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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

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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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# EFFICACY OF OSSEIN-HYDROXYAPATITE COMPLEX AS A PHARMACOLOGICAL CORRECTOR OF BONE LOSS (REVIEW)

**Olha Yakovleva, Oleh Hoina-Kardasevich, Nataliia Shcherbeniuk.**

*Vinnytsia National Pirogov Memorial Medical University, Ukraine.*

## Abstract.

The problem of osteoporosis is relevant due to the high frequency of its prevalence throughout the world. Complex mechanisms for maintaining bone mass biomass require various options for their pharmacological correction, so the range of proposed drugs is expanding. Among the debatable indications for the pharmacological correction of osteopenia and osteoporosis, the effectiveness and safety of the ossein-hydroxyapatite complex (OHC), which contributes to the preservation of mitogenic effects on bone cells, are specified. The literature review discusses aspects of the use of OHC: in traumatology and surgery for problematic complicated fractures, the impact of both excess and deficiency of hormonal regulators in postmenopausal women or in conditions of long-term pharmacotherapy with glucocorticoids, age-related as-pects from childhood to old age correction by OHC of accompanying bone tissue imbalance in pediatrics and geriatrics are considered, as well as the mechanisms of the positive effect of OHC in experimental data are clarified. Among the unresolved debatable issues of clinical protocols, various dose aspects, duration of therapy and clarification of indications in accord-ance with the requirements of personalized medicine continue to remain.

**Key words.** Osteoporosis, ossein-hydroxyapatite complex, fracture correction, glucocorticoid osteoporosis, postmenopausal osteoporosis, experimental osteoporosis.

## Review.

The problem of osteoporosis (OP) remains quite relevant in recent years. According to SCOPE (The Scorecard for Osteoporosis in Europe), in 2019 in Europe (European Union, plus Switzerland and the UK), 32 million people aged 50+ suffered from osteoporosis, equivalent to 5.6% of the total European population over the age of 50 years, or about 25.5 million women (22.1% of women over the age of 50) and 6.5 million men (6.6% of men over 50) [1].

OP is a multifactorial systemic metabolic disease of the skeletal system, characterized by a decrease in bone mass, and a violation of bone micro architectonics, leading to excessive bone fragility and a high risk of fractures. The danger of OP lies in the fact that, while asymptomatic, the disease is diagnosed already at the stage of complications — a low-energy fracture. Fractures are common and place a huge medical and personal burden on the elderly who suffer from them, and cause serious economic damage to the nation [2]. The number of people aged 50 years and older at high risk of osteoporotic fractures worldwide in 2010 was estimated at 158 million. Demographic shifts mean that this number is likely to double by 2040 [3].

The most common sites of osteoporotic fractures are the spine, hip, and distal radius. Hip fractures almost always result in hospitalization, recovery is slow, and rehabilitation is often incomplete. Vertebral fractures can occur without serious symptoms, but frequent recurrences result in disability. Distal radius fractures usually have a favorable prognosis [4]. The risk of a subsequent fracture is especially high in the first two years after the first fracture [5].

Throughout human life, starting from birth, there is a continuous process of bone remodeling, which ensures the complete renewal of the human skeleton 3-4 times in a lifetime. This process is provided by the main cells of bone tissue — osteoclasts, responsible for bone resorption, and osteoblasts, involved in the synthesis of new bone tissue. Normally, the processes of bone resorption and synthesis are balanced; when this balance is disturbed, osteoporosis develops. Diagnosis of the disease is based on the quantitative assessment of bone mineral density (BMD) using dual-energy X-ray absorptiometry (DEXA). The state of bone metabolism is assessed by biochemical markers of OP [6].

According to the classification of osteoporosis, it can have completely different causes, including 4 variants of primary osteoporosis and more than three dozen secondary processes, depending on diseases of different systems, age, gender, hormonal disorders, genetic disorders, and adverse events from drug therapy. This requires separate studies of the proposed approaches for pharmacotherapy, creates some doubts for unified recommendations and accordingly may lead to debatable problems for certain groups of patients.

