

# Benefits of Estrogen Replacement for Skeletal Muscle Mass and Function in Post-Menopausal Females: Evidence from Human and Animal Studies

## *Menopoz Sonrası Kadınlarda İskelet Kası Kitle ve Fonksiyonu için Östrojen Replasmanının Faydaları: İnsan ve Hayvan Araştırmaları Bulguları*

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### Abstract

Age related loss of skeletal muscle mass and strength accelerates with the onset of menopause in women. Recent evidence from human and animal studies provides compelling evidence for the role of estrogen based hormone replacement therapy (HRT) in maintaining and enhancing muscle mass and strength and protecting against muscle damage. The physiological mechanisms by which estrogen can positively influence skeletal muscle mass and strength and protect against post-damage inflammation and disruption are also beginning to emerge. These less well known benefits of estrogen for skeletal muscle coupled with other benefits of estrogen to bone and metabolic health in older females provide further incentives for HRT use to enhance overall health in post-menopausal women. New research also attests to the safety of shorter term HRT in younger post-menopausal females. Overall the benefits of HRT to muscle health and function could assist in offsetting age related loss of muscle mass and function and delay age related morbidity and their use for overall health benefits in aging females should continue to be evaluated.

**Key Words:** Aging, Estrogen, Health, Muscle function, muscle repair, Women

### Özet

Kadınlarda yaşa bağlı iskelet kas kütlesi ve güç kaybı menopoz başlangıcı ile hızlanır. İnsan ve hayvan çalışmalarından elde edilen yeni veriler kas kütlesi ve gücünün korunması ve kas hasarına karşı korumada östrojen hormon replasman tedavisinin (HRT) rolüyle ilgili ikna edici kanıtlar sunmaktadır. Östrojenin iskelet kas kütlesi ve gücünü olumlu yönde etkilemesinin fizyolojik mekanizmaları ve hasar sonrası inflamasyon ve bozulmaya karşı korunması da ilgi çekmeye başlamıştır. Östrojenin bu daha az bilinen yararları, yaşlı kadınlardaki kemik ve metabolik sağlık üzerine olan diğer yararları ile birleştiğinde, HRT'nin menopoz sonrası kadınlarda genel olarak sağlığı yükseltici olarak kullanılması için daha fazla teşvik sağlar. Yeni araştırmalar genç post-menopozal kadınlarda daha kısa süreli HRT güvenliğini kanıtlamaktadır. Genel kas sağlığı ve işlevine HRT'nin yararları, yaşa bağlı kas kütlesi ve fonksiyon kaybının ortadankaldırılmasında ve yaşa bağlı morbiditenin geciktirilmesini dengelemede yardımcı olabilir ve yaşlanan kadınlarda genel sağlık yararları için HRT kullanımı değerlendirilmeye devam edilmelidir.

**Anahtar Kelimeler:** Kadın, Kas fonksiyonu, Kas onarımı, Östrojen, Sağlık, Yaşlanma

### Introduction

With advancing age, muscle mass, muscle force and muscle repair capacity diminishes. The loss of muscle mass and muscle force in women accelerates relative to similar age males after the age of menopause [1]. In women in particular, the ability of muscle to generate force declines precipitously following menopause. Phillips et al. [2] demonstrated that males and females had similar adductor pollicis muscle strength (relative to muscle mass) until the age of female menopause. However, following the age of menopause, the

loss of muscle force relative to muscle mass accelerated much faster in women than similar aged men as age advanced.

In men, the loss of the sex hormone, testosterone has been linked to loss of muscle mass and force with aging [3] and the effects and mechanisms of testosterone in preserving muscle mass and function have been well documented [4, 5]. However, it is only more recently that positive effects of estrogen on skeletal muscle in females have become more established and well understood [4, 6, 7]. This review will cover recent research which documents the positive effects of estrogen and hormone replacement therapy (HRT) on skel-

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etal muscle mass, damage and repair indices and force generation in older females. This review will also discuss human and animal studies which outline further evidence for and potential mechanisms of the positive effects of estrogen on skeletal muscle. Finally, it will conclude with a brief overview of the overall health implications of HRT in aging females.

### **HRT and muscle function in aging females**

A number of earlier studies have reported beneficial effects of estrogen based HRT on skeletal muscle function in post-menopausal females. For example, Sipila et al. [8] and Taafe et al. [9] found evidence of enhanced muscle function and size in 50-57 year old post-menopausal women taking HRT relative to placebo controls in randomized control studies. Using a one year HRT intervention, Taafe et al. [9] reported that those subjects taking HRT increased muscle size, vertical jump height and running speed over the course of the study period, while those given a placebo either only maintained or had reductions in all of these measures over the same time period. Two other HRT or placebo groups of subjects who strength trained for the duration of the study both increased their muscle size, vertical jump height and running speed. However the HRT groups exhibited significantly greater gains [9].

