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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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LOW 25OHD IN ENDOMETRIOSIS- RISK FACTOR OR CONSEQUENCE?!

Nino Abesadze[1]*, Jenaro Kristesashvili[2], Arsen Gvenetadze[3].

[1]*Faculty of Medicine, Ivane Javakhishvili Tbilisi State University, 0162 Tbilisi, Georgia.*
[2]*Faculty of Medicine, Ivane Javakhishvili Tbilisi State University, 0162 Tbilisi, Georgia.*
[3]*Faculty of Medicine, Ivane Javakhishvili Tbilisi State University, 0162 Tbilisi, Georgia.*

Abstract.

Background: Active vitamin D-1.25OHD (1,25Dihydroxyvitamin D, calcitriol) in the endometrium of women with endometriosis seems to be enhanced compared to healthy controls. Evidence is insufficient on how this process reflects vitamin D metabolites-25OHD (25 Hydroxyvitamin D, calcifediol), 1.25OHD, and calcium blood concentrations.

Aim: Determination of vitamin D's significance in the pathogenesis of endometriosis by analyzing the levels of 25OHD, 1.25OHD, and calcium in patients with endometriosis before and after laparoscopic treatment.

Materials and Methods: This study is an anterograde comparative analysis, that investigates the variation of vitamin D metabolite and calcium levels between the preoperative assessment and the subsequent measurement following surgical treatment of endometriosis. Results before the intervention were also compared to the healthy control group. Levels of 25OHD,1.25OHD, and calcium before required surgical treatment and 3 months post-laparoscopy were measured. Data analyses were made using IBM SPSS 27.

Results: Women with endometriosis have significantly lower mean 25OHD (p-0.002) and a higher 1.25OHD ($p<0.001$) and total calcium levels (p-0.03) compared to controls. The endometriosis stage and size of endometrioma negatively correlate with 25OHD levels ($p<0.001$). After surgical removal of endometriotic lesions, 1.25OHD, and calcium showed a significant decrease whereas 25OHD blood concentrations increased statistically significantly. **Conclusion:** Women with endometriosis have a lower 25OHD, a higher 1.25OHD, and total calcium levels in the bloodstream compared to the control group. Usually, a low concentration of 25OHD is characterized by low/normal 1.25OHD and hypocalcemia. Hypercalcemia in the study group may be attributed to increased levels of active vitamin D- 1.25OHD, which seems to be the result of a higher conversion rate of 25OHD to 1.25OHD in the endometrium of women with endometriosis. Removal of endometriotic heterotopies was followed by significant changes, which could indicate that the levels of vitamin D metabolites have been influenced by endometriosis. It is reasonable to conclude, that diminished levels of 25OHD might be interpreted as an outcome of a high demand in endometriosis, instead of a risk factor.

Key words. Vitamin D, endometriosis, calcitriol, calcifediol, 25OHD, 1,25OHD.

Introduction.

Endometriosis is estrogen-dependent, progesterone-resistant chronic inflammatory disease, that affects nearly 10% of women in their reproductive years worldwide [1]. The prevalence of undiagnosed endometriosis seems to be higher than 10% due to the complexities associated with its diagnosis. The gold standard of diagnosis is surgical evaluation-laparoscopy. According to the latest systematic review, the prevalence of endometriosis depends on the diagnostic method. If the diagnostic method is laparoscopy-endometriosis is present in 20% of women, whereas via ultrasound or MRI (Magnetic Resonance Imaging) frequency of only 12% is detected [2-5]. Endometriosis affects many aspects of a woman's life, such as general health, reproductive health, sex life, social life, and work. Treatment of endometriosis requires a multidisciplinary approach. In many cases, oral medication is not enough to alleviate symptoms, and surgery is performed, but it also does not guarantee a recurrence-free life [6,7]. Consequently, for many women endometriosis stays unmanageable. According to the latest literature review, 11% of patients experience chronic pain after laparoscopic treatment and 22,6% of patients require repeated surgery [8]. Based on unsatisfactory diagnostic and treatment results, researchers are trying to explore innovative treatments and diagnostic strategies. Besides first-line treatment, some experimental ways of management are showing promising potential. One of them is active vitamin D-1,25OHD- calcitriol.

