Oxidative stress-related effects on various aspects of endometriosis

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Abstract

Endometriosis is a chronic and relatively common disease in women of childbearing age. Complications of this disease include a wide range of disorders. The cause of this disease is not known for sure, but several hypotheses have been proposed for it. In this disease, the entry of endometrial tissues into the peritoneal cavity causes oxidative stress through the Fenton reaction and inflammation in this site. Oxidative stress can be associated with many complications of endometriosis. In this review, an attempt has been made to discuss the effects of oxidative stress on various complications of this disease.

Introduction

Endometriosis is a hormone-inflammatory disease described by the presence of endometrial tissue outside the uterine cavity, with a prevalence of 6–10% in reproductive-age women, but as high as half when associated with chronic pelvic pain and infertility(1, 2). Several theories have been suggested to clarify the pathogenicity of endometriosis, which is delineated in Figure 1; the Sampson hypothesis presented in 1920 showed the retrograde menstruation through the fallopian tube into the peritoneal cavity principal reason for endometriosis(3, 4).

Some studies have shown endometriosis has an association with oxidative stress, characterized by a balance between the production of reactive oxygen species (ROS) and their neutralization by the antioxidant system(5-8). Oxidative stress has an essential role in the cell proliferation, inflammatory process, and the apoptosis prevention of the endometriotic cell(3, 9). Well-known inducers of oxidative stress are macrophages, erythrocytes, and apoptotic endometrial tissue, transplanted to the peritoneal cavity through retrograde menstruation(10). Fenton reaction can produce ROS through a catalytic form of iron. This process can provoke inflammatory responses and oxidative injury. As a result, the activity of macrophages and expression of nuclear factor-kappa B increase. All of these processes result in the upregulation of the expression of multiple proinflammatory genes such as cytokines, chemokines, adhesion molecules, growth, and angiogenic factors(8). Enzymatic and non-enzymatic antioxidant defenses and permitting an overall assessment of this process(11). The present study attempts to evaluate oxidative stress's role in the complications of endometriosis.

Physiology of reactive oxygen species

ROS are considered to be byproducts of cellular metabolism and normal physiologic processes. Some studies have shown that normal levels of ROS for sperm maturation, chemotaxis, acrosome reaction, zona pellucida binding, hyperactivation, capacitation, and sperm-oocyte fusion are needed. Additionally, ROS are crucial intermediaries that have some roles in gene regulation and vascular tone within the testis(12).

Oxidative stress and transcription factor

Intercellular ROS in the peritoneal activated macrophages can be generated due to proinflammatory molecules such as heme and iron. As a result of this phenomenon, transcription factors such as activator protein-1 (AP-1), CCAAT/enhancer-binding protein (C/EBP), signal transducer, and activator of

transcription (STAT), hypoxia-inducible factor-1 (HIF-1), and CCAAT/enhancer-binding protein (C/EBP), and nuclear factor kappa B (NF-kB) but not HNF can be activated. The transcription factor NF-kB activates proliferative, antiapoptotic, chemokines, growth and angiogenic factors, proinflammatory, adhesion molecules (such as VCAM-1, ICAM-1, and selectin E), and induction enzymes (iNOS and COX-2) genes in many cell types(13, 14). Agents that are induced in endometriosis by NF-kB and their function is shown in the table I.

Oxidative stress and VEGF

Some studies have reported endometriosis as an angiogenesis-dependent disease. Vascular endothelial growth factor (VEGF) as a mitogen has a crucial role in promoting angiogenesis in physiological and pathological conditions(8). In the endometrium, oxidative stress can enhance VEGF production, which by itself can promote the growth of endometrial implants and stimulate angiogenesis. Glycodelin has a crucial role in this process. Expression of glycodelin can be stimulated by oxidative stress, and it can enhance the expression of VEGF in the ectopic endometrial tissue(15).

Oxidative stress and autoantibody

Some studies have shown enhancement of autoantibody titers because of oxidative stress in the peritoneal fluid of endometriosis patients. Evidence suggested the presence of oxidative stress in the peritoneal cavity, and markers of increased lipid peroxidation, e.g., antibodies to the oxidized low-density lipoproteins, have been proposed to be increased in the endometriosis' patients(15). Evidence suggests the enhancement of titers of autoantibodies in women with endometriosis which results in an increase in serum autoantibody titers to oxidatively modified low-density lipoproteins(16). Oxidative stress products, such as lipid peroxides, can be generated from activated macrophages in the peritoneal cavity. Oxidized LDL and the peritoneal fluid of endometriosis patients can be involved in MCP-1 production by endometrial cells and peritoneal mesothelial cells. Accordingly, the growth of ectopic endometrium can be the result of the pre-oxidant environment in the peritoneal fluid and activated macrophages(17).

