

Drug-Induced Changes in the Gingival Tissue

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ABSTRACT

Introduction: Drug-induced gingivitis is caused by the administration of certain drugs such as hydantoin, calcium blockers, beta-blockers, cyclosporine, and oral contraceptives. The aim of this study was to evaluate the modifications linked to drug-induced gingivitis such as changes in color, volume, and consistency, and the clinical signs of periodontal disease. **Materials and methods:** The study was based on a questionnaire made up of 14 questions, formulated using colloquial language to increase addressability. **Results:** The most frequently used drugs were beta-blockers (37%), calcium channel blockers (33%), followed by anticonvulsants (18%), oral contraceptives (8%) and cyclosporine (4%). Color changes occurred in 81% of anticonvulsant treatments and 57% of oral contraceptives. Increases in the gingival volume were higher with anticonvulsants (73%) followed by cyclosporine (67%). Gingival consistency was higher with anticonvulsant treatments (90%), followed by calcium channel blockers (60%). Gingival changes and gingival bleeding during brushing were higher with anticonvulsant treatments, followed by beta-blocker medication. Spontaneous gingival bleeding had a higher prevalence in anticonvulsant treatments, followed by cyclosporine. **Conclusions:** The patients most affected by gingival enlargement were those under hydantoin treatment, followed by cyclosporine. Calcium channel blockers and beta-blockers had similar effects on gingival pathology. The intensity of the pathological changes that occurred secondary to the administration of these drugs was influenced by the dose, the duration of the treatment, and the association of several drugs. Early detection and management of gingival enlargement is important in order to allow patients to continue with their therapy, and also to increase their quality of life.

Keywords: gingival enlargement, hydantoin, calcium blockers, beta-blockers, cyclosporine, contraceptives

INTRODUCTION

Periodontal diseases include a large variety of conditions, some of which are induced by bacterial plaque, while others occur separately from biofilm build-up and may be modified or unaffected by it. The periodontal disease classification system of 1999 was the first to recognize the need to classify gingival diseases, but it had numerous flaws. This classification system did not define the state of periodontal

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health, which is a critical factor in establishing the diagnosis of periodontal diseases. The description of gingivitis was excessively complex because it included both predisposing factors and factors that modify the evolution of the disease in the diagnosis. In 2017, a new classification was proposed that helps clinicians in establishing the diagnosis of periodontal diseases. New concepts, such as periodontal health status, were introduced, both histologically and clinically. Also, a reduced methodology was adopted, which helps to classify gingivitis in two major categories: gingivitis caused by the dental biofilm (due to dental biofilm only; facilitated by systemic or local risk factors; drug-induced gingival hypertrophy) and gingival conditions not caused by the dental biofilm (such as genetic/developmental conditions; specific infective disease; inflammatory and immune disorders; reactive processes, malignant, endocrinological and nutritional disorders, but also traumatic lesions and pigmentation).^{1,2}

Nowadays, most people after a certain age receive a treatment that involves certain medication, which can have a multitude of adverse effects, with visible changes in the oral cavity. Drug-induced gingivitis is caused by the administration of drugs such as hydantoin, calcium blockers, beta-blockers, cyclosporine, and oral contraceptives.³ Patients who have been prescribed both calcium antagonists and cyclosporine show excessive hypertrophy of the gingival tissue due to the combined effects of the two drugs.⁴

Hydantoin, used in the treatment of epilepsy, produces gingival hyperplasia in most patients, especially in children.⁵ The association between hydantoin and gingival enlargement has been widely described. Other anticonvulsants, such as barbiturates, valproic acid, succinimides, and carbamazepine, may also induce gingival hyperplasia. However, the incidence of gingival hyperplasia associated with these agents is low compared to that of hydantoin-induced gingival enlargement. Of the 2 million patients taking hydantoin, approximately half had some degree of gingival hyperplasia, which may be related to the dosage, duration of treatment, and plasma levels of the drug.⁶ Hydantoin hyperplasia also occurs in the absence of plaque and calculus in patients with good oral hygiene. The presence of bacterial plaque, however, causes increased inflammation, which also increases gingival hypertrophy and hyperplasia.

