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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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ISOTRETINOIN THERAPY AND ITS EFFECT ON BONE HEALTH IN PATIENTS WITH ACNE VULGARIS

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Abstract.

Acne vulgaris is a common skin condition that affects mainly the dermal pilosebaceous glands, with symptoms range from open comedones to pustular cysts leading to inflammatory scars. Oral isotretinoin is used by dermatologists mainly for severe cases or resistance to topical treatments. This research determined bone health status in patients treated with a 6-month course of oral isotretinoin. The follow up duration of all 57 patients, 30 females and 27 males, who received a 0.5-1 mg/kg daily dose of oral isotretinoin through-out the study. The present investigation exhibited a significant decline in osteoblastic activity, markedly procollagen type 1 N-terminal propeptide (P1NP) and bone specific alkaline phosphatase (bsALP), accompanied by raised osteoblastic marker C-terminal telopeptide of type 1 collagen (bCTX), which suggests a shift towards bone resorption. Oxidative stress markers were also affected, with significantly decreased levels of glutathione (GSH) alongside elevated malondialdehyde (MDA). In addition, there were no such changes in liver function markers and parathyroid hormones (PTH). Such outcomes require a careful attention to bone health in patients with extended periods of oral isotretinoin therapy and in those with well-known skeletal disorders or risks.

Key words. Isotretinoin, acne vulgaris, bone health, retinoids, bone metabolism.

Introduction.

Acne vulgaris is a chronic inflammatory disorder of the skin with a prevalence as high as 85% among young patients. Acne vulgaris is associated with poor self-image leading to reduced self-esteem, anxiety and depression [1,2]. Topical retinoids, antibiotics or benzyl peroxide are considered as an effective treatment for mild to moderate cases of acne vulgaris. Systemic intervention is required for severe situations or not responding conditions to the topical therapy [3]. Isotretinoin is an oral systemic retinoid and is effective treatment for severe acne. Isotretinoin suppresses sebaceous gland secretion, keratinization and inflammation [2,4,5]. Despite the widespread use of isotretinoin, as the high prevalence of acne vulgaris in adolescents, the safety profile of the drug remains controversial because of the risk of teratogenicity and other mucocutaneous-related side effects [6,7]. Of all adverse effects, musculoskeletal pains and arthralgia accounted for 20% of the acne vulgaris patients on oral isotretinoin [8]. There is no controlled study examining the potential impact of isotretinoin on bone health among young individuals undergoing critical skeletal mineralized process.

Recent preclinical studies showed an accelerated bone resorption due to an increase in osteoclast activity in animals on high dose of isotretinoin [9,10]. However, human studies remain uncertain, but the relationship between retinoids and bone metabolism has shown increasing interest, as retinoids are associated with an increased risk of total fractures due to decreased bone mineral density following prolonged intake. This pleiotropic effect on bone mineralization occurs through interactions with nuclear receptors (RAR, RXR) that regulate the activities of osteoclasts and osteoblasts [11,12]. In contrast, other studies showed no significant bone mineral density changes or changes in bone turnover markers, such as osteocalcin, during therapy for 4-6 months of isotretinoin [13,14]. These conflict reports highlight methodological limitations in existing research, including inadequate control for confounders such as vitamin D and parathyroid hormone status.

The clinical importance of the potential effects of isotretinoin on skeletal profile for its target populations, which include adolescents and young adults whose peak bone mass attainment occurs between the ages of 13 and 20 [15]. Since most of acne vulgaris patients are adolescents and young adults, optimal bone mineralization is crucial to their growing bone health, especially when treating resistant cases that require high doses or multiple courses of retinoids. The current study measures levels of serum bone turn over markers, vitamin D3, parathyroid hormone (PTH), and oxidative stress markers to determine the possible impact of systemic intervention of isotretinoin on bone health in patients with acne vulgaris. Therefore, this research aims to clarify the skeletal safety profile of isotretinoin and provide information on the risk-benefit profile for clinicians, offering guidance on monitoring protocols for individuals at risk of osteoporosis or fractures.

Patients and Methods.