The treatment of OP requires long-term use of medications. Today, both agents that normalize the mineral composition of bone tissue and drugs that affect its organic basis are used. Previously, calcium preparations were included into the standards for the treatment of bone disorders: back in 1997, studies of its 5 different salts used in Western Europe, according to the results, did not differ much from each other, were accompanied by an increase in blood calcium levels and a decrease in parathyroid hormone (especially from carbonate and citrate calcium) [7].

Along with various options for pharmacotherapy with calcium preparations, vitamin D, bisphosphonates, strontium preparations, hormone replacement therapy, and other areas that have been sufficiently studied at the level of evidence-based medicine, a number of combined approaches for the correction of OP are proposed. The proposed bone biomaterials in the review of the Chinese authors are also diverse [8].

One of the less studied new directions in the treatment of OP includes OSTEOGENON — an ossein-hydroxyapatite complex (OHC) (830 mg per tablet), manufactured by Pierre Fabre Medicament Production, France. Ossein includes bone tissue remodulators: beta-transforming growth factor (21 ng), insulin-like growth factors type I (168 ng), type II (84 ng), osteocalcin (5.8 μg), type I collagen (216 mg), which are considered to be

mitogenic for bone cells. Hydroxyapatite contains 178 mg of calcium and 82 mg of phosphorus. Osteogenon has a dual effect on bone tissue metabolism: it stimulates osteoblasts and inhibits osteoclasts. These different actions physiologically complement each other and regulate the balance between bone resorption and bone tissue repair.

**Postmenopausal Osteoporosis.** By 2009, the first meta-analysis (1966-2008) comparing the efficacy of OHC and calcium supplements in postmenopausal women was published: out of 649 publications, 18 were selected for further review, then they were limited to 6 controlled RCTs, with a number of participants of 360 people (179 in osteogenon group and 181in the calcium carbonate group). OHC has been shown to be more effective in maintaining and increasing bone mineral density (BMD), with good tolerance: the frequency of adverse reactions is less than 4% (3.2% — constipation), against 13.4-18% of calcium preparations [2].

By 2014, there were several systematic reviews and meta-analyses of the effectiveness of OHC. In the sources Medline (1966-2013), Cochrane Controlled Clinical Trials Register, Embase, a number of randomized trials confirmed its benefits in reducing pain symptoms, accelerating fracture consolidation in postmenopausal women, with various bone disorders in comparison with dietary supplements and calcium carbonate [9,10].

In postmenopausal women, the ossein-hydroxyapatite complex was more effective than calcium triphosphate [11] or calcium carbonate [12], however, in early studies there were no clinical trials to assess the risk of fractures [2], therefore OHC was considered an alternative monotherapy in postmenopausal women and during pregnancy.

In a follow-up study of 74 perimenopausal women with osteopenia, the effect of OHC (1660 mg/day) and calcium carbonate (1200 mg/day) on pain syndrome and quality of life (VAS, VRS, and SF-36 questionnaire) was assessed. After 6 months of treatment, in the osteogenon group, back and knee pain scores were significantly reduced, and quality of life scores were significantly improved; in the calcium carbonate group, the changes were insignificant [13].

In SENIAL OP in 120 women over 65 years old, for the first time in Barcelona (2000-2004), the effect of the ossein-hydroxyapatite complex at a dose of 2 tablets twice (712 mg of elemental calcium/day) and calcium carbonate (1 g of elemental calcium/day) was compared; both groups received vitamin D (calcifediol 266 mcg). The study lasted 3 years. There was a significant increase in the level of osteocalcin in the blood, BMD in the group of ossein-hydroxyapatite complex [14].

In a study conducted in Ukraine, in 67 patients over 60 years of age with osteoporotic hip fracture, compared the effectiveness of endoprosthetics only with a combination of endoprosthetics and conservative correction with strontium ranelate (2 g/day, up to 3 months) and ossein-hydroxyapatite complex (6 tablets/day, up to 6 months). The clinical effect of combination therapy was already observed after 4 weeks of treatment, the authors recommend this approach for the treatment of osteoporosis and the prevention of instability of the endoprosthesis components [15].

