Review Article

Estrogen deficiency during menopause and its management: A current update

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ABSTRACT

Different phases of a woman's life: Puberty, menses, pregnancy, and menopause have varied influence on her oral health. During the menopause, women go through biological and endocrine changes, particularly in their sex steroid hormone production, affecting their health. Sex hormones strongly influence body fat distribution and adipocyte differentiation. Estrogens and testosterone differentially affect adipocyte physiology, but the importance of estrogens in the development of metabolic diseases during menopause is disputed. Estrogens and estrogens receptor regulate various aspects of glucose and lipid metabolism. Disturbances of this metabolic signal lead to the development of metabolic syndrome and a higher cardiovascular risk in woman. The absence of estrogens is a clue factor in the onset of cardiovascular disease during the menopausal period, which is characterized by lipid profile variations and predominant abdominal fat accumulation. However, influence of the absence of these hormones and its relationship to higher obesity in women during menopause is not clear. This systematic review discusses of the role of estrogens and estrogen receptors in adipocyte differentiation and its various effects and brief discussion on its management.

KEY WORDS: Estrogen hormone (estrogens/progestogens) replacement therapy, Menopause, Weight gain

INTRODUCTION

Menopause occurs when a woman stops ovulating and her monthly period (menstruation) stops.

As women age, into their 40s and 50s, there is a tendency to gain weight. During the menopause, women go through biological and endocrine changes, particularly in their sex steroid hormone production affecting their health.[1] Increasing distribution of abdominal fat is linking to the hormonal change in the perimenopause. Excess weight at midlife is associated with an increased risk of cardiovascular disease and diabetes. It is the result of irreversible changes in the hormonal and reproductive functions of the ovaries. Hormonal fluctuations affect more than a woman's reproductive system. Hormones have potent effects on the development and integrity of the skeleton and oral cavity.[2]

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BODY CHANGES AT MENOPAUSE

As we age, our muscles decrease in bulk and our metabolism slows down. These changes cancontribute to weight gain around the time of menopause. Other physical changes associated with menopause may include, mucosal changes such as oral dryness,vaginal dryness and skin changes such as loss of elasticity and loss of hair growth[3]. These changes may affect a woman's body image and self-esteems and increase her risk of depression and sexual difficulties. Taking steps to manage the symptoms of menopause can help.

ESTROGEN AND FAT DISTRIBUTION AT MENOPAUSE

A change in hormone levels, mainly estrogen, may influence body fat distribution. The increases in overweight and obesity in menopausal women are important public health concerns.[4] Estrogens deficiency enhances metabolic dysfunction predisposing to DM

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type 2, the metabolic syndrome, and cardiovascular diseases.[5,6]

Obesity and obesity-related disorders such as diabetes mellitus type 2 (DM type 2), cardiovascular disease, and hypertension are worldwide epidemics with a greater percentage of increase in developing countries.[7] Many genetic and epigenetic factors determine the pathophysiology of body fat accumulation.[8] The majority of these factors can be classified into different categories such as:

1. Factors responsible for the hormonal regulation of appetite and satiety;
2. Factors that regulate body glucose levels[9]
3. Regulators of basal metabolic rate[10]
4. Factors that control the quantity, disposition, and distribution of fat cells[11]
5. Modulators for the differentiation of progenitor cells[12] and
6. Those factors that determine adipocyte cell lineage.[13]

Unfortunately, there are a limited number of drugs for the treatment of obesity because the majority of new products have been recalled due to side effects.[14]

