



## Conference on ‘Nutrition and exercise for health and performance’ Symposium 2: Maintenance of muscle mass for healthy ageing

### Female hormones: do they influence muscle and tendon protein metabolism?

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Due to increased longevity, women can expect to live more than one-third of their lives in a post-menopausal state, which is characterised by low circulating levels of oestrogen and progesterone. The aim of this review is to provide insights into current knowledge of the effect of female hormones (or lack of female hormones) on skeletal muscle protein turnover at rest and in response to exercise. This review is primarily based on data from human trials. Many elderly post-menopausal women experience physical disabilities and loss of independence related to sarcopenia, which reduces life quality and is associated with substantial financial costs. Resistance training and dietary optimisation can counteract or at least decelerate the degenerative ageing process, but lack of oestrogen in post-menopausal women may reduce their sensitivity to these anabolic stimuli and accelerate muscle loss. Tendons and ligaments are also affected by sex hormones, but the effect seems to differ between endogenous and exogenous female hormones. Furthermore, the effect seems to depend on the age, and as a result influence the biomechanical properties of the ligaments and tendons differentially. Based on the present knowledge oestrogen seems to play a significant role with regard to skeletal muscle protein turnover. Therefore, oestrogen/hormonal replacement therapy may counteract the degenerative changes in skeletal muscle. Nevertheless, there is a need for greater insight into the direct and indirect mechanistic effects of female hormones before any evidence-based recommendations regarding type, dose, duration and timing of hormone replacement therapy can be provided.

#### Oestrogen: Hormone replacement therapy: Collagen: Muscle strength: Sarcopenia

Ageing is associated with a net loss of muscle mass, also in master athletes<sup>(1–3)</sup>. Since muscle mass is a significant determining factor for muscle strength and function, preservation of muscle mass during ageing is essential for preserving individuals’ ability to live independent lives. Muscle mass and strength are lower in women than in men<sup>(4–6)</sup>. Furthermore, women experience accelerated reduction in muscle mass, strength and function when they enter menopause<sup>(7–9)</sup>. The age-dependent accumulation of non-contractile tissue (fat, connective tissue) within skeletal muscle tissue increases after menopause<sup>(10,11)</sup> and this reduces muscle quality (strength relative to muscle cross-sectional area)<sup>(8,12,13)</sup>. Therefore, both the muscle

quality and skeletal muscle mass in women are negatively affected by the transition to the post-menopausal state. Since life expectancy is also higher in women than in men, women are particularly vulnerable to age-related frailty and morbidity. Therefore, it is important to evaluate the effectiveness of preventive strategies to postpone loss of muscle function in women. This will be all the more important in coming years due to the increasing numbers of post-menopausal women in developed countries who will challenge healthcare systems if preventive strategies to reduce physical disabilities are not implemented.

Loss of muscle mass takes place when the synthesis rate of structural contractile muscle proteins is lower

**Abbreviations:** ACL, anterior cruciate ligament; ER, oestrogen receptors; ERT, oestrogen replacement therapy; HRT, hormone replacement therapy; IGF-I, insulin-like growth factor-I; OC, oral contraceptive.

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than the breakdown rate. Furthermore, the turnover of structural muscle, tendon and ligament proteins may influence the composition and function of the tissue<sup>(14)</sup>. The aim of the present paper is to review the literature regarding the effect of (lack of) oestrogen/female hormones on muscle and tendon collagen protein turnover and mass. The present review will refer primarily to data from human trials. The direct effect of oestrogen on muscle strength and power, independent of the effect of muscle mass, is beyond the scope of the present review, but has been reviewed by others (for review, see<sup>(15,16)</sup>).

