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Clinical considerations regarding drug-induced gingival enlargement: a concise systematic review

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Abstract

Introduction: In the context of gingival conditions, certain medications can affect periodontal tissues by altering the inflammatory response and promoting gingival growth, resulting in gingival hyperplasia (GH) or gingival enlargement. **Objective**: It was to present the key clinical considerations regarding drug-induced gingival enlargement. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was conducted from March to April 2026 across the Web of Science, Scopus, Embase, PubMed, ScienceDirect, SciELO, and Google Scholar databases. A systematic review of the incidence of gingival hyperplasia and its relationship to the predictor phenytoin, nifedipine and cyclosporine A. The quality of the studies was assessed using the GRADE instrument, and the risk of bias was evaluated according to the Cochrane instrument. **Results and Conclusion:** According to the GRADE instrument, most studies presented homogeneous results, with X^2=78.5% > 50%. A total of 83 articles were found and submitted for eligibility analysis, with 21 final studies selected to compose the results of this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 33 studies with a high risk of bias and 13 studies that did not meet GRADE and AMSTAR-2 standards. It was concluded that drug-induced gingival overgrowth faces two therapeutic challenges: uncertain pathogenesis and a high recurrence rate. Analyzing the associations between medications and adverse reactions can help determine the treatment approach. Understanding the cytotoxicity thresholds of these medications is crucial for improving clinical outcomes and minimizing the incidence of gingival enlargement in patients requiring long-term therapy.

Keywords: Gingival enlargement. Gingival hyperplasia. Drugs. Medications. Cytotoxicity.

Introduction

In the context of gingival conditions, certain medications can affect periodontal tissues by altering the inflammatory response and promoting gingival growth, resulting in gingival hyperplasia (GH) or gingival enlargement [1-3]. Bacterial biofilm accumulation is a significant predictor of GH development, regardless of any association with medications, systemic diseases, or hormonal changes [3,4]. Even with good oral hygiene, a certain degree of drug-induced gingival enlargement may be observed in susceptible individuals [5].

In this context, GH is associated with various etiological factors, resulting in chronic inflammation triggered by local factors—such as plaque or calculus—or systemic factors, including chronic diseases, hormonal fluctuations, and medication use [6-8]. Physiologically, GH manifests as abnormal gingival tissue growth secondary to the use of systemic medications; these drugs can alter periodontal tissues by modifying their inflammatory and immune responses, particularly within the gingiva.

Prominent among the drugs involved are anticonvulsants, calcium channel blockers, and immunosuppressants. The most common agents capable of inducing gingival growth are phenytoin, nifedipine, and cyclosporine A. Erythromycin and oral contraceptives can also promote similar clinical presentations [9-11]. Consequently, hyperplastic gingival tissue exhibits characteristics similar to those

observed in all cases of gingival enlargement, whether drug-induced, hereditary, or idiopathic in origin [12-14]. Given this background, the aim of this study was to present the key clinical considerations regarding drug-induced gingival enlargement.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed at: 04/27/2026. The AMSTAR 2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed at: 04/27/2026.

Search Strategy and Sources

The literature search process was carried out from March to April 2026 and developed based on Web of Science, Embase, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors were used in health sciences (DeCS/MeSH terms): Gingival enlargement. Gingival hyperplasia. Drugs. Medications. Cytotoxicity. For further specification, the "Gingival enlargement" description for refinement was added during searches.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and Discussion

Summary of Findings

A total of 83 articles were found and submitted to eligibility analysis, with 21 final studies selected to compose the results of this systematic review. The listed studies were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=78.5%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 33 studies with a high risk of bias and 13 studies that did not meet GRADE and AMSTAR-2.

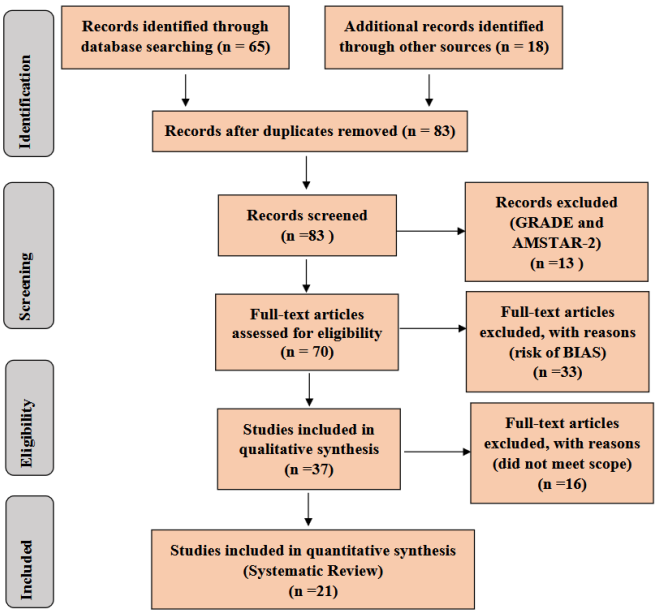

Figure 1. Flowchart showing the article selection process. Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph did not have a symmetrical behavior, suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the base of the graph and in studies with large sample sizes that are presented at the top.

