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Review Article

The Effect of Topical Estrogen in Skin Aging Process in Estrogen Deficiency Skin (EDS)

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Abstract:

Estrogen deficient skin (EDS): a skin condition characterized by dryness, dullness, atrophy, and pruritus of the skin. The causes of this condition are varying and are mostly seen in menopausal women in which estrogen hormone levels in the body drop. Other causes of estrogen deficient skin (EDS) such as medications, low function of pituitary gland or surgery, primary ovarian insufficiency, and other causes. Treatment varies from oral using replacement hormonal therapy which is lead to side effects to topical treatment using topical estrogen, isoflavones products, and methyl estradiol propanoate (MEP).

The article aims to outline the responsibility of estrogen hormone in the skin and the alterations that occur when there is a lack of estrogen in the body, in addition to alternative ways of treatment other than systemic estrogen, and represent the effect of each type of therapy on the estrogen-deficient skin (EDS).

Estrogen therapies are restrictedly used by obstetricians and gynecological physicians. Therefore, there is a lack of scientific studies on estrogen topical therapy and its effect on the skin for decades. Recently and with increasing interest in cosmetics worldwide, more studies come to light and new topical therapies are presented like methyl estradiol propanoate (MEP) because of the raising interest by the cosmeceutical company and dermatologist.

Keywords: estrogen deficient skin; methyl estradiol propanoate; topical estrogen

Introduction

Inspite of increase longevity, the women onset age remains constant for menopause, so they are expending most of their time in lives in a state of insufficient estrogen [1]. The changeover to post-reproductive from reproductive life is known as the transitional period of menopause and entitle a significant corner in the women's life, this transitional period is clinically important to start medical help if needed [2]. Menopause is known as menstrual period cessation for continues twelve months or more because of persistent ovarian failure, contributing to a significant estrogen level decrease [3]. The time of onset of menopause is multi-factorial and affected by genetic factors and environment such as sun exposure (UVA), also factors like diet, alcohol, tobacco smoking, anxiety, and in sufficient sleeping [4]. A deficiency of estrogen unfavorably affects various skin functions which appear as changes in skin such as dryness, loss of elasticity and wrinkles, atrophy, inappropriate healing, loss of physiological barrier, these changes can affect self-image and confidence in women [5]. Symptoms and signs of menopause treated by systemic and topical estrogen throughout decades, Hormone replacement therapy (HRT) from its name is therapy reverse the menopausal manifestations, such as dry and atrophied vagina, skin aging, hot flashes, reduction of muscle mass, bone loss, and sexual dysfunction [6]. Management with low dose oral estradiol versus placebo increases E2 and E1 levels in the serum by four to five times in perimenopausal and postmenopausal vasomotor symptoms woman, and Its effect in decreasing vasomotor symptoms number appears to be partially mediated by the raise in E1 and E2 in the serum upon oral administration of low dose estradiol [7]. postmenopausal experience increases body temperature and sweating specially in night, hot redness flash in around 70% of women [8], these symptoms are still most usefully relieved by estrogen hormonal therapy and its helpful in reducing bone loss which increases fracture risk, and has effect in treating genitourinary syndrome of menopause (GSM)[9]. There are various preparations of hormone therapy formulations used according to patient preference and side effects. Estradiol is a metabolite in the body that transformed into estrone during the first pass metabolism, and it's the main hormone circulating in the blood [10]. Systemic estrogen has significant

adverse effects which include an increase in coagulation factors and various inflammatory markers production snd thrombosis risks increased and hypertriglyceridemia[10]. Systemic estrogen can lead to endometrial hyperplasia and elevate cancer risk, in order to avoiding this risk progesterone therapy is used[10]. combined hormonal therapy with progestogen and estrogen offers a good utrine protection through continuous and intermittent cyclic combined hormonal therapy[9]. Finally, an intermittent combination of estrogen-progestogen constitutes of continues using of estrogen inturrpted by 3 days of progestogen, then repeated. Showed that the rate of amenorrhea is 80% after 1 year of intermittent progestogen dosing[10,11]. Age time of menopause of women when the systemic hormonal therapy started to play a major role in complication development, early started more saver [12]. In this review article, we will go over the significance of estrogen in the skin, the alterations that are linked to lack of estrogen, various substitutes for systemic estrogen therapy, and the outcomes of these treatments.

