Bachelor's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Neuromedicine and Movement Science

Valentine Herskedal
Malene Stokkereit Indrevåg
Marte Rogne Rishaug

The effect of hormone replacement therapy containing estrogen on muscle strength and muscle mass in postmenopausal women

Bachelor's thesis in Human Movement Science
Supervisor: Mireille Van Beekvelt
May 2022

NTNU
Norwegian University of
Science and Technology

Valentine Herskedal
Malene Stokkereit Indrevåg
Marte Rogne Rishaug

The effect of hormone replacement therapy containing estrogen on muscle strength and muscle mass in postmenopausal women

Bachelor’s thesis in Human Movement Science
Supervisor: Mireille Van Beekvelt
May 2022

Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Neuromedicine and Movement Science

NTNU
Norwegian University of
Science and Technology

Abstract

Background: Half of the world's population are women, who are likely to experience menopause in their lifetime. During menopause levels of estrogen hormones decrease, which can have a negative impact on skeletal muscle strength and muscle mass. Menopausal effects on skeletal muscle are a research area that has not been prioritized. The aim of this literature study is to investigate if HRT containing estrogen has an effect on muscle strength and muscle mass in postmenopausal women. **Methods:** The literature search was performed on PubMed 18.03.2022. The search criteria included menopausal women, HRT containing estrogen and skeletal muscle. The study design had to be an RCT or a clinical trial to be included. **Results:** Eight articles were included in this literature study. Four out of eight articles found an indication that HRT with estrogen had a significant effect on either muscle strength or muscle mass. **Conclusion:** Since the number of studies who found an association equalled the number of studies who did not, HRT´s role in affecting muscle strength and muscle mass is still unclear.

Abstrakt

Bakgrunn: Halvparten av verdens befolkning er kvinner, som sannsynligvis vil oppleve overgangsalderen i deres livsløp. I overgangsalderen synker østrogennivået, dette kan ha en negativ påvirkning på skjelettmuskelstyrke og muskelmasse. Overgangsalderens effekt på muskulatur er et forskningsområde som er blitt nedprioritert. Formålet med denne litteraturstudien er å undersøke om HRT som inneholder østrogen har en effekt på muskelstyrke og muskelmasse hos kvinner i overgangsalderen. **Metode:** Litteratursøket ble utført på PubMed 18.03.2022. Søkekriteriene inneholdt kvinner i overgangsalderen, HRT med østrogen og skjelettmuskulatur. Studiedesignet måtte være RCT eller klinisk forsøk for å bli inkludert. **Resultat:** Åtte artikler ble inkludert i dette litteraturstudiet. Fire av åtte artikler fant en indikasjon på at HRT med østrogen hadde en signifikant effekt på muskelstyrke eller muskelmasse. **Konklusjon**: Siden antall studier som fant en assosiasjon tilsvarte antallet studier som ikke gjorde det, er HRT sin rolle i påvirkningen av muskelstyrke og muskelmasse enda uklar.

Key words: Estrogen, Hormone replacement therapy, Menopause, Skeletal muscle strength, Skeletal muscle mass

Introduction

Historically, women have been largely excluded from clinical trials, despite making up half of the world's population. When studying diseases prevalent in both genders, Caucasian men were previously considered to be the norm study population. There was an assumption that there were no significant sex differences regarding medication response. Women were also viewed as confounding and more expensive test subjects because of their fluctuating hormone levels, as well as concerns of potential disadvantageous reproductive effects (Liu & Mager, 2016). Even though these assumptions have been discarded and the inclusion of women in clinical research is now regulated by law, the research on women's health is still scarce. Research efforts should therefore be magnified to match the vast amount of research conducted on men.

As women age, they can experience larger individual differences when it comes to overall health as opposed to younger women. Aging is associated with a natural decline in physiological functions, including muscle strength and mass. Decreased muscle mass and impaired muscle function are associated with functional limitations and disability, higher risk for mortality, and several other disadvantageous health outcomes among the older population (Sipilä et al., 2015). This decline does not occur at the same rate and age in men compared to women. An accelerated loss of muscle strength and mass appears to occur at an earlier age in women than men, around the time the women reach menopause. There is considerable evidence that this decline in muscle mass may be influenced by the decrease in estrogen levels which characterizes the menopausal years (Maltais et al., 2009).

