REVIEW PAPER

GINGIVAL ENLARGEMENT CAUSED BY CALCIUM CHANNEL BLOCKERS

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ABSTRACT

Calcium channel blockers, a group of drugs widely used in the treatment of cardiovascular patients, although effective, often cause gingival enlargement, a side effect that is rarely recognized in clinical practice and is not given sufficient importance. Gingival enlargement caused by calcium channel blockers can be localized or generalized, mild or severe. It can negatively affect patients' appearance, mastication, and speech, thus considerably reducing the quality of life of patients. Risk factors and pathogenesis of this side effect have been the subject of many studies but are still unknown, making this condition a major therapeutic challenge, especially if the cessation of the offending drug is not possible. This study aimed to review the etiology, potential risk factors, pathogenesis, clinical features, and therapy possibilities for gingival enlargement caused by calcium channel blockers.

Keywords: *Drug-induced gingival enlargement; calcium channel blockers; oral adverse effects.*

ABBREVIATIONS:

DIGE – Drug-induced gingival enlargement
CCBs – Calcium channel blockers
WHO – World Health Organization
DHPs – Dihydropyridines
non-DHPs – Non-dihydropyridines
SA node – Sinoatrial node
AV node - Atrioventricular node
MDR1 – Multidrug resistance protein 1
MMPs - Matrix metalloproteinases
TIMP - Tissue inhibitor of matrix metalloproteinases
HLA - Human leukocyte antigen
IL-1β – Interleukin 1β
IL-6 – Interleukin 6
ROS - Reactive oxygen species

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INTRODUCTION

Gingival enlargement is a disorder of the appearance and structure of the gingiva in terms of tissue size. Over the years, different types of gingival enlargements have been observed, divided based on etiological factors into inflammatory enlargements, enlargements associated with systemic diseases, neoplastic enlargements and drug-induced gingival enlargements. (1). Drug-induced gingival enlargement (DIGE) is a tissue-specific adverse effect (2) mainly associated with the usage of antihypertensive, immunosuppressive, and anticonvulsive drugs (3). The terms "gingival hyperplasia" and "gingival hypertrophy" were once used for this adverse effect; however, having a better insight into the pathogenesis and histological findings, the names "enlargement" and "overgrowth" were accepted (4, 5). DIGE often occurs within three months of commencing the therapy and predominantly affects anterior parts of the gingiva (6). Possible risk factors for DIGE can be grouped into the following categories: genetic, systemic, local, and drug-related (5). Alike other side effects of medicines in the oral cavity (xerostomia, altered taste, lack of taste, etc.), this side effect significantly affects patients' quality of life, so it should be borne in mind and given importance. Despite the fact that this adverse effect of different classes of drugs represents a major therapeutic problem, it is not truly recognized and evaluated in medical practice for many reasons. The objective of this article was to review the etiology of CCBs induced gingival enlargement, possible risk factors for its occurrence, pathogenesis, clinical features and treatment of DIGE.

Calcium channel blockers (CCBs)

Calcium channel blockers (CCBs) are a heterogeneous group of drugs that have been widely prescribed for many cardiovascular indications, including hypertension, angina pectoris, hypertrophic cardiomyopathy, and pulmonary hypertension (7). They can also be used in the treatment of Raynaud syndrome, migraine, and subarachnoid haemorrhage. CCBs are classified into two major categories, based on their chemical structure and physiologic effects: dihydropyridines (DHPs, e.g. nifedipine, amlodipine, isradipine), and non-dihydropyridines (non-DHPs, e.g. verapamil - phenylalkylamine, diltiazem - benzothiazepine) (8). Nifedipine, verapamil, and diltiazem belong to the first-generation of CCBs with a short duration of action; second-generation include manidipine and nicardipine; amlodipine and isradipine are third-generation of CCBs, with long-lasting action and far fewer side effects in comparison with the first-generation (5). CCBs inhibit the extracellular influx of calcium into the cells by blocking calcium channels located in the heart, smooth vascular muscles, and pancreas (8). This results in reduced blood pressure due to arterial vasodilatation and decreased heart rate and myocardial force (5). The dihydropyridines act as peripheral vasodilators, which is why they are mostly used for hypertension and migraine treatment (9). The DHPs are recommended as the first-line monotherapy for hypertension management (10). On the other hand, non-dihydropyridines affect the sinoatrial (SA) and atrioventricular (AV) nodes, leading to the slowing of cardiac conduction (8). Because of that particular effect, they are useful for hypertension and tachydysrhythmia treatment. CCBs are generally well absorbed orally but may exhibit low bioavailability due to cytochrome P450 3A4 metabolism in the liver, which might also be responsible for the interactions of CBBs with other drugs (8). The administration of CCBs is contraindicated in several cases. They should be avoided in patients with heart failure, AV blockade (second or third degree), severe hypotension, and sick sinus syndrome (11).