### Female hormone levels across the lifespan

Oestrogens are steroid hormones, which mediate their action by binding to a number of tissue receptors, including specific nuclear oestrogen receptors (ER;  $\alpha$  and  $\beta$ ) and plasma membrane-associated ER<sup>(17)</sup>. ER  $\alpha$  and  $\beta$  function as transcription factors once bound to their ligand. ER  $\alpha$  and  $\beta$  are expressed and localised within skeletal muscle tissue and in tendons and ligaments<sup>(18–23)</sup>, suggesting a direct effect of oestrogen.

The level of circulating oestrogen (17- $\beta$  estradiol), the primary female sex hormone, increases during puberty and is about four times higher in women than men during adulthood until menopause. Oestrogen and the other female hormones (progesterone, luteinising hormone, follicle-stimulating hormone) fluctuate during each menstrual cycle. The concentration of circulating oestrogen is relatively low during the early follicular phase (menses phase), increasing progressively in the late part of the follicular phase until ovulation. After this, the level decreases, but it is still maintained at a high level during the luteal phase until menses. The concentration of progesterone is low during the follicular phase, but markedly increased during the luteal phase. During pregnancy, both oestrogen and progesterone are markedly enhanced<sup>(24)</sup>. The level of oestrogen at the end of pregnancy is about 100 times or more higher than the level experienced during the late follicular phase. After delivery, the hormone levels drop again within a few days. Commonly, women in their mid-40s experience the menopausal transition where the level of female hormones and menstrual pattern become irregular. Menopause is defined by the permanent cessation of menstrual period and is experienced by women in their late 40s or early 50s. After menopause, oestrogen is reduced to a negligible level in most women. The implication of the latter is that women spend more than one-third of their life with low levels of oestrogen and progesterone.

### Sex differences in muscle mass and muscle protein turnover across the lifespan

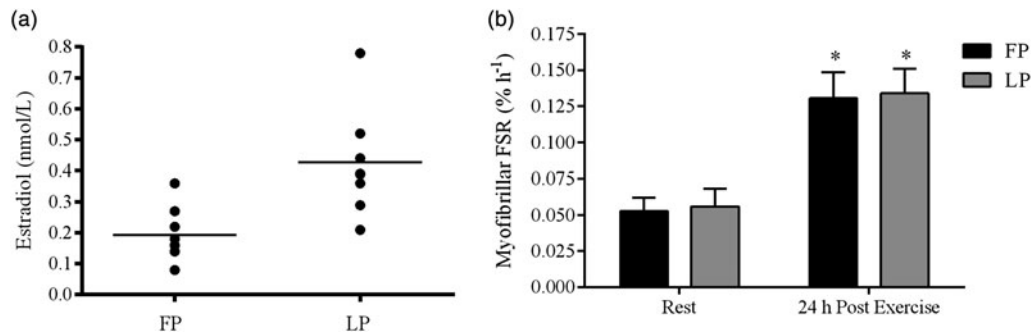
The sex difference in muscle mass becomes marked during the teenage years when boys experience accelerated muscle growth<sup>(25,26)</sup>. From young adulthood until the menopausal transition, skeletal muscle mass can at an individual level be changed positively or negatively by

training and immobilisation/disuse, but otherwise the sex difference in muscle mass is relatively stable until the age of about 50 years.

The observation of no major sex-related changes in relative muscle mass in young subjects is supported by the majority of published studies, which in young subjects report no sex difference in muscle protein synthesis in the post-absorptive state<sup>(27–31)</sup> in response to feeding<sup>(30,31)</sup> and strenuous exercise<sup>(31,32)</sup>. Similarly, the limited available data for measurements of muscle protein breakdown have shown no difference between young men and women<sup>(27,31)</sup> or muscle loss during disuse<sup>(33)</sup>. These observations may seem counterintuitive based on the anabolic effect of the male steroid testosterone<sup>(34)</sup> and women have a testosterone level that is 10–15-fold lower than in men<sup>(31)</sup> and do not experience an increase in circulating testosterone post-resistance exercise as has been seen in men<sup>(31,35)</sup>. Therefore, it can be hypothesised that other stimulating factors (e.g. oestrogen) in young women may compensate for the lower testosterone level since testosterone evidently supports muscle growth in response to resistance training<sup>(34)</sup>. Nevertheless, not all data from training studies suggest the response to regular strength training in muscle mass is equal between young men and women<sup>(36)</sup>. A greater increase in muscle volume was observed in eleven young men than in eleven young women after 9 weeks of knee extension exercises, three times weekly (also after adjustment for baseline muscle volume)<sup>(36)</sup>. Nevertheless, the latter findings are in conflict with several other strength training studies, which have reported no sex difference in muscle growth and strength gain<sup>(37–39)</sup>. Still, the number of studies, which have directly compared women and men in relation to the effect of strength training on muscle growth, is limited. Furthermore, the majority of studies include less than ten participants within each training group, which enhance the risk of statistical type II error.

