Journal of Aging Research & Clinical Practice©
*Volume 1, Number 2, 2012*

# ENDOMETRIOSIS AND NUTRITION – RECOMMENDING A MEDITERRANEAN DIET DECREASES ENDOMETRIOSIS-ASSOCIATED PAIN: AN EXPERIMENTAL OBSERVATIONAL STUDY

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**Abstract:** *Objective:* Typical treatments for endometriosis are either medical therapy or surgery. Our objective was to test whether a diet that closely followed Mediterranean nutritional recommendations would affect endometriosis-associated pain. *Design:* Prospective, experimental, observational study. *Setting:* Academic research institution. *Participants:* 68 women with laparoscopically diagnosed endometriosis. *Interventions:* Patients had to adhere to a nutrition regimen which included fresh vegetables and fruit, white meat, fish rich in fat, soy products, wholemeal products, foods rich in magnesium, and cold pressed oils; sugary drinks, red meat, sweets, and animal fats had to be avoided. *Measurements:* Change in subjective pain sensation, as measured by a Numeric Rating Scale (NRS; 0="no pain;" 10="very strong pain") after five months of diet. *Results:* Forty-three patients (63.2%) adhered to the nutrition regimen for over five months. The intention-to-treat analysis that included all patients showed a significant improvement of general pain symptoms based on the NRS (4.2±2.5 to 2.5±2.4; $p<0.01$). The group of patients who adhered to the study protocol (n=43, 63.2%) experienced a mean improvement in pain, with a NRS score from 4.2±3.0 to 2.0±2.3 ($p<0.01$). For the intention-to-treat group, a mean improvement was found in general condition, with a NRS score from 6.4±1.9 to 8.2±1.8 ($p<0.01$). For the study protocol group, NRS declined from 6.7±2.2 to 8.5±1.7 ($p<0.01$). Patients in the study protocol group also experienced significant improvement in dysmenorrhea, dyspareunia, and dyschezia ($p<0.01$). *Conclusion:* Endometriosis-associated pain symptoms may be influenced positively by a Mediterranean diet.

**Key words:** Endometriosis, nutrition, Mediterranean diet, chronic pelvic pain.

## Introduction

Endometriosis is the second most common benign, proliferative, gynecological disease, and is characterized by the accumulation of endometrial cells outside the uterine cavity (1). The main associated conditions are infertility and chronic pelvic pain (2). Therefore, endometriosis fulfills the criteria of a chronic disease: it lasts three months or more and it cannot be prevented by vaccines or cured by medication (3).

The relationship between chronic diseases and nutrition has become a topic of interest in the past few years. The World Health Organization states that over 30% of all cancer types are associated with nutrition (4). The American National Academy of Sciences estimates that 60% of all cancer types are related to nutritional factors (5). Since endometrial cells show a similar growth behavior to cancer cells, it might be hypothesized that endometriosis, too, can be influenced by nutrition (6). It has already been demonstrated that a diet rich in green vegetables and fresh fruit leads to a significant reduction in the risk for endometriosis; in contrast, there is an increased risk associated with a diet that includes beef and other red meat (7).

A genetic predisposition is likely for endometriosis. However, evidence suggests that also environmental factors including nutrition among many others substantially contribute to the development of this disease (8). Since endometriosis is an estrogen-dependent disease, prior work has attempted to discover a relationship between the phytoestrogens contained in many foods and endometriosis (9). An animal-testing study showed that the receptor-binding of estrogen could be blocked by phytoestrogens. Through this mechanism, the endometriosis cells are deprived of the substrate "estrogen," and therefore, proliferation of the endometrial focus is inhibited (10). Omega-3 fatty acids, as well, have been shown to have a positive effect on

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*Received October 17, 2011*
*Accepted for publication December 1, 2011*

endometriosis. As a dietary supplement, fish oil capsules containing the omega-3 polyunsaturated fatty acids, eicosapentaenoic acid and docosahexaenoic acid, were shown to decrease intraperitoneal PGE2- and PGF2-alpha production in an animal model of endometriosis and retard endometriotic implant growth (11).

To date, other investigations have been either observational and could not, therefore, provide a before-after comparison of the positive effect of individual foods, or examine the effect of dietary supplementations on endometriosis-associated pain. This is the first clinical trial designed to evaluate the relationship between the pain levels associated with endometriosis and nutrition.