Despite the fact that use of the calcium channel blockers is effective therapeutic option in antihypertensive, antianginal or antiarrhythmic manner, their effectiveness may be diminished by adverse effects (12).

Systemic adverse effects of CCBs

Adverse effects of CCBs can be predicted based on their pharmacological characteristics. Major side effects might be classified into several groups: vasodilation, gastrointestinal effects, metabolic reactions, and interactions with other drugs (mainly cardiac glycosides and beta-blockers) (13). Vasodilation is associated with headaches, palpitations, peripheral edema, and hypotension. Edema, headaches, and flushing are common adverse effects attributed to CCBs, especially nifedipine (13). Studies have also shown that nifedipine could cause reflex tachycardia (14). Gastrointestinal side effects include constipation, diarrhea, and nausea. Constipation has been reported in 12 to 42% of patients taking verapamil, so some of them stopped using it for this very reason. About 10% of patients experience dizziness, flushing, and weakness, during treatment (14). Some of the reported side effects of CCBs are transient hypotension, nasal congestion, and dermatological manifestations, such as dermatitis. All of these symptoms occur in less than 5% of patients (14). The idiosyncratic rash might sometimes be seen in the patients taking diltiazem, but it is very rare, and only 2% of patients report this kind of adverse effect (13). Still, all these side effects are not very frequent, especially when it comes to the new and improved generations of CCBs.

CCBs are - strongly linked, independent of generation, with gingival overgrowth (5). It is estimated that 30–50% of CCBs users experience gingival enlargement during the treatment (5). The first case of nifedipine-caused gingival overgrowth was documented in the mid-1980s (15). Amlodipine-caused gingival enlargement was first noted in 1994 (16). Newer generations of CCBs such as nicardipine, felodipine, and nitrendipine are also reported to have gingival enlargement as a side effect (16). One of the CCBs that has not been associated with gingival overgrowth is isradipine (5). A higher prevalence of CCBs-induced gingival enlargement might be related to concurrent therapy, such as statins (17). CCBs-induced gingival overgrowth might be noted in patients with dental implants, and also edentulous patients (18, 19). Table 1 shows the recommended dose of CCBs for hypertension and the prevalence of causing DIGE.

Table 1. Calcium channel blockers, their dosage and prevalence for inducing DIGE

Drug	Dosage for hypertension	Prevalence of gingival enlargement
Nifedipine	20 mg once or twice a day[72]	15-85%[1]
Amlodipine	5-10 mg once a day[72]	31.4%[21]
Diltiazem	90-180 mg twice a day[72]	2.2%[21]
Lercanidipine	10 mg once or twice a day[72]	13.3%[73]
Felodipine	2.5-10 mg once or twice a day[72]	12.5%[73]

PREVALENCE AND EPIDEMIOLOGY

It is difficult to determine the exact prevalence of DIGE due to many factors, such as neglect and non-reporting of this side effect, different indices for assessing gingival enlargement, focus on institutionalized versus outpatient population, due to which disease the patient takes the given medicine, age of the patient, combination therapy, periodic dental examinations and so on (4, 20). The first cases of DIGE caused by CCBs date from the 1980s, and the results from various prevalence studies are confusing, ranging from 20% to 83% (21-24). Data from the literature indicate that it is most commonly caused by nifedipine (15-85%). In comparison, diltiazem (2.2%) and amlodipine (31.4%) are less likely to provoke it (1, 21, 25). The different tendency of the drug within the group to cause this side effect is explained by the drug's pharmacokinetics, i.e., nifedipine is more lipophilic and passes through cell membranes faster, while amlodipine cannot do so without an active transport mechanism. Additionally, nifedipine's half-life allows it to reach the plasma levels necessary for the initiation of gingival enlargement. On the other hand, amlodipine has a long half-life (T1⁄2= 34 hours) and a steady plasma state (21, 25, 26).