Vitamin D receives a lot of attention nowadays. It has multiple functions almost in every cell and endometrium is not an exception. Enzyme 1-α-hydroxylase activates vitamin D - and converts 25OHD-calcifediol to 1,25OHD--calcitriol. While it has been classically understood that this activation occurs in the kidneys, current findings demonstrate that this conversion is detectable in numerous tissues, including the endometrium. The active form of vitamin D – (1.25OHD) calcitriol is a hormone and performs all the functions vitamin D has - via binding to a specific receptor -VDR (Vitamin D Receptor), which is found in the endometrium as well. Certain studies indicate that the metabolism of vitamin D may differ in individuals with endometriosis. There is a higher amount of 1- α -hydroxylase and VDR in the endometrium of patients with endometriosis compared to healthy women [9]. In 1989 Hartwell found higher plasma calcitriol levels in women with endometriosis compared to healthy controls (n-42) [10-12]. An important finding is that VDR is expressed in ectopic endometrium of endometriosis patients as well. Progesterone and calcitriol (1.25OHD) cooperate. CYP24A1 (vitamin D3 24-Hydroxylase) is a calcitriol deactivating enzyme, that causes calcitriol-induced self-limitation. Progesterone shows the ability to inhibit this CYP24A1. Consequently, progesterone may be the factor that allows calcitriol to work more effectively as an antiproliferative and anti-inflammatory factor [13-15]. Experimental treatment with calcitriol in some studies showed reduced size of endometriosis lesions. One study indicated that calcitriol positively impacted stromal cells in women suffering from endometriosis. Eutopic and ectopic stromal cells were investigated in vitro. Calcitriol reduced the proliferation and

invasion of cells [16]. An Analog of calcitriol-Elocalcitol was used in an experimental animal study to treat endometriosis. It affected the nuclear factor Kappa beta-NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells) pathway and reduced inflammation. NF-κB activation is an important step in the development and progress of endometriosis. It upregulates the adhesion of endometriotic cells outside of the endometrium [17,18]. Elocalcitol was used to treat endometriosis in disease-induced rats. In 3 weeks, this treatment reduced endometriotic lesions by 70% [19]. Additionally, an in Vitro experiment was carried out involving calcitriol on human endometriotic stromal cells, obtained from ovarian endometriomas. Treatment with calcitriol reduced inflammation. This study was also focused on vitamin D plasma levels and found no difference in plasma calcitriol levels of patients with and without endometriosis [20,21]. Notably, calcitriol increases progesterone in human granulosa cells by upregulating 3-βHSD (3β-Hydroxysteroid dehydrogenase) [22]. Also, active vitamin D upregulates the expression of HOXA10 (Homeobox A10) in stromal cells of the endometrium, which are transcription factors essential for implantation and decidualization [12]. These results could be explained by the fact that active vitamin D functions as both an anti-inflammatory and anti-proliferative factor, while also working in synergy with progesterone. Most studies indicate a negative correlation between endometriosis and 25OHD, suggesting vitamin D deficiency as a risk factor for endometriosis, research concerning calcitriol is notably scarce.

Aim.

Determination of vitamin D's significance in the pathogenesis of endometriosis by analyzing the levels of 25OHD, 1.25OHD, and calcium in patients with endometriosis before and after laparoscopic treatment.

Materials and Methods.

Study Design:

This study is an anterograde comparative analysis, that investigates the variation of vitamin D metabolite and calcium levels between the preoperative assessment and the subsequent measurement following surgical treatment of endometriosis. Results before the intervention were also compared to the healthy control group. The total sample consisted of 50 women. Participants were divided into 2 groups. Group I -60%(n30) - were fertile women with surgical and histomorphological confirmed endometriosis, while Group II - 40%(n20) were healthy controls. The study continued from the 2023 spring until the January 2024.

Study population.

Inclusion criteria:

For the Group I -surgical and histopathological confirmed diagnosis of endometriosis.

For the Group II– healthy reproductive status-confirmed with gynecological examination, ultrasound, and medical history.

Exclusion criteria: For both groups were infertility, any serious chronic disease, genetic disease, PCOS, diabetes mellitus of any type, thyroid gland hormonal dysfunction, any hormonal or anti-hormonal treatment past 3 months, vitamin D supplementation past 6 months, frequent sun exposure past 3 months, pregnancy or lactation past 3 months, morbid obesity, bariatric surgery.

