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Body composition and muscle performance during menopause and hormone replacement therapy

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ABSTRACT. Menopausal transition is characterized by ovarian failure and its consequent decrease in female sex steroid production. Earlier studies suggest that an increase and redistribution of body fat during menopause predispose women to cardiovascular disease and metabolic syndrome. In addition, peri- and post-menopausal women seem to have less lean body mass (LBM) compared with pre-menopausal women. Accordingly, a changing ovarian hormonal status may accelerate the loss of muscle mass and result in decreased muscle performance and functional capacity. Hormone replacement therapy (HRT) has been used to treat menopausal symptoms and as a primary prevention therapy in chronic conditions. Inconsistent findings have, however, been published on the effects of HRT on body composition in post-menopausal women. Some studies clearly suggest that HRT counteracts menopause-related changes in body composition whereas others fail to show any difference between post-menopausal HRT users and abstainers. Although cross-sectional studies show conflicting results concerning the association between HRT and muscle performance, experimental trials suggest that deterioration in muscle force during menopause can be prevented by HRT. In the future, longitudinal data need to be collected to confirm changes in body composition and muscle performance during menopausal transition irrespective of age. Although HRT seems to have beneficial effects on body composition and muscle performance in healthy post-menopausal women, there is considerable variation in the effects of HRT between different studies. The underlying mechanism of HRT action on muscle performance is still unclear.
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INTRODUCTION

Aging can be characterized by changing endocrine activity. Dysfunction of the pancreas and thyroid is of clinical importance, and these age-associated conditions are often treated as a disease. There are also other endocrine systems that show decreased production of hormones during aging. These physiological changes are related to normal aging and therefore the deprivation is not necessarily treated with hormone replacement therapy (HRT) (1). Somatopause is characterized by a gradual deprivation of GH/IGF-I axis due to a changing hypothalamus and pituitary status. Adrenopause, decreased levels of plasma dehydroepiandrostenedion (DHEA), and dehydroepiandrostenedion sulphate (DHEAS) result in a decreased conversion of these steroids into sex hormones in peripheral tissues, mostly in fat. Menopause is an age-induced condition of female hypogonadism that is characterized by ovarian failure and a rapid and dramatic decrease in female sex hormone production (2).
Menopausal transition seems to be the most dramatic and abrupt age-induced endocrinologic event. The decrease in the production of female gonadal steroids also seems to occur earlier than the deprivation observed in other endocrine systems. The average menopausal age, 51 yr, has not changed notably over time despite the obvious increase in life expectancy. Today, women may spend nearly one third of their life in a sex hormone deficient state.
It has been suggested that the menopausal hormonal deprivation is associated with changes in metabolism and body composition that adversely influence chronic conditions such as osteoporosis, cardiovascular diseases and metabolic syndrome. In addition, there exists some evidence that sex hormone deficiency is related to poor muscular performance in post-menopausal women. A decrease in muscle per-

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formance during peri-menopause predisposes women to decreased functional capacity and disability. Disability can be characterized by weakness, impaired mobility, and decreased physical activity, all of which are risk factors for the previously mentioned chronic conditions. Strategies aimed at preventing changes in body composition and muscle performance during menopause might, therefore, be effective in decreasing the risks of chronic conditions, disability and frailty in aging women.

Post-menopausal HRT has been prescribed by physicians for several decades in order to relieve menopausal symptoms. Several studies have also suggested that HRT plays an important role in the primary prevention of osteoporosis (3) and cardiovascular disease (4). However, over the last few years, more critical opinions have been expressed on the potential benefits and risks associated with HRT (e.g. 4).

The role of female sex steroids in body composition has been investigated quite extensively whereas the published data on the effects of post-menopausal HRT on muscle performance in middle-aged and older women are still scanty. This review focuses on the effects of menopause-related changes on female sex steroids, body fat, total and regional lean mass, and skeletal muscle performance. In addition, the effects of post-menopausal HRT on body composition and muscle performance will be addressed. Finally, the potential mechanisms by which female sex steroids could act on skeletal muscle in peri- and post-menopausal women are discussed.

