Fontys Paramedic University of Applied Sciences

Programme Physiotherapy

"Is strength training superior to hormone replacement therapy to increase the bone mineral density in postmenopausal women?"

A Systematic Literature Review

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Bachelor Thesis*
*Version: 1.0

Preface

Writing the current literature review was the final step to finish the bachelor program of physiotherapy at the Fontys Paramedic University of Applied Sciences in Eindhoven. The preparation for this thesis began in July 2013. First, the university handed out a list with different topics and students had to apply for three topics of their choice. One of the topics I choose for was about strength training and physiology of aging. I was interested in this topic because during my study we had the topic strength training and physiology of aging, but there was little information about the relation between aging and strength training. Therefore I wanted to deepen my knowledge about this topic. In my opinion it is a topic, which is relevant for physiotherapy practice because as a physical therapist you have to know, which effects strength training has on the aging process. After I was allocated to this topic I was looking up my notes from my studies, to come up with a research question. In the last year of my studies one of the topics was about postmenopausal women and bone loss. I read in an article that strength training increases bone mineral density and therefore I wanted to figure out if strength training would be an effective treatment tool to stop bone density loss in postmenopausal women. As a co-intervention I choose hormone replacement therapy, because it is the most common treatment tool against bone density loss in postmenopausal females. Finally I made up the following research question: "Is strength training superior to hormone replacement therapy to increase the bone mineral density in postmenopausal women?" In the current literature review I gave my best to answer the current research question.

The last years, as a student were an amazing time for me. I got to know a lot of people and places during my study time and internships. The English stream and especially my class were like a family and therefore I wanted to thank them for this great time. Further I wanted to thank my family to support me to do this study. Last but not least, I thank my supervisor Anke Lahaije and classmates Jane Tammearu, Cedrik Hollmann, Domenica Zink and Paul Herzeg for the help and feedback they provided during this literature review.

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Summary

Introduction. Postmenopausal osteoporosis leads to millions of fractures annually, which are considered with high morbidity and mortality. To prevent postmenopausal bone loss, hormone replacement therapy is prescribed. Nowadays, it is known that this medication can have side effects and is no long-term treatment tool against bone loss. Thus, conservative treatment methods against bone breakdown are needed. It is known that a major stress to bone can stimulate bone formation and therefore strength training seems to be an alternative treatment tool. The aim of this literature review is to find out if strength training would be a favourable treatment tool compared to hormone replacement therapy to increase the bone mineral density in postmenopausal women.

Research question. "Is strength training superior to hormone replacement therapy to increase the bone mineral density in postmenopausal women?"

Method. Prior to literature search a search string was made and therefore the most relevant keywords were postmenopausal women, strength training, hormonal replacement therapy and bone mineral density. Included were full text randomized controlled trials published in English. Relevant articles were identified on databases such as PubMed, CINAHL and Science Direct. For methodological quality assessment the PEDro scale was used and a best evidence synthesis was done to define the level of evidence.

Results. The results were based on four low quality randomized controlled trials. A total amount of 204 postmenopausal women were divided into strength training or hormonal replacement therapy groups. The focus was laying on the strength training group. Bone mineral density was measured at the lumbar spine, hip and femur by dual-energy X-ray absorptiometry or computed tomography scans. Measurements were taken at the baseline and after 12 months.

Conclusion. There were indicative findings that strength training was superior to hormonal replacement therapy to increase the bone mineral density at the greater trochanter in postmenopausal women. Further no evidence was found that ST was superior to HRT to increase bone mineral density in postmenopausal females.

Key words. Postmenopausal women, strength training, hormone replacement therapy, bone mineral density

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Introduction

According to the National Osteoporosis Foundation (NOF), Osteoporosis (OP) means "porous bone" and is a disease[1] caused by increased bone breakdown[2] resulting in loss of bone density.[1, 2] Therefore the bone becomes weak and the risk to have a fracture is higher.[3] The cause of increased bone breakdown is mostly related to the natural process of aging.[3] In general more women than men have fractures caused by OP[4] and predominantly postmenopausal females are affected.[3] Postmenopausal OP is caused by estrogen deficiency, leading to an imbalance between bone break-down and bone formation, resulting in bone loss.[4]

In Europe, the United States and Japan, OP affects around 75 million people resulting in 8.9 million fractures per year.[5] Bone fractures caused by OP, cost the world wide health care systems around 19 billion dollars per year.[6] Due to a rise in the elderly population[7] experts predict that by 2025 the costs will rise to 25.3 billion dollars.[6] Not only do these fractures burden the health care systems, but they can have a negative impact on the individual person sustaining the fracture.[2] Particularly hip[1,3] and spine[3] fractures are associated with high morbidity and mortality in postmenopausal women.[3] According to the NOF, 24 percent of the amount of patients over 50, who had a hip fracture, died within a year following the fracture and 50 percent never regained full function again.[1] In many cases OP is not detected beforehand, but is diagnosed after a person suffered from a bone fracture.[6] These fractures can occur from minimal trauma such as bumping into furniture or even by movements without external influences.[6] Another problem is that bone loss is irreversible,[1] but there is the possibility to prevent or slow down further degeneration by early diagnosis and adequate treatment.[2] To prevent the risk of fractures as much as possible, the Clinical Guideline for OP recommends that all postmenopausal women should be screened for OP.[2] Assessment of bone mineral density (BMD) could be done by dual-energy X-ray absorptiometry (DXA) or computed tomography (CT) scans.[8] DXA is the golden standard and is commonly used in the clinical environment.[8] After measurements are done, the outcome of the BMD of the patient is compared to a reference measurement, which is defined by the world health organization (WHO).[2] OP is diagnosed if the BMD of the patient is equal to or higher than 2.5 standard deviation below the reference norm.[9]

Common sites of the body to establish the likelihood of OP are the spine,[2,7,10] hip[2,7] and femur.[10] To prevent bone loss and the risk of fractures, hormonal replacement therapy (HRT) is a common treatment tool prescribed to postmenopausal women.[11] Medication often consists of estrogen and progesteron supplements, which are delivered orally or non orally.[11] A randomized controlled trial (RCT) from the "Women´s Health Initiative" found that estrogen plus progestin increased BMD in postmenopausal women and hence reduced fracture risk.[12] Benefits of HRT besides the fact that it protects bone loss, are reduction of menopausal symptoms such as hot flushes and vaginal dryness.[11] The use of HRT is not recommended to women over the age of 60[13] and the NOF recommends to keep the dosage as low as possible,[2] since the use of HRT increases the risk of cancer, venous thrombo-embolism and strokes.[13] Moreover the NOF states that HRT has no long-term effect in protection of bone loss.[2] Therefore, it is important to offer women with higher risks of fractures alternative treatment methods, once HRT cannot be continued.[2]

It is assumed that strength training (ST) is beneficial for bone development and maintenance.[2] Stress to bone by increased load over time activates bone remodeling and therefore the bone mass becomes thicker and stronger to resist the load.[2,14] A RCT done by Wallace et al. (2000) concluded, that ST seemed to be most suitable to strengthen the skeleton and therefore reduced the risks of fractures.[15] As reported in two other previous studies, both done by Kohrt et al. (1995,1998), the combined effects of HRT and weight bearing exercises showed beneficial effects on bone mineral density in postmenopausal females.[16,17] Nevertheless HRT seems to bear health risks for postmenopausal females.[13] As HRT involves health risks[13] and has no long term effect on bone strength,[2] it is important to know for the future, if ST is a better choice of treatment compared to HRT. This leads to the following research question: “Is strength training superior to hormone replacement therapy to increase the bone mineral density of postmenopausal women?”