Menopause

It's a normal pathway of aging for women. It defined as 12 months cessation of menstruation since women's last menstrual cycle. years before menopause, women usually developedmenstrual cycle changes, got hot flashes and other symptoms, known as transitional period of menopause (perimenopause). This period usually begins around the age of 45 until the age of 55 years old, it's lenght ranges about seven years but can last for fourteen years, the age of onset and the duration, and symptoms of menopause are different depending on geographical region, ethnicity, socioeconomic status, women of poor socioeconomic status have an earlier onset of menopause 13. The term estrogen deficient skin (EDS) is now more used, it's more entire than menopause, including all women who have estrogen deficiency by other causes than menopause like drugs, surgery, or other causes.

menopausal period Symptoms and signs

Women's body parts require the estrogen hormone for many functions. When estrogen levels begin to decline various symptoms appear, and these symptoms differ in severity from one woman to another. The first of these symptoms is changes in menstrual period, which may become more or less than usual, heavy bleeding, or bleeding between cycles. A very common symptom is hotness and redness (hot flashes) which can continue years after the menopause, vasomotor symptoms and insomnia due to menopause can be treated by cognitive behavioral therapy CBT [14]. A study on Mexican women supported that using 20 mg citalopram can improve vasomotor and urogenital syndrome in menopausal women [15]. In addition, many women experience Sleep disturbances and trouble getting a good night's sleep. Some simple technics like foot massage were found to increase sleep duration and decrease anxiety and fatigue, also progressive muscle relaxation and health education counseling enhance vasomotor symptoms and insomnia, as well resistance training improves the quality of life and postural control in postmenopausal women [16,17,18]. Moreover, Mood changes can occur as some women will experience depression or stress disorders during menopause. Estrogen deficiency led to vaginal dryness which can make sex uncomfortable, sexual desire is also affected in menopause women could be less or more interested in sex, vaginal dryness and other symptoms of menopause have been shown to improve when using a 190 mg combination of soy and hop [19]

Estrogen deficiency manifestations of the skin

Commonly used term now is estrogen deficient skin EDS, it's more entire than menopause because include all women who have estrogen deficiency other than menopause such as surgical ovarian removal, or side effect of drugs like chemotherapy. Estrogen hormone is very essential for skin functioning, and well-being. Historically in the 1920s, the two scientists Adolf Butenandt and Edward Adelbert Doisy first discovered estrogen [20]. The name estrogen or oestrogen derives from Greek "oestros" which is mean the period time of sexual activity in female of mammals, "genos" means generation or producing [21]. It is a steroid sex hormone which mainly produced by ovaries in females of reproductive age and the peripheral tissue in postmenopausal age. Estradiol is the most common form and is approved by FDA as hormone replacement therapy (HRT) [22]. the three main estrogens are estrone, estriol, and estradiol another estrogen which produce during pregnancy exclusively called estetrol(E4). The estrogen makes their action through the estrogen receptor (ER), it is intracellular like other steroid hormones receptors, action of estrogen depends on presence of estrogen receptors in the cells. Estrogen receptors present in some cell tissues Like the uterus, ovaries, and breast, Estrogen has two receptors alpha (ERα) and beta (ERβ), which have been expressed in the skin [23]. However, stimulation of ERα is interestingly related to breast and other reproductive cancers [24]. This area makes selective targeting of ERβ open the door to a new intervention in the future.

Functions of estrogen in the skin

Process of wound healing

As we age, our skin becomes more sensitive and prone to trauma, as well as decreased healing after injury, age-associated delayed wound healing is a serious health problem in elderly patients. many studies tried to identify the causes of impaired healing in the elderly, one of these causes is estrogen deficiency which is supposed to have an important role in delayed wound healing. Delayed wound healing in elderly both female and male patients can be accelerated by topical estrogen[25]. But a recent randomized, placebo-blind study done on a preoperative child with hypospadias found no obvious improvement with topical estrogen[26].

Collagen synthesis

Skin is an important protective barrier organ that protects the body from outer environmental hazards, but like other body organs it goes through the aging process with time, one of those signs of aging is loss of thickness with age, shown that topical estrogen increases epidermal thickness and type I collagen[27]. Collagen, the primary component of connective tissue, is the body's principal structural protein making about 25% to 35% of the whole-body protein. The body's type I collagen is thought to be the most prevalent kind [28]. Collagen also is a main structural element of the skin and provided it with strength and tension. The two forms of collagen most frequently seen in the skin are type I and type III [29]. Skin collagen is significantly affected after menopause due to estrogen-deficient, it continues to decline 15-18 years postmenopausal by 1-2% and 1.1% loss of skin thickness per year [30].

Skin moisture

Aging skin is more prone to dryness due to loss of moisturized agents, these moisturizers are involved in several factors which help restore skin moisture (1) acidic PH of the skin surfaces provides an important barrier and antimicrobial effects on the skin[31]. (2) sweat is possible that maintain skin hydration and prevents thermal regulation[32]. (3) hyaluronic acid is important for anti-aging, anti-wrinkles, and improving skin hydration[33]. (4) sebum lubricates the skin and makes it more moisturized [34].

