, but we lack strong data on this. Bone studies in MM have shown that early bone fractures are common within the first weeks and observed in about 15 % within 3 months [40]. This is assumed to cause deterioration of physical function. Patients undergoing HDT-SCT can experience loss in function during treatment. Potentially, such loss can be prevented or minimised by exercise [41]. Other treatments than HDT-SCT, typically offered to patients over the age of 65-70 years, are less intensive, but still may affect the physical function as well. Since the patients are older and may be frail [42] early detection of physical decline and subsequent early prevention by providing exercise interventions is of importance.

Our study accommodates the gap of knowledge of physical function in newly diagnosed patients with MM. Although our cohort is relatively large, further research is needed if we want to establish evidence of the physical function limitations. This could have implications for clinical practice, either by identifying patients at risk at group or individual level, and then establish an exercise regimen aiming at preventing physical decline and thereby importantly maintaining independence and quality of life.

Conclusions

Newly diagnosed patients with MM have reduced physical function compared to the normal population, except for grip strength. In particular, bone disease and fractures influence the physical function.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study is approved by the Ethical Scientific Committee in Region Zealand (SJ-422), registered 11 December 2014 and by the Danish Data Protection Agency (REG-122-2014), registered 30 December 2014. Written informed consent are obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors´ contributions

RFL designed the work, did the analyses and interpretation of data, and drafted the manuscript, made changes revision, and finalised the manuscript. MJ, LRM, UCF, and NA designed the work, contributed to analyses, interpretation of data, and revision of the manuscript. UCF and NA recruited participants. SM contributed to data analyses and interpretation of data, and revision of the manuscript. All authors approved the final manuscript.

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List of abbreviations

MM	Multiple Myeloma
ECOG	Eastern Cooperative Oncology Group
HDT- SCT	High Dose Therapy with Stem Cell Transplantation
6MWT	Six-minute-Walk-Test
SST	Sit-to-Stand-Test
EMMY	Exercise in Multiple MYeloma

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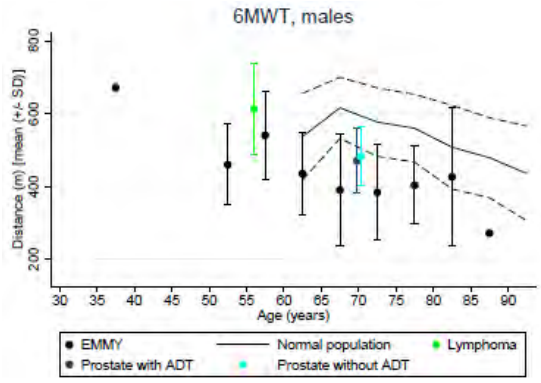
Table 1. Patient demographics in the total study population and according to gender.

Patient characteristics	**Total N = 100**	**Male n =58**	**Female n = 42**
Age, years			
Mean (SD)	67.7 (10.3)	68.1 (10.7)	67.1 (9.8)
Median (range)	69 (38-90)	70 (38-89)	67.5 (49-90)
Age groups, years (n (%))			
≤ 39	1 (1)	1 (2)	0 (0)
40-49	3 (3)	1 (2)	2 (5)
50-59	20 (20)	11 (19)	9 (21)
60-69	28 (28)	15 (26)	13 (31)
70-79	35 (35)	22 (38)	13 (31)
80-89	12 (12)	8 (14)	4 (10)
≥ 90	1 (1)	0 (0)	1 (2)
ECOG performance status[a] (n (%))			
0-1	85 (85)	46 (79)	39 (93)
≥ 2	15 (15)	12 (21)	3 (7)
Bone disease	73 (73)	44 (76)	29 (69)
Bone disease with restriction for tests or exercise	41 (41)	23 (40)	18 (43)
Fracture (n (%))	33 (33)	19 (33)	14 (33)
Non-vertebral fracture (n (%))	9 (9)	3 (5)	6 (14)
Vertebral fracture (n (%))	24 (24)	16 (28)	8 (19)
Pain from non-vertebral fracture (n=9)	5 (55)	0	5 (83)
Mild	2 (22)	0	2 (33)
Moderate	1 (11)	0	1 (17)
Functional	2 (22)	0	2 (33)
Pain form vertebral fracture (n=24)	19 (79)	13 (81)	6 (75)
Mild	4 (17)	2 (13)	2 (25)
Moderate	8 (33)	7 (44)	1 (13)
Functional	7 (29)	4 (25)	3 (38)
Pain relieving drugs (n (%))			
None	45 (45)	28 (48)	17 (40)
Non-opid/mildly pain relieving drugs[b]	31 (31)	14 (24)	17 (40)
Moderately pain relieving drugs[c]	11 (11)	6 (10)	5 (12)
Strong pain relieving drugs[d]	13 (13)	10 (17)	3 (7)
Walking aid (n (%))			
Yes	17 (17)	9 (16)	8 (19)
No	81(81)	47 (81)	34 (81)
Missing	2 (2)	2 (3)	0 (0)
Working (n (%))			
Yes	20 (20)	16 (28)	4 (10)
No	78 (78)	40 (69)	38 (90)
Missing	2 (2)	2 (3)	0 (0)
Working status (n (%))			
Working	20 (20)	16 (28)	4 (10)
Retired	56 (56)	29 (50)	27 (64)
Early retirement	3 (3)	1 (2)	2 (5)
Off work sick, full time	14 (14)	8 (14)	6 (14)
Un-employed	1 (1)	0 (0)	1 (2)
On social security	1 (1)	0 (0)	1 (2)
Other reason	2 (2)	1 (2)	1 (2)
Missing	3 (3)	3 (5)	0 (0)

[a]ECOG; Eastern Cooperative Oncology Group. [b]non-opioid drugs. [c]opioid drugs but less or maximum equivalent to 20 mg morphine per day. [d] opioid drugs equivalent to more than 20 mg morphine per day.

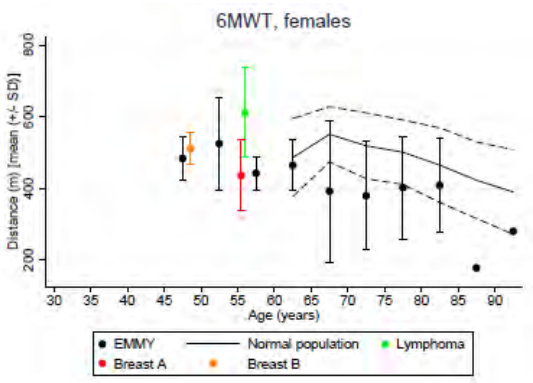
Figure 1a-d. Age group and gender specific Six-Minute-Walk-Test and Sit-to-Stand-Test in EMMY population.

a.



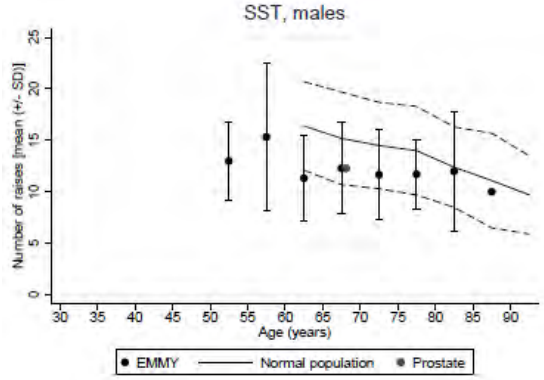
Normal [26]. *Lymphoma* [29]. *Prostate (+/- ADT)* [30].

b.



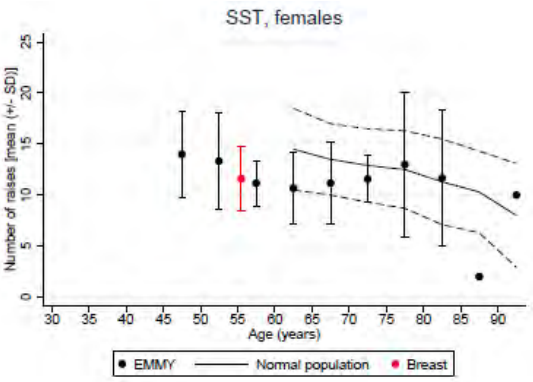
Normal [26]. *Lymphoma* [29]. *Breast A* [32]. *Breast B* [33].

c.



Normal population [26]. *Prostate* [31].

d.

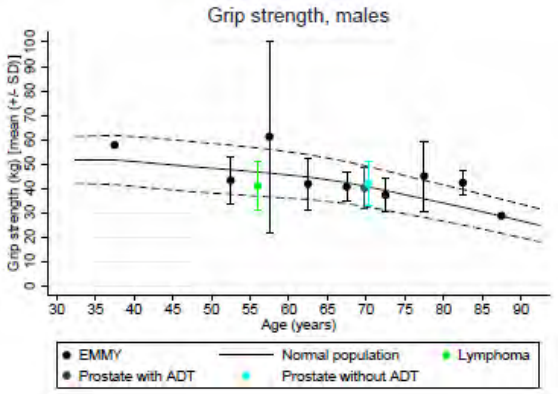


Normal population [26]. *Breast* [32].

EMMY data are illustrated by means and SD-bars (within the five year intervals) and reference values from the normal populations are illustrated by curves (full line indicates mean and dotted lines are +/- SD).

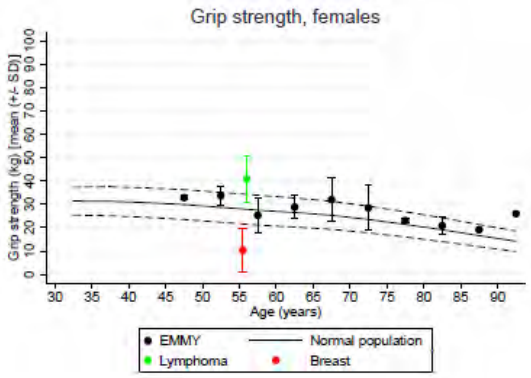
Figure 2a-d. Age group and gender specific grip and knee extension strength in EMMY population.

a.



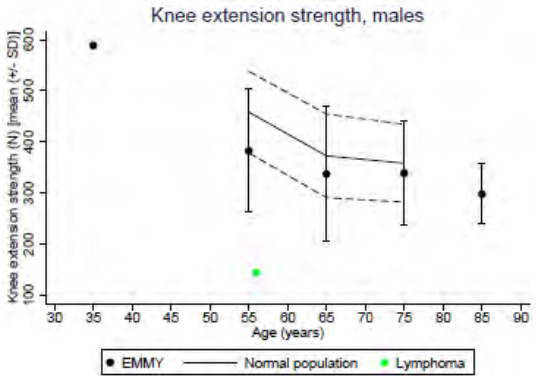
Normal [27]. *Lymphoma* [29]. *Prostate (+/- ADT)* [30].

b.



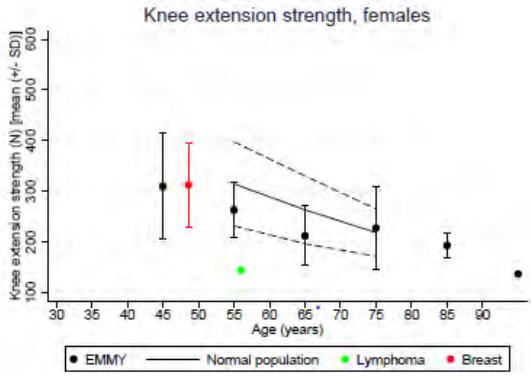
Normal [27]. *Lymphoma* [29]. *Breast* [32].

c.



Normal [28]. *Lymphoma* [29].

d.



Normal [28]. *Lymphoma* [29]. *Breast* [33].

