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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 ВИНТИ 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 ВИНТИ 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. Корректур авторам не высылаются, 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 computer-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 საყურადღებო!

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, შემავსებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრაფიის ფოტოსურათები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგების 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 ფხიხლებში 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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BIOMARKERS OF BONE REMODELING AND INFLAMMATION IN CHRONIC PERIAPICAL LESIONS: A NARRATIVE REVIEW

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Abstract.

Background: Chronic periapical lesions are inflammatory conditions that cause ongoing destruction of the alveolar bone. While microbial infection is known to be the initial cause, the complex interplay between the types of microbes present, immune responses, factors affecting the whole body, and bone remodeling processes is not yet fully understood.

Objectives: This narrative review summarizes current evidence on how bone metabolism changes in chronic periapical lesions. It also examines the roles of inflammatory mediators, osteoimmune pathways, systemic factors, and imaging techniques in understanding how the disease progresses and how well it can heal.

Methods: A narrative search was performed across electronic databases, including PubMed, Scopus, and Web of Science, for relevant studies. These studies investigated chronic periapical lesions, bone metabolism markers, inflammatory pathways, vitamin D levels, systemic factors, and imaging assessments. We analyzed evidence concerning biomarkers of bone formation and resorption, osteoclast activation, and bone remodeling mechanisms.

Results: Current evidence shows that biofilms in root canals trigger the release of pro-inflammatory substances. This leads to higher levels of RANKL and lower levels of osteoprotegerin (OPG), which encourages the development of osteoclasts and the breakdown of bone matrix. Markers of bone resorption, such as CTX and TRACP5b, are frequently reported as elevated, while markers of bone formation, including BALP, osteocalcin, and PINP, show variable or minor changes. Systemic factors like vitamin D deficiency, diabetes, smoking, and alcohol consumption are observationally associated with impaired healing. Cone-beam computed tomography (CBCT) offers a better volumetric assessment compared to traditional X-rays.

Conclusions: Chronic periapical lesions are characterized by a complex osteoimmune imbalance. While integrating biomarkers with advanced imaging represents a promising research avenue, further validation is required before these strategies can be implemented in routine clinical practice.

Key words. Chronic apical periodontitis, periapical lesions, bone metabolism, osteoimmunology, RANKL/OPG pathway, vitamin D, biomarkers, CBCT.

Introduction.

Periapical lesions comprise a spectrum of acute and chronic inflammatory pathologies of endodontic origin that develop around the tooth apex and may result in resorption and destruction of the surrounding alveolar bone [1]. Microbial infection of the root canal system plays a central role in the initiation and progression of apical periodontitis, with microorganisms and their products contributing to inflammatory responses in the periapical tissues and subsequent periapical bone destruction [1,2]. Within this pathological spectrum, apical periodontitis is a highly prevalent disease worldwide, with systematic review and meta-analysis data demonstrating a substantial prevalence across diverse adult populations [2]. Persistent periapical inflammation may contribute to the development of periapical cysts, which are associated with the proliferation of epithelial cell rests of Malassez in the context of chronic inflammatory stimulation [1,3]. Histologically, periapical cysts are characterized by a fibrous connective tissue wall lined by non-keratinized stratified squamous epithelium and may contain cholesterol clefts. Their detection and radiographic assessment can be supported by conventional periapical radiography and cone-beam computed tomography (CBCT), with CBCT demonstrating greater sensitivity for the detection of periapical lesions than conventional periapical radiography in certain clinical settings [4,5].