During the menopausal transition, muscle loss is accelerated in women<sup>(40)</sup>, after which the rate of muscle loss slows down<sup>(25,41)</sup>. The accelerated loss of muscle mass during the post-menopausal transition occurs even though a higher post-absorptive muscle protein synthesis rate is observed in post-menopausal women than in pre-menopausal women and age-matched men<sup>(42,43)</sup>. These results suggest that the net negative muscle protein balance in post-menopausal women is caused by an up-regulation of skeletal muscle protein breakdown rate, although this hypothesis has not directly been tested in human subjects. However, catabolic genes (e.g. MuRF1 and FOXO<sub>3</sub> mRNA expression) are up-regulated in ageing muscle in women<sup>(43,44)</sup>, which may help to explain the counterintuitive observation of loss of muscle mass even though the post-absorptive muscle protein synthesis rate is enhanced in post-menopausal women.

A reduced responsiveness to anabolic stimuli such as exercise and feeding when female hormone levels decline at menopause may be an alternative explanation for the net loss of muscle mass in elderly women. In line with this notion, post-menopausal women experience a diminished anabolic response to feeding<sup>(45,46)</sup> and resistance exercise<sup>(46,47)</sup> compared with young subjects and



**Fig. 1.** Plasma estradiol (a) and resting and post-exercise myofibrillar fractional synthesis rates (FSR) (b) in the follicular phase (FP) and luteal phase (LP) of the menstrual cycle. Straight line in (a) represents the average estradiol level. \* $P < 0.05$ . Significantly different from contralateral resting leg within each menstrual phase. Copyright © 2006 The American Physiological Society. Used with permission<sup>(32)</sup>.

age-matched men. Also, the accumulated response to resistance exercise training (three times per week in 26 weeks) has been reported to be lower in elderly women than in elderly men<sup>(48)</sup>. In agreement, after a 10-week unilateral knee-extension strength-training programme, including fifty-four men and eighty-two post-menopausal women (50–85 years) a significant greater training-induced increase in muscle volume was observed in men than women, which corresponded to 9.1 % in men and 7.5 % in women<sup>(49)</sup>. In contrast, training studies including women without regard to use of hormone replacement therapy (HRT) and with less than ten subjects in each group have not been able to observe significant differences between old women and men in response to resistance training<sup>(50)</sup>, which may be related to lack of statistical power.

#### Influence of female hormones on skeletal muscle

In comparative studies, including women and men, it is not possible to test the isolated effect of the individual sex hormones on skeletal muscle. Furthermore, when testing young women, several hormones fluctuate during the menstrual cycle and inter-individual levels of female hormones exhibit great variation. This may be due to genetic factors as well as nutritional status<sup>(51)</sup>. In a cross-sectional trial, we did not observe any differences in the myofibrillar protein synthesis rate in eight young females tested 2–3 d after the onset of menses (the follicular phase), and seven females tested in the luteal phase 4 d after a positive ovulation test<sup>(32)</sup>. In the luteal phase compared with the early follicular phase, circulating oestrogen was on average twice as high and the progesterone markedly higher, but there was great variation and overlap in oestrogen between the phases (Fig. 1). Therefore, to elucidate a clear effect of oestrogen on muscle protein synthesis rate independent of progesterone, it would have been more appropriate to measure the synthesis rate in the early follicular phase *v.* late the late follicular phase in a cross-over trial. Another approach could be to administer estradiol and progesterone separately to post-menopausal women who have an existing low circulation

