

Vitamin D plus epigallocatechin gallate: a novel promising approach for uterine myomas

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Abstract. – OBJECTIVE: Uterine myomas are the most common benign tumors in females. Most myomas are asymptomatic and require no intervention or further investigations; however, almost a third of women with myomas will require a therapy. Treatment options include pharmacological approaches or surgery, and depend on symptomatology, size, number and desire for future pregnancy. Minimally invasive procedures or alternative medical treatments for handling myomas are preferred, when possible, to the radical abdominal surgery. Vitamin D and epigallocatechin gallate (EGCG) recently proved effective in the management of these benign tumors. Our aim was to verify the effect of combined oral vitamin D and EGCG supplementation in symptomatic women with myomas.

PATIENTS AND METHODS: Symptomatic women with myomas were enrolled in this pilot study and divided in two groups: one group treated daily with two tablets of 25 µg vitamin D + 150 mg EGCG + 5 mg vitamin B6, for 4 months; the other group received no treatment (control), for the same period. Volume, number of myomas as well as severity of symptoms (SS) and quality of life (QoL) were analyzed.

RESULTS: The total myoma volume significantly decreased by 34.7% in the treated group, whereas it increased by 6.9% in the control group. An improvement in the QoL of women treated with vitamin D, EGCG and vitamin B6 was reported along with a reduction of the SS.

CONCLUSIONS: The combined supplementation of vitamin D and EGCG seems to be an optimal approach for the management of myomas and correlated symptoms. For the first time, we showed the cooperative effectiveness as a promising and novel treatment for myomas.

Key Words:

Uterine myoma, Uterine fibroids, Leiomyoma, Vitamin D, Epigallocatechin gallate, EGCG.

Introduction

Uterine myomas, also named uterine leiomyomas or uterine fibroids, are monoclonal tumors

of the smooth muscle cells of the myometrium. They are the most common benign uterine neoplasm and are classified by their size, shape and location in the uterine cavity¹. Myomas consist of accumulation of collagen, fibronectin and/or proteoglycan that may form in or on the uterus. They develop in women of childbearing age, mainly between 35 and 50 years. The worldwide incidence of myomas ranges between 5.4% to 77%, as it may vary in different ethnic groups. Indeed, African American women have 3-4 times higher risk of developing myomas, compared to Caucasian^{2,3}. Recent molecular studies suggest that there may be different phenotypes of myoma disease⁴.

The exact cause of myomas is still unknown, but their development and growth seem to be under the influence of steroid hormones. Estrogens and progesterone, through their nuclear receptors, are the main factors initiating uterine muscle differentiation and abnormal growth, leading to myoma pathogenesis^{5,6}.

The development of myomas varies greatly in relation to age, heredity, obesity, hormonal and environmental factors. Additional environmental factors, such as diet (particularly vitamin D deficiency) and toxins, are the subjects of ongoing investigations. Myomas often develop asymptotically; however, they may be associated with an increased risk of menorrhagia, dysmenorrhea, chronic pelvic pain, compression of the surrounding organs, painful sexual intercourse, infertility, recurrent abortion, preterm delivery and anemia^{1,7,8}.

Transvaginal ultrasound is the gold standard method for diagnosis⁹. In a small portion of women, regression of untreated myomas may be observed during the premenopausal period or during pregnancy or postpartum involution. In menopause, when the hormone levels decrease, the risk for new myomas decreases as well.

