GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 4 (349) Апрель 2024

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

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.

GEORGIAN MEDICAL NEWS
No 3 (348) 2024

Содержание:

GEORGIAN MEDICAL NEWS
No 4 (349) 2024

THE IMPACT OF SYSTEMIC DRUGS ON DENTAL IMPLANT OSSEOINTEGRATION: A REVIEW

Vullnet Fazliu[1,2], Aferdita Gashi-Rizaj[3], Yll Krasniqi[2]*, Venera Bimbashi[4,5].

[1]*Department of Oral Surgery, UBT – Higher Education Institution, Prishtina, Republic of Kosovo.*

[2]*Private dental Clinic "OSS Dental Art's" Prishtina, Republic of Kosovo.*

[3]*Department of Pediatric Dentistry, UBT – Higher Education Institution, Prishtina, Republic of Kosovo.*

[4]*Department of Prosthodontics, University Dentistry Clinical Center of Kosovo.*

[5]*Department of Prosthodontics Alma Mater Europaea, Campus College Rezonanca, Prishtina, Republic of Kosovo.*

Abstract.

The process of osteointegration of dental implants is a biological process. Systemic therapy can interfere with this process, affecting the growth and breakdown processes of the bone and ultimately leading to implant failure. This literature review focuses on specific groups of systemic drugs that directly impact osteointegration.

Materials and methods: The research in electronic literature was conducted using the National Library of Medicine's PubMed/MEDLINE database from March 2000 to February 2024. The following MeSH (Medical Subject Headings) terms were used: "implant osseointegration," "bisphosphonates," "non-steroidal anti-inflammatory drugs," "glucocorticoids," "proton pump inhibitors," and "selective serotonin reuptake inhibitors (SSRIs)." This search yielded 1,258 articles on implant osseointegration. Among these, 30 articles met our criteria for implant osseointegration and bisphosphonates, 2 articles for non-steroidal anti-inflammatory drugs (NSAIDs), 7 articles for glucocorticoids, 14 articles for proton pump inhibitors (PPIs), and 14 articles for selective serotonin reuptake inhibitors (SSRIs).

Conclusion: Clinicians considering implant therapy should be mindful of potential medication-related implant failures. The present systematic review has identified an association between proton pump inhibitors (PPIs), nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), glucocorticoids, and bisphosphonates with an increased implant failure rate.

Key words. Osteointegration, Bisphosphonates, Non-steroidal anti-inflammatory drug, SSRIs, proton pump inhibitors, dental failure.

Introduction.

In the past three decades, there has been a notable rise in demand for dental implants as a solution for tooth loss, largely due to advancements in endodontic treatment. Dental implants offer immediate restoration of function and aesthetics for patients who have lost teeth [1]. However, it's important to recognize that dental implants may not be suitable for every patient. As clinicians, we must meticulously evaluate patients, considering not only their dental health but also their systemic conditions and medications. Systemic diseases and medications used in their treatment can significantly impact the osseointegration process of dental implants [2,3]. Therefore, thorough assessment and consideration of these factors are imperative to ensure successful treatment outcomes.

Data on drug use incidence in the USA from 2000 to 2008 revealed a notable increase in the utilization of various therapies [4]. The percentage of Americans who had taken one, two, or five prescription medications saw significant growth during this period. Specifically, the percentage of individuals receiving one medication increased from 44% in 2000 to 48% in 2008. Similarly, the percentage of those receiving two medications rose from 25% to 31%, while the percentage of individuals taking five medications increased from 6% to 11% over the same period [4]. Hence, to mitigate the risk of dental implant failures and address the influence of medications on the osseointegration process, thorough pre-operative assessment is essential.

Materials and Methods.

