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Major clinical considerations regarding the drug-induced gingival overgrowth: a systematic review

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Abstract

Introduction: Some systemic medications can affect the periodontal tissues, modifying their inflammatory response and promoting gingival growth, which causes gingival hyperplasia (GH). This can be intensified when two drugs are used synergistically, worsening the GH picture. **Objective**: It was to perform a systematic review on the incidence of gingival hyperplasia and its relation to the predictors of phenytoin, nifedipine and cyclosporine A. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was conducted from December 2025 to January 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:** According to the GRADE instrument, most studies presented homogeneous results, with X^2=70.8% > 50%. A total of 62 articles were found and submitted for eligibility analysis, with 20 final studies selected to compose the results of this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 02 studies with a high risk of bias and 10 studies that did not meet GRADE and AMSTAR-2 standards. It was found that gingival growth in patients with kidney transplantation was associated with a significant increase in gingival hyperplasia (GH) and also with other pathologies leading to the use of drugs such as phenytoin, nifedipine and cyclosporin A. However, G H can be mistakenly mistaken for gingival hyperplasia. The name "gingival growth and / or gingival hypertrophy" is a function of histological study, the occurrence of increased extracellular matrix synthesis, mainly in collagen, and increase in the size and number of fibroblasts present in the tissue. Scientific research has shown that Ciclosporin A can modify the metabolism of the gingival and bone tissue and the composition of the oral biofilm, the flow and composition of the gingival fluid. **Conclusion:** The surgeon-dentist should be aware during the anamnesis to the cases of patients who use medications that induce gingival hyperplasia, such as anticonvulsants. It is imperative for the dentist to understand the general condition and the limitations of each patient, so that he can control and cure the most varied oral manifestations, in order to maintain a good quality of life in his patient.

Keywords: Gingival hyperplasia. Gingival overgrowth. Drug. Medicine. Clinical trials.

Introduction

Periodontal disease is characterized by inflammation of the supporting tissues of the teeth, caused by bacteria. The gingival inflammatory process promotes the apical migration of the junctional epithelium, allowing the advancement of plaque to the subgingival region, causing periodontitis, which is a disease characterized by loss of periodontal insertion

and bone resorption [1,2]. Some drugs of systemic use can affect the periodontal tissues, modifying their inflammatory response and promoting gingival growth, which causes gingival hyperplasia (GH) [3,4]. This can be intensified when two drugs are used synergistically, worsening the GH picture [4].

The accumulation of bacterial biofilm or calculus is, in many cases, the essential condition for the development of gingival hyperplasia, regardless of association with drugs, systemic diseases, or hormonal changes. The degree of gingival increase seems to be related to the patient's susceptibility and to the level of oral hygiene, with a positive and significant correlation between gingival hyperplasia and poor oral hygiene [2].

In the observation of patients with excellent oral hygiene, gingival growth and the formation of pseudobolsas are dramatically reduced or absent [3]. However, even with good oral hygiene, some degree of drug gingival increase can be observed in susceptible individuals, although in many cases it is difficult to detect the changes. Rigorous oral hygiene, controlling local irritant factors, can often limit severity to clinically insignificant levels [3,5], on the other hand, patients with precarious oral health may not develop gingival drug hyperplasia [5].

In this context, gingival hyperplasia presents several clinical manifestations and is associated with different etiological factors, resulting in a chronic inflammation, triggered by local factors such as plaque or calculus, or systemic factors such as chronic diseases, hormonal variations, and medication use [6-8]. Gingival hyperplasia refers to an abnormal growth of the gingival tissues secondary to the use of systemic medicines, which can alter the periodontal tissues, modifying the inflammatory and immune response of these, mainly the gingiva. The anticonvulsants, calcium channel blockers, and immunosuppressants are listed. The most common are phenytoin, nifedipine, and cyclosporin A, which may induce gingival growth, in addition to erythromycin and oral contraceptives, promoting similar clinical aspects [9-11]. Thus, hyperplastic gingival tissue shows characteristics similar to those observed in all gingival increases, both those induced by medicine, as well as hereditary or idiopathic ones [12-14].

The present study aimed to systematically review the incidence of gingival hyperplasia and its relation to the predictor phenytoin, nifedipine, and cyclosporin A.

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: 01/22/2026. The AMSTAR 2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed at: 01/22/2026.

Search Strategy and Sources

The literature search process was carried out from December 2025 to January 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 hyperplasia. Gingival overgrowth. Drug. Medicine. Clinical trials*. For further specification, the "*Gingival hyperplasia*" 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 62 articles were found and submitted to eligibility analysis, with 20 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=70.8%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 02 studies with a high risk of bias and 10 studies that did not meet GRADE and AMSTAR-2.

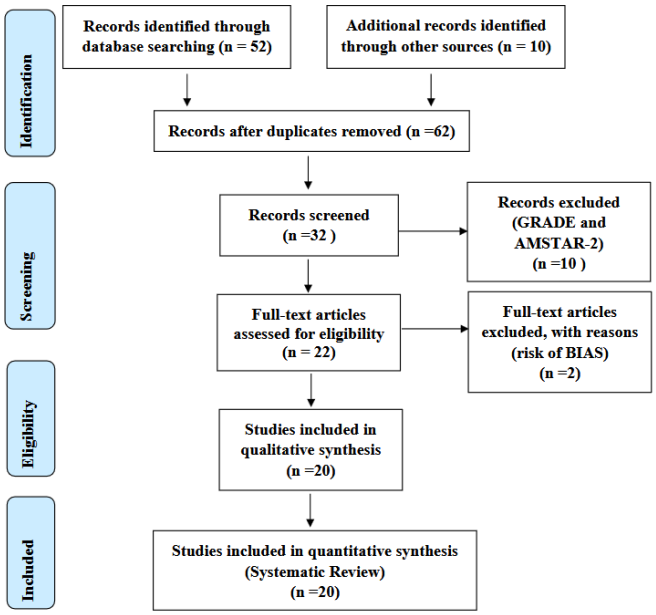

Figure 1. Flowchart showing the article selection process. Source: Own authorship.

