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Review

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Endometriosis and food habits: Can diet make the difference?

Ilaria Soave[1], Tommaso Occhiali[2], Jean-Marie Wenger[3], Nicola Pluchino[3], Donatella Caserta[1] and Roberto Marci[3,4,5]

Abstract

Endometriosis is a chronic, inflammatory, estrogenic-dependent disease characterized by the presence of endometrial glands outside the uterine cavity, affecting approximately 2%–10% of women in reproductive age and 30%–50% of women in general. Despite the high prevalence of the disease, not much is known about etiology, possible risk factors, and an adequate and satisfactory therapy. In the past years, many studies have focused on food intake (nutrients and food groups) and on its possible correlation with endometriosis, demonstrating how diet could be identified as a possible risk factor. Comprehensive searches in the largest medical information databases (Medline-PubMed, Embase, Lilacs, and Cochrane Library) were conducted using the Medical Subject Heading terms "diet," "food," "nutrition," "fatty acids," vitamins," "fruit," "vegetables," "coffee," "caffeine," "fish," "soy food," "dairy products," "tea," "curcumin" combined with "endometriosis." Purpose of this review is to revise the literature, in order to determine potential modifiable risk factors of the disease.

Keywords

Endometriosis, diet, nutrition, food habits, diet component, dietary intervention

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Introduction

Endometriosis is a chronic, inflammatory, estrogenic-dependent disease characterized by the presence of endometrial glands outside the uterine cavity.[1] The endometrial tissue, although outside its natural location, almost keeps the same features of the eutopic one. Therefore, it is responsive to estrogen and progesterone, it is able to grow under hormonal stimulation, and it often invades the adjacent tissues (bowels, ovaries, bladder, and pleural cavities).[2] Typical symptoms of the disease are pelvic pain, dysmenorrhea, dyspareunia, dysuria, dyschezia, and/or infertility. Sometimes, it could also be completely asymptomatic.[3] The disease affects 2%–10% of women of reproductive age and 30%–50% of women in general, but the actual prevalence is yet unknown, since a laparoscopic diagnosis is usually required.[1,2] Despite the high prevalence of the disease, not much is known about etiology and possible risk factors and so far an adequate and satisfactory therapy is lacking. Several theories have been presented, ranging from altered organogenesis[4] to retrograde menstruation.[5]

In the past years, many studies have focused on food intake (nutrients and food groups) and on its possible correlation with endometriosis, demonstrating how diet could be identified as a possible modifiable risk factor given its influence on hormonal levels, immune and

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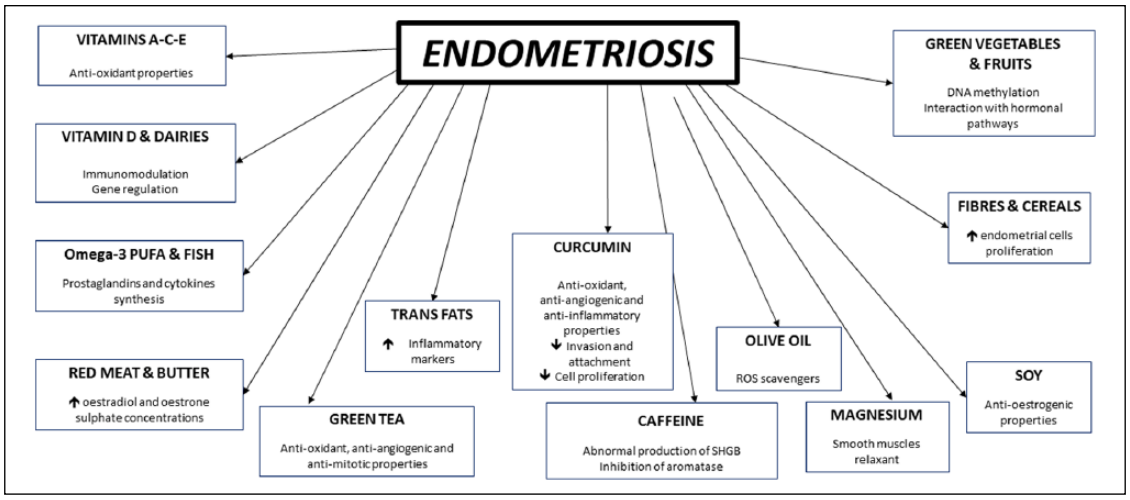

Figure 1. Food-related processes potentially involved in the pathogenesis of endometriosis.
SHBG: sex hormone binding globulin.

inflammatory activity, and smooth muscle contraction. In the last decades, there has been a change in eating habits. Western diets often include refined and processed foods with low consumption of vegetables and fruits. Furthermore, with the advent of agriculture, pesticides and organochlorines (e.g. polychlorobiphenyls), considered additional risk factors for endometriosis, may accidentally be ingested by consuming fruits, vegetables, meat, and dairy products.[6–9]

Aim of this review is to revise the literature, in order to determine potential modifiable risk factors of the disease. Figure 1 summarizes the food-related processes potentially involved in the pathogenesis of endometriosis, and Table 1 summarizes the main characteristics of considered studies.