Calcium antagonists are a group of drugs used in the treatment of cardiovascular diseases that inhibit the influx of calcium ions through the cell membrane of cardiac cells and smooth muscles, blocking the intracellular mobilization of calcium. This leads to the dilation of coronary arteries and arterioles, thus improving the oxygenation of the heart muscle and reducing blood pressure by dilating peripheral vessels. Secondary to the administration of some of

these drugs, gingival hyperplasia may occur.⁷ The treatment of cardiovascular diseases with calcium channel inhibitors may have different effects in the oral cavity. It may restore cellular metabolism and stimulate cell proliferation in the gingiva. Histologically, calcium channel blocker-related gingival hyperplasia is characterized by an increase in the number of fibroblasts that closely resemble hydantoin-induced hyperplasia, a predominantly lymphocytic nonspecific inflammation. After a long-term treatment with amlodipine, mispositioned teeth were observed on both arches, which may lead to tooth extractions.⁸ In the case of gingival hyperplasia caused by calcium antagonists, dental practitioners will not recommend stopping such a vital treatment, instead they will treat it with appropriate local therapy.⁹

Beta-blocker medication produces gingival enlargement in the lowest percentage of all antihypertensive medications. Research shows that some beta-blockers can still cause gingival hyperplasia, but with a very low prevalence rate of around 7.4%.¹⁰

Cyclosporine is an immunosuppressant administered to prevent the rejection of transplanted organs and for the treatment of autoimmune diseases. Gingival hyperplasia occurs in 30% of patients who receive this drug, more often in children.¹¹ Several techniques for gingival hyperplasia have been proposed, including dose reduction or substitution of medication, but also optimal oral hygiene programs and surgical treatment. Nevertheless, each of these approaches may have contraindications, and dose reduction or the use of alternative drugs is not possible in all situations. Other medicines may also have side effects. Surgery is only used for cosmetic reasons, and oral hygiene procedures can be used only for disease control in patients developing cyclosporine A-induced gingival hyperplasia but cannot inhibit its development.¹²

Oral contraceptives are used by approximately 50 million women worldwide. Numerous systemic and oral adverse reactions have been identified in patients who are under oral contraceptive treatment. Studies have found that the use of oral contraceptives is associated with a higher prevalence of gingival inflammation, attachment loss, and progression of periodontal disease.¹³ Both estrogen and progesterone are known to cause increased gingival exudate, edema, and inflammation.¹⁴ Women taking oral contraceptives for more than 1–2 years have been found to present gingival bleeding on probing, deeper periodontal pockets, and significant attachment loss. This indicates that the longer the duration of oral contraceptive use, the poorer the periodontal health status.

Due to the controversies surrounding the side effects of certain drugs on the gingival tissue and drug-induced gin-