level of oestrogen and progesterone. Accordingly, Smith *et al.*<sup>(43)</sup> in a parallel-randomised controlled trial enhanced circulating estradiol to a level that corresponded to the mid-to-late-follicular phase by administering transdermal oestrogen replacement therapy (ERT) or administered progesterone in a dose that enhanced circulating progesterone to a level corresponding to the mid-luteal in young girls. The administration of progesterone was associated with a 50 % increase in muscle protein synthesis rate, whereas ERT did not affect muscle protein synthesis rate in the post-absorptive state. This suggests that oestrogen may not have any marked effect on the post-absorptive muscle protein synthesis rate<sup>(43)</sup>. Nonetheless, oestrogen may reduce muscle protein breakdown and/or enhance sensitivity to anabolic stimuli. In support of the former, HRT has been reported to reduce muscle loss or increase muscle mass and strength in post-menopausal women in several, but not all<sup>(52–54)</sup>, randomised controlled trials<sup>(11,55–57)</sup>. Furthermore, positive associations have been observed between serum estradiol and muscle mass and strength in post-menopausal women<sup>(55)</sup>. In line with this, a twin study, including thirteen pairs of monozygotic post-menopausal twin pairs showed that use of HRT was associated with greater muscle power and higher walking speed than no use of HRT after a 1-year intervention<sup>(58)</sup>. In addition, in a randomised controlled trial lean tissue cross-sectional area was increased significantly (6.3 %) after 12-month administration of HRT compared with the control group (0.7 %), which underline that HRT influence muscle protein balance positively<sup>(57)</sup>. In further support of an oestrogen mediated reduction in skeletal muscle breakdown, HRT has been reported to counteract post-menopausal-related enhancement of protein degradation<sup>(59)</sup>. In a randomised double-blinded trial, reduction in lean body mass along with transcriptional changes in the ubiquitin–proteasome system was observed in women in the early post-menopausal years after a 1-year intervention<sup>(59)</sup>. In contrast, amongst the women receiving HRT during the intervention period, lean body mass was increased and no transcriptional changes in the ubiquitin–proteasome system were observed<sup>(59)</sup>. Therefore, there are several findings, which suggest that ERT/HRT may indirectly

influence skeletal muscle protein turnover and counteract the age-related loss of muscle mass and strength. In addition, it should be noted that oestrogen is an antioxidant and sarcolemma membrane stabiliser, which may positively influence the contractile properties of skeletal muscle and protect against muscular damage. Moreover, oestrogen lowers the age-related increase of pro-inflammatory cytokines<sup>(60)</sup> that otherwise may contribute to muscle loss by increasing muscle breakdown<sup>(61)</sup>. Accumulation of fat in the skeletal muscle may also be counteracted by ERT/HRT<sup>(11)</sup>, thus reducing the impairment of muscle quality observed in the elderly<sup>(12)</sup>.