Materials and methods

The largest medical information databases (Medline–PubMed, Embase, Lilacs, and Cochrane Library) were searched using the Medical Subject Heading (MeSH) terms "diet," "food," "nutrition," "fatty acids," vitamins," "fruit," "vegetables," "coffee," "caffeine," "fish," "soy food," "dairy products," "tea," "curcumin" combined with "endometriosis" (date of last search: October 2017). In total, 392 papers were identified, and data were extracted independently by two investigators (I.S. and T.O.). Only those papers that were published as full-length articles in English language were considered, and the relative reference lists were systematically searched. After duplicates removal and the exclusion of some papers based on title and abstract, 24 articles were assessed for eligibility. Review articles, commentaries, and papers on the effect of diet on endometriosis-related symptoms were further excluded. Figure 2 shows the flow diagram of the search strategy.

Vitamins A-C-E

Few studies investigated the relationship between A-C-E vitamins intake and endometriosis, and no statistically significant association was found.[23,24] Vitamins (mostly C and E), due to their great anti-oxidant effect, play an important role on lipid peroxidation, which is a key process in chronic inflammatory diseases.[27] Lipid peroxidation could be triggered out by reactive oxygen species (ROS), which activate growth-related pathways that promote cellular proliferation and angiogenesis.[28] This potential correlation has suggested a possible role of ROS also in the proliferation of endometriotic cells. In 2009, Labrinoudaki et al.[29] evaluated 66 patients undergoing laparoscopy for different reasons (unexplained infertility, pelvic pain, adnexal masses, or tubal ligation). All patients were investigated for endometriotic foci during laparoscopy and 45 of them were diagnosed with endometriosis (13 at stages I–II and 32 at stages III–IV). Four oxidative stress markers (heat shock protein 70, heat shock protein 70b′, thioredoxin, and ischemia-modified albumin) were measured in the serum of each of the 66 patients participating in the study: in women affected by endometriosis, an increased systemic oxidative stress has been found. In line with these observations, Mier-Cabrera et al.[18] proposed a high anti-oxidant diet (150% of the suggested daily intake of vitamin A, 660% of the recommended daily intake of vitamin C, and 133% of the recommended daily intake of vitamin E) for 4 months to 37 women affected by endometriosis. At the end of the 4 months, they found reduced levels of oxidative stress markers, enhanced anti-oxidant activity, and increased vitamins concentration in peripheral blood compared to controls (women without endometriosis). Using a Food Frequency Questionnaire, they also investigated vitamins and minerals intake. A significant lower intake of A-C-E vitamins was found in patients affected by endometriosis. In addition, a recent study published in 2012 has shown, on murine models, the ability of retinoic acid—a

Table 1. Main characteristics of considered studies.

References	Study design	Sample size		Dietary assessment	Results
		Cases	Controls		
Grodstein et al.[10]	Case control	180 infertile women with endometriosis	3833 healthy fertile women	–	Coffee ↑
Bérubé et al.[11]	Case control	329 women with laparoscopically confirmed endometriosis (minimal/mild)	262 infertile women without endometriosis	FFQ on caffeine and alcohol intake	Coffee ↑
Britton et al.[12]	Case control	280 women with endometrioid ovarian cysts	347 age- and hospital-matched women	FFQ	Vegetable fats ↑ PUFA ↑
Parazzini et al.[13]	Case control (two studies)	504 women with laparoscopically confirmed endometriosis	504 women admitted for acute non-gynecological, non-hormonal, and non-neoplastic conditions	FFQ	Vitamin A= Vitamin D= Green vegetables ↓ PUFA= Red meat ↑ Butter= Coffee=
Heilier et al.[14]	Case control	176 women with peritoneal endometriosis[15] or deep endometriotic nodules[15]	88 women without endometriosis	FFQ	Vitamin D= Red meat= PUFA=
Tsuchiya et al.[16]	Case control	79 women with laparoscopically confirmed endometriosis	59 women without endometriosis with unexplained infertility	Urine test	Soy ↓
Matalliotakis et al.[17]	Case control	535 women with endometriosis	200 infertile women	Data were collected from patients' medical records	Coffee ↑
Mier-Cabrera et al.[18]	Case control	83 women with endometriosis	80 fertile women without endometriosis	FFQ	Vitamins A-C-E ↓
Sesti et al.[19]	Randomized study	Women with surgically treated endometriosis divided into four groups: placebo,[20] GnRHa,[20] OC,[21] and dietary supplementation[20]	–	Gynecological examination 18 months after surgery	PUFA=

(Continued)

Table 1. (Continued)