Normally, the size of preexisting formations may reduce. Most myomas are asymptomatic and require no intervention or further investigations (“watching and waiting”); however, almost a third of women with myomas require treatment due to symptoms. Indeed, they are generally severe and affect women’s quality of life (QoL). Treatment options for myomas depend on symptoms, size, number and desire for future pregnancy. Surgery, such as myomectomy, hysterectomy, myolysis, uterine artery embolization (UAE) and magnetic resonance imaging-guided focused ultrasound surgery (MRgFUS), is generally adopted for large myoma. According to the American Journal of Obstetrics and Gynecology, more than 400,000 hysterectomies were performed in the United States in 2015. Hysterectomy may cause short term and long term sequelae, and in a minor portion of operated women even death (between 0.4-1.1 per 1000 surgeries)¹⁰. The conservative management mainly consists of medical treatment such as selective progesterone receptor modulators (sPRMs), gonadotropin-releasing hormone agonist (GnRHa), hormones such as estroprogestins or progestogens, non-steroidal anti-inflammatory drugs (NSAIDs), and tranexamic acid. This interventional therapy is preferred with mild symptomatology, and it is commonly used for reducing pain and blood loss during menstruation. In particular, ulipristal acetate (UPA), a sPRM, is effective in controlling the bleeding and reducing the number of surgical procedures^{11,12}. However, concerns about the adverse estrogenic activity and liver toxicity were raised¹³⁻¹⁶. Recently, the role of two natural molecules, vitamin D and epigallocatechin gallate (EGCG), in managing myomas has been investigated. Hypovitaminosis D is associated with a higher prevalence of myomas, and correlated with their severity¹⁷. Administration of vitamin D in insufficient women (serum level <30 ng/mL) proved to restore the normal vitamin D status and to reduce the mild symptoms of myomas¹⁸. Likewise, the daily administration of EGCG for 4 months reduced the myoma size in premenopausal women¹⁹. Therefore, there is considerable interest in further investigating the role and the possible synergistic effect of vitamin D and EGCG in the treatment of myomas. This study aims to investigate the effects of a combined oral supplementation of vitamin D and EGCG in women presenting with symptomatic myomas.

Patients and Methods

This was a pilot study involving women with myomas, referring to our Outpatient Unit between March and October 2019. All women enrolled gave their oral informed consent after the explanation of the study purpose. This study was conducted following the Ethical Principles of the Helsinki Declaration and the national laws. Subjects were included in the study if they were: 18 years of age or older, in premenopausal stage, with at least one myoma ≥ 2 cm³ (intramural, subserosal and/or submucosal) detected by vaginal and abdominal ultrasound, with moderately severe myoma-related symptoms, and do not require treatment other than regular observation. The exclusion criteria of the study were: pregnant women or intended to become pregnant during the following four months, currently breastfeeding, with severe anemia or medical morbidity, eligible to surgery, elevated liver enzymes, treatment (within the past 3 months) of hormones (estrogen, progestin, oral contraceptives), corticosteroids, food supplements having possible hormonal effects, use of sPRMs or GnRH analogues within the past 6 months. In this pilot study we enrolled 30 women with myomas. Patients were divided in two groups: one group (15 patients) treated by oral route with one tablet of 25 μ g vitamin D + 150 mg EGCG + 5 mg vitamin B6 (Delphys, Farmares S.r.l., Rome, Italy), twice a day for 4 months. The second group (15 patients) received no treatment (control), for 4 months. The primary outcome was the change of myoma volume analyzed by transvaginal ultrasonography (TVU), and/or transabdominal ultrasonography. The secondary outcomes were the variation of the number of myomas, distress by bleeding during the menstrual period, pressure feeling in the pelvic area, sense of fatigue, QoL and the severity of symptoms (SS). The subjective experience of bleeding was indicated as heavy, medium and normal, through a self-administered bleeding assessment. The SS and QoL were evaluated with a questionnaire consisting of 37 questions in the LiKert format, divided in 2 parts. The first part is composed of 8 questions evaluating the SS, with points (1 to 5) assigned to each answer option. This domain allows raw total scores from 8 to 40 with an increase in the score proportional to the SS. The second part evaluated the QoL, divided in six areas (concern, daily activities, changes in mood and energy, self-control, self-consciousness and sexual function). This domain consists

Table I. Clinical characteristics of patients by group at baseline.