A reduced sensitivity to anabolic stimuli in post-menopausal women may provide an alternative explanation for the accelerated loss of muscle mass in the early menopause. Several observations support that oestrogen has an important positive role in regards to increasing sensitivity to training, reducing exercise-induced muscle damage and improving recovery (discussed later). Part of this positive effect may be explained by the idea that oestrogen seems to be important for satellite cell expansion, differentiation, and self-renewal and thereby muscle function<sup>(62,63)</sup> (for review see<sup>(64)</sup>). Therefore, the reduction in oestrogen at menopause may compromise satellite cell function and have negative impact on the training response and increase the risk of sarcopenia<sup>(64)</sup>. In addition, in a cross-sectional study that included oral ERT users we observed an increase in myofibrillar protein synthesis rate in response to resistance exercise<sup>(47)</sup>. In contrast, age-matched post-menopausal controls with estradiol concentration under the analytic threshold showed no change in myofibrillar protein synthesis rate when measured 24 h post-exercise, even though the women had performed a very strenuous bout of unilateral knee extensor exercise (ten sets of ten repetitions, corresponding to ten to twelve repetitions maximum (10–12 RM))<sup>(47)</sup>. Moreover, Taaffe *et al.*<sup>(11)</sup> observed a synergistic effect when combining training with HRT (oestrogen and synthetic progesterone) on leg muscle cross-sectional area compared with no HRT or training alone. Furthermore, transcriptional data from analysis of muscle samples from post-menopausal women support positive synergetic effects of training and use of HRT on skeletal muscle mass<sup>(65,66)</sup>, and animal data show that oestrogen is important for regaining muscle mass in ovariectomised rats after muscle loss<sup>(67–69)</sup>.

Oestrogen may also influence the response to training in young girls, but probably not when combined with a high circulating level of progesterone, as in the luteal phase. No difference in the myofibrillar protein synthesis rate in response to an acute bout of strenuous exercise is observed between girls in the early follicular phase where circulating oestrogen and progesterone are low compared with the mid-luteal phase where both hormones are elevated<sup>(32)</sup> (Fig. 1). Also, animal data indicate that the individual effect of oestrogen and progesterone on net muscle protein balance may counteract each other when present simultaneously (as in the luteal phase) (see review<sup>(70)</sup>). In the follicular phase, especially in the late part of the follicular phase, only oestrogen is enhanced. This may hypothetically induce an enhanced possibility for muscle growth if resistance training is

performed in this phase of the menstrual cycle. In support, Wikström-Frisén *et al.*<sup>(71)</sup> observed greater improvements in muscle strength and muscle mass in response to 4 months resistance training in girls who had undertaken intensified resistance exercise training (five times per week) during the follicular phase compared with girls who undertook intensified resistance exercise training in the luteal phase. This observation is supported by others<sup>(72,73)</sup>, but not all<sup>(74)</sup>. In general, the number of studies within the area is still limited. In addition, in the most well-controlled study by Wikström-Frisén *et al.*<sup>(71)</sup> with fifty-nine participants who completed the training protocol, the groups consisted of a mix of non-users and users of oral contraceptives (OC), which makes it difficult to separate between the effects of endogenous and synthetic female hormones. Nevertheless, it should be noted that the OC users who experienced an increase in muscle growth and strength when training in the first 2 weeks of the pill-circle primarily used triphasic OC with a low content of synthetic progesterone in the first part of the pill period.

In young women, a lower myofibrillar protein synthesis rate was observed in women using OC containing a constant amount of ethinyl estradiol and gestagen (third generation OC) compared with non-users of OC<sup>(75)</sup>. In contrast, myofibrillar protein synthesis rate in the non-users of OC and users of second generation OC containing ethinyl estradiol and norgestimate was comparable<sup>(75)</sup>. These observations indicate that the synthetic type of progesterone (gestagen) have differential (anti-) androgen effects on myofibrillar protein synthesis rate when combined with ethinyl estradiol. However, mostly the type of OC is not reported in the literature or type of OC has not been taken into account in the data analysis. The present data underline the importance of clarifying the specific effect of the different types of OC on skeletal muscle in future studies.

In summary, oestrogen may be important for muscle maintenance and muscle growth in response to training in young and post-menopausal women regardless of no potential direct effect of oestrogen on muscle protein synthesis at rest in the post-absorptive state<sup>(43)</sup>. However, future human trials need to clarify the individual female hormones' effect on net muscle protein balance alone and in combination under differential circumstances (e.g. in the post-absorptive state, in response to protein feeding and/or in response to exercise/training).