References	Study design	Sample size		Dietary assessment	Results
		Cases	Controls		
Missmer et al.[22]	Prospective cohort study	1199 women with laparoscopically confirmed endometriosis	586,153 person/years US registered nurses	FFQ	Vegetable fat= Monounsaturated fat= PUFA= Trans fat ↑ Omega-3 ↓
Savaris and Do Amaral[23]	Case control	25 women with laparoscopically confirmed endometriosis	20 women without endometriosis	FFQ	Vitamins A-C-E ↓ Fibers ↓ PUFA ↓
Trabert et al.[24]	Case control	284 women with mild/severe endometriosis	660 women without endometriosis	FFQ	Vitamin D= Green vegetables= Fruit ↑ Red meat= Dairy products ↓ Trans fats= PUFA=
Khanaki et al.[25]	Case control	46 women with endometriosis	74 healthy women	Serum phospholipid fatty acid profile	PUFA=
Harris et al.[26]	Prospective cohort study	1385 women with laparoscopically confirmed endometriosis	Healthy woman	FFQ	Vitamin D ↓ Magnesium ↓

↑: increase of endometriosis risk; ↓: decrease of endometriosis risk; =: no association; FFQ: Food Frequency Questionnaire; PUFA: polyunsaturated fatty acids; GnRHa: gonadotropin-releasing hormone analogue; OC: oral contraceptive.

metabolite of vitamin A—to inhibit the growth of endometriotic implants by reducing pro-inflammatory cytokine levels and increasing anti-inflammatory protein concentration, suggesting another possible therapeutic option.[19]

Vitamin D and dairy products

A biological role of vitamin D in the pathogenesis of endometriosis seems plausible but complex (Figure 3). Higher levels of 25-hydroxyvitamin-D3 (25-OHD) in the serum of women affected by endometriosis were found by Somigliana et al.,[30] regardless of season, age, and ongoing therapy. Authors also described a biological gradient that showed differences, although not statistically significant, depending on the stage of the disease. However, other studies did not confirm this association.[31,32] Trabert et al.[24] in 2011 reported an inverse association between endometriosis risk and dairy food. Along this line, in a prospective study published by Harris et al.,[26] it is reported that women consuming more than three servings of dairy products per day had a lower risk to be diagnosed with endometriosis. Furthermore, the authors correlated predicted plasma 25(OH)D levels and risk of endometriosis, and an inverse correlation was found. Indeed, women with higher concentration of 25(OH)D had 24% less risk of developing endometriosis. No relationship between cheese and milk was found in previous studies.[13,14]

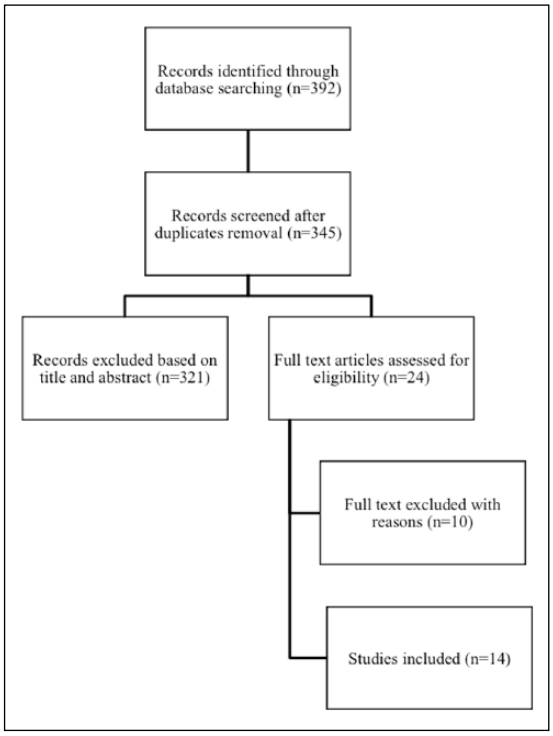

Figure 2. Flowchart of the search strategy.

Endometriosis meets some of the criteria for autoimmune disease, including increased association with other autoimmune diseases, familial occurrence, immunological dysfunction in B and T cells, and possible genetic susceptibility.[33–35] Activated immune cells like macrophages, dendritic cells, and CD4+ and CD8+ lymphocytes synthesize the enzymes necessary for the two hydroxylation steps of vitamin D3 (1-α hydroxylase and 24-hydroxylase) and widely express the vitamin D receptor (VDR), a nuclear receptor that controls the transcription of more than 900 genes.[36,37] Hence, 1,25-dihydroxyvitamin-D3 (1,25(OH)2D), the metabolite that best reflects vitamin D nutritional status, could be produced locally, suggesting an autocrine/paracrine role of vitamin D on the immune system.[38] Vitamin D metabolites, given their effect on immune system cells, could, therefore, be considered as immune modulators. In fact, 1,25(OH)2D inhibits the production of interleukin-12 (IL-12), IL-2, tumor necrosis factor (TNF), and interferon (pro-inflammatory