	Treated T ₀ Mean ± SEM	Control T ₀ Mean ± SEM	p-value
Age	37.27 ± 1.15	37.67 ± 1.71	0.8475
Height	165.73 ± 1.78	167.73 ± 1.09	0.3469
Weight	62.13 ± 2.21	64.00 ± 1.64	0.5023
BMI (kg/m ²)	22.67 ± 0.64	22.72 ± 0.49	0.9542
N° myomas	23	21	
Mean n° myomas	1.53 ± 0.19	1.40 ± 0.19	0.6256
Volume myomas cm ³	10.84 ± 1.16	10.17 ± 1.43	0.7188
SS	22.67 ± 1.76	27.13 ± 2.04	0.1086
QoL	91.60 ± 5.55	84.93 ± 6.13	0.4270

The baseline characteristics of patients in the two groups (Treated with Vitamin D + EGCG vs. Control). The groups were well matched, with no significant difference. A p -value ≤ 0.05 was considered statistically significant. All data resulted non-significant. *Abbreviations:* BMI, body mass index; SS, severity of symptoms; QoL, quality of life; SEM, standard error of the mean.

of 29 answer options allowing the gross total scores from 29 to 145. The higher the score, the better the QoL in relation to health. A complete medical history was collected from all women; a careful physical examination, ultrasound instrumental evaluation and compilation of questionnaires were performed at baseline (T₀) and after 4 months (T₁). From all visible myomas identified, the total myoma volume was calculated through the Voluson™ E8 ultrasound (GE Healthcare). All the clinical data collected in the study were analyzed anonymously.

Statistical Analysis

Statistical analysis was performed using unpaired t -test (2018 GraphPad Software, La Jolla, CA, USA) when comparing two groups, with the results expressed as mean \pm standard error of the mean (SEM). Intragroup comparisons were assessed by one-way ANOVA analysis for repeated measures; values are indicated as mean \pm SEM. Wilcoxon–Mann–Whitney test was used for QoL and SS analyses; values are indicated as median, 25th and 75th percentile. Level of statistical significance was achieved with p -value ≤ 0.05 .

Results

We enrolled 30 women with myomas aged between 28 and 46 years old. The clinical characteristics of patients by group at baseline (T₀) are illustrated in Table I. At T₀ the two groups were comparable for all parameters. No patients dropped out in either group. No adverse effects ascribable to the treatment were recorded

throughout the study period. The total number of myomas in the treated and control group was 23 and 21, respectively. In the treated group the incidence of intramural, subserosal and submucosal myomas was 43.75%, 12.5%, 43.75%, respectively. In the control group 47.4% were intramural, 10.5% subserosal and 42.1% submucosal. A significant reduction was observed in the volume of myomas (from 10.84 \pm 1.16 cm³ at baseline to 8.04 \pm 0.85 cm³ after 4 months of treatment, $p < 0.0001$) in the treated group (Figure 1). The reduction of volume was independent of the type of myomas. In the control group, myomas volume significantly fluctuated from 10.17 \pm 1.43 cm³ at T₀, to 10.94 \pm 1.50 cm³ after

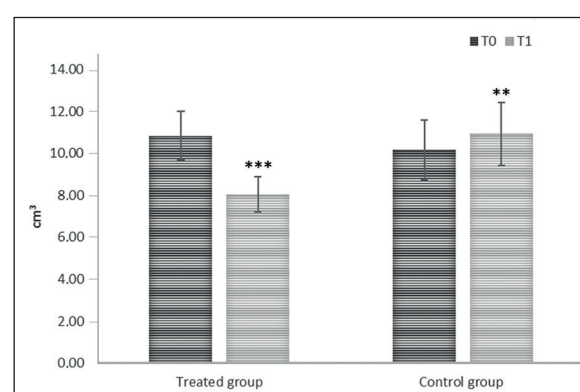


Figure 1. Volume of myomas in the groups at baseline and after the 4-month study period. Volume of myomas is indicated (mean \pm SEM) as cm³ at baseline (T₀) and at the end of the study (T₁), in the treated and control group. Treated group (vitamin D + EGCG for 4 months); control group (no treatment for 4 months). A p -value ≤ 0.05 was considered statistically significant. *Significance T₁ vs. T₀.