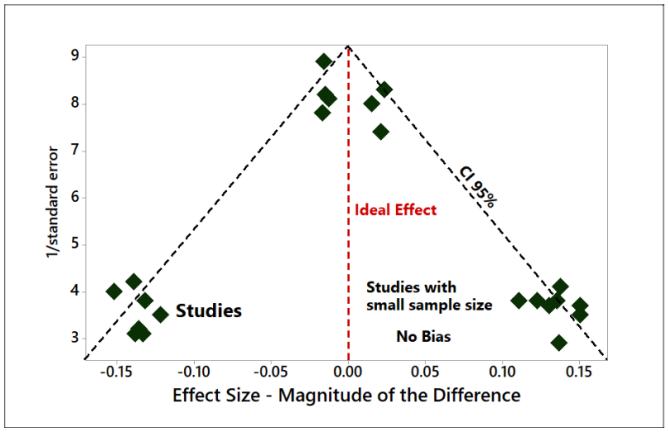

Figure 2. The non-symmetrical funnel plot suggests risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=21 studies). Source: Own authorship.

Major Approaches and Results

Certain drugs predispose patients to gingival overgrowth by modifying immune and inflammatory responses. Key examples include anticonvulsants, calcium channel blockers, and certain immunosuppressants (such as cyclosporine A – CPA) [1,2]. Also, phenytoin and nifedipine are particularly notable among these. The term gingival hypertrophy (GH) or gingival enlargement is based on histological findings, such as increased extracellular matrix synthesis (primarily collagen) and an increase in both the size and number of fibroblasts within the tissue. Scientific research has demonstrated that CPA can alter the metabolism of gingival and bone tissues, as well as the composition of oral biofilm and the flow and composition of gingival fluid [15-18].

Moreover, the CPA+nifedipine combination in patients receiving renal transplantation shows that arterial hypertension is very constant; there was a large increase in the use of this drug in patients with autoimmune diseases [4]. Renal transplantation is most often applied to patients who are already on dialysis, although it is possible to do so before initiating dialysis. Cyclosporin A, when used in the long term, can lead to a manifestation of localized or generalized gingival hyperplasia. The gingival papillae appear lobulated and enlarged, and the teeth may be partially covered with gingival tissue [4-6].

The tissue increase can promote the impaction or deviation of the teeth, thus leading to malocclusion, besides the presence of false periodontal pockets. The gingival hyperplasia induced by the use of CPA can be observed from the third month of drug use and microscopically presents features that differentiate it from other modalities of hyperplasia, such as elongated epithelial crests, atrophic and mononuclear inflammatory infiltrate distributed more intensely in the region of the lamina own [19].

In this context, most of the studies analyzed indicate that GH has a high incidence in kidney transplant patients. In patients affected by chronic renal failure, systemic alterations also influence oral manifestations that interfere with oral hemostasis. The patient with Chronic Renal Disease presents systemic and oral manifestations that reflect in the dental treatment of the same. Thus, these patients are predisposed to suffer a wide variety of oral problems such as periodontal disease, uremic stomatitis, enamel anomalies, premature tooth loss, and xerostomia [17].

In renal transplant patients and users of CPA + nifedipine, periodontal problems go beyond gingival augmentation, and there is also significant bone loss in most of the patients examined. Making it clear that the dental surgeon will have to work together as a physician to provide a better quality of life for these patients through drug substitution, surgical therapy, and self-management of the dental biofilm. Another study determined the efficacy of metronidazole as a gel in reducing CPA-induced gingival hyperplasia in patients with heart transplantation [20].

Its long-term efficacy has been demonstrated in the control of inflammation as well as in the depth of the pockets. However, being used only as an additional procedure to conventional therapy [20]. In this sense, the studies confirm that the drugs of systemic use can alter the morphology and physiology of the periodontal tissues [21]. Therefore, oral hygiene of good quality is essential to avoid aggravation of GH, but it does not have sufficient action to eradicate it [1-3].

The use of nifedipine suggests that monitoring of GH in patients is also important. The potential risk of nifedipine following the long-term use of a calcium channel blocker has been demonstrated [6]. These drugs are widely used in the management of gestational hypertensive disorders. As an example, a case of a 27-year-old woman presented with GH at the 27th week of gestation during hospitalization due to pre-eclampsia. Has used nifedipine for hypertension in the last 9 weeks. Nifedipine was discontinued and replaced with methyldopa, and after 48 hours, GH improved. She gave birth two weeks later, and GH resolved completely without surgical intervention [6].