**Glucocorticoid Osteoporosis.** The mechanisms of this OP variant are complex and varied. Cytoplasmic glucocorticoid receptors take place on osteoblasts, realizing direct effects on bones: protein and collagen synthesis slows down, RNA synthesis in osteoblasts decreases, proliferation of osteoblast precursors decreases; on the contrary, the activity of osteoclasts is increased, as well as the secretion of parathyroid hormone, with a decrease in absorption in the intestine and reabsorption in the kidneys of calcium and phosphorus. In addition, the synthesis of active forms of vitamin D decreases. In steroid OP, damage to the bones of the axial skeleton (spine, ribs, bones of the cranial vault), pelvic bones is typical; stunted growth in children [16].

Among the early studies in the Czech Republic (292 patients — 207 women and 85 men) showed a negative effect of glucocorticoids (GC) on vitamin D metabolism, which leads to secondary hyperparathyroidism and increased bone resorption by osteoclasts. It was shown that women had steroid OP 2.5 times more often, especially in combination with other factors (hypercalciuria, immobilization). Against the background of complex therapy of steroid OP with calcium, vitamin D, OHC, bisphosphonates, an increase in BMD and a significant reduction in the number of fractures were obtained [17].

Among the secondary OP, OP in rheumatological patients, first of all, hormonal glucocorticoid (GC), often secondary to rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis and other systemic connective tissue diseases, acquires relevance. Even minimal doses of GC in such patients lead to osteopenia, which develops in the absence of preventive protection of patients [18,19]. According to the EULAR 2007 data on systemic GC therapy for rheumatic diseases, the diagnosis of OP is made when BMD in DEXA (T-index) decreases by 1.5 standard deviations from peak bone mass, this requires earlier control, including against the background of baseline calcium and vitamin D preparations [19].

The effectiveness of Osteogenon was compared with the calcium-vitamin D combination in 47 patients with rheumatoid arthritis (48.94% of patients received GC at a dose of 5-10 mg/day), divided into 2 groups. The frequency of osteopenia in these patients reached 51.1% (T-score -1.55+0.31); OP was detected in 31.9% of patients (T-score — 2.89+0.25); normal parameters of the BMD were only in 17% of patients; the duration of the observation was 6 months. One group received Osteogenon against the background of basic therapy — 2 tablets 2 times/day, calcium dose 712 mg/day; the second group is a calcium preparation with vitamin D (1000 mg and 800 IU). The results confirmed the effectiveness of osteogenon: improvement in well-being, a significant decrease in vertebrogenic pain syndrome after 6 months by 35.4% (against 9.1% in the comparison group). The increase in BMD in patients with OP was 6.9%, in patients with osteopenia 2.97% (against 1.79% and 1.54%, respectively, in the calcium-vitamin D group [19].

**Osteoporosis in Children.** One of the options for steroid OP is its development in children with a nephrotic variant of glomerulonephritis, the basic therapy of which includes prednisolone, and methylprednisolone pulse therapy is not excluded. For the correction of children's hormonal OP, complex

preparations of calcium-vitamin D3 with microelements, and vitamins (Calcitonin, Cigapan, etc.) have been proposed [16].

There have been separate studies of OP in children involved in sports. It has been shown that excessive physical activity is a risk factor for the formation of OP, although the majority of pediatricians, as the survey showed, think otherwise. When analyzing the international databases PubMed/Medline for 2011-2015, only 33 publications in this area were found [20].

Other factors contributing to the development of OP in children include: nutritional deficiencies (deficiency of protein, calcium, polyhypovitaminosis), a number of diseases, smoking, alcohol abuse, beer, as well as negative drug effects, against the background of the great needs of a growing organism. Diagnosis is based on DEXA results (Z-scores less than -2.0 SD), in addition to changes in biochemical bone markers. Even more difficult is the correction of these disorders with drugs, taking into account a number of restrictions on their use in sports [20].