4 month-period observation ($p < 0.001$) (Figure 1). A trend towards significance is observed between the volume of treated myomas vs. controls at T_1 ($p = 0.0930$). The number of myomas did not change from T_0 to T_1 (end of study) in both groups, showing an unvaried mean \pm SEM (1.53 ± 0.19 in the treated group and 1.40 ± 0.19 in the control group, with a non-significant difference in between groups, Table II). Table II illustrates the incidence of the main myoma-related symptoms expressed in percentage (%) at T_0 and T_1 , in the treated and the control group. Changes from T_0 to T_1 of QoL in the treated group showed increase (31, median value), while the control group showed slight decrease (-1, median value); changes from T_0 to T_1 between the two groups were statistically different ($p < 0.0001$) (Figure 2A). Changes from T_0 to T_1 of SS in the treated group showed reduction (-7, median value), while the control group showed no variation (0, median value); from T_0 to T_1 between the two groups were statistically different ($p < 0.0001$) (Figure 2B).

Discussion

The goal of this study was to investigate whether the combined treatment with vitamin D, EGCG and vitamin B6 improves the status of myomas as well as the QoL in women affected by these benign tumors. We observed a significant reduction in the volume of myomas (34.7%) in the treated group and, conversely, an increase in tumor size in the control group (6.9%). Furthermore, we reported an improvement of women's QoL after treatment with vitamin D, EGCG and vitamin B6 along with a reduction of the SS.

Even though myomas are often asymptomatic, nearly 30% of patients may show many debilitating symptoms, with an important impact on their QoL. Such perceived worsening of QoL was described in a recent survey study, showing increased discomfort in women with symptomatic uterine myomas, with respect to the asymptomatic ones²⁰. Commonly, when myomas are asymptomatic no interventions are prescribed; however, the follow-up is advisable for monitoring size and growth. Considering the onset of myoma-related symptoms, pharmacological therapy or surgical procedure are recommended. Myoma size, number and desire for future pregnancy are the main factors to be considered when choosing a therapeutic strategy. Surgical procedures or pharmacological interventions are valuable in order to eliminate the symptoms of myomas and avoid possible serious complications, but the development of novel approaches to manage these benign tumors of the female genital tract is highly sought. As mentioned previously, the action and potential mechanisms of vitamin D and EGCG on myomas were considerably investigated. Vitamin D is a fat-soluble secosteroid hormone primarily involved in the regulation of calcium and bone health. However, it plays a role in different areas such as immunology, oncology, dermatology, rheumatology, hematology, endocrinology, obstetrics and reproductive medicine²¹⁻²⁹.

The main source of vitamin D is the endogenous production in the skin upon sunlight exposure, but dietary intake (fish oils, fatty fish, fortified foods, and vitamin supplements) also represents an essential source in humans. Low levels of 25-hydroxyvitamin D, 25(OH)D, are correlated with a number of tumors like lung,

Table II. Incidence of number, type of myomas and correlated symptoms at visit 1 and visit 2.

	Treated T_0 n° patients (%)	Treated T_1 n° patients (%)	Control T_0 n° patients (%)	Control T_1 n° patients (%)
Myomas intramural	7 (43.75%)	7 (43.75%)	9 (47.4%)	9 (47.4%)
Myomas subserosal	2 (12.5%)	2 (12.5%)	2 (10.5%)	2 (10.5%)
Myomas submucosal	7 (43.75%)	7 (43.75%)	8 (42.1%)	8 (42.1%)
Normal bleeding	3 (20 %)	5 (33.3 %)	3 (20 %)	3 (20 %)
Heavy bleeding	8 (53.3 %)	0 (0 %)	6 (40 %)	6 (40 %)
Medium bleeding	4 (26.7 %)	10 (66.7 %)	6 (40 %)	6 (40 %)
Fatigue	10 (66.7 %)	3 (20 %)	8 (53.3 %)	8 (53.3 %)
Pelvic pain	8 (53.3 %)	1 (6.7 %)	8 (53.3 %)	8 (53.3 %)

Incidence is expressed as the percentage (%) of subjects having the type of myoma or the correlated symptoms in each group at the two timepoints (T_0 , baseline or T_1 , after 4 months); n, number of subjects.