Most women reach menopause between ages 45 and 55. Menopause is defined by World Health Organization as "the permanent cessation of menstruation resulting from loss of ovarian follicular activity" (World Health Organization, 1981). Postmenopause is defined as the period after 12 months without menstrual periods. In the postmenopausal period the ovaries produce lower levels of estrogen and progesterone hormones. A decline in these hormones often cause menopausal symptoms such as hot flashes, sleep problems, sexual disturbances, mood changes and depression (World Health Organization, 1981). This decline may also influence skeletal muscle which is an estrogen-responsive tissue affected by circulating estrogen levels. Estrogen has been shown to influence fiber size, overall muscle weight, muscle regeneration, contractility, and to induce minimal changes in fiber-type distribution (Haizlip et al., 2015). These findings are the origins of the increasing interest on how effects of low estrogen levels in postmenopausal women may affect their physical health and muscular function.

Hormone replacement therapy (HRT) can relive the menopause symptoms that are caused by the lack of hormone production in the ovaries. Commonly implemented HRT includes estrogen alone as the active substance or combined with progesterone and are mostly consumed as tablets or through skin patches. There are both positive and negative effects to HRT, therefore should women considering treatment, discuss it with a doctor. HRT can reduce the risk of all-cause mortality, osteoporosis and improve quality of life (Xu et al., 2020). HRT can cause several undesirable side effects, such as headaches, nausea, mood swings, troubles with indigestion and vaginal bleeding. Recent studies suggest a beneficial role for HRT, where a supplementation with estrogen and progesterone, could induce pathways by which estrogen could assist skeletal muscle maintenance and remodelling (Haizlip et al., 2015).

The decline in skeletal muscle strength and mass followed by menopause, may be a consequence of the menopausal change in the hormonal environment and it is uncertain if HRT has a beneficial effect regarding this decline. HRT has been used in clinical practice for over 70 years (Xu et al., 2020). As previously mentioned, women's health needs to be prioritized to increase their quality of life. If HRT with estrogen influences muscle function, it could help many postmenopausal women by maintaining or improving their muscle strength and muscle mass.

Previous meta-analyses have received different findings regarding HRT´s effect on muscle strength. A meta-analysis from 2009 (Greising et al., 2009) found a beneficial association, unlike another from 2020 that found no association, or that the effect size was too small to identify any significance (Xu et al., 2020). This literature study stands out by investigating studies evaluating both muscle strength and mass, where some included training interventions. The aim of this literature study is to investigate whether HRT containing estrogen has an effect on skeletal muscle strength and skeletal muscle mass in postmenopausal women.

Methods

The literature search was performed on 18.03.2022 and collected from PubMed. The keywords “hormone replacement therapy” AND “estrogen” AND “menopause “AND “skeletal muscle” provided a result of twenty original articles that were of interest for this research review. Inclusion and exclusion criteria were used to narrow the initial search. The search criteria that applied to the search were randomized controlled trials (RCT), clinical trials, humans and females. The selected studies had to be published in English, be conducted on menopausal women, include HRT with estrogen and measure skeletal muscle strength and muscle mass directly. The articles that did not fulfil the inclusion criteria were excluded, which left us with eight remaining articles in this literature study.

Results

Eight studies investigated the effect of different types of HRT on skeletal muscle strength and muscle mass. The common denominator of all HRT´s was that they included estrogen. There were four studies that evaluated HRT´s effect on both skeletal muscle strength and muscle mass, whereas four studies evaluated HRT´s effect only on muscle strength. The different types of HRT´s and dosages used in the included articles are presented in Table 1 to give an insight to the different interventions used. Table 2 presents a quick overview of the different article’s characteristics. Hereafter the findings in each of the articles will be elaborated in further details.

Table 1: An overview of the hormone replacement therapy used in the included studies

Author, year	**Estrogen (type)**	**Estrogen (mg)**	**Progesterone (type, mg)**	**Others (mg)**	**Application**	**Duration**
Dayal et al. (2005)	Conjugated equine estrogen	0.625	---	Droepiandrosten edione (50)	Tablets	3 mo
Taaffe et al. (2005)	Kliogest (combination pill)	2	Norethisterone acetate (1)	---	Tablet	1 y
Uusi-Rasi et al. (2005)	Optional	Optional	Optional	Optional	Optional	9 y
Ribom et al. (2002)	Menorest	4.3	Gestapuran (2.5)	---	Plaster and tablet	6 mo
Sipilä et al. (2001)	Kliogest (combination pill)	2	Norethisterone acetate (1)	---	Tablet	1 y
Skelton et al. (1999)	Prempak C (combination pill)	0.625	Norgestrel (0.15)	---	Tablet	1 y
Heikkinen et al. (1997)	Estrogen valerate	2	Medroxyprogesterone acetate (10 or 20)	---	Tablets	24 mo
Armstrong et al. (1996)	Prempak C (combination pill) or Premarin	0.625	Prempak C: Norgestrel (0.15)	Sandocal: Calcium (1000)	Tablets	11 mo