MENOPAUSAL CHANGES IN SEX HORMONES

The average menopausal age, and thus the cessation of the woman's reproductive life, is largely controlled by the genes. Snieder et al. (5) showed that 63% (95% confidence interval 53-71%) of the variance in the average menopausal age is determined by genetic factors. Menopausal transition is initiated by exhaustion of ovarian follicles and age-induced changes in hypothalamo-pituitary unit (1, 6). During the menopausal transition, cyclic estradiol production is replaced by a very low level of constant ovarian estradiol synthesis. Circulating estrone, which is synthesised from the adrenal steroids androstenedion, DHEA, and DHEAS in peripheral tissue, becomes the most abundant estrogen in serum after menopause. Rannevik et al. (2) showed that the serum concentrations of estradiol and estrone decrease by 67 and 35%, respectively, during the first 6 menopausal months. During the following post-menopausal years, the estradiol and estrone concentrations continue to decrease, but they do so at a slower rate. The secession of ovulatory cycles and luteinization of follicles during menopause also results in the decreased synthesis of ovarian progesterone (6).

In concert with the decreased estrogen concentrations, an increased production of gonadotrophins, follicle stimulating hormone (FSH), and LH secreted by anterior pituitary lobe is also observed (1, 2). This is due to the decreased inhibition of the hypothalamo-pituitary unit by ovarian sex steroids and inhibin. Rannevik et al. (2) showed that more than 95% of their subjects had elevated serum FSH and LH levels after the first 6 post-menopausal months. Therefore, serum FSH level is often used as an indicator of menopausal status.

Circulating testosterone in post-menopausal women originates from the ovary and peripheral aromatization of androstenedion, DHEA, and DHEAS. Serum testosterone and adrenal steroid concentrations decrease slightly (14-18%) during the first menopausal year (2). Thereafter only very small changes are observed in the concentrations of serum androgens.

BODY COMPOSITION AND MUSCLE PERFORMANCE IN PRE- AND POST-MENOPAUSAL WOMEN

Age-induced changes in body composition have widespread consequences on an individual's health and functional capacity. Previous studies in women suggest that changes in body composition coincide with menopause and that at least some of these changes are explained by the deprivation of female sex steroid production.

Body fat

There is an overwhelming amount of evidence in the literature showing that post-menopausal women have higher total body fat mass, fat percentage and a greater accumulation of central fat than pre-menopausal women (e.g. 7-11). It has also been suggested that clinically relevant changes in body composition already occur during menopausal transition (peri-menopause). Total body fat mass and fat percentage are greater in peri-menopausal women compared with pre-menopausal women (8, 12). Greater central body fatness and less fat in the legs in peri- compared with the pre-menopausal women suggest more android distribution of fat already during middle age. A 6-yr follow-up study by Poehlman et al. (13) confirms the results obtained from the cross-sectional data. Women who spontaneously stopped menstruating had a greater increase in fat mass,

assessed using underwater weighting (UW), than did women who remained pre-menopausal.
Earlier studies collectively suggest that menopause is characterized by changes in body fat. Whether these changes are due to female sex hormone deprivation or aging *per se* is still unclear. A regression analysis performed on cross-sectional data showed that significant age-independent changes in body fat mass, fat percentage and the amount of central fat were related to the menopausal status and the number of years since menopause (9). On the other hand, conflicting data have also been published. For example, Douchi et al. (7) and Wang et al. (14) have suggested that adiposity and fat redistribution in women are merely related to age and not to menopausal status.