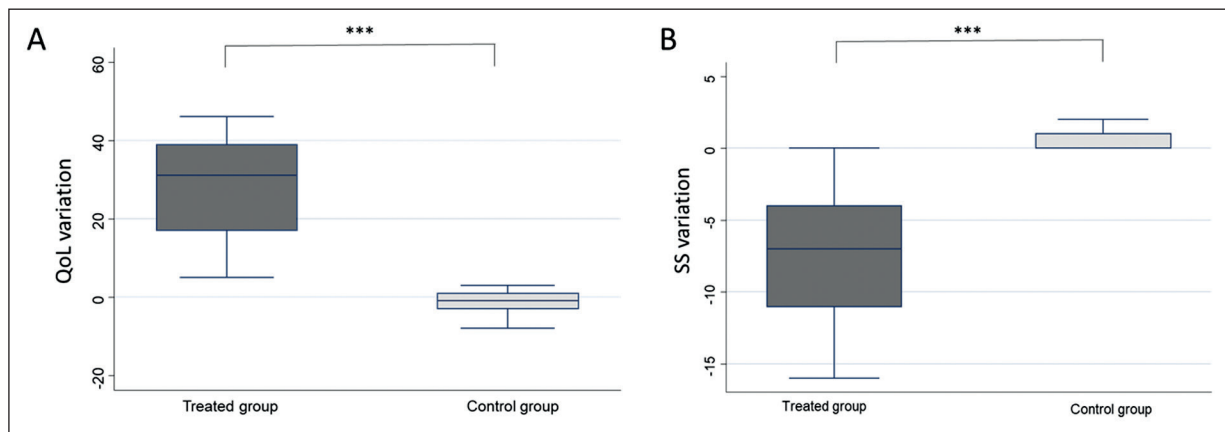


Figure 2. Variation of quality of life (QoL) and severity of symptoms (SS) in women with myomas. Data are presented as box plots. **A**, Variation of quality of life (QoL). **B**, Variation of severity of symptoms (SS). Variation is determined between the changes from T_0 to T_1 in each group, through the evaluation of the patients' responses in the questionnaires. Treated group (vitamin D + EGCG for 4 months); control group (no treatment for 4 months). Wilcoxon–Mann–Whitney test were used for the analyses. A p -value ≤ 0.05 was considered statistically significant.

lymphomas, colon, and breast cancers³⁰⁻³⁴. A number of studies have investigated the role of vitamin D also in the growth of myomas, either *in vitro* or *in vivo* animal models. According to Sharan et al³⁵, vitamin D inhibits the growth of human uterine leiomyoma (HuLM) cells *in vitro* through the down-regulation of the proliferating cell nuclear antigen (PCNA), the cyclin-dependent kinase 1 (CDK1, key player in cell cycle regulation), B-cell lymphoma 2 (BCL-2, the regulator of apoptosis) and the catechol-O-methyltransferase (COMT) expression³⁶. The same team corroborated these findings in Eker rats, showing a reduction of myoma size after 3 weeks of subcutaneous injection with 1,25-dihydroxyvitamin D₃, 1,25(OH)₂D₃. Blauer et al³⁷ demonstrated that 1,25(OH)₂D₃ (100 nM) *in vitro* inhibits the growth of myometrial and myoma cells by 62%. All these molecular pathways involved in the onset and the development of myomas may be useful for new thrilling breakthrough in the treatment of myomas³⁵⁻³⁹. Al-Hendy et al⁴⁰ suggested that 1,25(OH)₂D₃ could be a potent antiestrogenic agent in tumors, reducing the expression of sex steroid receptors in HuLM cells. Sabry et al¹⁷ report that low vitamin D levels in serum are correlated with the severity of myomas and with their increased. Further clinical studies^{18,39} showed that supplementation of vitamin D₃, in symptomatic women presenting with myomas and hypovitaminosis D (serum level <30 ng/mL), restores the normal vitamin D serum levels and reduces myoma size.