Other studies have also reported muscle related functional improvements with HRT. For example, Naessen et al. [10] found significantly better postural balance in older females taking estrogen replacement relative to those not taking HRT. Isometric muscle strength was also enhanced by HRT in post-menopausal females as measured by adductor pollicis strength [11].

However, not all earlier studies which examined potential HRT replacement effects on muscle strength or size in older women, reported positive results. Hansen et al. [12] provided post-menopausal women with estrogen for over one year. While bone mineral density increased and fat mass decreased in the HRT group increases in muscle mass in the HRT group did not reach statistical significance (0.09) relative to the control group [12]. Another study found no significant effect of HRT on muscle performance or balance in older females [13], while a different study noted no significant strength gains for women performing weight bearing exercises for nine months while on HRT [14]. Sarcopenia is the loss of muscle mass due to age related loss of muscle fibers [3]. Kenny et al. [15] also found little effect of two years of HRT on the incidence of sarcopenia in post-menopausal females relative to non HRT taking control.

The lack of positive results from some of these studies has been suggested to be related to a number of factors including lack of control of subject estrogen dosage, diet, activity levels, age and medications [16]. Brown [16] suggested that sarcopenia studies may need to be much longer than

two years in duration to demonstrate results and that more intense resistance exercises rather than walking exercises may be more likely to demonstrate positive results of HRT on muscle strength. Nevertheless controversy and conflicting findings on HRT efficacy in producing positive responses in skeletal muscle function and mass in older females remained.

Over the last few years however, commentators have noted that several recent studies on HRT and muscle function in older females have, "tipped the balance toward a positive and measureable impact of HRT" [17] and have elucidated some potential mechanisms by which these effects can be achieved [4, 18]. The most compelling of these more recent studies involves the assessment of 15 pairs of monozygotic female twins aged 55-56 years [7]. One of each twin pair was a long time HRT user while the other twin was not. The twins using HRT had significantly more muscle power, higher vertical jump, faster walking speed, greater lean body mass and less fat mass than their non-HRT using twins [7]. Because of the robust nature of this experimental design which minimizes genetic and physiological variation between HRT users and non-users, the potential to demonstrate HRT benefits to muscle function were enhanced and positive results were demonstrated [17].

Two other recent studies by Dieli-Conwright and colleagues [19, 20] have further strengthened the case for positive HRT effects on skeletal muscle in post-menopausal women. The first of these studies reported that women taking HRT had significantly up-regulated pro-anabolic mRNA expression and mRNA signalling in muscles of sedentary women relative to those not taking HRT [19]. This included mRNA coding for MyoD, myogenin, and Myf5 as well as the suppression of mRNA for the negative regulator of muscle mass, myostatin. In addition, a single bout of eccentric exercise induced significantly greater responses in muscle expression of these mRNA as well as mRNA related to regulation of protein turnover in women taking HRT than in their non-HRT using counterparts. These findings point to an enhanced pro-anabolic muscle environment in both sedentary and exercising women exposed to HRT and pointing to a potential mechanism by which HRT manifests positive effects on muscle mass and function. Another recent study also demonstrated that yearlong exposure to HRT increases expression of genes associated with the insulin-like growth factor-1 (IGF-1) signalling cascade in post-menopausal females [21]. IGF-1 is a potent signal for muscle hypertrophy and satellite cell activation [22] and as such, these findings point to another likely mechanism by which HRT can positively influence skeletal muscle mass.

Dieli-Conwright et al. [20] also reported that HRT could minimize indices of muscle damage, such as the post-eccentric exercise rise in blood creatine kinase (CK) and lactate

dehydrogenase (LDH) activities as well attenuate markers of inflammatory signalling in muscles of older females. These findings suggest that HRT will also act to attenuate exercise induced muscle damage and inflammation in post-menopausal females.

A recent meta-analysis of 29 human studies which examined that potential effect of HRT on muscle force also concluded that on balance, studies indicate that estrogen exposure has the ability to significantly increase acute muscle force by mechanisms beyond just increases in muscle mass [23]. The current weight of evidence suggests that estrogen and HRT have positive effects on muscle mass, muscle function and muscle force and power generation in older females and that these benefits can translate into positive health and lifestyle benefits for post-menopausal women [16, 24].