The biological repercussions of chronic periapical infections may extend beyond local tissue boundaries, with observational studies highlighting potential links to systemic inflammatory responses [6]. Epidemiological and integrative data suggest an observational association between untreated apical periodontitis and cardiovascular parameters, such as endothelial markers [6]. This systemic burden is characterized by a continuous spillover of pro-inflammatory mediators and bacterial byproducts into the bloodstream, which may contribute to systemic endothelial stress [6,7]. A primary molecular mechanism driving this link is oxidative stress; severe periapical inflammation induces both local and systemic oxidative stress through the excessive production of reactive oxygen species (ROS) and lipid peroxidation, which is biologically linked to vascular health [7,8]. Consequently, clinical evidence demonstrates that non-surgical endodontic therapy can modify these serum inflammatory markers, decreasing peripheral biomarkers,

though these changes primarily reflect localized inflammatory reduction rather than definitive cardiovascular disease prevention [7,9]. The systemic modulation of periapical and periodontal health is further influenced by metabolic diseases and lifestyle-related factors, which may affect host responses, inflammation, and bone metabolism. Clinical and epidemiological evidence indicates an association between diabetes mellitus and an increased prevalence of radiolucent periapical lesions in root-filled teeth [10]. This association may be related, at least in part, to diabetes-associated alterations in immune responses, inflammation, and tissue repair [10]. In addition to systemic metabolic diseases, lifestyle factors such as tobacco smoking may exert additional inflammatory and toxicological stress. In an experimental animal model, chronic cigarette smoke inhalation enhanced periapical bone resorption associated with apical periodontitis, potentially through increased inflammatory responses and osteoclast-mediated bone resorption [11]. Furthermore, endocrine dysfunctions, including alterations in thyroid function, have been associated with periodontal health outcomes, providing indirect biological insights regarding alveolar bone dynamics [12].

Finally, broader evidence from umbrella and systematic reviews indicates potential associations between apical periodontitis and a range of chronic systemic diseases, with inflammatory pathways representing a possible common biological link between local oral infection and systemic health [13,14].

At the intersection of systemic bone metabolism and chronic oral inflammation, vitamin D status emerges as an important factor influencing skeletal health and inflammatory responses. Vitamin D plays an important role in maintaining bone health and may contribute to the regulation of immune and inflammatory processes; accordingly, lower serum vitamin D levels have been associated with chronic inflammatory periodontal conditions and impaired skeletal health [15,16].

When a vitamin D deficiency occurs, it frequently triggers secondary hyperparathyroidism, where elevated levels of parathyroid hormone (PTH) serve as a clinical marker of bone fragility, significantly accelerating alveolar bone resorption and tissue destruction within periodontitis and endodontic pathologies [17,18]. Vitamin D status and its supplementation dynamically modulate systemic serum levels of bone turnover markers and bone remodeling responses in humans [19]. Because of these tight biological links, ensuring adequate vitamin D status may support bone metabolism and healing responses, and clinical observations suggest that vitamin D optimization may be associated with improved healing of periapical lesions following endodontic treatment [20]. Although clinical data specifically targeting endodontic lesions remain evolving, observational evidence extrapolated from periodontal surgical outcomes suggests that baseline vitamin D status may influence postoperative bone recovery dynamics [21]. Conversely, when biochemical markers such as osteocalcin, CTX-1, and bone alkaline phosphatase are altered due to metabolic deficiencies, patients present with lower bone mineral density and a substantially increased risk of persistent periapical lesions [3,22].

Historically, periapical lesions have been evaluated using conventional two-dimensional radiographs; however, modern

cone-beam computed tomography (CBCT) provides significantly higher prospective accuracy and sensitivity in detecting early cortical bone loss and tracking the true dimensional extent of periapical paths [5,23]. Alongside advanced imaging, assessing localized structural alterations in the alveolar bone relies on detecting specific biochemical profiles; tissue-specific bone resorption biomarkers and altered levels of salivary or serum mineral components (partly extrapolated from periodontal models) are associated with lesion dynamics [24,25].