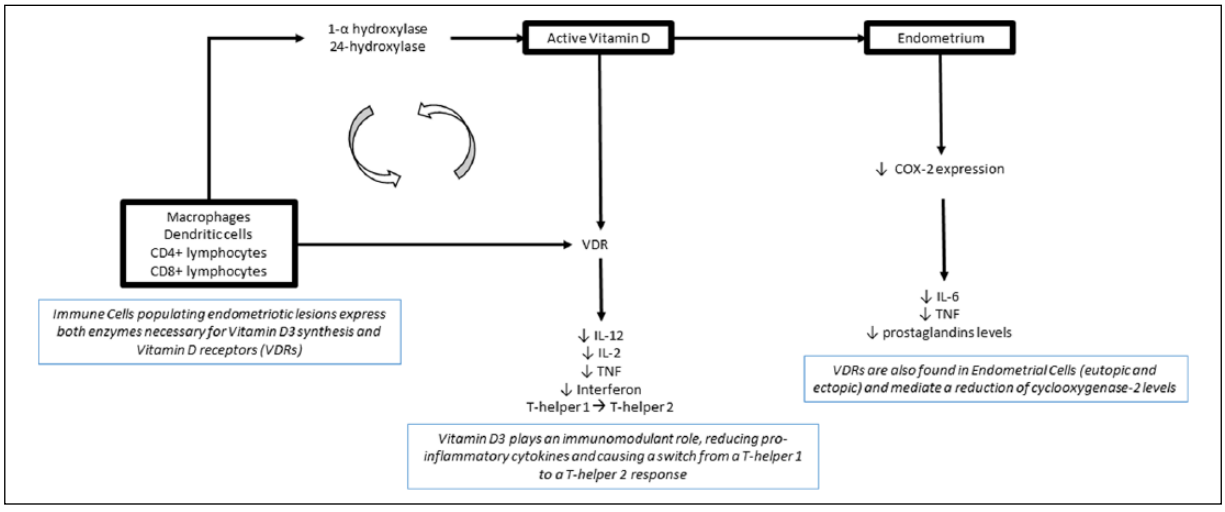

Figure 3. Effects of vitamin D on endometriotic lesions.
VDR: vitamin D receptor; TNF: tumor necrosis factor; COX: cyclooxygenase.

cytokines), favoring a T-helper 2-type immunity and diminishing T-helper 1 function.[39–41]

The link between vitamin D and autoimmune diseases is supported by two main observations:

1. Vitamin D deficiency is associated with an increased risk of pathologic conditions with an autoimmune component (e.g. multiple sclerosis, systemic lupus erythematosus, type 1 diabetes, rheumatoid arthritis, inflammatory bowel disease).[42]
2. Some autoimmune diseases show seasonal exacerbations (generally with a peak in late winter), correlating with changes in serum vitamin D concentrations.[43]

However, despite the fact that endometriosis may have some common features with autoimmune diseases, the relationship with vitamin D remains complex. Indeed, patients affected by endometriosis do not show any seasonal flares and do not have vitamin D deficiency, as would have been expected, but normal[31,32] or high 25-OHD levels.[30,44]

Vitamin D is also involved in uterine physiology. Actually, stromal endometrial cells take part in vitamin D metabolism. These cells are able to synthesize 1,25(OH)2D, thanks to the expression of the active form of 1-α hydroxylase.[45] At the same time, stromal cells express VDR, making the endometrium both a site of 1,25(OH)2D extra renal synthesis and a target of 1,25(OH)2D. In particular, it has been shown that in the endometrium, vitamin D could suppress COX-2 expression, thus reducing IL-6, TNF, and prostaglandin levels.[46] In a study published in 2007, Agic et al.[31] analyzed the deregulation of vitamin D pathway in the eutopic endometrium. Endometrial biopsies from 10 women affected by endometriosis (laparoscopically confirmed) were sampled, and VDR, 1-α-hydroxylase, and 24-hydroxylase mRNA levels were assessed. Affected women showed an increased mRNA expression when compared to controls (endometrial biopsies from five healthy women), suggesting an acceleration in vitamin D metabolism, decreasing its anti-inflammatory and immune regulatory effect, thus reducing the final immune tolerance.

Concerning the possible role of vitamin D in the pathogenesis of endometriosis through gene regulation, a higher expression of osteopontin (OPN) was found in patients affected by endometriosis.[47,48] OPN is an extracellular structural protein mainly expressed in bone and dentin,[49] and also in the uterus and decidua,[50] where it is involved in implantation and decidualization processes.[51] Higher levels of plasma OPN and greater expression of OPN mRNA in patients with endometriosis have been reported by Cho et al.[47] Moreover, a recent study found a greater expression in OPN in the luteal secretory endometrium of women with endometriosis.[48]

Magnesium

Most dietary magnesium comes from vegetables, especially from dark green leafy vegetables. Other foods that are good sources of magnesium are milk, bananas, nuts, and whole grains. Magnesium deficiency has been reported among women with premenstrual syndrome and with a history of miscarriage, suggesting that it may play a role in reproductive function.[52,53] Moreover, high intake of magnesium seems to be associated with lower levels of systemic inflammatory markers.[54] In a study published by Mathias et al.,[55] authors reported that fallopian tubes of women affected by endometriosis exhibit spasmodic contractions, described as "seizure activity." Considering that magnesium acts as smooth muscle relaxant, it may be related to the pathogenesis of endometriosis through its influence on retrograde menstruation.[56,57] In line with this assumption, Harris et al.[26] found an inverse relationship between magnesium intake (especially from food sources) and risk of endometriosis.

