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Research Article

Repercussions of the Anti-inflammatory Diet on Endometriosis Control

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Abstract

Endometriosis is an inflammatory pathology characterized by the growth of endometrial tissue outside the uterus, resulting in chronic pelvic pain and infertility. As a result, it has been observed that diet can influence the pathophysiology of this disease by attenuating the inflammatory environment. In this context, this study aims to summarize the influence of diet as a complementary therapy for endometriosis. To this end, a narrative review was carried out using the BVS, Embase, and Cochrane databases, including articles available in full in Portuguese, English, and Spanish published in the last 5 years. According to the literature, a diet can have pro-inflammatory properties in patients with endometriosis, such as a diet rich in saturated fatty acids, and anti-inflammatory properties, involving polyunsaturated fatty acids, in order to influence the metabolism of prostaglandins. It is concluded that endometriosis is a chronic inflammatory disease that can be modulated with the adoption of anti-inflammatory dietary habits that can impact women's quality of life in the long term.

Introduction

Endometriosis is an inflammatory pathology characterized by the growth of functional and hormone-dependent endometrial tissue outside the uterus, which can result in menstrual changes, chronic pelvic pain, and infertility [1]. It is therefore believed that this clinical condition affects between 6% and 10% of menopausal women and between 50 and 60% of adolescent and adult women with pelvic pain, as well as being responsible for around 50% of the causes of infertility.

According to the National Health Surveillance Agency (ANVISA), endometriosis affects 1 in 10 women between the ages of 25 and 35, who come down with pelvic pain that coincides with the menstrual period, a fact that is normalized, resulting in late diagnosis and treatment in around 7 years [2].

The clinical picture of endometriosis varies widely and is confused with other pathologies, such as pelvic inflammatory disease and irritable bowel, and is characterized as a benign disease that presents with a lesion in the ovary or endometrioma and foci of endometrial growth (Figure 1) that can reach the intestine, peritoneum, bladder and adjacent organs, resulting in non-specific symptoms [3]. In women

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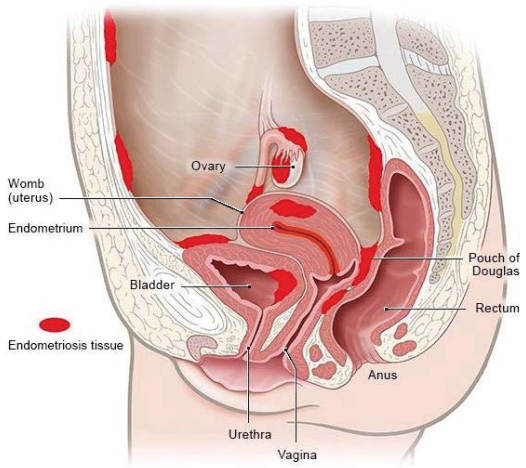

Figure 1: Possible foci of endometriosis. Source: Adapted from [13].

who are oligosymptomatic, infertile, or in the early stages of the disease, diagnosis can be late, which results in thousands of underdiagnosed cases that become chronic and compromise quality of life [4].

The spectrum of signs and symptoms of this inflammatory disease, the non-correspondence of symptoms with the stage of the disease, and the limitation of the use of imaging tests due to cost-effectiveness mean that the diagnosis of endometriosis is postponed for years, as well as resulting in 5 or more consultations until the start of specific treatment or the referral of women to specialized centers [5].

Thus, the choice of drug therapies for endometriosis takes into account the inflammatory pathophysiology of the disease and the responsiveness to hormones, in addition to the fact that the physiological conditions of the pregnancy and menopause period are associated with the resolution of the resulting chronic pain [6]. In other words, the prescription of progestogen analogs and Combined Oral Contraceptives (COCs), which simulate hormonal conditions similar to those of pregnancy, and GnRH agonists, which promote the suppression of endogenous estrogen and resemble menopause [4].

On the other hand, the literature shows that aspects related to lifestyle changes, especially in relation to an anti-inflammatory diet, are important as a complement to pharmacological therapy, with the aim of approaching the disease through different therapies. That said, it has been observed that a selective diet can influence the course of endometriosis pathophysiology, such as inflammation and prostaglandin metabolism [7]. This diet is related to the consumption of oral omega-3 polyunsaturated fatty acids, a dietary supplement approved by the Food and Drug Administration (FDA) that has a suppressive action on endometrial cells [8].