ESTROGENS AND ESTROGEN RECEPTORS IN FAT METABOLISM

The hormones help integrate metabolic interaction among major organs that are essential for metabolically intensive activities such as reproduction and metabolic function. Sex steroids are required to regulate adipocyte metabolism and also influence the sex-specific remodeling of particular adipose depots.[15] In humans, the factors that control fat distribution are partially determined by sex hormones concentrations.[16] Men, on average, have less total body fat but more central/intra-abdominal adipose tissue, whereas women tend to have more total fat that favors gluteal/femoral and subcutaneous depots.[17] Weight and fat abdominal distribution differ among women of reproductive age and menopausal women.[18] The decrease in estrogen levels in menopausal women is associated with the loss of subcutaneous fat and an increase in abdominal fat.[19] The importance of estrogens in subcutaneous fat accumulation is evident; in fact, estrogen hormonal therapy in men also increases the amount of subcutaneous fat.[20,21] In humans, 17-β-estradiol (e2) is the most potent estrogen followed by estrone (e1) and estriol (e3).[22] The expression of genes that encode the enzymes in estrogen synthetic pathway such as aromatase and reductive 17β-hydroxysteroid dehydrogenases (17β-hsd) is critical for e2 formation.[23] Protein products of several genes with overlapping functions may reductive 17β-hsd activities in peripheral tissues. Estrogens function is mediated by nuclear receptors that are transcription factors that belong to the superfamily of nuclear receptors. Two types of estrogen receptors (ers) have been identified, the alpha (erα) and beta (erβ) receptors.[24,25] The classical genomic action mechanism of er action typically occurs within hours, leading to the activation or repression of target genes. The classical genomic action mechanism of er action typically occurs within hours, leading to the activation or repression of target genes[26] although it was considered that the action of e2 was subject to an action in gene expression regulation. Several mechanisms of membrane-signaling activation can explain rapid responses to e2. The rapid actions include activation of kinase, phosphatase, and phospholipase that can mediate calcium-dependent signaling and can mediate downstream non-genomic physiological responses such as effects on cell cycle, cell survival, and energy metabolism.[27] Human subcutaneous and visceral adipose tissues express both erα and erβ,[28,29] whereas only er has been identified in brown adipose tissue [30,31] Erα plays a major role in the activity of adipocytes and sexual dimorphism of fat distribution. Female and male mice that lack er have central obesity, have severe insulin resistance, and are diabetic.[32,33] Although not all studies are in agreement, polymorphism of erα in humans has been associated with risk factors for cardiovascular diseases.[34] Lipolysis in humans is controlled primarily by the action of β-adrenergic receptors (lipolytic) and α2a-adrenergic receptors (antilipolytic). Estrogen seems to promote and maintain the typical female type of fat distribution that is characterized by accumulation of adipose tissue, especially in the subcutaneous fat depot, with only modest accumulation of intra-abdominal adipose tissue.[35] Estradiol directly increases the number of antilipolytic α2a-adrenergic receptors in subcutaneous adipocytes. Visceral adipocytes exhibit a high α2a/β ratio, and these cells are stimulated by epinephrine; in contrast, no effect of estrogen on α2a-adrenergic receptor MRNA expression was observed in adipocytes from the intra-abdominal fat depot.[36] However, it is important to highlight that the effects of estrogens differ on the route of administration and the lipolytic influence of estrogens on fat accumulation affects specific regions of the body. E2 may also increase beta-adrenoreceptor expression through erα.[37] These results provide a mechanism insight for the effect of e2 on the maintenance of at distribution with an increase of lipids as energy source, which partially promotes fat reduction in abdominal fat. This effect occurs through the facilitation of fat oxidation in the muscle by the inhibition of lipogenesis in the liver and muscle through the regulation of peroxisome proliferator-activated receptor γ (pparγ) and an increase in lpl expression.[38,39] E2 also increases muscle oxidative capacity by means of the regulation of acyl-CoA

oxidase and uncoupling proteins (ucp2-ucp3), which enhances fatty acid up take without lipid accumulation. Therefore, E2 improves fat oxidation through the phosphorylation of ampkinase (ampk) in muscle and myotubes in culture.[40]