Furthermore in the current literature review following sub questions are included “Does strength training increase bone mineral density in postmenopausal women?” and “Does hormone replacement therapy increase bone mineral density in postmenopausal women?” If there is a favourable outcome for ST, it could push physiotherapists to offer ST programmes to postmenopausal women, in order to increase BMD, thus lowering health care costs in the end.

Method

Databases and Search Strategy

The search for this literature review was performed from November 2013 till April 2014. Research was done in databases PubMed, CINAHL and Science Direct. Literature was searched by search terms and/or search strings (appendix I). This search strategy was first developed for PubMed and adapted for CINAHL and Science Direct. Search terms were combined by boolean operator (and/or). Moreover search filters were activated to narrow the search. In PubMed the search filters were activated to RCT, female subjects, full text, humans and middle aged or older than 45. In CINAHL additional search options were limited to full text, RCT, middle aged and female. In Science Direct search options were limited to journals and only topics, which were relevant to the inclusion criteria (BMD, patient, physical activity, postmenopausal women, bone mass, bone mineral, HRT, osteoporosis, bone loss, woman, bone density, femoral neck, exercise, replacement therapy, bone health, and exercise program) were chosen. Before literature search started inclusion and exclusion criteria were formulated (table 1).

Table 1. Inclusion and exclusion criteria

Inclusion criteria	***Exclusion criteria***
● RCT´s, which compare ST and HRT conducted in postmenopausal females measured on BMD ● Participants included were healthy (except from including low bone density and OP) postmenopausal females ● Therapy should be provided to a group of more than two participants ● BMD has to be measured with DXA or CT ● Articles published in English ● RCT´s available with full text	● Studies with only the abstract available ● Studies conducted in postmenopausal women having a disease (except from including low bone density and OP) ● Studies, which have not been done on humans ● Studies, which have not been done on postmenopausal women ● Studies, which are not measuring BMD
RCT's=randomized controlled trials, ST= strength training, HRT=hormonal replacement therapy, BMD=bone mineral density, OP=osteoporosis, DXA=dual energy X-ray absorptiometry, CT=computed tomography	

Literature Search

Study selection included following steps: (I) Screened the title, (II) Read the abstracts, (III) Read full text articles (IV) Searched by references listed in included full text articles (snowball method). Both the inclusion and exclusion criteria were applied during the whole literature search. If articles could not be accessed in the above-mentioned databases, Bieb.nu and Google Scholar were used to get the full text studies.

Collection of Data and Quality Assessment

After collecting literature, which passed the upper mentioned steps, the methodological quality of the included studies were assessed by using the PEDro scale[18] The scale consisted of 11 questions, which were answered with "yes" or "no" depended if the criteria was satisfied or not. In this literature review, individual studies scored on the PEDro scale, were considered with nine till ten as "very good", six till eight as "good", four and five as "reasonably good" and zero till three as "poor" quality (table 2).[19]

Table 2. Methodological quality according to the Pedro scale[19]

Pedro score	***Methodological quality***
● 0-3 points ● 4-5 points ● 6-8 points ● 9-10 points	● Poor ● Reasonably good ● Good ● Very good

Method of Extraction

To extract the various data from the included articles a data extraction table (appendix II) was made. For the data extraction the study characteristics and study outcomes were assessed.

Best Evidence Synthesis

To summarize the evidence about the effectiveness of ST compared to HRT on the BMD in postmenopausal women, a best evidence synthesis (BES) was performed, based on the criteria adjusted by Steultjens et al. (2003).[20] No evidence was stated, when the total number of the included articles that showed evidence within the same category of methodological quality and study design was less than 50 percent.[20] In this literature review a P-value ($p \leq 0.05$) was considered as significant.
Furthermore classification was adjusted by the author in order to be able to use Steultjens et al. (2003).[20] Studies with a "very good" or "good" methodological quality were classified as "high quality" studies and articles with a "reasonably good" methodological quality as "low quality" studies. The level of evidence was classified according to Steultjens et al. (2003) [20] (table 3).

Table 3. Level of evidence[20]

Level of evidence	*Definition*
Strong evidence	● Consistent and statistically significant results measured in minimal two high quality RCT's
Moderate evidence	● Consistent and statistically significant results measured in minimal one high quality RCT and minimal one low quality RCT or high quality CCT
Limited evidence	● Statistically significant results measured in minimal one high RCT ● Consistent and statistically significant findings in outcome measures in minimal two high quality CCT´s
Indicative findings	● Statistically significant result or process measured in at least one high quality CCT or low quality RCT ● Consistent and statistically significant result or process measured in at least two OD's with sufficient quality
No or insufficient evidence	● All other studies, which do not met the upper mentioned points ● Conflicting results among RCT´s and CCT´s ● No eligible studies
RCT'(s)=randomized controlled trial(s), CCT'(s)=controlled clinical trial(s),OD's=other design studies	

Results

A total number of 518 articles were found after search filters were activated. Science Direct provided the most articles with a number of 197, followed by PubMed with 193 and CINAHL with 128. After titles were screened in the databases a total number of 18[16,17,21-36] articles were checked for the abstract. From these 18[16,17,21-36] articles, eight were found in Science Direct, six in PubMed , two in CINAHL and two by reference screening. Subsequently, 12 articles dropped out. Articles dropped out because they compared ST to control groups[21-25] or low-impact exercises[26] or home exercise groups[27] or untrained groups[28] or premenopausal women were included,[29,30] one study only combined ST with HRT[31] and in another study there was no relevant information of BMD.[32] Six articles were screened for the full text.[16,17,33-36] Finally a total number of four[33-36] were included, three[33,34,36] provided by PubMed and one[35] by Science Direct. Two articles,[16,17] found by reference screening were excluded because end results between the ST group and HRT group were not presented[16] or assignment to groups was not randomized.[17] Inclusion and exclusion criteria were applied within the whole search procedure (figure 1).