RISK FACTORS

Drug-induced gingival enlargement does not occur in all patients taking CCBs, and the prevalence and severity of the clinical features vary from patient to patient. Therefore, it is possible to talk about risk factors or favoring factors for the occurrence of this side effect, in addition to the nature of the drug (27).

Regarding the age of the patients, when using CCBs, it cannot be taken as a risk factor, having in mind that these drugs are prescribed to patients who belong to the middle-aged population and the elderly. Certain studies have identified age as a risk factor, but only in the case of combination therapy with CCBs and cyclosporine (21, 27).

Gender can be a risk factor in the sense that this side effect occurs more than three times often in men, which is associated with the potential existence of a serum threshold for initiation, and that this threshold is lower in men. Nifedipine has also been shown to cause the conversion of testosterone to an active metabolite that stimulates fibroblasts. Animal model studies have also shown that male animals are more prone to gingival enlargement than females (21, 26, 27). Also, men's lifestyle and habits may be associated with a higher risk, i.e., with pre-existing factors related to hypertension (smoking, alcohol consumption, diabetes mellitus, low-density lipid) (5, 28).

Dose regimen of the drug is considered an inadequate predictor of gingival changes, and it may be more reliable to take into account the patient's weight when determining the dose dependence of this side effect. Previous studies conclude that there is probably a particular threshold concentration of drug in the serum necessary to trigger these changes, but that it is individual and varies from person to person (27, 29, 30). Nifedipine-induced gingival enlargement occurs at doses of 5 mg/day, 10 mg/day, or 20–40 mg/day, and amlodipine even at doses of 2.5 mg/day for extended periods of time (5, 28, 31-33). Regarding the duration of therapy, it is acknowledged that more prolonged therapy may increase cell exposure to the drug, modifying apoptosis and causing increased cell viability and growth (33, 34).

Dental plaque is one of the leading causes of all inflammatory periodontal diseases, and it has been proven that its presence worsens drug-induced gingival enlargement. It has already been established that poor oral hygiene correlates with the severity of the changes. It has been determined that dental plaque is a relevant co-factor in developing this side effect (27, 35, 36). However, since mostly cross-sectional studies have been performed, it has not been fully established whether dental plaque is only the predisposing factor or whether its amount increases due to the existence of gingival changes that impede good oral hygiene (27). The first

hypothesis is supported by the fact that DIGE is topically associated with dentate regions, and thus where there is inevitably a certain amount of dental plaque (5, 35). Risk factors for DIGE may also include local factors that promote plaque accumulation, such as teeth malposition, inadequate fillings and prosthetic restorations, and the presence of calculus (5, 37). Important information is also that nifedipine achieves a higher concentration in inflamed gingival tissue, directly affecting keratinocytes (33, 38).

Although insufficiently researched, genetic predisposition is considered one of the risk factors for the development of DIGE. Since CCBs are metabolized via cytochrome P450, it is thought that the polymorphism of the cytochrome P450 gene that affects enzyme activity may represent a specific individual risk factor for DIGE (25, 27). As a consequence, despite taking the same dose of the drug, due to the different function, there will be a different concentration of the drug in the serum and tissue, which may explain why only certain patients have DIGE (5, 28, 39). Also, it has lately been pointed out that multidrug resistant (MDR1) gene polymorphism can modify the inflammatory response to the presence of these drugs (25, 33, 40).

PATHOGENESIS

The exact etiology and pathogenesis of this side effect of the drugs are still not fully recognized. Over the years and as a result of numerous studies, there are certain proposed theories and pathways of DIGE.

Based on the histological analyses, various groups of medications induce lesions with different characteristics. Anticonvulsants, such as phenytoin, lead to fibrosis, immunosuppressant-induced lesions mainly have an inflammatory component, while antihypertensive drugs, like calcium channel blockers (CCBs), provoke the mixed type of lesions (41).

The basis of drug-induced gingival enlargement is fibrosis, i.e., increased production of the extracellular matrix of connective tissue where collagen fibers predominate. Collagen synthesis takes place under the regulation of matrix metalloproteinases (MMPs), and tissue inhibitor of matrix metalloproteinases (TIMP), while collagen degradation occurs via collagenases (extracellular pathway) or phagocytosis (intracellular pathway). As CCBs affect calcium metabolism by reducing Ca2+ influx, folic acid intake is reduced. Reduced amounts of folic acid in the cell lead to an increase in TIMP concentration, which reduces the concentration of MMPs necessary for collagenase activation, thus preventing the degradation of collagen fibers. Due to the reduced degradation of the fibers, their accumulation occurs. One of the other proposed mechanisms is an increased production of the extracellular ground substance due to the increased presence of glycosaminoglycans (22, 35, 42-45).