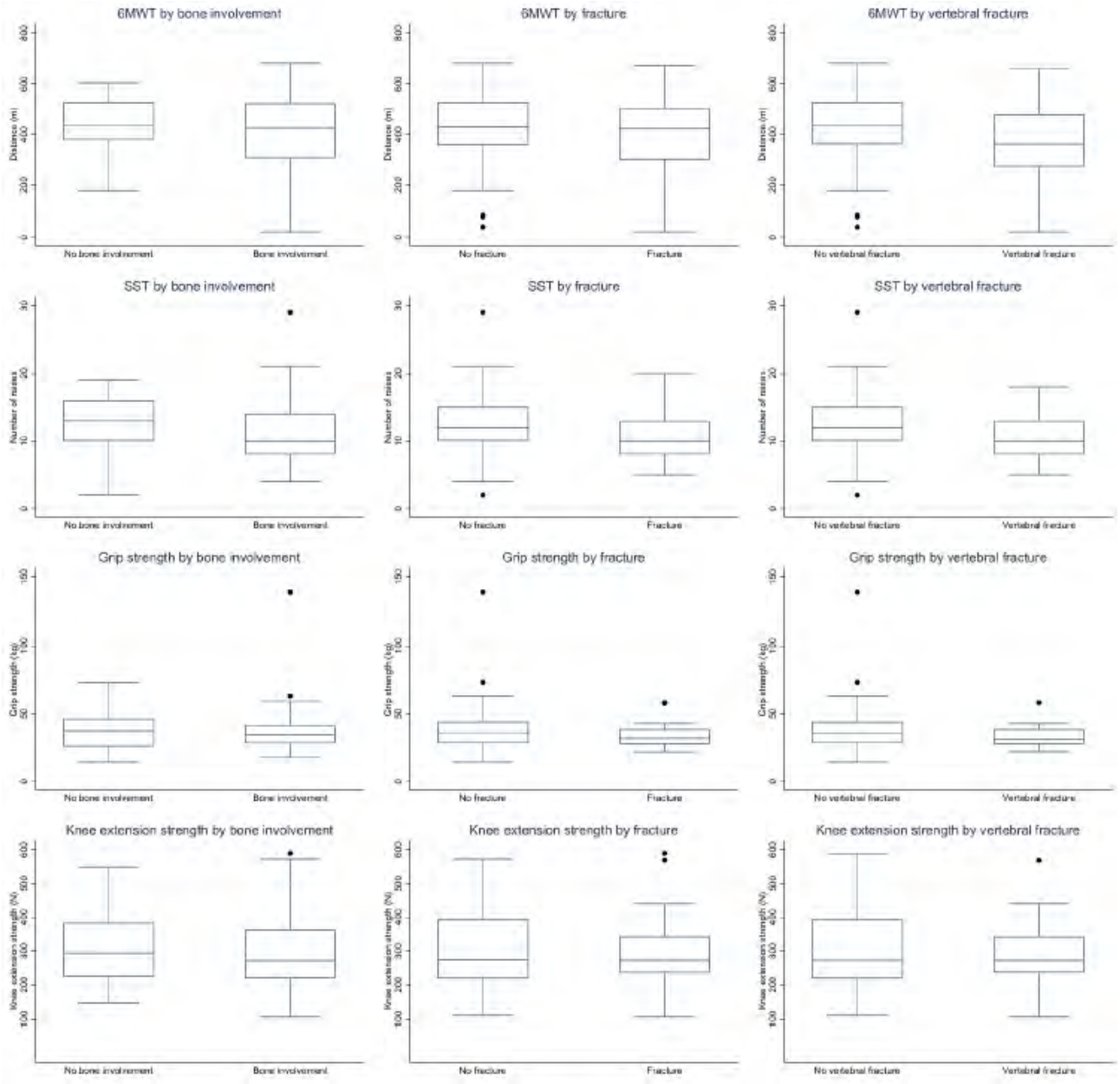
EMMY data are illustrated by means and SD-bars (within the five years intervals for grip strength and ten year intervals for knee extension strength) and reference values from the normal population are illustrated by curves (full line indicates mean and dotted lines indicate +/- SD).

Table 2 Estimates (mean (SD)) for Six-Minute-Walk-Test, Sit-to-Stand-Test, grip and knee extension strength.

Gender	**Age group**	**6MWT** (distance in meters)		**SST** (number of raises)		**Grip strength** (kilograms)		**Knee extension strength** (Newton)	
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Males	35-39	1	671.75 (.)	0		1	57.70 (.)	1	588.90 (.)
	40-44	0		0		0		0	
	45-49	0		0		0			
	50-54	5	460.24 (111.79)	4	13.00 (3.83)	5	43.20 (9.51)	11	382.71 (120.27)
	55-59	6	540.68 (120.18)	6	15.33 (7.17)	6	61.18 (39.35)		
	60-64	6	435.32 (113.46)	6	11.33 (4.18)	6	41.77 (10.61)	13	337.37 (132.51)
	65-69	9	389.74 (153.62)	7	12.29 (4.46)	9	40.62 (5.92)		
	70-74	12	383.96 (130.49)	12	11.67 (4.38)	13	37.18 (6.73)	20	338.96 (101.95)
	75-79	8	403.42 (107.28)	7	11.71 (3.35)	8	44.92 (14.26)		
	80-84	6	426.44 (189.02)	6	12.00 (5.83)	6	42.28 (5.01)	7	298.39 (59.32)
	85-89	1	272.00 (.)	1	10.00 (.)	1	28.70 (.)		
	90+	0		0		0		0	
Females	35-39	0		0		0		0	
	40-44	0		0		0		2	310.05 (104.58)
	45-49	2	483.68 (61.77)	2	14.00 (4.24)	2	32.85 (1.06)		
	50-54	3	525.17 (128.83)	3	13.33 (4.73)	3	33.70 (4.19)	9	262.76 (54.87)
	55-59	6	442.35 (47.28)	6	11.17 (2.23)	6	25.28 (7.33)		
	60-64	4	464.40 (69.78)	3	10.67 (3.51)	4	28.83 (5.02)	10	212.13 (58.41)
	65-69	8	392.34 (197.78)	6	11.17 (3.97)	9	31.98 (9.24)		
	70-74	11	379.78 (150.43)	9	11.56 (2.30)	11	28.50 (9.57)	12	227.53 (81.65)
	75-79	2	402.18 (143.80)	2	13.00 (7.07)	2	23.00 (0.71)		
	80-84	3	408.77 (132.39)	3	11.67 (6.66)	3	20.87 (3.57)	4	192.98 (23.79)
	85-89	1	178.02 (.)	1	2.00 (.)	1	19.10 (.)		
	90+	1	280.00 (.)	1	10.00 (.)	1	26.00 (.)	1	136.60 (.)

Note: Knee extension strength is reported in 10 year age groups. SD cannot be estimated, if only one observation.

Figure 3. Box plots for Six-Minute-Walk-Test, Sit-to-Stand-Test, and the strength measures according to bone status.



Appendix III – Paper III

Exercise in newly diagnosed patients with multiple myeloma – a randomized, controlled trial of effects on physical function, physical activity, pain and quality of life

Authors

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Abstract

Background: Physical exercise in patients with hematological cancer has been shown to be feasible, safe and beneficial for the patients, but exercise studies in patients with multiple myeloma are sparse, especially around the time of diagnosis, and in patients undergoing treatments other than High Dose Therapy with Stem Cell transplantation. The myeloma bone disease poses special challenges in planning and performing exercise intervention in this disease.
The aim was to study the effect of individualized exercise on physical function, physical activity, quality of life and pain in patients newly diagnosed with multiple myeloma.
Methods: This was a two-center, single-blinded, randomized controlled trial assessing a ten-week exercise intervention. Systematic assessment of the bone disease was done. Outcomes were knee extension strength, Six-Minute-Walk-Test, 30 sec Sit-to-Stand-Test, grip strength, number of daily steps, quality of life and pain, all measured pre and post intervention, and number of daily steps was also measured during the intervention period.
Results: Eighty-six participants were eligible for evaluation, 44 in intervention group and 42 in control group, hereof 58 % males, mean age (SD) in years 67.3 (10.3), presence of bone disease 74%. Overall, there were no statistically significant differences between intervention group and control group. The knee extension strength significantly declined in the control group. The muscle strength of lower extremities (30 sec Sit-to-Stand-Test) and aerobic capacity increased in both groups. Upper body strength and level of physical activity did not change. Global quality of life changed in a positive direction in both groups. Perception of pain changed in a positive direction among controls. Possible reasons for the non-significant results of the intervention may be contamination in the control group, non-adherence to the intervention, sub-optimal intensity, or pain caused by exercise.
Conclusion: No significant effects of exercise in newly diagnosed patients with multiple myeloma were found. Muscle strength declined or were unchanged, while functional measures, 30 sec Sit-to-Stand-Test and Six-Minute-Walk-Test increased. Quality of life improved, whether or not patients were receiving exercise intervention.

Background

Multiple myeloma (MM) is a plasma cell cancer in the bone marrow that primarily affects older adults. Incidence and prevalence have increased due to the aging population and because survival has improved due to more effective therapies (1–4). In Europe, the incidence of MM is 5.72 per 100,000, and the median age at diagnosis is 68 years (1). At the time of diagnosis, most patients have symptomatic disease that requires treatment within few days.

At diagnosis, the patient´s physical function of aerobic capacity and muscle strength (age and gender specific) are inferior to the normal population (submitted, unpublished data).

Besides the reduced function from the onset of the diagnosis, the patients start treatment that may influence their physical function and quality of life negatively.

Physical exercise in patients with hematological cancer has been shown to be feasible and safe, and yielding benefits for aerobic capacity, muscle strength, quality of life, psychosocial wellbeing, treatment-related symptoms, fatigue, and body composition, before, during, and after stem cell transplantation (5–8). Still, exercise studies in the field of hematological malignancies are sparse, (9,10), particularly in patients with MM (11).

Patients with MM experience more symptoms and more severe symptoms than patients with other hematological malignancies, not least among the older patients, negatively affecting QoL (12). Servadio et al. (13) focused on quality of life in patients with MM and the possible benefits of physical activity, and they found positive effects on quality of life, including treatment side effects.

Bone destruction is a hallmark of MM seen at diagnosis in up to 79% of the patients (14). It is caused by an imbalance between osteoclast (increased absorption) and osteoblast (decreased formation) activity (15). This imbalance is induced by the myeloma cells and leads to lytic bone lesions (67% of the patients), pathological fractures (26% of the patients), or vertebral compression fractures (22% of the patients) (14). Many patients have more than one abnormality (14). The bone destructions are the major cause for the bone pain, experienced by 58% of the patients at diagnosis (14). Almost all patients receive intravenous bisphosphonates to reduce the risk of progressive bone disease, pain, and fractures (16,17). Still, the bone disease is a challenge in clinical practice, particularly at diagnosis, where pain hampers physical activity, and larger lytic lesions cause doubt as whether exercise is safe or recommendable. In the Danish MM guideline it is stated regarding physical activity that dynamic exercise without causing pain is recommended to prevent further decalcification of the bones. In addition, there is a precaution, where patients are told not to lift any more than three kilograms in the active phase of the disease (18). In our research we challenge the precautions by differentiation, depending on the degree and site of bone disease, but still with precautions in line with the guidelines.

Former exercise studies in patients with MM have only investigated the younger patients who are fit to undergo high dose therapy with stem cell support (HDT-SCT) (19–22). The studies are summarized in the review by Gan et al. (11), with inclusion of studies investigating exercise before, during and after HDT-SCT. They concluded that exercise was feasible and safe, and that the possible benefits include psychological, physiological, and physical outcomes, as well as quality of life, but they also emphasized the need for more research to establish the effect of exercise (11). Particularly, elderly patients with MM have not been studied, and in fact they may potentially be even more challenged on their physical function, e.g. due to natural age decline. Furthermore, there is a gap in the literature concerning exercise studies that investigate early initiated exercise at diagnosis. In our study, we introduced differentiated, individualized prescription of exercise, depending on the present bone disease. We have shown this strategy to be feasible and safe in our feasibility study (data accepted for publication October 2019), and we have shown that it is possible to include elderly patients, and patients with bone destructions.
Here we report efficacy data from our randomized, controlled trial that compared early initiated, individualized physical exercise intervention, combining supervised exercise sessions and home-based exercise and physical activity, to standard of care in patients newly diagnosed with MM. The aim was to study the effect of individualized exercise on physical function, physical activity, quality of life and pain in patients newly diagnosed with multiple myeloma.

Methods

Study Design

This was a randomized controlled study with blinded outcome assessors, taking place in two university hospitals. Patients were screened for eligibility at time of diagnosis, based on inclusion and exclusion criteria. Inclusion criteria were patients >18 years, newly diagnosed with MM planned to start first-line treatment. The patients had to speak and understand Danish. Exclusion criteria were spinal cord compression, unstable vertebral fracture (SINS score >12) (23), untreated cardiac failure or untreated cardiac arrhythmia, severe chronic cardiac failure (NYHA 3-4), other severe comorbidity that would not permit physical exercise, and psychological or psychiatric disorders. Informed consent was obtained from all participants included in the study.
According to standard care, all participants at diagnosis were evaluated with CT scan of the skeleton or skeletal survey. The hematologist performed a systematic assessment of the impact of the bone disease to determine, if there were any restrictions regarding the physical tests or exercise. This assessment was based on the principles of Mirels´ scoring system (24) and captured site, size of osteolytic lesions, and if applicable, time since fracture, and the degree of pain.

The study was approved by the Ethical Scientific Committee in Region Zealand (SJ-422), and the Danish Data Protection Agency (REG-122-2014) and was in accordance with the ethical standards of the 1964 Helsinki Declaration. It was registered at ClinicalTrials.gov. (ID NCT02439112).

Procedure

An overview of the study procedure is illustrated in Figure 1. The block randomization (externally conducted) was stratified according to treatment (planned HDT-SCT versus non HDT-SCT), ECOG performance status (PS 0-1 versus PS≥2), and study site.