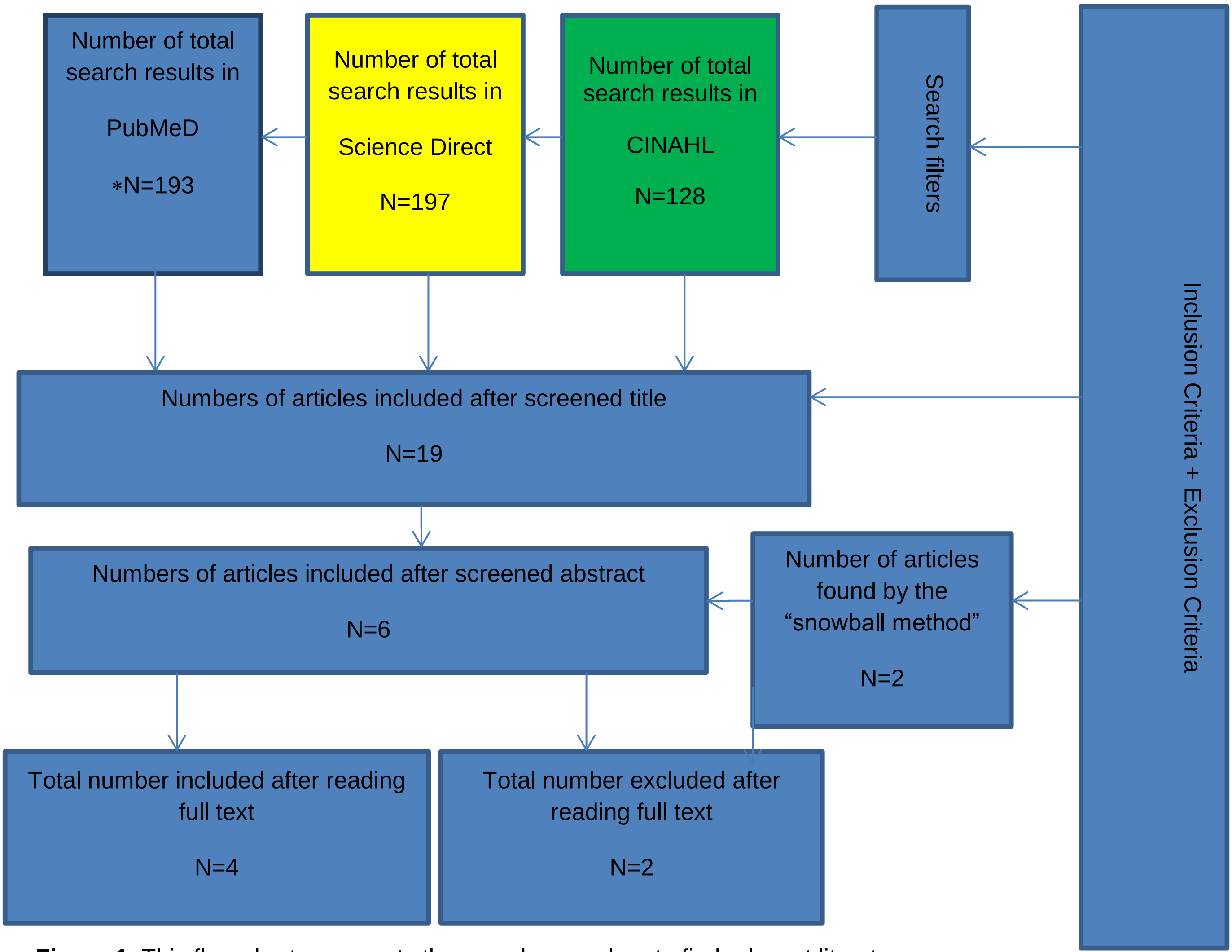

Figure 1. This flow chart represents the search procedure to find relevant literature

∗ N=number

To assess the methodological quality the Pedro scale was applied to the remaining four included articles.[33-36] The overall rating on the PEDro score of the articles is attached (appendix III). Three studies were a partial RCT[33,35,36] and one study was a full RCT.[34] One study received five points[33] and three studies scored four points.[34,35,36] All studies had a fair methodological quality and were classified as low quality studies.[33-36]

Data Extraction and Findings

The most relevant outcomes are summarized in tables, which show the study characteristics (table 4), study interventions (table 5) and study outcomes (table 6). Data were extracted from the data extraction tables (appendix III).

Table 4. Summarized study characteristics (studies were ordered according to their relevance or according to the alphabet of the surname of the first author)

Author and the year of study	Type of study/Pedro score	Average age of postmenopausal women in years	Number of postmenopausal women
Going et al. (2003)[33]	● RCT / 5	● 54-56	● ST: BL: N=91 / CS: N=71 ● HRT: BL: N=73 / CS.: N=65
Cheng et al. (2002)[34]	● RCT / 4	● 50-57	● ST: BL: N=20 / CS: N=12 ● HRT: BL: N=20 / CS: N=15
Maddalozzo et al. (2007)[35]	● RCT / 4	● 51-52	● ST: BL: N=35 / CS: N=29 ● HRT: BL: N+35 / CS: N=34
Milliken et al. (2003)[36]	● RCT / 4	● 54-57	● ST: BL: N=26 / CS: N=25 ● HRT: BL N=21 / CS: N=21

RCT=randomized controlled trial; ST=strength training; HRT=hormonal replacement therapy; BL=baseline; N=number; CS=completed study

Study Characteristics

All articles were RCT's with a fair methodological quality,[33-36] All women were in the middle age[37] between 50-57 years and passed their menopause.[33-36] There were significant differences ($p \leq 0.05$) at baseline in BMD[35] and age.[36] The number of participants ranged from 40 till 164 per study and the total number of subjects was 204.[33-36] The drop-out rate varied between zero and 20.[33-36]

Table 5. Summarized study interventions (studies were ordered according to their relevance or according to the alphabet of the surname of the first author)

Author and the year of study	Intervention protocol of ST group	Intervention protocol of HRT group
Going et al. (2003)[33]	● Duration: 12 months, 3 times a week ● Measurement at baseline and after 12 months ● Supervision: yes ● Warm up: stretching, balance and aerobic weight-bearing activities ● Working phase: leg press, squats, lat. pull downs, lat. rows, back extension, arm dumbbell presses and rotatory torso, 2 sets of 6-8 rep. of 70%-80% of 1RM ● Circuit training: moderate impact activities, stair climbing and step boxes with weight vests ● Adaptation of 1 RM every 6-8 weeks ● Cooling down: stretching, balance and ancillary resistance exercises	● Duration: 12 months ● Measurement at baseline and after 12 months ● HRT was prescribed by primary care providers, using estrogen or progesterone ● Calcium supplementation: 800mg per day for each participant (inclusion ST group) ● Participants used a log book for recording intake, complications and changes in relation to medication
Cheng et al. (2002)[34]	● Duration: 12 months, 2 times a week ● Measurement at baseline and after 12 months ● Supervision: yes ● Homework, 4 times a week ● Additional information: including circuit training and high-impact aerobic dance periods ● Warm up: 10 min., stretching activities ● Working phase: chest fly, lat. pull down, military press, seated down and biceps curl	● Duration: 12 months ● Measurement at baseline and after 12 months ● Medication: every participant got 1 tablet of estradiol and noretisterone acetate per day
Maddalozzo et al. (2007)[35]	● Duration: 12 months, 2 times a week ● Measurement at baseline and after 12 months ● Supervision: yes ● Warm up: 2 sets of 10-12 rep. at 50% of 1RM ● Working phase: squats and deadlifts, 3 sets of 60-75% of 1RM (set1= 8 rep., set2= 10 rep., set3= 12 rep.), ● Adaptation of 1 RM every 8 weeks ● Rest Phase: between sets = 60 sec. between sets ● Cooling down: 10 min. flexibility exercise	● Duration: 12 months ● Measurement at baseline and after 12 months ● Medication prescribed by physician ● Participants used a log book for recording intake, complications and changes in relation to medication
Milliken et al. (2003)[36]	● Duration: 12 months, 3 times of 75 min. each set ● Measurement at baseline and after 12 months	● Duration: 12 months ● Measurement at baseline and after 12 months

	● Supervision: yes ● Warm up: 20min. of aerobic weight-bearing activities ● Working phase: 35 min. of RT including leg press, squats, seated one- arm dumbbell presses, back extension, rotatory torso, seated rows, and lat. pull downs, 2 sets of 6-8 rep. at 70-80% of 1RM. ● Adaptation of 1 RM every 6 weeks Cooling down: 10 min. stretching	● Medication prescribed by physician and consists of different forms of estrogen ● Calcium supplementation: 800mg per day for each participant (inclusion ST group)

Lat=lateral, 1 RM=one repetition maximal, ST=strength training, HRT=hormone replacement therapy, RT=resistance training Rep=repetitions, Min=minutes, Mg=milligram, Sec=second,%=percent

Study Interventions

Relevant for this literature review was that studies were comparable because all had a total duration of 12 months and measurements of BMD were done at baseline and after 12 months.[33-36] Moreover the intervention protocol of the ST group had a similar structure.[33-36]

Table 6. Summarized study outcomes, (studies were ordered according to their relevance or according to the alphabet of the surname of the first author)