## Patients and methods

### *Patient population*

Figure 1 provides an overview on the patient flow. In 160 women, the diagnosis of endometriosis had been ascertained by laparoscopy at the Department of Gynecology and Obstetrics of the Medical University Vienna, Austria, during the years 2003 and 2004. In all of these patients, all evidence of ovarian and peritoneal disease had been excised completely. In 2006, i.e. a minimum of 24 months after surgery, their contact data were retrieved by retrospective chart review and all patients for whom these data were available were contacted by telephone. Participants in the trial needed to meet the following inclusion criteria: (i) laparoscopic surgery for endometriosis and conservative treatment with retention of the uterus and the ovaries; (ii) patients were experiencing endometriosis-associated pain postoperatively and had to be willing to comply with the nutritional recommendations. Women who met one of the following exclusion criteria were not included in the trial: (i) presence of other known gastrointestinal and urologic diseases that might cause painful pelvic symptoms; (ii) a diagnosis of concomitant neoplasia or current/chronic pelvic inflammatory disease; (iii) administration of estrogen-suppressing drugs such as oral contraceptives, danazole, or GnRH analogues in the 3-6 months before dietary therapy. Patients were allowed to use non steroidal anti-inflammatory drugs if required; (iv) women who had undergone any kind of re-operation for endometriosis (including patients who had undergone removal of the ovaries or the uterus); (v) women with any eating disorders.

### *Study design*

The study participants were surveyed by telephone twice. The first survey focused on the current nutritional habits of the endometriosis patients before the start of any diet. Further questions included: the current weight and height; smoking habits; subjective pain sensation; general condition; questions as to the degree of pain for specific pain symptoms, such as dysmenorrhoea, dyschezia, dyspareunia, and dysuria; and questions concerning the frequency of consumption of various foods (specified in portions, and alcohol consumption classified as "daily," "3-6 times/week," "1-2 times/week," "rarely," or "never"). Data on the site of endometriosis and the revised American Fertility Society (rAFS) score were derived from retrospective chart review (12).

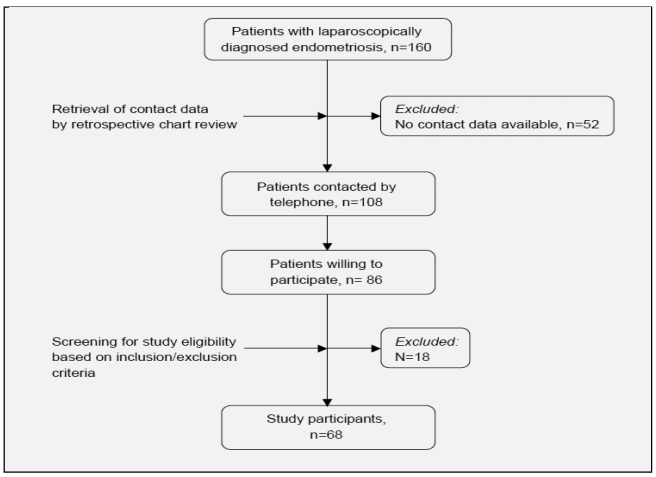


**Figure 1.**

The second survey was administered five months later, and covered the same issues as the first, but also focused on the following questions: whether patients had adhered to the dietary recommendations; change in subjective pain sensation; change in general condition; and change in individual pain symptoms, such as dysmenorrhoea, dyschezia, dyspareunia, and dysuria.

Pain degrees were specified on a Numeric Rating Scale (NRS) (13). The NRS ranged from "0" (no pain at all) to "10" (the worst imaginable pain). The patients' general condition was also evaluated by with an NRS: "0" indicated that the patient was in very poor general condition and "10" indicated that the patient was in very good general condition.

A Mediterranean diet was recommended and explained to the patients. The study participants were to eat fresh fruit, fresh vegetables, and fish three times a week, particularly fatty fish and fish high in omega-3 fatty acids, such as salmon, tuna, sardines, or anchovies. Meat consumption was to mainly include white meat, such as chicken or turkey. Equally, wholemeal, soy, seed, and grain products were to be consumed several times a week. Foods high in magnesium and cold pressed oils, primarily extra-virgin oils, were also recommended. Patients were advised to drink a minimum of 1.5 liters of non-alcoholic fluids. The consumption of red meat, animal fats in general, sweet foods, and sugary drinks, and some milk products, such as hard cheese, salt, and

alcohol, had to be avoided (see Figure 2).

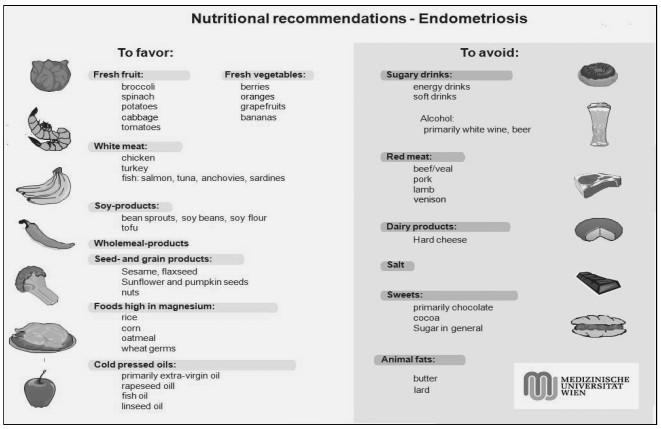


**Figure 2.**

## *Statistical analysis*

Variables were described by frequencies and mean ± standard deviation (SD). Statistical analysis was performed using the chi-square and Wilcoxon rank-sum test. Differences were considered statistically significant if $p < 0.05$. Statistical analysis was performed using SPSS 15.0.1 for Windows (SPSS Inc., 1989-2006).