Green vegetables and fruits

The role of fruit and vegetable consumption in endometriosis development has been extensively investigated with inconsistent results. Two major studies focused on green vegetables and fruit consumption, and their relationship with endometriosis. Parazzini et al.[13] considered the number of servings/week and found that patients with higher intake of green vegetables had a significantly reduced risk of developing the disease. On the other hand, a recent case-control study published in 2011 concluded that the higher the number of servings/day of fruit, the higher the risk of endometriosis, but no association was found with vegetables.[24] Vegetables, in particular green vegetables, contain lipotropic agents (such as methionine, choline, folate, and vitamin B6) that could influence gene expression and alter DNA methylation.[58,59] A diet poor in these nutrients could lead to molecular alterations and epigenetic abnormalities that may be involved in the pathogenesis of endometriosis.[60,61] Hypomethylation of CpG (cytosine–phosphate–guanine) genetic sequences, as a consequence of epigenetic alterations, is responsible for increased transcription and expression of steroidogenic factor 1 (SF 1) and estrogen receptor 1 β (ER-β), which in turn favors a milieu where inflammation and cellular growth are promoted.[62] Several studies underlined the relationship between lipophilic environmental chemicals and endometriosis. Higher concentrations were found in patients affected by the disease.[8,20,21,63] In addition, vegetables, but principally fruit, may also contain organochlorines that have been shown to interfere with estrogen and androgen receptors function, altering several hormonal pathways: this could explain why some authors found a positive association between higher fruit intake and endometriosis.[20,24]

Soy and phytoestrogens

Soy is a common aliment in Japan and in Southwestern Asia that contains phytoestrogens which are able to interact with estrogen receptors, either with estrogenic or antiestrogenic effect.[64] Due to the connection between endometriosis and estrogen level, a case-control study was conducted in Japan. Authors reported that women with a higher urinary concentration of daidzein and genistein, two isoflavones belonging to the phytoestrogen group, had a lower risk of severe endometriosis (stages III and IV).[16]

Red meat and butter

Red meat is a source of saturated fats and, when consumed in high doses, it is also responsible for a modest raise in estradiol and estrone sulfate concentrations,[65] leading to higher circulating levels of steroid hormones,[66] finally promoting the disease sustainment. Butter represents another main source of saturated fats. Several studies have investigated the possible relationship between red meat, butter, and saturated animal fat and endometriosis, but the obtained results are controversial.[12,22,23] While Parazzini et al.[13] linked red meat, but not butter, with an increased risk of endometriosis, Heilier et al.[14] associated butter, but not red meat, with the disease. Nevertheless, the study published by Trabert et al.[24] found no statistical association between endometriosis and red meat.

Olive oil and monounsaturated fats

Olive oil is a source of monounsaturated fats, anti-oxidants, and micronutrients. It is particularly rich in oleic acid and phenols. Oleic acid is quite resilient to oxidation when compared to other unsaturated fatty acids, and phenols are thought to be potent scavengers of ROS.[67] Monounsaturated fatty acids are commonly found in red meat, whole milk dairies, sesame oil, corn oil and popcorn, wholegrain, wheat cereal, nuts, lard, olives, and avocados. Parazzini et al.[13] found no association between the consumption of olive oil and endometriosis.

Similarly Missmer et al.[22] found no connection between vegetable fat or monounsaturated fatty acids intake and endometriosis incidence. A positive correlation between monounsaturated fats and endometriosis is reported by Britton et al.:[12] an elevated risk of ovarian endometrioid cyst was found in the group of women with the highest intake of vegetable fat with no change after adjustment for polyunsaturated fat intake.

Trans fats

Trans fats are unsaturated fats, uncommon in nature, but frequently found in food production processes. Margarine, chocolate, cookies, crackers, and fried chicken contain high concentration of trans fats. In people with a diet rich in trans-unsaturated fatty acids, the markers of systemic inflammation (e.g. TNF, IL-6, C-reactive protein) are shown to be higher suggesting that a modulation of the inflammatory response by trans fats could promote the development of endometriosis.[68] According to data gathered by Missmer et al.,[22] the diagnosis of endometriosis is much more likely in women with a higher consumption of trans fats (up to 48%) when compared with controls, but Trabert et al.[24] did not report any association.