It is worth mentioning that studies have analyzed the correlation of nutrition on the pathogenesis of endometriosis and on the inflammatory state of the disease, such as a diet based on antioxidants, as they minimize free oxygen radicals and, consequently, inflammation [6]. On the other hand, a diet rich in carbohydrates is associated with a pro-inflammatory state, which can aggravate the main symptom of the disease, which is chronic pain [9]. With this in mind, considering the influence of diet on the progression of endometriosis and as a potential complementary therapy to pharmacological therapy, this study aims to summarize the repercussions of an anti-inflammatory diet on the control of endometriosis.

Methodology

Characterization of the research

This is a narrative, qualitative, and descriptive review, in which bibliographic studies on a particular subject are analyzed and synthesized in order to provide a relevant and current theoretical reference, as well as gather new perspectives on a specific topic [10]. In order to construct the research question, the PICO strategy (Population, Intervention, Control, and Outcomes/Outcome) was used, resulting in the research question: "What are the repercussions of an anti-inflammatory diet on the control of endometriosis?"

Conducting the research

The review was carried out during the months of November and December 2023, in the electronic databases Embase, Cochrane, and VHL aimed at indexing scientific journals and articles. The keywords provided by the Health Sciences Descriptors (DeCS) and the Boolean operators used in the search were: endometriosis AND diet OR nutrition AND inflammation, with the search languages being Portuguese and English, involving articles from the last 5 years. The papers were then selected by title, followed by reading the abstract and then the full text, original articles that dealt with endometriosis in the dietary context, as well as the influence of food as an anti-inflammatory therapy, were selected. The exclusion criteria were duplicate studies, review articles, and articles involving animals which, after full reading, did not answer the research question.

Summary of results

Based on the search criteria, 123 articles were found and, at first, reviews and studies involving animals were excluded, followed by other articles excluded by title and abstract and, finally, after a thorough reading, 8 articles were selected to make up the state of the art. This was followed by an analysis of the theoretical basis of each study, as well as an observation of the general characteristics of the articles, highlighting the most relevant points to be synthesized in the current narrative review.

As this is a review article, it was not necessary to submit the study to an ethics and research committee, as the analysis was based on secondary data already published in other articles.

Theoretical background

Understanding Endometriosis

Endometriosis is a chronic, inflammatory gynecological disease in which endometrial tissue grows outside the uterine cavity, resulting in local inflammation, compression, and

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obstruction of other organs, generating chronic pain and, in advanced cases, infertility [4]. In other words, it corresponds to ectopic endometrial tissue outside the uterine cavity and myometrium and can be found in the pelvic and abdominal cavities, adhered to the peritoneum, ovary, bladder and/or intestines [1].

In a study [3] that worked with a sample of 153 women with endometriosis, the most prevalent symptoms were: dyspareunia (65.4%), dysmenorrhea (88.2%), and infertility (52.9%) and, when endometrial tissue appears in non-reproductive organs, the associated complaints are: dyschezia, hematochezia and dysuria.

The causes that explain endometriosis have not yet been fully elucidated and may vary in terms of the manifestations and bodily responses to ectopic endometrial implants, whose progression is not restricted to a single pathway and may regress, progress, or stabilize [11]. The symptoms associated with endometriosis usually appear in adolescence or early adulthood, and they also manifest cyclically with the hormonal variations of the menstrual cycle, as the growth of endometrial tissue is estrogen-dependent [12].

With regard to treatment, the choice of method should take into account the expression of each symptom and the site affected by the disease, as well as including the desire to become pregnant or not, the patient's age, and possible surgical complications. Treatment with combined contraceptives aims to slow down the progression of the disease and is used as the first choice for women who want contraceptive protection associated with mild symptoms of endometriosis, as it reduces dysmenorrhea and helps to reduce endometriomas [4].

Thus, the hormonal drugs cited in the literature - such as isolated progestogens, combined oral contraceptives, gestrinone, danazol, and GnRH - have similar effects in relieving pelvic pain. In addition, there is surgical treatment to remove endometrial foci in the case of women who have not responded to drug treatment and suffer from progressive pelvic pain [1].

Pathophysiology of endometriosis

In principle, endometriosis is a common, inflammatory, and debilitating gynaecological disease that can lead to the occurrence of many chronic pathologies, such as pelvic pain, dysmenorrhoea, and infertility, characterized by the presence of endometrial tissue outside the uterus, affecting the ovaries, fallopian tubes, bladder, and more distant tissues [14] (Figure 2).

Despite being recognized as an inflammatory disease, the pathogenesis of endometriosis and the origin of chronic pain and other symptoms remain poorly understood. However, it is known that some hormonal, neurological, and systemic inflammatory factors may be related to the pathophysiology of this condition [15].

