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Adipose Tissue Metabolism and Effect of Postmenopausal Hormone Therapy on Change of Body Composition

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1. Introduction

Obesity is a process by which excess energy accumulates and results in increasing fat deposition in various parts of the body. Obesity is associated with economic, social, and lifestyle factors, and is commonly induced by imbalanced energy intake and consumption of high calorie foods or low physical activity. Obesity is a worldwide issue in public health that significantly increases the risk for type 2 diabetes, metabolic syndrome, atherosclerosis, and cardiovascular disease.

Body weight increases with aging in both genders, irrespective of the baseline weight in normal and obese individuals [1]. This increase in body weight is attributed to a reduction in energy expenditure with decreased physical activity. The global prevalence of obesity has been reported to be higher in females than males [2]. A US population survey estimated that approximately two thirds of women 40 - 60 years of age are overweight or obese [3].

In addition to aging, the menopause is considered an important factor for contributing to altered adiposity in women. Menopause is defined as a decline in endogenous estrogen production from the ovaries, and clinically represents cessation of menstruation and loss of fertility. Estrogen loss is the most significant event impacting a variety of physiologic and psychological changes in women. In the peri- or postmenopausal period, a change in adiposity has been well described. Weight gain during the menopausal transition has been scrutinized as a critical factor to midlife body weight in women [1]. Several observational studies have shown increased weight gain during the menopausal transition [4, 5]. A number of clinical trials have demonstrated a significant association between menopausal status with changes in anthropometry, blood pressure, lipid profile, and glucose/insulin metabolism [6-11], which can be linked to increased cardiovascular morbidity and mortality during the postmenopausal period [12].

Given the collective evidence on the change in adiposity across the menopausal transition, the roles of sex hormones, especially estrogen, are of increased interest in understanding the regulation of adiposity. This review discusses the association between estrogen and adiposity, and the interaction of estrogen with other biological metabolites and substances

involved in obesity. In addition we summarize evidence for the effect of postmenopausal hormone therapy (HT) on changes in body composition.

2. Adipose tissue

Adipose tissue has a vital role in the lives of mammals. The primary function of adipose tissue is to store excess energy within the body in the form of free fatty acids (FFAs) and heat production. However, adipocytes are currently regarded as an independent endocrine organ since the metabolic and endocrine actions have been revealed.

In mammals, two types of adipose tissue exist (white adipose tissue [WAT] and brown adipose tissue [BAT]) [13]. WAT represents the major component of adipose tissue and provides most of the total body fat [13]. Moreover, WAT is the main source of FFAs that are available as energy substrates for generation through oxidative phosphorylation of adenosine triphosphate (ATP) high-energy bonds [13, 14]. Excess WAT in the upper parts of the body (android type obesity) represents a strong risk factor for some inflammatory pathologies [15]. In contrast, accumulation of WAT in lower body parts (gynecoid type obesity) is not associated with metabolic complications [13, 15].

In contrast to WAT, BAT participates in energy expenditure from non-oxidative phosphorylation in the form of heat for cold adaption [16]. The uncoupling of phosphorylation in BAT is attributed to the activity of uncoupling protein-1, which is expressed on the mitochondrial membrane, by creating a proton leak that depletes the electrochemical gradient needed for oxidative phosphorylation [14, 16]. BAT represents a smaller number of fat cells that have a rich vascular supply, which can respond more rapidly to sympathetic nervous system stimulation, and elicits heat production, rather than ATP production from nonshivering cold adaptive thermogenesis [14, 16]. In humans, BAT helps to maintain body temperature in newborns, but BAT regresses with increasing age and is completely lost in adulthood [17, 18]. Recently, Virtanen et al. studied BAT deposition in healthy adults using the glucose analogue, ^{18}F-flurodeoxyglucose, uptake by PET and computed tomography [18]. Metabolically-active BAT depots in paracervical and supraclavicular adipose tissue, which can be induced in response to cold and sympathetic nervous system activation, has been reported [14, 16, 18]. The presence of BAT in human adults is of potential interest in understanding the mechanism of obesity, and may provide a rationale for pharmacologic and gene expression manipulation to combat human obesity [14, 18, 19].

