REVIEW ARTICLE

The role of oxidative stress in menopause

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ABSTRACT

This review will discuss the concept of reproductive aging, which includes the definition of menopause, its symptoms, and predisposing conditions. It will elaborate upon the contributory factors implicated in the pathogenesis of menopause, focusing most prominently on oxidative stress. Specifically, this paper will explain how oxidative stress, in the form of free radicals and antioxidant deficiencies, has been directly linked to the decline of estrogen during reproductive aging. Additionally, this paper will elaborate upon the treatment options aimed at mitigating the menopausal symptoms and hormonal deficiencies that can lead to various disease processes. Treatment options such as hormonal therapy, antioxidant supplementation, and lifestyle modification have been explored for their effectiveness in treating and preventing the symptoms and sequelae of menopause. The majority of information in this review was obtained through PubMed and the National Library of Medicine. While most references in this paper are original research articles, a limited number of references are comprehensive reviews on the topic.

Key Words: Antioxidants, cardiovascular disease, catalase, estrogen, hormonal therapy, hot flashes, malonaldehyde, menopause, osteoporosis, oxidative stress, phytoestrogens, reproductive aging, superoxide dismutase, Vitamin A, Vitamin C, Vitamin E

INTRODUCTION

Menopause, a form of reproductive aging, is defined as the permanent cessation of ovarian follicular activity and eventually, the menstrual cycle.[1,2] Normally, menopause is a natural process of the body; however, it can be the result of other causes such as surgery, chemotherapy, or iatrogenic insult.[1] Additionally, two hormones (progesterone and estrogen) integral to reproductive aging are no longer produced during menopause.[3-5] Specifically, the decline and eventual cessation of estrogen production has been shown to cause a variety of symptoms during menopause, affecting each woman differently. These include hot flashes, night sweats, breast tenderness, vaginal dryness, irregular menses, mood changes, vaginal atrophy, osteoporosis, heart disease, and sometimes premature ovarian failure.[6] Many therapies have targeted this hormonal decline in estrogen and have also expanded to include lifestyle modifications, such as diet and exercise.[7] Additionally, foods rich in antioxidants have been shown to be of great benefit in women experiencing menopausal symptoms because they help to eliminate oxidative stress within the body. Overall, this paper will discuss in great detail the stress of free radicals and antioxidant deficiencies, both of which play a role in the pathogenesis of menopause.[3]

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METHODS

The majority of information in this review was obtained through English-only articles from the PubMed and National Library of Medicine databases. Only literature containing up-to-date and relevant information on the topic was selected, starting from 1988 to 2013. Specifically, the following key terms were used to generate the literature search for this review paper: Menopause, oxidative stress, antioxidants, estrogen, free radicals, herbal antioxidants, pharmacotherapy, hormonal therapy, phytoestrogens, osteoporosis, cardiovascular disease, and vasomotor disturbances. While most references in this paper are original research articles, a limited number of references are comprehensive reviews on the topic.

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HORMONAL AND CHEMICAL IMBALANCES OF MENOPAUSE

Menopause is a gradual process that occurs over a period of years in females who are typically between 45–55 years of age. It marks the beginning of a woman's age-related fertility decline via a decrease in the number of ovarian follicles produced.[2] This change in reproductive potential is the direct result of a decline in production of hormones by the ovaries, which causes physical manifestations that negatively impact the quality of life of menopausal women.[3] In regards to the hormonal changes that occur, the earliest involves a rise in follicle stimulating hormone (FSH) followed years later by a rise in luteinizing hormone (LH).[4] Studies have attributed this rise in FSH during menopause to a decreased production of inhibin B, a dimeric glycoprotein that suppresses FSH.[8] Specifically, this compound was found to decline during both the follicular and luteal phases of the menstrual cycle, causing a rise in the FSH levels, and is therefore considered an early indicator of reproductive aging.[3] Overall, these hormonal imbalances resulting from the permanent cessation of ovarian function contribute to significant changes in the menstrual bleeding patterns during the perimenopausal period.[6]