In this sense, it is clear that chronic inflammation has been proposed in several studies as an enhancer of the pathophysiological mechanism of endometriosis [16]. This is because the pro-inflammatory condition of endometriosis triggers an increase in cytokine and growth factor concentrations, as well as leading to a decrease in cell apoptosis and an increase in angiogenesis [17].

As evidence of this, in recent decades, researchers have

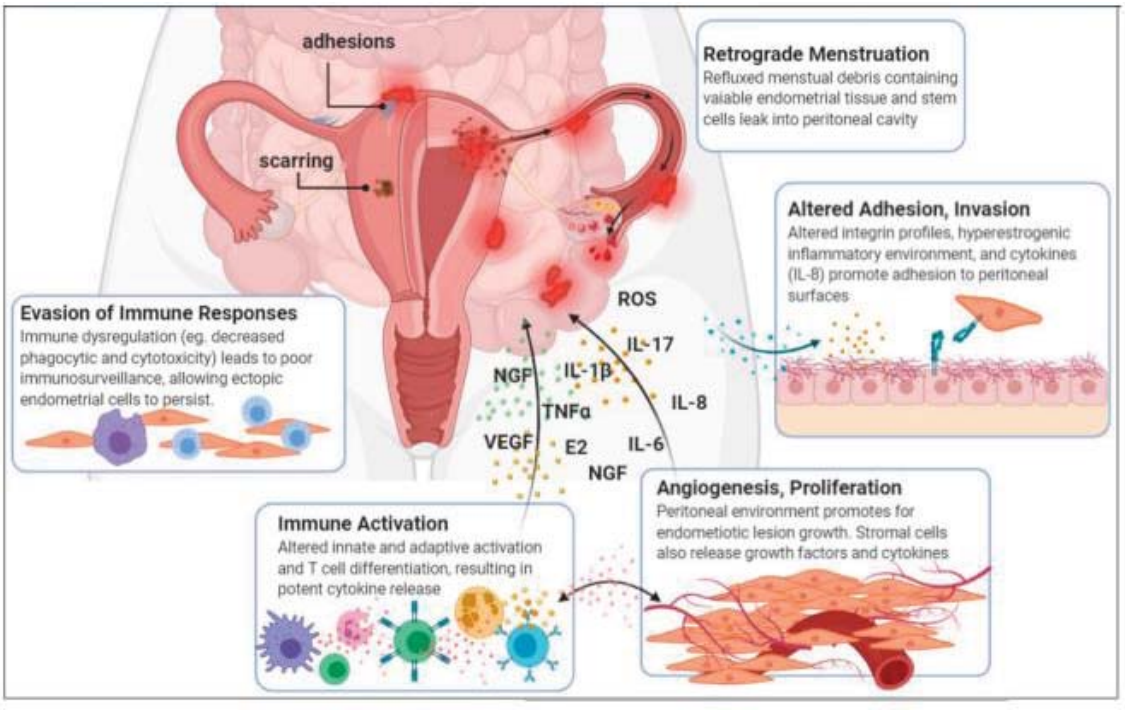

Figure 2: Pathophysiology of endometriosis. Source: Adapted from [21].

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been able to find the presence of inflammatory mediators such as interleukin (IL)-1 beta, IL-6, and Tumor Necrosis Factor-alpha (TNF-α) in the endometrial tissue of women with endometriosis, demonstrating that inflammation plays a crucial role in the pathogenesis of endometriosis, as these cytokines positively regulate the production of human endometrial haptoglobin in women with endometriosis [14].

In addition, the macrophages that infiltrate the ectopic lesions through chemokine-induced recruitment express typical markers of alternative activation, promoting neoangiogenesis and facilitating the growth of endometriosis by increasing the levels of vascular endothelial growth factor in the peritoneal fluid [18].

Furthermore, the chronic inflammatory state of endometriosis activates nociceptors, resulting in central and peripheral sensitization [7]. Consequently, the altered inflammatory microenvironment characteristic of endometriotic tissue may be related to hyperalgesia and the persistence of chronic pain [19].

In addition, women with endometriosis have been reported to have significant changes in oxidative stress parameters [20]. This factor induces a cytotoxic effect, increased cell membrane permeability, enzyme activation, DNA damage, and cell death, so pain in women with endometriosis is related to the response to tissue injury, the resulting inflammatory process, and oxidative stress [7].

Finally, in addition to these factors, high serum estrogen levels can contribute to the production of prostaglandins and the development of cell proliferation, favoring inflammation and the intensification of endometriosis [7]. As a result, because it is a chronic inflammatory disease dependent on oestrogen, the greatest risk of endometriosis occurs between the ages of 25 and 35, given that the density of serum hormone levels, especially oestrogen, normally decreases at the age of 35 [19].