Author and the year of study	Measurement tool for BMD	Significant ($p \leq 0.05$) or not significant ($p>0.05$) changes from the baseline to month 12, ST group	Significant ($p \leq 0.05$) or not significant ($p>0.05$) changes from the baseline to month 12, HRT group	Significant ($p \leq 0.05$) different effects on BMD between ST and HRT groups
Going et al. (2003)[33]	● DXA outcomes expressed in g/cm^2	● Femoral neck: ns ● Greater trochanter: s ● Lumbar spine L2-L4: ns	● Femoral neck: ns ● Greater trochanter: ns ● Lumbar spine L2-L4: s	● Greater trochanter: ST > HRT
Cheng et al. (2002)[34]	● CT outcomes expressed in mg/cm^3	● Proximal femur: s ● Mid femur: ns	● Proximal femur: s ● Mid femur: ns	● NS
Maddalozzo et al. (2007)[35]	● DXA outcomes expressed in g/cm^2	● Lumbar spine L1-L4: s ● Greater trochanter: s ● Femoral neck: ns ● Total hip: ns	● Lumbar spine L1-L4: ns ● Greater trochanter: ns ● Femoral neck: ns ● Total hip: ns	● Lumbar spine: ST>HRT ● Greater trochanter ST>HRT
Milliken et al. (2003)[36]	● DXA outcomes expressed in g/cm^2	● Greater trochanter: ns ● Wards triangle: s ● Femoral neck: ns ● Lumbar spine: ns	● Trochanter: ns ● Wards triangle: s ● Femoral neck: s ● Lumbar spine: s	● Femoral neck: ST< HR ● Wards triangle: ST<HRT ● Lumbar spine: ST< HRT

g/cm^2=grams per square centimeter, mg/cm^3=milligrams to cubic centimeter, BMD=bone mineral density DXA=dual energy X-ray absorptiometry, CT=Computed tomography, ST=strength training, HRT=hormone replacement therapy, ns=not significant, s=significant

Best Evidence Synthesis

All articles had a fair methodological quality and therefore were classified by the author of this paper as low quality studies.[33-36] Thus, all studies were treated the same way in the BES.[33-36]

Evidence regarding Research Question. Two low quality studies stated that ST showed significant differences (p≤0.05) on BMD at the greater trochanter compared to HRT[33,35] and one low quality study did not found significant differences (p>0.05).[36] Therefore indicative findings existed that ST was superior to HRT to increase BMD at the greater trochanter in postmenopausal women.[33,35,36] One low quality study stated that ST showed significant differences (p≤0.05) in BMD at the lumbar spine compared to HRT[35] and two low quality studies did not found significant differences (p>0.05).[33,36] Thus, no evidence was stated, that ST was superior to HRT to increase BMD at the lumbar spine after 12 months training.[33,35,36] No significant differences (p>0.05) were found in BMD at the femoral neck,[33,35,36] proximal femur,[34] mid-femur,[34] total hip[35] or wards triangle[36] when ST was compared to HRT.[33-36] Following there was no evidence that ST was superior to HRT in the upper mentioned body regions. [33-36]

Evidence regarding Sub Questions. Two low quality studies stated that ST showed significant differences (p≤0.05) after 12 months on the greater trochanter,[33,35] while one low quality study did not.[36] Thus, there were indicative findings that ST was effective to increase BMD at the greater trochanter after 12 months training in postmenopausal women.[33,35,36] One low quality study found that ST showed significant differences (p≤0.05) after 12 months training at the lumbar spine,[35] while two low quality studies did not.[33,36] Thus, there was no evidence that ST was effective to increase BMD at the lumbar spine in postmenopausal women.[33,35,36] There were indicative findings that ST was effective to increase BMD at the proximal femur[34] and wards triangle.[36] No evidence was found that ST showed significant effects (p≤0.05) to increase BMD at the femoral neck,[33,35,36] mid femur[34] or total hip.[35] Two low quality studies stated that HRT showed significant effect (p≤0.05) on BMD at the lumbar spine,[33,36] while one low quality study did not.[35] There were indicative findings that HRT increased BMD at the lumbar spine in postmenopausal women.[33,35,36] One low quality study found that HRT had significant effects (p≤0.05) on BMD at the femoral neck,[36] whereas two low quality studies did not.[33,35] So therefore no evidence was stated that HRT increased BMD at the femoral neck in postmenopausal women.[33,35,36] Two studies respectively found that HRT showed significant differences (p≤0.05) on BMD at the proximal femur[34] and wards triangle.[36] Thus, there were indicative findings that HRT increased BMD at the proximal femur and wards triangle in postmenopausal women.[34,36] No evidence was found that HRT increased BMD at the greater trochanter,[33,35,36] mid femur[34] or total hip.[35]

Other Findings. One low quality study found that HRT showed significant (p≤0.05) better effect to increase BMD at the wards triangle than ST. [36] Therefore there were indicative findings that HRT was superior to ST to increase BMD at the wards triangle in postmenopausal females.[36] One low quality study found that HRT showed significant differences (p≤0.05) in BMD at the femoral neck and lumbar spine compared to ST.[36] While two low quality studies did not found significant differences (p>0.05) in BMD at the femoral neck or lumbar spine between groups.[33,35] Hence, there was no evidence stated that HRT was superior to increase BMD at the femoral neck or lumbar spine in postmenopausal women.[33,35,36]

Discussion

The aim of this study was to systematically review if ST was superior to HRT to increase BMD in postmenopausal women. After finishing the search procedure, four low quality RCT's were included.[33-36] Therefore in the BES all studies were equally treated.[33-36] To give an answer to the research question, by combining the results of each study the conclusion was as follow:

1) There were indicative findings that ST was superior to HRT to increase BMD at the greater trochanter in postmenopausal women.[33,35,36]
2) No evidence was stated, that ST was superior to HRT to increase BMD at the lumbar spine,[33,35,36] femoral neck,[33,35,36] proximal femur,[34] mid femur,[34] total hip[35] or wards triangle[36] in postmenopausal females.

All articles were classified as low quality studies and therefore treated equally in the current literature review.[34-36] However, there was one article, which scored higher on the PEDro scale[33] than the other studies.[34-36] As shown in the method of the studies, three articles were partially randomized.[33,35,36] Therefore it was discussable, if studies should been classified as RCT's.[33,35,36] Since randomization occurred within groups,[33,35,36] it was relevant enough for this literature review. The reason for partial randomization was that women already did or did not take HRT before they participated in the studies.[33,35,36] Thus, women who were in the HRT group took medication for a longer period of time when compared to the time-span women spent with ST, [33,35,36] and therefore bone density loss stopped earlier in HRT-users than non-HRT users.[35] This lead to differences in BMD at the baseline between groups as reported in the study by Maddalozzo et al. (2007).[35] Further, in the study by Milliken et al. (2003), there were significant differences at baseline between the groups in age.[36] Women, who underwent HRT were younger than females that participated in the ST group.[36] As bone loss generally increases with age,[37] younger women had thicker BMD compared to the older females.[36] It can be assumed that this was one of the reasons why in the study by Milliken et al.(2003), HRT was superior to ST to increase BMD in postmenopausal women.[36] Another reason could be that similar as in the study of Maddalozzo et al. (2007),[35] women that were in the HRT group took medication for years already before the participated in the study.[36] Therefore it can be assumed that, bone loss already stopped before they started in the study.[36] In the study by Cheng et al. (2002) women got the same amount and type of medication,[34] while in the other studies HRT was prescribed individual for each participant by the primary health care provider.[33,35,36] Consequently, in the study of Cheng et al. (2002) most drop out occurred because of side effects from HRT.[34] This study[34] also differed from the other studies[33,35,36] that it used CT scans to measure BMD.[34] Since DXA is the golden standard[8] it can be that outcomes were less reliable.[34] Moreover, CT scans differed from DXA that BMD is expressed in another unit.[8] However, this had no influence for the evaluation of the results itself because the P-value was relevant to compare outcomes between studies.[33-36] Results could be influenced by calcium supplementations, differences between eligibility criteria and different treatment protocols.[33-36] Some studies provided calcium supplementations to all participants, to test BMD better.[33,36] Thus, it could be that studies, which did not use calcium supplementations, missed changes in BMD.[34,35] Moreover, studies differed in eligibility criteria such as exclusion of participants with a history of bone fractures or osteoporosis and exclusion of women participated in regular weight lifting.[33,36] Relevant differences between ST interventions were that two studies used seven exercises for leg, arm, back and trunk muscles, [33,36] one study included five exercises for arm and leg muscles,[34] and Maddalozzo et al. (2007) only choose for the squat and dead lift.[35] Moreover some studies gave circuit training and homework.[33,34] Obviously, this differences could have influenced BMD and therefore made the overall outcomes of studies less comparable.[33-36] Following outcomes are more discussed in detail.