## Results

The patients in the study collective were 35.3 ± 11.2 years of age. According to the rAFS classification, many patients (32/68, 47.1%) suffered from Stage I endometriosis. Stages II, III, and IV were found for 13 (19.1%), 4 (5.9%), and 19 (27.9%) of cases, respectively.

Before the start of the study, the patients had an average BMI of 22.7 ± 7.6 kg/m$^2$, and, after the dietary regimen, an average BMI of 22.5 ± 8.3 kg/m$^2$ (n.s.). Forty-nine of the 68 surveyed women (72.1%) maintained their weight during the study period, 12 gained weight (17.6%), and seven lost weight (10.3%). Details on weight changes during the study period are shown in Table 1.

**Table 1**
Weight before and after the study period

| | Before study period | After study period | p |
|---|---|---|---|
| Weight category (BMI) | n (%) | n (%) | |
| Underweight (<19.0 kg/m$^2$) | 8 (11.8) | 7 (10.3) | 0.189 |
| Normal weight (19.0-24.0 kg/m$^2$) | 45 (66.2) | 48 (70.6) | |
| Overweight (24.1-30.0 kg/m$^2$) | 10 (14.7) | 8 (11.8) | |
| Obesity (>30 kg/m$^2$) | 5 (7.4) | 5 (7.4) | |

Twenty-five study participants (36.8%) had not adhered to the recommended dietary regimen. As an explanation, 19 of these stated that they had either turned to classical treatment options or had become pregnant during the study period (amenorrhea due to pregnancy: n=5; amenorrhea due to use of depot gestagens: n=6; use of oral contraceptives: n=2; further surgical interventions: n=2; in vitro fertilization treatment: n=4). Six women did not state any reasons why they had not adhered to the diet. However, in an intention-to-treat analysis, all 68 patients were included (see Table 2). A significant relief of general pain (NRS 4.2 ± 3.0 vs. 2.0 ± 2.3; $p<0.01$), as well as an improvement in the general condition (NRS 6.7 ± 2.2 vs. 8.5 ± 1.7; $p<0.01$), were found.

**Table 2**
Intention-to-treat analysis: symptom load before and after the study period (as measured by the Numeric Rating Scale)

| | Before study period | After study period | p |
|---|---|---|---|
| General pain | 4.2 ± 2.5 | 2.5 ± 2.4 | 0.003 |
| General condition | 6.4 ± 1.9 | 8.2 ± 1.8 | 0.005 |
| Dysmenorrhea | 4.6 ± 2.8 | 2.9 ± 2.5 | <0.001 |
| Dyspareunia | 1.8 ± 2.2 | 0.9 ± 1.3 | 0.011 |
| Dyschezia | 2.9 ± 3.1 | 2.0 ± 2.5 | 0.032 |

A post-hoc power analysis for general pain was performed with a given significance level of 0.5, a sample size of 68 and an effect size of 0.586 and revealed a power of 99.9%.

## Discussion

The results of this study show a clear tendency toward a relationship between the alleviation of pain sensations in endometriosis patients, which included general pain, dysmenorrheal, dyspareunia and dyschezia, and a Mediterranean nutritional regimen. Our data are in accordance with previous reports. In an observational study, a diet rich in green vegetables and fresh fruit was found to lead to a significant reduction in risk for endometriosis development; in contrast, there was an increased risk associated with a diet that included beef and other red meat (7). As systematically reviewed in the Cochrane database, omega-3-fatty acids, as well as magnesium, have been shown to be more effective than placebo in improving dysmenorrhea (14).

The Mediterranean diet recommended to our study participants was thought to improve endometriosis-associated pain symptoms via various mechanisms: Fish, as well as cold-pressed oils, primarily extra virgin olive oils, were recommended because of their anti-inflammatory effect. Extra virgin olive oil, which contains the substance oleocanthal, displays a similar structure to the molecule ibuprofen, and both take effect via the same mechanism, i.e., cyclooxygenase inhibition. The inflammation cascade can thus be influenced by a shift from the inflammation-promoting prostaglandins to the leukotrienes (15). The recommendation to eat fish once or

twice a week was also focused on possible anti-inflammatory effects. The recommended fish types were ranked according to the content of omega-3 fatty acids, eicosapentaenoic acids, and dexosahexaenoic acids these fish contain (salmon, tuna, sardines, and anchovies).