The intervention group received usual care concerning ergonomic guidance and transfers, and in addition, the exercise intervention. The intervention was ten weeks and consisted of eight supervised exercise sessions (typically 75 minutes) combined with home-based exercise, including physical activity. The intervention was designed according to the Danish recommendations for persons >65 years and for patients with cancer (25,26), which is in accordance with international guidelines for bone health and older adults (27–31). The intervention was a structured exercise program taking the assessment of the bone disease into consideration if this gave rise to any restrictions, based on the recommendations by Galvão et al. (32), although modified regarding weight-bearing exercise. The exercise program included warm-up, aerobic exercise, strengthening exercises and static stretching exercises. The patient had to perform the exercise program 3 times/week and physical activity with moderate intensity for 30 minutes per day (for 10 continuous minutes, as a minimum), the other four days of the week. For further details about the exercise program we refer to Table A in Appendix.

The control group received usual care consisting of an information leaflet on the importance of and suggestions on being physically active and ergonomic guidance on how to lift and perform transfers properly. Usual care could include a physician-ordered rehabilitation plan.

Measures

Outcome measurements were collected at two time points; baseline (T1) and post-intervention (T2). Primary outcome was knee extension strength (33,34). This was measured by a dynamometer (Lafayette Manual Muscle Tester), which was perpendicularly fixated to a bench by a strap. The participant was sitting on the bench with hip and knee flexion of 90° and arms resting on the side. Then the strap with the dynamometer was placed around the participant´s lower leg. The lower border of the dynamometer was placed five centimeters from the top of the lateral malleolus. Secondary outcomes were Six-Minute-Walk-Test (35,36), 30 sec Sit-to-Stand-Test (37,38), grip strength (37,39), quality of life by EORTC-QLQ-C30 (40), and pain by Brief Pain Inventory (41). Number of daily steps were collected at four activity time points (A-T); Baseline (A-T1), week 4 (A-T2), week 7 (A-T3) and week 11 (A-T4) (Figure 1) by accelerometers (ActivPal Micro).

Statistical methods

Power calculation with significance level, $\alpha = 0.05$, 80% power, $\beta = 0.20$ and a minimum clinical difference of mean(SD) 7 kg(13.1) (corresponding to 69 N(128.5) in the knee extension strength (22) (increase of 23%) showed that the number of patients needed was estimated to 44 patients in each group (intervention and control). Taking a drop-out rate of 15% into account, 102 patients needed to be included.

We report categorical characteristics as counts and proportions, and numerical characteristics as means and standard deviations, respectively, and medians with inter quantile range. Outcomes were compared between groups by two-sample t-test for individual time points and by mixed effects linear regression models, including the patient as random intercept, for longitudinal comparisons. Relative changes were compared between groups by Wilcoxon rank sum test. Normality assumptions were ascertained by quantile plots. P-values below 0.05 were considered statistically significant, and analyses were performed in Stata 15.1.

Results

Sample Characteristics

Of 158 patients screened, 33 did not fulfill the inclusion- and exclusion criteria, and 24 patients declined to participate (Figure 2). One patient was not included for other reason. In total, 100 patients were included. They were randomized to intervention group (n=54) or control group (n=46). Two patients never started the intervention. Eight participants from the intervention group and four participants from the control group, respectively, were lost to follow-up during intervention period, leaving 86 participants for post-intervention evaluation (intervention group, n=44 and control group, n=42).

The included subjects were 49 males (58%) and 37 females (42%). Mean age (SD) was 67.3 (10.3) years, IQ range 59-74 years. HDT-SCT was planned for 57% of the patients. The majority (74%) had bone disease, with involvement of the spine being most common and present in 30% (Table 1). The two groups were comparable in all baseline characteristics; only patients in the CG had more bone involvement of the thoracic spine and/or costae (Table 1).

Around one third of the participants did not use pain relieving drugs (39%), and another one third used mild drugs (31%). During the intervention period 15% of the participants needed an up-grade in dose intensity of analgesic drugs, whereas 13% had a down-grade in dose intensity. This, without any differences between the groups (Table 1).

During the intervention period, the majority (92%) received treatment with a Bortezomib-based regimen. Around one third experienced peripheral sensory neuropathy (CTC-grade 1 in 23.3%,

CTC-grade 2 in 11.6%). Diarrhea and constipation occurred in 8% and 17% of the participants, respectively. Twenty per cent of the participants were hospitalized during the intervention period, most frequently caused by infections. There was no difference between the groups in the need for hospitalization (Table 1).

Two participants in the CG, and one in the IG, had a vertebral fracture during the intervention period. Two participants in the CG had non-vertebral fractures during the intervention period; this was not observed in the IG. One participant in the CG received pain-relieving radiotherapy for non-vertebral bone fracture during the intervention period; this was not given to anyone in the IG. During the intervention period, one participant from the IG and four from the CG received other structured exercise therapy in their local community. As of yet, we are still missing data on this from seven participants. At this point, we have not yet data on this from nine participants.

Physical Outcomes

The results of the four physical outcome measures are shown in Table 2. Knee extension strength (primary outcome) showed a decline in both groups. This was a trend in the IG ($p=0.092$), and in the CG the decline was statistically significant ($p=0.014$). No difference between the IG and the CG ($p=0.648$) was found. Grip strength declined in both groups, but neither of them was statistically significant, neither within nor between groups.

The functional tests (SST and 6MWT) showed a statistically significant increase in the SST in both groups; almost two raises in the IG ($p=0.009$) and 1.5 raises in the CG ($p=0.022$), but a difference between groups was observed ($p=0.707$). In 6MWT we found a statistically significant increase in both groups of about 40 meters (IG, $p=0.001$, and CG, $p<0.001$), without difference between groups ($p=0.900$). Whether the participants had symptomatic bone disease with the need for restriction in exercise intervention or not, did influence physical outcome measures (Figure 3). Accelerometer-based activity at baseline (A-T1) and during and after the intervention period is shown in Figure 4. The figures indicate an early, but not sustained increase in steps in the IG. No significant differences within or between groups were noticed.

Patient-Reported Outcomes

Self-reported physical activity and exercise are shown in Table 3. The only significant finding was that subjects in the IG reported more physical exercise at T2 compared to T1, approximately one hour ($p=0.012$). However, no between groups differences in reported exercise or physical activity were observed.

Participants in both groups reported equally improved global QoL after the intervention period. QoL are summarized in Table 4. The functional domains reached a statistically significant increased score within the IG regarding physical function ($p=0.016$) and emotional function

(p<0.001). In the control group emotional function (p<0.001) and role function (p=0.050) had statistically significant better scores.

In the symptom domains the participants in the IG perceived statistically significant decreased pain (p<0.001) but increased insomnia (p=0.028). Pain was statistically reduced in the CG as well (p=<0.001), and the CG also reported significantly less appetite loss (p=0.004). Between groups analysis showed more insomnia (p=0.006) post intervention in the IG compared to the CG.

The pain severity rates are also shown in Table 4. In the IG the item "worst pain" significantly decreased, whereas in the CG statistically significant less pain was reported in all items. Between groups analysis indicated less "here and now" pain in the CG compared to the IG.

In total, 92% of possible sessions were completed (Table 5). The primary cause of cancellation was disease condition, but other reasons were present as well, including miscommunication regarding planning, and no medical treatment on the day of exercise (data not shown). In total, 86 % of the participants in the IG filled in the diary registration, but nearly half of them had incomplete registrations (Table 5). According to the registrations, only half of the participants adhered to home-based exercise sessions and physical activity, respectively. Adjustments of the exercise program had to be made during the intervention; both progression and regression were needed.

There were no serious adverse events in either of the two groups (Table 5). Five non-serious adverse events were registered, but only one was considered to be related to exercise (excessive load), and three led to discontinuation.

Discussion

The aim was to study the effect of individualized exercise on physical function, physical activity, quality of life and pain in patients newly diagnosed with multiple myeloma. Overall, the results were negative, given that we did not observe unequivocally better physical function or activity after the intervention.

The knee extension strength, which was significantly reduced in the CG compared to baseline. However, it was reduced in the IG as well, although insignificantly, and between groups analysis showed no difference between the groups. Grip strength was unchanged in both groups. The functional measures; SST and 6MWT, showed an improvement in both groups without between groups differences, whereas the levels of physical activity based on accelerometer measurements and on self-reported measures did not indicate behavioral differences between the groups. However, the IG reported increased physical exercise training at end of intervention.

We found a positive change in global QoL in both groups, which can be explained by the effect of initiated anti-myeloma treatment. Pain reported by the Brief Pain Inventory changed significantly towards less reported pain in the CG. The IG reported less evidently reduced pain, but it was

significantly reduced for perception of "worst pain". At the end of the intervention period patients in the CG reported less "here and now" pain than patients in the IG. Thus, the supervised exercise sessions, and perhaps the home-based sessions, may have caused more pain. The incomplete diary registrations can, as mentioned, be due to non-adherence, and the pain may be a reason for non-adherence.

Overall, our primary end point and most of the secondary end points did not document benefit of our intervention, but some significant differences were found within groups. However, it can be discussed if these differences are relevant in a clinical perspective. The knee extension strength declined significantly in the CG, whereas the observed decline in the IG was not significant. The decline was -19.6 N (relative change 6%) and -26.9 N (relative change 5%) in the intervention group and the control group, respectively. These estimates are in contrast to the Minimal Important Difference of 69 N used in the power calculation (69 N), corresponding to a relative change of 23%, based on the study by Groeneveldt et al. (22). Later, a larger randomized study was published by Persoon et al. (42), where the mean change was 28.3 NM, relative change 16% in the intervention group, and 21.4 NM, relative change 12% in the control group. Both studies (22,42) were conducted in younger patients after HDT-SCT/stable phase. Because the time of intervention was after HDT-SCT the patients may have been more affected by treatment and untrained, and thus more sensitive to exercise training due to physiological mechanisms (43). On the other hand, our cross-sectional study of physical function at time of diagnosis (submitted study) showed that the younger patients might be more affected on their physical function than the older patients, which could speak in favor of the opposite, although physical function is not necessarily associated with trained/untrained conditions.

Concerning SST, an increase of two raises is considered a minimum clinically important difference, although in study populations other than cancer (44,45). Despite the fact that the populations are not absolutely comparable to the population in our study, we assume that an increase of two raises is reasonable. In our study we reached statistically significant increases within both groups, but the minimum important difference of two raises for identifying clinically relevant changes were not reached for the means in the groups, and there were no differences between the groups.

In 6MWT, the minimum clinically important difference ranges across the literature, but in a study in patients with chronic obstructive pulmonary disease with almost similar mean age (SD) (COPD, 70.3(8.5)), gender distribution (61% males) and rehabilitation period (7 weeks), the minimum clinically important difference was 25 meters (absolute change) and a relative change of 14% (46). A review in patients with cardio pulmonary disease speaks in favor of a minimum clinically important difference of 50 meters (47). On the basis of these studies we consider the within group improvements in the IG and the CG of around 40 meters (absolute change) and a relative changes of 26% (IG) and 39% (CG) to be significant findings, although the study populations vary.

Overall, the QoL data showed identical findings in the IG and the CG. Global QOL improved significantly in both groups and was also clinically significant for both groups, based on an observed improvement in score above 10 (48).

Methodological Considerations

Because of the aim of investigating the effect of our intervention, the single blinded, randomized controlled trial design is a proper design, and a strength for the study. We did our best to maintain the blinding of the assessors. The participants were carefully informed not to reveal whether they belonged to the IG or the CG. It is a limitation that we did not systematically register whether we succeed in maintaining the blinding. We succeeded in to including participants who are representative of newly diagnosed patients with MM in clinical practice. Patient median age, age range and presence of lytic bone disease were as expected in a population-based cohort (14). However, we were challenged by a long inclusion period. Several things might explain this. First, there is no doubt that some patients were missed because of acute hospitalization at diagnoses due to complications, e.g. renal failure, with need of immediate treatment. Upfront consideration of inclusion in an exercise study will have low priority in many situations. Secondly, some eligible patients were probably missed due to lack of awareness of the study among treating physicians and nurses. We could have chosen another screening procedure by asking The Danish Health Authority permission to screen referrals and thereby increase focus on eligible patients. However, the included cohort is, as stated, representative of newly diagnosed patients, and our randomized design compensates for potential minor selection biases.

In keeping with the power calculation, we planned to include 102 patients, but managed to include 100 patients within the stipulated inclusion period. The drop-out rate and missing evaluations were low, and we therefore succeeded in evaluating data from 86 patients (the estimate was 88). We cannot eliminate a type II error on the effect of the intervention.