Methods.

In Group I blood for evaluation was drawn before surgery and then 3 months after laparoscopy. At the same season of the year, we tested Group II participants. Laparoscopy was performed by experienced surgeon-gynecologists on any day of the menstrual cycle. Method of surgical intervention included excision of ovarian endometriomas, lysis of adhesions, and endo-coagulation of endometriosis lesions.

In both groups, was measured 25OHD, 1,25OHD, total and ionized calcium levels in serum, using 1,25-Dihydroxyvitamin D3 (Calcitriol) ELISA Kit for the quantitative measurement of 1,25-Dihydroxyvitamin D3 (Calcitriol) concentrations in serum, plasma, and other biological fluids. Tests were done following the manufacturer's instructions. The reference range for 1,25OHD in females was considered 18-78pg/ml. Serum 25(OH)D level of ≥30 ng/ml was considered a normal level, 20 to 29 ng/ml as vitamin D insufficiency and 25(OH)D <20 ng/ml as a deficiency [23]. The normal level for calcium was considered 1.15-1.29 mmol/l for ionized calcium and 2.15-2.5mmol/l for total calcium.

All participants from Group I signed informed consent before the planned surgical intervention and Group II before the assessment. Study groups signed confirmation, that the first sample for laboratory would be frozen at -20°C until the end of the study and they won't have access to vitamin D and calcium results. All study participants agreed not to take vitamin D and calcium supplements for the next 3 months. Patients who required hormonal treatment were excluded from the study (n-3). Patients were not planning pregnancy and were advised to use non-hormonal contraception methods. Both groups had to fill out questionnaires. Information about the menstrual cycle and genital pain was also analyzed. Participants had to rate pain during, before, or after menstruation from 0 to 10 points, using a "Numeric Pain Rating Scale", where 0 was no pain, 1-3 mild, 4-6 moderate, and 7-10 severe pain. To rate pain during sexual intercourse participants had to choose between -no pain, rare, and frequent pain options. Also, they were asked to fill out a questionnaire for FRAX (Fracture Risk Assessment Tool). Calculation was done without BMD. Only low-risk women for osteoporosis were included (<10% for major osteoporosis fractures and <2% for hip fractures).

The study was approved by the ethics committee.

Statistical analysis.

Statistical analysis was done using IBM SPSS Statistics-Version 27. Correlation for continuous variables was made with Pearson correlation analysis. Categorical and continuous variables were compared with the use of an independent Student's t-test and for multiple group comparison we used a one-way ANOVA test. For the prospective study, where similar tests were made twice - at 1st timepoint and after 3 months – a two-sample paired t-test was used. p-value < 0.05 was considered as statistically significant.

Results.

Description of sample:

In the current study mean body weight, BMI and age of study participants were equal and comparable. The mean BMI- in the study group – was 23.7kg/m2, and in healthy controls -24kg/m2 (p-0.7); the mean age in the endometriosis group- was 26, and in the healthy group-27.4(p-0.42). There was no significant difference in age and BMI between the endometriosis and healthy group. Participants with obesity were excluded from the study due to the possible impact of body weight on 25OHD levels. The BMI range in the total study group was 18-29kg/m2.

Vitamin D and endometriosis:

In this prospective study patients with endometriosis had significantly (p-0.002) lower mean 25OHD levels than healthy controls. The mean 25OHD level in Group I was -14.4ng/ml and in Group II-23.8ng/ml. The mean 1.25OHD level in the endometriosis group was - 94.4pg/ml, statistically significantly higher (p <0.001) comparing healthy women -31.5pg/ml (Table 1).

Table 1. *Results of vitamin D metabolites and calcium in study and control group.*

	GROUP I *Women with endometriosis* (n30)	GROUP II *Healthy controls* (n20)	Significance *P*
Calcifediol 25OHD ng/ml	14.4±9.3	23.8±10.5	0.002
Calcitriol 1.25OHD pg/ml	94.4±43.6	31.5±12	<0.001
Total Calcium mmol/l	2.5±0.38	2.3±0.12	0.03
Ionized Calcium mmol/l	1.23±0.5	1.21±0.39	0.27

We analyzed results according to seasons to exclude seasonal influence on 25OHD levels. The study was conducted from spring 2023 until the end of autumn 2023. In each of these 3 seasons, 25OHD was significantly lower and 1.25OHD higher in Group I compared to Group II.