In the complex treatment of osteoporotic fractures, an important place is given to the medical correction of bone remodeling. The appointment of OHC for the treatment of fractures in children with delayed formation of peak bone mass (BMD deficit 10-20% relative to the age norm), 6 tablets/day during the year, contributed to the normalization of calcium and alkaline phosphatase levels in the blood, an increase in BMD by 2-3% in the region of the femoral neck and 3-6% in the spine. Extension of therapy for another year led to the normalization of BMD in accordance with the age norm (according to DEXA) [21].

**Immobilization Osteoporosis.** A number of studies have been conducted to clarify the comparative effectiveness of osteogenon in immobilization osteoporosis. Thus, in 65 patients with terms after a high-energy injury from 4 months to 7 years, the comparative effectiveness of pharmacological correction of bone remodeling was specified (when compared in the group of osteogenon, calcium with vitamin D3 or only in surgical treatment), in 61 patients had an initial decrease in BMD to the level of osteoporosis (DEXA method, with a Z-score from -2.5 SD to -5.3 SD). Osteogenon was used after 21 days of surgical correction, 6 tablets/day for up to 3 months, then 3 tablets/day for another 3 months, doses in the comparison group for similar periods: calcium 1000 mg and 400 IU vitamin D3, then 500 mg and 200 IU (i.e., patients in both groups received the same daily amount of elemental calcium). During osteogenon therapy, the BMD of the operated limbs after 6 months increased by 5.5%, after 1.5 years — by 9.7%; terms of consolidation of false joints of the thigh were reduced by 2 months, lower legs - by 3 months. During calcium therapy with vitamin D3, an increase in BMD was observed only after 1.5 years by 1.8%, and the time for the fusion of the femur and lower leg bones decreased by 15% and 30%, respectively. During therapy with both osteogenon and calcium with vitamin D3, acceleration of bone remodeling processes was noted: after 6 months of treatment, the bone resorption marker CrossLaps in the osteogenon group was 3.1 times higher than in the comparison group; in the calcium group with vitamin D3 - 2.8 times higher than the comparison group. The dynamics of CrossLaps excretion after 6 months were different: in the groups of osteogenon and calcium with vitamin D3 — an increase in the indicator, in the comparison group - a decrease [22].

In the first 3 months, osteogenon contributed to a 3.9-fold decrease in the level of parathyroid hormone in the blood, but there was an increase after 6 months, as a reflection of the bone remodeling activation factor. Taking into account the provision of normal bone formation by macroergs (anaerobic glycolysis), the activity of LDH, then MDH, increased during osteogenon therapy. In the blood, the growth factors of this drug caused an increase in MCHC (the average concentration of hemoglobin in an erythrocyte), a decrease in the nuclear index, and indicators of anisocytosis. Vitamin D3 was characterized by stimulation of the immune system: there was an increase in phagocytosis and HCT test, with significant correlations with parathyroid hormone, CrossLaps, and granulocytosis [22,23].

The study of the effect of osteogenon on the consolidation of pseudoarthrosis of long bones complicated by immobilization OP was carried out in 73 patients in 2006-2009 (age 20-55 years) in 3 groups: osteogenon in 17 patients (at doses of 3-6 tablets/day for up to 6 months), calcium with vitamin D3 in similar doses (23 patients) and a group without pharmacological correction (33). In both groups of pharmacotherapy, there was an increase in the activity of acid and alkaline phosphatases, and a decrease in the level of parathyroid hormone compared with the control group. However, the activation of the metabolic activity of osteoblasts in patients treated with calcium and vitamin D preparations was shorter in contrast to patients treated with osteogenon. The use of osteotropic drugs in the postoperative period contributed to a reduction in the time of consolidation (by 28.6-34.3%) and the total duration of treatment compared with the control group. The absence of metabolic correction in patients led to bone loss, osteogenon contributed to the increase in BMD of the operated limb [23].