Furthermore, recent scientific mapping confirms that untreated odontogenic infections can quickly expand into extensive fascial spaces if local microbial loads are not completely eradicated [26]. To improve treatment outcomes and maximize root canal disinfection favoring periapical bone recovery, modern clinical research is exploring adjunctive therapies; for instance, using a diode laser alongside conventional irrigation has demonstrated high efficacy in eliminating persistent intracanal biofilms and supporting healing rates in chronic apical periodontitis [27]. This narrative review aimed to synthesize current evidence on the biological mechanisms underlying bone remodeling and osteoimmune dysregulation in chronic periapical lesions. Specifically, this review aimed to examine the role of inflammatory mediators and the RANKL/OPG pathway in periapical bone resorption; evaluate the clinical importance of biomarkers that indicate bone formation and resorption; assess how systemic factors influence endocrine, metabolic, and lifestyle-related factors, such as vitamin D status, diabetes, smoking, and alcohol consumption, on disease progression and healing; and explore how advanced imaging techniques, especially cone-beam computed tomography (CBCT), might be used to monitor changes in periapical bone and assess treatment results. By combining these biological, systemic, and diagnostic viewpoints, this review also aimed to pinpoint current gaps in knowledge and highlight new possibilities for using biomarkers and personalized strategies to manage chronic periapical lesions.

Methods.

To ensure comprehensive narrative synthesis of the literature for this narrative review, a structured literature search was conducted across major electronic databases, including PubMed/MEDLINE, Scopus, and Web of Science up to January 2026. The search strategy was designed to identify peer-reviewed literature addressing the intersection of endodontic pathology, bone metabolism, osteoimmune mechanisms, bone turnover biomarkers, systemic modifying factors, and advanced diagnostic imaging. As this is a narrative review, the methodology focuses on providing a comprehensive overview rather than adhering to formal PRISMA systematic review protocols.

The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords, where applicable, using the Boolean operators AND and OR. The core search concepts included combinations of the following terms: ("chronic apical periodontitis" OR "periapical lesions" OR "radicular cyst") AND ("bone metabolism" OR "osteoimmunology" OR "RANKL/OPG") AND ("vitamin D" OR "biomarkers" OR "bone turnover markers") AND ("cone-beam computed tomography" OR "CBCT"). The electronic search was supplemented by manual

screening of the reference lists of relevant retrieved articles and reviews to identify additional relevant studies that might have been omitted during the initial database search. No strict publication-year restriction was applied in order to provide an appropriate historical context for the development of the field; however, particular emphasis was placed on recent and high-impact literature, especially studies published during the past two decades. Titles and abstracts were independently screened by two authors, followed, where appropriate, by assessment of the full texts against the predefined eligibility criteria. Any disagreements regarding study relevance or eligibility were resolved through discussion and consensus between the two authors.

Inclusion and Exclusion Criteria.

Appropriate eligibility criteria were established to maintain the scientific relevance of the synthesized evidence.

Inclusion Criteria: The scope was limited to peer-reviewed primary research articles, randomized and non-randomized clinical trials, cohort studies, case-control studies, cross-sectional observational studies, and relevant systematic reviews. Eligible studies had to investigate the molecular mechanisms of periapical bone destruction, local and systemic biomarkers of bone turnover, or the clinical utility of advanced imaging modalities (specifically CBCT) in diagnosing or monitoring these lesions. Only studies published in the English language were considered.

Exclusion Criteria: Editorials, conference abstracts, technical notes, case reports with limited sample sizes, and studies utilizing poorly defined diagnostic criteria for periapical lesions were excluded from the final synthesis. Given the narrative nature of this synthesis, formal risk-of-bias assessment tools were not applied across all retrieved studies; however, methodological characteristics were qualitatively considered during evidence synthesis.

Results.

Local Inflammatory Profiles and Bone Metabolism Biomarkers:

The evaluation of molecular markers in chronic periapical pathology reveals a distinct shift in bone turnover and localized immune responses.

Bone Resorption vs. Formation: Narrative evidence indicates that C-terminal telopeptide of type I collagen (CTX) serves as the most sensitive marker for bone resorption, whereas procollagen type I N-terminal propeptide (PINP) and bone-specific alkaline phosphatase (BALP) predominantly reflect bone formation pathways.

Periapical Cysts Characteristics: In an observational clinical setting, patients presenting with periapical inflammatory cysts demonstrated elevated CTX levels and concurrent vitamin D (25OHD) deficiency, while BALP and osteocalcin exhibited limited clinical variations.