Femur: Greater Trochanter. There were indicative findings that ST was superior to HRT to increase BMD at the greater trochanter in postmenopausal females.[33,35,36] Comparing the individual studies there were differences between the study populations.[33,35,36] In two studies, which found significant differences,[33,35] more women participated compared to one study, which stated no significant outcome.[36] It can be assumed that results taken from a study including more participants, are more likely to be reliable.[33,35]

There was no significant difference on BMD at the baseline between groups.[33,35,36] When comparing the studies, which stated that ST was more effective than HRT,[33,35] to the study of Milliken et al. (2003) there were no relevant differences between study interventions and measurement tools.[36] All studies included exercises, which loaded the greater trochanter such as the squat and leg press.[33,35,36] ST was done two[35] or three[33,36] times a week and overall intensity was 60 to 80 percent of one repetition maximum (1RM).[33,35,36] No significant differences were found regarding calcium supplementations[33,36] and DXA was used as a measurement tool.[33,35,36] Most differences were found between the studies, which both stated that ST was superior to HRT.[33,35] Therefore it is not known why studies had different outcomes.[33,35,36]

Femur: Wards Triangle and Proximal Femur. No evidence was found that ST was superior to HRT to increase BMD at the wards triangle[36] and proximal femur.[34] Nevertheless, there were indicative findings that 12 months of ST increased BMD at the wards triangle[36] and proximal femur.[34] A limitation was that no further studies were found, that took measurements from this side of the femur and therefore no comparison could be made.

Femur: Femoral Neck. No evidence was found that ST had beneficial effects at the BMD on the femoral neck of postmenopausal women.[33,35,36] Milliken et al. (2003) stated that HRT was superior to ST to increase BMD at the femoral neck in postmenopausal women,[36] but no further evidence was found to support those findings.

Femur: Wards Triangle and Proximal Femur. There was limited evidence that ST increased BMD at the wards triangle[36] and proximal femur.[34] A limitation was that no further studies were found to compare these outcomes.

Femur: Mid Femur and Total Hip. The findings regarding the mid femur[34] and the total hip[35] were limited, because respectively one study[34,35] took measurements and no effects were found that ST or HRT was beneficial.

Lumbar Spine. No evidence was found that ST was superior to HRT to increase BMD at the lumbar spine in postmenopausal females.[33,35,36] However, one study done by Maddallozzo et al. (2007) found that ST was superior to HRT to increase BMD at the lumbar spine in postmenopausal women.[35] There were differences between the study by Maddallozzo et al. (2007)[35] and other studies,[33,36] which did not support the findings by Maddallozzo et al. (2007).[35] The differences were that in the study by Maddalozzo et al. (2007) training consisted of lower intensity, more repetitions and less exercises,[35] compared to the other studies.[33,36] Moreover, the performance of exercises differed between studies.[33,35,36] In the study by Maddalozzo et al. (2007) patients were clearly instructed to do a concentric lift (1-2 seconds) and an eccentric lift (2-3 seconds).[35] While in the other two studies, patients were not clearly instructed how to do their exercises.[33,36] Another point was that the warm up phase consisted of two sets of 10-12 repetitions at 50 percent of 1RM,[35] while in the other two other studies stretching,[33] balance exercises[33] and aerobic weight-bearing activities[33,36] were used. After comparing the study interventions between studies it can be assumed that training at lower intensity, more repetitions and including an eccentric phase had more beneficial effects on BMD at the lumbar spine, after 12 months training than higher intensity and lower repetition training.[33,34,36] Comparing the HRT and ST group in the study by Maddalozzo et al. (2007), the HRT group had thicker BMD at baseline and women took medication longer than the exercise programme lasts.[35] The end result in this study[35] was that ST was superior to HRT and therefore it can be concluded that the improvement of BMD at the lumbar spine reacted faster and more intensive on ST than HRT.[35]

There were indicative findings that HRT was effective to increase BMD at the lumbar spine in postmenopausal women.[33,36] This findings might be related to the fact that HRT was applied for a longer period of time than ST.[33,36]

Comparison with other Studies

There were indicative findings in the current literature review that 12 months of ST increased BMD at the greater trochanter in postmenopausal women.[33,35,36] This statement was supported by Kerr et al. (1996), who reported similar outcomes after one year of progressive ST in postmenopausal women.[38] Kerr et al. (1996) found that there were correlations between the type of exercise and the site where BMD increased.[38] The study reported that one year ST, including the leg press, increased BMD at the greater trochanter.[38] The conclusion of Kerr et al. (1996)[38] matched with the outcomes of the study done by Going et al. (2003),[33] which used the leg press and reported that BMD at the greater trochanter increased after one year ST. Another finding by Kerr et al. (1996) was that one year ST increased BMD at the wards triangle,[38] which supported the findings of this current literature review.[36]

In this current literature review there was no evidence that ST was superior to HRT to increase the BMD at the lumbar spine in postmenopausal females. However, in the study by Maddallozzo et al. (2007) it was reported that ST carried out for one year was superior to HRT to increase the BMD at the lumbar spine in postmenopausal females.[35] A RCT done by Bocalini et al. (2010) found that 24 weeks of ST maintained the BMD at the lumbar spine in postmenopausal females.[39] At the same time, women that did not participate ST lost BMD at the lumbar spine.[39] Since ST increased[35] or at least maintained[39] the BMD at the lumbar spine in postmenopausal women, it can be concluded that ST might be an effective treatment tool, which stops bone loss or even increases BMD at the lumbar spine.[35,39]

In the current literature review there were indicative findings that one year ST increased BMD at the proximal femur in postmenopausal females.[34] This was not supported by a RCT done by Bassey et al. (1995).[26] This study stated that there were no significant changes on the BMD at the proximal femur after one year of ST in postmenopausal women.[26] Hence, the findings of the current literature review that one year ST increased BMD at the proximal femur in postmenopausal women,[34] were not matched by the findings by Bassey et al. (1995)[26] and therefore not definite conclusion on that matter can be drawn.[26,34]

Further findings were that in study by Milliken et al. (2003) HRT was superior to ST to increase BMD at the lumbar spine, femoral neck and wards triangle.[36] This findings were supported by two other studies, which stated that HRT applied for two[40] till three[41] years showed significant increases on BMD at the lumbar spine[40,41] and femoral neck.[40] Therefore it can be assumed that HRT might be a beneficial treatment tool to increase BMD at the lumbar spine,[36,40,41] and femoral neck.[36,41]

Further conclusion were made that ST was the favourable treatment tool to increase BMD at the greater trochanter,[33,35,36] while HRT is better to increase BMD at the wards triangle.[36] However, it cannot be stated whether ST or HRT would be the better total treatment to increase BMD in postmenopausal women.[33-36] Additionally, it can be hypothesized that women would rather take medication than participate regularly in an exercise program.[34,35] This is suggested due to the fact that the participation rate in the ST group was lower than in the HRT group.[34,35]