The present study is a prospective multicenter cohort study conducted in dermatology clinics across Mosul city from April 2025 to January 2026. Ethical approval was assured from the Collegiate Committee for Medical Research Ethics at the University of Mosul (Code: CCMRE-PHA-25-10) and verified for compliance with the Declaration of Helsinki of the World Medical Association. The inclusion criteria were newly diagnosed patients with severe acne vulgaris with no prior treatment for the condition. Patients presenting with mild to moderate acne vulgaris, those with chronic medical diseases or on any concurrent medication, pregnant or breastfeeding females were excluded from the study. An informed written consent form was obtained from all participants after the purpose of the study was explained to them. Moreover, participants were asked to report the development of any musculoskeletal-related symptoms throughout the study period.

The assessment of eligibility of patients was initially administered through a research questionnaire, and then approved by the clinical evaluations of dermatologists using the

Table 1. *The demographic characteristics of the study groups.*

Parameter	Baseline	AV3	AV6
BMI (kg/m²)	23.13 ± 0.26	22.75 ± 0.25	22.80 ± 0.24
GAGs score	33.54 ± 0.28	19.27 ± 0.47*	10.77± 0.67*

Results are represented as Mean ± SEM.
*Groups differ significantly ($p < 0.05$) compared to the baseline.

Table 2. *Effects of isotretinoin therapy on bone turnover markers.*

Bone Turnover Markers	Baseline	AV3	AV6
P1NP (ng/ml)	57.07 ± 4.97	47.44 ± 3.09	44.46 ± 2.67*
bsALP (U/L)	29.73 ±1.43	26.61 ± 1.22	25.3 ± 1.27*
bCTX (pg/ml)	323.10 ± 19.26	364.20 ± 16.15	395.60 ± 21.28*

Results are represented as Mean ± SEM.
*Groups differ significantly ($p < 0.05$) compared to the baseline.

Table 3. *Effects of isotretinoin therapy on liver function tests.*

Liver Function Tests	Baseline	AV3	AV6
ALP (U/L)	81.24 ± 1.30	81.35 ± 1.04	80.8 ± 1.26
AST (U/L)	23.10 ± 0.55	23.58 ± 0.63	24.70 ± 0.68
ALT (U/L)	25.60 ± 0.83	26.11 ± 0.74	27.23 ± 0.78
TSB (mg/dL)	0.68 ± 0.01	0.69 ± 0.01	0.71 ± 0.01

Results are represented as Mean ± SEM.

Table 4. *Effects of isotretinoin therapy on oxidative stress markers.*

Oxidative Stress Markers	Baseline	AV3	AV6
MDA (µmol/L)	2.12 ± 0.08	2.47 ± 0.09*	2.42 ± 0.08*
TAC (µmol/L)	1.27 ± 0.01	1.21 ± 0.02	1.24 ± 0.02
GSH (µmol/L)	6.11 ± 0.15	5.53 ± 0.15*	5.34 ± 0.15*

Results are represented as Mean ± SEM.
*Groups differ significantly ($p < 0.05$) compared to the baseline.

Table 5. *Effects of isotretinoin therapy on PTH and vitamin D.*

Biochemical Markers	Baseline group	AV3	AV6
PTH (pg/ml)	21.21 ± 1.09	20.44 ± 0.90	19.13 ± 0.87
Vitamin D (ng/ml)	19.92 ± 0.93	20.51 ± 0.83*	23.21 ± 0.94*

Results are represented as Mean ± SEM.
*Groups differ significantly ($p < 0.05$) compared to the baseline.

Global Grading Acne System [16]. A total of 57 patients (27 males and 30 females) were enrolled in the study, meeting the criteria of severe acne vulgaris.

Blood was collected from each participant at baseline and following a period therapy of 3 months and 6 months, and stored at -20°C until used for the biochemical assay. The ALLSHENG Microplate reader AMR-100 was used to measure serum P1NP (Procollagen Type 1 N-terminal Propeptide), bsALP (Bone-Specific Alkaline Phosphatase), bCTX (C-terminal telopeptide of type-1 collagen), serum vitamin D and serum parathyroid hormone (PTH) using ELISA kits provided by Shanghai Ideal Company (China). A chromate spectrophotometer/ microplate reader (USA) was used to quantify serum MDA (Malonaldehyde), Solarbio Life Science (China) provided the ELISA kit. TAC (Total Antioxidant Capacity) and GSH (Glutathione) were obtained from SUNLONG (China) and assessed using Biosan ELISA microplate reader (USA). Serum ALP (Alkaline phosphatase), AST (Aspartate aminotransferase), ALT (Alanine aminotransferase), and TSB (Total serum bilirubin) supplied by CORMAY (Poland), which were tested using an ACCENT 200 device following the manufacturer's instructions.