The research in electronic literature was carried out applying the biomedical search engine "National Library of Medicine" PubMed/MEDLINE database from March 2000 to February 2024. The following MeSH (Medical Subject Headings) terms were used: "implant osseointegration," "bisphosphonates," "non-steroidal anti-inflammatory drugs," "glucocorticoids," "proton pump inhibitors," and "selective serotonin reuptake inhibitors (SSRIs)." This search yielded 1,258 articles on implant osseointegration. Among these, 30 articles met our criteria for implant osseointegration and bisphosphonates, 2 articles for non-steroidal anti-inflammatory drugs (NSAIDs), 7 articles for glucocorticoids, 14 articles for proton pump inhibitors (PPIs), and 14 articles for selective serotonin reuptake inhibitors (SSRIs).

The articles were chosen by evaluating the titles and abstracts of those containing the term "drug impact osteointegration" in the title. Articles pertaining specifically to clinical applications within general dentistry and its various application fields were manually searched in relevant prominent journals. Additionally, the reference lists of included studies were screened with no language restrictions. The inclusion criteria established for this review were as follows: all case reports, case series, original research papers, review papers, in vivo studies, and controlled clinical trials examining the influence of medications on the osseointegration process, along with comprehensive pre-operative assessments utilized in dentistry-related studies.

Osteointegration.

The process of osseointegration of dental implants is a biological phenomenon that leads to a direct bond between the jawbone and the implant surface, excluding the incorporation of connective tissue [5]. This process progresses through distinct stages including hemostasis, inflammation, proliferation, and

remodeling. It is imperative for the success of osseointegration to eliminate iatrogenic or systemic biological factors that could adversely affect the bone-implant connection.

Certain systemic drugs that we have analyzed and found to have an impact on the process of osseointegration of dental implants include:

- Selective serotonin reuptake inhibitors (SSRIs)
- Bisphosphonates
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Glucocorticoids
- Proton pomp inhibitors

Bisphosphonates.

These drugs are commonly prescribed for the treatment of various bone pathologies such as osteoporosis, multiple myeloma, Paget's disease, and bone metastases. They significantly interfere with the process of osseointegration due to their effects on bone metabolism at the cellular level. Specifically, these medications inhibit the osteoclast cell cycle, thereby preventing bone resorption, which is essential for the initiation of new bone formation [3,6].

The method of administration for these therapies is typically oral or intravenous. One characteristic of these treatments is their long duration of action, as they are retained within the bone. For example, Alendronate, a prominent drug in bone pathology, can remain effective for up to 10 years. However, despite their efficacy in treating bone disorders, these medications can pose significant complications during oral surgical procedures such as implant placement or tooth extraction. One notable complication is osteonecrosis of the jaw, which has been documented in cases where patients undergo oral surgery. Even after 8 weeks post-surgery, healing may not occur, leading to bony exposure of the jaw. It's important to note that this complication can occur even in patients who have not undergone radiotherapy in the maxillofacial region [7].

The treatment protocol for such cases necessitates individualized approaches, albeit challenging. However, adhering to preventive procedures can significantly mitigate complications, including the risk of osteonecrosis. These preventive measures encompass administering antibiotics, local irrigation with antimicrobial solutions, thorough wound cleaning, application of plasma rich in platelets, and hyperbaric oxygen therapy. Based on a comprehensive literature review, it is imperative for patients to undergo routine oral cavity examinations [6,7]. Whenever possible, minimally invasive procedures should be favored. In cases requiring dental implant placement, it is recommended to discontinue systemic drug therapy three months before and three months after the intervention. Additionally, the application of a temporary prosthesis is advised to safeguard against potential postoperative wound injuries.

According to the Maxillofacial and Oral Surgical Association, dental implants are contraindicated in patients undergoing intravenous bisphosphonate therapy. However, for patients receiving oral bisphosphonate therapy, the contraindication for implant placement varies depending on the duration of treatment. Patients who have recently initiated oral bisphosphonate therapy or have been under treatment for up to three years are not necessarily contraindicated for implant placement. However, for those who have been undergoing therapy for a prolonged period, such as 10 years, the incidence of bone osteonecrosis becomes evident [8].