The etiophysiopathogenesis of drug GH is not yet fully understood, but it is multifactorial [1-4]. The hypotheses presented suggest that there is stimulation of fibroblast cell proliferation, alteration in the metabolism of degradation and collagen production, and the accumulation of intracellular calcium with a variation in the individual tissue response [1,2,6]. Another proposed mechanism for side effects from the use of anticonvulsants is the production of inactive collagenase from fibroblasts, causing a decrease in collagen turnover [7].

Besides, folic acid deficiency caused by phenytoin could cause degenerative changes in the sulcular epithelium and exacerbate the inflammatory response [8]. Among the etiological factors of this pathology, in addition to individual susceptibility, genetic predisposition [1,4,10], hormonal factors, pharmacological characteristics of the drugs involved, as well as the time of ingestion of this drug, the main factor is the accumulation of dental biofilm, resulting from poor oral hygiene. However, the role of the dental biofilm in the gingival growth induced by drugs still remains contradictory, although adequate oral hygiene is a primary factor for the control of this pathology [9,10].

The use of phenytoin, however, is not free from

adverse effects, with GH being one of the most common that affect the oral cavity. There may also be increased blood glucose, mental confusion, hair growth on the body and face, insomnia, nausea, and blood pressure drop [11,12]. This drug can affect the periodontal tissues, modifying the immune-inflammatory response of the same, mainly of the gingiva [13,14]. Within cells, phenytoin acts in the direct suppression of the sodium and potassium pump, decreasing the hyperexcitability of the neurons in the motor cortex [15].

Another observation is that edentulous areas are generally not affected; however, significant hyperplasia may be observed under poorly adapted prostheses and around implants [5]. The color of the gingiva varies from normal to hyperemic [6]. In the absence of inflammation, the enlarged gingiva is firm, and the coloration is similar to normal mucosa; the surface can be flat, dotted, or granular. With inflammation, the affected gingiva becomes dark red and edematous, with a friable surface, bleeds easily, and occasionally become ulcerated. Nodules similar to pyogenic granuloma are occasionally observed in the presence of severe inflammation [7]. Bacterial plaque control is associated with the prevention and regression of associated inflammatory gingival increase [7,8].

As phenytoin is used more often in young patients, drug GH is more common in people under 25 years of age, and the greater risk occurs when the drug is used in young individuals, especially adolescents [2]. In general, there is no predilection for ethnicities and genders, and their onset ranges from two weeks to three months at the beginning of the medication, with maximum severity between 12 and 18 months, but the change is usually more observed after 3 to 6 months of drug use [3,4].

The severity of hyperplasia tends to increase as the concentration of phenytoin increases, and there is a direct correlation with serum levels of the drug [5]. Identification of the use of these drugs in the anamnesis is essential for the diagnosis, since antiepilepticassociated hyperplasias, such as phenytoin, and calcium channel antagonists, such as nifedipine, are similar. At the histological level, the hyperplastic gingival tissue shows features similar to those observed in all gingival increases, both those induced by drugs and those hereditary or idiopathic. At the microscopic level, these alterations are constituted by keratinized stratified squamous epithelium showing areas of acanthosis and thin epithelial projections that extend deeply towards the conjunctiva [6].

Discontinuation of aggressive medication by the patient's physician often leads to paralysis and possibly regression of gingival enlargement; substitution of the drug with another may also be beneficial [3,4]. If the doctor responsible for the patient allows the substitution of the drug [5]. If drug use is imperative, professional cleaning, frequent reassessment, and home plate control are important. Antiplatelet agents, such as chlorhexidine, are beneficial in preventing plaque development and associated gingival hyperplasia [7].

Finally, as a prophylactic and curative measure, the use of systemic or topical folic acid has been shown to have positive effects on gingival hyperplasia in some cases. In cases of patients taking phenytoin, supplemental folic acid treatment 1 to 5 g / day should be done concomitantly [2].

Limitation

More randomized controlled clinical trials and other clinical studies are needed to better verify the findings in the literature, as well as to close the information gaps.

Conclusion

It was concluded that drug-induced gingival overgrowth faces two therapeutic challenges: uncertain pathogenesis and a high recurrence rate. Analyzing the associations between medications and adverse reactions can help determine the treatment approach. Understanding the cytotoxicity thresholds of these medications is crucial for improving clinical outcomes and minimizing the incidence of gingival enlargement in patients requiring long-term therapy.

CRediT

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The authors declare no conflict of interest.

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Application of Artificial Intelligence (AI)

Not applicable.

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