Table 2: Characteristics of the original studies

Author, year	Study design	Participants (n, age)	Groups	Duration	Means of measuring	Exercise	Results
Dayal et al. (2005)	Clinical trial	32, 44 -70 y 32 Completed	4 groups: HRT with ET (n=5), HRT with only DHEA (n=12) HRT with ET and DHEA (n=9) CON (n=6)	3 mo	MS: Handgrip strength test, isometric and isokinetic tests by dynamometer MM: CSA by MRI (ankle plantar flexors)	No	MS - MM -
Taaffe et al. (2005)	RCT	80, 50-57 y 51 completed	4 groups: HRT (n=20) Ex (n=20) HRTEx (n=20) CON (n=20)	1 y	MS: isometric knee extensor strength MM: CSA by CT (quadriceps and posterior muscles)	Yes	MS ↑ MM ↑
Uusi-Rasi et al. (2005)	Clinical trial (Follow up study)	80, 61+-0,9 y 80 completed	3 groups: HRT (n=43) CON (n=37)	9 y	MS: maximum isometric strength (leg extension and forearm flexion) by strain-gauge dynamometers	No	MS ↓
Ribom et al. (2002)	RCT	40, 60-78 y 34 completed	2 groups: HRT (n=20) CON (n=20)	6 mo	MS: Hand grip strength, isokinetic knee flexion/extension	No	MS -
Sipilä et al. (2001)	RCT	80, 50-57 y 52 completed	4 groups: HRT (n=20) HRTEx (n=20) Ex (n=20) CON (n=20)	1 y	MS: Knee extension torque MM: CSA by CT (quadriceps femoris and ankle flexors and extensors)	Yes	MS ↑ MM ↑
Skelton et al. (1999)	Clinical trial	102, 53-67 y 85 completed	2 groups: HRT (n=50) CON (n=52)	1 y	MS: MVF of adductor pollicis MM: CSA of adductor pollicis	No	MS ↑ MM -
Heikkinen et al. (1997)	Clinical trial	78, 49-55 y 76 completed	3 groups: HRT1 (n=13) + HRTEx1 (n=13) HRT2 (n=13) + HRTEx2 (n=13) CON (n=13) + CONEx (n=13)	24 mo	MS: maximal isometric strength (back extensor and flexor)	Yes	MS ↑
Armstrong et al. (1996)	RCT	116, 45-70 y 108 completed	2 groups: HRT + (Calcium) (n=57) CON (Calcium) (n=59)	11 mo	MS: Leg extensor power and hand grip strength	No	MS -

MS = muscle strength; MM = muscle mass; ↑ = Increase; ↓ = Decrease; - = No significant effect; HRT = Hormone replacement therapy; Ex = Exercise; HRTEx = Hormone replacement therapy + exercise; CON = Control; CONEx = Control group + exercise; MRI = Magnetic resonance imaging; CSA = muscle cross sectional area; CT = Computed tomography; MVF = Maximal voluntary force; BIA = bioelectrical impedance.

Dayal et al. (2005) conducted a prospective, randomized double-blind study to evaluate the effect of combined conjugated estrogen (ET) and dehydroepiandrostenedione (DHEA) hormone replacement on muscle mass and strength in postmenopausal women, among other factors. The study consisted of 32 postmenopausal women (44-70 years old). All participants were enrolled for 12 weeks and had not been exposed to HRT for at least 60 days prior. The participants were divided into 4 groups: HRT with ET (n=5), HRT with DHEA (n=12), HRT with ET and DHEA (n=9) and control (n=6). Muscle mass was determined by magnetic resonance imaging (MRI), while muscle strength was determined by right-hand grip strength test, as well as isometric and isokinetic tests by dynamometers. Only one of several tests, regarding muscle strength showed a significant improvement of the lower calf surface area in the HRT with ET-treated group. Except for this improvement, muscle strength and mass were unchanged in all groups.