Fat-free mass

The association between menopause and lean body mass (LBM) or fat-free mass (FFM) has also been investigated quite intensively. However, considerable methodological differences exist among studies and, therefore, in the definition of the LBM and FFM. Some studies make use of measures that include the whole musculoskeletal structure in the determination of FFM, such as UW and bioelectrical impedance (BIA). Other studies utilize techniques which are capable of separating fat-free soft tissue from the bone mineral mass (dual-energy X-ray absorptiometry, DXA or multi-frequency BIA). While none of these studies have utilized medical imaging modalities such as computerized tomography (CT) or magnetic resonance imaging (MRI), several studies have been published on the relationship between age and CT- or MRI-measured skeletal muscle mass. Due to the capability of separating intramuscular fat from the lean muscle tissue, CT and MRI give rather specific estimates of regional muscle mass.
Aging is characterized by reduced muscle mass (sarcopenia) after the age of 50. Sarcopenia is a consequence of several neuromuscular events occurring at the cellular and molecular levels. Older subjects have a reduced number of slow twitch oxidative and fast twitch glycolytic muscle fibers together with decreased fast twitch fiber cross-sectional area (CSA) compared with younger subjects (15). Intramuscular fat infiltration (15) and increased amount of connective tissue (16) is observed together with sarcopenia.
Cross-sectional data collected by DXA have shown that post-menopausal women have less lean mass in the whole body, trunk and lower extremity regions than do pre-menopausal women (7-9, 12, 13, 17). The loss of LBM seems to start during the menopausal transition (12, 13), suggesting that sarcopenia is associated with menopausal status and is, at least partly, independent of age (7, 9, 12-14, 17). The 6-yr follow-up study by Poehlman et al. (13) also showed that women who experienced menopause lost more FFM compared with age-matched women who remained pre-menopausal. Conflicting findings have also been observed. For example, Toth et al. (10) assessed total body FFM and skeletal muscle mass using DXA, and found no difference between pre- and early post-menopausal (6-60 months) women.

Muscle performance

Although the studies referred to earlier did not include specific measurements of skeletal muscle mass, the results obtained from LBM and FFM suggest that a changing ovarian hormonal status is one of the factors that trigger sarcopenia. The association between menopause and decreased energy expenditure (13) may be due to the loss of metabolically active tissue, predisposing women to metabolic syndrome. It also appears that sarcopenia is the major cause for age-related decrease in muscle performance, increasing susceptibility to fracturing, disability, and frailty.
Muscle strength declines during aging. The annual decline is approximately 1% in middle-aged men (18) and 2% in men over 65 yr (19). In healthy, older women, the annual decline in strength is approximately 1 to 2% (19, 20). Although a decline in muscle strength is observed in both genders, women may experience a more rapid decline during the menopausal transition.
A cross-sectional study by Samson et al. (21) showed an accelerated non-linear decline in isometric knee extension strength and hand grip strength in women over the age of 55. In contrast, they reported that men had a more gradual and linear strength decline over the age range of 20-90 yr. In addition, Phillips et al. (22) suggest that the specific force (i.e. strength-to-muscle-area ratio) of the *adductor pollicis* muscle declines dramatically in women around the time of menopause while in men, the decline starts much later – at the age of 60 yr. Other studies investigating the relationship between muscle strength and age have not shown any notable difference in strength decline between the genders (e.g. 23, 24) probably because these studies were not designed to capture the possibility of strength changes during the menopausal transition.

BODY COMPOSITION, MUSCLE PERFORMANCE AND HRT

Studies investigating the relationship between HRT, body composition and muscle performance

vary with respect to their design, measurement technique, the particular HRT used, and the subjects under investigation. A major concern with these cross-sectional studies is the lack of HRT standardization. Women accepted into the HRT groups have used different preparations for different lengths of time. It is notable that some reports do not even list the preparations used. However, it has been suggested that the association between body composition and HRT is dependent on the drug and combination of drugs included in the HRT (25, 26).

Body fat

Studies comparing HRT users with HRT abstainers show conflicting results in the relationship between body fat and HRT. For example, Site et al. (27) observed that total body fat mass and visceral adipose tissue CSA were lower in a group of 50-71 yr old HRT users compared with non-users. Lower total body fat mass and fat percentages were also observed in a group of younger (46-55 yr old) HRT users compared with non-users (28). On the other hand, some other studies have not shown any difference in the total or regional fat mass or fat percentage between post-menopausal women on HRT and women with no recent history of replacement therapy (25, 29, 30).