Calcium and Endometriosis:

In Group I the mean level of total calcium was -2.5mmol/l and the mean level of Ca++ was -1.23 mmol/l. vs group II total calcium-2.3mmol/l and Ca++ -1.21mmol/l. The difference between Group I and II in total calcium levels was statistically significant (p-0.03), whereas Ca++ doesn't differ significantly. (p-0.27) (Table I).

33.3% of endometriosis patients had a total calcium level above the reference range and 20% had elevated Ca++ levels, while only 5% of healthy women had elevated total and Ca++ levels.

Asrm stage, phenotype, and Vitamin D:

The location of endometriosis is in connection with vitamin D. Mean 1.25OHD in ovarian endometriosis was 101.8 pg/ml, in deep infiltrative endometriosis-82pg/ml, in deep endometriosis with ovary affected- 78pg/ml, and in the healthy group -31.5 pg/ml The difference in 1.25OHD levels between endometriosis phenotypes was significant (<0.001). 25OHD levels between the different forms of endometriosis were also not the same (p-0.02). When endometriosis affects both ovaries or ovary and deep pelvic structures together-25OHD shows to be lower than in case of isolated deep or ovarian endometriosis.

Patients from Group I were divided according to the endometriosis stages considering ASRM classification. 23.3%(n7) of patients had stage II endometriosis, 43.3% (13) - stage III, and 33.3% (10)-stage IV. Mean 25OHD was lowest in stage IV patients -7.6ng/ml. In milder-stage III and II endometriosis mean 25OHD was 17.76ng/ml and 18.2ng/ml respectively – practically similar. The difference between mild (II) and severe (III and IV) forms was significant (p-0.001).

1.25OHD levels between the stages did not differ significantly (p-0.08).

The size of ovarian endometrioma was in negative correlation with 25OHD (r =-0.600; p-0.005) and did not show any association with calcitriol.

Menstrual cycle and Vitamin D:

We compared 25OHD levels within Group I (n30) between the follicular and luteal phases of the menstrual cycle. In the luteal phase mean 25OHD was significantly higher-26.7ng/ml than in the follicular phase-12.7ng/ml (p-0.03) in endometriosis patients. Those with irregular menstrual cycle had the lowest concentration of 25OHD-11.2ng/ml.

Inside Group II (n20) participants had similar mean 25OHD levels in the 1st and 2nd phases -23.9ng/ml in the luteal vs 23.8ng/ml in the follicular phase.

Pain and Vitamin D:

The frequency of genital pain during or after intercourse in both groups was analyzed. 33.3% of women from Group I – had dyspareunia regularly, 20% of patients- rarely, and 46.7% of women with endometriosis -were pain-free during sexual intercourse. Only 5% of healthy women, reported rare dyspareunia. We compared patients inside Group I and women with rare and regular pain show to have similar calcitriol levels-101 pg/ml, 105 pg/ml, whereas pain-free participants with endometriosis had a lower mean level of 1.25OHD-84.7 pg/ml. 25OHD was not associated with dyspareunia.

Dysmenorrhea was present in 100% of endometriosis patients and 10% of healthy controls. In Group I, the severity of pain was inversely associated with 25OHD levels (p-0.01 r=-0.449), but not with calcitriol. In healthy controls, we observed the same tendency of an inverse association between dysmenorrhea and 25OHD, but this negative correlation was insignificant (p-0.09 r=-0.382).

The individual feeling of pain was not connected with the endometriosis stage, phenotype, regularity of the menstrual cycle, or brown discharge.

Re-Test Results:

After 3 months from 1st test, vitamin D metabolites and calcium levels were repeated in the study group. Mean 1.25OHD in Group I after surgical treatment was significantly decreased compared to the first assessment (p<0.001). 25OHD levels in

Group I were significantly (p<0.001) increased after surgical treatment-from the level of 14.4ng/ml to the 18ng/ml. In Group I total calcium significantly decreased (p-0.002) after surgery (Table N2).