EGCG is a plant compound, the most abundant catechin in tea. It is mainly found in green tea, but small quantities are present also in onions, apples, grapes, plums, hazelnuts, pecans, and carob powder. Recently, its use has been linked to a great and positive impact on health, raising the attention of researchers worldwide. Catechins are a group of bioflavonoids, well known for their antioxidant and anti-inflammatory activity⁴¹⁻⁴³ as well as for the prevention of certain chronic conditions that include heart diseases, diabetes, and cancers^{44,45}. The chemopreventive potential of EGCG, through the induction of apoptosis and promotion of cell growth arrest, was demonstrated in different districts such as skin, lung, liver, breast, prostate, stomach, mammary gland and colon⁴⁶⁻⁵¹. Zhang et al⁵² investigated its potential activity on HuLM cell line, showing antiproliferative action, in a time and dose dependent manner, and induction of apoptosis. Different pathways were reported, from the modulation of the expression of several gene through multiple signaling pathways such as BCL2, BCL2A1 and cyclin D1 (inhibition), cyclin dependent kinase inhibitor 1A and 2B (CDKN1A, CDKN2B), mouse double minute 2 homolog (MDM2) and tumor protein p53 (enhancement) to an inhibited expression of PCNA and CDK4, as well as to an increment of the proapoptotic BAX expression in a dose-dependent manner. In a clinical trial, the administration of oral EGCG for 4 months to premenopausal women with myomas (≥ 2 cm³) resulted in a significant reduction of tumor

volume¹⁹. These data agree with our results. However, in our study, a major reduction of myoma volume was observed after the combined treatment with vitamin D and EGCG. We also found significant improvement in all QoL aspects and SS, including daily activities, sexual function, bleeding and pelvic pain. Interestingly, when comparing the QoL of patients after the use of vitamin D plus EGCG *vs.* EGCG alone (from earlier studies, Roshdy et al¹⁹), the combination seems more effective (31% and 18.53%, respectively). These findings provide a novel and safe therapeutic alternative to other medical treatments.

Conclusions

The oral supplementation of vitamin D plus EGCG and vitamin B6 might have a considerable impact on female reproductive health. Indeed, avoiding surgical treatments allows women to maintain fertility and prevents complications at the gynecological level. This simple, nonsurgical, approach seems appropriate to improve QoL, in a condition where the health-related condition is considerably impaired. Furthermore, these findings suggest that observing a myoma (“watching and waiting”) might not be the best choice and an alternative would be preferred. Indeed, considering these preliminary data, vitamin D, EGCG and vitamin B6 could be used to treat myomas, preventing a possible growth during the observation period. Furthermore, this novel combination could be administered along with other pharmacological therapy, or as pre-treatment before surgery, reducing the side effects on patients. This might also help to decrease the volume of myomas, avoiding surgical complications and lowering the risks for the patients. Further controlled studies, with a larger randomized cohort and different ethnic groups, are required to validate these encouraging results. Besides, new pre-clinical and clinical studies are necessary to clarify how these two molecules work together as well as to identify the appropriate dosage of each compound for an effective therapy in women with myomas. In this paper, we showed for the first time the effectiveness of a combined supplementation with vitamin D and EGCG in the management of myomas and the correlated symptoms, opening new therapeutic scenarios and propelling further related investigations.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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