Experimental trials have also failed to show consistent results regarding the effects of HRT on body fat in post-menopausal women. Some of the studies show that estrogen implants (50 mg), estradiol/norethisterone acetate and estradiol valerata/cyproterone acetate for 3 to 36 months have beneficial effects on body fat distribution in on the average 50 to 55-yr-old women (31-33). Other trials, however, have not shown any difference in the amount of body fat between women assigned to conjugated equine estrogen/medroxyprogesterone (34, 35) or estradiol/norethisterone acetate (36, 37) treatment and control or placebo groups.

Fat-free mass

In most cross-sectional studies, no significant difference is observed between HRT users and non-users in the total or regional lean mass, or the body cell mass assessed using DXA, BIA, or CT (e.g. 25, 27-30). However, Dittmar (25) conducted a more detailed analysis on the drugs included in the HRT and found that body cell mass was higher in women on HRT, including estradiol-based and testosterone-derived gestagen compared with the women not on HRT. In the same study, the body cell mass of the women using either conjugated equine estrogens or progesterone-derived gestagens did not differ from that of the HRT abstainers.

A selection of experimental trials on the effects of HRT on fat-free and skeletal muscle mass in healthy post-menopausal women is reviewed in Table 1. In our double-blinded, placebo-controlled trial (36), 12 months of estradiol/norethisterone acetate treatment induced there was a significant increase in LBM (2.4%), measured using BIA, in 6-60 months post-menopausal women compared with a placebo group (–0.6%). We also found that the CT-measured lean tissue CSA of knee extensor muscles increased on average by 5.8% and that of the lower leg muscles increased by an average of 6.8% due to HRT while the changes in the placebo-treated women were 0.4 and 3.7%, respectively. Other studies also suggested that 3-12 month course of estradiol/norethisterone acetate (33, 38) and 3 yr of estradiol valerate/cyproterone acetate (32) induce a significant increase in LBM (32, 33) and muscle mass (38) in 50-55 yr old women compared with placebo and control groups. On the other hand, no change has been observed in total body or leg lean tissue mass after 6 months of HRT including estradiol/norethisterone acetate (37), or after 2 to 3 yr of estradiol implants (31), or conjugated equine estrogens with medroxyprogesterone (34) in women with a mean age of 52 yr. Experimental trials fail to show consistent results on the role of particular HRT drugs on either LBM or muscle mass in post-menopausal women (Table 1). Before any firm conclusions are made on this topic the effects of different pharmaceutical products should be tested in the same clinical trial.

Muscle performance

Only a few studies have investigated the role of female sex steroids in muscle performance among middle-aged and older women, and the results obtained from these studies are somewhat conflicting. In the study by Phillips et al. (22), a group of women, aged 42-72, on either combined estrogen/progestin or estrogen therapy had greater specific force of the *adductor pollicis* muscle than did a group of similar aged women who were not on HRT. A positive association between serum estrogen concentration and grip strength in the average 56- and 58-yr-old women has also been reported (39, 40). On the other hand, Taaffe et al. (30) and Seeley et al. (41) showed no difference in lower-body muscle strength and functional capacity between HRT users (mostly conjugated estrogens) and non-users over the age of 65. Accordingly, the muscle strength of women who, on average, were 14 yr post-menopausal and who had been undergoing HRT for an average of 11 yr, did not differ from that

Table 1 - *Summary of experimental studies on the effects of hormone replacement therapy on fat-free and skeletal muscle mass in post-menopausal women.*