3. Deposition and distribution of adipose tissue

Deposition of the fat mass has a different pattern between the genders. Young males have little subcutaneous fat and do not show a central-peripheral difference [20], whereas women of reproductive age have more subcutaneous fat than men at all measured subcutaneous regions [21]. In addition, with an increasing severity of obesity, adipose tissue thickness is higher in the central regions in men, but women exhibit a peripheral deposition [20]. This pattern of fat deposition is altered in women across the menopausal transition; specifically, the total amount of body fat increases, and the peripheral fat shifts around the abdomen. Furthermore, the change in visceral adipose tissue has been ascribed to both chronologic aging and menopause [22, 23]. The results from a clinical study with 156 healthy women

during 4 years of follow-up showed an increase in visceral adipose tissue and total body fat, and a 32% reduction in fat oxidation during the menopausal transition [4]. In the study, the subcutaneous adipose tissue increased in accordance with age independent of menopausal status, while the findings of increased visceral adipose tissue and total body fat were noted only in postmenopausal women. This distinctive physiologic change in amount and distribution of fat in women is noteworthy because the central fat deposition has a more deleterious effect on the development of cardiovascular and metabolic disease [24, 25].

Although the exact mechanism regarding fat redistribution after menopause remains unclear, the phenomenon with declining estrogen level may be due to alterations in adipose tissue metabolism [4]. Several studies have shown that estrogen directly promotes subcutaneous fat accumulation [26], and the loss of estrogen by menopause is associated with an increase in central fat. Several longitudinal studies lend support in suggesting that estrogen plays an important role in regulating body fat distribution. Postmenopausal women who receive estrogen replacement have significantly lower waist-to-hip ratios and less visceral adipose tissue than women who have never received estrogen replacement therapy [27, 28].

In experimental studies, 17β-estradiol (E2) has been shown to regulate adipose tissue by increasing the number of adipocytes through effects on proliferation and differentiation [29, 30]. The number and size of adipocytes is a determining factor for adiposity, and the adipocyte size is balanced by lipogenesis and the lipolysis pathway. Palin et al. have found a direct regulatory effect of E2 on the expression of lipoprotein lipase (LPL) and hormone-sensitive lipase (HSL) in human subcutaneous abdominal adipose tissue [31]. LPL is a major modulator of lipid deposition as triglycerides into adipocytes, and HSL is the rating-limiting enzyme involved in the process of lipolysis. Therefore, the direct effect of estrogen on these enzymes might lead to fat redistribution in postmenopausal women.

As other mechanisms suggest, the role of the estrogen receptor (ER) is focused on estrogen-related action on the regulation of adiposity. Adipocytes express two main subtypes of ERs (alpha [ERα] and beta [ERβ]). ERα was discovered first, and the biological effects of ERα on adiposity have been thoroughly described. ERα is considered to be essential for genomic actions of E2 on the regulation of body fat [32]. Because the hypothalamic nuclei that regulate energy homeostasis express ERα, E2 action could affect adiposity [33-35]. An animal study conducted by Heine et al. demonstrated that glucose intolerance, hypertrophy, and hyperplasia of adipocytes are induced in ERα knockout mice [36], thus supporting a critical role of ERα in determining adiposity.

In contrast, the biological implications of the more recently discovered ERβ have been less revealing than ERα. The binding affinity of estrogen to ERα and ERβ is known to be similar, but the two subtypes of ER only have 56% identity in the ligand binding domain [26, 37, 38]. Therefore, different or competitive roles between both ERs have been repeatedly suggested. Naaz et al. studied the role of ERβ in adipose tissue [39] in mice with ERαKO. When compared to the results generated in ERαKO mice, it was shown that removing E2/ERβ signaling induced a decrease in body weight, the amount of fat, and adipocyte size. Therefore, the authors suggested a potential role for ERβ in regulating adiposity, as well as ERα, but with opposing actions. Thus, the roles for ERs in adipocytes might be an interesting target to further elucidate the estrogen effects on regulating adiposity.

4. Proinflammatory cytokines production

Obesity is a low grade systemic inflammatory state; several studies have addressed adipocyte-related mechanisms involved in regulating proinflammatory [15, 40] and adipocyte-specific cytokines. Systemic chronic inflammation is due to an inflammatory response in adipose tissues that are under quick expansion, and in which macrophages and adipocytes are activated and stimulate the production of proinflammatory cytokines and adipokines [41]. Visceral WAT is considered a main source of inflammation related to obesity. Obese subjects with higher visceral fat exhibit monocyte-chemotactic protein (MCP)-1 expression and infiltration of macrophages in visceral fat compared to subcutaneous fat [42]. Also, several *in vivo* studies have shown higher levels of plasminogen activator inhibitor (PAI)-1, IL-6, and TNF-α in visceral obesity [43, 44].