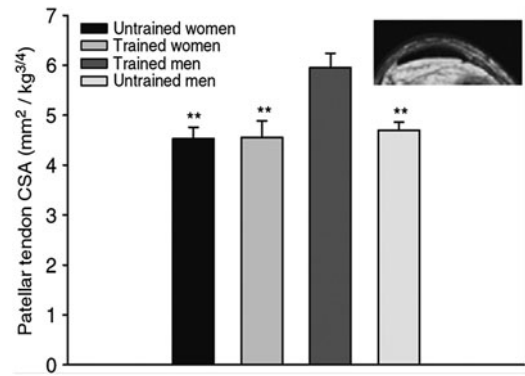
### Influence of female hormones on tendon and ligaments

Any influence of female hormones on the biomechanical properties of tendon and ligaments will have impact on locomotion<sup>(76)</sup>. Therefore, it is interesting to note that sex differences are observed in connective tissue. However, the effect of individual female hormones alone and combined on skeletal muscle connective tissue is a puzzle, which may be related to differential direct and indirect effects of endogenous and exogenous female hormones<sup>(77,78)</sup>.



Tendon structural quality seems to be lower in women than in men<sup>(79–82)</sup>. Isolated female tendon fascicles rupture at a lower load compared with fascicles from men<sup>(79)</sup>. Also, a lower tendon dry mass per mg tendon wet weight<sup>(80)</sup> and a higher expression of type III collagen mRNA<sup>(81)</sup> in women compared with men has been reported. In line with these observations, tendon stiffness during maximal loading is lower in women, indicating less resistance to deformation during loading<sup>(82)</sup>. Reduced tendon and ligament stiffness may explain why muscle damage after eccentric non-weight-bearing muscle contractions is lower in women than in men because of reduced tensile loading of the myofilaments during muscular contractions<sup>(83,84)</sup>. Conversely, reduced stiffness may also help to account for the observed 2–8 times higher risk of sustaining an anterior cruciate ligament (ACL) rupture in active women than in comparably active men<sup>(85,86)</sup>. The idea that oestrogen may negatively impact tendon and ligament resistance against rupture during loading is further supported by the findings that load to failure is significantly lower in ACL from rabbits treated with a high dose of oestrogen than in controls<sup>(87)</sup>. Nevertheless, in regard to tendinopathy, ERT/HRT may be beneficial for post-menopausal women in preventing tendinopathy, especially in active elderly women<sup>(88)</sup>.

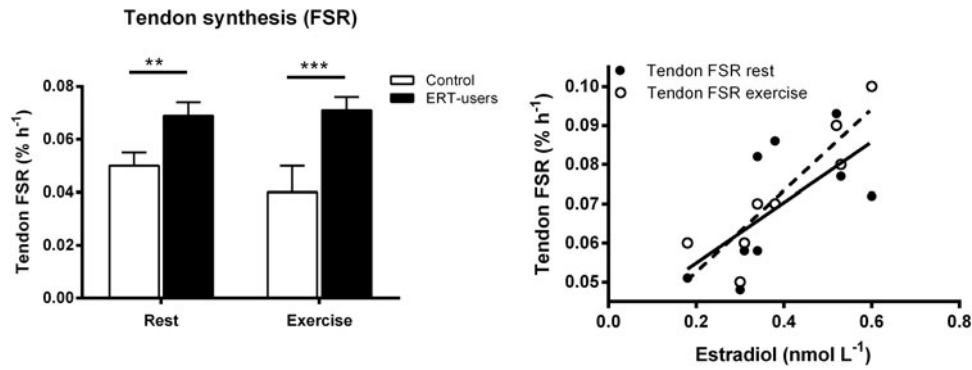
Sex may also influence the ability of tendons and ligaments to respond to training. Collagen is the most abundant structural protein in tendons and ligaments, and the tendon collagen synthesis rate is markedly lower in women than in men both at rest and in response to acute exercise<sup>(89)</sup>. Furthermore, in a cross-sectional trial, we included young untrained controls and experienced female and male runners who had been running at least 40 km/week for the previous 5 years (men average 58 km/week and women average 54 km/week)<sup>(90)</sup>. The results showed that the weight-normalised cross-sectional area of the patellar tendon and Achilles tendon in trained and untrained women were comparable<sup>(90)</sup>. In contrast, the cross-sectional area of the tendons in trained men were greater than untrained and trained women, but also greater than untrained men<sup>(79,90)</sup>. These data indicate that the hypertrophic effect of regular exercise on the patellar and Achilles tendons is lower in young trained women than in similarly trained men<sup>(79,90)</sup> (Fig. 2). Based on these findings, we hypothesised that oestrogen has an inhibiting effect on tendon and ligament collagen synthesis, which was supported by some<sup>(91)</sup>, but not all animal findings<sup>(92)</sup> dependent on species. Nevertheless, we found that elderly women using ERT had a higher tendon collagen synthesis than age-matched post-menopausal women, and that the estradiol level correlated positively with the tendon collagen synthesis rate (Fig. 3)<sup>(14)</sup>. Therefore, the higher tendon collagen synthesis in men compared to women may be caused by a dominating effect of another factor (e.g. testosterone). But on comparing women to women the higher tendon collagen synthesis rate in ERT users than in non-users was associated with a relatively lower tendon stiffness<sup>(14)</sup>. Similarly, we observed in a group of female handball players a negative correlation between serum estradiol and tendon stiffness (adapted from<sup>(93)</sup>).