The role of nutrition as a complementary therapy

Pro-inflammatory diet: Some factors associated with the diet may have properties considered to be pro-inflammatory in patients with endometriosis, for example, a diet with high amounts of saturated fatty acids and carbohydrates, and low amounts of polyunsaturated fatty acids (especially omega-3 fatty acids), flavonoids, and antioxidants [18]. As a starting point, we can cite the results of the Nurses' Health Study II, which shows that the consumption of red meat possibly increases painful symptoms, as it reduces estrogen transporters resulting in greater availability of this hormone in circulation, which stimulates the progression of endometriotic foci that are hormone-dependent [7].

In a study of thirty-one women diagnosed with endometriosis and suffering from gastrointestinal disorders, twenty-eight of them (90.3%) had nickel (Ni) in their oral mucosa and were diagnosed with allergic contact mucositis due to Ni, while three of the thirty-one (9.7%) patients did not have nickel in their oral mucosa. After three months on a low-nickel diet, all gastrointestinal, extraintestinal, and gynecological symptoms decreased significantly [15].

In this context, nickel (Ni) in high concentrations can be toxic, inducing inflammatory and allergic disorders, for humans the main source of the element is in foods such as tomatoes, cocoa, beans, mushrooms, green leafy vegetables, whole wheat flour, soybeans, corn, onions, garlic, shellfish, nuts, canned foods [15].

Furthermore, a study carried out using data from the National Health and Nutrition Examination Survey with participants from the general US population concluded that those with the highest Dietary Inflammatory Index (DII) scores had a 57% higher risk of endometriosis than those with the lowest DII scores [16]. This is due to the high levels of systemic inflammation caused by the pro-inflammatory diet, which can affect the markers C-reactive protein, IL-6, IL-8, and TNF-α, collaborating for the implantation of endometrial cells, growth, invasion, and angiogenic properties of ectopic lesions [18].

Anti-inflammatory diet: The main treatments for endometriosis are based on hormonal medication and surgical removal of lesions [7]. However, around 75% of symptoms recur after surgery, and ovarian suppressant drugs have several side effects similar to those of menopause and/or are contraceptives, which generates the need for alternatives to promote patients' quality of life [8].

Studies are progressively analyzing the importance of therapy strategies that address all demands, including aspects related to quality of life. This trend is demonstrated in the analysis of the impact of changes in dietary patterns on controlling the symptoms of chronic diseases such as endometriosis. Over the last decade, it has been observed that diet can influence various mechanisms involved in endometriosis, such as inflammation, prostaglandin metabolism, and estrogen regulation [7].

In this sense, it is important to consider that an ideal therapy for endometriosis includes reducing painful symptoms, reducing the size of the lesion, and limiting side effects. These criteria are met by oral omega-3 polyunsaturated fatty acids, a dietary supplement approved by the Food and Drug Administration (FDA), which participate in the regulation of prostaglandin metabolism and cytokine physiology, potentially producing anti-inflammatory lipid mediators [8].

In this sense, quantitative and qualitative analysis of dietary intake is valid, since inflammatory processes play a significant role in the pathogenesis and progression of endometriosis [20]. In addition, in vitro studies have shown that oral omega-3 polyunsaturated fatty acids have a suppressive effect on endometrial cell survival [22].

Among the dietary habits analyzed, a prospective study included 35 women with endometriosis to analyze the role of the Mediterranean Diet (MD) on the perception of pain in endometriosis and on oxidative stress. This dietary pattern is based on a daily intake of fruit, vegetables, whole grains, and vegetable fats, and a weekly intake of fish, poultry, legumes,

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and eggs, as well as moderate portions of dairy products and limiting red meat and foods with added sugar. Thus, the results of the study showed a trend toward a relationship between adherence to DM and minimization of chronic non-menstrual pelvic pain (p = 0.06), dyspareunia (p = 0.04), dysuria (p = 0.04) and dyskinesia (p < 0.001) in the first three months of the diet [7].

It is therefore understood that dietary therapies can be effective in promoting the quality of life of patients with endometriosis, considering, for example, that omega-3 polyunsaturated fatty acids have the potential to reduce the painful symptoms associated with endometriosis, reduce the size of the lesion, preserve the patient's ability to conceive and have minimal side effects [22].