Recent studies have shown the inhibitory role of estrogen to the inflammatory response in adipose tissue, and cardiovascular and nervous systems [35]. ERα is located in cytokine-producing cells, such as macrophages and microglia, and several *in vitro* studies have reported that E2/ ERα decreases the number of pro-inflammatory cytokines [35, 45, 46]. Another *in vivo* study has demonstrated that both ERα and ERβ regulate proinflammatory cytokine and chemokine production through E2-dependent and independent mechanisms [47].

Because energy expenditure is related to inflammation, a role for nuclear receptor kappa B (NF-κB) has been suggested. NF-κB is a protein complex that controls transcription factor, and is known to have a crucial role in regulating immune responses to infection or stress. NF-κB induces the transcription of inflammatory cytokines, such as TNF-α, IL-1, IL-6, and MCP-1 [41]. In the classical pathway, NF-κB is mediated through IKKβ-induced phosphorylation and proteasome-mediated degradation of IkBα [48]. The other pathway is the activation by hypoxia in the absence of IkBα degradation, a pathway in adipocytes and macrophages which contributes to chronic inflammation in the adipose tissues of obese subjects [41, 49]. Limited evidence has proposed an inhibitory effect of E2 via ERα on NF-κB [50, 51], which partially explains the anti-inflammatory properties of estrogen.

5. Adipokine expression/secretion

Adipokines are a family of cytokines which include leptin, resistin, adiponectin, and TNF-α and are primarily secreted from adipocytes. These adipokines are released from different tissues and organs, and are not exclusively produced by WAT [14, 52].

Leptin, the product of the *ob* gene, has been shown to be a key metabolic hormone in regulating appetite body weight and energy homeostasis [53, 54]. In humans, circulating leptin levels have a parallel correlation with the amount of body fat. In addition, serum levels of leptin have been shown to be higher in women than men [55]. This finding has been hypothesized to be due to a different pattern in fat deposition between the genders and/or the effects of a different hormonal milieu [56]. With respect to the change in leptin levels according to menopausal status, data are inconsistent; some data have shown no change in leptin levels between the pre- and post-menopause [57], while other studies have demonstrated a decrease in leptin levels during the menopausal transition [58, 59]. Some investigators have suggested that the low amount of visceral fat compared with subcutaneous fat in the genders [60, 61] makes it unlikely that the leptin secretion rates from these two depots differ, and may therefore be the cause for the sexual dimorphism in leptin concentrations, suggesting an important role for sex steroid hormones [53]. According to

recent data derived from healthy pre- and post-menopausal women, postmenopausal women had increased levels of tissue plasminogen activator antigen (tPA), MCP-1, and adiponectin [24]. Furthermore, an increase in intraabdominal fat was correlated with C-reactive protein, tPA, and leptin, and negatively with adiponectin levels. The results imply that during the menopausal transition, women have adverse changes in inflammatory markers and adipokines which correlate with increased visceral obesity.

Several animal studies have indicated a stimulatory effect of estrogen on leptin expression and secretion in rat adipose tissues [59, 62]. Machinal et al. reported that there are regional differences in leptin expression between subcutaneous and deep fat tissues in rats, and that leptin secretion increased in the deep fat tissue tissues [63]. Based on one study involving human adipocytes, estrogen is likely to stimulate leptin expression [53]. In a previous study, the association between ER and adipokine expression in 3T3-L1 adipocytes was investigated [64]. The results showed that ERα has a stimulatory effect on leptin expression, while the expression of ERβ is inversely correlated with leptin expression. Therefore, discordant findings regarding the estrogen effect on leptin expression/secretion from other studies can be explained by the different expression of the two ER subtypes, which have opposite actions on the expression of leptin. In addition, if there are regulating factors (genetic or environmental) for ERα or ERβ expression in adipocytes, this may explain how the different expression of ER in adipose tissue can affect the diverse obesity phenotypes.

Adiponectin is a 30 kDa protein secreted abundantly from adipocytes [65, 66], and functions to exert anti-diabetic and anti-atherogenic properties. The serum adiponectin levels are decreased in obese individuals, metabolic syndrome, and type 2 DM [67, 68]. Similar to leptin, circulating adiponectin levels show a sexual dimorphism with higher levels in women than men [69]. Although the estrogen effects for adiponectin expression are limited, some *in vitro* studies have reported no direct regulatory effect in humans and mouse adipocytes [64, 70].