As a preventive measure, prophylactic antibiotic therapy should be administered, with a combination of penicillin or metronidazole along with a broad-spectrum antibiotic such as a quinolone. Additionally, mouthwash containing Chlorhexidine 0.12% should be used twice daily for two weeks. Given the prolonged retention of bisphosphonate therapy in bone tissue, monitoring the level of Type 1 collagen Carboxy-terminal telopeptide in the blood is crucial. Elevated levels of this telopeptide indicate collagen degradation, necessitating preventive measures [9]. Surgeons must possess comprehensive knowledge of these drugs, including their pharmacological, pharmacodynamic, pharmacokinetic, and mechanistic aspects, to effectively manage patients undergoing bisphosphonate therapy.

Based on scientific studies analyzed by Freitas and collaborators in 2016, comprising 15 studies including 8 retrospective, 1 prospective, and 6 other cases, a total of 1339 patients were analyzed, with 3748 implants placed. Among these, 152 implants failed, and 78 cases of osteonecrosis were reported [10]. These findings underscore the importance of distinguishing between patients undergoing intravenous and oral administration of bisphosphonates when considering invasive oral surgical interventions, including dental implants. Intravenous administration presents a contraindication for such procedures, whereas for patients under oral administration, it is crucial to assess the duration of therapy and implement preventive measures to mitigate the risk of osteonecrosis prior to oral surgical interventions [10]. The risk of developing bisphosphonate-related osteonecrosis of the jaw and experiencing implant failure or loss is higher in patients receiving intravenous bisphosphonate therapy. Therefore, it is crucial to conduct a thorough analysis of the patient's complete medical history. If bisphosphonate therapy is confirmed, the duration of treatment and the route of administration must be carefully considered [11].

Nonsteroidal anti-inflammatory drugs.

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of medications known for their anti-inflammatory, analgesic, and antipyretic effects. In oral surgical interventions, NSAIDs are primarily utilized for managing postoperative pain. Their mechanism of action involves the inhibition of cyclooxygenase enzymes (COX1, COX2, and COX3), which directly interferes with the synthesis of prostaglandins and thromboxane. Prostaglandins serve as inflammatory mediators that play a crucial role in bone metabolism. Therefore, the inhibition of their synthesis by NSAIDs can disrupt the repair mechanisms of bone tissue [11-13].

According to a long-term study by Marquez-Lara et al., analyzing the effects of peri-operative non-steroidal anti-inflammatory therapy, dental implant osseointegration failures were observed [14]. Out of 197 implants that failed over an extended period, 44% of the failures occurred in patients who received NSAID therapy before the operation, while 38% occurred in patients who did not receive any nonsteroidal anti-inflammatory medication [12,13]. Additionally, the group

receiving NSAID therapy exhibited a 3.2 times higher rate of bone loss compared to the group not receiving NSAID therapy, with a loss of less than 30% of the total bone height [14,15].

Proton pump inhibitor drugs.

Proton pump inhibitor drugs, such as Omeprazole, Pantoprazole, and Esomeprazole, are commonly prescribed for the treatment and prevention of gastrointestinal pathologies such as peptic ulcers, gastroesophageal reflux disease (GERD), and Heliobacter pylori infection [16]. These medications function by suppressing stomach acidity through the inhibition of the proton pump (H+/K+ ATPase). Notably, this proton pump is not limited to the gastrointestinal tract but also exists in the bones of the body [17].

These drugs exert their indirect effects on bone density and the osseointegration process of dental implants through multiple mechanisms. By inhibiting stomach acid production, they disrupt calcium homeostasis, leading to decreased calcium absorption. Consequently, this reduction in calcium absorption contributes to a decline in bone density. Moreover, proton pump inhibitors also affect the activity of osteoclasts, further impacting bone metabolism and potentially interfering with the osseointegration process of dental implants [18,19].

During our literature review, we examined various scientific studies focusing on patients receiving proton pump inhibitor (PPI) therapy. For instance, Wu conducted a study involving 799 patients who received a total of 1773 dental implants, with 133 implants in 58 PPI users and 1640 implants in 741 non-users [19]. The study found that implant failure occurred at a rate of 6.8% in PPI users compared to 3.2% in non-users. Additionally, Ursomanno conducted a study examining bone level loss in 635 patients with a total of 1480 implants. Among PPI users, a bone level loss of 1.60 mm was observed, whereas non-users experienced a loss of 1.01 mm [20].