**Fig. 2.** The MRI determined patellar tendon cross-sectional area (CSA) for trained and untrained men and women normalised to body mass. Trained men had a greater CSA than untrained men ( $P < 0.01$ ); however, note that trained women had a similar CSA compared with untrained women<sup>(79,90)</sup>. Copyright 2007 John Wiley and Sons. Used with permission.

Furthermore, a significantly higher knee joint laxity was observed in women in their third trimester (week 30) compared with 5–7 weeks postpartum. Knee joint laxity was reduced in thirty-eight of forty women postpartum<sup>(24)</sup>. The latter observation underlines the fact that biomechanical properties can change over a relatively short time. In a well-controlled trial, Lee *et al.*<sup>(94)</sup> collected blood samples seven times during a menstrual cycle and measured anterior tibia displacement simultaneously. In the late follicular phase, when the level of serum estradiol peaks and progesterone is low, they observed significantly greater knee laxity compared with other time points during the menstrual cycle. This observation is confirmed by others<sup>(95–97)</sup> and is connected with a greater risk of sustaining an ACL rupture in the late follicular phase of the menstrual cycle<sup>(98,99)</sup>. It seems surprising that tissue structure is able to change within days. However, results from engineered ligaments have shown that short-term exposure to oestrogen (48 h) can inhibit the activity of the crosslinking enzyme lysyl oxidase<sup>(100)</sup>. As a result, the tissue structure was destabilised, the relative stiffness was lowered and the ultimate stress before rupture was reduced<sup>(100)</sup>. Notably, this finding comes from a study that involved engineered ligaments, so further research is needed to confirm whether similar inhibition of the cross-linking enzyme in tendon and ligaments takes place in human subjects *in vivo*.

Administration of OC to young women seems to have opposite effect of tendon and ligaments than HRT to postmenopausal women<sup>(78)</sup>. In OC users, tendon collagen synthesis rate is lower than in age-matched controls<sup>(101)</sup>. This is in contrast to the higher tendon collagen synthesis rate observed in elderly women using ERT compared with age-matched controls<sup>(14)</sup>. Furthermore, use of OC is associated with lower ACL elasticity in several studies<sup>(102,103)</sup>, but not all<sup>(104)</sup>. This is also contrary to the lower relative tendon stiffness in elderly ERT users<sup>(14)</sup>. The influence of OC on tendon and ligaments seem to influence injury risk. A case-control study including 4497 operatively treated patients after ACL rupture and 8858 age-matched