Resistin is a cysteine-rich protein that was originally described as an adipose-derived protein in rodents that links obesity to insulin resistance [71]. However, in human data, the relationship of resistin with obesity and insulin metabolism is still debated. A widely reported biological role of resistin is the regulatory effect involved in inflammatory processes. In addition to adipocytes, resistin is induced by lipopolysaccharides and TNF-α in macrophages [72]. The other data showed that resistin induces or is induced by IL-6 and TNF-α via NF-κB in human monocytes [73, 74]. Data on estrogen effects for resistin expression are limited. In a mouse adipocyte model, the regulatory effect of 17β-E2 on resistin expression is discordant [64, 75].

Recently described novel adipokines, such as visfatin, retinol binding protein-4, and omentin, have been shown to exert some metabolic properties, but their biological actions linked to obesity and interactions with estrogen need to be elucidated.

6. Postmenopausal hormone therapy and change in body composition

Hormone therapy (HT) is widely used for the treatment of menopausal symptoms and preventing bone loss in postmenopausal women. Estrogen replacement, when combined with various progestogens for endometrial protection, has been established as a conventional formulation. The benefit of HT is known to reduce vasomotor symptoms,

prevent osteoporotic fractures, and improve well-being and quality of life during the menopausal period. In contrast, the risks for breast cancer and thromboembolic disease may increase, and cardiovascular effects remain controversial.

As previously mentioned, aging and menopause in women are related to an increase in body fat and redistribution of fat mass to the central portion of the body. These changes are linked to an increase in metabolic and cardiovascular disease after the menopause. Therefore, it has been continuously questioned and theorized that HT may have a favorable effect on change in body composition and anthropometries in postmenopausal women. With respect to this issue, data are still debated. In a meta-analysis of 24 RCTs, no effect of ET or HT on body weight was described [76]. However, subsequent studies suggested some beneficial effects of HT on body composition. A sub-study of the estrogen plus progestin trial of the Women's Health Initiative (WHI) investigated whether or not postmenopausal HT affects age-related changes in body composition [77]. The WHI study was originally designed to evaluate the risks and benefits of HT (EPT/ET) with an enrollment of 16,608 postmenopausal women between 1993 and 1998 [78]. The sub-analysis included 835 women who had whole-body dual-energy X-ray absorptiometry scans for measurement of body composition at baseline and year 3. Based on the results of the study, women who received EPT lost less lean soft tissue mass (-0.04 kg) than women who received placebo (-0.44 kg) 3 year after intervention. Furthermore, less upper-body fat distribution was noted in the EPT group than the placebo group (ratio of trunk to leg fat mass, -0.025 for the EPT group and 0.004 for the placebo group, $P = 0.003$). The investigators concluded that EPT has a favorable effect by reducing central fat deposition, but the real health benefits of this effect remains to be confirmed due to the small size of the effect. In a randomized, single-blind study, the effects of HT on body fat composition were studied in 59 postmenopausal women (mean age 49.9 ± 3.8 years) [79]. The participants were assigned into the following three groups according to the type of HT: transdermal estradiol (E2)/norethisterone acetate (NETA); transdermal continuous E2/ oral medroxyprogesterone acetate (MPA); and oral continuous E2/NETA. The results showed that all types of HT caused a significant decrease in WC, subcutaneous fat, and WHR. Thus, HT reduced fat deposition in the central part of the body, and such an effect was more marked in women with a WC ≥ 88 cm and subcutaneous fat ≥ 33 cm. Another placebo-controlled study investigated the effects of oral continuous E2/NETA on anthropometric changes and serum leptin levels in postmenopausal women [80]. In agreement with a previous study, WC and HC decreased significantly in the E2/NETA group, while the body weight (BW) increased in the placebo group. With this reduction in central fat deposition, the serum leptin levels were positively related to the changes in subcutaneous fat tissue. The authors advocated that HT may have a protective effect on CVD via a slimming effect on the central region in postmenopausal women.

Although the effect of postmenopausal HT on the change of body composition is not clearly understood, the limited data have suggest that HT has a small, but significant effect on preventing an android fat shift (central fat depot) regardless of the body weight.