In addition to changes in FSH and LH levels, there is a substantial decrease in the amount of estrogen produced during menopause. Acting as a lipophilic hormone, estrogen normally helps to promote female secondary sexual characteristics, such as breast development and female patterned hair growth. It not only plays a pertinent role in the female reproductive system, but also induces a variety of beneficial effects in other areas of the body.[9] Specifically, this hormone increases hepatic production of binding proteins like sex hormone binding globulin, maintains appropriate fluid balance in the body by allowing for salt and water retention, promotes coagulation, and it allows for a favorable lipid profile via increases in high density lipoprotein (HDL) and decreases in low density lipoprotein (LDL).[9,10]

Estrogen's release is mediated by FSH produced from the anterior pituitary gland, which in turn stimulates the granulosa cells of the ovary to synthesize estrogen. Specifically, in the ovary, estrogen is produced from the conversion of androgens via the enzyme aromatase[11] [Figure 1]. Moreover, estrogen is synthesized in three forms: Estradiol, estriol, and estrone.[12] Specifically, 17β-estradiol is the most common and potent form of estrogen predominating during the premenopausal and perimenopausal periods; whereas estrone, the much weaker form, is prevalent during the postmenopausal phase. The latter form of estrogen is normally produced from the conversion of androstenedione in adipose tissue and the liver.[13] In addition to being produced in the ovaries and a portion of the ovary known as the corpus luteum, estrogens are synthesized in smaller amounts by other tissues, such as adrenal glands, fat cells, breast tissue, and hepatocytes.[12]

Another reproductive hormone that declines significantly during menopause is progesterone. Also lipophilic in nature, progesterone promotes the secretory stage of the endometrium in order to prepare the uterus for implantation and decreases the maternal immune response to allow for the body's acceptance of pregnancy.[5,14] Moreover, this hormone thickens cervical mucus so it is impenetrable to sperm, inhibits lactation during pregnancy such that its fall after delivery triggers milk production, and decreases the contractility of the uterine smooth muscle. Overall, it is evident that a wide variety of hormonal and chemical changes occur in the female body as a result of menopause.

IMPLICATIONS OF OXIDATIVE STRESS IN MENOPAUSE

Oxidative stress plays an integral part of the aging process and results from the overproduction of free radicals such as reactive oxygen species (ROS), which overwhelm the body's antioxidant defense mechanisms. Normally, antioxidants neutralize ROS and thus help to prevent over exposure from oxidative stress.[15,16] However, as the body ages, antioxidant levels decline, leaving the human body susceptible to a variety of age-related pathologies, such as non-alcoholic liver cirrhosis and atherosclerotic heart disease.[17,18] This decline combined with a gradual loss of estrogen in the female reproductive system is

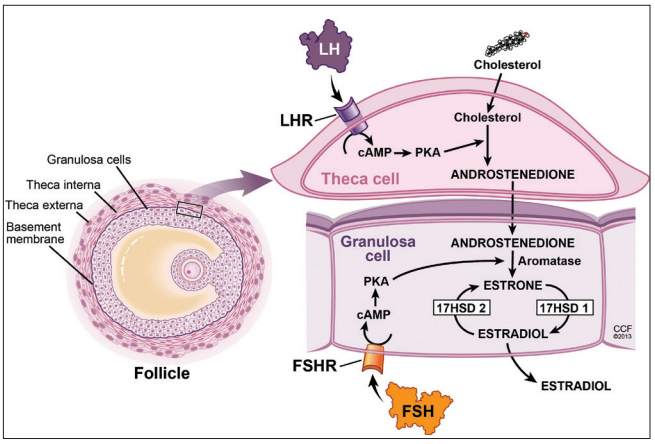

Figure 1: Two cell theory of estrogen production: Luteinizing hormone stimulates the production of androstenedione from cholesterol in the theca cells. This androgen is then transported to the granulosa cells, where it is converted to estrone. Follicle stimulating hormone then promotes the conversion of estrone to 17β-estradiol in the ovaries