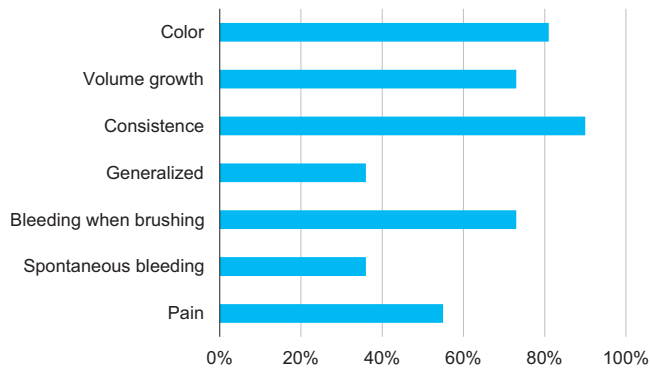


FIGURE 1. Gingival changes due to hidantoin

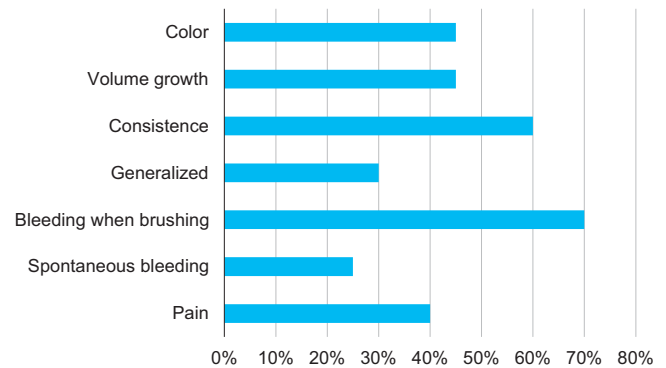


FIGURE 2. Gingival changes due to calcium blockers

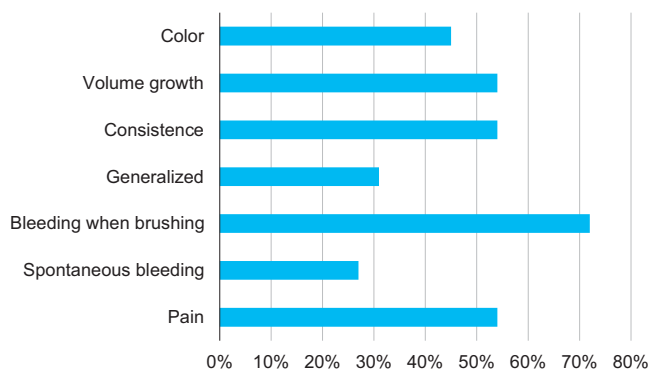


FIGURE 3. Gingival changes due to beta-blockers

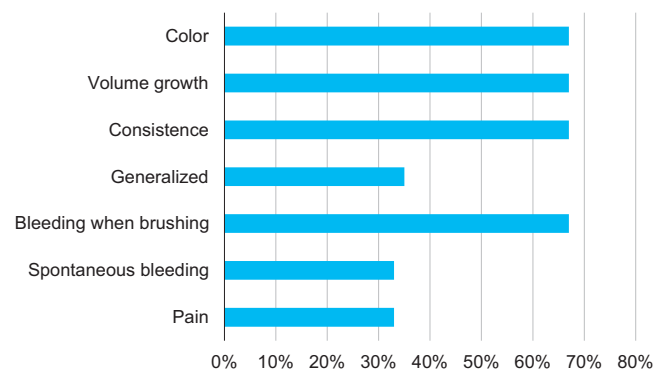


FIGURE 4. Gingival changes due to cyclosporine

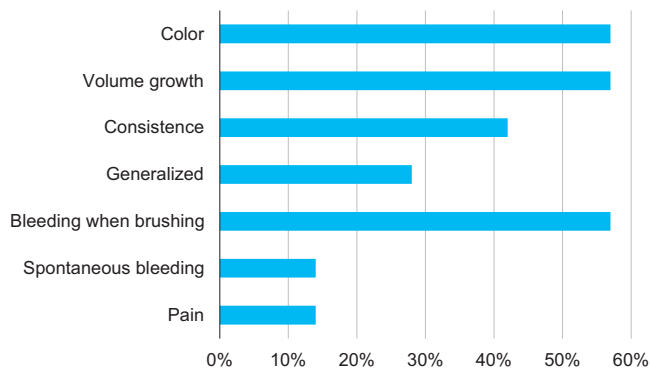


FIGURE 5. Gingival changes due to contraceptives

gival hyperplasia, we decided to evaluate the modifications linked to drug-induced gingivitis.

MATERIALS AND METHODS

The study took place between April 2020 and June 2021 at the Faculty of Dental Medicine of the “George Emil Palade” University of Medicine, Pharmacy, Science and Technology of Târgu Mureș, Romania. Due to the COVID-19 pandemic, our study was based on a questionnaire made up of 14

questions using colloquial language (for example: “increase in the volume of the gum” for gingival hypertrophy) to increase addressability. In the absence of a clinical examination, the questions were formulated according to the structure of an anamnestic questionnaire in order to guide the results toward formulating the most realistic conclusions possible regarding periodontal health. The first two questions referred to personal characteristics such as age and sex. Questions 3–7 referred to drug treatments that could induce changes in periodontal structures. Through questions 8–10, we wanted to detect the changes in color, volume, and consistency that appeared at a periodontal level. Questions 11–14 were related to the observation of relevant clinical signs that would suggest the installation of periodontal diseases: bleeding when brushing and the presence of gingival pain.

RESULTS

The majority of the patients were men (58.4%) aged between 50 and 69 years (68%). The most frequently used drugs were beta-blockers (37%), calcium channel blockers (33%), anticonvulsants (18%), oral contraceptives (8%), and cyclosporine (4%).

