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The Role of Antioxidant Supplementation in Endometriosis Therapy

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Abstract

Endometriosis is a benign, estrogen-dependent disorder, characterized by the presence of ectopic lesions in extra-uterine regions of body, including the ovaries, peritoneum, and even the thoracic cavity. Though the pathophysiology of endometriosis is relatively unknown, disease itself is characterized by cell survival, oxidative stress, cellular proliferation, excessive adhesion, inflammation, and angiogenesis [Matsuzaki]. Though endometriomas are not malignant, this atypical tissue can spread throughout the female reproductive tract, causing chronic pain, infertility, and abnormal bleeding. Approximately 1 in 10 women suffer from endometriosis [1]. Despite the prevalence of endometriosis, current treatment methods include surgery, oral contraceptives, gonadotropin-releasing hormone agonist therapy (GnRH), anti-inflammatory medications, danazol, and aromatase inhibitors [1]. While these treatment methods aim to resects preexisting ectopic lesions, cause ovarian estrogen synthesis down regulation, and lessen cytokine-mediated inflammatory pain. Despite these interventions, endometriosis often can recur after cessation of therapy; therefore, novel medical therapies, such as statins, metformin, and antioxidant therapy, could have the potential to alleviate the symptoms and progression of endometriosis. This article is a brief review of relevant and novel antioxidant treatments for endometriosis and their possibility to increase and improve treatment options.

Introduction

Endometriosis is a common benign disease characterized by extra-uterine implantation of endometrial-like tissue within the ovaries, peritoneum, rectum, pelvis, and thoracic cavity. While some women remain asymptomatic, its symptoms and signs include infertility, chronic pain, irregular bleeding, and dyspareunia in approximately 8% of women of reproductive age and up to 50% of infertile women [1,2]. While the pathophysiologic mechanism of endometriosis is still unclear, the disease is characterized by abnormal cellular proliferation, invasion, and inflammation due to presence of reactive oxidative stress. These atypical processes underlie the signs and symptoms of this disease; therefore, treatment for endometriosis is targeted to address the various aspects of its pathogenesis.

The management of endometriosis is currently as recommended by the European Society of Human Reproduction (ESHRE) guidelines [2]. These guidelines for endometriosis therapy include oral contraceptive medications, GnRH agonists, progestogens, analgesics, danazol, anti-progestogens, aromatase inhibitors, and conservative or non-conservative surgical approaches. The treatment approach for patients is highly dependent on the severity of the patient's symptoms. Traditionally, surgical interventions, such as resection and nerve transection, are considered in patients with confirmed endometriosis who do not respond to medical therapy [ASRM].Surgical methods aimed to removed endometriosis are considered more effective than non-invasive means [1]. Surgery has been shown to significantly reduce pain, a major symptom of endometriosis [ASRM] and can offer improvements in fertility [1,3]. Though these interventions have been shown to be effective, the relapse rate of endometriosis post-surgery, the most aggressive treatment, is still roughly 22% at 2 years and 40-50% after five years [4]. Though the current therapeutic means offer benefits to patients, recent literature on endometriosis treatment suggests that other novel medical approaches, especially in antioxidant therapy, may be able to supplement the established treatment guidelines [3].

The Role of Antioxidants

All Though the pathogenesis of endometriosis is still not fully elucidated, the disease is associated with oxidative stress and an abnormal increase in reactive oxidative species (ROS). ROS are volatile molecules that interact with biological molecules to activate apoptotic mechanisms and cell death [5]. ROS are typically neutralized by physiological means; however, patients

with endometriosis have an altered balance of prooxidant and antioxidant molecules. For example, oxidative markers, such as Cu, ceruloplasmin, 8-hydroxyl-2-deoxyguanosine, and total oxidant status, may be elevated in endometriosis patients [6]. Moreover, serum total antioxidant status and thiol levels were significantly lower ($p<0.001$) [7,8]. This evidence demonstratesthat the low antioxidant levels may be integral to the etiopathogenesis of endometriosis. Previous literature on antioxidant therapy suggests that the beneficial properties of antioxidants may reduce endometriosis-related symptoms and oxidative damage.

The Evidence for Antioxidant Therapy

Based on the role of oxidative stress in endometriosis, antioxidant use has been studied as a means to improve patient outcomes in endometriosis. Current research assesses the antioxidant characteristics of vitamin E, vitamin C, epigallocatechin-3-gallate (EGCG), resveratrol, melatonin, andcerum oxide nanoparticles. Analysis of the antioxidative benefits of these therapies were determined by outcomes both in animal and human studies, such as symptomatic reduction, pain alleviation, lesion size reduction, and number of lesions.