**Fig. 3.** Left: Patellar tendon collagen fractional synthesis rates (FSR) at rest and 25 h after exercise in post-menopausal women who used oestrogen replacement therapy (ERT) and post-menopausal women who did not use ERT (control)  $**P < 0.01$  and  $**P < 0.001$ , unpaired *t* test, control v. ERT users. Right: Relationship between tendon FSR and serum (s)- estradiol in ERT users at rest ( $r^2$  0.41,  $P = 0.06$ ) and post-exercise ( $r^2$  0.80,  $P < 0.001$ )<sup>(14)</sup>. Copyright© 2009 The American Physiological Society. Used with permission.

controls with no ACL injury concluded that the relative risk for sustaining an ACL injury was lower in OC-users<sup>(105)</sup>. The latter may be explained by OC users having a lower endogenous level of estradiol and they do not experience a peak in estradiol during the pill-period as do non-users of OC. Still, it has not been clarified whether synthetic estradiol (ethinyl estradiol) or the synthetic gestagens in OC influence tendon and ligament collagen turnover directly or indirectly. It is noteworthy that, use of OC is associated with markedly lower insulin-like growth factor-I (IGF-I) levels in young female OC users<sup>(101)</sup>. IGF-I enhances tendon collagen synthesis<sup>(106)</sup>. Therefore, the lower IGF-I level in OC-user may be a major explanatory factor in regards to the lower tendon collagen synthesis rate<sup>(101)</sup>. The IGF-I level is already relative low in elderly women<sup>(107)</sup>. Therefore, the further small reduction in IGF-I induced by oral ERT in elderly women may have negligible influence on tendon collagen synthesis rate, whereas the stimulating influence of an enhanced estradiol level on tendon collagen synthesis may overrule the consequence of a lowered IGF-I level in elderly ERT-users<sup>(78)</sup>.

It is noteworthy that the presented findings have focused on the effect of female hormones on ACL, Achilles or patellar tendon. It is too simple to assume that female hormones influence the structure and biomechanical properties equally in all tendons and ligaments, independent of anatomical position and function (e.g. stabilisation or elastic properties). Differential distribution of ER in different tissues may, for example, induce differential effects on collagen protein turnover<sup>(108)</sup>. Furthermore, there are many types of OC and HRT with either estradiol or ethinyl-estradiol, and different types of synthetic progesterone with differential androgenic properties. Nevertheless, the latter has not been elucidated in regards to the effects on tendon and ligament collagen synthesis rate, and only sparsely in regards to the effect on myofibrillar protein synthesis rate<sup>(75)</sup>.

In conclusion, sex differences in muscle protein turnover in young subjects seem to be negligible. Still,

oestrogen may play an important role for obtaining a positive anabolic effect of training. However, oestrogen also reduces tendon and ligament stiffness, which for the young female athletes probably enhance the risk for ACL rupture. In postmenopausal, administration of ERT/HRT has beneficial effects on skeletal muscle protein maintenance and may improve sensitivity to anabolic stimuli and thereby enhance muscle mass and strength. Furthermore, ERT/HRT may be beneficial for post-menopausal women in preventing tendinopathy and reduce tendon stiffness. Nevertheless, individual's risk profile should be considered before initiating HRT/ERT and it must be underlined that no evidence-based optimal dose, type of ERT/HRT, duration or timing of initiation of treatment is currently outlined. Therefore, currently, post-menopausal women should be recommended to follow evidence-based guidelines for diet and regular resistance training (with or without use of HRT/ERT), since these are well-documented strategies for counteracting age-related loss of muscle mass and function, but also other age-related degenerative changes in men and women<sup>(109–111)</sup>. Furthermore, physically active post-menopausal women report fewer symptoms related to menopause than sedentary women<sup>(112)</sup>.

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**Conflict of Interest**

None.

### Authorship

M. H. conducted the literature search and drafted the paper.

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