The changes that appeared in the gingival tissue due to the administration of these medications are presented in Figures 1–5. The most frequent changes in patients undergoing hydantoin treatment included changes in consistency, color, and also bleeding (Figure 1). For subjects treated with calcium channel blockers, the most frequent change was in consistency and bleeding while brushing (Figure 2), which was similar to those treated with beta-blockers (Figure 3). On the other hand, subjects undergoing treatment with cyclosporine more frequently presented changes in color and volume growth, but also changes in consistency and bleeding (Figure 4). The use of oral contraceptives triggered bleeding during brushing, changes in color and consistency (Figure 5).

DISCUSSION

The results of our study showed that color changes occurred in 81% of anticonvulsant treatments and 57% of oral contraceptives. Increases in the gingival volume were higher in patients receiving anticonvulsants, followed by cyclosporine. Gingival consistency was higher in subjects undergoing anticonvulsant treatments, followed by calcium channel blockers. Gingival changes and gingival bleeding during brushing were higher with anticonvulsant treatments, followed by beta-blocker medication. Spontaneous gingival bleeding had a higher prevalence in anticonvulsant treatments, followed by cyclosporine.

Many studies were conducted concerning the side effects of drugs on the gingival tissue. A retrospective study found only 147 cases of drug-induced gingival hyperplasia (0.04% of all cases). Patients were more frequently male (58.5%), aged between 40 and 69 years. The evolution was favorable in 47.5% of cases. The most common “suspected” drugs were calcium channel blockers (30.6%), followed by immunosuppressants (15.2%) and anticonvulsants (10.1%). Gingival hyperplasia has also been reported with less well-known periodontal drugs (mycophenolate mofetil, valproic acid, clarithromycin, ethinylestradiol, levonorgestrel, desogestrel etc.).¹⁵

Another study found that genetic factors and patient susceptibility are important for the etiopathogenesis of amlodipine-induced hyperplasia. Genetic predisposition may influence drug interactions, cells characteristics, plaque-induced inflammation, functional heterogeneity of gingival fibroblasts, collagenolytic activity, drug-receptor binding, collagen synthesis, and many other factors. Since most types of pharmacological agents involved in amlodipine-induced hyperplasia can have negative effects on the flux of calcium ions across cell membranes, it has been

postulated that these agents can interfere with collagenase synthesis and function.¹⁶ A recent in vitro study showed that treating human gingival fibroblasts with cyclosporine in relevant doses leads to significantly lower levels of MMP-1 and MMP-3 secretion. This will contribute to the accumulation of extracellular matrix components.¹⁶

Treatment with other antihypertensive medication, such as angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and beta-blockers, produces changes at the gingival level less often compared to calcium channel blockers.^{17,18} Therefore, in patients at risk for developing drug-induced gingivitis or those who already did, replacing calcium channel blockers with other antihypertensive drugs is a treatment option.¹⁹

Another study showed that drug-induced gingival hyperplasia occurs mainly in medical therapy with phenytoin, the antihypertensive drug nifedipine, and the immunosuppressant cyclosporine in 50% of the people who take this kind of medication. Gingival enlargement induced by drugs is an important oral health issue, particularly if insufficient attention is paid to oral hygiene by dentists or the patients themselves. This may occur due to a miscommunication between patients and physicians.²⁰

Excessive gingival enlargement causes both physical and psychological suffering. Generally, the increase in gingival volume is limited, but severe cases can also occur when the gingival tissue completely covers the teeth, thus interfering with chewing and speaking. Gingival enlargement can also lead to depression and anxiety, especially when it causes esthetic problems, affecting the smile and facial expressions.²¹

CONCLUSIONS

The patients most affected by gingival enlargement are those under hydantoin treatment. After hydantoin, cyclosporine is the drug with the most adverse side effects on the periodontium. Calcium channel blockers and beta-blockers have similar effects on gingival pathology. The intensity of the pathological changes in the gingival tissue that occur secondary to the administration of these drugs is influenced by the dose, the duration of the treatment, and the association of several drugs. Early detection and management of gingival enlargement is important in order to allow patients to continue with their therapy, and also to increase their quality of life.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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