Cytokine and Osteoclastogenesis Activation: Chronic apical periodontitis lesions are consistently characterized by increased expression of pro-inflammatory cytokines, including interleukins (IL-1 β , IL-6, and IL-17) and tumor necrosis factor- α (TNF- α). This sustained inflammatory environment

triggers osteoclastogenesis via the activation of the receptor activator of nuclear RANKL/OPG signaling pathway.

Oxidative Stress and Clinical Standardization: Systematic data confirms that apical periodontitis is strongly linked with elevated reactive oxygen species (ROS) and increased local and systemic oxidative stress markers. However, despite a consistent association between multiple bone or inflammatory biomarkers and apical periodontitis, pronounced study heterogeneity continues to limit formal clinical standardization.

Systemic Comorbidities and Modifying Health Factors:

Periapical pathology does not occur in isolation; its severity and biomarker expression are significantly modulated by systemic health status and chronic metabolic diseases.

Clinical observational data demonstrates that diabetes enhances the expression of bone resorption biomarkers specifically altering RANKL and OPG dynamics in patients diagnosed with apical periodontitis.

Systemic bone density loss appears to have a compounding effect on periapical tissues, as evidence suggests that osteoporosis may increase both the overall prevalence and structural severity of apical periodontitis.

Systemic Health Links: Extensive evidence from umbrella and systematic reviews suggests an observation association between chronic apical periodontitis and multiple systemic conditions, underscoring that periapical inflammation may present potential systemic health interactions mediated by circulating inflammatory markers.

Exogenous toxicological factors play a detrimental role in accelerating tissue destruction in experimental models of apical periodontitis.

In experimental models of apical periodontitis, chronic exposure to alcohol was found to intensify localized inflammation, resulting in increased bone resorption driven by elevated levels of TNF- α , RANKL, and tartrate-resistant acid phosphatase (TRAP)-positive osteoclasts.

Similarly, experimental evaluation in rat models revealed that cigarette smoke exposure significantly elevates TRAP expression, thereby amplifying osteoclast activity and escalating alveolar bone destruction.

Therapeutic interventions and targeted supplementation demonstrate a direct capacity to mitigate inflammation and restore balanced bone signaling.

In prospective clinical evaluations involving complex cohorts, such as patients with concurrent cardiovascular disease and apical periodontitis, the administration of root canal treatment successfully reduced high-sensitivity C-reactive protein (CRP) alongside other systemic inflammatory biomarkers, supporting localized periapical healing. Preliminary clinical evidence from a randomized trial indicates that targeted Vitamin D supplementation may enhance the radiographic healing rate of periapical lesions, though broader clinical validation is required before establishing routine protocols.

At a narrative level, complete periapical bone healing is determined to be highly dependent on the successful restoration of balanced osteoimmune signaling specifically involving Wnt, transforming growth factor-beta (TGF-beta), and the RANKL/OPG axis alongside the subsequent activation of regenerative pathways. Table 1 represents a curated summary of key

representative studies rather than an exhaustive systematic repository.

Discussion.

The Osteoimmune Imbalance: RANKL/OPG Axis and Cytokine Networks:

This review highlights a complex, interconnected system where bone metabolism and the host immune system interact dynamically to regulate tissue destruction within chronic periapical lesions. From a pathophysiological standpoint, apical periodontitis is characterized by a persistent biomolecular imbalance in which localized bone resorption significantly exceeds bone formation, a phenomenon triggered by intracanal microbial factors, sustained host immunopathology, and systemic metabolic conditions [1,2,6,26]. Root canal biofilms are central to periapical bone destruction because they activate the host's osteoimmune response. These intricate microbial

communities release endotoxins, such as lipopolysaccharide (LPS) and lipoteichoic acid, which infiltrate the periapical space and trigger severe localized inflammation [2,27]. Neutrophils and macrophages, acting as early cellular responders, create a self-sustaining cycle that maintains the recruitment of white blood cells and promotes ongoing inflammatory signals [2]. This chronic inflammatory microenvironment is marked by a notable elevation of pro-inflammatory cytokines at the local site, including interleukin-1 beta (IL-1 β), IL-6, IL-17, and tumor necrosis factor-alpha (TNF- α) [2]. These cytokines act as powerful upstream signals that directly modulate the RANKL/RANK/OPG axis [2,6]. When local levels of receptor activator of nuclear factor- κ B ligand (RANKL) increase, they encourage the development, fusion, and activation of pre-osteoclasts [1,2]. In contrast, the decoy receptor osteoprotegerin (OPG), which typically prevents RANKL from binding to RANK, is frequently downregulated. This shifts the local RANKL/

Table 1. Summary of key representative studies investigating bone turnover biomarkers, inflammatory pathways, and systemic modifiers in chronic periapical lesions.