Polyunsaturated fatty acids

Polyunsaturated fat can be found essentially in algae, fish, nuts, leafy greens, seeds, and krill. Simopoulos[69] showed that among polyunsaturated fatty acids (PUFA), omega-6 PUFA and omega-3 PUFA are the most prevalent in human diet.

Inflammation plays a key role in endometriosis, and omega-3 PUFA and omega-6 PUFA are involved in prostaglandin and cytokine synthesis.[70] As the balance between 6-PUFA and 3-PUFA oscillates toward one or the other, so does the profile of prostaglandins production: arachidonic acid (AA), a 6-PUFA, is a precursor of pro-inflammatory molecules, where eicosapentaenoic acid (EPA), a 3-PUFA, is proved to be associated with a lower pro-inflammatory power. 3-PUFA are commonly found in fish, fish oils, and vegetables. A low ratio of omega-6/omega-3 fatty acids could reduce the risk of chronic inflammatory diseases, including endometriosis. Currently, a 2:1 to 4:1 ratio is suggested, although a general consensus is lacking. Before the age of industrialization, this ratio was around 1:1 to 2:1, because of the great consumption of vegetables and seafood. Nowadays, these ratios are around 10:1 to 50:1, as a result of the great consumption of refined foods and of the reduced rates of fruits, vegetables, and seafood.[25] Prostaglandin E2 (PGE2), the main prostaglandin derived from AA, can modulate the steroidogenesis process, the production of cytokines, the activity of macrophages, and the synthesis of metalloproteinases, and can promote angiogenesis. In addition to that, along with estradiol, IL-1, and vascular endothelial growth factor (VEGF), PGE2 can also influence COX-2 synthesis that may promote the growth of endometriotic lesions.[62,71] However, a study conducted in 2001 found that the in vitro survival rates of endometrial cells were lower in those exposed to EPA when compared with those cultured in media with no PUFA.[72] In animal studies conducted on mice and rabbits, a diet rich in omega-3 PUFA showed promising effects, such as the reduction of lesions size and number with decreased levels of pro-inflammatory cytokines (e.g. PGE2 and prostaglandin F2 (PGF2)) in the peritoneal fluid.[73–75] Attaman et al.,[76] while studying the immunological profile of induced endometriotic lesions in transgenic murine models with high

levels of endogenous 3-PUFA, found that IL-6 intralesional expression was particularly variable. Considering that IL-6 plays a central role in angiogenesis and metastatic diffusion in some human malignancies, it could be speculated that systemic host 3-PUFA levels may be involved in the early stage of endometriosis. Up to now, epidemiological studies conducted on humans showed no statistically significant association between PUFA and endometriosis, but a slight trend for a reduced risk could be observed.[14,22,24] Missmer et al.[22] observed a reduced risk of endometriosis in women with higher intake of 3-PUFA; even more, a lower consumption of trans fats in favor of 3-PUFA granted a further reduction in terms of risk of developing the disease. A reduced risk, although not statistically significant, was also found in other studies.[14,24] On the other hand, no link was found by Trabert et al.,[24] and a strong association with endometriotic cyst development was observed by Britton et al.[12] A cross-sectional study published in 2012[25] analyzed the phospholipid fatty acid profile of patients affected by endometriosis. When compared to controls (healthy women), no differences were found in serum phospholipid levels, but the EPA/AA ratio appeared to be an important factor in endometriosis severity ($r=0.34$, $p=0.006$). In a comparative study, Sesti et al.[19] evaluated the chance of recurrence of symptomatic endometriotic lesions after conservative surgical treatment in patients with stage III and stage IV endometriosis. After surgery, patients were randomized to receive a placebo ($n=65$) or a medical treatment with gonadotropin-releasing analogues or continuous monophasic estroprogestin ($n=65$ and 64, respectively) or dietary supplementation (fish oil, vitamins, mineral salts, lactic ferments, $n=65$) for 6 months. No differences were found in terms of rapidity of recurrence, but patients who underwent hormonal suppression therapy and dietary therapy reported an amelioration in nonmestrual pelvic pain.

Fibers and cereals

Fibers and cereals are central nutrients in many countries' diet. Fibers have the ability to increase the excretion of estrogens and, consequently, to reduce the concentration of bioavailable estrogens,[77] and cereals are able to slow down gastric emptying, reducing the insulin peak. Actually, insulin can, directly or indirectly, stimulate endometrial cell proliferation, along with the circulating levels of estrogens.[78] Several studies found no association between endometriosis and fibers, and whole grains intake.[12,13,24] Only a Brazilian study observed that women with endometriosis had a higher fiber intake when compared to the control group.[23]