Theories about the genetic predisposition of the patient for the occurrence of this side effect (cytochrome P450, human leukocyte antigen - HLA and MDR1 gene polymorphisms) exist, and this knowledge would be important when identifying patients at risk (25, 27, 33, 40, 46).

The fact is that drugs that cause gingival enlargement induce reparative processes in the gingival tissue accompanied by inflammation, which further induces fibrosis present within the extracellular matrix. Secondary drug-induced inflammation may be necessary for the onset of fibrotic processes but not for further progression. Certain reparative and proliferative phenotypes of macrophages and proinflammatory cytokines, such as interleukin 1β (IL-1β) and interleukin 6 (IL-6), have been shown to increase in the presence of DIGE, indicating an inflammatory component of this side effect, as a reaction to drugs (43, 47, 48). They are thought to have a synergistic effect by acting on fibroblasts and stimulating collagen fiber formation and glycosaminoglycan synthesis (35, 43, 49). In the case of amlodipine-induced gingival enlargement, increased synthesis of B-cell lymphoma 2 oncoprotein, which inhibits keratinocyte apoptosis, was observed (5, 45).

The interdental papilla is the site of the most considerable accumulation of bacterial biofilm but also the greatest DIGE. Due to its structure and constant exposure to aggravating factors, there are several molecules at this site that participate in the wound healing process, such as surface receptors, procollagen type 1, fibronectin, glycosaminoglycans, and growth factors. In the development of DIGE, it is uncertain that a deregulated cytokine imbalance provides a significant contribution (43, 50, 51).

The possible influence of androgens in the pathogenesis of DIGE is indicated by the fact that there are more androgen receptors in the gingival tissue of patients with this side effect (25, 52). Also, nifedipine directly induces the conversion of testosterone to 5 α-dihydrotestosterone, the active metabolite which further targets specific fibroblast subpopulations, stimulating collagen production or preventing degradation (1, 5, 21, 35, 53, 54).

One of the new aspects of consideration in the pathogenesis of DIGE is oxidative stress. It has been shown that reactive oxygen species (ROS) and shifted oxidative status are closely related to the progression of fibrotic changes, and their increase leads to stabilization of the extracellular matrix and increased resistance to degradation (43). A recent study suggests that DIGE inducing drugs may increase ROS production and that antioxidant status disorder participates in the progression of DIGE (56).

CLINICAL FEATURES

The drug-induced gingival enlargement usually commences between the third and sixth month from the beginning of therapy, progresses gradually, and reaches a plateau phase between 9 and 12 months (4, 35, 43, 56). The enlargement can be generalized or localized, but most often it affects the labial side of the gingiva of the front teeth, which is explained by the greater exposure of this part of the gingiva to

irritating factors and dental plaque (5, 25, 43, 56). In the initial stages, nodular thickening of the interdental papilla (horizontal growth) occurs, which later spreads coronally (vertically) and can cover the entire surface of the clinical crown. With further disease progression, the surrounding surfaces can be affected, i.e., the marginal gingiva can also be altered, and the entire gingival surface acquires a lobular appearance (4, 5, 25, 35, 43, 56, 57). In cases of mild enlargement, patients usually do not feel pain, but in serious cases, discomfort may occur during mastication (5, 32). In the beginning, the gingiva is light pink in color, lobular and enlarged, without bleeding. However, due to the formation of pseudopockets and difficult maintenance of hygiene of those places, inflammation is almost always combined, so the gingiva changes color to red and bluish-red discolorations, with smooth surface, and a pronounced tendency to bleeding is noticed. (5, 25, 35, 57.). Depending on the severity and progression of the disease, patients may experience aesthetic problems, difficulties in speech and mastication, a constant feeling of a foreign body between the teeth, halitosis, all of which significantly reduces the quality of life (5, 25, 33, 35). The onset of gingival enlargement promotes the accumulation of dental plaque, and the components and host response to dental plaque worsen the clinical picture of DIGE, so it represents a perpetuating cycle (43). As a result of poor hygiene, inflammation, caries, and periodontal disease can occur, ultimately leading to bone and tooth loss (5, 25, 33, 35). The increased potential for plaque retention may also jeopardize systemic inflammation and thus raise the risk of cardiovascular complications in patients taking CCBs (27).