highly associated with the various sequelae of menopause such as heart disease, vasomotor disturbances, and osteoporosis.[18,19] The marked reduction in estrogen has been shown to increase levels of oxidative stress in the body, depending on the concentration and chemical structure of this hormone. Specifically, at high concentrations, estrogen tends to have a beneficial antioxidant effect by inhibiting the 8-hydroxylation of guanine DNA bases. However, at low concentrations, this hormone has pro-oxidant like effects, especially when its chemical structure contains a catechol. These effects include breaks in genetic material, formation of DNA adducts, and oxidation of bases.[20] Additionally, serum concentrations of inflammatory cytokines and pro-oxidant biomarkers such as glutathione, 4-hydroxynenal, and malonaldehyde were found to be higher in postmenopausal women than in premenopausal women.[21] The elevation of cytokines and pro-oxidant makers suggests that there is a high degree of oxidative stress in the postmenopausal state.[21,22]

Cardiovascular effects of menopause

Estrogen has been shown to play a physiologic role in the cardiovascular system by protecting against heart disease. This is facilitated via its atheroprotective effect on plaque stabilization and collateral vessel formation.[23,24] This hormone also has favorable effects on insulin, glucose, and lipoprotein levels in the serum.[24] However, because the antioxidant effect of estrogen is lost once women reach menopause, the incidence of atherosclerosis increases.[17] This is due to a variety of factors, one of which is a higher level of oxidized LDL in the blood.[21,24] Also, there is an overexpression of the angiotensin receptor, AT-I, in menopausal women, which contributes to the endothelial dysfunction and increased vasoconstriction seen in atherosclerosis.[25] Additionally, studies have shown that postmenopausal women have low levels (<1 μM) of nitric oxide, a natural vasodilator in the body. Such low levels have been shown to play a role in cardiovascular disease by allowing for more smooth muscle proliferation, inflammation, and atherogenic effects on the vasculature.[26,27] The higher levels of nitric oxide normally seen in premenopausal women provide cardioprotective effects and inhibit the propagation of smooth muscle typically seen in heart disease.[27] Furthermore, the marked reduction of estrogen during menopause increases free fatty acid levels. This makes postmenopausal women more susceptible to the metabolic syndrome and insulin resistance, both of which are implicated as risk factors for cardiovascular disease.[28] Thus, it is evident that the effects of declining estrogen and other substances during menopause can predispose women to cardiovascular disease.

Vasomotor disturbances

Oxidative stress is also involved in the pathogenesis of menopausal symptoms, such as vasomotor disturbances. These disturbances include hot flashes or night sweats. Hot flashes are defined as a sudden feeling of warmth usually over the face, neck, and chest. During a hot flash, the metabolic rate temporary increases, which often results in sweating, panic, and irritability.[29,30] Throughout menopause, there are repeated episodes of such vasomotor disturbances, which results in a prolonged increase of the metabolic rate. This increase has been show to contribute to the formation of oxidative stress by placing a hindrance on antioxidants and their function in neutralizing ROS.[29]

Osteoporosis

Osteoporosis is defined as a reduction in bone mineral density, which occurs when there is an imbalance between the creation of new bone and removal of old bone. A decline in estrogen has been shown to play a major role in this decreased bone mass during the onset of menopause, especially because it has a variety of protective effects on bone marrow and bone cells.[31,32] This can be seen via estrogen's significant impact on bone-resorbing osteoclasts, which are cells involved in the breakdown of organic bone and removal of mineralized matrix. In particular, this hormone allows for increased bone formation by reducing the production and function of these osteoclasts as well as increasing osteoclast apoptosis. This effect on the osteoclastic cells of the bone is facilitated via estrogen's inhibition of two signaling molecules, RANKL and CSF-1, which are involved in osteoclast differentiation and survival.[31-34] However, due to the estrogen deficiency during menopause, this beneficial effect on the bone is lost.

