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**Drug-induced gingival overgrowth in cardiovascular patients**

Bajkovec L *et al*. DIGO in cardiovascular patients

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**Abstract**

Drug-induced gingival overgrowth (DIGO) is a pathological growth of gingival tissue, primarily associated with calcium channel blockers and immunosuppressants. Consequently, it is mainly seen in cardiovascular and transplanted patients. Nifedipine remains the main calcium channel blocker related to the development of this unpleasant side-effect. As for immunosuppressants, cyclosporin is the leading causative agent, whereas other drugs from this drug-group, including tacrolimus, have better safety profiles. Accumulated collagen with inflammatory infiltrates is the histological hallmark of this condition. Several factors are involved in the pathogenesis and can increase the risk, such as male gender, younger age, pre-existing periodontal inflammation, and concomitant use of other DIGO-inducing medications. Patients with DIGO may experience severe discomfort, trouble with speech and mastication, pain, and teeth loss, aside from cosmetic implications. Furthermore, these patients also have an increased risk for cardiovascular diseases. The interdisciplinary approach and cooperation with dental care experts are necessary for patient management. Treatment includes discontinuing the drug and switching to one with a better profile, improving oral hygiene, and surgical removal of enlarged tissue. Recognizing the potential of commonly used medications to cause DIGO and its effect on patients' health is necessary for early detection and adequate management of this complication.

**Key Words:** Drug-induced gingival overgrowth; Calcium channel blocker; Nifedipine; Calcineurin inhibitor; Cyclosporin; Cardiovascular

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**Core Tip:** Drug-induced gingival overgrowth is a side-effect of the drugs such as calcium channel blockers and immunosuppressants, commonly used in cardiovascular and transplanted patients. The condition is multifactorial and mainly depends on the potential of the used drug to cause gingival changes and the state of oral hygiene. Patients who develop drug-induced gingival overgrowth may experience severe discomfort and pain in addition to troubles with mastication, speech, and maintaining oral hygiene. Since it significantly reduces the quality of life, preventive and curative measures should be implemented as part of a care plan for patients at risk.

**INTRODUCTION**

Drug-induced gingival overgrowth (DIGO) is a pathological growth of the gingiva characterized by the accumulation of connective tissue that primarily affects the anterior regions of the maxilla and mandibula[1-3]. The first large DIGO case series was described in 1939, showing DIGO in 68 out of 119 patients treated by antiepileptic drug phenytoin[4].

Since then, various medications showed to be associated with this side-effect[5]. Although more than 20 different drugs are now known to cause DIGO, it most frequently results from calcium channel blockers (CCBs) and immunosuppressants[6,7]. Antiepic drugs (*e.g.*, phenytoin, valproic acid, phenobarbital, vigabatrin) are recognized as a prominent group of medications causing DIGO, although in recent years, cases of DIGO resulting from these drugs were less frequently reported[8].

Cardiovascular and transplanted patients are at particular risk due to the extensive use of CCBs alone or in combination with immunosuppressants[9,10]. Significant variability among patients medicated with the same drugs is observed[1], indicating the importance of additional risk factors involved in the pathogenesis. Genetic factors, male gender, bacterial plaque, and gingival inflammation are associated with increased DIGO risk[11]. Aside from the cosmetic effect, which is the most apparent feature, patients who develop DIGO experience difficulty maintaining oral hygiene, pronunciation, and mastication. Simultaneously, the extensive disease can cause pain and loss of the teeth. As a result, quality of life is reduced significantly[12,13]. Since this side-effect is not rare in a group of cardiovascular patients, oral health needs to be emphasized and included as part of a care plan for patients treated with the drugs mentioned above.

**CLINICAL FEATURES AND PATHOGENESIS**

DIGO usually starts as painless enlargement of interdental papillae and progresses towards facial and lingual margins, covering the teeth crowns. Fully developed, it forms generalized changes throughout the mouth, affecting the anterior gingiva the most[5], although it can also occur as a localized lesion[14]. A possible explanation for the predominance of lesions in anterior regions could be higher exposure of anterior gingiva to the irritation resulting from plaque[15]. DIGO initially appears as pink, lobulated, and thickened gingival tissue without concomitant inflammation, with no tendency to bleed[5,16]. In its course it becomes inflammated with red or bluish-red discolorations with increased bleedings[5]. As it progresses, it spreads both vertically and horizontally and affects mastication and speech[14].

In advanced forms, enlarged gingiva may even interfere with the occlusion[5]. Patients with DIGO have problems maintaining oral hygiene, which leads to susceptibility to infections and periodontal disease and may result in the loss of the teeth[14]. A weakened immune system predisposes to more severe periodontal disease and puts patients on immunosuppressants at additional risk[17]. Furthermore, periodontitis may potentially carry a risk for cardiovascular diseases, including myocardial infarction, peripheral artery disease, stroke, and heart failure. In theory, possible mechanisms behind this association could be dissemination of oral pathogens into the bloodstream and invasion of cardiovascular organs and tissues to induce inflammatory response on a local and systemic level[18]. Additionally, periodontitis is associated with endothelial dysfunction, an important factor in atherosclerosis development[18,19]. Aside from the functional impairment and cardiovascular risk, gingival changes also represent a significant esthetic problem for the patients[14].