Pathohistologically, parakeratosis of the squamous epithelium with acanthosis and elongated epithelial ridges is noted in DIGE. Within the lamina propria of connective tissue, various fibroblasts, increased vascularization, infiltration by various inflammatory cells (dominant plasma cells and fewer lymphocytes), as well as accumulation of extracellular matrix proteins such as collagen, amorphous ground substance, and glycosaminoglycans are observed (5, 35, 43, 57-59). An increase in the volume of gingival tissue is more in line with changes in connective tissue than epithelial proliferation, which is why the former name "gingival hyperplasia" is rejected (4, 5, 35, 57).

TREATMENT

Keeping in mind the mechanism of occurrence of this side effect, the best therapy method would be replacing the drug that caused DIGE with some of the drugs from another category of antihypertensives, such as beta-blockers, diuretics or angiotensin-converting enzyme inhibitors that are not associated with DIGE (4, 25, 35, 60, 61-63). Another option is to prescribe isradipine or verapamil, which are related to a much smaller percentage of this side effect, according to the results of previous studies (35, 60, 62). However, if hypertension is successfully regulated by a drug that causes DIGE, both the patient and the physician are often reluctant to change the prescribed therapy, so this may be one of the problems regarding this therapeutic approach (25, 35). It is also essential that relapse after surgical and conservative treatment occurs in a high percentage in patients who have not replaced the drug, but also in those who have had very poor oral hygiene (35, 62).

In addition to discontinuing the therapy, one of the first therapeutic methods should be the elimination of dental plaque, having in mind the possible influence of dental plaque in the pathogenesis of DIGE, as well as the impact on the worsening of the clinical appearance (4, 25, 62, 64). Therefore, conservative treatment is necessary, which includes full mouth debridement, scaling and root planning, as well as training and motivation of the patient to maintain good oral hygiene (4, 5, 35, 62, 65, 66). The combination of regular professional plaque control and good oral hygiene in less severe cases of DIGE can lead to a reduction in the degree of enlargement and a general improvement in periodontal health. In this way, the risk of loss of clinical attachment level, which exists due to the increased accumulation of bacterial biofilm because of the existence of pseudopockets, is reduced (4, 5, 35, 62, 67). These measures are also necessary to prevent the recurrence of this side effect (5, 62, 66, 67).

However, in many cases, after the change of therapy and the application of the conservative treatment, DIGE persists. In these cases, it is necessary to apply the surgical treatment, which involves gingivectomy and gingivoplasty or periodontal flap surgery (4, 25, 62, 64). Excess tissue is removed through surgery, thus eliminating pseudopockets, returning tissue contour, appearance, and function. After the surgery, patients can adequately maintain oral hygiene, which is necessary to prevent recidivism (35, 62). The use of carbon dioxide laser is suitable in these cases due to accuracy in cutting, better hemostatic and antimicrobial effect, minimal edema and postoperative pain, as well as dry field and improved visibility (4, 5, 25, 35, 68, 69).

Since the latest research results indicate the potential role of ROS in the pathogenesis of DIGE, in the future, one of the possible preventive and therapeutic methods may be the administration of a scavenger of ROS, such as vitamin E (56).

Unfortunately, the incidence of recurrence is 40% (4, 25, 35, 62) within the first 18 months after the treatment (4, 70), which makes DIGE a major therapeutic problem. The most significant risk factors for recurrence are younger age, gingival inflammation and irregular visits to the dentist (4, 5, 69, 70). It is also concluded that regular use of chlorhexidine oral rinse (0.12%) after surgery helps prevent reappearance by inhibiting plaque accumulation and gingival inflammation (4, 68, 71).

CONCLUSION

Calcium channel blockers are often prescribed medicines primarily used in the treatment of hypertension, a disease with a high prevalence. CCBs-induced gingival enlargement is a side effect that is often neglected, and patient's quality of life is reduced due to its appearance. Since the

pathogenesis and risk factors are still not fully elucidated, clinicians need to approach these patients with special care. Also, close cooperation of the patient, physician, and periodontist during the treatment of DIGE is necessary, especially if the replacement of therapy with another drug, although it is the best option, is not possible.

CONFLICT OF INTEREST

All authors of the manuscript declare there is no conflict of interest regarding this paper.

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