As stated earlier, the menopause induced hormonal deficit has been linked to an increase in inflammatory cytokines within the serum such as tumor necrosis factor (TNF)-α, interleukin (IL)-4, IL-10, and IL-12. These cytokines stimulate osteoclast and osteoblast formation, leading to increased bone turnover and eventually, bone loss.[22] Specifically, TNF-α, produced from macrophages and granulocytes, negatively impacts the bone by contributing to increased osteoclast formation. This occurs via direct stimulation of pro-osteoclastogenic activity of stromal cells.[22] Additionally, the high levels of FSH during menopause stimulate osteoclast differentiation and TNF-α production, both of which play an important role in osteoporotic bone loss.[35] Overall, it is evident from the role of pro-inflammatory cytokines and estrogen in bone remodeling that oxidative stress is a major contributor to bone density loss in osteoporosis.

Effects of oxidative stress on menopause

In healthy, premenopausal women there is usually an

appropriate balance between free radical species and antioxidant mechanisms. As such, the level of oxidative stress in these women is not sufficient enough to affect the ovaries until the onset of menopause. In the aforementioned paragraphs, it has been stated that menopause creates a pro-oxidant state in the body due to the decline of the natural antioxidant, estrogen.[9,15] Consequently, the question often arises if oxidative stress can lead to menopause. The majority of studies have shown that oxidative stress alone in premenopausal women cannot induce menopause, but rather can lead to a variety of pathologies. Specifically, studies have reported that oxygen radicals have an important physiologic role within the ovary. However, the continuous synthesis of these harmful agents over time may lead to an increased cumulative risk of ovarian pathology. This includes premature ovarian failure, which is suggested to be exacerbated under conditions of reduced antioxidant status such as infection and autoimmune disease.[36]

TREATMENT OPTIONS FOR MENOPAUSE

Menopausal hormone therapy

MHT has been extensively researched as a potential treatment for the debilitating symptoms and sequelae of menopause. The aim of hormonal therapy is to enhance antioxidant defense mechanisms and decrease levels of oxidative stress in postmenopausal women.[37] A variety of researchers have found an association between MHT and its beneficial effect on oxidative stress. As such, most studies favor its administration to menopausal women. However, due to the fact estrogen has antioxidant and pro-oxidant characteristics, as well as a multitude of adverse side effects, some studies have not approved its use for the treatment of menopausal symptoms. A few studies even suggest that MHT has no significant effects on oxidative stress levels.[38,39]

Hormonal therapy has been shown to improve a variety of menopause-induced pathologies in the body, such as atherosclerotic heart disease. Specifically, the estrogen-progestin pill has been shown to reduce the risk of cardiovascular disease by opposing atherosclerosis. This is carried out via estrogen's downregulation of inflammatory markers such as chemokines and cell adhesion molecules.[24] Furthermore, it has been shown to potentially stabilize atherosclerotic plaques by reducing the expression of matrix metalloproteinases and the production of plasminogen activator inhibitor-1.[40] MHT also aids the cardiovascular system by downregulating both angiotensin receptor gene expression and smooth muscle proliferation. The former effect helps to lower blood pressure, while the latter aids in the prevention of atherogenesis. Additionally, the high concentrations of estrogen in MHT promote the dilation of vessels through the production of prostacyclin, inhibition of endothelin synthesis, and blockage of calcium channels.[40,41]

In addition to its advantageous effect on the cardiovascular system, hormonal therapy has been shown to have a similar effect on vasoactive biomarkers. For example, a study conducted on healthy postmenopausal women demonstrated that MHT given for 1 year significantly reduced levels of catecholamines, mean blood pressure, and LDL cholesterol while increasing levels of nitrite and nitrate. This suggests that MHT has a cardiovascular benefit in those who are menopausal.[38] Interestingly, it also showed that the amount of oxidative stress in the body was not greatly altered by 12 months of MHT usage. This was measured via the oxidative stress biomarker 8-epi $PGF_{2\alpha}$, which did not significantly differ from its baseline value.[38] Other studies discussing the effect of hormonal therapy on oxidative stress showed decreases in serum lipid peroxides and upregulation of overall antioxidant status. Overall, it is clear that a definitive relationship exists between MHT and oxidative stress levels; however, the nature of this relationship cannot be confirmed.[42,43]