The Mediterranean Diet mainly recommends fish rich in omega-3 fatty acids and extra virgin olive oils, which have an anti-inflammatory effect. In addition, in the study, the daily fiber intake of women with endometriosis was below the recommended levels. Therefore, an increase in fiber intake was promoted through the consumption of fruits, vegetables, and whole grains, in order to regulate the fecal excretion of excess estrogen. This approach was based on the understanding that high serum estrogen levels related to endometriosis lead to the production of prostaglandins, favoring inflammation and the proliferation of the disease. Thus, adopting a Mediterranean dietary pattern, rich in fruit, vegetables, legumes, whole grains, and fish, is a possible non-pharmacological therapeutic intervention for endometriosis [7].

In addition, a prospective cohort study showed an inverse relationship between magnesium intake and the risk of endometriosis (RR = 0.86, 95% CI: 0.73 - 1.01; p = 0.007), which indicates the potential therapeutic use of magnesium. In addition, vitamin C was highlighted for its antioxidant and anti-inflammatory effects, benefits associated with minimizing the oxidative stress characteristic of endometriosis. Therefore, the intake of vitamins and minerals can play an important role in the therapeutic strategy [20].

Discussion

Although its pathogenesis is poorly understood, it is known that endometriosis is a multifactorial chronic disease influenced by genetic, pro-inflammatory, hormonal, immunological, systemic, and environmental factors. Risk factors include family history, long menstrual cycle, low parity, and low physical activity [15].

In addition, studies show that endometriosis is intrinsically related to an inflammatory process, tissue damage, oxidative stress, and high estrogen levels [7]. These factors are responsible for causing the symptoms of endometriosis, such as chronic non-specific pain, dysmenorrhea, dyspareunia, dysuria, and the risk of infertility [16].

At this juncture, after analyzing various studies, it was observed that because endometriosis is a multifactorial disease with a concomitant inflammatory pattern, the dietary intake of patients has an influence on some of the symptoms presented, so a complementary approach to treatment would be conducted focused on minimizing inflammatory processes in general, in order to reduce uncomfortable symptoms [9].

In this way, pro-inflammatory foods should be avoided, since changing some dietary patterns can reduce inflammatory markers by mitigating the chemical signals of prostaglandins that are responsible for painful stimuli [23].

Furthermore, it is necessary to continue researching diets as part of therapeutic strategies, as dietary patterns have shown important benefits in reducing the symptoms of chronic diseases, such as endometriosis [7].

Of particular note at this juncture is the intake of oral omega-3 polyunsaturated fatty acids and the consumption of foods rich in fiber, vitamins, and minerals. This is mainly due to the regulation of prostaglandins and antioxidant Properties [20]. However, studies are still needed to define the appropriate levels of supplementation for controlling endometriosis symptoms [22].

Conclusion

It is clear that the prevalence of endometriosis is high, as it is a disease that is still underdiagnosed and thought of as a diagnosis of exclusion, especially in patients with infertility and chronic pelvic pain who often do not respond to the recommended pharmacological therapy. As such, treatment should always be individualized, taking into account studies and protocols that show the effectiveness of different therapeutic regimes and patients' quality of life.

Regarding the role of diet as a complementary therapy, it was observed that the consumption of antioxidant nutrients, additional fatty acids, and a combination of vitamins and minerals, in addition to reducing the consumption of red meat, has influenced the modulation of endometriosis. That is, the consumption of foods with anti-inflammatory properties interferes with the pathophysiology of this chronic disease in the long term. On the other hand, studies have shown that a pro-inflammatory diet contributes to the production of inflammatory cytokines and prostaglandins that enhance the disease's unwanted symptoms, such as chronic pain.

Therefore, the inclusion of anti-inflammatory dietary habits, such as the consumption of omega-3 fatty acids, fruits, vegetables, legumes, whole grains, fish, and fiber, as well as the exclusion of ultra-processed foods containing saturated fatty acids and carbohydrates, is a non-pharmacological therapeutic intervention with important repercussions in modulating the inflammatory state of the disease and promoting the quality of life of patients with endometriosis.

In this context, there is a consensus in the literature that endometriosis is a multifactorial chronic disease, and its pathophysiology is still complex and poorly understood, which makes diagnosis and treatment difficult, especially when it comes to the influence of diet on the progression or prevention of this disease. Furthermore, despite the studies and theories

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linking biological mechanisms and the effect of dietary profiles on the improvement or worsening of endometriosis symptoms, these studies still lack robust epidemiological evidence.

Authors' contribution

SO, BG, CS, LD, JA: Conception, organization, writing of the work, critical review, and approval of the final manuscript.

SF: Conception, critical review and approval of the final manuscript.

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