A potential reason for not observing an effect could be the broad inclusion criteria. We included all ages, allowed all different anti-myeloma treatments, and had no restriction based on performance status. At study planning this was a conscious choice. The study should reflect daily practice, and thus, the results would have high external validity. Although we stratified our randomization according to planned treatment, performance status and study site, it is still a very heterogeneous group of patients, and this can be a challenge when assessing their physical function and physical activity. The patients' performance and behavior may vary considerably.

We found that the self-reported activity levels as well as the objectively measured levels of physical activity in the IG and the CG were identical but extremely variable, as reflected by high standard deviations of the mean in the number of measured steps. Possible reasons for the lack of difference can either be lack of effect in the IG (maintaining level of physical activity) or it can be

contamination in the CG. Contamination was pointed out as a reason for non-significant effects in the studies by Persoon et al. (42). The simple fact of being included in an exercise study may increase focus on possible benefits of exercise and thereby motivate patients in the CG to be more active. A weakness is that we do not know exactly what kind of exercise and/or physical activity the CG performed. In the IG, we attempted to document the extent of exercise and physical activity in the intervention group, but almost half of the patients had incomplete registrations, and the missing registrations we observed were more than in our feasibility study (not yet published data). We do not know if incomplete registrations reflect non-adherence to exercise, or forgotten registration.

More participants in the CG were assessed to have bone destructions in the thoracic spine and/or costae compared to the IG. We would expect that bone destructions cause less physical activity and exercise, which is supported by the findings in our cross-sectional study of physical function in patients with MM (not yet published data). The observation that more patients in the CG had destructions in the thoracic spine and/or costae could potentially be a bias for our outcome findings, but that would most likely be in favor of the IG, and should therefore not challenge our overall findings. However, symptomatic bone destructions will probably affect the feasibility and potential benefit of exercise. We therefore analyzed outcome measures according to whether the included subjects had bone destructions that affected test and training procedures or no symptomatic bone disease (Figure 3). These sub-cohort analyses did not indicate any differences in the efficacy of training intervention. Of course the results of these sub-analyses should be interpreted with caution.

An important issue is if our training intensity was optimal. We found a need for both progression and regression of the exercise intensity during the intervention period, which made it difficult to know whether we achieved the desired intensity over time. This speaks in favor of a patient group, where individualization is important. There are both strengths and limitation in the randomized controlled trial. It is a strength that we have described the intervention in a structured way and manage the bone disease in a structured way as well, but at the same time these structured ways also limit the magnitude of possibilities for individualization.

Conclusion

Our randomized, controlled trial did not find significant efficacy on physical function or physical activity of early initiated, supervised exercise in patients with newly diagnosed multiple myeloma. Physical function in terms of muscle strength in lower extremities and aerobic capacity declined from time of diagnosis and in the following 3 months, regardless of receiving exercise intervention or not. As expected, global quality of life improves over time after initiation of anti-myeloma

treatment. Exercise studies in multiple myeloma are still warranted and should particularly address the potential benefit in older patients after end of treatment.

Authors´ contribution

RFL designed the work, did the analysis and interpretation of data and drafted the work, and made changes after revision. MJ designed the work, contributed to analysis and interpretation of data, and revised the manuscript. LRM designed the work contributed to analysis and interpretation of data, and revised the manuscript. UCF designed the work and revised the manuscript. SM assisted the analysis and contributed to interpretation of data, and revised the manuscript. NA designed the work, contributed to interpretation of data, and revised the manuscript.

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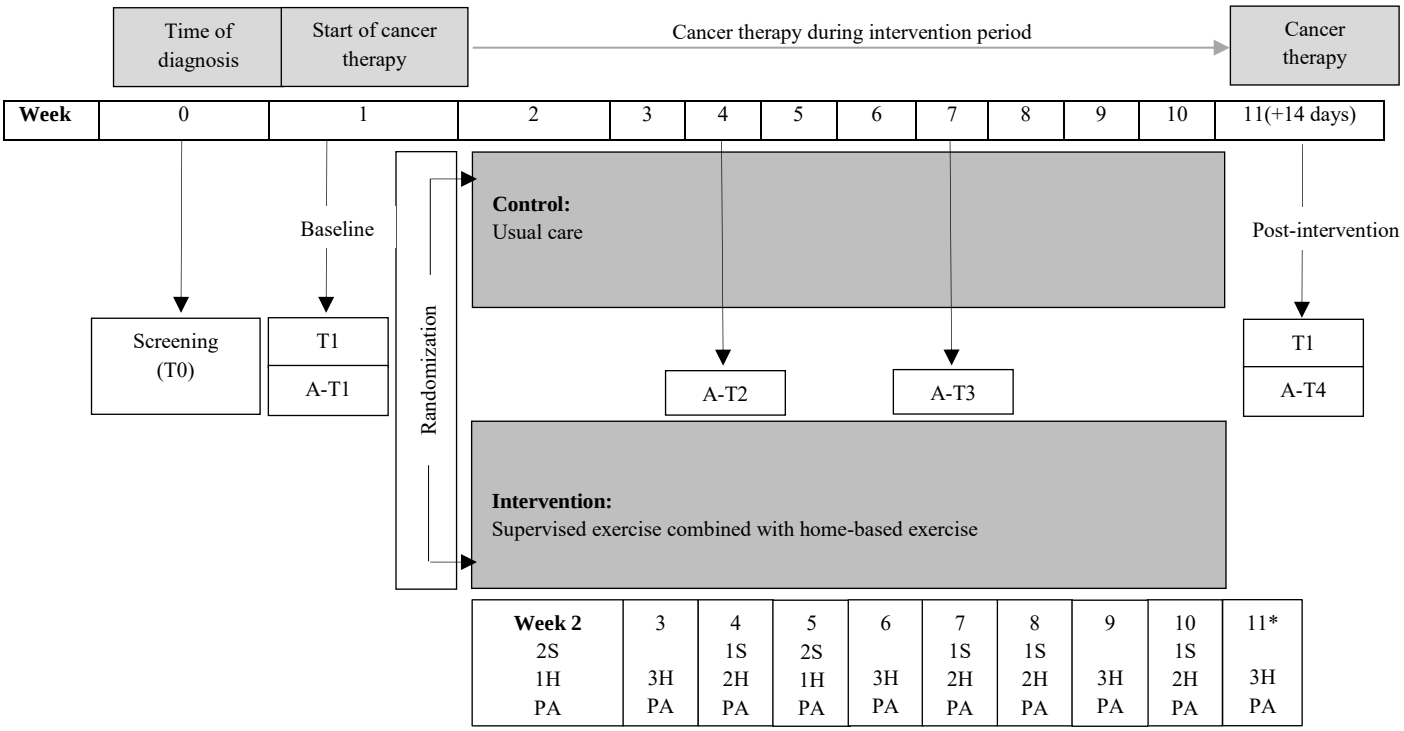
Figure 1. Overview of the randomized, controlled feasibility study from time of diagnosis and screening (T0), through baseline measurements (T1), intervention period and time of post-intervention measurements (T2). Time of physical activity measurements are illustrated by A-T1, A-T2, A-T3, and A-T4.



T0; Time 0 (time of screening).

T1; Time 1 (physical tests at baseline test).

T2: Time 2 (physical tests post-intervention).

A-T1; Activity-Time 1 (accelerometer measures at baseline).

A-T2; Activity-Time 2 (accelerometer measures at week 4).

A-T1; Activity-Time 3 (accelerometer measures at week 7).

A-T4; Activity-Time 4 (accelerometer measures post-intervention).

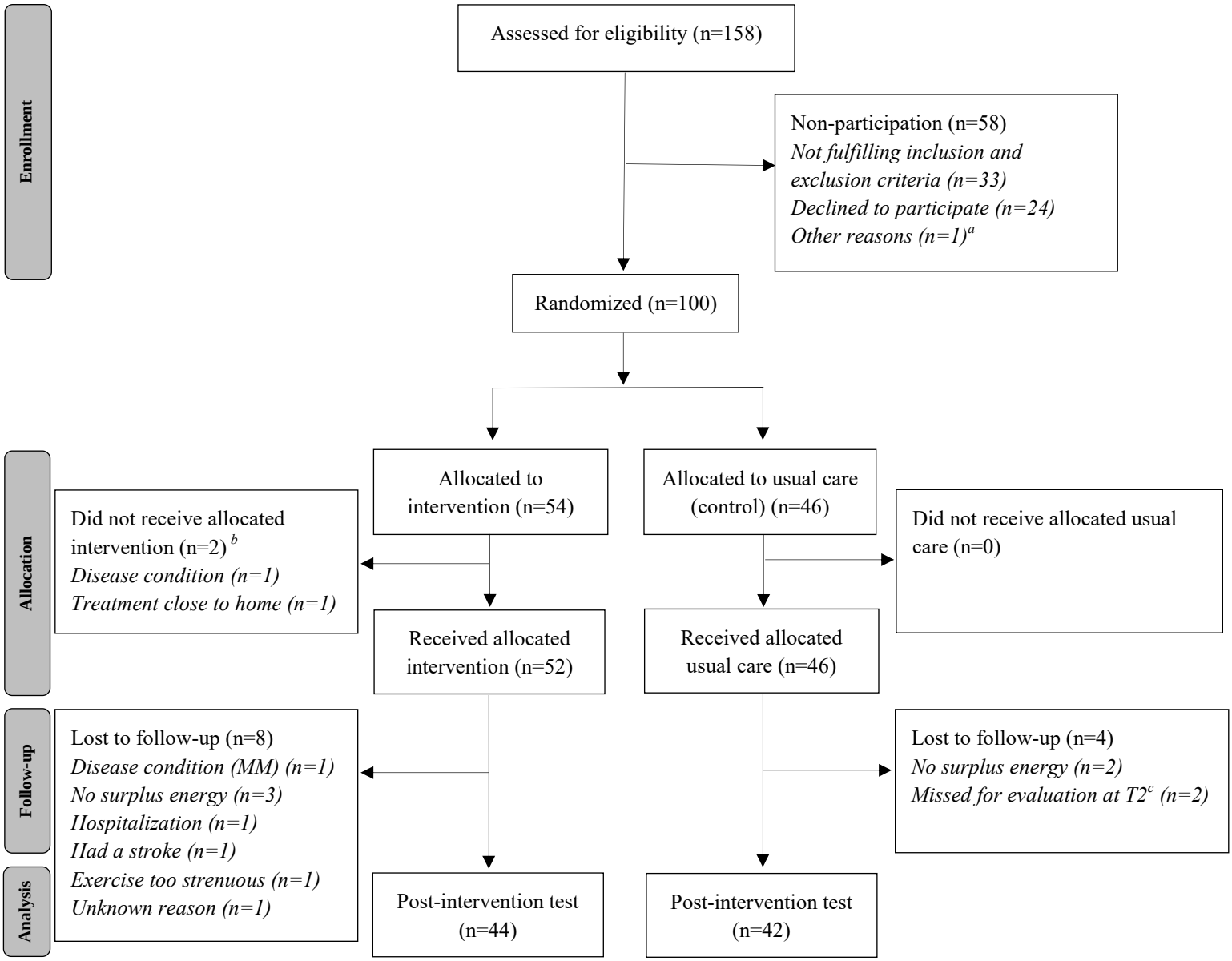
1S and 2S; Supervised exercise session one or two times weekly, respectively.

H1, H2 and H3; Home-based exercise session one, two or three times weekly, respectively.

PA; Physical activity taking place the remaining four days, where exercise sessions are not conducted.

**The test procedure can, but will not necessarily be performed in week 11. This means that in some cases, the participant will not perform a full week of exercise in week 11 before performing the post intervention test.*

Figure 2. Flowchart of the inclusion to the study, based on the CONSORT 2010 Flow Diagram.



[a] *One participant fulfilled the inclusion criteria, but declined to participate afterwards, including use of data.*
[b] *Two participants were randomized before baseline test, and therefore allocated too early. This must be considered a randomization failure.*
[c] *T2; Time 2 corresponding to physical tests post-intervention.*

Table 1. Patient demographics and medical characteristic for the total study population, the intervention group, and the control group at baseline, as well as characteristics during the intervention period.