**Aseptic Necrosis.** Generalization of the problem of aseptic necrosis of the femoral head was reflected in the Clinical guidelines in 2020 [24]. The authors emphasized the relevance of this situation: in the UK 1989-2003 the incidence of pathology reached 1.4-3.0 per 100,000 population [25], in the USA by 2000 — 300,000-600,000 patients [26], in Japan - the incidence is 1.9 per 100,000 population [27], and young working age suffers, with a male predominance of 3:1. The options for diagnosis and pharmacotherapy, surgical treatment are determined by the international classification of osteonecrosis (ARCO) [28]. Basic therapy from the first days of treatment includes daily intake of calcium and vitamin D preparations, with the recommendation to use the ossein-hydroxyapatite complex, in doses of 2-4 tablets/day, under the control of blood calcium levels every 3 months, lasting up to a year. The level of 25-OH vitamin D in the blood must be kept at least 40 ng/ml. This therapy is combined with the appointment of bisphosphonates, although this pathology is not mentioned in the annotation to them (off-label intake). When more than 50% of the femoral head is affected, total joint replacement is required [24].

In Dentistry in rheumatoid arthritis, diagnosed generalized periodontitis is also accompanied by impaired bone metabolism and calcium-phosphorus metabolism, negative dynamics of

bone markers — acid and alkaline phosphatases, which were eliminated by OHC in 6 months of therapy in 123 patients [29]. Authors from Belarus are expanding their understanding of the mechanisms of influence of drugs based on synthetic hydroxyapatite in dentistry, including osteogenon [30].

In a number of experimental dental studies, a search was made for drugs that could inhibit the resorption processes of bone tissue and exhibit a periodontal protective effect. Rats with pre-modeled osteoporosis and periodontitis were treated with osteotropic therapy with six drugs, incl. osteogenon. The experiment lasted 4 months. It was found that in the osteogenon group, the highest level of acid glycosaminoglycans involved in bone tissue repair was found in the thigh bones (67.34%), the lowest in the lower jaw (20.27%); the highest level of glycosaminoglycans in the bones of the lower jaw (59.76%) was found in the Teraflex group [31].

The combined pathology of osteochondrosis of the spine and periodontal disease, which has been widespread in recent years, also mutually aggravates the mechanisms of their development, which was shown in an experiment in rats: when modeling osteochondrosis in the cervical intervertebral discs for 120 days of observation, histological methods convincingly proved the growing damage to periodontal tissues. Comparison of the treatment complex (including osteogenon 75.6 mg/kg up to 30 days) with the traditional approach to periodontal therapy showed its advantages: reduction of inflammation, perivascular resorption of bone tissue in the alveolar processes of the jaws, the presence of only individual foci of bone lysis, a decrease in the number of osteoclasts with an increased size of osteoblasts, i.e. increase in bone tissue regeneration [32].

## Conclusion.

1. Disturbances in the balance between resorption and regeneration of bone tissue (osteopenia, osteoporosis) have a complex pathogenesis, which differs depending on the underlying disease, which makes it difficult for real comparability and effectiveness of osteotropic drugs.

2. Among a number of proposed methods of pharmacotherapy, attention is drawn to the ossein-hydroxyapatite complex, the composition of which is able to stimulate adequate bone formation.

3. Evidence of the efficacy and safety of the ossein-hydroxyapatite complex is given in the review for problems of traumatology in various types of fractures, in rheumatology, in long-term hormonal therapy with glucocorticoids, in dentistry, in the age aspect and in experimental data.

4. The received recommendations for the use of osteogenon differ in different doses and duration of therapy, which contributes to the continuation of research in specific conditions, in accordance with the requirements of personalized medicine.