The documented primary acne lesions included comedones, nodulocystic lesions, pustules, and papules, which were observed across the forehead, right and left cheeks, nose, chin, upper back, and chest. Oral isotretinoin (20 mg capsule, Douglas, New Zealand) 0.5 mg/kg/day was initially prescribed for all participants during the first month. The oral dose was then subsequently escalated to 1 mg/kg/day for the remaining period of the treatment.

Statistical analysis.

All data are expressed as mean ± standard error of mean (SEM) and analyzed by GraphPad Prism 8.0 software. Repeated measures analysis of variance (one-way ANOVA) followed by Tukey's post hoc multiple comparison test was conducted on the data to compare the baseline and post-treatment groups for 3 and 6 months. A statistically significant difference with a P value of less than 0.05 was considered.

Results.

A total of 57 patients (27 males and 30 females) with an average age 20.77 ± 0.33 years. These individuals were enrolled in this study cohort and were divided into three groups; the (pre-treatment) baseline group, consisting of patients diagnosed acne vulgaris before the treatment, AV3 group, including patients with acne vulgaris who had received isotretinoin therapy for three months, and AV6 group, comprising acne vulgaris patients who had completed six months of isotretinoin therapy. The demographic characteristics of the study population, including body mass index (BMI) and GAGs score are summarized in Table 1.

At baseline, mean serum P1NP, bsALP, and bCTX levels were 57.07, 29.73, and 323.10, respectively. Following a period therapy of 3 months, there was a modest reduction in serum P1NP and bsALP with an increased bCTX levels, however, all these changes were not statistically significant compared to baseline. At 6 months, both P1NP and bsALP decreased by 22% (44.46) and 14.9% (25.30), respectively, compared to baseline ($p= 0.04$ for both), while bCTX levels showed a significant increase by 8.5% (395.6) compared to baseline ($p=0.02$) (Table 2).

Table 3 showed that serum ALP, AST, ALT, and TSB did not change significantly following 3 and 6 months of isotretinoin therapy compared to baseline.

Baseline serum MDA, TAC, and GSH were 2.12, 1.27, and 6.11, respectively. Following the three months of isotretinoin therapy, MDA increased significantly in the AV3 group compared with baseline ($p= 0.01$). The current study found that there is a significant reduction in GSH levels in AV3 group with unchanged TAC levels compared to baseline. The six months course of oral isotretinoin treatment, patients exhibited further increase in MDA levels (14%) with a reduction in in GSH readings by 12% and unchangeable levels of TAC compared to baseline statistics, as seen in Table 4.

Table 5 demonstrated that the PTH differences among groups were not significantly changed. The values of vitamin D3 were insufficient (less than 30 ng/ml) in 89.5% of patients showing a significant increased levels after six months courses of oral therapy.

Discussion.

This study evaluates the skeletal health status in acne patients on oral isotretinoin therapy through measuring bone turn over markers, PTH, oxidative stress and vitamin D3 levels. The present findings revealed that the therapeutic oral dose of 0.5-1 mg/kg/day of isotretinoin over the period of six months is associated with statistically significant changes in blood levels of bone remodelling and oxidative stress markers. Whereas, PTH and liver function tests were not affected.

The current study showed a decreased blood levels of bone formation markers (P1NP and bsALP) at the end of six months treatment period with oral isotretinoin. In contrast, higher levels of bone resorption marker bCTX were detected. These outcomes suggest shifting the remodelling balance towards a net bone resorption relative to formation. The consequences of such shifting raised a question regarding the skeletal safety profile of systemic isotretinoin, particularly for treating young adults who are in there ongoing bone growth age [17,18]. The 13-cis-retinoic acid of isotretinoin shares structural similarities with vitamin A, of which excess links to decreased osteoblastic bone formation and increased osteoclastic bone resorption [19,20]. Studies in humans and animals have shown that high dietary consumption of vitamin A and systemic isotretinoin has been associated with osteoporosis and increased fracture risk [12,21]. These effects are caused by a biological mechanism linked to the direct interaction between osteoclasts and osteoblasts. Isotretinoin alters the genetic transcription of skeletal remodelling by binding to nuclear retinoic receptors and retinoic X receptors. Retinoids suppress osteoblast differentiation and promote osteoclastogenesis, leading to an uncoupling of bone formation and resorption [22,23]. The changes in bone turnover markers observed in the present study may be explained by such an imbalance.