Skin wrinkles

Is a typical and natural process linked to aging skin that results in epidermal thickness and loss of skin suppleness, some theories suggested that skin wrinkles are due to Misrepair-accumulation, in which skin wrinkles developed as a result of incorrect repairs to collagen and elastic fibers [35,36].

Treatments

Hormone replacement therapy (HRT)

Menopausal symptoms vary in severity from one woman to another, using hormone replacement therapy (HRT) can reverse some of those symptoms but at the same time sometimes it carries risks and unwanted side effects. In the last update, to address menopausal symptoms over 65 women, american college of obstetrics and gynecology (ACOG) has approved the replacement

hormonal therapy using [37,38]. under 60 years old women who use a combination of HRT and PMB, endometrial cancer is quite low detected. Even if other diagnoses are much more likely, putting a woman on a pathway for cancer suspected diagnosis stresses and worry her and might lead to an initial inquiry that is more invasive. Women who began taking hormone replacement therapy (HRT) or changed their regimen during or after 6 months from it and have postmenopausal bleeding should be evaluated on a less urgent way. In appropriate way, it gives the extremely low endometrial carcinoma incidence in women under the age of 60[39] According to a nationwide study by the women's health initiative (WHI), oral hormone replacement treatment increases the ischemic stroke risk, but topical estrogen has no effect and vaginal estrogen decreases it [40]. When hormone replacement therapy (HRT) is started aroud 10 years or more after the onset of menopause, there is a very low decrease in ischemic heart diseases expected and the risk of stroke is increased. If HRT is started about (10 years) or less post menopausalonset, there is approximately no benefits in reduction of ischemic heart diseases[41]. Continuous hormonal treatment with estrogen and progesterone was found to decrease the incidence of endometrial cancer [42]. Depending on the type of hormone replacement and how long it has been used, studies on the connection between HRT and breast cancer might vary. In comparison to bioidentical hormones, conjugated equine estrogen (CEE), medroxyprogesterone acetate (MPA) has been proven to somewhat lower the risk of breast cancer[43]. women have a hysterectomy who take equine estrogen alone experience a low incidence of breast cancer. However, if it is combination with medroxyprogesterone, breast cancernoma risks increased relatively [44]. Topical estrogen products are widely used nowadays by many women with symptoms of estrogen-deficient skin in the form of wide cosmeceutical products to improve aging skin. It's interesting to note that research using skin surface texture (SST) analysis on Japanese women with climacteric or estrogen insufficiency symptoms, low dose estradiol gel applied on the forearm site, and placebo on the cheek found that improvement of skin surface texture fine-ness (using several ridges) after 4 weeks in the forearm, and improvement of cheek skin texture after 8 weeks, suggesting that topical estradiol carry systemic effects [45].

Isoflavones products

Groups of a plant-derived nonhormone closely related to phytoestrogen which is a substance structurally similar to estradiol(17-β-estradiol), isoflavones produced by members of the bean family Fabaceae. In a study done in ovariectomized rats treated with systemic genistein aglycone, Isoflavone from soy proved successful in treating aging symptoms [46]. A double-blind, randomized clinical study using two groups of postmenopausal women and topical treatments of 0.01%17-estradiol gel on one group and 4% genistein gel on the other group for 24 weeks revealed that isoflavones have an impact on the production of hyaluronic acid. The estrogen group had higher levels of hyaluronic acid than the genistein group, but both groups had higher levels overall [47]. Additional randomized double-blind research using estradiol and genistein topically and measuring enhancement in collagen production in postmenopausal women showed raised the of (type I, III) collagen in both groups, but the estrogen group is greater than the genistein group [48].

Equol

Is a bacterial metabolized from daidzein isoflavone which has estrogenic and antioxidant activity [49]. Many studies have found that equol has a favorable impact on postmenopausal women's skin, intake of equol supplementation in Japanese postmenopausal women improves skin aging [50].

Topical methyl estradiol propanoate MEP

MEP is a non-hormonal estrogen receptor agonist. The benefit of MEP is that it is broken down into inactive metabolites which enter the circulation without being absorbed unlike which avoid the side effect of estrogen [51]. MEP was shown by the double-blind randomized pilot trial to be efficient and secure, 80 women, aged 53 to 80, who had not had periods for three to ten years for 14 weeks duration, showed a noticeable reduction in roughness, increase elasticity, and improve general skin texture in the group who received MEP compare with control, increase in fibroblast estrogen receptor staining[51]. Many skin cosmetics interest companies started to add methyl estradiol propanoate (MEP) to skin care regimens, an experienced trial was done to evaluate the effectiveness of the Emeplle skin care regimen containing MEP, found that skin aging in younger women improved significantly at 8 weeks, older women improved at 20 weeks [52].