Coffee

Coffee represents one of the most diffused pharmacologically active substance in the world. Due to its wide consumption, its potential repercussion on human health has been widely studied. Exactly, caffeine seems to affect the hepatic production of the sex hormone–binding globulin, reducing the concentration of the bioavailable testosterone.[79,80] Furthermore, it may also impede the conversion of androgens to estrogens by inhibiting aromatase function.[81] Based on these assumptions, it has been hypothesized that coffee intake may have a possible role in hormone-dependent diseases (e.g. endometrial and breast cancer).[82,83] Concerning its link with endometriosis, all the studies published so far have lead to weak results, and only two studies reported a statistically significant positive correlation between coffee intake and endometriosis.[11–14,16,17] A recent meta-analysis,[15] published in 2014, confirmed the lack of association, but several bias came up: (a) the majority of the studies did neither report an estimation of caffeine intake nor gave any information on coffee variety or method of preparation; (b) coffee intake was based on patients' self-reports; and (c) endometriosis represents an heterogeneous clinical entity both for location and stage, and the available data do not allow to investigate the effect of coffee on site and extent of the disease.

Green tea

Epigallocatechin-3-gallate (EGCG) is the most abundant polyphenol in green tea, which is one of the most consumed beverages in the world. Given its strong anti-oxidant, anti-angiogenic, and anti-mitotic properties, a possible therapeutic role of green tea in the treatment of different kinds of cancers has been taken into consideration.[84,85] Given the fact that endometriosis shares with neoplasms many steps of the carcinogenetic process (mutation, cell proliferation, cell invasion, and apoptotic cell death), researchers proposed to study the effect of EGCG on endometriotic lesions. Despite the encouraging results obtained in vitro and on animal models (summarized in Table 2), to date there are no published studies conducted on humans. The first study that analyzed the possible effect of EGCG on endometriosis was published in 2008.[86] Laschke et al. found that green tea is able to suppress estrogen-stimulated activation and proliferation of endometrial cells and to influence VEGF expression in vitro. Furthermore, it is able to inhibit angiogenesis in endometriotic implants in vivo, and this may explain the regression of the lesions observed after the treatment. From this study on, the anti-angiogenic properties of green tea have been widely demonstrated. In a study published in 2009, microvessels' size and density and mRNA levels of VEGF in endometriotic lesions have been found to be significantly reduced after EGCG treatment.[87] In 2011, the same research group found that EGCG significantly reduces the expression of vascular endothelial growth factor C (VEGFC) and VEGF receptor 2 (VEGFR2), and down-regulates the VEGFC/VEGFR2 angiogenic pathway.[88] Two other studies on animal models observed a reduction in size and weight of endometriotic

Table 2. Main characteristics of studies conducted in vitro or on animal models focused on green tea effects.

References	Study type	Results
Laschke et al.[86]	In vitro (endometrial cells)	↓ E2-stimulated activation ↓ Proliferation ↓ VEGF expression
	In vivo (endometriotic lesions)	↓ Angiogenesis ↓ Blood perfusion Induces regression of the lesion
Xu et al.[87]	Animal study (subcutaneous transplant of human endometrial tissue from women with endometriosis in immunocompromised mice)	↓ Lesion size ↓ Glandular epithelium, eccentrically distributed ↓ Angiogenesis (endometriotic implants and adjacent tissue) ↓ Microvessels size and density ↓ mRNA levels of VEGFA ↑ Lesion apoptosis ↑ mRNA levels of NFKB ↑ mRNA levels of MAPKI
Xu et al.[88]	Animal study (subcutaneous or intraperitoneal inoculations of human endometrial tissue from women with endometriosis in immunocompromised mice)	↓ Microvessels in endometriotic implants Suppresses the expression of VEGFC and VEGF receptor
Wang et al.[89]	Animal study (subcutaneous transplant of homologous endometrium in mice)	↓ Growth of endometrial implants ↓ Lesion size and weight ↑ Lesion apoptosis Inhibits functional and structural microvessels
Ricci et al.[90]	Animal study (surgical induction of endometriosis in mice)	↓ Mean number and volume of the established lesions ↓ Cell proliferation ↓ Vascular density ↑ Lesion apoptosis
Matsuzaki and Darcha[91]	In vitro (endometrial and endometriotic stromal cells)	Inhibits cell proliferation (greater in endometriotic stromal cells), migration, and invasion ↓ Fibrotic markers
	In vivo (endometriotic implants)	Prevents the progression of fibrosis

E2: estradiol; VEGF: vascular endothelial growth factor; VEGFA: vascular endothelial growth factor A; NFKB: nuclear factor kappa B; MAPKI: mitogen-activated protein kinase I; VEGFC: vascular endothelial growth factor C.

lesions with reduced vascular density and cell proliferation after the treatment with EGCG.[89,90] In addition, it is well known that endometriosis is characterized by an abnormal inflammatory response that could lead to the formation of fibrosis. Recently, Matsuzaki and Darcha[91] reported that the treatment with EGCG significantly reduces the expression of fibrotic markers and inhibits cell proliferation, migration, and invasion of endometrial and endometriotic stromal cells in vitro and prevents the progression of fibrosis in vivo.