Importantly, parathyroid hormone levels were unchanged throughout the study, indicating a stable calcium-phosphate balance with adequate bone mineralization status in this cohort study. Additionally, the levels of ALT, AST, ALP, and TSB remained within the normal limits during the period of study, confirming a liver safety profile for isotretinoin at therapeutic doses over six months. Collectively, these changes on bone health status are not due to hyperparathyroidism or hepatic dysfunction, but may indicate a direct skeletal effect of isotretinoin.

Clinical case reports have shown a negative skeletal impact of isotretinoin, including diffuse idiopathic skeletal hyperostosis, hyperostosis, and premature epiphyseal closure, especially with long-term or high-dose isotretinoin [24-26]. The present study contributes to the body of literature by showing that even a conventional standard regimen of isotretinoin carries a risk when given over an extended period or to susceptible individuals. Notably, no patients reported any significant musculoskeletal symptoms throughout the study. Nevertheless, the asymptomatic nature of the early bone loss necessitates the need for close observation, particularly in patients with additional risk factors such as low body mass index, low physical activity, or concurrent use of corticosteroids [27,28]. While routine evaluation of bone mineral density is not required for all patients, but should be considered for those with long or repeated therapy.

Over the course of 6 months of therapy with isotretinoin, serum levels of MDA, a byproduct of lipid peroxidation, were increased, suggesting elevated oxidative stress. In contrast, GSH, a key intracellular antioxidant, was decreased, indicating a reduction in antioxidant defense under prolonged exposure to reactive oxygen species. This shift is in line with the imbalance response between oxidants and antioxidants produced by isotretinoin [29]. Oxidative stress is known to prevent osteoblastic differentiation and activity with promoting osteoclastogenesis, likely via modulation of the RANK/RANKL/OPG pathway, and reduce expression of osteoblast differentiation markers such as ALP and osteocalcin [30]. Thus, the observed imbalance of systemic redox status may be influenced by the effects of retinoids.

Despite the significant elevated concentrations of vitamin D, they were just above the sufficiency threshold. Although this modest elevation rules out vitamin D deficiency as a confounder, it is unlikely to fully counteract the oxidative stress effects on stimulating osteoclast activity or suppressing osteoblast function. Thus, the activity of isotretinoin on bone remodelling seems to override the mild supportive effect of adequate vitamin D levels. Additionally, the increase in vitamin D over the follow-up periods that extended into winter months, when serum vitamin D expected to be declined because of diminished sunlight exposure [31,32], could be due to self-initiated supplementations, lifestyle factors, or even the buffering effects of maintaining proper calcium homeostasis to counteract negative effects on bone metabolism. The standardized evaluations of vitamin D and/or A supplementations, dietary intake, sun exposure and even lifestyle modifications, all of which might also alter bone remodelling process, should be considered in future studies.

In light of our results, patients should be counselled regarding the skeletal safety profile of isotretinoin therapy. Clinicians might opt to measure the baseline serum of vitamin D3 with possible supplementation of calcium and vitamin D3 to minimize the negative effects of prolonged isotretinoin therapy for high-risk individuals.

A key limitation of the present prospective longitudinal cohort study is the absence of matched age and sex healthy control not receiving isotretinoin. This longitudinal design considered each participant baseline values as own control, reducing inter-individually variations with measurements obtained at 3 and 6 months following treatments. However, it cannot totally rule out the potential impact of temporal changes or other extrinsic factors on bone remodelling or oxidative stress markers. Future studies involving a matched control group would help to differentiate drug-related effects from natural physiological variations.

Conclusion.

In conclusion, management of severe acne vulgaris patients with standard isotretinoin therapy over six-month treatment periods is associated with bone remodelling imbalance favors the increase in bone resorption over bone formation in combination with increased oxidative stress. There were no significant changes in liver function and PTH suggest early phase of bone resorption that can be overlooked by clinicians in prolonged therapy.

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Ethics approval and consent to participate.

Ethical approval for this study was obtained from the Collegiate Committee for Medical Research Ethics at the University of Mosul (Code: CCMRE-PHA-25-10) and the study was conducted in accordance with the Declaration of Helsinki of the World Medical Association. All participants were provided with clear explanation of study objectives, and written consent was requested was obtained from each participant.

Competing interests.

The authors declare that they have no competing interests.

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