Discussion

Drop of ovarian function, synthesis and release of estrogen hormone is occure naturally after menopause [53] this significantly alters the features of the EDS [54]. Evidence indicating that estrogens are necessary for sebum generation, better stratum corneum mechanical function, and increased elastin and collagen content supports estrogen's in maintaining skin structure and function[55]. many research on the impact of estrogen replacement on estrogen-deficient skin EDS has also been conducted, with much of them focusing on the effects of estrogen systemically through the oral or parental route[56]. While estrogen supplementation has positive effects on the skin, it raises the possibility of getting malignancies including breast, ovary, and endometrium cancers. To assess the effectiveness of topical administered estrogens, an increasing number of studies have been conducted. Numerous researchers have reported no systemic effects after topical estrogen application[57]. For instance, another study recorded a decrease in redness and hotness (hot flash) occurrences postmenopausal following the application of a topical formula that included estradiol, showed that topical treatments may affect systemically [57]. Progesterone does not need to be added to provide uterine protection, even after applying estrogen directly through the vulvar and vaginal routes. When compared to a placebo, topical vaginal estrogen applying didn't increase incidence of endometrial hyperplasia or the carcinoma risks in a cohort study including 4162 women[48]. As compared systemic therapy of estrogen, systemic absorption with topical estrogen treatment is not high and the risk of thrombosis doesn't increased[58]. EDS is not usually treated with topical estrogens it is presently unknown if their administration might have an undesirable systemic effect[59]. Recently, it has been investigated if it is concessible to mimic the good benefits of estrogen using plant hormones or isoflavones. A form of natural sources isoflavonoid known as soy isoflavones is nearly entirely produced by plants in the Fabaceae family, which also includes red clover, lentils, and soybeans[60]. Genistein is the isoflavone that is most prevalent.

Isoflavones are categorized as phytoestrogens, or dietary estrogens, in mammals because They resemble 17-B estradiol in features and maybe affects the estrogen receptor[60]. Revealed that in terms of correcting menopausal skin abnormalities, isoflavones may be as effective as estrogen replacement treatment. Additionally, studies have demonstrated that some phytoestrogens function like estrogens when applied topically because they promote the growth of the epidermis, encourage the production of collagen, and lessen the enzymatic breakdown of collagen [61]. The strong affinity that isoflavones (namely genistein) have for ERβ, which is more often present in the skin, bones, and cardiovascular systems [62] has a weak affinity for ERα, which is present in the breasts and uterus [63]. In reality, Tamoxifen and raloxifene are categorized as selective estrogen receptor modulators, and isoflavones also fall into this group because of their capacity to be tissue-selective [64]. While reducing the negative effects of systemic estrogen, isoflavones are showing promise in the treatment of estrogen-deficient skin EDS, albeit bigger well-controlled research is required. Due to its more constrained receptor specificity, genistein is anticipated to entail an even lower risk than local estrogens, which have minimal systemic absorption and consequent hazards. Despite research demonstrating topical estrogens' and isoflavones' anti-aging properties, isoflavonoids' biological potency is substantially lower than synthetic estrogens[65]. According to the efficacy study's lead investigator, MEP significantly improved roughness (P0.001), dullness (P0.001) elasticity (P=0.001) and atrophy (P=0.003) and from baseline at week 14 compared to vehicle. In the biopsy sub-study, four out of nine individuals showed an increase in fibroblasts stained for the estrogen receptor, Postmenopausal women may benefit cosmetically from the

innovative idea of a safe and effective soft estrogen face cosmeceutical[51]. Another study shown The Emepelle Night Cream and Serum formulations were well-liked by the study's participants. By around 8 weeks, younger patients had considerably enhanced. Significant improvements were noticed by week 20 in individuals who had been in menopause for a long time, indicating the possibility that MEP might activate latent estrogen receptors[52].

Conclusion

Estrogen has potent effects on the skin that promote its elasticity and smoothness. It stimulates collagen and elastin production. Also helps maintain the skin's barrier function and enhances skin texture. When estrogen level falls, many of these functions deteriorate.

Topical estrogen is more effective than isoflavones in treating estrogen deficiency symptoms but it was proved that topical estradiol applied to the skin has systemic effects. Furthermore, topical Methy Estradiolpropanoate (MEP) was found to improve skin aging in women without systemic side effects.

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