Reference	Group: mean age (SD or range), yr	No.	Menopausal status, mo or FSH mean (SD) or range	Treatment	Intervention time (mo)	Technique	Outcome	Mean effect, change, %	Comments
Aloia et al (1995)	H: 51.2 (0.7)	30	6-72 mo	CE 0.625 mg· d^{-1} 25d, MPA 10 mg·d^{-1} 10 days	~36	DPA	LBM, kg·yr^{-1} (SD)	-3.1 (0.3) *	Statistics: one-way ANOVA
	C: 52 (0.6)	36		Calcium carbonate				-2.3 (0.4) *	
	P: 53.4 (0.6)	28		Placebo				-2.2 (0.3) *	
Davis et al (2000)	E: 50.1 (3.8)	17	>12 mo/ >15 IU·l^{-1}	E_2 implant, 50 mg + MPA 5-10 mg or NA 2.5 mg	24	DXA	FFM	0.7	Progestin for those with intact uterus, N not given; single blind design
	ET: 52.0 (3.1)	15		E+testosterone implant 50 mg +MPA 5-10 mg or NA 2.5 mg				12.5 *	
Gambacciani et al (2001)	H: 49.5 (0.7)	18	11 (1) mo/ 75 (5) IU·l^{-1}	E_2V 2 mg·d^{-1} 21 d, CPA 1 mg· d^{-1} 10 days	36	DXA	LBM Leg LM Trunk LM Arm LM	3.6 * -1 0 4.5	Subjects had no history of earlier HRT 6 mo prior the study; subjects were not randomized
	C: 49.8 (0.8)	13	10 (1) mo/ 75 (6) IU·l^{-1}	Calcium carbonate 500 g·d^{-1}			LBM Leg LM Trunk LM Arm LM	-10 * -4.8 -4.6 * -2.3	
Jensen et al (1986)	H_{high}: 50.2 (44-54)	40	33, 6-62 mo	E_2 4+E 2 mg·d^{-1} 22 d, E_2 1+E 0.5 mg·d^{-1} 6 d, NA 1 mg·d^{-1} 10d	12	UCE	UCE, %·$24h^{-1}$/ BW	14 #	
	H_{medium}: 52.4 (46-56)	42	46, 29-62 mo	E_2 2+E 1 mg·d^{-1} 22d, E_2 1+E 0.5 mg·d^{-1} 6 d, NA 1 mg·d^{-1} 10 d				5 #	
	H_{low}: 53.0 (48-55)	23	44, 28-58 mo	E_2 2 mg·d^{-1} 22d, E_2 1 mg·d^{-1} 6 d, NA 1 mg·d^{-1} 10d				5 #	
	P: 50.7 (46-55)	23	45, 29-62 mo	Placebo				-5	
Sipilä et al (2001)	Ex: 53.4 (1.9)	12	6-60 mo/ >30 IU·l^{-1}	High-impact exercise ~ 2·wk^{-1}	12	BIA CT	LBM QLCSA LLCSA	2.2 # 1.9 3.1	Double blind design; Continuous administration of NA
	H: 53.5 (1.8)	15		Estradiol 2 mg·d^{-1}+ NA 1 mg·d^{-1}			LBM QLCSA LLCSA	2.4 # 5.8 # 6.8	
	ExH: 54.0 (2.1)	10		Ex + H			LBM QLCSA LLCSA	2.4 # 7.0 # 9.2 #	
	P: 53.2 (1.9)	15		Placebo			LBM QLCSA LLCSA	-0.6 0.4 3.7	
Skelton et al (1999)	H: 60.9 (3.2)	37	60-180 mo	CE 0.625 mg· d^{-1} 28 d, N 0.15 mg·d^{-1} 10 days	13	Anthropo-metry	*Adductor pollicis* CSA	~ -0.8	
	C: 60.6 (3.3)	48						~ -1	
Sørensen et al (2001)	H: 55 (3)	16	~72 (48) mo/ 81 (27) IU·l^{-1}	E_2 4 mg·d^{-1} 22 d, E_2 1 mg·d^{-1} 6 d, NA 1 mg·d^{-1} 10 d	3	DXA	LBM (kg)	0.35 (0.86) #	Cross-over design with 3 mo washout period
	P: 55 (3)			Placebo				-1.0 (1.6) *	
Walker et al (2001)	H: 51.9 (3.3)	15	>6 mo/ 75 (21) µmol l^{-1}	E_2 2 mg·d^{-1} 22 d, E_2 1 mg·d^{-1} 6 d, NA 1 mg·d^{-1} 10 d	6	DXA	LBM X LegLM X	0.5 0	Open design
	P: 52.3 (2.4)	15	77 (31) µmol·l^{-1}	Placebo			LBM X LegLM X	0.8 0.8	

#: significantly different from P or C; *: significantly different from zero or baseline; X: personal communication; BIA: bioelectrical impedance; C: control; CE: conjugated estrogens; CT: computerized tomography; CSA: cross-sectional area; DXA: dual x-ray absorptiometry; DPA: dual photon absorptiometry; E: estriol; Ex: exercise group; ExH: exercise and hormone replacement therapy; ET: estrogen+testosterone group; E_2: estradiol; E_2V: estradiol valerata; H: hormone replacement therapy; LLCSA: lean CSA of lower leg muscles; mo: months; MPA: medroxyprogesterone acetate; N: norgestrel; NA: noretisterone acetate; P: placebo; QLCSA: lean tissue CSA of the quadriceps muscle; UCE: urinary creatinine exertion rate; d: days.

of the women at equal menopausal status and age but without a history of HRT (29).