	Total group N=86	**Intervention group (IG) n =44**	**Control group (CG) n =42**	**IG vs. CG p-value**
AT BASELINE				
Gender (n (%))				
Male	49 (57%)	26 (59%)	23 (55%)	0.685
Female	37 (43%)	18 (41%)	19 (45%)	
Age (years)				
Mean (SD)	67.3 (10.3)	68.2 (9.1)	66.3 (11.5)	0.399
Median (range)	68 (38-90)	68 (52-87)	68 (38-90)	
IQ range	(59-74)	(61-74)	(58-74)	
EOCG performance status (n (%))				
0-1	76 (88%)	38 (86%)	38 (90%)	0.552
≥2	10 (12%)	6 (14%)	4 (10%)	
Subtype (n)[a]				
IgG/IgA/LC/NS	54/18/13/1	26/10/8/0	28/8/5/1	0.686
Planned treatment (n (%))				
HDT-SCT	49 (57%)	23 (52%)	26 (62%)	0.367
Non HDT-SCT	37 (43%)	21 (48%)	16 (38%)	
Bone involvement (n (%))	64 (74%)	35 (80%)	29 (69%)	0.265
Bone disease with restriction for tests or exercise (n (%))				
Thoracic spine and/or costae	22 (26%)	7 (16%)	15 (36%)	0.035
Lumbar spine	18 (21%)	8 (18%)	10 (24%)	0.521
Either thoracic spine/costae or lumbar spine	26 (30%)	10 (23%)	16 (38%)	0.121
Pelvis and/or femoral bone	6 (7%)	4 (9%)	2 (5%)	0.361
Humeral bone(s)	5 (6%)	3 (7%)	2 (5%)	0.522
Pain relieving drugs (n (%))				
None/mild/moderate/strong[b]	39/29/9/9	17/17/6/4	22/12/3/5	0.493
Body Mass Index				
Mean (SD)	25.6 (4.6)	26.2 (5.4)	24.9 (3.5)	0.205
Median (range)	24.7 (17.8-44.6)	24.8 (17.8-44.6)	24.5 (18.3-38.9)	
IQ range	(22.7-27.5)	(22.6-28.2)	(22.7-26.6)	
DURING THE INTERVENTION PERIOD				
Given treatment (n (%))				
With Bortezomib	79 (92%)	39 (89%)	40 (95%)	0.434
Without Bortezomib	7 (8%)	5 (11%)	2 (5%)	
Toxicity during intervention period				
Peripheral neuropathy (n)				
CTC-grade 1/2/3/4	20/10/0/0	14/6/0/0	6/4/0/0	0.094
Diarrhea (n)				
CTC-grade 1/2/3/4	5/2/1/0	1/2/1/0	4/0/0/0	0.143
Constipation (n)				
CTC-grade 1/2/3/4	13/4/0/0	9/2/0/0	4/2/0/0	0.584
Patients hospitalized due to infection (n (%))	20 (23%)	13 (30%)	7 (17%)	0.158
Fractures (n (%))				
Vertebral	3 (3%)	1 (2%)	2 (5%)	0.612
Non-vertebral	2 (2%)	0 (0%)	2 (5%)	0.236
Radiotherapy (n (%))				
Vertebral	0 (0%)	0 (0%)	0 (0%)	NA
Non-vertebral	1 (1%)	0 (0%)	1 (2%)	0.488
Change in pain relieving drugs (n (%))				
Up-grade in intensity	12 (15%)	6 (14%)	6 (14%)	0.573
Down-grade in intensity	11 (13%)	6 (14%)	5 (12%)	

NA; Not applicable

Table 2. Measures of physical function at baseline (T1) and post-intervention (T2) according to intervention group (IG) and control group (CG) as well as within group differences, and between groups differences with corresponding p-values and relative changes (RC) from baseline to post-intervention.

	IG (TP1) n=44	**IG (TP2) n=44**	**Within IG**	**CG (TP1) n=42**	**CG (TP2) n=42**	**Within CG**	**Between groups**	**P-value for RC between groups**
Knee extension strength (Newton)								
Mean (SD)	304.2 (117.5)	282.6 (113.6)		295.4 (113.08)	270.8 (103.88)			
Mean diff.(p-value)			-19.6 (0.092)			-26.9 (0.014)	-7.3 (0.648)	
RC (mean% (SD))			-0.06 (0.30)			-0.05 (0.24)		0.799
Knee extension strength (Nm/kg body weight)								
Mean (SD)	4.2 (1.54)	4.0 (1.66)		4.03 (1.41)	3.55 (1.35)			
Mean diff.(p-value)			-0.20 (0.210)			-0.34 (0.024)		
RC (mean% (SD))			-0.05 (0.30)			-0.04 (0.25)	-0.14 (0.528)	0.906
Grip strength (kilogram)								
Mean (SD)	36.1 (13.29)	34.0 (11.11)		38.6 (18.0)	37.2 (20.96)			
Mean diff. (p-value)			-2.1 (0.083)			-1.3 (0.48)	0.8 (0.742)	
RC (mean% (SD))			-0.03 (0.30)			-0.03 (0.17)		0.205
30 sec Sit-to-Stand-Test (number of raises)								
Mean (SD)	12.5 (4.5)	14.1 (5.3)		11.0 (3.89)	12.5 (4.85)			
Mean diff.(p-value)			1.9 (0.004)			1.5 (0.022)	-0.4 (0.707)	
RC (mean% (SD))			0.22 (0.52)			0.24 (0.49)		0.949
6 Min-Walk-Test (meter)								
Mean (SD)	435.5 (134.7)	476.7 (114.9)		409.5 (147.16)	451.6 (119.89)			
Mean diff. (p-value)			44.1 (0.001)			42.1 (<0.001)	-2.2 (0.900)	
RC (mean% (SD))			0.26 (0.63)			0.39 (1.65)		0.902

Missing values: Nine for knee extension strengths (N), twenty for knee extension strengths (Nm/kg), one for grip strength, twelve for 30 sec Sit-to-Stand-Test, and one for Six-Minute-Walk-Test. Difference between the two knee extension strength measures is caused by missing weights.

Figure 3. Physical outcome measures at baseline (T1) and post intervention (T2) for participants in the control group (CG) and intervention group (IG) with bone disease (left side) and no bone disease (right side).

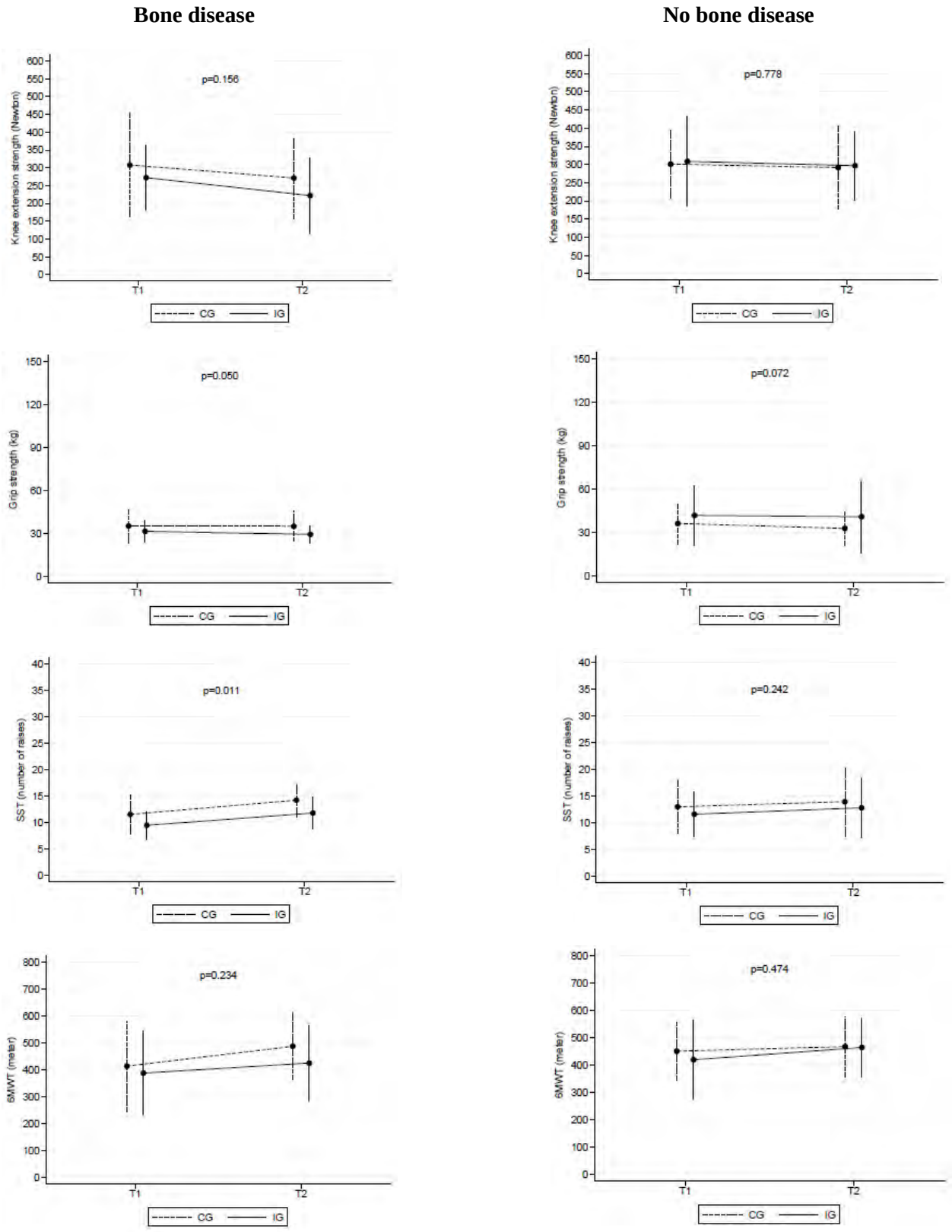


Figure 4. Measures of physical activity (steps per day) at baseline (T1/A-T1), week 4 (A-T2), week 7 (A-T3), and week 11 (T2/A-T4) according to intervention group and control group. P-values are reported between groups (intervention group (IG) and control group (CG)) and within groups across all four time points.

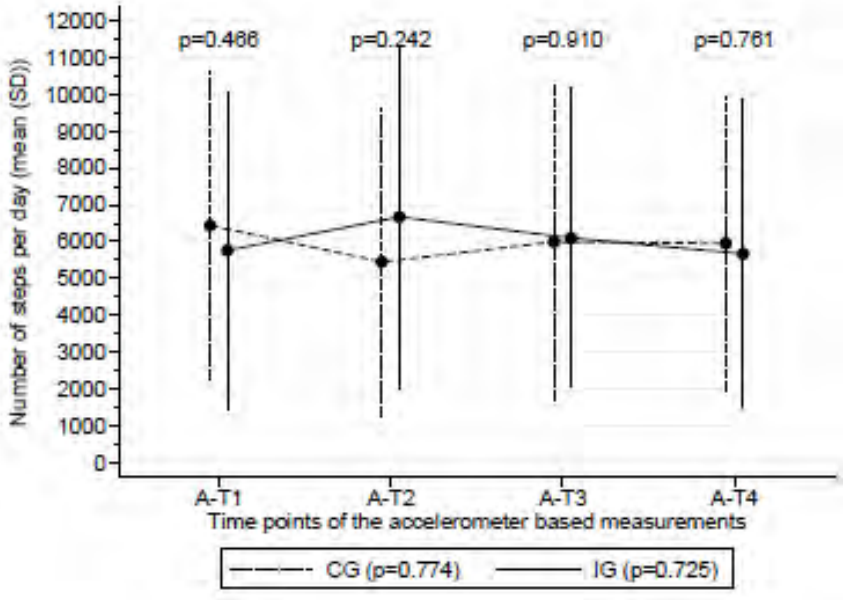


Table 3. Self-reported physical activity at baseline (T1) and post intervention according to intervention group (IG) and control group (CG), as well as within group differences, and between groups differences with corresponding p-values and relative changes (RC) from baseline to post-intervention.

Self-reported physical activity and exercise	**IG (T1) n=44**	**IG (T2) n=44**	**Within IG**	**CG (T1) n=42**	**CG (T2) n=42**	**Within CG**	**Between groups**
Physical activity, min/week							
Mean (SD)	373 (449)	472 (559)		393 (434)	453 (432)		
Mean diff. (p-value)			73 (0.227)			61 (0.467)	19 (0.854)
RC (mean%)			0.65 (1.44)			-1.23 (2.42)	
Physical exercise, min/week							
Mean (SD)	78 (128)	133 (152)		75 (169)	104 (139)		
Mean diff. (p-value)			56 (0.016)			26 (0.399)	30 (0.391)
RC (mean%)			0.38 (2.38)			1.06 (4.28)	

[a]*Physical activity; Physical activity in a daily living perspective, lasting for ≥10 min.*
[b]*Physical exercise; Exercise with perception of breathlessness.*

Table 4. Measures of quality of life and pain at baseline (T1) and post-intervention (T2) according to intervention group (IG) and control group (CG) as well as within groups differences, and between groups differences with corresponding p-values and relative changes (RC) from baseline to post-intervention.