Study	Study Design	Population / Model	Main Biomarker(s)	Principal Findings
Cazzolla et al., 2025	Observational clinical study	Patients with periapical inflammatory cysts	25OHD, CTX, BALP, Osteocalcin	Vitamin D deficiency and elevated CTX were associated with periapical inflammatory cysts, whereas BALP and osteocalcin showed limited differences.
Braz-Silva et al., 2019	Literature review	Chronic apical periodontitis	IL-1 β , IL-6, TNF- α , IL-17, RANKL/OPG	Chronic lesions exhibit elevated inflammatory cytokine levels and activation of osteoclastogenesis via the RANKL/OPG pathway.
Matos-Sousa et al., 2024	Systematic review	Human studies	Multiple inflammatory and bone biomarkers	Biomarkers are consistently associated with apical periodontitis, although study heterogeneity limits clinical standardization.
Schini et al., 2023	Narrative review	Bone metabolism	CTX, PINP, BALP, Osteocalcin	CTX is the most sensitive marker of bone resorption, while PINP and BALP primarily reflect bone formation.
Georgiou et al., 2021	Systematic review	Human and experimental studies	ROS, oxidative stress markers	Apical periodontitis is associated with increased local and systemic oxidative stress.
Sarmento et al., 2020	Clinical observational study	Diabetic and non-diabetic patients	RANKL, OPG, bone resorption markers	Diabetes enhances expression of bone resorption biomarkers in apical periodontitis.
Maraş et al., 2026	Randomised clinical trial	Patients with apical lesions	Vitamin D supplementation	Vitamin D supplementation accelerated radiographic healing of apical lesions.
Martins et al., 2025	Systematic review (animal studies)	Experimental apical periodontitis	TNF- α , RANKL, TRAP-positive osteoclasts	Chronic alcohol exposure intensified inflammation and increased bone resorption.
Veiga Vasques et al., 2024	Experimental animal study	Rats	TRAP, inflammatory markers	Cigarette smoke significantly increased osteoclast activity and alveolar bone destruction.
Bhardwaj et al., 2025	Prospective clinical study	Patients with cardiovascular disease and AP	hs-CRP, inflammatory markers	Root canal treatment reduced systemic inflammatory biomarkers and promoted healing.
Reiser et al., 2026	Narrative review	Periapical lesions	Wnt, TGF- β , RANKL/OPG	Bone healing depends on restoration of balanced osteoimmune signalling and activation of regenerative pathways.
Pestana de Vasconcelos et al., 2024	Systematic review	Human studies	Osteoporosis and AP	Osteoporosis may increase the prevalence and severity of apical periodontitis.
Pinto et al., 2023	Umbrella review	Chronic diseases and AP	Systemic inflammatory markers	Strong evidence supports an association between apical periodontitis and several systemic diseases.
Venugopal et al., 2025	Systematic review	Observational studies	Systemic inflammatory markers	Chronic apical periodontitis demonstrates clinically relevant systemic health associations.

Note: Table 1 represents a curated summary of key representative studies illustrating core biological themes, rather than an exhaustive systematic repository.