Strength and Limitations of Research

Strengths were that all articles specified the eligibility criteria, the results of between-group statistical comparison and point measurements and variability of outcomes were given.[33-36] Some studies found significant ($p \leq 0.05$) differences at the baseline,[34-36] but for this literature review relevant were differences on BMD[35] and age.[36]

In the current literature review there were indicative findings that ST was superior to HRT to increase the BMD in postmenopausal females. It is a limitation that no further studies could be found, which supported those findings. Another weakness was that only one study included the proximal femur,[34] mid femur[34] ward's triangle[36] and total hip[35] and therefore this results could not have been compared. Articles scored relatively low on the Pedro score and no study was blinded and there was no concealed allocation.[33-36] In the study of Cheng et al. (2002) there was a double-blind manner between HRT groups, but there was no blinding between ST or HRT so therefore blinding was not a relevant for this review. [34] In two studies key outcomes were obtained from 85 percent of subjects,[35,36] while in the other studies there were to many drop outs.[33,34] Only one study analysed key outcomes by "intention to treat".[33]

This literature review was done by an inexperienced researcher (JG) carried out the search procedure and did the final evaluation. However, the rating of the PEDro score (appendix III) done by the researcher (JG) of this paper were compared with the PEDro score outcomes of the Physiotherapy evidence database.[42] Resulting in a strong point for the current literature review, because the outcomes of the author (JG) matched the results of the Physiotherapy evidence databases.[42] However, it is advisable to treat conclusions with caution, because potential articles might have been missed during literature research.

Implications for further Research

This systematic literature review showed that to come to a conclusion regarding the main question “Is ST superior to HRT to maintain or increase BMD in postmenopausal women?” further research is needed. Moreover more research could be done to investigate how much intensity and which kind of exercises would have the best effect against bone density loss in the postmenopausal years.

Conclusion

In conclusion, one year ST was superior to HRT to increase BMD at the greater trochanter in postmenopausal women. HRT was superior to ST to increase BMD at the wards triangle in postmenopausal females. Besides that, no evidence was found and therefore no conclusion could be made if ST or HRT is the better choice of treatment.

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Appendices

Appendix I. Keywords and Search Terms

Search numbers	Search terms
#1 #2 #3 #4 #5	postmenopausal women postmenopausal female older women older female #1 OR #2 OR #3 OR #4
#6 #7 #8 #9	strength training resistance training weight lifting #6 or #7 or #8
#10 #11 #12	Hormone replacement therapy Estrogen replacement therapy #10 OR #11
#13 #14 #15	Bone mineral density Bone mass measurement #13 OR #14
#16	Randomized controlled trial

Search string	*HITS*
#5 AND #9 AND #12 AND #15 AND #16	PubMED: 193 CINAHL: 197 Science Direct: 128

Appendix II. Data Extraction Tables

Going et al. (2003): Effects of exercise on bone mineral density in calcium-replete postmenopausal women with and without hormone replacement therapy[32]

Study characteristics

Method	**Criteria for Study Inclusion**	**Intervention protocol EX+NHRT**	**Intervention protocol HRT+NEX**
Partially randomization: • Women using HRT (n=159) were randomized to 2 groups: HRT+EX (n=86) or HRT+NEX (n=70) • Women not using HRT (n=161) were randomized to 2 groups: EX+NHRT (n=91) or NEX+NHRT (n=70) • Participants agreed to maintain level of physical activity (except in ET group) and continued normal dietary intake and to consume calcium intake • Calcium supplementation: 800mg per day for each participant • Average age of the EX+NHRT: 55.8±4.7 • The average age of the HRT+NEX: 54.9±5 • Number of final participants of EX+NHRT: n=71 • Number of final participants of HRT+NEX: n=65 • No significant (P>0.05) differences at the baseline between groups	• Age (40-65 y.), surgical or natural menopause (3-10.9 y.), BMI<33kg/m^2, non-smoker, no history of osteoporotic fractures, BMD of measurement sides greater than Z-score -3.0, women undergoing HRT (1-5.9 y.) , women not undergoing HRT (>1 year), cancer free last 5 y. (exclusion skin cancer), not using medication that alter BMD, no beta-blockers or steroids, Calcium intake>300mg per day, less than 120 min. physical activities per week, no weight lifting or similar activities	• Duration: 12 months, 3 times a week • Supervision: study trainers, who were trained according to the exercise protocol and meet weekly with an investigator • Additional trainers were monitoring training in log books • Warm up: 10 min. stretching, balance and aerobic weight-bearing activity • Working phase: using free weights and machines, leg press, hack squats, smith squats, lat. pull-downs, lat. rows, back extension, arm dumbbell presses and rotatory torso, 2 sets of 6-8 rep. of 70%-80% of 1RM • Circuit training: 20-25 min. moderate impact activities (walk/jog, skipping, hopping) and stair climbing and step boxes with weight vests • Adaption of 1 RM every 6-8 weeks • Cooling down: stretching, balance and ancillary resistance exercises using bands and balls	• HRT was prescribed by primary care providers, using oral estrogen (32%), estrogen and progesterone (51%) and transdermal estrogen or progesterone (12%) • Participants were asked to maintain the same amount whole study and if chances occur report them. • Assessment of HRT (type and regime) 6-months intervals **Measurement tool for BMD** • DXA (were used to measure BMD expressed in g/cm^2 • Sites of measurements were lumbar spine (L2-L4), femur (neck and trochanter) and total body BMD • Subjects were scanned twice at each measurement period and the mean of the two measurements was used for analyses • Scan analyses was done by one certified technician • Calibration was done daily to account for potential BMD variations due to machine errors

HRT= hormonal replacement therapy, EX= exercise, N= Number, NEX= no exercise, NHRT= non hormonal replacement therapy, ET= exercise therapy, mg= milligram, y= year, BMI= body mass index, kg/m^2= kilogram per square meter, BMD= bone mineral density, Z-score = statistical measurement of a score relationship to the mean in a group of scores, min= minute, lat.= lateral (sideward). Rep.= repetitions, 1RM= one repetition maximum, DXA= dual energy X-ray absorptiometry, g/cm^2 = gram per square centimetre, L2= lumbar spine segment two, L4= lumbar spine segment four

Going et al. (2003): Effects of exercise on bone mineral density in calcium-replete postmenopausal women with and without hormone replacement therapy[32]
Study outcomes

BMD expressed in g/cm^2 at the baseline, group EX+NHRT • Femoral neck: 087±0.13 • Greater trochanter: 0.74±0.11 • Lumbar spine L2-L4: 1.12±0.18		**BMD expressed in g/cm^2 at the baseline, Group HRT+NEX** • Femoral neck: 0.89±0.1 • Greater trochanter: 0.77±0.10 • Lumbar spine L2-L4: 1.17±0.13
Average changes in BMD expressed in g/cm^2 from baseline to 12 months, group EX+NHRT • Femoral neck: 0.005±0.036 • Greater trochanter: 0.008±0.024 • Lumbar spine L2-L4: 0.000±0.028		**Average changes in BMD expressed in g/cm^2 from baseline to 12 months, group EX+NHRT** • Femoral neck: 0.007±0.029 • Greater trochanter: 0.000±00.032 • Lumbar spine L2-L4: 0.011±0.028
Significant (P≤0.05) changes from the baseline to month 12, Group EX+NHRT • Femoral neck: ns • Greater trochanter: s • Lumbar spine: ns	**Significant (P≤0.05) changes from the baseline to month 12, Group HRT+NEX** • Femoral neck: ns • Greater trochanter: ns • Lumbar spine: s	**Significant (P≤0.05) different effects on BMD between EX+NHRT and HRT+NEX groups** • *Greater trochanter: EX+NHRT> HRT+NEX*