In another study conducted by Charcovic, which involved 999 patients and a total of 3559 dental implants, 178 implants were reported to have failed. Among these failures, 12.0% (30 out of 250) occurred in PPI users, while 4.5% (148 out of 3309) occurred in non-users [21].

Ultimately, decisions regarding the placement of dental implants in patients using PPIs should be made on a case-by-case basis, taking into account the individual patient's overall health status, risk factors, and the potential benefits and risks of the procedure. Close collaboration between the patient's dental and medical providers is essential in ensuring the best possible outcomes [22,23]. PPIs inhibit proton pumps not only in the stomach but also in osteoclasts within bone. This inhibition reduces the acidification necessary for bone resorption, impairing osteoclast function and disrupting normal bone remodeling. Over time, these effects can lead to decreased bone density and an increased risk of fractures and osteoporosis. Therefore, the impact of PPIs on bone health is an important consideration, particularly for patients requiring long-term PPI therapy [21-23].

Glucocorticoid drugs.

The glucocorticoid drugs work by inhibiting inflammatory processes, which are often associated with autoimmune diseases [24]. These medications mimic the action of natural steroids produced by the body and are typically used when the body's own anti-inflammatory response is insufficient to manage autoimmune conditions effectively. By suppressing inflammation, glucocorticoids help alleviate symptoms and reduce the immune system's attack on the body's own tissues in autoimmune diseases [25,26].

Therefore, the use of glucocorticoid therapy, especially at high supraphysiological levels and for extended periods, can potentially interfere with the osseointegration process of dental implants [27]. This highlights the importance of careful consideration and monitoring of glucocorticoid therapy in patients undergoing dental implant procedures. Prednisone and Prednisolone are intermediate-acting corticosteroids that have a longer duration of action compared to Dexamethasone, which is a long-acting corticosteroid [28]. Their prolonged presence in the body can lead to more pronounced suppression of bone formation by osteoblasts, thereby potentially impairing the process of osseointegration. However, it's important to note that the choice of corticosteroid and its dosage should be carefully evaluated based on individual patient factors, the specific condition being treated, and the desired therapeutic outcomes [28].

The blockade of the B-Catenin/Wingless pathway leads to several effects, including an increase in the level of reactive oxygen species (ROS) and the production of the Activating Receptor of the binding factor kappa-B (RANK), which is the main mediator in the process of bone resorption [29]. RANK stimulates osteoclast formation and activity, leading to increased bone resorption. Preosteoclasts, which express RANK, interact with osteoblasts to form a complex that promotes osteoclast differentiation and maturation. Ultimately, this dysregulation of bone remodeling results in excessive bone resorption and decreased bone formation, contributing to bone loss and potentially impairing processes such as osseointegration of dental implants [30].

Firstly, the decrease in osteoblast secretion of Osteoprotegerin (OPG) reduces its availability to bind with RANKL receptors, resulting in an imbalance favoring bone resorption over formation. This imbalance further exacerbates bone resorption. Additionally, the apoptosis of osteocytes, the main cells responsible for maintaining bone health and integrity, leads to poor bone quality. The reduction in osteoblasts, osteocytes, and OPG levels, combined with increased osteoclast function, results in less formed bone and increased bone resorption [30]. Moreover, the decrease in vascular endothelial growth factor (VEGF) further contributes to bone complications such as osteoporosis or osteonecrosis. These effects collectively impair the creation of adequate bone, which is crucial for successful osseointegration of implants [31]. Overall, clinical trials investigating implant failure caused by glucocorticoids highlight the importance of considering the potential impact of systemic medications on bone health and implant outcome. They may delay the process of osseointegration, which is essential for the successful integration of dental implants with the surrounding bone. Moreover, the clinical trials have reported longer healing times and decreased implant stability in patients receiving glucocorticoid therapy. Glucocorticoids can lead to a decrease in bone quality, including reduced bone mineral density and alterations in bone microarchitecture. These

changes may compromise the stability and longevity of dental implants [32,33]. It have been suggested that glucocorticoid use may increase the risk of peri-implantitis, an inflammatory condition that affects the soft and hard tissues surrounding dental implants. This complication can contribute to implant failure [34].

Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) are a type of antidepressant commonly used to treat major depressive disorders and anxiety disorders. They are the most widely prescribed antidepressants globally [35]. The SSRIs, including Prozac, Paxil, Lexapro, Zoloft and Celexa, are medications developed to block the reuptake of serotonin, thereby increasing its levels to treat depression [36]. Approximately 3.8% of the global population suffers from depression, with 5% of adults affected (4% of men and 6% of women), and 5.7% of adults over the age of 60. Around 280 million people worldwide are living with depression [37]. Serotonin (5-hydroxytryptamine 5-HT) is a monoamine neurotransmitter in the brain that plays a role in promoting feelings of well-being and happiness [38]. In bone metabolism, serotonin regulates the activity of bone cells by interacting with receptors such as 5-HT1B, 5-HT2B, and 5-HT2C, as well as serotonin transporters (5-HTTs) [35]. This results in intricate signaling pathways within osteoblasts and osteoclasts, influencing various aspects of bone remodeling. Hence, SSRIs inhibit serotonin transporters (5-HTTs) on bone cells, leading to a direct adverse impact on metabolism and bone formation [39]. Previous studies on SSRIs have shown that using these medications reduces bone formation, thereby increasing the risk of bone fractures. The inhibition of 5-HT reuptake leads to enhanced osteoclast differentiation and suppressed osteoblast proliferation, resulting in a decrease in overall bone mass and bone mineral density [39,40].

The case report by Grün et al. suggests a potential association between SSRIs and the failure of osseointegrated dental implants in a premenopausal Caucasian woman. However, it's important to note that this case report represents only a single instance and does not establish a definitive causal relationship between SSRIs and implant failure. Further research is needed to determine the precise mechanisms by which SSRIs might impact implant success rates and to evaluate any potential confounding factors that could contribute to implant failure in similar case (41). The study conducted by Wu X et al., concluded that SSRI treatment was linked to a greater risk of osseointegrated implant failure. They also noted that other factors, such as implant diameter, bone augmentation, and smoking habits, could significantly influence implant survival rates (42).

Conclusion.

Clinicians considering implant therapy should be mindful of potential medication-related implant failures. The present systematic review has identified an association between proton pump inhibitors (PPIs), nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), glucocorticoids, and bisphosphonates with an increased implant failure rate. Further research is warranted to investigate the effects of these medications as potential confounders for implant outcomes.

Competing interests.

The authors declare no conflict of interest.

Funding.

This research did not receive any specific grant from founding agencies in the public, commercial, or not-for profit organization.