Figure 1 | Osteoimmune pathways and systemic modifiers in chronic periapical lesions

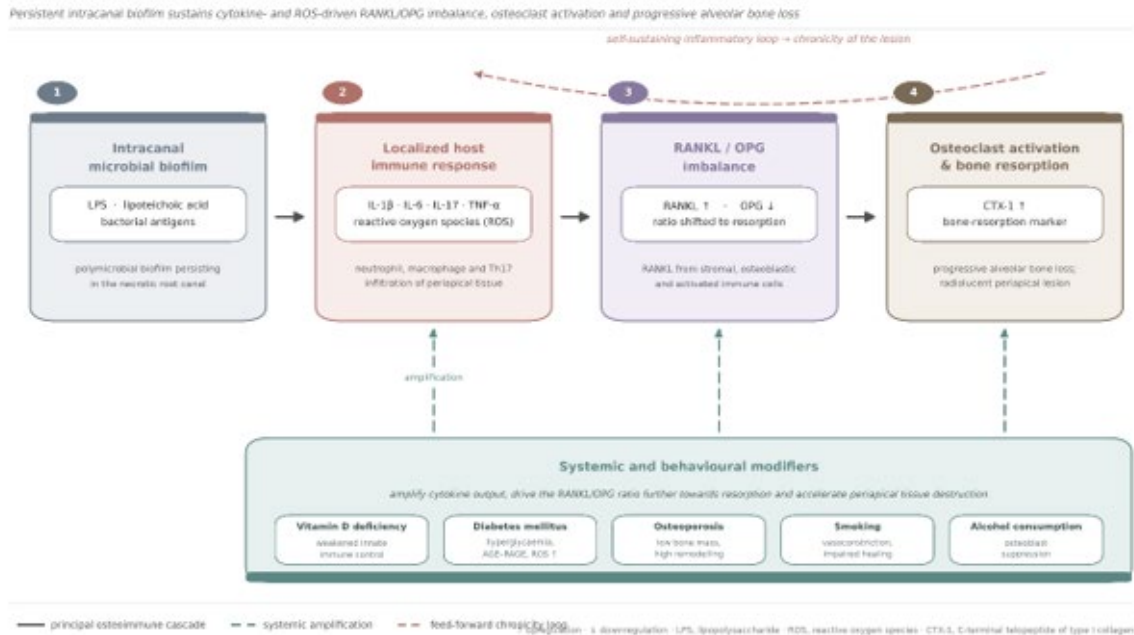


Figure 1. Osteoimmune pathways and systemic modifiers in chronic periapical lesions.

Persistent intracanal microbial biofilms release bacterial antigens like LPS and lipoteichoic acid that trigger a localized host immune response, driving the production of pro-inflammatory cytokines such as IL-1 beta, IL-6, IL-17, TNF-alpha and reactive oxygen species ROS. This inflammatory cascade alters the RANKL OPG ratio toward bone resorption, leading to osteoclast activation and progressive alveolar bone loss marked by elevated CTX-1. Systemic and behavioral modifiers including vitamin D deficiency, diabetes mellitus, osteoporosis, smoking, and alcohol consumption further amplify cytokine output and accelerate tissue destruction.

OPG ratio upward, serving as a direct molecular indicator of active bone breakdown [1,2]. Proinflammatory cytokines and endotoxin-stimulated macrophages also increase the release of destructive matrix metalloproteinases and cathepsin K, which degrade type I collagen, the main structural component of the jawbone [2,24]. While these enzymatic pathways mediate local tissue degradation, specific biomarkers of bone resorption, such as C-terminal telopeptide of type I collagen (CTX-1), require careful interpretation as they may also reflect broader skeletal turnover rather than isolated periapical destruction [3]. Interestingly, markers of bone formation, including bone-specific alkaline phosphatase (BALP) and osteocalcin (OC), show limited clinical variations in patients with periapical inflammatory cysts [1]. BALP, an enzyme essential for depositing hydroxyapatite, and OC, which binds calcium in the matrix, fail to increase dynamically enough to keep pace with osteoclastogenesis [3]. However, looking toward future diagnostic paradigms, advanced digital technologies can frameworks represent an emerging direction in dental medicine [28].

Systemic, Endocrine, and Metabolic Modifiers of Jawbone Homeostasis:

Periapical bone remodeling is not merely a localized event; it appears to be influenced by the patient's systemic health status, endocrine balance, nutritional factors, and exogenous lifestyle habits [6,13,14]. Among the systemic metabolic comorbidities, diabetes mellitus stands out as a critical clinical factor that accentuates localized bone resorption. The chronic hyperglycemic environment alters the RANKL/OPG

balance, suppressing osteoblastic bone repair and accelerating immunoexpression of bone resorption biomarkers, which directly delays periapical healing and manifests as larger radiolucant areas in root-filled teeth [10,29].