Experimental studies investigating the effects of HRT on muscle performance suggest that HRT either prevents the strength decline or improves the muscle strength in healthy post-menopausal women, regardless of the number of years since menopause. An open trial by Greeves et al. (42) showed a significant decline in muscle strength during 10 months of follow-up in women who were 12-36 months post-menopausal. In the same study, strength decline was prevented by HRT including various different preparations. The preventive effect of HRT was, however, only observed in isometric and slow isokinetic (1.05 $rad \cdot s^{-1}$) knee extension strength, whereas no significant interaction was observed in grip or fast isokinetic (>2.09 $rad \cdot s^{-1}$) knee extension strength. Heikkinen et al. (43) also observed an increase in isometric back extensor muscle strength after 2 yr of estradiol valerata/medroxyprogesterone acetate treatment in a group of post-menopausal women aged 49-55 yr. In somewhat older women (10 yr post-menopausal on average), a significant decline of 2.9% was observed in *adductor pollicis* muscle strength during a 1-yr follow-up. In contrast, women on HRT, including conjugated estrogen/norgestrel, increased muscle strength by 12.4% with no change in muscle CSA (44).

In our placebo-controlled study on the effects of HRT on skeletal muscle performance in early post-menopausal (6-60 months) women (36), the administration of estradiol with continuous norethisterone acetate for 6 months increased isometric knee extension force by an average of 8%, whereas the placebo group showed a mean decrease of 4%. In the same study, leg extensor power, assessed by vertical jumping height, showed a mean increase of 7% in the HRT group compared with a decrease of 6% in the placebo group. In the women who continued for 12 months in the study, the knee extension force in the HRT group returned to the baseline level, whereas the leg extensor power was still an average of 7% higher compared with the baseline value. The placebo-treated women had a mean decrease of 8 and 5%, respectively, in the extension force and power after 12 months of follow-up.

The leg extensor power results of our study are of great interest because muscle power is highly predictive of functional disability in the older population. An adequate amount of muscle strength produced in a short period of time is important in several activities of daily living. It has also been suggested that muscle power declines earlier and faster than muscle strength – the average annual decline in leg extensor power is approximately 3.5% in women over the age of 65 (45).

Suggested mechanism for female sex steroid action on skeletal muscle tissue

Only a limited number of studies have suggested mechanisms by which female sex steroids may act on skeletal muscle tissue in women. However, a considerable amount of data exists on the mechanism of action of estrogens in non-muscle tissue in women and muscle tissue in experimental animals. These studies suggest that female sex steroids have complex mechanisms of action including estrogen receptor mediated, non-genomic mediated, and possibly also non-receptor mediated pathways (46). The presence of the hormone specific receptors in the skeletal muscle cell is required for the direct action of female sex steroids on the muscle. Decades ago, experimental animal studies showed that rabbit (47), rat (48-50), and bovine (51, 52) skeletal muscle tissue contains estrogen receptors, suggesting that skeletal muscle is a target tissue for this hormone. Kahlert et al. (26) also showed that the rat L6, and mouse Slo8, and C2C12 myoblasts contain functional estrogen receptors. In the same study, estrone induced a significant myoblast growth, whereas estradiol had no effect. In addition, both estrone and estradiol induced an expression of transcription factors in proliferating myoblasts.

Only a limited number of publications exist on the presence of steroid hormone receptors, including estrogen and progesterone receptors, in human skeletal muscle. Saartok et al. (53) showed that the *erector spinae* muscle of scoliotic patients, aged 9-35, contained androgen and glucocorticoid receptors, whereas estrogen receptors were undetectable.