## REFERENCES


1. Kanis JA, Norton N, Harvey NC, et al. SCOPE 2021: a new scorecard for osteoporosis in Europe. Arch Osteoporos. 2021;16:82.
2. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to prevention and treatment of osteoporosis. Osteoporosis Int. 2014;25:2359-2381.
3. Odén A, McCloskey EV, Kanis JA, et al. Burden of high fracture probability worldwide: secular increases 2010-2040. Osteoporos Int. 2015;26:2243-2248.
4. Kanis JA, Cooper C, Rizzoli R, et al. Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019;30:3-44.
5. Kanis JA, Johansson H, Odén A, et al. Characteristics of recurrent fractures. Osteoporos Int. 2018;29:1747-1757.
6. Orlenko VL. Pathogenetic substantiation of bisphosphonates use in postmenopausal osteoporosis. Trauma. 2014;15:27-35.
7. Deroisy R, Zartarian M, Meurmans L, et al. Acute changes in serum calcium and parathyroid hormone circulating levels induced by the oral intake of five currently available calcium salts in healthy male volunteers. Clin Rheumatol. 1997;16:249-253.
8. Qu H, Fu H, Han Z, et al. Biomaterials for bone tissue engineering scaffolds: a review. RSC Advances. 2019;9:26252-26262.
9. Castelo-Branco C, Ciria-Recasens M, Cancelo-Hidalgo M, et al. Efficacy of ossein-hydroxyapatite complex compared with calcium carbonate to prevent bone loss: a meta-analysis menopausae. J North American Menopause Society. 2009;16:984-991.
10. Castelo-Branco C, Guardia JD. Use of ossein-hydroxyapatite complex in the prevention of bone loss: a review. 2014:29-37.
11. Albertazzi P, Steel SA, Howarth EM, et al. Comparison of the effects of two different types of calcium supplementation on markers of bone metabolism in a postmenopausal osteopenic population with low calcium intake: a double-blind placebo-controlled trial. Climacteric. 2004;7:33-40.
12. Ruegsegger P, Keller A, Dambacher MA. Comparison of treatment effects of ossein-hydroxyapatite compound and calcium carbonate in osteoporotic femals. Osteoporos Int. 1995;5:30-34.
13. Castelo-Branco C, Davila J, Alvarez L, et al. Comparison of the effects of calcium carbonate and ossein-hydroxyapatite complex on back and knee pain and quality of life in osteopenic perimenopausal women. Maturitas. 2015;81:76-82.
14. Ciria-Recasens M, Blanch-Rubio J, Coll-Batet M, et al. Comparison of the effects of ossein-hydroxyapatite complex and calcium carbonate on bone metabolism in women with senile osteoporosis: a randomized, open-label, parallel-group, controlled, prospective study. Clin Drug Investig. 2011;31:817-824.
15. Shimon NM, Litvak VV, Shimon MV, et al. Conservative therapy in comprehensive treatment of elderly patients after hip replacement. Trauma. 2014;15:80-81.
16. Dlin VV. Steroid osteoporosis in children with glomerulonephritis: principles of treatment and prevention. Pediatric pharmacology. 2003;1:31-34.
17. Kocian J. Steroid osteoporosis. Vnitr Lek. 1998;44:86-92.
18. Gough AK, Lilley J, Eyre S, et al. Generalized bone loss in patients with early rheumatoid arthritis. Lancet. 1994;344:23-27.