Taaffe et al. (2005) examined the effect of whether HRT, alone or combined with exercise, affected skeletal muscle strength and muscle mass among other factors in menopausal women in RCT. The study included 80 healthy postmenopausal women (50-57 years old), which were randomly assigned to 4 groups (n = 20 per group): HRT, HRT combined with exercise (HRTEx), exercise (Ex) and control for 1 year. The study was double blinded where the subjects received either HRT or placebo daily. The exercise groups were given a high-impact training program for lower extremities. Muscle strength was determined by a knee extensor strength test, while muscle mass was determined by muscle cross-sectional area (CSA) of the quadriceps and posterior muscles measured by computed tomography (CT). A total of 51 women completed the study. The results showed a significant mean increase in quadriceps and posterior muscle CSA for all groups. The HRTEx group showed the largest increase, followed by HRT, Ex and lastly the control group showing only a small change in muscle CSA. Also, the HRTEx group showed the largest increase in knee extensor strength with 37.7 Nm, compared to the control group that had a 21.7 Nm reduction. Both the HRT and Ex groups had a positive effect where the Ex group increased the most.

Uusi-Rasi et al. (2005) conducted a 9-year follow-up study evaluating factors influencing bone characteristics and physical performance, including muscle strength during postmenopausal years. A population of 80 healthy, non-smoking, peri-menopausal women (61 ± 0.9 years) that originally had participated in a randomized, controlled exercise intervention trial, attended follow-up measurements 9 years later. At enrolment, 43 of the women were HRT users and therefore made up the HRT group, while 12 women who had been using HRT for 3.7 ± 2.2 years but hadn't received HRT for at least 1 year, and the remaining 25 women not using HRT, made up the control group. The study evaluated changes in muscle strength by measuring maximum isometric strength of the leg extension and dominant forearm flexion by dedicated strain-gauge dynamometers. Changes in isometric arm flexors had a significant mean decrease (95% confidence interval) of 32.9%, whereas isometric leg extension strength showed no significant change after the 9 years.

Ribom et al. (2002) conducted a double blinded, prospective, placebo-controlled trial that evaluated if HRT could influence muscle strength in postmenopausal women (60-78 years old). The study consisted of 40 healthy postmenopausal women who were randomly assigned into two groups: HRT (n = 20) and control (n = 20). The HRT group (67.5 ± 4.8 years) administered an HRT plaster and tablet daily, while the placebo group (67.7 ± 4.8 years) would receive a placebo treatment, both for a duration of 6 months. Hand grip strength, isokinetic knee flexion and extension were used to determine if HRT influenced muscle strength. Physical activity levels were measured and remained unchanged during the study. A total of 34 women completed the study. The results showed that both groups had a significant increase in right-hand grip strength, while only the HRT group showed a significant increase in left-hand grip strength. Despite these results, there was no significant difference in muscle strength between the HRT and the placebo group.

Sipilä et al. (2001) conducted a randomized, double-blinded placebo-controlled trail, to evaluate effects of HRT and high-impact physical exercise on skeletal muscle strength and mass in postmenopausal women. The study population consisted of 80 healthy women (50-57 years old). The subjects were randomized to one of four groups: HRT, HRTEx, Ex and control. HRT or placebo was administered one tablet per day for 1 year. The HRTEx and Ex groups conducted a progressive physical training program including two supervised and four at-home workouts a week. The non-exercise groups were instructed not to change daily routines or physical activity levels. Changes in skeletal muscle strength was determined by knee extension torque, while changes in muscle mass were determined by lean tissue CSA of the quadriceps measured through CT. A total of 52 women completed the trial. The results showed that muscle mass and muscle strength were improved by HRT. The HRTEx group had a significant increase in knee extension torque with 8.3% compared to the control group which had a decrease of 7.2%. The HRT group showed a positive increase in knee extension torque after 6 months, but after 12 month there were no visible effect. Lean tissue CSA of the quadriceps muscle was significantly increased in the HRT (6.3%) and HRTEx (7.1%) groups compared to Ex (2.2%) and control (0.7%) groups. Lower leg lean tissue CSA also had a higher increase in the HRTEx group (9.1%) compared to Ex (3.0%) and control (4.1%) groups.

Skelton et al. (1999) conducted a randomized open trial where HRT was used to assess changes in adductor pollicis muscle strength and mass in postmenopausal women. The study consisted of 102 healthy postmenopausal women (53-67 years old) and lasted for 6-12 months. The subjects were randomly divided into an HRT group (n = 50, 60.9 ± 3.2 years) or a control group (n = 52, 60.6 ± 3.3 years). Both muscle strength and muscle mass were measured in the adductor pollicis 8 times during the study. To measure muscle strength, maximal voluntary force (MVF) was used, while CSA of the adductor muscle was used to determine muscle mass. 85 women completed the trail. The results showed a significant increase in muscle strength in the HRT group. MVF increased in the HRT group (12.4 ± 1.0% (mean ± SEM)) compared to the control group who experienced a slight decline (2.9 ± 0.9%). The increase in muscle strength was not affected by the results from CSA regarding muscle mass, as it did not significantly increase during the study.