REFERENCES

1. Mericske-Stern RD, Taylor TD, Belser U. Management of the edentulous patient. Clin Oral Implants Res. 2000;11:108-25.
2. Brånemark PI. Introduction to osseointegration. In: Brånemark PI, Zarb GA, Alberkasso T, editors. Tissue integrated prostheses: osseointegration in clinical dentistry. Chicago: Quintessence Publishing. 1985:11-76.
3. Chadha GK, Ahmadieh A, Kumar S, et al. Osseointegration of dental implants and osteonecrosis of the jaw in patients treated with bisphosphonate therapy: a systematic review. J Oral Implantol. 2013;39:510-20.
4. D'Ambrosio F, Amato A, Chiacchio A, et al. Do Systemic Diseases and Medications Influence Dental Implant Osseointegration and Dental Implant Health? An Umbrella Review. Dent J (Basel). 2023;11:146.
5. Moy PK, Medina D, Shetty V, et al. Dental implant failure rates and associated risk factors. Int J Oral Maxillofac Implants. 2005;20:569-77.
6. Hwang D, Wang HL. Medical contraindications to implant therapy: part I: absolute contraindications. Implant Dent. 2006;15:353-60.
7. Migliorati CA. Bisphosphonates and oral cavity avascular bone necrosis. J Clin Oncol. 2003;21:4253.
8. Marx RE. Pamidronate (aredia) and zoledronate (zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg. 2003;61:1115-7.
9. Rogers MJ, Gordon S, Benford HL, et al. Cellular and molecular mechanisms of action of bisphosphonates. Cancer Suppl. 2000;88:2961-78.
10. Russell RGG, Watts NB, Ebetino FH, et al. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporos Int. 2008;19:733-59.
11. de-Freitas NR, Lima LB, de-Moura MB, et al. Bisphosphonate treatment and dental implants: A systematic review. Med Oral Patol Oral Cir Bucal. 2016;21:e644-51.
12. Luo JD, Miller C, Jirjis T, et al. The effect of non-steroidal anti-inflammatory drugs on the osteogenic activity in osseointegration: a systematic review. Int J Implant Dent. 2018;4:30.
13. Kalyvas DG, Tarenidou M. Influence of nonsteroidal anti-inflammatory drugs on osseointegration. J Oral Sci. 2008;50:239-246.
14. Marquez-Lara A, Hutchinson ID, Nuñez F, et al. Nonsteroidal anti-inflammatory drugs and bone-healing: a systematic review of research quality. JBJS Rev. 2016;4.
15. Gomes FIF, Aragão MGB, de Paulo Teixeira Pinto V, et al. Effects of nonsteroidal anti-inflammatory drugs on osseointegration: a review. J Oral Implantol. 2015;41:219-230.
16. Aghaloo T, Pi-Anfruns J, Moshaverinia A, et al. The Effects of Systemic Diseases and Medications on Implant Osseointegration: A Systematic Review. Int J Oral Maxillofac Implants. 2019;34:s35-s49.