PERIMENOPAUSE AND MENOPAUSE AS ESTROGEN DEFICIENCY

In addition, there is a persistent, non-scientific conflation of perimenopause and menopause, their symptoms (ambiguously called "menopausal symptoms"), and their therapies. If discussing perimenopausal symptoms, menometrorrhagia, mastalgia, headaches, and nausea should take center stage.[41] These two life phases do share hot flushes and night sweats (that is, vasomotor symptoms) and vaginal dryness, although vaginal dryness occurs in perimenopause for unknown reasons. However, hormonally, perimenopause and menopause are as different as chalk and cheese. Compared with premenopausal women, estrogen levels are erratically higher in perimenopause and stably lower in menopause; progesterone levels silently decline and become lower in the perimenopausal years before the last flow.[42] In contrast to conventional wisdom, perimenopause begins with changes in experiences within regular cycles at a time when estrogen levels are already higher and progesterone levels already lower than in premenopause. Vasomotor symptoms, which are a key adverse experience of both perimenopause and menopause, are discussed in a way that creates confusion, include no primary physiological references, and allude to the old hypothesis that low estrogen levels cause these symptoms.[43] Why, then, do perimenopausal women experience vasomotor symptoms when they "have rather high levels of estrogens?"[44] The authors state that: "Hypothalamic insensitivity to estrogens also explains why menopausal symptoms - such as hot flushes and night sweats - commonly occur at this stage (perimenopause)… as well as why exogenous estrogens are effective in reducing the symptoms."[44]

MENOPAUSE AND CARDIOVASCULAR DISEASE

As women get older, their risk of cardiovascular (heart and blood vessel) disease increases. This may be partly due to the postmenopausal tendency to put on weight around the abdomen. Body fat stored within the abdominal wall and around the internal organs (visceral fat) is a risk factor for the development of cardiovascular disease. Hormone replacement therapy may reduce the risk of cardiovascular disease by preventing the accumulation of abdominal body fat.

In addition, estrogen replacement boosts "good" blood cholesterol (high-density lipoproteins) and lowers "bad" blood cholesterol (low-density lipoproteins).[44]

ORAL MUCOSA AND FEMALE SEX HORMONES

Menopause affects the oral tissues in the same way as it alters the other systems. Alterations in the oral cavity are due to aging as well as hypoestrogenism. [45] Oral mucosa resembles vaginal mucosa in its histology as well as its response to estrogens. Sex hormone receptors have been detected in the oral mucosa and salivary glands.[46] Estrogen can affect oral mucosa directly or through neural mechanism, thus altering the periodontal health in menopausal women. The oral problems may include a paucity of saliva, leading to xerostomia, burning mouth syndrome, increase in incidence of dental caries, dysesthesia, taste alterations, atrophic gingivitis, periodontitis, and osteoporotic jaws.[47]

MANAGEMENT OF MENOPAUSAL SYMPTOM

Behavioral Treatment of Vasomotor Symptoms

Common sense measures to address vasomotor symptoms include portable fans, lowering the ambient temperature, wearing layered clothing, avoiding tobacco, alcohol, caffeine, and spicy foods as well as ingesting cool drinks.[48] An RCT of 187 symptomatic menopausal women found that clinical hypnosis was associated with a 74.2% of reduction in hot flushes, compared with a 17.1% of reduction in women randomized to structured attention control ($P < 0.001$).[49] The effectiveness of acupuncture, exercise, yoga, paced respiration, relaxation training, and mindfulness-based stress reduction has not been established.[50-53]

HORMONAL PRESCRIPTION MEDICATIONS

Hormone Replacement Therapy

Literature was also reviewed to explore the benefit of hormone (estrogens/progestogens) replacement therapy (HRT) on oral symptoms and signs in postmenopausal women. In a study by Volpe *et al*., conjugated estrogens were administered to one group of postmenopausal women with oral discomfort. They observed that HRT improved subjective and objective symptoms in more than 50% of patients.[54] Forabosco *et al*. evaluated the effect of HRT on symptoms of oral discomfort in postmenopausal women and concluded that oral discomfort may be related to steroid hormone withdrawal only in some postmenopausal women and treatment with estrogens may improve

the clinical picture in this group of women only. Immunohistochemical identification of estrogen receptors may help to identify patients for whom HRT may be beneficial.[55]