In addition to the anti-inflammatory effect, the composition of the dietary change was also designed to have a eupeptic effect. Therefore, fibers were emphasized for five months, in order to shorten the transit time through the intestinal tract. Furthermore, the intake of magnesium was emphasized, which is known to be able to prevent an increase in the intracellular calcium level, which is important for muscular contraction (16, 17). Consequently, a low intracellular calcium level can advance the relaxation of the uterus, and thereby, might decrease chronic pelvic pain.

It should be particularly emphasized that the adherence to the nutritional recommendations was self-reported by each individual patient. They were able to decide independently whether they wanted to adhere strictly to the specific nutritional suggestions. This clearly distinguishes the recommended dietary regimen change from conventional therapy options for endometriosis. The high level of self-determination provided to the women in the course of this study is considered a major motivational factor for the actual participation in the study. The general organismic and dialectical theory of intrinsic motivation by Deci and Ryan suggests that an action is emotionally connotated in a more positive way as soon as one's own actions are self-determined and can be self-modulated (18). This fact is especially important for endometriosis patients, who often experience much suffering, involving a number of consultations with different practitioners, before they actually receive the diagnosis of endometriosis.

The adherence to a dietary regimen generally supports the autonomy of the patient, not only because they can decide for themselves whether they want to adhere to the dietary recommendations, but also because they are not under strict supervision while following the nutritional suggestions. The nutritional recommendations for this study were therefore purposely divided into the two categories "favor" and "avoid." There were no "dos" and "don'ts" involved, but rather, recommendations. If the patients had to adhere to strict dietary rules, there would be a great risk of becoming too occupied with eating habits. From a psychological perspective, this type of effect, in conjunction with the intake of food, should always be avoided because it can adversely interfere with day-to-day life to a large extent (18). Thus, work performance or social contacts could have been negatively affected. The avoidance of "dos" and "don'ts" in the course of the dietary change should also intensify the patients' attitude toward their own bodies. During the telephone surveys, it soon became apparent that the majority of women had already decided which nutritional products they felt had a positive or a negative impact on their sense of well-being (data not shown). These concepts were also supported by the nutritional recommendations, perhaps encouraging continuation after the study ended.

The prescribed nutritional recommendations in this study are generally recognized as a "healthy diet." By changing eating behavior for the benefit of healthy nutrition, general physical well-being increases naturally, and pain is then better tolerated. Whether the participating patients actually experienced an improvement in pain levels because of the consumption of individual foods that are specifically protective against endometriosis, or whether the sensation of pain being alleviated was due to a higher degree of physical fitness, cannot be clearly determined. In this regard, a placebo effect should also be considered. Although the exact psychological process of the placebo effect has not yet been scientifically researched (19), it is safe to assume that, in the course of this study, some patients experienced pain alleviation solely because of the awareness of the necessity to improve nourishment, which is, in turn, due to an unconscious motivation (18). However, even if the alleviation of pain was produced by a placebo effect, it can still be seen as a success, as even the evocation of a placebo effect is considered to be a positive result.

It cannot, however, be assumed that the success of the dietary change is entirely attributable a placebo effect. It is unlikely that this could have been maintained over a period of five months, as was the case in this study. In a controlled, double-blind, randomized trial, Sutton et al. demonstrated that the effect of a placebo effect subsides after six months, at the latest (20). Sixty-three women with minimal to moderate endometriosis, divided into two groups, underwent either a laser ablation of endometriotic deposits and uterine nerve ablation by laparoscopy or a simple diagnostic laparoscopy. Patients in the laser laparoscopy group experienced statistically significant pain relief compared to the group with expectant management at six months after surgery.

We are aware of the fact that the patients' compliance was difficult to assess since the dietary alterations had only been suggested, especially in regard to nutrients such as magnesium or omega-3 fatty acids. Moreover, we cannot rule out whether only a subset of the components of the recommended Mediterranean diet may actually be causally associated with endometriosis-associated pain. Notably, the study was not randomized. We consider these factors study limitations. Despite that, we were able to demonstrate a significant decline in pain scores that, in our opinion, is due to the recommended dietary alterations.

In conclusion, the results of our study, which demonstrate an association between endometriosis and nutrition, are to be seen in the light of specific limiting

factors. Nevertheless, we demonstrate that a Mediterranean diet might lead to symptom relief in patients who suffer from endometriosis.

*Acknowledgments:* None.

*Disclosure statement:* All authors declare that they have no commercial interest, financial interest, and/or another relationship with manufacturers of pharmaceuticals, laboratory supplies, and/or medical devices or with commercial providers of medically related services.

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