In order to determine the effect of vitamin E and C, 46 women with endometriosis-related pain were given a combination of vitamin E (1200 IU) and vitamin C (1000mg) for two months. Vitamin E is a fat-soluble antioxidant that prevents the formation of the vitamin E radicals, and vitamin C was added to this regimen because it functions to recycle the vitamin E radial to vitamin E. After this randomized control trial, 43% of the patients reported a reduction in chronic pelvic pain, suggesting that vitamin E and C may offer noticeable pain reduction even in short time frames ($P=0.0055$). The patients in the control group did not experience any decrease in pain [9]. While Santanam et al. [9] attributed the effects of vitamin supplementation to its anti-oxidative and anti-inflammatory properties, there was no clear physiologic mechanism stated in the article. However, the work of Durak et al. [10], may offer some insight. In a rat model, experimentally induces endometriotic cysts were treated with differing doses of vitamin C (0.5mg, 1.25mg, and 2.5mg) to determine if vitamin C supplementation would alter the volume and weights of these lesions. The cysts from group treated with 2.5mg of vitamin C were significantly reduced in weight and volume [10]. This evidence suggests that antioxidants, such as vitamin C, may reduce endometriosis symptoms by reducing lesion size.

In addition to vitamins, epigallocatechin-3-gallate (EGCG) may also impact the size of endometriomas as well as selectively inhibit neovascularization in these lesions. EGCG is a commonly found polyphenol in green tea. In other fields, it has been found to prevent tumor formation through initiating apoptosis and cell cycle arrest [11]. Therefore, Matsuzaki et al. [12] assessed its effect in endometriosis. Cell samples for 55 endometriosis patients were treated with EGCG and analyzed via rt-PCR, cell proliferation assays, in vitro migration and invasion assays. EGCG significantly reduced proliferation, cell migration, and invasion of endometriotic cells [12]. Though EGCG appears to offer benefits for endometriosis patients, its low bioavailability through ingestion of pure EGCG or green tea consumption limits its use as a drug.

Like EGCG, resveratrol, another natural therapy, may also improve endometriosis symptoms. Resveratrol is known anti-proliferative agent and antioxidant found in grapes and red wine. Ricci et al. [13] studied the effects of both EGCG and resveratrol on endometriosis as potential natural therapies. They investigated in a mouse model, 56 mice completed surgical induction of endometriosis and were treated with either resveratrol and EGCG for four weeks. Both interventions reduced the mean number and volume of established lesions ($P<0.005$). Though both treatments were effective in decreasing cell proliferation, reducing vascular density, and increasing apoptosis, results due to resveratrol ($p<0.01$) were more significant than those due to EGCG ($p<0.05$) [13]. While the mechanism of action associated with resveratrol is not completely understood, Amaya et al. [14] studied its dose-dependent impact on endometrium. In addition to its antioxidant properties, resveratrol functions as a phytoestrogen. It has different estrogen action based on concentrations; in low concentrations, it acts agonistically. However, in high concentrations, it functions antagonistically. Because endometriosis is an estrogen-dependent disease, high levels of resveratrol was shown to reduce proliferation of xenografts of human endometrium in mice [14].

Another naturally produced substance, melatonin, is also suggested to have potent effects on endometriotic lesions. Melatonin has several properties, including free radical scavenging, stimulation of antioxidants, and increasing the efficacy of electron chain function [15,16]. In humans, it is produced in the pineal gland, and has been shown to decrease oxidative damage [15]. To understand the role of melatonin, Yilmaz et al. [16], implanted endometriotic lesions in twenty rats and treated ten with melatonin and ten with saline (control). The outcome measures of this study were volume and weights of the lesions. In the experimental group, the lesion volume ($p<0.01$) and weights were significantly decreased ($p<0.05$), showing that melatonin causes lesion regression [16].

Another novel antioxidant therapy includes the use of cerium oxide in order to impact the progression of endometriosis. Cerium oxide has radical-scavenging characteristics that could offer benefit to endometriosis patients. Chaudhury et al. [17] utilized cerium oxide nanoparticles to improve endometriosis-related effects in a mice model. Mice with endometriosis treated with cerium oxide nanoceria were found to have lower levels of ROS and higher levels of total antioxidant capacity (TAC). Cerium oxide not only has antioxidant properties, but also has regenerative traits. This process of regeneration makes one dose of cerium oxide more appealing than the use of other antioxidants. While this study shows the effect of cerium oxide

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nanoparticles in endometriosis, there is also a concern for toxicity when using these nanoceria.