The interaction between female sex steroids and the receptors of the other hormones or enzymes has been suggested as a possible mechanism for estrogen action on skeletal muscle. Earlier studies have shown that estradiol can enhance the androgen receptor interaction in rat skeletal muscle (54) and modulate insulin action at the insulin receptor level, thereby participating in the regulation of glucose metabolism (55). Moreover, a recent study by Joe and Ramirez (56) showed that estradiol has a high binding affinity to glyseraldehyde-3-phosphate dehydrogenase (GAPDH) and that both estradiol and progesterone regulate the catalytic activity of the GAPDH – an important enzyme in glycolysis. If female sex steroids improve insulin-mediated glucose uptake and utilization in skeletal muscle, functional capacity and muscle performance may be associated with the concentration of available female sex steroids.

Recently, the association between the renin-angiotensin converting enzyme (ACE) genotype and physical performance has been investigated. ACE

degrades vasodilator agents and generates vasoconstrictor angiotensin II. A local renin-angiotensin system has been also found in skeletal muscle (57). Montgomery et al. (58) showed that subjects with ACE insertion (I) genotype had a greater anabolic training response than did subjects with one or more depletion (D) alleles. The authors suggested that II genotype is a marker for low ACE activity that may be associated with enhanced metabolic efficiency. Accordingly, Woods et al. (59) showed that a significant gain in muscle force due to the HRT (conjugated estrogens/norgestrel) was strongly influenced by ACE genotype. HRT induced greater changes in the force of the *adductor pollicis* muscle in post-menopausal women with the ACE II (16%) and ACE ID (14.3%) genotypes than women with the ACE DD (7.8%) genotype. This interesting finding suggests that HRT combined with low serum and tissue ACE activity may provide the greatest benefits in preventing deterioration in muscle performance and functional capacity in peri- and post-menopausal women.

CONCLUSIONS

When investigating the association between menopausal hypogonadism and body composition and performance, healthy pre-, peri-, and early post-menopausal women are the most desirable groups of subjects to study. With advancing age, the deprivation of several other endocrine systems may interfere in the relationship between hypogonadism and body composition and performance and thereby distort the results.

Previous literature suggests that climacteric is characterized by increased fatness and a shift towards central android fat distribution. An increase in fat tissue occurs together with a loss of fat-free lean tissue. A decrease in skeletal muscle mass is associated with a decreased muscle performance and functional capacity. The changes in body composition and performance may predispose women to an increased risk of chronic conditions, disability and frailty. The observations concerning changes in body composition and performance during menopause are mainly based on cross-sectional designs. Longitudinal studies with more sophisticated measurement techniques (e.g. CT and MRI) are needed to confirm previous results and to capture changes that are due to the sex-hormone deprivation irrespective of age. Moreover, when the menopausal status of the subjects is defined, menstrual status with serum concentration of FSH and estrogen should be measured and reported.

Previous literature has failed to show consistent data regarding the effects of HRT on body composition during climacteric despite intensive research efforts performed on this topic. There is also a lack of consistent findings concerning the effects of the particular pharmaceutical product or drug used in the HRT on body composition in post-menopausal women. On the other hand, the few experimental studies investigating the effects of HRT on muscle performance have suggested that HRT has a beneficial influence on skeletal muscle irrespective of the drug used. Despite this observation, additional carefully designed trials are needed to confirm the positive effects of HRT on muscle performance. In experimental trials, post-menopausal women have been assigned to 3-36 months of HRT, control, or placebo treated groups. The placebo-controlled design is, however, questionable when using cyclical HRT preparations because these medications induce withdrawal bleeding and, consequently, the subjects will be aware of the active hormone in the pills.

It is quite obvious that female sex steroids have many effects on different organs and systems extending beyond the essential role of these hormones in the control of reproductive function. The mechanism by which female sex steroids act on skeletal muscle performance in women is still unclear. Female sex steroids have complex mechanisms of action and therefore more research is needed to explore all the pathways by which female sex steroids could act on skeletal muscle in peri- and post-menopausal women.

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