	IG (T1) n=44	IG (T2) n=44	Within IG	CG (T1) N=42	CG (T2) N=42	Within CG	Between groups	Missing
QUALITY OF LIFE								
EORTC-QLQ-C30								4
Global QoL								
Mean (SD)	54.7 (25.3)	65.3 (21.3)	10.9 (0.024)	54.7 (23.94)	65.5 (18.1)	10.9 (0.002)	-0.4 (0.941)	
Median (range)	58.3 (0-91.7)	66.7 (16.7-100)		58.3 (0-100)	66.7 (33.3-100)			
IQ range	33.3-75.0	50.0-83.3		33.3-66.7	50.0-83.3			
RC (mean%)			0.43 (1.09)			0.36 (0.65)	0.764	
Functional domains								
Physical functioning								1
Mean (SD)	73.7 (25.6)	79.5 (19.0)		70.1 (20.3)	74.6 (19.3)			
Mean diff. (p-value)			5.8 (0.016)			4.52(0.116)	-1.3 (0.726)	
Role functioning								1
Mean (SD)	57.1 (33.1)	64.3 (30.7)		51.1 (36.73)	61.6 (32.44)			
Mean diff. (p-value)			7.1 (0.106)			10.5 (0.050)	3.3 (0.632)	
Emotional functioning								3
Mean (SD)	6.9 (17.1)	84.72(18.9)		71.7 (19.7)	83.5 (16.5)			
Mean diff. (p-value)			8.5 (<0.001)			11.7 (<0.001)	3.3 (0.380)	
Cognitive functioning								3
Mean (SD)	87.9 (19.6)	88.9 (18.3)		83.7 (20.80)	86.8 (16.08)			
Mean diff. (p-value)			2.1 (0.492)			2.8 (0.207)	0.5 (0.890)	
Social functioning								3
Mean (SD)	82.5 (24.7)	82.5 (22.4)		78.0 (26.4)	80.6 (21.5)			
Mean diff. (p-value)			2.2 (0.426)			2.5 (0.495)	0.6 (0.890)	
Symptoms domains								
Fatigue								1
Mean (SD)	38.4 (29.3)	39.8 (24.1)		44.2 (27.2)	36.7 (23.6)			
Mean diff. (p-value)			1.5 (0.702)			-7.5 (0.076)	-9.0 (0.116)	
Nausea and vomiting								1
Mean (SD)	11.5 (16.7)	8.3 (15.7)		6.1 (12.0)	8.5 (13.8)			
Mean diff. (p-value)			-3.2 (0.260)			2.4 (0.262)	5.6 (0.113)	
Pain								1
Mean (SD)	37.3 (33.5)	19.4 (22.4)		47.7 (32.9)	24.0 (23.9)			
Mean diff. (p-value)			-17.9 (<0.001)			-23.8 (<0.001)	-6.0 (0.371)	
Dyspnoea								2
Mean (SD)	23.6 (28.13)	26.3 (31.70)		23.5 (25.50)	19.4 (27.44)			
Mean diff. (p-value)			2.9 (0.574)			-3.8 (0.415)	-6.6 (0.338)	
Insomnia								2
Mean (SD)	23.0 (28.0)	33.3 (27.6)		33.3 (34.5)	22.2 (29.1)			
Mean diff. (p-value)			10.3 (0.028)			-10.7 (0.071)	-21.0 (0.006)	
Appetite loss								2
Mean (SD)	15.08 (24.6)	15.08 (28.7)		27.1 (31.1)	13.2 (26.4)			
Mean diff. (p-value)			0.00 (1.000)			-14.3 (0.004)	-14.4 (0.028)	
Constipation								2
Mean (SD)	23.0 (30.8)	23.8 (30.0)		23.3 (32.2)	17.1 (26.6)			
Mean diff. (p-value)			0.8 (0.847)			-6.7 (0.128)	-7.5 (0.212)	
Diarrhea								4
Mean (SD)	8.3 (16.5)	8.9 (18.3)		9.1 (16.7)	14.7 (23.4)			
Mean diff. (p-value)			0.7 (0.833)			5.6 (0.180)	5.0 (0.354)	
Financial difficulties								4
Mean (SD)	4.2 (11.2)	4.0 (13.2)		5.4 (19.2)	9.3 (18.3)			
Mean diff. (p-value)			-0.1 (0.956)			3.9 (0.048)	4.0 (0.159)	
BRIEF PAIN INVENTORY								
Pain severity rate[a]			Mean diff (p)			Mean diff (p)	Mean diff (p)	
Worst	3.7 (2.9)	2.7 (2.5)	-1.0 (0.040)	4.6 (3.4)	2.8 (2.7)	-1.8 (0.001)	-0.8 (0.292)	2
Least	1.3 (1.3)	1.4 (1.5)	0.1 (0.801)	1.7 (2.1)	0.9 (1.2)	-0.8 (0.015)	-0.9 (0.045)	6
Average	2.6 (2.3)	2.2 (2.1)	-0.5 (0.314)	3.1 (2.6)	2.0 (2.1)	-1.2 (0.004)	-0.7 (0.261)	3
Now	1.8 (2.00)	1.5 (2.0)	-0.3 (0.376)	2.7 (3.0)	0.9 (1.6)	-1.8 (<0.001)	-1.5 (0.013)	5
Composite score	2.4 (1.9)	2.0 (1.9)	-0.5 (0.221)	3.0 (2.45)	1.7 (1.5)	-1.4 (<0.001)	-1.0 (0.067)	2
Pain interference[b]	2.5 (2.5)	2.2 (2.5)	-0.3 (0.468)	2.8 (2.4)	1.7 (1.9)	-1.1 (<0.001)	-0.8 (0.162)	2

EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

[a]*Pain severity is rated by four items: Worst within the last 24 hours, least within the last 24 hours, average generally, and now. The composite score is the mean of the four pain items.*

[b]*Pain interference covers seven items of daily activities: General activity, walking, work, mood, enjoyment of life, relations with others, and sleep. The pain interference mean score is the mean score of the seven items.*

Table 5. Adherence to the intervention and the individual components (supervised exercise sessions, home-based exercise sessions, and physical activity) and adverse events.

	IG n = 44
Adherence to supervised exercise session	
Sessions completed (n (%))[a]	325 (92%)
Adjustments of the exercise program	
Progression of exercise program (n (%))	16 (36%)
Regression of exercise program (n (%))	11 (25%)
No progression or regression (n (%))	4 (9%)
Both progression and regression (n (%))	13 (30%)
Adherence to home-based exercise sessions (n (%))[b]	414 (50%)
Adherence to physical activity[c]	813 (51%)
Diary registration (n (%))	
All weeks	18 (41%)
Some weeks	20 (45%)
No weeks	6 (14%)
Adverse events (n)	5
Consequences of the adverse events	
None	0
Discontinuation of the SES (n)	3
Patient had to be seen by medical doctor	1
Other	1

[a]*Out of 352 possible sessions (eight sessions for each participant).*
[b]*Out of 836 recommended sessions, based on a period of nine weeks.*
[c]*Out of 1584 recommended sessions, based on a period of nine weeks.*

Appendix

Table A. Exercise intervention; mode, intensity, duration, and progression

Mode	Intensity	Duration per session	Progression
Exercise program, three times per week			
Warm up	10-11 RPE[a]	5 min	-
Aerobic exercise[b]	12-13 RPE	20 min	↑ intensity to 14-16 RPE
Strengthening exercise *Five exercises for the lower extremities*[c] *Three exercises for the upper extremities*[d] *One exercise for truncus*[e]	Three sets of 12-15 reps	30-45 min	↑ weight to three sets of 10-12 reps
Stretching *Three muscle groups of the lower extremities*[f]	30 sec static	5 min	-
Physical activity. four times per week			
Preference of the participant	12-13 RPE	30 min. at least for 10 continuous min	14-16 RPE A possibility, but not standard

[a]*RPE, Rate of Perceived Exertion; Reps, repetitions.*

[b]*Aerobic exercise: If not possible to do aerobic exercise for 20 min on the stationary bike during the supervised session, the progression is an increase in total time (up to 20 min).*

[c]*Knee extension in sitting position, knee flexion in standing position, hip extension in prone position, toe raising in standing position, knee bent OR raise from chair.*

[d]*Arm lift in frontal plane OR circulation of shoulders in standing position, elbow extension in supine position and elbow flexion in standing or sitting position.*

[e]*Static in supine with knees bent OR supine position with knee bent and lift of foot with press from opposite hand.*

[f]*Femoral muscles (standing position), hamstring muscles (standing or sitting position), calf muscles (standing in front of wall).*

Appendix IV – Literature search strategy

Appendix IV.
Search strategy in PubMed and EMBASE to the literature search in the field of multiple myeloma and exercise.

<table>
<tr><th colspan="4">PubMed</th></tr>
<tr><th>Search terms for the multiple myeloma population</th><th>Antal hits</th><th>Search terms for the exercise focus</th><th>Antal hits</th></tr>
<tr><td>Multiple myeloma[Mesh] OR
Multiple myeloma*[Title/Abstract] OR
Plasma cell myeloma*[Title/Abstract] OR
Myelomatosis[Title/Abstract] OR
Myelomatoses[Title/Abstract] OR
Kahler disease*[Title/Abstract] OR
Myeloma-multiple*[Title/Abstract]</td><td>50077</td><td>Exercise [Mesh] OR
Exercise[Title/Abstract] OR
Exercises[Title/Abstract] OR
Physical activity[Title/Abstract] OR
Physical activities[Title/Abstract] OR
Physical exercise[Title/Abstract] OR
Physical exercises[Title/Abstract] OR
Exercise training*[Title/Abstract] OR
Gymnastic[Title/Abstract] OR
Circuit based exercise*[Title/Abstract] OR
Endurance training*[Title/Abstract] OR
High intensity interval training*[Title/Abstract] OR
Resistance training*[Title/Abstract] OR
Strength training*[Title/Abstract] OR
Exercise therapy [Mesh] OR
Exercise therapy[Title/Abstract] OR
Exercise therapies[Title/Abstract] OR
Synonyms derived from MeSH Terms
Remedial exercise*[Title/Abstract] OR
Rehabilitation exercise*[Title/Abstract]</td><td>472980</td></tr>
<tr><td colspan="4">”Population” (n=50077) AND ”exercise focus” (n=472980)
and limited to publication date back to 01.01.1989
↓
121 hits

Based on title/abstract</td></tr>
</table>

Appendix IV, continued…

EMBASE			
Search terms for the multiple myeloma population	**Antal hits**	**Search terms for the exercise focus**	**Antal hits**
Multiple myeloma		Exercise OR Aerobic exercise OR Circuit training OR Closed kinetic chain exercise OR Dynamic exercise OR Endurance training OR Exercise intensity OR High intensity interval training OR Muscle exercise OR Open kinetic chain exercise OR Resistance training OR Static exercise Kinesiotherapy	295482
”Population” (n=) AND ”exercise focus” (n=295482) and limited to publication date back to 01.01.1988 ↓ **186 hits**			

Appendix V – Overview of the results from literature search

Appendix V. *Overview of original studies and reviews identified by the literature search on exercise in patients with multiple myeloma*

ORIGINAL STUDIES

Author and year of publication	Focus of interest Design	Study population (n) Time point of investigation	Overall conclusion
Coleman et al. 2003 (78)	Exercise adherence. Pilot/feasibility.	N=24 During treatment.	Contributions to successful implementation: Flexibility of prescriptions, simplicity of the exercise equipment, and frequent encouragement from health care professionals.
Coleman et al. 2003 (66)	Feasibility. Effect on fatigue, mood, and sleep.	N=24 During treatment.	Feasible. May be effective.
Coon et al. 2004 (76)	Facilitators and barriers.	N=21 During treatment.	Facilitators: Belief in the benefit of exercise, personal commitment, desire to help themselves, prophylactic Epoetin alfa, and advice. Barriers: Symptoms and complications, and receiving chemotherapy. Environment and pain were both facilitators and barriers.
Jones et al. 2004 (61)	Association between exercise and QoL. Survey. Retrospective design.	N=156 After treatment, but retrospectively asked about three periods; pre-diagnosis, during and after.	The more exercise, the higher QoL. Low percentage of patients are exercising during and after treatment.
Coon et al. 2004 (72)	Feelings, beliefs, and experiences regarding adherence to an exercise program. Qualitative naturalistic (constructionist).	N=21 During treatment.	Beliefs, social context and experience influenced the adherence.
Jones et al. 2006 (74)	Determinants for exercise intentions. Cross-sectional survey.	N=70 After treatment.	Attitude and perceived behavioral Control correlated with exercise intentions.
Coleman et al. 2008 (67)	Effect related to stem cell collection transfusion, recovery, and response Randomized controlled trial.	N=120 During treatment.	Reduction in number of transfusions and in number of attempts at stem cell collection.
Coleman et al. 2012 (68)	Effect on fatigue, sleep, and physical performance. Randomized, controlled trial.	N=187 During treatment.	No/minimal effect in fatigue, insomnia, and physical performance.