Heikkinen et al. (1997) examined the effect of 1- or 3-monthly sequential combinations of HRT on muscle strength in postmenopausal women, among other factors. The subjects were 78 healthy postmenopausal women that were 49-55 years old (52.5 ± 1.5 years) and participated in the study for a duration of 24 months. Three groups (n=26 per group) were randomly distributed, into two HRT groups and one control group. HRT1 and HRT2 would compare two estrogen-progestin regimens, while the control group received placebo. Each group was then divided equally into two subgroups: non-exercise and exercise. The exercise group received guidance and encouragement to physical activity, as opposed to the non-exercise groups. There were 9 dropouts in the study, but 76 participants were included in the efficacy analyses. Muscle strength was determined by maximal isometric strength in the back extensor and flexor muscles at 12 and 24 months. Results showed a significant association between baseline and follow-up measurements of isometric back extensor and flexor strength in both HRT groups ($P<0.001$). The main strength-augmentation occurred the first year, followed by a slight decrease the second year. A significant increase in flexor strength was observed in both exercise and non-exercise groups receiving HRT, where the exercise groups had the greatest increase in muscle strength. HRT had a beneficial effect on skeletal muscle strength, especially pronounced in women who had low muscle strength in the beginning of the study.

Armstrong et al. (1996) conducted a RCT which investigated whether there is a difference in effect between oral HRT plus calcium, compared to calcium only, on muscle performance including muscle strength, balance and falls in 116 postmenopausal women (45-70 years old). All the subjects recently (< 3 months) had a distal radial fracture. The subjects were divided into two groups. The test group (n = 57, 60.5 ± 6.3 years) received HRT and calcium, while the control group (n = 59, 61.3 ± 5.8 years) received calcium only for 48 weeks. Changes in muscle strength was determined by evaluating changes in leg extensor power and hand grip strength. The subject's activity levels were measured to ensure that no substantial differences in exercise had occurred during the study. Both groups were moderately active. According to the results, there were no significant changes in muscle strength that could be attributed to HRT. There were also no observed changes in grip strength in the HRT group, despite a significant change in oestradiol levels after 48 weeks. The control group showed a significant increase of 4.2% (95% confidence interval 0.7-7.6%) in leg extensor power, in comparison to the HRT group, who showed no changes.

Discussion

The eight included articles investigated the effect of different types of HRT including estrogen on muscle strength and muscle mass in postmenopausal women. All studies evaluated HRT´s effect on muscle strength, where four articles found a positive association, three found no association, and one found a negative association. Four studies also focused on muscle mass, where two of the studies found a positive association, while the two others found no effect. The different findings demonstrate that the results are inconsistent. In addition to the main findings regarding muscle strength and mass, there were also three articles that discovered that HRTEx could enhance HRT´s effect. There could however be factors influencing all these findings, which will be addressed in further detail.

The intervention time between studies

The included studies in this literature study all have different lengths of intervention time. The majority of the studies had an intervention time of 1 year. The shortest study lasted for 12 weeks and the longest for 9 years. Outcomes from shorter interventions may be considered as temporary in comparison to longer interventions. Normally, it is recommended to try HRT treatment for a minimum of 3 months to reach full effect of relieving menopausal symptoms, as well as stopping when the symptoms pass, usually after a few years (National Health Services, 2017).

A long intervention time is beneficial when it comes to obtaining accurate results. The follow-up study by Uusi-Rasi et al. (2005) may therefore have a better chance at providing a correct estimate of HRT's long-lasting effect on the muscles, due to the long intervention time of 9 years. This study did, however, not find any association between HRT and muscle strength, and a negative association in dominant forearm flexion strength. These results may provide evidence that HRT with estrogen does not have any significant long-lasting effects on skeletal muscle strength outweighing the effects of aging. The four studies finding an effect all had an intervention time of 1-2 years, while the three additional studies finding no associations lasted for 3-11 months. This could imply that an HRT intervention may provide a positive association when applied for a duration lasting 1 year minimum. However, there is no basis in this literature study to say how long this positive effect may last, exceeding the 1-2 year period, other than being likely to decrease earlier than 9 years of HRT usage. This can indicate that a positive effect of HRT is only temporary and may at some point be caught up by the natural effects of aging.