17. Mazer-Amirshahi M, Mullins PM, van den Anker J, et al. Rising rates of proton pump inhibitor prescribing in US emergency departments. Am J Emerg Med. 2014;32:618-622.
18. Metz DC. Potential uses of intravenous proton pump inhibitors to control gastric acid secretion. Digestion. 2000;62:73-81.
19. Wu X, Al-Abedalla K, Abi-Nader S, et al. Proton Pump Inhibitors and the Risk of Osseointegrated Dental Implant Failure: A Cohort Study. Clin Implant Dent Relat Res. 2017;19:222-232.
20. Ursomanno BL, Cohen RE, Levine MJ, et al. Effect of Proton Pump Inhibitors on Bone Loss at Dental Implants. Int J Oral Maxillofac Implants. 2020;35:130-134.
21. Chrcanovic BR, Kisch J, Albrektsson T, et al. Intake of Proton Pump Inhibitors Is Associated with an Increased Risk of Dental Implant Failure. Int J Oral Maxillofac Implants. 2017;32:1097-1102.
22. Mullin JM, Gabello M, Murray LJ, et al. Proton pump inhibitors: actions and reactions. Drug Discov Today. 2009;14:647-60.
23. Liu J, Li X, Fan L, et al. Proton pump inhibitors therapy and risk of bone diseases: An update meta-analysis. Life Sci. 2019;218:213-223.
24. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol. 2011;335:2-13.
25. Kleiman A, Tuckermann JP. Glucocorticoid receptor action in beneficial and side effects of steroid therapy: lessons from conditional knockout mice. Mol Cell Endocrinol. 2007;275:98-108.
26. Fraser LA, Adachi JD. Glucocorticoid-induced osteoporosis: treatment update and review. Ther Adv Musculoskelet Dis. 2009;1:71-85.
27. Fu JF, Bushutski JD, Al-Hezaimi K, et al. Statins, glucocorticoids, and nonsteroidal anti-inflammatory drugs: their influence on implant healing. Implant Dent. 2012;21:362-7.
28. Caramori G, Mumby S, Girbino G, et al. Corticosteroids. Nijkamp and Parnham's Principles of Immunopharmacology. 2019:661-688.
29. Staehlke S, Haack F, Waldner AC, et al. ROS Dependent Wnt/β-Catenin Pathway and Its Regulation on Defined Micro-Pillars-A Combined In Vitro and In Silico Study. Cells. 2020;9:1784.
30. Kitaura H, Marahleh A, Ohori F, et al. Osteocyte-Related Cytokines Regulate Osteoclast Formation and Bone Resorption. Int J Mol Sci. 2020;21:5169.
31. Weinstein RS. Glucocorticoid-induced osteoporosis and osteonecrosis. Endocrinol Metab Clin North Am. 2012;41:595-611.
32. Bencharit S, Reside GJ, Howard-Williams EL. Complex prosthodontic treatment with dental implants for a patient with polymyalgia rheumatica: a clinical report. Int J Oral Maxillofac Implants. 2010;25(6):1241–5. [PubMed: 21197503]
33. Carr AB, Revuru VS, Lohse CM. Risk of Dental Implant Failure Associated With Medication Use. J Prosthodont. 2019 Aug;28(7):743-749. doi: 10.1111/jopr.12773. Epub 2018 Mar 5. PMID: 29508502.
34. Kochar SP, Reche A, Paul P. The Etiology and Management of Dental Implant Failure: A Review. Cureus. 2022 Oct 19;14(10):e30455. doi: 10.7759/cureus.30455. PMID: 36415394; PMCID: PMC9674049.
35. Tsapakis EM, Gamie Z, Tran GT, Adshead S, Lampard A, Mantalaris A, Tsiridis E. The adverse skeletal effects of selective serotonin reuptake inhibitors. Eur Psychiatry. 2012 Apr;27(3):156-69. doi: 10.1016/j.eurpsy.2010.10.006. Epub 2011 Feb 3. PMID: 21295451.
36. Liu B, Anderson G, Mittmann N, To T, Axcell T, Shear N. Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people. Lancet. 1998 May 2;351(9112):1303-7. doi: 10.1016/s0140-6736(97)09528-7. PMID: 9643791.
37. World Health Organization. Depression. World Health Organization.2023, June 5. https://www.who.int/news-room/fact-sheets/detail/depression
38. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature. 2008 Oct 16;455(7215):894-902. doi: 10.1038/nature07455. PMID: 18923511; PMCID: PMC2721780.
39. Diem SJ, Blackwell TL, Stone KL, Yaffe K, Haney EM, Bliziotes MM, Ensrud KE. Use of antidepressants and rates of hip bone loss in older women: the study of osteoporotic fractures. Arch Intern Med. 2007 Jun 25;167(12):1240-5. doi: 10.1001/archinte.167.12.1240. PMID: 17592096.
40. Wu X, Al-Abedalla K, Rastikerdar E, Abi Nader S, Daniel NG, Nicolau B, Tamimi F. Selective serotonin reuptake inhibitors and the risk of osseointegrated implant failure: a cohort study. J Dent Res. 2014 Nov;93(11):1054-61. doi: 10.1177/0022034514549378. Epub 2014 Sep 3. PMID: 25186831; PMCID: PMC4212463.\
41. Grün P, Pfaffeneder-Mantal F, Schneider B, Bandura P, Grün AS, Turhani D. Are selective serotonin reuptake inhibitors responsible for the failure of osseointegrated titanium-zirconium and one-piece zirconia dental implants in a premenopausal Caucasian woman? - A case report. Advances in Oral and Maxillofacial Surgery.2022 Dec (8): 100381. doi.org/10.1016/j.adoms.2022.100381
42. Wu X, Al-Abedalla K, Rastikerdar E, Abi Nader S, Daniel NG, Nicolau B, Tamimi F. Selective serotonin reuptake inhibitors and the risk of osseointegrated implant failure: a cohort study. J Dent Res. 2014 Nov;93(11):1054-61. doi: 10.1177/0022034514549378. Epub 2014 Sep 3. PMID: 25186831; PMCID: PMC4212463.