Systemic Dose

In women with an intact uterus, treatment with estrogen alone is associated with an elevated risk of endometrial neoplasia with dose and duration of treatment directly related to the magnitude of this risk. When adequate progestogen is combined with estrogen, risk of endometrial neoplasia is not higher than in untreated women. In the Women's Health Initiative clinical trial, at a mean of 5.6 years of follow-up, the use of continuous oral conjugated equine estrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg daily was associated with a risk of endometrial cancer similar to placebo (hazard ratio 0.81 [95% CI, 0.48–1.36]),[56] and risk was significantly reduced after 13 years of cumulative follow-up. A large, long-term Finnish observational study noted that while continuous concomitant progestin therapy is associated with a risk of endometrial neoplasia lower than seen in women not using HRT, sequential progestin therapy (e.g., 14 days each month) was associated with an elevated risk.[57] Long-cycle progestin therapy (e.g., 14 days every 3 months) was associated with a further elevation in risk of endometrial cancer. Neither route nor type of progestin appeared to affect the risk of endometrial neoplasia,[58] although additional research is needed on non-medroxyprogesterone formulations. Based on these observations, combination of estrogen-progestin therapy is generally employed when systemic HRT is prescribed to women with an intact uterus.

In 2013, a formulation combining 0.45 mg conjugated equine estrogens with the estrogen agonist-antagonist bazedoxifene (20 mg) was approved by the FDA for the treatment of vasomotor symptoms and the prevention of osteoporosis among women with an intact uterus. In a 12-month trial, rates of endometrial hyperplasia and amenorrhea among women allocated to this combination formulation were similar to those randomized to placebo.[59]

Although clinical trials of conjugated equine estrogens - bazedoxifene have not suggested that this formulation increases risk of breast cancer, trials have not been large or long enough to adequately assess this association. In contrast with estrogen-progestin therapy, which increases mammographic breast density and breast tenderness, bazedoxifene has not been found to increase breast density or tenderness.[60]

In the United States, the most commonly used oral estrogens for systemic treatment of menopausal symptoms are estradiol and conjugated equine estrogens. Standard doses of oral estradiol and conjugated equine estrogens are 1.0 mg and 0.625 mg, respectively.[28] Higher and lower doses of these formulations are also available.

Transdermal estradiol formulations are also available. Skin patches represent the most commonly used transdermal estradiol formulations. Patches releasing 0.0375 and 0.05 mg estradiol daily are considered standard dose. Patches with higher and lower doses are also available. Ultra-low-dose patches which release 0.025 mg or 0.014 mg estradiol daily are also available. In addition, transdermal estradiol gels, emulsion, and spray are available in a variety of doses.[29] A 3-month vaginal estradiol-releasing ring can also be used for systemic estrogen therapy (ET): The ring releasing 0.05 mg estradiol daily is considered standard dose.

Although estrogen injections as well as estrogen pellets have been used to treat menopausal symptoms, serum estradiol levels associated with the use of these formulations have not been well characterized. Accordingly, the use of oral or transdermal estrogen formulations is recommended. Estrogen pellets are not FDA approved.

The indications and contraindications for the use of menopausal hormone therapy and related medications are summarized in Box 1.[61]

NON-HORMONAL PRESCRIPTION MEDICATIONS

Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (more commonly used to treat depression) as well as anticonvulsant medications (more commonly used to treat neuropathic pain) are increasingly being used off-label in the non-hormonal management of vasomotor symptoms. In RCTs, paroxetine, escitalopram, citalopram, venlafaxine, desvenlafaxine, gabapentin, and pregabalin have been effective in treating vasomotor symptoms. Low-dose p oxetine mesylate currently represents the only non-hormonal formulation FDA approved for the treatment of vasomotor symptoms.[62]

The antidepressants best studied in the treatment of vasomotor symptoms agents are paroxetine mesylate and venlafaxine. Lower doses of these agents than those used to treat psychiatric disorders are often effective in treating hot flushes. Although these medications may cause nausea, headache, and dizziness, these side effects are less common than when the same medications are used to treat psychiatric conditions; furthermore, these side effects often subside within several weeks of initiating treatment.[63]

In RCTs, gabapentin at daily doses ranging from 900 to 2400 mg has been found more effective than

Box 1: Menopausal Hormone Therapy/Related Medications: Indications and Contraindications*

SYSTEMIC ESTROGEN THERAPY (oral, transdermal, and high-dose vaginal formulations)