Study design and sample size

All included studies in this research review were RCT´s and clinical trials. RCT is considered to be the gold standard when it comes to measuring the effectiveness of an intervention or treatment. RTC achieves a reliable assessment of effectiveness through concealed and randomized allocation, binding, intention-to-treat analysis, and adequate sample size (Hariton & Locascio, 2018). Regarding sample size, it can be a potential weakness or strength when it comes to an article's reliability and validity. The sample size in this literature study varied from 32 to 116 participants, which is a considerable difference. Six of the original studies had sample sizes greater than 78, while the remaining two articles had 40 or less. There is reason to believe that a larger sample size could provide a better estimate, unlike smaller sample sizes which could make it difficult to determine if the result is a true finding.

Validity and reliability of the measure methods

The studies included in this literature review, used varying tools as means of evaluating changes in muscle strength and muscle mass. The different ways of quantifying the changes could potentially affect the results of the studies, and some means of measuring may have a higher reliability or validity than others.

The most common tools for measuring changes in skeletal muscle strength in the studies were a dynamometer, testing either extension or flexion of leg strength or knee torque, as well as hand grip strength. Dynamometers are known to have a high test-retest reliability and are therefore often used in clinical testing. According to a review, hand grip tests are well suited tests for older people, and are a good measure of muscle strength (Roberts et al., 2011). These tests have shown to have predictive validity and low scores are associated with falls, reduced health-related quality of life and increased mortality. Another review reported that dynamometers assessing upper and lower limb muscle strength and voluntary activation, exhibit good intra-rater reliability in isometric and isokinetic strength in most samples (correlation coefficients ≥0.90) (Nuzzo et al., 2019). It should be noted that dynamometer-tests could be influenced by various factors such as correct size adaptation, hand/leg dominance, frequency of testing, time of day, posture, joint position, rest periods and encouragement of the subject, all affecting the inter-rater reliability of the tests.

Muscle mass was measured by MRI and CT in the included studies to determine muscle CSA. A recent study by Faron et al. (2020) comparing analysis of body composition using CT and MRI has found that these methods can be used interchangeably for skeletal muscle assessment, and may therefore not have a significant impact on the individual studies results (Faron et al., 2020).

Confounding factors: physical activity and progesterone

When investigating if HRT with estrogen has an effect on muscle strength and mass, there are several confounding factors that could play a role in the outcome of the study. A confounding factor could be the subjects' physical activity. It is known that physical activity and exercise has a direct effect on muscular strength and mass. In five of the studies, it was reported that the subject's physical activity was monitored through either questionnaires, interviews, or diaries. Although questionnaires have a moderate reliability and could be affected by bias, it gives the researchers some insight in the variability of physical activity throughout the intervention. However, it should be noted that due to the randomization in all original studies it could be argued that bias in these factors would have no or minimal effects on the results.

The artificial forms of progesterone, progestogen, and progestin are secondary components included in most of the studies that use HRT. Progesterone is added to reduce the risk of hyperplasia and cancer in the endometrium in the uterus (Campagnoli et al., 2005). However, potential effects progesterone could have on muscles should be taken into consideration. A RCT by Smith et al. (2014) found that progesterone treatment increased the muscle protein synthesis rate by approximately 50% ($P<0.01$), not affected by estrogen treatment and unchanged in the control group (Smith et al., 2014). This could indicate that progesterone potentially has an additional effect on muscle strength, creating interference in the original studies results.

The combination of HRT and exercise

Three studies discussed whether HRT combined with exercise may be more beneficial on muscle strength and muscle mass than HRT alone. Two of three investigated HRT´s effect on both muscle strength and mass combined with exercise, while the last study only looked at muscle strength. All three found an association, where HRT combined with exercise gave the largest increase in muscle strength and/or mass. The results also indicate that HRT could have a positive effect without adding training intervention, since HRT groups had the second largest increase in muscle strength and/or mass. It should be mentioned that Heikkinen et al. (1997) registered that the effects of HRT on muscle strength were especially prominent in those who were weakest in the beginning of the studies. Regarding the exercise intervention, the improvement in the weakest participants could be due to change in activity level. These results indicate that HRT with estrogen does influence muscle strength and mass but can be enhanced in combination with exercise.

Side effects and risk of HRT

HRT is known to relieve menopausal symptoms and is argued to potentially effect muscular strength and/or mass. However, there are a few possible side effects of HRT including bloating, breast soreness, nausea, leg cramps, headaches, mood swings, depression, acne, body ache, troubles with digestion and vaginal bleeding. Usually these will pass within a few weeks, but some might find them troublesome. Serious risks are also reported, most known is the increased risks of breast cancer (estrogen-only HRT), blood clots and stroke, but these are very small (National Health Services, 2017). Tablets are the most common form of HRT and are usually prescribed as 1 tablet a day. The study by Ribom et al. (2002), used patches to administer HRT. It should be mentioned that using patches does not increase risk of blood clots, unlike tablets. Patches also help to avoid some side effects, such as indigestion. Most women consider the benefits of HRT to outweigh the risks associated (National Health Services, 2017).