Table 2. *Results of vitamin D metabolites and calcium before and after surgical treatment of endometriosis.*

	GROUP I 1ST test *(pre-surgery)*	GROUP I 2nd test *(post-surgery)*	Significance *P*
Calcifediol 25OHD ng/ml	14.4±9.3	18±8.7	<0.001
Calcitriol 1.25OHD pg/ml	94.4±43.6	49.9±23.5	<0.001
Total Calcium mmol/l	2.5±0.38	2.34±0.19	0.002
Ionized Calcium mmol/l	1.23±0.5	1.22±0.04	0.3

Improvement in hypercalcemia was observed, and only 10% from Group I were left with elevated total calcium levels after removal of endometriotic lesions vs 33% of hypercalcemia before surgery. The hypocalcemia rate decreased after surgery from 6.7% - at the first evaluation to 3.3%-after laparoscopy.

All results were adjusted to seasons, and it was determined that there was no seasonal influence on our findings.

Discussion.

According to our study results, women with endometriosis have significantly (p-0.002) lower mean 25OHD compared to healthy controls. This finding is in agreement with the majority of the observational studies and meta-analyses which found lower 25OHD levels in women with endometriosis compared to controls and mainly consider vitamin D deficiency as a risk factor for endometriosis [24,25]. Interventional research shows no benefit of simple cholecalciferol supplementation in endometriosis [26]. This suggests a complex relationship between vitamin D and endometriosis. Vitamin D supplementation lacks benefits in case of many diseases, associated with vitamin D deficiency. This led the Endocrine Society to change the guidelines, and current recommendations don't support routine supplementation. Furthermore, they are against routine testing of 25OHD because optimal levels, which could improve disease outcomes are not defined yet [27]. This indicates that further research is needed to confirm the extra-skeletal functions of vitamin D. Vitamin D status estimation requires greater accuracy, and focusing on 25OHD alone may lead to misdiagnosis. 1.25OHD is an active form of vitamin D, which is the primary effector of all the functions vitamin D has. We found 1.25OHD concentration to be significantly higher in the bloodstream of patients with endometriosis than controls. Very few studies are focused on active vitamin D concentrations in the bloodstream of women with endometriosis. As far as we are informed, in 1989 Hartwell was the first researcher, who investigated women with endometriosis have elevated 1.25OHD in their blood [28]. After Hartwell there is another study from 2007 analyzing 1.25OHD in women with endometriosis, which also found higher 1,25OHD levels compared to controls, but not statistically significant [29]. Our findings concerning calcium levels in endometriosis align with the most recent randomized study from 2024, which identifies a correlation between endometriosis and hypercalcemia [30]. 33% of patients with endometriosis from our study have elevated calcium levels vs 5% from the control group and the mean total calcium is significantly higher in women with endometriosis. There is little evidence about calcium in endometriosis and some outcomes disagree with our results-receiving low/normal calcium concentration [31].

Our observation indicates that the phenotype and stage of endometriosis are associated with 25OHD levels. The lowest levels of 25OHD are found in more severe forms of endometriosis, namely when the disease affects deep pelvic structures together with the ovary or both ovaries. The lowest 25OHD was identified in stage IV endometriosis. The size of ovarian endometrioma is also related to 25OHD serum levels and shows a significant inverse association. Most studies could not find an association between vitamin D and the stage of endometriosis. One observation indicates that individuals with severe endometriosis have lower levels of 25OHD compared to those with mild form, however, this finding was not statistically significant [24,31].

Higher 1.25OHD, but not 25OHD in the endometriosis group was associated with dyspareunia within our study, and lower 25OHD with dysmenorrhea. Certain evidence about similar results exists regarding 25OHD and pain. In one study pelvic pain was linked to low 25OHD levels, independently from endometriosis status [32]. Even supplementation with vitamin D has shown to be beneficial for pain relief [33,34]. According to our results, there is no cyclic fluctuation of vitamin D in healthy women. However, in the endometriosis group, the tendency of higher 25OHD in the luteal phase was prominent. Our research did not reveal a difference in active vitamin D levels between follicular and luteal phases. Prior research suggests higher expression of both -VDR (vitamin D receptor) and 1-α -hydroxylase in the healthy endometrium, in the second phase of the menstrual cycle, specifically in the implantation window period [11,12]. Consequently, they suggest that the activation and reception of vitamin D may follow a cyclical pattern, associated with progesterone. However, our study did not find a reflection of this phenomenon in the bloodstream.