- Indications: Management of moderate-to-severe vasomotor symptoms (prevention of osteoporosis among women at high risk of osteoporotic fracture who are unable to tolerate standard preventive medications)
- Contraindications:

Absolute: Unexplained vaginal bleeding; liver dysfunction or disease; history of deep venous thrombosis or pulmonary embolism; known blood clotting disorder or thrombophilia (transdermal may be an option in some women at elevated risk for venous thrombosis); untreated hypertension; history of breast, endometrial cancer, or other estrogen-dependent neoplasia; known hypersensitivity to hormone therapy, or history of CHD, stroke, or TIA. Concomitant progestational therapy should be prescribed when a uterus is present

Relative: high triglycerides (>400 mg/dL, 4.5 mmol/L) or gallbladder disease (oral estrogen should be avoided, but transdermal estrogen may be an option); elevated risk of breast cancer (5-year breast cancer risk> 5% by NCI or IBIS assessment BC:

CE/BAZEDOXIFENE

- Indications: Same indications as above: An additional FDA-approved option for women with concerns about breast tenderness, breast density, or uterine bleeding with conventional therapy
- Contraindications:

Absolute and relative: Same as above

LOW-DOSE VAGINAL ESTROGEN

- Indications: Treatment of the genitourinary symptoms of menopause, including vaginal dryness and dyspareunia
- Contraindications (absolute): Unexplained vaginal bleeding; known or suspected breast cancer or endometrial cancer, or other estrogen-dependent neoplasia. For some women with a personal history of breast cancer, use might be considered after consultation with the patient's oncologist; however, particular caution is appropriate among women taking aromatase inhibitors. Although concomitant progestational therapy is not recommended, endometrial evaluation should be performed if any vaginal spotting or bleeding occurs

OSPEMIFENE

- Indications: Treatment of genitourinary symptoms of menopause, including vaginal dryness and dyspareunia, among women preferring an oral treatment.
- Contraindications (absolute): Same as for low-dose vaginal estrogen. Also should not be used in patients with the past or current venous or arterial thromboembolic disease, severe liver disease, or those using estrogens or estrogen agonists/antagonists

*See product labeling for more comprehensive listing. CHD: Coronary heart disease, TIA: Transient ischemic attack, FDA: U.S. Food and Drug Administration, NCI: National Cancer Institute, IBIS: International Breast Cancer Intervention Study

placebo in treating hot flushes. The recommended dose is 900 mg/day in three divided doses, with a starting dose of 300 mg/d. Likewise, pregabalin (a newer formulation similar to gabapentin) has been found to effectively treat vasomotor symptoms. The recommended dose is 75 mg twice daily, with a starting dose of 50 mg/day. Both of these medications can produce dose-related dizziness and sedation.[62]

STELLATE GANGLION BLOCK

Stellate ganglion block has been assessed in the treatment of vasomotor symptoms. A small RCT of 40 postmenopausal women compared the effects of stellate ganglion block with a sham injection. The resulting overall frequency of vasomotor symptoms was similar in the active and sham groups. However, the frequency of moderate-to-severe hot flushes as well as that of objectively measured symptoms was reduced significantly more by the active than by the sham treatment.[64]

WOMEN WITH EARLY MENOPAUSE

Women who experience spontaneous or induced menopause (caused by surgery, chemotherapy, or other factors) in their 40s or younger face more severe vasomotor symptoms than women reaching menopause at the mean age (51–52 years), and are at higher risk for osteoporosis, and possibly coronary heart and neurodegenerative disease. Although little clinical trial data inform the management of women with early menopause, the use of systemic menopausal HRT or oral contraceptives is appropriate in the absence of contraindications. When systemic HRT is used in this patient population, higher than standard doses are often appropriate.[65]

CONCLUSION

Menopause affects a woman's oral and general health for the same reasons as for other body systems. To reduce the obesity pandemic, we consider that using menopause hormonal therapy with the lowest effective dose and for the shortest duration may be a possible coadjutant therapy. Future research should focus on identifying critical brains where ERs regulate body weight homeostasis and delineate the intracellular signal pathways that are required for the actions of estrogens. Large randomized controlled studies are needed to document significant effect of HRT and other interventions in menopausal women.

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