There are a considerable number of risks and side effects associated with MHT. These include increased risk of a pulmonary venous embolism, stroke, and cardiovascular events as well as a high incidence of estrogen-dependent breast, ovarian, and endometrial cancers.[39] It has been suggested that there is a certain window during the postmenopausal period in which MHT is most beneficial. Outside this time frame, estrogen intake can have detrimental effects on the body. The timing of MHT is crucial because the longer menopause continues, the greater the estrogen deficiency, which leads to a decreased activity of estrogen receptors. This reduced receptor activity, in turn, leads to severe endothelial dysfunction and eventually decreased vascular responsiveness as well as decreased effectiveness of MHT.[44]

Overall, current research indicates that postmenopausal women should use the lowest possible dose of MHT due to the aforementioned side effects.[45] However, long-term use of MHT may prevent cardiovascular disease if started in women at the onset of menopause. As such, the benefits of this pharmacotherapy seem to outweigh the risks for women under 60-year-old.[46]

Selective estrogen receptor modulators

SERMs are a class of compounds that act on the estrogen receptor, exhibiting agonistic actions of estrogen in some tissues and antagonistic actions in others. Two examples of SERMs are raloxifene and tamoxifen.[47] The former drug has antagonistic action in the uterus and breast,

but agonistic action on the bone. Thus, the main use of raloxifene is to prevent and treat osteoporosis. Tamoxifen, however, acts as an agonist of estrogen receptors in the uterus but has antagonistic effects on the breast. Thus, its main use is to treat breast cancer. Similar to estrogen, raloxifene acts as an antioxidant due to the phenolic rings comprising its chemical structure.[47,48] Specifically, raloxifene's mechanism of action aims at decreasing nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, an enzyme that produces free radical species. This is facilitated via the downregulation of rac1 protein, which is required for NAPH oxidase activation.[49]

Additional beneficial effects of this SERM includes an increase in superoxide dismutase levels, a free radical scavenger, an increase in nitric oxide release, and a compound that suppresses smooth muscle proliferation and atherogenesis. Furthermore, raloxifene improves the lipid profile by preventing macrophage lipid oxidation and it also decreases levels of pro-oxidant biomarkers with the blood, such as malonaldehyde.[49,50] Additionally, raloxifene may play a protective role in the cardiovascular system by improving endothelial function and decreasing blood pressure levels as demonstrated in a study conducted on hypertensive rats.[50] Overall, by targeting the estrogen-mediated pathways, harmful results of oxidative stress can be prevented in postmenopausal women.

Exercise

Exercise has been shown to modulate levels of oxidative stress within the body through a variety of mechanisms. Studies have reported transient increases in ROS concentrations following acute aerobic and anaerobic exercise. However, this increased oxidative stress may serve as a necessary signal for upregulation of antioxidant defense mechanisms and eventual reduction of free radical species.[50,51] Specifically, exercise training has been associated with reduced basal oxidant production and free radical leak during oxidative phosphorylation, both of which contribute to the high oxidative stress levels seen during menopause.[51] Moreover, physical activity has been shown to alleviate menopausal symptoms and sequelae, such as sweating, anxiety, depression, hot flashes, osteoporosis, and cardiovascular disease.[52,53] In particular, one study reported that postmenopausal women had higher levels of oxidative stress associated with increased fat content than women who were premenopausal. Therefore, exercise in this population is helpful to reduce body fat, which is highly beneficial in augmenting the antioxidant capacity of the body.[54,55] Overall, exercise has been proven to be a valuable, cost-effective option in alleviating menopausal symptoms and improving the redox balance in healthy, postmenopausal women.[7]