After surgical removal of endometriosis tissue, significant changes occurred - 1.25OHD and total calcium decreased and 25OHD increased, compared to the first assessment.

For a clearer understanding of the results obtained, it would be beneficial to review normal vitamin D and calcium homeostasis. The major circulating form of vitamin D is 25OHD-calcifediol, which is converted into active form-1.25OHD-calcitriol, classically in the kidney. This conversion requires enzyme 1-α-hydroxylase. 1.25OHD is a hormone and main ligand of VDR (vitamin D binding receptor). When 25OHD levels are low, calcium absorption falters and hypocalcemia arises. Via a negative feedback loop, hypocalcemia causes elevated parathyroid hormone (PTH), which tries to increase vitamin D activation and raise plasma calcium levels back to normal. Once calcium levels are increased to the reference range, PTH

returns to normal concentration and stops further activation of vitamin D-conversion of 25OHD to 1.25OHD [35,36]. Within a normal endometrium, vitamin D activation also occurs. In endometriosis, local enhanced activation of 25OHD to 1.25OHD due to elevated levels of enzyme 1- α -hydroxylase in endometrial cells was identified [37,38]. Notably, VDR (vitamin D receptor) is expressed in both - eutopic and ectopic endometrium of endometriosis patients and it's higher in eutopic endometrium. This could be a sign of decreased reception of ectopic endometrium to calcitriol and explain a higher calcitriol demand due to its anti-inflammatory and antiproliferative properties in endometriosis [11]. Significant activation of vitamin D in the endometrium of women with endometriosis could result in excessive uptake of 25OHD from the bloodstream, potentially leading to a deficiency in vitamin D's major circulating form. Therefore, vitamin D deficiency could be viewed as an outcome rather than a risk factor in endometriosis. Excessive activation may lead to elevated levels of 1.25OHD in the bloodstream, thereby affecting calcium homeostasis. There are conditions, from which we have to differentiate our results - primary and secondary hyperparathyroidism. Classically in case of secondary hyperparathyroidism due to 25OHD deficiency calcium is low and 1.25OHD normal [39]. For better accuracy, we compared mean calcitriol levels in Group I and II's same degree of 25OHD deficiency. In case of severe deficiency 25OHD <10ng/ml -in Group I mean 1.25OHD level was- 90.7pg/ml vs Group II – 15pg/ml. The difference is significant ($p<0.001$). This supports the conclusion that the elevated levels of 1.25OHD observed in Group I are not a compensatory response to secondary hyperparathyroidism, as such response would manifest similarly across both groups with the same degree of 25OHD deficiency. We couldn't exclude primary hyperparathyroidism due to technical difficulties from our study and it could theoretically lead to the results we get at the first assessment in the study group - elevated 1.25OHD and calcium. The main argument is that it is a rare disease and if present, then it should manifest with the same frequency in both groups. Besides, a decrease in 1.25OHD and calcium after endometriosis excision excludes the presence of primary hyperparathyroidism. This suggests that the primary factor that causes these changes is endometriosis itself. We propose that vitamin D deficiency in endometriosis is a consequence rather than a predisposing factor. Therefore, cholecalciferol supplementation should be approached with caution to prevent further increase in calcium levels. On the other hand, progesterone may decrease 1.25OHD deactivation and increase reception, [40] consequently treatment with progestins can worsen hypercalcemia and affect bone metabolism. Some studies already focused on this point and show minimal/significant decrease in bone mineral density (BMD) after long-term treatment with dienogest [41,42]. These findings may serve as valuable support for future research, particularly concerning calcitriol analogs. Distinct regulatory mechanisms in endometriosis underscore the importance of vitamin D in endometriosis. We assume that the increased demand for vitamin D serves as a form of self-protection in endometriosis.

Conclusion.

Women with endometriosis have a lower 25OHD, a higher 1.25OHD, and total calcium levels in the bloodstream compared to the control group. Usually, a low concentration of 25OHD is characterized by low/normal 1.25OHD and hypocalcemia. Hypercalcemia in the study group may be attributed to increased levels of active vitamin D- 1.25OHD, which seems to be the result of a higher conversion rate of 25OHD to 1.25OHD in the endometrium of women with endometriosis. Removal of endometriotic heterotopies was followed by significant changes, which could indicate that the levels of vitamin D metabolites have been influenced by endometriosis. Reasonable to conclude, that diminished levels of 25OHD might be interpreted as an outcome of a high demand in endometriosis, instead of a risk factor.