#### **Positive effects of estrogen on skeletal muscle; mechanisms from animal studies**

The recent studies demonstrating HRT benefits to skeletal muscle in older females confirm ongoing reports of the positive effects of estrogen on attenuation of skeletal muscle damage and inflammation and enhancement of muscle mass and muscle force from animal studies. Animal studies have also shed light on some of the potential mechanisms by which estrogen and HRT may benefit skeletal muscle.

Numerous animal studies have reported reduced muscle structural damage and diminished muscle membrane disruption following potentially damaging exercise in rodents when they are exposed to estrogen [6, 25-27]. Findings include diminished CK release from muscle, reduced disruption of muscle structural proteins such as dystrophin and desmin and diminished activation of lysosomal enzymes in female rodents or ovariectomized female rodents with estrogen replacement relative to ovariectomized rodents without estrogen replacement [6, 28]. Estrogen is an antioxidant and membrane stabilizer and as such it has the potential to protect muscle membranes from exercise induced muscle damage and to attenuate inflammatory responses [6, 29]. Estrogen has been repeatedly been found to diminish post-exercise inflammation and infiltration of muscle by leukocytes such as neutrophils and macrophages [30-32].

The attenuation of membrane disruption and inflammatory responses such as leukocyte infiltration can act to reduce secondary muscle damage following exercise since inflammatory responses can be responsible for further muscle damage prior to initiation of muscle repair [29, 33]. Neutrophils and macrophages which act to remove damaged tissue by generating powerful oxygen radicals and hypochlorous acid and releasing inflammation and repair regulating cytokines will ultimately help facilitate muscle repair. However some of these actions will also cause potential further damage

to muscle [33]. By attenuation of some of these responses, estrogen may potentially diminish the damaging effects of inflammation consequent to muscle injury [29].

Stabilization of muscle membranes by estrogen can also act to suppress activation of lysosomal and non-lysosomal proteases in muscles [6, 29]. Post-exercise suppression of calpain (a non-lysosomal protease) activation and beta-glucuronidase (a lysosomal protease) activation and the consequent potential diminishing of further secondary muscle damage has been repeatedly demonstrated in ovariectomized female animals with estrogen replacement relative to non-estrogen replaced controls [32, 34, 35]. In addition to protection of muscle membranes, estrogen may also act to stabilize post-exercise muscle calcium homeostasis via its ability to increase nitric oxide synthase (NOS) activity and thereby enhance nitric oxide (NO) synthesis and signalling within muscle [36]. NO has the potential to attenuate calcium entry into cardiac muscle following ischemia-reperfusion injury by stabilizing L-type calcium channels in the sarcolemma and by enhancing calcium uptake by sarcoplasmic reticulum calcium pumps (SERCA). It has been suggested that this is one of the mechanisms by which estrogen enhances protection of cardiac muscle consequent to ischemia-reperfusion injury [36]. Since calcium is also a potent activator of lysosomal proteases in skeletal muscle and since as noted above, activation of these proteases is attenuated post-exercise skeletal muscle, it is possible that estrogen may also be enhancing positive NO signalling in skeletal muscle [24]. Estrogen has also been reported to diminish damage and inflammation consequent to ischemia-reperfusion injury in skeletal muscle of ovariectomized rats [37].

Heat shock proteins (HSPs) are important facilitators of post-synthesis muscle protein assembly and maintenance of protein structure when stressed by heat, trauma or exercise [38]. Estrogen will enhance basal muscle HSP content and thereby provide a further level of protection against potential damage induced by exercise [39]. All of these potential benefits of estrogen could also be providing muscles of post-menopausal females with added protection and resulting in the reported reduced indices of muscle damage and inflammation seen in older women taking HRT [19].

It is well known that estrogen supplementation is a positive influence for muscle and lean carcass development in cattle [40]. Muscle satellite cells are largely responsible for muscle repair, growth and hypertrophy and their involvement in estrogen stimulated growth of cattle has been demonstrated [40]. It has also been demonstrated that estrogen will increase activation and proliferation of skeletal muscle satellite cells following exercise in ovariectomized female rats beyond that seen by exercise alone [34, 35]. Estrogen signalling of muscle satellite cell activation and proliferation

is mediated via estrogen receptor-alpha located on skeletal muscle which may in turn activate a number of possible signalling pathways including IGF-1 signalling, NO signalling or activation of the phosphor-inositide-3 kinase/protein kinase B (PI3K/Akt) pathway which then act to positively influence muscle satellite cells [35-41]. In this regard, it has also been demonstrated that recovery of atrophied rodent hindlimb muscle is prevented by ovariectomy and facilitated by estrogen replacement, with estrogen signalling muscle re-growth possibly via Akt and IGF-1 signalling pathways [42]. Ovariectomy also prevents satellite cell activation in skeletal muscle of rats following exercise, suggesting that estrogen presence is obligatory for muscle growth in female animals [35]. It is possible that similar mechanisms are at work in the ability of estrogen and HRT to induce muscle mass enhancement in post-menopausal women [6].