DIETARY TREATMENT OF MENOPAUSE

Consumption of foods rich in antioxidants may be helpful in enhancing the beneficial effects of pharmacotherapy for postmenopausal patients.[56,57] Specifically, women who cannot tolerate the adverse side effects of MHT or are prone to develop estrogen-dependent breast cancer may find it advantageous to use dietary antioxidants to control the symptoms of menopause. Supplementation with antioxidants will not only improve the quality of life of menopausal women exposed to high amounts of oxidative stress, but also from other lifestyle-related factors such as smoking, stress, excessive alcohol consumption, and unhealthy eating habits.[57] The following antioxidants were found to be beneficial to women in the perimenopausal and postmenopausal phases: Vitamin C, Vitamin E, phytoestrogens, melatonin, *Acanthopanax senticosus*, klamin, Curcuma *longa*, grape polyphenols, and lycopene. Only the most relevant antioxidants will be discussed.

Vitamin C and E

Two dietary vitamins, vitamin C (ascorbic acid) and E (α-tocopherol), can be used to thwart the onset of various disorders associated with an age-related decrease in estrogen. Rich in their antioxidant capacity, these vitamins scavenge free radicals and neutralize oxidative stress.[58] One study assessing the effect of these vitamins on postmenopausal women found higher levels of the oxidative stress marker, malonaldehyde, and lower levels of the antioxidant enzymes, catalase and superoxide dismutase, in those who did not incorporate vitamin C and E in their diet.[59] These vitamins were not only helpful in achieving a favorable redox balance in the body, but they also are associated with a reduced risk of cardiovascular disease. This is mediated via their inhibition of cholesterol synthesis and LDL-cholesterol oxidation.[58,60]

In regards to the symptoms of menopause, both vitamins have been shown to reduce the intensity and number of hot flashes via promotion of adrenal function. This allows for increased hormonal production, specifically estrogen, allowing for a greater antioxidant defense system in postmenopausal women. When considering vitamin C alone, its intake has been associated with a protective effect on bone. This can be seen through its suppressive action on osteoblast and osteoclast activity, which thereby prevents accelerated bone turnover and eventual bone loss.[61,62]

However, at high doses, vitamin C and E have deleterious effects on the body. Specifically, large quantities of vitamin C (>2,000 mg/day) have been suggested to cause diarrhea, abdominal cramps, bloating, nausea, vomiting, and kidney stones.[61] While high doses of vitamin E (>1,000 mg/day) may increase the risk of bleeding by

having an anticoagulant-like effect on the body and may also increase the risk of birth defects. Thus, when using vitamin C and E to quell the adverse effects of menopause, it is important that appropriate dosages be used.[56]

CONCLUSION

Within the female reproductive system, menopause is a key physiological phenomenon associated with eventual cessation of ovarian function and thus, the menstrual cycle. During this time period, estrogen becomes deficient, which is an established antioxidant in the body. This leads to oxidative stress in various tissues due to the release of ROS, leading to the development of a variety of symptoms and pathologies that characterize menopause. Specifically, oxidative stress has been linked to an increased risk of osteoporosis and cardiovascular disease and a greater frequency of vasomotor symptoms. Therefore, a multitude of therapies have been employed to target this estrogen deficit and unfavorable redox balance, the most promising of which are MHT therapy and SERMs. However, for those who cannot tolerate the adverse side effects of these pharmacological therapies, exercise and antioxidant supplementation can also be used to quell the symptoms of menopause. However, further investigation needs to be done regarding the efficacy and safety of these various treatments when used in clinical practice. Overall, because a wide variety of treatment options are now available to prevent and reverse the negative effects of oxidative stress associated with reproductive aging, the specific treatment selected should be chosen based on the history and clinical presentation of the patient.

TAKE HOME MESSAGE

Though the levels of oxidative stress rise inevitably in menopause due to declining levels of estrogen, this article has put forth methods that women can use to curb the deleterious sequelae effects of this condition.

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