Future studies

Through conducting this literature search, we came across an indication that HRT combined with exercise could provide a more beneficial effect on postmenopausal women's muscle strength and mass, than HRT alone. As this was not the aim of the study, only three articles included training interventions. It would be interesting to conduct more research on this aspect to evaluate various training interventions and thereby find the most suitable training regimen on the musculoskeletal system for menopausal women. There was also an implication that HRT might have a positive effect on skeletal muscle strength after receiving HRT for a duration of at least 1-2 years, and that it is unknown how long this positive effect may last. More research is needed to pinpoint the duration of this potential positive association, and whether this effect is beneficial enough to outweigh the side effects of HRT.

Research conducted on postmenopausal women is scarce, which could be due to the potential side effects and risks of HRT that influence the screening criteria. According to the literature, many women are interested in participating, but are excluded. By including a more diverse group of postmenopausal women in a controlled environment it could expand the research field. This literature study does not incorporate the entire field of literature existing on this topic and may therefore be lacking. A bigger overview of the existing literature might give a more precise interpretation of whether HRT containing estrogen does in fact have a positive effect on muscle strength and muscle mass.

Conclusion

This literature study included eight articles which addressed whether HRT containing estrogen, has an effect on skeletal muscle strength and skeletal muscle mass in postmenopausal women. Four studies showed a beneficial effect of HRT on muscle strength and/or mass, while four showed no associations or effects. HRTEx was shown to be the most beneficial intervention, although it should be noted that HRT alone also had a more beneficial effect than exercise in isolation. After evaluating the strengths and weaknesses of the included studies, it was apparent that one should be critical of the results, both for the studies finding an association and the ones who did not. Differences in the studies approaches could have affected the study's results. The varying findings of the individual studies are inconclusive. Additional research is necessary before results can have any practical implications of HRT with estrogen as a treatment to counteract the menopausal effects on skeletal muscle strength and mass.

Literature

Armstrong, A. L., Oborne, J., Coupland, C. A. C., MacPherson, M. B., Bassey, E. J. & Wallace, W. A. (1996). Effects of Hormone Replacement Therapy on Muscle Performance and Balance in Post-Menopausal Women. *Clinical Science*, *91*(6), 685–690. https://doi.org/10.1042/cs0910685

Campagnoli, C., Clavel-Chapelon, F., Kaaks, R., Peris, C. & Berrino, F. (2005). Progestins and progesterone in hormone replacement therapy and the risk of breast cancer. *The Journal of Steroid Biochemistry and Molecular Biology*, *96*(2), 95–108. https://doi.org/10.1016/j.jsbmb.2005.02.014

Dayal, M., Sammel, M. D., Zhao, J., Hummel, A. C., Vandenbourne, K. & Barnhart, K. T. (2005). Supplementation with DHEA: Effect on Muscle Size, Strength, Quality of Life, and Lipids. *Journal of Women's Health*, *14*(5), 391–400. https://doi.org/10.1089/jwh.2005.14.391

Faron, A., Sprinkart, A. M., Kuetting, D. L. R., Feisst, A., Isaak, A., Endler, C., Chang, J., Nowak, S., Block, W., Thomas, D., Attenberger, U. & Luetkens, J. A. (2020). Body composition analysis using CT and MRI: intra-individual intermodal comparison of muscle mass and myosteatosis. *Scientific Reports*, *10*(1), 11765. https://doi.org/10.1038/s41598-020-68797-3

Greising, S. M., Baltgalvis, K. A., Lowe, D. A. & Warren, G. L. (2009). Hormone Therapy and Skeletal Muscle Strength: A Meta-Analysis. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *64A*(10), 1071–1081. https://doi.org/10.1093/gerona/glp082

Haizlip, K. M., Harrison, B. C. & Leinwand, L. A. (2015). Sex-Based Differences in Skeletal Muscle Kinetics and Fiber-Type Composition. *Physiology*, *30*(1), 30–39. https://doi.org/10.1152/physiol.00024.2014

Hariton, E. & Locascio, J. J. (2018). Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. *BJOG: An International Journal of Obstetrics & Gynaecology*, *125*(13), 1716–1716. https://doi.org/10.1111/1471-0528.15199