Estrogen may also increase muscle strength and force production independent of increases in muscle mass. Several recent studies in rodents demonstrated that ovariectomy results in up to a 20 percent reduction in titanic muscle force which is restored upon estrogen replacement [43, 44]. These changes are independent of the effects of estrogen on animal activity levels [45]. A recent meta-analysis of a large number of animal studies also concludes and confirms that estrogen will significantly enhance muscle force development capacity [23]. In a recent review, Lowe et al. [4] report on their research findings demonstrating that muscle fibres from ovariectomized mice that are exposed to estrogen have significantly more myosin heads in strong binding configuration during muscular contraction relative to muscles from ovariectomized mice without estrogen exposure. This estrogen induced increase in myosin strong binding fraction is solely responsible for enhancement of muscle strength due to estrogen exposure since the force per actin-myosin crossbridge is unaffected by estrogen exposure or estrogen loss [4, 44]. It is suggested that the ability of estrogen to act as an antioxidant may reduce myosin susceptibility to oxygen radical induced alteration in function and thus positively influence myosin strong binding affinity during muscle contraction [4, 46]. It is also quite possible that these factors and mechanisms may account for the increased muscle force potential reported in studies with HRT in post-menopausal females.

#### **Health effects of estrogen in post-menopausal females**

Human studies have demonstrated that young adult females oxidize relatively greater amounts of fat and less carbohydrate than males when exercising at the same relative intensity [47]. In addition, recent research has shown that post-menopausal females exhibit increased incidence of type

2 diabetes, reduced insulin sensitivity, increased fat mass and increased systemic inflammatory markers [48]. These same features are seen in ovariectomized rodents, suggesting that estrogen may play a role in reducing the incidence of type 2 diabetes, insulin insensitivity and weight gain in aging females [48]. Human studies have suggested that HRT may protect against obesity-induced insulin resistance in older women in part by inducing increases in heat shock proteins (HSPs) [49-51]. These data suggest that estrogen and HRT could help limit the onset of type 2 diabetes in aging females [24, 49].

The positive association of bone mass and density with estrogen in older women has been well established in the scientific literature [16]. Bone mineral loss accelerates following menopause in women and this accelerated bone loss is prevented by HRT [16, 52]. Exercise and HRT may also independently and additively help maintain bone mineral density in aging females [16].

The overall health benefits and drawbacks of HRT in older women has been controversial, particularly since the publication in 2004 of the Women's Health Initiative study which reported a higher incidence of stroke in women on HRT containing both progesterone and estrogen without substantially increasing other health benefits [53]. However this study examined a wide age range of post-menopausal women. A recent follow up on this study concluded that in younger post-menopausal women with hysterectomies, the use of HRT for up to 6 years was not associated with increased risk of cancer, stroke or increases in total mortality [54]. Others have also suggested that the greatest benefits of HRT to skeletal muscle may be seen in women nearer the age of menopause [16].

Estrogen has been shown to provide damage protection in a range of other tissues, beyond muscle and bone, including cardiac, neural, hepatic and vascular tissues [6]. Evidence from animal and human studies have suggested that if HRT is not initiated proximal to ovariectomy or menopause, the protective effects of estrogen on neural and vascular tissues is lost [55, 56]. If these same effects hold true in skeletal muscle, and other tissues, this may help explain why younger post-menopausal females may benefit most from timely HRT following onset of menopause. It may also explain the lack of health benefits from HRT in the 2004 Women's Health Initiative study since most of the subjects of this study initiated HRT well distal to menopause [55].

#### **Conclusion**

The weight of evidence from human and animal studies demonstrates that estrogen based HRT will have significant beneficial effects on skeletal muscle mass, strength and protection from damage in older women. Benefits to skeletal

muscle may be most evident in younger post-menopausal females and those who initiate HRT proximal to menopause. The benefits of HRT in maintaining muscle function and mass may help offset aging related loss of muscle mass and strength and may help prolong the ability of aging females to maintain a functioning independent lifestyle. These benefits coupled with other known benefits of HRT in maintaining bone mineral density, and diminishing the risks of type 2 diabetes and weight gain in older women, coupled with new evidence for HRT safety, particularly in younger post-menopausal females, could suggest that the benefits of limited HRT use could be an important adjunct for maintaining overall health in aging women.

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