BMD= bone mineral density, g/cm^2 = gram per square centimeter, EX= exercise, NHRT= no hormonal replacement therapy, ±= standard deviation, L2= lumbar spine segment two, lumbar spine segment four, NEX= no exercise, P= p-value

Cheng et al. (2002): Change in bone mass distribution induced by hormone replacement therapy and high-impact physical exercise in post-menopausal women[33] Study characteristics

Method	Criteria for Study Inclusion	Intervention protocol EX	Intervention protocol HRT
• Randomization: after baseline measurement 80 women were randomized into 4 groups: • EX (n=20), HRT (n=20), • EX+HRT (n+20) and control (n=20) • Age of participants: 50-57 y. • The number of final participants of EX: n=12 • The number of final participants of HRT: n= 15 • Participants (except EX group) were asked to keep their normal level of physical activity and their normal diet. • The number of final participants of EX: n=12 • The number of final participants of HRT: n=15 • Main reason for exclusion or dropping out: lack of time or interest(n=7), health concerns (n=6), side-effects HRT(n=9), inadequate participation rate in ex (n=6) • No significant ($p>0.05$) differences at the baseline on BMD between groups	• No cardiovascular or locomotor system problems, BMI <33kg/m^2, • Not using estrogen, fluoride, calcitonin, bisphosphonates and steroids (not in the previous 2 y. and not more than 6 months in total), • Last menstruation at least 0.5 y. ago but not longer than 5 y., no contraindications for EX or HRT,	• Duration: 12 months, 2 times a week • Supervision: yes • Homework: 4 times a week • Additional information:supervised program included 5 circuit training periods, each lasting 8-10 weeks. These periods were interrupted by 3 high impact aerobic dance periods with 2 week duration each. There was a total summer pause of 5 weeks. • Warm up: 10 min. of stretching activities • Working phase: chest fly, lat. pull down, military press, seated down and biceps curl, • Circuit training: 3-4 rounds of skipping, bounding, hopping , drop jumps and leaping activities, which were split up in two different periods. • Home work: hoping, jumping, bounding, lower back and abdominal exercises	• Double-blind manner: • Participants in group HRT received 1 tablet of estradiol (2mg) and noretisterone acetate (1mg).per day. • Participants not receiving HRT got placebo tablets. **Measurement tool for BMD** • CT scans were used to measure BMD expressed in mg/cm^3 • Quality assurance was done by calibration before each person was measured and phantoms were scanned before baseline and follow up measurements • Scans were taken from the proximal femur, mid femur, tibia shaft divided into total tibia and cortical bone and proximal tibia

EX= exercise, HRT= hormonal replacement therapy, N= number, Y= year, BMI= body mass index, kg/m^2= kilogram per square meter, CT= Computed tomography, mg/cm^3 = milligrams to cubic centimetres, Lat= latissimus , Min= minute BMD= bone mineral density

Cheng et al. (2002): Change in bone mass distribution induced by hormone replacement therapy and high-impact physical exercise in post-menopausal women[33] Study outcomes

BMD expressed in mg/cm³ at the baseline, group EX • Proximal femur: 301 (37) • Mid femur: 849 (43)		**BMD expressed in mg/cm³ at the baseline, Group HRT** • Proximal femur: 311 (32) • Mid femur: 865 (26)
BMD expressed in mg/cm³ after 12 months, group EX • Proximal femur: 306 (33) • Mid femur: 849 (36)		**BMD expressed in mg/cm³ after 12 months, Group HRT** • Proximal Femur: 326 (32) • Mid femur: 869 (29)
Significant (P≤0.05)changes from the baseline to month 12, group EX • Proximal femur: P≤0.05 • Mid femur: P>0.05	**Significant (P≤0.05) changes from the baseline to month 12, group HRT** • Proximal femur: P≤0.05 • Mid femur: P>0.05	**Significant (P≤0.05) different effects on BMD between EX and HRT groups** No significant findings

mg/cm^3 = milligrams to cubic centimetre, BMD= bone mineral density, EX= exercise, HRT= hormone replacement therapy, P= p-value

Maddalozzo et al. (2007): The effects of hormone replacement therapy and resistance training on spine bone mineral density in early postmenopausal women[34] Study characteristics

Method	Criteria for Study Inclusion	Intervention protocol RT+NHRT	Intervention protocol HRT+NRT
Partially randomization: • Subjects (self-selected HRT or non-HRT use) had previously participated in a one-year follow-up observational study • Women using HRT were randomized to 2 groups: HRT+NRT (n=35) or HRT+RT (n=37) • Women not using HRT were randomized to 2 groups: RT+NHRT (n=35) or NRT+NHRT (n=34) • Average age of the RT+NHRT: 52.3±3.3 • Average age of the HRT+NRT: 51.8±2.9 • Number of final participants of RT+NHRT: n=29 • Number of final participants of HRT+NRT: n=34 • Reasons for drop out: stopped taking HRT (n=3), start taking HRT (n=2), moved out of area (n=5), personal reasons (n=4) and no participation exercise program (n+5) • Significant ($p \leq 0.05$) differences at the baseline on BMD at the lumbar spine between groups	• Women experienced menopause 0-36 m., Follicle-stimulating hormone levels > 40 mIU/mL, BMI (19-30 kg/m ^{2}), taking 0.625 mg estrogen or no HRT, no inclusion of non-HRT users who had taken HRT previously more than 12 m., no hypertension or metabolic diseases, no stain medication for hypercholesterolemia, no multiple sclerosis or osteoarthritis or musculoskeletal disorders	• Participants: postmenopausal women, not using HRT • Duration: 12 months, 2days a week • Supervision: personal trainer • Warm up: 2 sets of 10-12 rep. at 50% of 1RM • Working phase: squats and deadlifts, 3 sets of 60-75% of 1RM (set1= 8 rep., set2= 10 rep., set3= 12 rep.), Rep. were performed at a speed of 1-2 sec. for the lifting phase and 2-3 sec. for the lowering phase • Adaption of 1 RM every 8 weeks • Rest Phase: between sets = 60 sec. • Cooling down: 10 min. flexibility ex.Participants: postmenopausal	• Participants: postmenopausal women, who started HRT at their MP and continued for the duration of the study. • Participants used a log book for recording intake, complications and changes in relation to medication. • Duration: 12 months • **Measurement tool for BMD** DXA was used to measure bone area expressed in g/cm ^{2} of lumbar spine (L1-L4), proximal femur (total hip, femoral neck and greater trochanter), and whole body composition.

HRT= hormonal replacement therapy, NRT= no resistance training, RT= resistance training, n= number, NHRT= non hormonal replacement therapy, m= months, *mIU/mL* = milli-international units per millilitre, BMI= body mass index, kg/m ^{2}= kilogram per square meter, Rep= repetition, 1RM= one repetition maximum, sec= second, min=minute, ex=exercise, DXA= dual energy X-ray absorptiometry, g/cm ^{2} = gram per square centimetre, L1= lumbar spine segment one, L4= lumbar spine segment four, Maddalozzo et al. (2007) The effects of hormone replacement therapy and resistance training on spine bone mineral density in early postmenopausal women[34] Study outcomes