Heikkinen, J., Kyllönen, E., Kurttila-Matero, E., Wilén-Rosenqvist, G., Lankinen, K. S., Rita, H. & Väänänen, H. K. (1997). HRT and exercise: effects on bone density, muscle strength and lipid metabolism. A placebo controlled 2-year prospective trial on two estrogen-progestin regimens in healthy postmenopausal women. *Maturitas*, *26*(2), 139–149. https://doi.org/10.1016/S0378-5122(96)01098-5

Liu, K. A. & Mager, N. A. D. (2016). Women's involvement in clinical trials: historical perspective and future implications. *Pharmacy Practice*, *14*(1), 708. https://doi.org/10.18549/PharmPract.2016.01.708

Maltais, M. L., Desroches, J. & Dionne, I. J. (2009). Changes in muscle mass and strength after menopause. *Journal of Musculoskeletal & Neuronal Interactions*, *9*(4), 186–197.

National Health Services. (2017, oktober 23). *Hormone replacement therapy (HRT)*. Nhs.Uk. https://www.nhs.uk/conditions/hormone-replacement-therapy-hrt/

Nuzzo, J. L., Taylor, J. L. & Gandevia, S. C. (2019). CORP: Measurement of upper and lower limb muscle strength and voluntary activation. *Journal of Applied Physiology*, *126*(3), 513–543. https://doi.org/10.1152/japplphysiol.00569.2018

Ribom, E. L., Piehl-Aulin, K., Ljunghall, S., Ljunggren, Ö. & Naessén, T. (2002). Six months of hormone replacement therapy does not influence muscle strength in postmenopausal women. *Maturitas*, *42*(3), 225–231. https://doi.org/10.1016/S0378-5122(02)00079-8

Roberts, H. C., Denison, H. J., Martin, H. J., Patel, H. P., Syddall, H., Cooper, C. & Sayer, A. A. (2011). A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age and Ageing*, *40*(4), 423–429. https://doi.org/10.1093/ageing/afr051

Sipilä, S., Finni, T. & Kovanen, V. (2015). Estrogen Influences on Neuromuscular Function in Postmenopausal Women. *Calcified Tissue International*, *96*(3), 222–233. https://doi.org/10.1007/s00223-014-9924-x

Sipilä, S., Taaffe, D. R., Cheng, S., Puolakka, J., Toivanen, J. & Suominen, H. (2001). Effects of hormone replacement therapy and high-impact physical exercise on skeletal muscle in post-menopausal women: a randomized placebo-controlled study. *Clinical Science (London, England: 1979)*, *101*(2), 147–157.

Skelton, D. A., Phillips, S. K., Bruce, S. A., Naylor, C. H. & Woledge, R. C. (1999). Hormone replacement therapy increases isometric muscle strength of adductor pollicis in post-menopausal women. *Clinical Science (London, England: 1979)*, *96*(4), 357–364.

Smith, G. I., Yoshino, J., Reeds, D. N., Bradley, D., Burrows, R. E., Heisey, H. D., Moseley, A. C. & Mittendorfer, B. (2014). Testosterone and Progesterone, But Not Estradiol, Stimulate Muscle Protein Synthesis in Postmenopausal Women. *The Journal of Clinical Endocrinology & Metabolism*, *99*(1), 256–265. https://doi.org/10.1210/jc.2013-2835

Taaffe, D. R., Sipila, S., Cheng, S., Puolakka, J., Toivanen, J. & Suominen, H. (2005). The effect of hormone replacement therapy and/or exercise on skeletal muscle attenuation in postmenopausal women: a yearlong intervention. *Clinical Physiology and Functional Imaging*, *25*(5), 297–304. https://doi.org/10.1111/j.1475-097X.2005.00628.x

Uusi-Rasi, K., Sievänen, H., Heinonen, A., Beck, T. J. & Vuori, I. (2005). Determinants of changes in bone mass and femoral neck structure, and physical performance after menopause: a 9-year follow-up of initially peri-menopausal women. *Osteoporosis International: A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, *16*(6), 616–622. https://doi.org/10.1007/s00198-004-1724-0

World Health Organization. (1981). *Research on the menopause : report of a WHO scientific group [meeting held in Geneva from 8 to 12 December 1980]*. World Health Organization. https://apps.who.int/iris/handle/10665/41526

Xu, Y., Deng, K.-L., Xing, T.-F., Mei, Y.-Q. & Xiao, S.-M. (2020). Effect of hormone therapy on muscle strength in postmenopausal women: a systematic review and meta-analysis of randomized controlled trials. *Menopause (New York, N.Y.)*, *27*(7), 827–835. https://doi.org/10.1097/GME.0000000000001538

Norwegian University of
Science and Technology