Curcumin

Curcumin (diferuloylmethane) represents the most active polyphenol in turmeric, a common substance used as spice, color, and flavor all around the world, especially in Asia. Since ancient times, curcumin has been used to treat several human diseases, including gynecological problems,[92] and recently various studies conducted in vitro or on animal models have documented its anti-oxidant, anti-inflammatory, anti-angiogenic, and anti-metastatic properties.[93–97] According to the literature, so far there are only few studies that have examined the impact of curcumin on endometriotic lesions. In 2013, Zhang and colleagues investigated the effect of different concentrations of curcumin on endometriotic cells. Normal endometrial stromal and epithelial cells and endometriotic stromal and epithelial cells were isolated and cultured, and after intervening with curcumin (10, 30, and 50 μmol/L), a dose-dependent reduction in growth and number of endometriotic stromal cells was seen.[98] Another study published in 2012 by Kim et al. supported the anti-inflammatory effect of curcumin on endometriosis. Indeed, authors reported that a treatment with curcumin is able to reduce the production of several anti-inflammatory cytokines (such as IL-6, IL-8, and monocyte chemoattractant protein-1) and to inhibit the activation and translocation of nuclear factor kappa B in human ectopic endometriotic stromal cells. Moreover, a suppression of mRNA and total protein expression of cell adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), was found.[99] Curcumin seems also able to influence

expression and serum concentration of different MMPs (matrix metalloproteinases), molecules involved in cell invasion and attachment. Jana et al.[100] have reported that curcumin nanoparticles combined or not with letrozole are able to reduce serum levels of MMP-2 and MMP-9, and to down-regulate MMP-3 expression in endometriotic mice.[101] The same group also investigated the ability of curcumin to interfere with cell proliferation and apoptosis in surgically induced endometriosis.[101] Endometriotic foci were surgically implanted in murine models in a two-phase experiment; 72 h prior surgical implantation (phase 1), mice were treated with three different doses of curcumin (12, 24, and 48 mg/kg bw), and in the 5 days after surgery (phase 2), they received either a 48-mg/kg bw dose of curcumin or celecoxib. Curcumin showed two beneficial effects. It reduced the development of endometrial glands on the peritoneum and increased the expression of pro-apoptotic factors. In particular, curcumin shifted the balance between pro- and anti-apoptotic factors toward the former. In a previous study, the authors also examined the anti-oxidant effect of curcumin on endometriosis.[99] They found that the administration of letrozole and curcumin, or curcumin alone to mice with surgically induced endometriosis was associated with lower levels of ROS and lipid peroxidation. An increased total anti-oxidant activity was also reported.

The anti-angiogenic activity of curcumin has also been investigated only on animal models. Few studies report that curcumin could be able to reduce VEGF levels both in the serum and in the ectopic endometrium, and to diminish the microvascular density in endometriotic lesions.[100,102,103]

A recent study published by Signorile et al.[104] investigated the effect of a combination of extracts of different plants (including quercetin, curcumin, parthenium, nicotinamide, 5-methyltetrahydrofolate calcium salt, and omega-3/6) in patients affected by stage IV endometriosis. The aim of the study was to evaluate the effect of these supplements on endometriosis-related symptomatology using a Visual Analogue Scale (VAS) administered to patients before and after the treatment. In addition, 17-beta-estradiol, PGE2, and CA125 were dosed (measured in both occasions on day 21 of the menstrual cycle); 90 women were enrolled and divided into three groups: group 1 (30 patients) received all supplements, group 2 (30 patients) only received linseed oil and 5-methyltetrahydrofolate calcium salt, and group 3 (30 patients) received a placebo and was used as a control group. All patients underwent a dietetic regimen during the 3 months of the study with a consistent reduction in milk/dairy products and meat servings. The intake of caffeine, alcohol, gluten food, margarine, and saturated fats was also reduced, and soy, aloe, and oats were prohibited. A significant reduction of endometriosis-related symptoms along with a significant decrease in the absolute values of all the lab parameter analyzed was observed in group 1. Groups 2 and 3 showed no changes in symptom degree after treatment.

Summary and conclusion

Epidemiological data concerning the association between diet and endometriosis are growing but still limited and inconsistent. From the data collected herein, a high variability of the results is noticeable and the presence of bias must be considered. In fact, most of the time, data are gathered from patients using self-administered questionnaire. Furthermore, different studies use different pools of patients (healthy/already affected/already effected and divided into subgroups), increasing the difficulty of comparing results regarding a topic—diet—which already has an incredible amount of confounding factors, from food–food interaction to personal predispositions. In addition, some data are only available from animal studies and are yet to be proven in human subjects. Moreover, the disease itself is not fully understood and has different stages that could react differently to the same nutrient. In conclusion, given the public health implication of the topic and the possible beneficial effect of a certain type of diet on endometriosis, further studies in this area are definitely required.

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