Conclusion

Endometriosis is a chronic, estrogen-dependent condition that affects nearly 10% of women of reproductive age, causing pain, irregular bleeding, and infertility. This disease is treated by various medications, which function to reduce estrogen levels and inflammation, and surgery to remove the endometriotic lesions. However, despite this wide array of therapy, there is still high rate of relapse after surgery, the first line therapy for symptomatic patients [4]. Because of this phenomenon, there may be a need to improve outcomes for endometriosis patients. The current and previous literature focuses on the efficacy of antioxidant therapy in the treatment and mitigation of endometriosis. Antioxidants function by removing the free radial species, upregulating antioxidant enzymes, and reducing oxidative damage. Relevant antioxidants include vitamin E and C, EGCG, resveratrol, melatonin, and cerium oxide. These molecules have been shown to reduce the symptoms and progression of endometriosis mainly in experimental animal models. However the studies highlight the potential of the antioxidants enlisted in the article for use in women with endometriosis. There is a need for further well designed and adequately powered studies to assess the newer antioxidants in women suffering from this debilitating disease.

References

1. Gupta S (2015) Endometriosis: a comprehensive update. Springer.
2. Dunselman GAJ, Vermeulen N, Becker C, Hooghe TD, De Bie B, et al. (2014) ESHRE Guideline : Management of Women With Endometriosis. Hum Reprod 29(3): 400-412.
3. E Society, H Reproduction (2013) Management of women with endometriosis. p. 1-97.
4. Guo S (2009) Recurrence of endometriosis and its control. Hum Reprod Update 15(4): 441-461.
5. Ménézo Y, Dale B, Cohen M (2010) DNA damage and repair in human oocytes and embryos: a review. Zygote 18(4): 357-365.
6. Gupta S, Sinha A (2016) Potential Markers of Endometriosis : Latest Update. J Genit Syst Disord 5: 3.
7. Turgut A, Özler A, Görük NY, Tunç SY, Lu OEĞ, et al. (2013) patients with advanced-stage endometriosis. pp. 1472-1478.
8. Choi YS, Cho S, Seo SK, Park JH, Kim SH, et al. (2015) Alteration in the intrafollicular thiol-redox system in infertile women with endometriosis. Reproduction 149(2): 155-162.
9. Santanam N, Kavtaradze N, Murphy A, Dominguez C, Parthasarathy S (2013) Antioxidant supplementation reduces endometriosis-related pelvic pain in humans. Transl Res 161(3): 189-195.
10. Durak Y, Kokcu A, Kefeli M, Bildircin D, Çelik H, et al. Effect of vitamin C on the growth of experimentally induced endometriotic cysts. J Obstet Gynaecol Res 39(7): 1253-1258.
11. Singh BN, Shankar S, Srivastava RK (2011) Green tea catechin, epigallocatechin-3-gallate (EGCG): Mechanisms, perspectives and clinical applications Catechin backbone. Biochem Pharmacol 82(12): 1807-1821.
12. Matsuzaki S, Darcha C (2014) Antifibrotic properties of epigallocatechin-3-gallate in endometriosis. Hum Reprod 29(8): 1677-1687.
13. Singla JJ, Ricci AG, Olivares CN, Bilotas MA, Basto JI (2013) Natural therapies assessment for the treatment of endometriosis. Hum Reprod 28(1): 178-188.
14. Amaya SC, Savaris RF, Filipovic CJ, Wise JD, Hestermann E, et al. (2015) Resveratrol and Endometrium : A Closer Look at an Active Ingredient of Red Wine Using In Vivo and In Vitro Models. Reprod Sci 21(11): 1362-1369.
15. Reiter RJ, Tan D, Mayo JC, Sainz RM, Leon J (2003) Melatonin as an antioxidant : biochemical mechanisms and pathophysiological implications in humans. Acta Biochem Pol 50(4): 1129-1146.
16. Yilmaz B, Kilic S, Aksakal O, Egemen I, Tanrisever GG, et al. (2015) Melatonin causes regression of endometriotic implants in rats by modulating angiogenesis, tissue levels of antioxidants and matrix metalloproteinases. Arch Gynecol Obstet 292(1): 209-216.
17. Chaudhury K, Singh AK, Das S, Kumar A, Seal S (2013) Mitigation of endometriosis using regenerative cerium oxide nanoparticles, Nanomedicine Nanotechnology. NanoMedicine 9(3): 439-448.

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