Tibolone is a synthetic steroid hormone that exerts estrogenic, androgenic, and progestogenic properties. The biological actions of tibolone are mediated through the metabolites of tibolone (3α-OH-tibolone, 3β-OH-tibolone, and Δ^4-isomer) by binding estrogen or progesterone receptors in multiple target tissues and organs (brain, bone, breast, and endometrium). Based on several randomized trials, tibolone has shown comparable

effects with traditional estrogen therapy (ET)/HT on relieving vasomotor symptoms/ genital atrophy, improving the quality of life, and preventing bone loss in postmenopausal women [81-84]. Currently 4 studies have shown the effects of tibolone on BW or body composition in postmenopausal women. In a 2-year follow up study comparing three regimens of HRT, tibolone had a stable effect on body fat and lean mass [85]. However, the fat mass increased (+3.6%) and the lean body mass decreased (-1.7%) in the control group. Another study demonstrated that tibolone significantly increased fat-free mass by 0.85 kg and total body water by 0.78 liter during a 1-year observation period [86]. The authors reported an effect of tibolone on preventing a decline in lean body mass, but mentioned the need for a long-term observational study.

Arabi et al. compared the effects of tibolone with EPT (E2/NETA) on changes in body composition and bone densitometry in postmenopausal women [87]. Both EPT and tibolone increased lean body mass, whereas the android fat and android obesity index decreased.

Tibolone might provide further benefits in increasing lean body mass and decreasing the fat component. Steroid hormones exert their action by binding to an intra-nuclear receptor [88]. Therefore, like estrogen, tibolone might have a direct effect on skeletal muscle by binding to ERα or ERβ expressed within human skeletal muscle [88-90]. In addition, tibolone increases the serum IGF-1 levels [91], which promotes muscle protein synthesis, and increases the number of myogenic satellite cells and the proliferation of myogenic satellite cells. The anabolic effect of tibolone on muscle has been suggested to be mediated in part by local IGF-1, independent of the serum IGF-1 level [92].

7. Summary

Adipose tissue is the largest endocrine organ in the human body. The amount and distribution of adipose tissue reflects energy balance. Adipose tissue also releases a variety of biologically active molecules or cytokines. Adipocyte metabolism and physiology have been extensively studied over recent years, but the exact mechanism and effect of sex steroid hormones involved in regulating adiposity remain to be defined.

Current data give evidence that estrogen appears to have direct effects on cell proliferation or differentiation for adipocytes, and in regulating key enzymes involved in fat deposition. Another possible mechanism involves the hormonal or paracrine effects by secretion of various adipokines and cytokines, in which interactions with estrogen are promising and need additional studies.

At present, it is not known whether or not HT provides a significant effect on modulating fat mass or preventing fat redistribution. Furthermore, in recent years the HT formulations have been changed to include lower doses of estrogen (< 50 μg) in combination with new progestins. The effects of the currently used HT regimens on changes in body fat composition are limited and require more data. Tibolone includes estrogenic, androgenic, and progestogenic properties which may affect the body composition (adipose tissue or lean mass) differently than conventional HT.

The respective roles of sex steroid hormones and their receptors (ER subtypes and PR) on body fat distribution could be an interesting target for understanding the estrogen effect on adiposity, and may provide selective therapeutic approaches, such as hormonal manipulation for adiposity related to estrogen change throughout the menopausal period.

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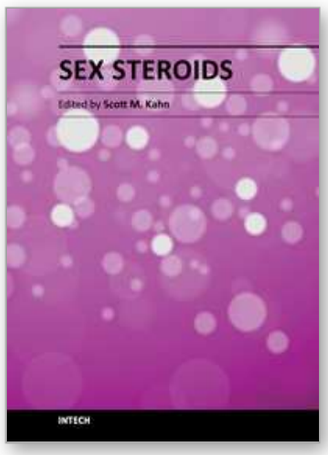

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This book, entitled "Sex Steroids", features a valuable collection of reviews and research articles written by experts in signal transduction, cellular biology, diseases and disorders. "Sex Steroids" is comprised of four sections, "The Biology of Sex Steroids", "Sex Steroids, Memory, and the Brain", "Sex Steroids and the Immune Response", and "Therapy"; individual chapters address a broad range of recognized and predicted functions and applications of sex steroids. "Sex Steroids" is intended to provide seasoned veterans as well as newcomers to this area of research with informative, resourceful, and provocative insights. Readers of "Sex Steroids" should emerge with an appreciation and understanding of the multitude and complexity of biologic processes attributed to these important hormones, and possible future directions of research in this fascinating and ever evolving field.

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