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Conflict of Interest.

Authors declare no conflict of interest.

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25OHD-ის დაქვეითებული დონე ენდომეტრიოზის დროს - რისკ-ფაქტორი თუ შედეგი?!

ნინო აბესაძე[1], ჯენარო ქრისტესაშვილი[2], არსენ გვენეტაძე[3]

[1]მედიცინის ფაკულტეტი, ივანე ჯავახიშვილის სახელობის თბილისის სახელმწიფო უნივერსიტეტი, 0162 თბილისი, საქართველო

[2]მედიცინის ფაკულტეტი, ივანე ჯავახიშვილის სახელობის თბილისის სახელმწიფო უნივერსიტეტი, 0162 თბილისი, საქართველო

[3]სამედიცინო ფაკულტეტი, ივანე ჯავახიშვილის სახელობის თბილისის სახელმწიფო უნივერსიტეტი, 0162 თბილისი, საქართველო

აბსტრაქტი

აქტუალობა: ენდომეტრიოზის მქონე ქალების ენდომეტრიუმში აქტიური D ვიტამინის -1.25OHD (1,25 დიჰიდროქსივიტამინი დ, კალციტრიოლი) ჭარბი წარმოქმნა აღინიშნება ჯანმრთელ ქალებთან შედარებით. არ მოიპოვება საკმარისი მტკიცებულებები იმის შესახებ, თუ რა ასახვას ჰპოვებს ეს პროცესი D ვიტამინის მეტაბოლიტების-25OHD(25ჰიდროქსივიტამინი დ, კალციფედიოლი), 1.25OHD და კალციუმის დონეზე სისხლში. მიზანი: D ვიტამინის მნიშვნელობის განსაზღვრა ენდომეტრიოზის პათოგენეზში-25OHD-ის, 1.25OHD-ისა და კალციუმის დონის შეფასებით ენდომეტრიოზის მქონე პაციენტებში ლაპაროსკოპიულ მკურნალობამდე და მის შემდეგ. მასალები და მეთოდები: კვლევა არის ანტეროგრადული, შედარებითი ანალიზი, რომელიც იკვლევს D ვიტამინის მეტაბოლიტების კონცენტრაციის ცვალებადობას სისხლში, ენდომეტრიოზული ქსოვილის ქირურგიულ ამოკვეთამდე და მის შემდეგ. საწყისი მონაცემები შედარდა ჯანმრთელი ქალების საკონტროლო ჯგუფსაც. განისაზღვრა 25OHD,1.25OHD და კალციუმის დონე გეგმიურ ქირურგიულ მკურნალობამდე და ლაპაროსკოპიიდან 3 თვის შემდეგ. მონაცემთა ანალიზი გაკეთდა IBM SPSS 27-ის გამოყენებით. შედეგები: ენდომეტრიოზის მქონე ქალებს ჯანმრთელ ქალებთან შედარებით სარწმუნოდ დაბალი(p-0.002) 25OHD - კალციფედიოლის დონე და მომატებული(p<0.001) 1.25OHD-კალციტრიოლის კონცენტრაცია აქვთ სისხლში. ასევე სარწმუნოდ მაღალია (p-0.03) ენდომეტრიოზით დაავადებული ქალების საერთო კალციუმის დონე საკონტროლო ჯგუფთან შედარებით. ენდომეტრიოზის ხარისხი და ენდომეტრიომის ზომა უარყოფით კორელაციაშია 25OHD-ის მაჩვენებელთან (p<0.001). ენდომეტრიოზული დაზიანებების ქირურგიული ამოკვეთის შემდეგ 1.25OHD-კალციტრიოლის და საერთო კალციუმის დონე სისხლის შრატში სარწმუნოდ დაქვეითდა, ხოლო 25OHD-კალციფედიოლის კონცენტრაციამ მოიმატა. დასკვნა: ენდომეტრიოზის მქონე ქალებს აღენიშნებათ 25OHD-ის დაქვეითებული, ხოლო 1.25OHD-ისა და საერთო კალციუმის მომატებული დონე სისხლში, საკონტროლო ჯგუფთან შედარებით. კლასიკურად D ვიტამინის დეფიციტს, ანუ 25OHD-ის დაქვეითებას ახასიათებს ჰიპოკალცემია და 1.25OHD-ის ნორმალური კონცენტრაცია სისხლში. ჰიპერკალცემია, ჩვენი კვლევის საკვლევ ჯგუფში, აიხსნება აქტიური D ვიტამინის (1.25OHD) ჭარბი კონცენტრაციით, რაც თავის მხრივ ენდომეტრიოზის მქონე ქალების ენდომეტრიუმში კალციფედიოლის (25OHD) კალციტრიოლად (1.25OHD) აქტიური გარდაქმნით უნდა იყოს გამოწვეული. ენდომეტრიოზული ჰეტეროტოპიების ამოკვეთის შემდომ სარწმუნო ცვლილებები მიუთითებს, რომ D ვიტამინის მეტაბოლიტების დონეზე გავლენას თავად ენდომეტრიოზი ახდენს. 25OHD-ის დაქვეითებული დონე განხილულ უნდა იქნას, როგორც მისი ჭარბი მოხმარების შედეგი ენდომეტრიოზის დროს და არა რისკ-ფაქტორი.