The role of nitric oxide (NO) induced by ROS

Oxygen free radicals have the ability to induce nitric oxide. Different studies show that No has different effects on implantation and ovarian function(17). Harmful effects on sperm motility, toxicity to embryos, and inhibition of implantation can be expected from high NO levels(18, 19). As a free radical agent, No has a significant role in regulating apoptosis(20). Additionally, the enhancement of activity and number of macrophages is related to releasing more cytokines and other immune mediators, such as NO. For the first time, it was reported that NO enhancement is accompanied by the augmentation of activity and the number of macrophages in low-grade inflammation(21). mRNA expression of nitric oxide synthase (NOS) in the epithelial glands of the human endometrium is periodic. The level of NO and NOS in the endometrium of endometriosis' patients are higher than the endometrium of ordinary women(22-24).

A study has reported the higher NOS activity of peritoneal macrophages, higher peritoneal fluid NO levels, and higher protein expression of peritoneal macrophage inducible NOS in infertile women with endometriosis. This study shows that peritoneal macrophages produce more NO in response to immune stimulation in vitro express higher levels of NOS. Moreover, this kind of macrophage has more NOS enzyme activity. Additionally, enhancement of expression of endothelial NOS in the glandular endometrium of patients with endometriosis has been(22, 23). The iNOS isoforms in tissues of patients with endometriosis is also reported(24). There are studies that show abnormal stimulation of endothelial NO synthase can be the result of different cytokines secreted from immune cells, endometrial cells, or macrophages stimulate endothelial NO synthase to release NO(10, 22, 25). This abnormal stimulation can release a high level of NO, resulting in inhibition of implantation(26).

Moreover, during the menstrual cycle of endometriosis' patients, the expression of endothelial NO synthase in their endometrium will increase(27). NO is an essential molecule for normal reproductive biological processes like sustaining pregnancy at physiological levels(28). According to a hypothesis in endometriosis patients,

stimulation of macrophages for releasing NO can be the result of IL-10, which is augmented within earlier stages of endometriosis(29). Three types of NO synthase produce NO from the conversion of L-arginine to L-citrulline. NOS1, neuronal form, NOS2, the inducible form, and NOS3, the endothelial form(30).

The peritoneal macrophages can move to different parts of the female reproductive system, including fallopian tubes in which fertilization happens. Regarding this subject, these macrophages can cause a more significant risk of infertility because of the increased capacity of macrophages for producing NO(31). It has also been reported that in women with endometriosis-associated infertility, peritoneal macrophages express higher NO synthase2. Additionally, they have higher NO-synthase enzyme activity, and they can produce more NO in response to immune stimulation in vitro(32).

Oxidative stress and cancer

There is a link between the increased ROS and almost all cancers(33). This link is the result of ROS's effect on MAPK signaling pathways which can cause cell proliferation. According to the linkage between the proliferation of cancer cells and ROS and regarding increased ROS production in endometriosis, we can conclude that ROS has an outstanding role in regulating cell proliferation in endometriosis(34-36).

Oxidative stress and fibrosis

There is a linkage between the enhancement of expression of genes encoding profibrotic such as TGF-1β and iron and the iron-mediated generation of ROS(37, 38). TGF-β, as an inflammatory cytokine, can induce inflammatory changes and fibrotic in different organs(39). Changes in iron metabolism have some roles in developing fibrosis and chronic inflammation(40). Liver in the humans and animal models are great examples of the linkages between tissue fibrosis and upregulation of TGF-β and iron(41). The kidney and the heart are other possible organs that iron may play a role in tissue fibrosis and TGF-β upregulation(42, 43). Additionally, the vital effect of TGF-β in the growth of endometriosis has been found in both in vivo and in vitro studies(44).

Oxidative stress and infertility

Infertile women with endometriosis have some macrophages that had more inflammatory mediators and iNOS activity. These features of this kind of macrophages can have some roles in infertility related to endometriosis(31). These kinds of macrophages can produce high levels of NO, which can have some deleterious effects on fertility in different ways. A study shows that changes in peritoneal fluid might influence all these reproduction steps(21, 45, 46). According to the deleterious effects of high levels of NO, fertility of women with endometriosis can be improved by either blocking NO effects or reducing the peritoneal fluid NO production(31).

Conclusion

It has been reported that in the peritoneal fluid of endometriosis' patients, there are activated macrophages and growth factors and high concentrations of cytokines. These conditions have been toxic to embryo survival and sperm function. ROS can mediate these conditions. Moreover, it can have some relations with iron concentrations in peritoneal fluid. Novel therapeutic strategies must regulate intracellular ROS signaling to inhibit the adverse effects of ROS-induced endometriosis-promoting events. According to features of antioxidants, they may inhibit early events of the development of endometriosis.

Conflict of Interests

The authors declare that they have no competing interests.

Data Availability Statement

The data used to support the findings of this study are available from the corresponding author upon request.

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No.

Author contribution

H.A. writing manuscript A.Y. data collection F.Z. and A.J. editing. All authors read and approved the final manuscript.

Figure 1. Theories as to how endometriosis develops

Table 1. Molecules that are induced in endometriosis by NF-kB factor and their function

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