19. Kuryata AV, Karavanska IL, Lysunets TK, et al. Effect of «Osteogenon» on bone mineral density and dynamics of pain in patients with rheumatoid arthritis. Orthopaedics, traumatology, and prosthetics. 2014;2:58-62.
20. Kljuchnikov SO, Kravchuk DA, Ogannisyan MG. Osteoporosis in children and its relevance for pediatric sports medicine. Rossiyskiy Vestnik Perinatologii I Pediatrii. 2017;62:112-120.
21. Rodionova SS, Krivova AV. Osteogenon in the combined treatment of fractures. The difficult patient. 2007;5:15-18.
22. Trifonova EB, Osipenko AV, Gylnazarova SV, et al. Effect of osteotropic therapy on bone remodelling at patients witn immobilization osteoporosis. Journal "Modern Problems of Science and Education". 2015;3.
23. Gylnazarova SV, Kuznetsova OA, Trifonova YB, et al. Influence of Some Bone-Seeking Agents on Consolidation of Pseudarthrosis of Long Bones and Mineral Density of Injured Extremity. Pain Joints Spine. 2011;4:101-112.
24. Torgashin AN, Rodionova SS, Shumsky AA, et al. Treatment of aseptic necrosis of the femoral head. Clinical guidelines. Rheumatology Science and Practice. 2020;58:637-645.
25. Cooper C, Steinbuch M, Stevenson R, et al. The epidemiology osteonecrosis: finding from the GPRD and THIN databases in UK. Osteoporos Int. 2010;21:569-577.
26. Lieberman JR, Berry DJ, Mont MA, et al. Osteonecrosis of the hip: management in 21st century. Instr Course Lect. 2003;52:337-355.
27. Ikeuchi K, Hasegawa Y, Seki T, et al. Epidemiology of nontraumatic osteonecrosis of the femoral head in Japan. Mod Rheumatol. 2015;25:278-281.
28. Yoon BH, Mont MA, Koo KH, et al. The 2019 Revised Version of Association Research Circulation Osseous Staging System of Osteonecrosis of the Femoral Head. J Arthroplasty. 2020;35:933-940.
29. Kovalyshyn HV, Rozhko MM. Calcium-phosphorus exchange and bone metabolism in generalized periodontitis, which occurs on the background of rheumatoid arthritis in patient, who live in environmentally unfavorable territories. Bulletin of Problems of Biology and Medicine. 2020;3:326-331.
30. Baitus NA. Synthetic osteoplastic preparations based on hydroxyapatite in dentistry. Bulletin of the Vitebsk State Medical University. 2014;13:29-34.
31. Hodovana OI. Histochemical investigation of glycosaminoglycans of the mandibular alveolar process in pharmacological correction of experimental osteoporosis and periodontitis. Ukrainian Dental Almanac. 2016;1:7-11.
32. Kulygina VM, Tepla TO, Korol AP. Experimental rationale for method of complex treatment of parodontal disease in cervical intervertebral disk lesions. Reports of Morphology. 2016;22:258-264.

**РЕЗЮМЕ**

**ЭФФЕКТИВНОСТЬ ОССЕИН-ГИДРОКСИАПАТИТНОГО КОМПЛЕКСА КАК ФАРМАКОЛОГИЧЕСКОГО КОРРЕКТОРА ПОТЕРИ КОСТНОЙ ТКАНИ (ОБЗОР)**

**ЯКОВЛЕВА ОА, ГОЙНА-КАРДАСЕВИЧ ОЮ, ЩЕРБЕНЮК НВ.**

*Винницкий национальный медицинский университет им. Н.И. Пирогова, Украина.*

Проблема остеопороза актуальна в связи с высокой частотой его распространенности во всем мире. Сложные механизмы сохранения биомассы костной массы предполагают различные варианты их фармакологической коррекции, поэтому спектр предлагаемых лекарственных препаратов расширяется. Среди дискуссионных показаний к фармакологической коррекции остеопении и остеопороза уточняются эффективность и безопасность оссеин-гидроксиапатитного комплекса (ОГК), способствующего сохранению митогенных влияний на костные клетки. В обзоре литературы рассматриваются аспекты применения ОГК: в травматологии и хирургии при проблемных осложненных переломах, влияние как избытка, так и дефицита гормональных регуляторов у постменопаузальных женщин или в условиях длительной фармакотерапии люкокортикоидами, рассматриваются возрастные аспекты от детства до старости коррекции ОГК сопутствующего в педиатрии и гериатрии дисбаланса костной ткани, а так же уточняются механизмы позитивного влияния ОГК в экспериментальных данных. Среди нерешенных дискуссионных вопросов клинических протоколов продолжают оставаться различные дозовые аспекты, длительность терапии и конкретизация показаний по требованиям персонализированной медицины.

**Ключевые слова:** остеопороз, оссеин-гидроксиапатитный комплекс, коррекция переломов, глюкокортикоидный остеопороз, постменопаузальный остеопороз, экспериментальный остеопороз.