საკვანძო სიტყვები: ვიტამინი D, ენდომეტრიოზი, კალციტრიოლი, კალციფედიოლი, 25OHD, 1,25OHD.

Низкий уровень 25OHD при эндометриозе — фактор риска или следствие?!

Нино Абесадзе[1], Дженаро Кристесашвили[2], Арсен Гвенетадзе[3]

[1]Медицинский факультет, Тбилисский государственный университет имени Иване Джавахишвили, 0162 Тбилиси, Грузия

[2]Медицинский факультет, Тбилисский государственный университет имени Иване Джавахишвили, 0162 Тбилиси, Грузия

[3]Медицинский факультет, Тбилисский государственный университет имени Иване Джавахишвили, 0162 Тбилиси, Грузия

Абстракт

Актуальность: Активность витамина D-1.25OHD в эндометрии женщин с эндометриозом, по-видимому, повышена по сравнению со здоровыми женщинами. Недостаточно данных о том, как этот процесс отражается на концентрации метаболитов витамина D - 25OHD, 1,25OHD и кальция в крови. **Цель**: определение значения витамина D в патогенезе эндометриоза путем анализа уровней 25OHD, 1,25OHD и кальция у больных эндометриозом до и после лапароскопического лечения. **Материалы и метод:** Данное исследование представляет собой антероградный сравнительный анализ, в ходе которого изучаются различия в уровнях витамина D между предоперационной оценкой и последующими измерениями после хирургического лечения эндометриоза. Результаты до вмешательства также сравнивались со здоровой контрольной группой. Были измерены уровни 25OHD, 1,25OHD и кальция до хирургического лечения и через 3 месяца после лапароскопии. Анализ данных проводился с использованием IBM SPSS 27. **Результаты:** Женщины с эндометриозом имеют значительно более низкие средние значения 25OHD (p-0,002) и более высокие уровни 1,25OHD (p<0,001) и общего кальция (p-0,03) по сравнению с контрольной группой. Стадия эндометриоза и размер эндометриомы отрицательно коррелируют с уровнем 25OHD (p<0,001). После хирургического удаления эндометриоидных образований 1,25OHD вместе с кальцием показали значительное снижение и последующее увеличение концентрации 25OHD в крови.

Вывод: женщины с эндометриозом имеют более низкий уровень 25OHD, более высокий 1,25OHD и общий кальций по сравнению с контрольной группой. Обычно низкий уровень 25OHD характеризуется низким/нормальным уровнем 1,25OHD и гипокальциемией. Гиперкальциемию в исследуемой группе можно объяснить повышенным уровнем активного витамина D-1,25OHD, что, по-видимому, является результатом более высокой скорости конверсии 25OHD в 1,25OHD в эндометрии женщин с эндометриозом. Удаление эндометриоидных гетеротопий сопровождалось значительными изменениями, которые могли указывать на влияние эндометриоза на уровни метаболитов витамина D. Низкий уровень 25OHD можно интерпретировать как результат эндометриоза, а не как фактор риска.

Ключевые слова: витамин D, эндометриоз, кальцитриол, кальцифедиол, 25OHD, 1,25OHD.