Appendix X, continued…

Author and year of publication	Focus of interest Design	Study population (n) Time point of investigation	Overall conclusion
Craike et al. 2013 (62)	Barriers. Cross-sectional study, based on The Australian Myeloma Impact Survey.	N=229 During treatment.	Strongest barrier was fatigue (37.8 %), Other barriers were injuries, pain, other health conditions, age-related decline in physical ability, lack of knowledge about safe physical activity, lack of confidence in physical ability, fear or injury, and interpersonal factors (costs, exercising alone, lack of time).
Groeneveldt et al. 2013 (69)	Feasibility. Safety. Effect. Single-arm study.	N=37 After treatment.	Exercise was feasible and safe. High attendance and adherence. Beneficial effects in QoL, fatigue, and muscle strength.
Craike et al. 2013 (71)	Benefits and barriers. Qualitative study.	N=24 After treatment.	Benefits: Symptom control, recovery, psychological benefits. Barriers: Diseaese-related symptoms, treatment-related side effects, and low self-motivation.
Hung et al. 2014 (79)	Impact of exercise (and nutrition) counselling. Randomized, controlled trial.	N=37 (mixed diagnoses) After treatment (at discharge).	Effect regarding avoiding weigth loss and improvement in QoL.
Shallwani et al. 2015 (75)	Compliance and non-compliance. Retrospective study.	N=41 During treatment,	High compliance was associated with improvements in fatigue Non-compliance: History of pathological fracture, spinal cord compression, radiation.
Bartels et al. 2015 (80)	Feasibility and safety. Single-center prospective longitudinal feasibility study.	N=25 (mixed diagnoses) During and after treatment.	Feasible and safe.
Craike et al. 2017 (73)	Physcial activity preferences. Role of clinicians. Qualitative study.	N=24 After treatment.	Low- to moderate-intensity after treatment Flexible programs need to be flexible, concerning individual preferences, functional status, and treatment schedules.
Persoon et al. 2017 (70)	Effect. Multicenter randomized controlled trial.	N=109 After treatment.	No significant beneficial effects.
Persoon et al. 2018 (77)	Process evaluation.	N=109 After treatment.	Satisfactory implementation. Exercise in local physiotherapy practice was possible. Patient and physiotherapist were satisfied with the intervention. Dose was adequate for a part of the exercise, and unknown in another part. Must be addressed in future research.

Appendix X, continued…

Author and year of publication	Focus of interest Design	Study population (n) Time point of investigation	Overall conclusion
Servadio et al. 2019 (81)	Association with QoL.	N=175 After treatment.	Physcial active had better QoL, lower fatigue, and fewer treatment-relatede side effects. No association with psychological symptoms.
van Dongen et al. 2019 (82)	Long-term effectiveness and cost-effectiveness. Randomized controlled trial.	N=109 After treatment	No effect on physical fitness and fatigue. Not cost-effective from a societal perspective.

REVIEWS

Author and year of publication	Focus of interest Type of review.	Included studies (n) Time point of literature search	Overall conclusion
Smith et al. 2015 (64)	Knowledge of physical activity in all stages of multiple myeloma. Map the literature. Future research directions. Scoping review.	14 papers included Two of them in smoldering myeloma.	Literature is limited. The role of physical activity in disease prevention of/transition to multiple myeloma. Gender and treatment specific physical activity interventions. More randomized controlled trials evaluating type and dose of physical activity in different health parameters.
Gan et al. 2016 (65)	Quantitative and qualitative evidence. Methodological quality of studies. Literature review.	7 papers included. Two of them in smoldering myeloma. Search period was January 1998 to July 2013.	Potential improvement in physiological, psychological, physical, exercise performance outcomes, and QoL. Safe and feasible. True efficacy unclear. Weak methodological quality.

Appendix VI – Structured assessment of the bones

	EMMY Exercise in Multiple Myeloma	Hæmatologisk Afd. Roskilde Sygehus
Projektnr. 15-000068	Pt.id.nr. (påføres af projektleder)	Label

Vurdering af knoglepåvirkning hos patienter, som har samtykket til deltagelse/registrering i EMMY studie

Der sættes kryds i ja i "Betydning for træning", hvis ét af nedenstående følgende kriterier for det enkelte site er opfyldt. **Ved tvivl** om tolkning konfereres telefonisk med Niels Abildgaard, **mobil 23 22 15 84 / 23 30 45 85**	
Rørknogler	• Moderat **eller** funktionel smerte og med påvist/mistænkt osteolyse/destruktion/fraktur • Osteolyse med size >2/3 **eller** cortical udtynding uanset om den er med eller uden smerte • Osteolyse med size 1/3 – 2/3 med smerte, men uanset grad af smerte • Fraktur uanset om den er med eller uden smerte
Pelvis	• Osteolyse >2 cm i acetabulum loft **eller** >1/3 i rami • Fraktur
Columna/costae	• Frisk sammenfald/fraktur **eller** sammenfald/fraktur af ukendt alder med smerte

Site		**Pain** **Hvis ja, hvilken grad**		**Osteolyse** **Hvis ja, hvilken størrelse**		**Betydning for træning**
Femur	Højre	□ nej □ ja	□ milde □ moderate □ funktionelle	□ nej □ ja	□ < 1/3 □ 1/3 – 2/3 □ >2/3 □ cortical udtynding □ fraktur	□ nej □ ja
	Venstre	□ nej □ ja	□ milde □ moderate □ funktionelle	□ nej □ ja	□ < 1/3 □ 1/3 – 2/3 □ >2/3 □ cortical udtynding □ fraktur	□ nej □ ja
Humerus	Højre	□ nej □ ja	□ milde □ moderate □ funktionelle	□ nej □ ja	□ < 1/3 □ 1/3 – 2/3 □ >2/3 □ cortical udtynding □ fraktur	□ nej □ ja
	Venstre	□ nej □ ja	□ milde □ moderate □ funktionelle	□ nej □ ja	□ < 1/3 □ 1/3 – 2/3 □ >2/3□ cortical udtynding □ fraktur	□ nej □ ja
Pelvis		□ nej □ ja	□ milde □ moderate □ funktionelle	□ nej □ ja	□ små, usikre osteolyser □ >2 cm osteolyser i acetabulum loftet □ >1/3 i rami □ fraktur	□ nej □ ja
Thoracal columna og/eller costae		□ nej □ ja	□ milde □ moderate □ funktionelle	□ nej □ ja	□ mistanke om nylig sammenfald (<6 uger) □ vertebrale osteolyser □ costafraktur □ sternumfraktur	□ nej □ ja
Lumbal columna		□ nej □ ja	□ milde □ moderate □ funktionelle	□ nej □ ja	□ mistanke om nylig sammenfald (<6 uger) □ sammenfald ukendt alder □ osteolyser	□ nej □ ja

□ **Patienten har ingen knoglepåvirkning og dermed ingen begrænsninger ift. træning**

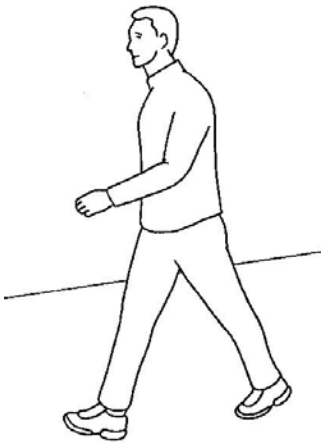
Appendix VII – Example of an exercise program

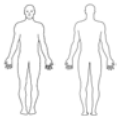
Køge

Example of the exercise program

Af: Rikke Faebo Larsen

No image



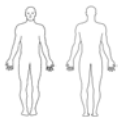


1. OPVARMNING, gang

Gå med halvlange skridt.

1: Intensity: 50 %, Time: 0 Sec

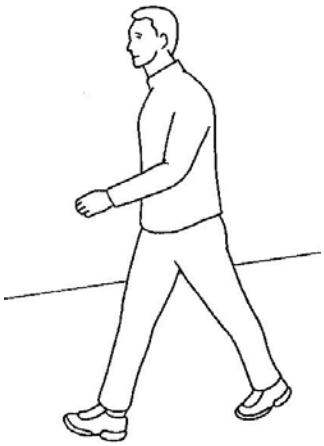
2: Intensitet: Svagt forpustet. Flydende samtale.

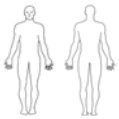


2. OPVARMNING, kondicykel

1: Intensity: 50 %, Time: 0 Sec

2: Intensitet: Svagt forpustet. Flydende samtale





3. KONDITION, gang

Gå med halvlange skridt.

1: Intensity: 50 %, Time: 0 Sec

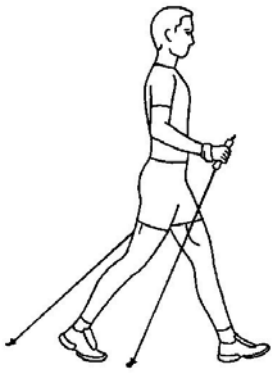
2: Intensitet: Lettere fopustet. Kan samtale

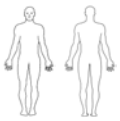
Køge

Example of the exercise program

Af: Rikke Faebo Larsen

No image



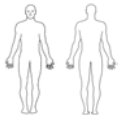


4. KONDITION, stavgang.

Gå fremad med strakt, let foroverbøjet ryg og lave afslappede skuldre. Hold armene indtil kroppen og hold løst fat om stavene. Sving armene skiftevis frem og tilbage. Stavene sættes i jorden på højde med hælen på den modsatte fod og skal pege skråt bagud under hele armbevægelsen. Læg pres på staven indtil hånden er bag kroppens midterlinje. Gå med lette og lange skridt. Find dit eget tempo og rytme. Ved hjælp af stavene får du en god gangrytme og en bedre holdning.

1: Intensity: 50 %, Time: 0 Sec

2: Intensitet: Lettere forpustet. Kan samtale.



5. KONDITION, cykle

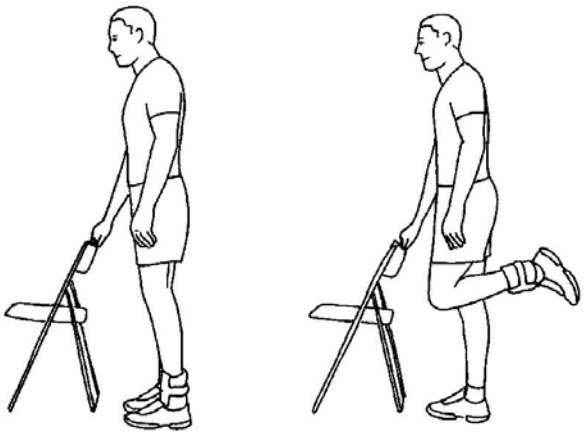
Intensitet: Lettere forpustet. Kan samtale.

6. STYRKE. Siddende knæstrækning med vægtmanchet

Sid på en stol med ret ryg og en vægtmanchet rundt om ankelen.
Stræk ud i knæet.
Sænk langsomt ned igen.
Hold ryggen ret.

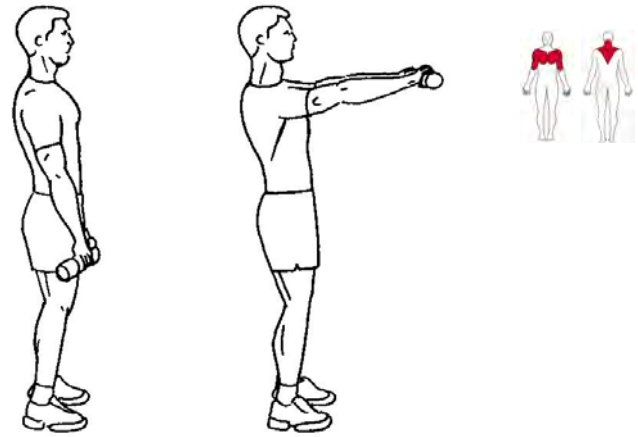
Antal kg pr. ben: , Antal sæt: , Antal gentagelser:

No image



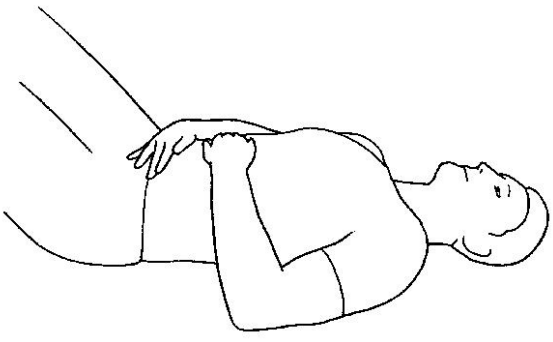
7. STYRKE. Knæbøjning med vægtmanchet

Stå støttet til en stol og hav en vægtmanchet rundt om anklen på det ene ben.
Bøj i knæet og før foden op mod bagdelen.
Sænk foden roligt ned igen.
Stå uden at holde, hvis du kan.
Antal kg pr. ben: , Antal sæt: , Antal gentagelser:



8. STYRKE, løft af strakt arm (med håndvægte)

Stå med en håndvægt i den ene hånd.
Løft armen frem foran kroppen.
Du kan enten skifte hånd mellem hvert løft eller efter 1 sæt.
I alt skal der tages 3 sæt med hver arm.
Antal kg. pr. hånd: , Antal sæt: , Antal gentagelser pr. arm:



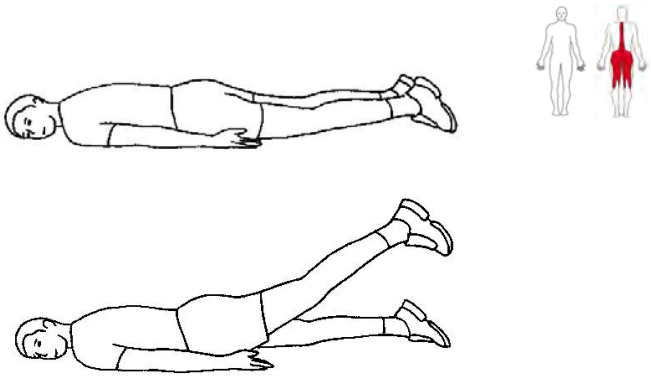
9. STYRKE, selvspænding af mave- og rygmuskler

Lig på ryggen med lænden i gulvet, placér hænderne på maven, én over og én under navlen.
Træk den nederste del af maven 1 -2 cm ind mod rygsøjlen, uden at den øverste hånd bevæger sig.
Knib i bækkenbunden samtidig.
Antal sæt: , Antal gentagelser:

No image

10. STYRKE, mave

Lig på ryggen med bøjede ben.
Lænden skal holdes fladt i gulvet.
Knib i bækkenbunden.
Løft det ene ben og før knæet til modsatte hånd.
Pres hånd og knæ let mod hinanden og hold samtidig stillingen i ryg og bækken.
Kom roligt tilbage til udgangsstillingen.
Antal sæt: , Antal gentagelser: , Antal sekunder hvor stillingen holdes:



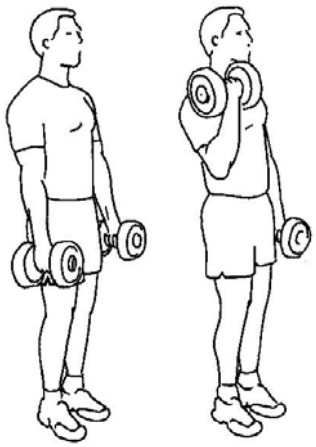
11. STYRKE, Maveliggende etbensløft

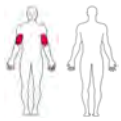
Lig på maven.
Løft benene skiftevis op mod loftet.
Antal sæt: , Antal gentagelser pr. ben:

12. STYRKE, liggende albuestrækning (med én håndvægt)

Lig på ryggen med håndvægt i den ene hånd og 90 graders bøj i skulder og albue.
Stræk ud i albuen til armen bliver strakt og peger lige op mod loftet.
Bøj i albuen og sænk langsomt tilbage til udgangsstillingen.
Skift til modsat hånd efter 1 sæt.
Ialt skal der tages 3 sæt med hver arm.
Antal kg: , Antal sæt: , Antal gentagelser:

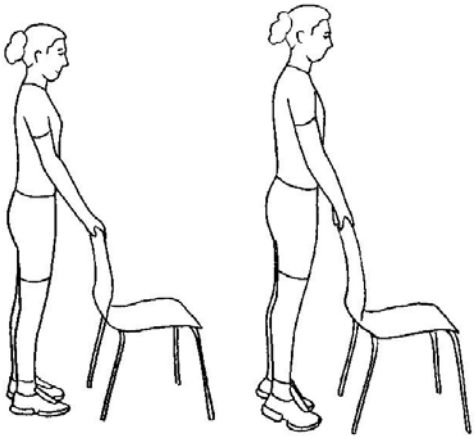
No image

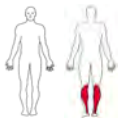




13. STYRKE,stående albuebøjning (med håndvægte)

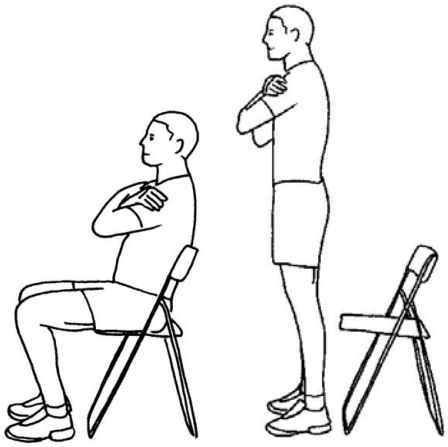
Stå med håndvægten hængende ned langs siden.
Bøj i albuen og løft håndvægten helt op mod brystet samtidig med at du drejer den udad.
Du kan enten skifte hånd mellem hvert løft eller efter 1 sæt.
I alt skal der tages 3 sæt med hver arm.
Antal kg pr. hånd: , Antal sæt: , Antal gentagelser pr. arm:

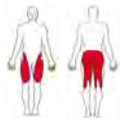




14. STYRKE, tåhævning (med støtte)

Stå bag en stol og støt med hænderne på stoleryggen.
Gå op på tæerne med begge ben.
Hælene skal hæves fra underlaget.
Sænk roligt tilbage til stående stilling igen.
Antal sæt: , Antal gentagelser:

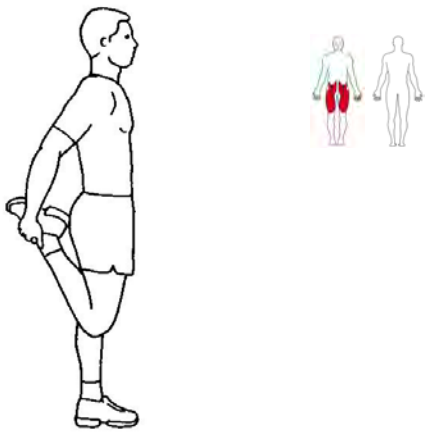




15. STYRKE, rejse sig (uden armlæn)

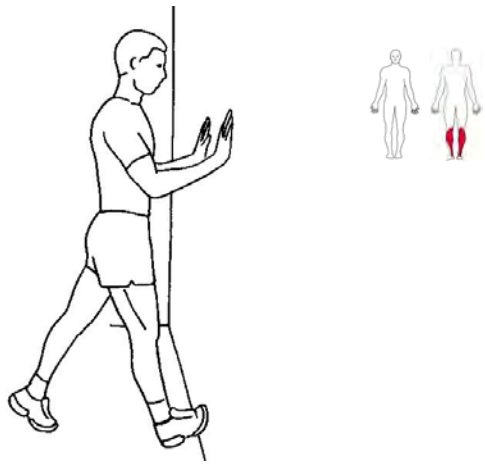
Sid på en stol med armene over kors foran brystet.
Rejs dig op til stående.
Antal sæt: , Antal gentagelser:

No image



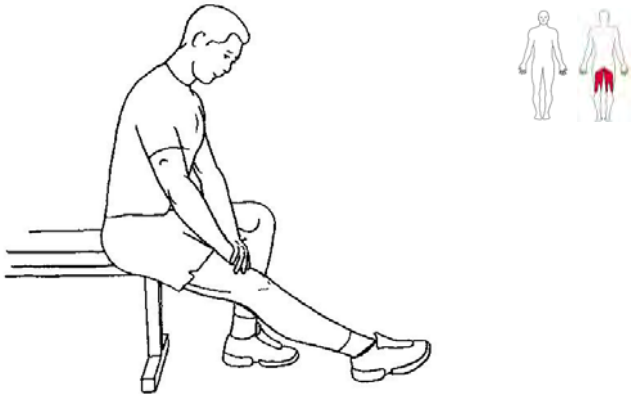
16. UDSPÆNDING, forside af lår og hofte

Stå med strakt krop. Fat den ene ankel og træk hælen mod balden. Pres hoften frem til der mærkes et stræk på forsiden af låret. Sørg for at holde knæene samlet. Hold 30 sek. og byt ben.



17. UDSPÆNDING, læg

Støt dig mod væggen og placer den ene fodsål op mod væggen med hælen i gulvet. Benet skal være strakt. Pres hoften roligt frem til der mærkes et stræk på bagside af underbenet. Hold 30 sek. og byt ben.



18. UDSPÆNDING, lårets bagside

Sid på kanten af en bænk og stræk det ene ben med foden vippet opad.. Placer hænderne over knæet og pres forsigtigt ned således at knæet strækkes helt. Eventuelt kan overkroppen lænes frem for at skabe ekstra stræk, men ryggen skal holdes ret. Hold 30 sek. og byt ben.

Appendix VIII – Exercise diary

TRÆNINGSDAGBOG

Sådan udfylder du træningsdagbogen.

Planlagte træningsdage

Du har aftalt med fysioterapeuten hvilke dage du skal træne – og om det er træningsprogrammet eller om det er at være fysisk aktiv.
De aftalte dage er markeret med et kryds (X).
Hvis det er træningsprogrammet du skal lave, udfylder du de blå felter.
Hvis det er at være fysisk aktiv, udfylder du de lilla felter.

Hvor meget af den planlagte træning / Hvor meget af den planlagte fysiske aktivitet?

Der skal kun sættes kryds ved én smiley.

□ ☺ *helt program*
□ 😐 *delvist program*
□ ☹ *intet program*

Hvordan?

Dvs. hvor meget træning / fysisk aktivitet af gangen?

□ *Opdelt* - *sæt X her, hvis du har delt træningen eller aktiviteten op i løbet af dagen*
□ *Ikke opdelt* - *sæt X her, hvis du har udført træningen eller aktiviteten på én gang*

Afvigelser fra dagens træning eller aktivitet

Her kan du notere, hvis der for eksempel er nogle øvelser, du ikke har kunnet lave, eller hvis du for eksempel har lavet færre gentagelser end planlagt eller træningen på andre måder har været anderledes end det planlagte. Du skal også notere, hvis du slet ikke har trænet eller været fysisk aktiv

Begrundelse for afvigelse

Hvis du har skrevet afvigelser ned, så skriv begrundelsen her. Det kunne for eksempel være, at du blev utilpas undervejs, var øm eller fik smerter, eller hvad der nu kan være årsagen til, at det ikke blev helt som planlagt.

Øvrige bemærkninger

Her kan du skrive generelle kommentarer, for eksempel at du blev træt efter træningen, fik mere energi, fik forbedring eller forværring af bivirkninger eller hvad der ellers har præget din træning eller din dag.

TRÆNINGSDAGBOG

Pt.id.nr.:		**Navn:** **Cpr.nr.:**						
HJEMME-TRÆNING	**UGE** **DATO**	**MANDAG** **/**	**TIRSDAG** **/**	**ONSDAG** **/**	**TORSDAG** **/**	**FREDAG** **/**	**LØRDAG** **/**	**SØNDAG** **/**
Trænings-program	**Planlagte træningsdage**							
	Hvor meget af den planlagte træning? ☺ *helt program* 😐 *delvist program* ☹ *intet program*	□ ☺ □ 😐 □ ☹	□ ☺ □ 😐 □ ☹	□ ☺ □ 😐 □ ☹	□ ☺ □ 😐 □ ☹	□ ☺ □ 😐 □ ☹	□ ☺ □ 😐 □ ☹	□ ☺ □ 😐 □ ☹
	Hvordan?	□ *Opdelt* □ *Ikke opdelt*	□ *Opdelt* □ *Ikke opdelt*	□ *Opdelt* □ *Ikke opdelt*	□ *Opdelt* □ *Ikke opdelt*	□ *Opdelt* □ *Ikke opdelt*	□ *Opdelt* □ *Ikke opdelt*	□ *Opdelt* □ *Ikke opdelt*
Fysisk Aktivitet	**Planlagte dage for fysisk aktivitet**							
	Hvor meget af den plan-lagte fysiske aktivitet? ☺ *mindst 30 min i alt* 😐 *10 min til maks. 30 min* ☹ *mindre end 10 min*	□ ☺ □ 😐 □ ☹	□ ☺ □ 😐 □ ☹	□ ☺ □ 😐 □ ☹	□ ☺ □ 😐 □ ☹	□ ☺ □ 😐 □ ☹	□ ☺ □ 😐 □ ☹	□ ☺ □ 😐 □ ☹
	Hvordan?	□ *Opdelt* □ *Ikke opdelt*	□ *Opdelt* □ *Ikke opdelt*	□ *Opdelt* □ *Ikke opdelt*	□ *Opdelt* □ *Ikke opdelt*	□ *Opdelt* □ *Ikke opdelt*	□ *Opdelt* □ *Ikke opdelt*	□ *Opdelt* □ *Ikke opdelt*
Afvigelser fra dagens træning eller aktivitet								
Begrundelse for afvigelse fra dagens træning eller aktivitet								
Øvrige bemærkninger								