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.

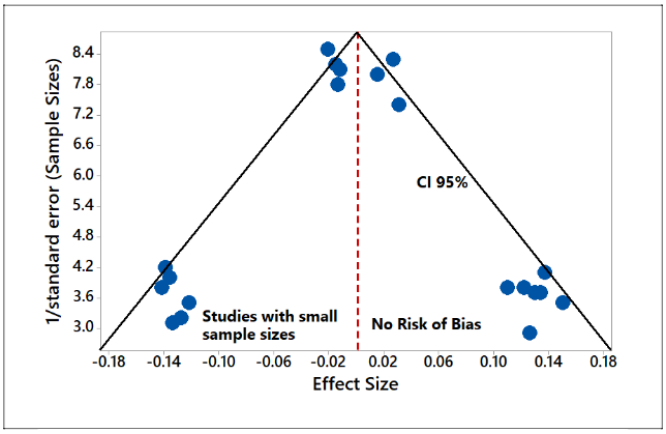

Figure 2. The non-symmetrical funnel plot suggests risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=20 studies). Source: Own authorship.

Development and Discussion

The present study pointed out that some patients use systemic drugs, which can affect the periodontal tissues, modifying their inflammatory and immune response, mainly the gingiva, causing drug-induced gingival growth [1,2]. Drugs associated with gingival hyperplasia are an adverse reaction related to the systemic use of anticonvulsant medications, calcium channel blockers, and some immunosuppressants such as cyclosporin A (CPA). Thus, quality hospital care requires a multiprofessional team capable of offering comprehensive care to the hospitalized individual. In periodontics, it is important to know the aspects of drug use, which may present gingival hyperplasia, and secondly, there may be manifestations of perioral hyperesthesia [2].

After careful consideration of the main literature on gingival hyperplasia (GH) and its pharmacological predictors, it was found that an increase in patients with kidney transplantation and also with other pathologies leading to the use of drugs such as phenytoin, nifedipine, and cyclosporin A. However, GH can be erroneously mistaken for gingival hyperplasia. The name "gingival growth and/or gingival hypertrophy" is a function of histological study, the occurrence of increased extracellular matrix synthesis, mainly in collagen, and an increase in the size and number of fibroblasts present in the tissue. Scientific research has shown that CPA can modify the metabolism of the gingival and bone tissue and the composition of the oral biofilm, the flow and composition of the gingival fluid [15-18].

In this context, CPA is a cyclic peptide composed of 11 amino acids, produced by the fungus *Tolypocladium inflatum*. Its action is inhibited by the proliferation of T lymphocytes. However, CPA is associated with undesirable side effects, including nephrotoxicity, lymphoma, and gingival growth. Several cases of gingival growth caused by the use of CPA have been described in the literature [16]. CPA is primarily metabolized in the liver, and a small part is eliminated through the urine. It is a medically immunosuppressant used in patients receiving organ transplantation, such as kidneys, liver, skin, and heart, used to prevent rejection of the transplanted organ in order to improve graft survival preventing rejection [17-18].

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].

Thus, the tissue increase can promote the

impaction or deviation of the teeth, thus leading to malocclusion, besides the presence of false periodontal pockets [19]. 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. 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].

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].

Despite this, not all patients treated with phenytoin develop gingival growth, the prevalence of this undesired effect being approximately 50% for patients receiving phenytoin, while for cyclosporine A and nifedipine, the percentages are around 30% and 20%, respectively [1-3]. However, it is controversial whether there is any relationship between the dose and the risk or severity of hyperplasia [4].

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 antiepileptic-associated 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].

In this sense, it is necessary to detail the conclusive diagnosis of GH, since some non-neoplastic proliferative processes, such as pyogenic granuloma, giant cell peripheral lesion, papilloma, and condylomata acuminata, may be similar. Thus, it is necessary to perform the biopsy to exclude other lesions from the differential diagnosis and confirm the diagnostic hypothesis [5].

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]. Thus, 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].

Also, prophylactic oral hygiene measures are necessary to control local oral factors in order to minimize the effects of local inflammation and / or systemic factors [2]. If gingival growth occurs, in spite of these preventive measures adopted, this professional should schedule a new scaling, curettage, dental and periodontal polishing before beginning the removal of hyperplasias, which may or may not be necessary [8].

Finally, to differentiate GH from gingival fibromatosis (GF), it is necessary to know that GF is characterized by a large increase in the gingival dimension that extends above the dental crowns. The causes of GF may be of genetic origin, but GH may occur alone or as part of a syndrome, or of an acquired origin, from specific drugs administered systemically [8].

Limitation

There are still gaps in information regarding the incidence and prevalence of gingival hyperplasia under medication use, especially when patients have comorbidities and the duration of drug use. 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

The surgeon-dentist should be attentive during the anamnesis to the cases of patients who take medications that induce gingival hyperplasia, such as anticonvulsants. As there is no possibility of predicting which patients will develop this problem, interdisciplinary work with the attending physician should be advocated in order to protect the patient against adverse effects. It is up to the professional to accompany the patient through plaque control, scaling, and oral hygiene instructions, preventing and treating cases of gingival growth. It is imperative for the dentist to understand the general condition and the limitations of each patient, so that he can control and cure the most varied oral manifestations, in order to maintain a good quality of life in the patients.

CRediT

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