In addition to metabolic diseases, toxicological modifiers related to patient lifestyle habits play a detrimental role in speeding up tissue destruction. However, it is essential to note that much of the available evidence regarding chronic alcohol consumption and tobacco smoke inhalation stems from experimental animal models or observational studies in periodontal populations. While animal models demonstrate that alcohol and cigarette smoke alter host immune pathways, elevate TNF- α and RANKL, and compromise local microvascular circulation to increase alveolar osteoclast activity, these findings represent biological plausibility and cannot be directly translated into the exact magnitude of clinical effects in human apical periodontitis. Similarly, while systemic endocrine conditions like thyroid disorders alter systemic bone turnover, direct clinical evidence specifically linking thyroid dysfunction to chronic periapical lesions remains limited and relies largely on indirect extrapolated data from periodontal research. Furthermore, while conditions such as periapical cysts, apical periodontitis, and periodontal disease share common immune-inflammatory mechanisms, they represent distinct clinical entities and their diagnostic markers should not be used interchangeably.

Endocrine Regulation via Vitamin D and Parathyroid Hormone:

Central to these systemic influences is the metabolic status of Vitamin D [25(OH)D], which exerts potent endocrine,

anti-inflammatory, and antimicrobial actions within periapical pathologies. In deficient states, the physiological suppression of local pro-inflammatory networks is lost, leading to ongoing infection and increased osteoclast activation [3,15]. Vitamin D deficiency has been observationally associated with lower bone mineral density, chronic inflammatory responses, and a significantly higher prevalence of large, destructive periapical cysts and lesions [3,16,31]. Furthermore, vitamin D deficiency and inadequate dietary intakes frequently trigger secondary hyperparathyroidism; elevated serum levels of parathyroid hormone (PTH) serve as a prominent marker of bone fragility, accelerating bone loss and fracture risks across adult populations [16-18]. While preliminary clinical trials suggest that Vitamin D supplementation may support radiographic healing rates, observational associations do not establish direct causality, and routine Vitamin D supplementation should be viewed as a promising adjunctive consideration rather than an established clinical standard of care or a universally required therapeutic target [20,32].

Integrating Volumetric Imaging with Biomarker Profiling and Interventional Outcomes:

A primary clinical challenge in endodontics is distinguishing between active, progressing periapical lesions and stable, healing tissues. Standard two-dimensional periapical radiographs are fundamentally limited in detecting early mineralized bone loss and significantly underestimate the true volumetric extent of periapical and periodontal defects [4,5,23]. Cone-beam computed tomography (CBCT) effectively resolves these diagnostic limitations by offering precise three-dimensional volumetric measurements, which are critical for accurate pre-operative status assessment and long-term monitoring [4,5,23]. Combining this advanced three-dimensional imaging with biochemical analysis provides a promising conceptual framework, though currently an area of ongoing research rather than an established clinical diagnostic algorithm. Because bone turnover markers follow distinct timelines during healing phases, a persistent radiolucency seen on a CBCT scan can be clinically deemed benign and healing if accompanied by a notable biological drop in bone resorption markers and a simultaneous stabilization of structural matrix proteins [1,5,33]. The clinical efficacy of endodontic treatment is clearly evident both locally and systemically. Successfully removing the microbial biofilm through non-surgical root canal treatment eliminates the primary localized stimulus driving osteoclastic activity. In patients presenting with complex comorbidities, such as concurrent cardiovascular disease, successful endodontic intervention has been associated with reductions in systemic inflammatory risk markers, including high-sensitivity C-reactive protein (hs-CRP) and circulating serum cytokines [9,13,14]. However, while reductions in systemic surrogate biomarkers are observed post-treatment, current evidence does not demonstrate that endodontic therapy directly prevents cardiovascular disease or atherosclerosis, and these observational associations must not be interpreted as definitive causal effects [6,9,13,14]. Furthermore, to optimize clinical outcomes, modern protocols increasingly utilize advanced adjunctive methods; implementing a diode laser alongside conventional irrigation provides high efficacy