BMD expressed in g/cm^2 at the baseline, group RT+NHRT • Lumbar spine L1-L4: 0.974±0.13 • Greater trochanter: 0.682±0.09 • Femoral neck: 0.745±0.09 • Total hip: 0.891±0.10		**BMD expressed in g/cm^2 at the baseline, Group HRT+NRT** • Lumbar spine :L1-L4: 1.01±0.12 • Greater trochanter: 0.667±0.09 • Femoral neck:0.765±0.08 • Total hip: 0.885±0.11
BMD expressed in g/cm^2 after 12 months, group RT+NHRT • Lumbar spine L1-L4: 0.974±0.13 • Greater trochanter: 0.682±0.09 • Femoral neck: 0.745±0.09 • Total hip: 0.891±0.10		**BMD expressed in mg/cm^2 after 12 months, group HRT+NRT** • Lumbar spine L1-L4:1.02±0.12 • Greater trochanter: 0.662±0.09 • Femoral neck: 0.745±0.08 • Total hip: 0.882±0.10
Average changes in BMD expressed in g/cm^2 from baseline to 12 months, group RT+NHRT • Lumbar spine L1-L4: 0.43±4.3% • Greater trochanter: 0.43±3.5% • Femoral neck: -1.2±4.3% • Total hip:-0.30±3.1%		**Average changes in BMD expressed in g/cm^2 from baseline to 12 months, group HRT+NRT** • Lumbar spine L1-L4: -0.66±3.2% • Greater trochanter: -0.60±4.6% • Femoral neck: -1.2±3.3% • Total hip: -0.79±2.9%
Significant (P≤0.05) changes from the baseline to month 12, Group RT+NHRT • Lumbar spine L1-L4: P≤0.05 • Greater trochanter: P≤0.05 • Femoral neck: P>0.05 • Total hip: P>0.05	**Significant (P≤0.05) changes from the baseline to month 12, Group HRT+NRT** • Lumbar spine L1-L4: P>0.05 • Greater trochanter: P>0.05 • Femoral neck: P>0.05 • Total hip: P>0.05	**Significant (P≤0.05) different effects on BMD RT+NHRT and HRT+NRT groups** • Lumbar spine L1-L4: RT+NHRT>HRT+NRT • Greater trochanter: RT+NHRT>HRT+NRT

g/cm^2 = gram per square centimetre, BMD= bone mineral density, RT= resistance training, HRT= hormone replacement therapy, P= p-value, , L1= lumbar spine segment one, L4= lumbar spine segment four, NRT= non-resistance training, ±= standard deviation

Milliken et al (2003): Effects of exercise training on bone remodeling, insulin-like growth factors, and bone mineral density in postmenopausal women with and without hormone replacement therapy[35] Study characteristics

Method	Criteria for Study Inclusion	Intervention protocol EX+NHRT	Intervention protocol HRT+NEX
Partially randomization: • Subjects 94 (self-selected HRT or non-HRT use) were randomized to 2 groups: HRT+NRT (n=21) or HRT+RT (n=17) • Women not using HRT were randomized to 2 groups: EX+NHRT (n=26) or NEX+NHRT (n=30) • Average age of the EX+NHRT: 56.9±4.6 • Average age of the HRT+NRT: 54.4±4.6 • Number of final participants of EX+NHRT: n= 25 • Number of final participants of HRT+NEX: n=21 • Participants agreed to maintain level of physical activity (except in EX group) and continue normal dietary intake and to consume calcium intake • Calcium supplementation: 800mg per day for each participant to adequately test the effects of EX intervention • Significant ($p \leq 0.05$) differences at the baseline in age between groups	• Women who are taking HRT (between 1 y. and 3.9y.), Women who are not taking HRT for at least 1 y., postmenopausal status 3-10 y., age 40-65 y., less than 120 min. weight bearing ex per week for at least 1 y., no drugs altered BMD except HRT, no smokers, no osteoporosis, exclude if BMI > 32.9 or <19.0, no undergoing of cancer treatment in the last 5 y., excluded if unwilling to underwent randomization, excluded if history of eating disorder or musculoskeletal disorder or history of bone fractures or contraindication to exercise intervention	• Duration: 12 months, 3 times of 75 min. each set. • Supervision: yes • Warm up: 20min. of aerobic weight-bearing activity (jumping, skipping, while wearing weight vests) • Working phase: 35 min. of RT including leg press, squat, seated one- arm dumbbell presses, back extension, rotatory torso, seated rows, and lat. pull downs. 2 sets of 6-8 rep. at 70-80% of 1RM. • Adaption of 1 RM every 6 weeks • Cooling down: 10 min. stretching	• Medication prescribed by physician • Types of medication: estrogen transdermal patch (n=3), unopposed estrogen (n=23), estrogen plus testosterone (n=2) **Measurement tool for BMD** DXA was used to measure bone area expressed in g/cm^2 of lumbar spine, whole body and right proximal femur. Scans were taken at the baseline, 6 m and 12 m.

HRT= hormonal replacement therapy, EX= exercise, n= Number, NEX= no exercise, NHRT= non hormonal replacement therapy, mg= milligram, y= year, BMD= bone mineral density, BMI= body mass index, min= minutes, 1RM= one repetition maximum, DXA= dual energy X-ray absorptiometry, g/cm^2 = gram per square centimetre, m= months

Milliken et al. (2003) Effects of exercise training on bone remodelling, insulin-like growth factors, and bone mineral density in postmenopausal women with and without hormone replacement therapy[35] Study outcomes

BMD expressed in g/cm² after 12 months, group EX+NHRT • Greater trochanter: 0.739±0.109 • Wards triangle: 0.743±0.119 • Femoral neck: 0.836±0.109 • Lumbar spine: 1.104±0.159		**BMD expressed in g/cm² at the baseline, Group HRT+NEX** • Greater trochanter: 0.752±0.116 • Wards triangle: 0.764±0.141 • Femoral neck: 0.864±0.134 • Lumbar spine 1.144±0.134
BMD expressed in g/cm² after 12 months, group EX+NHRT • Trochanter: 1.3±5.5 • Wards triangle: 0.1±6.6 • Femoral neck: 0.6±5.1 • Lumbar spine: 0.3±4.2		**BMD expressed in mg/cm² after 12 months, group HRT+NEX** • Greater trochanter: -0.1±6.1 • Wards triangle:1.4±7.4 • Femoral neck: 0.6±5.7 • Lumbar spine: 1.2±4.6
Significant (P≤0.05) changes from the baseline to month 12, Group EX+NHRT • Greater trochanter: P>0.05 • Wards triangle: P≤0.05 • Femoral neck: P>0.05 • Lumbar spine: P>0.05	**Significant (P≤0.05) changes from the baseline to month 12,Group HRT+NEX** • Greater trochanter: P>0.05 • Wards triangle: P≤0.05 • Femoral neck: P≤0.05 • Lumbar spine: P≤0.05	**Significantly (P≤0.05) different effects in BMD EX+NHRT versus HRT+NEX** Femoral neck: EX+NHRT< HRT+NEX Wards triangle: EX+NHRT< HRT+NEX Lumbar spine: EX+NHRT< HRT+NEX

BMD= bone mineral density, g/cm² = gram per square centimetre, EX= exercise, NHRT= non-hormonal replacement therapy, HRT= hormonal replacement therapy, NEX= non-exercise, P= p-value
±= standard deviation

Appendix III. PEDro Scores

Author	1)∗	2)	3)	4)	5)	6)	7)	8)	9)	10)	11)	Score
Going S. (2003)[34]	Yes	1	0	1	0	0	0	0	1	1	1	5
Cheng S. (2002)[35]	YES	1	0	1	0	0	0	0	0	1	1	4
Maddalozzo GF. (2007)[36]	Yes	1	0	0	0	0	0	1	0	1	1	4
Milliken LA.[37]	Yes	1	0	0	0	0	0	1	0	1	1	4

1) Eligibility criteria 2) Randomization 3) Concealed allocation 4) Similar at baseline 5) Blinding all subjects 6) Blinding therapists 7) Blinding assessors 8) Measured key outcome more than 85 percent of subjects 9) All subjects received intervention as allocated or intention to treat 10) Results between group statistical comparison 11) Point measurement and measures of variability

∗ Criteria one was not used to calculate the total PEDro score

1=criteria was eligible
2=criteria was not eligible