in eradicating persistent intracanal biofilms and promoting accelerated tissue repair [27]. This comprehensive approach underscores that complete periapical bone healing depends heavily on eliminating local irritants to enable targeted metabolic, molecular, and clinical recovery [1]. Future research should therefore explore the integration of these technologies with CBCT-based volumetric analysis and biomarker profiling to improve diagnostic accuracy, longitudinal monitoring, and individualized treatment planning in patients with periapical disease.

Methodological Challenges, Study Limitations, and Research Directions:

Despite the strong biological rationale for using biomarkers in clinical diagnostics, several significant obstacles remain. It is critical to distinguish between biomarkers of pathophysiological mechanisms and validated diagnostic tools, as involvement in disease pathways does not automatically confer clinical diagnostic utility. The main challenge is the wide variation in research methods used, especially in the types of samples collected (such as gingival crevicular fluid, saliva, periapical fluid, or blood) and the testing platforms employed [2,24]. While local fluids like saliva provide a minimally invasive view into the oral microbiome, systemic biomarkers like CTX-1, parathyroid hormone, and active Vitamin D are highly responsive to wider skeletal, postmenopausal, and nutritional changes [16,17,33]. Furthermore, much of the existing research carries a risk of bias because critical confounding factors, such as smoking, alcohol consumption, medication use, age, socioeconomic variables, and dental caries indexes, are not always adequately controlled for [11,13,30]. Additionally, the current literature is constrained by publication bias, language restrictions in study selection, heterogeneity in study designs, and a reliance on indirect extrapolations from periodontal and systemic bone research. Future long-term studies should focus on standardized panels of multiple biomarkers. These panels should integrate local cytokines and oxidative stress markers with advanced CBCT volumetrics to fully achieve personalized patient management centered on osteoimmunity [1,5,24].

Conclusion.

In summary, this review emphasizes that the development and healing of chronic periapical lesions are controlled by a dynamic, localized bone-immune system that is closely linked to overall metabolic and endocrine health. By outlining the molecular processes of bone destruction and repair in apical periodontitis, we can reach several key conclusions:

Periapical bone destruction stems from a significant imbalance in bone remodeling. The local inflammatory response to root canal biofilms alters the RANKL/OPG ratio, favoring the formation of osteoclasts. This localized breakdown is characterized by elevated markers of bone resorption, whereas markers of bone formation do not dynamically increase to match the rate of destruction.

The turnover of bone in the periapical region is modulated by broader systemic modifiers. Addressing nutritional status, such as optimizing Vitamin D levels, and managing systemic metabolic conditions like diabetes mellitus may serve as promising adjunctive measures to support host immune

responses and periapical healing. Conversely, animal models and observational data suggest that exposure to cigarette smoke and chronic alcohol consumption negatively influence alveolar tissue preservation, though clinical translation requires further validation.

While standard two-dimensional radiographs remain the primary post-treatment imaging tool, three-dimensional CBCT volumetric analysis provides superior accuracy in detecting lesion resolution. Integrating CBCT volumetric tracking with localized biochemical profiling represents a compelling future research direction to help distinguish active from healing tissues, though it requires standardized clinical validation before widespread implementation.

Clinical Implications and Future Outlook.

Achieving optimal endodontic outcomes requires thorough microbial biofilm eradication alongside considerations of host systemic health. While routine adjunctive systemic therapies remain an area of ongoing investigation, evaluating overall patient metabolic stability may support local tissue repair.

To translate these biological insights into future practice, research must focus on standardizing non-invasive biomarker collection methods (such as gingival crevicular fluid or saliva) and validating multi-biomarker panels in well-controlled longitudinal trials. Furthermore, combining standardized biochemical profiles with advanced 3D volumetric imaging—and potentially prospective digital diagnostic tools—may eventually facilitate personalized, precision-guided endodontic management.

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