Etiopathology of DIGO is multifactorial and not fully understood[2,20]. Genetic factors (cytochrome P450, HLA, and MDR1 gene polymorphisms) influence the interindividual difference in gingival response to DIGO-inducing drugs and could have a role in identifying patients at risk[2,21,22]. The main histological finding in DIGO is the accumulation of collagen in the gingiva's extracellular matrix, along with the infiltration of inflammatory cells[1]. Most of the DIGO-inducing drugs act as inhibitors of calcium ion influx[23]. An inhibited influx of cations into fibroblasts causes a decrease in cation-dependent folic acid uptake. Folic acid is necessary for the proper function of matrix metalloproteinases, which activate collagenase. With no collagenase, there is no collagen breakdown, and it accumulates in connective tissue[1]. Furthermore, studies demonstrated a drug-induced increase in glycosaminoglycans[1] and collagen[24] production along with the proliferation of gingival fibroblasts[25]. These changes are mainly mediated by inflammatory cytokines that are a part of an inflammatory response to drugs[23]. Inflammatory infiltrates found in the gingiva mainly consist of plasma cells[26]. Periodontal status is a significant predictor of DIGO, as bacterial plaque induces inflammation. A significant correlation was found between bacterial plaque and a higher risk for DIGO in patients treated with CCBs or cyclosporin[1,15,27]. In gingival tissue of patients with CCBs-associated DIGO, higher expression of androgen receptors accompanied with higher levels of type I collagen were detected, implying androgens' role in its pathogenesis[28].

**DIGO-INDUCING DRUGS**

The first CCB-DIGO cases date from the early 80-ties, primarily associated with nifedipine[29] and later with the use of other CCBs such as verapamil, diltiazem, amlodipine, and felodipine[30]. Early studies demonstrated the highest prevalence in patients on nifedipine (6.3%), which remains to date the leading cause of DIGO in this drug group. Other CCBs, such as amlodipine (1.7%) and diltiazem (2.2%), have a lower potential to cause DIGO[31]. The various prevalence of DIGO among different CCBs may be a consequence of pharmacokinetic characteristics, as nifedipine is more lipophilic, so it passes through cell membranes more quickly and has a half-life which allows it to reach peak levels in the plasma needed for the initiation of gingival changes[31]. However, the prevalence of DIGO caused by CCBs varies in various studies, as for CCBs in general, it ranges between 10%-20%[32]. It amounts from 15% to 85%[33,34], for nifedipine, meaning that there are additional influencing factors. Male gender, drug dosage, smoking, periodontal status, previous myocardial infarction, and concomitant use of diuretics or antiepileptic drugs increase the risk of developing DIGO in CCBs users[12,31,35]. However, drug dosage depends mostly on pharmacokinetics and pharmacodynamics and is thought to be an unreliable predictor[36]. The majority of cases develop in the first six months of therapy, with the greatest occurrence in the first month, whereas the incidence decreases with long-term use[12]. On the other hand, the study of Hatahira *et al*[13] detected a median time to onset of 262 d, so long-term monitoring is still needed for patients who will develop the changes later. DIGO occurs less often using other antihypertensive drugs, such as angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and beta-blockers[3,37]. Therefore, in patients at risk for developing DIGO or those who already did, switching to CCBs with better safety profiles or other antihypertensive drugs is a treatment option.

Cyclosporin and tacrolimus, from the group of calcineurin inhibitors, are the leading cause of DIGO among immunosuppressive drugs[38]. Cyclosporin was the primary immunosuppressive drug in heart-transplant patients since 1980[39]. Many heart transplant recipients (8.3%-67%) develop gingival enlargement, most of whom are treated with cyclosporin[40]. The role of cyclosporin as an inducing drug in DIGO development is well known and recognized[41]. Gingival changes in patients treated with cyclosporine show symmetry between mandibula and maxilla and within the jaw, while incisors and canines are affected the most[15]. According to the research of Hatahira *et al*[13], 70% of gingival overgrowth is attributed to cyclosporin. On the other hand, tacrolimus is another immunosuppressant often used as an alternative to cyclosporin in primary or rescue therapy[27]. It is 100 times more potent and tends to cause some side-effects common to other immunosuppressants[27,42]. However, it less often causes gingival overgrowth, and changes are less severe than those caused by cyclosporin[27]. The prevalence of DIGO among tacrolimus treated patients is around 14%[27,43]. DIGO can be detected as soon as 1-3 mo after immunosuppressive therapy initiation, and the plateau phase is reached at 9-12 mo[44]. However, gingival changes resulting from tacrolimus use appear later compared to cyclosporin, as in various studies, no changes were observed before 90 d of treatment[38,45]. Interestingly, immunosuppressants differ from other DIGO-inducing drugs since high inflammation levels and low fibrosis mostly mediate the changes[46]. Some of the predisposing factors among cyclosporin users are male gender, gingivitis, bacterial plaque, and higher cyclosporine concentrations[15,22]. Furthermore, younger patients are more frequently affected by DIGO[15], and high rates have been reported among the group of pediatric heart-transplant patients treated with cyclosporin[39,47,48]. Younger age was also a risk factor for more severe changes in patients on tacrolimus[27]. Different therapeutic patterns and higher potential of fibroblasts to proliferate and produce collagen in a group of younger patients could be a possible explanation[15,49]. Additionally, a higher risk for DIGO in tacrolimus users was observed in patients with the worse periodontal state, those previously medicated with cyclosporin[27], and a longer duration of tacrolimus therapy[50]. The occurrence and severity of changes also depend on the concomitant use of other medications. Simultaneous use of cyclosporin and CCBs doubles the risk for DIGO, compared to using cyclosporin alone (51.9% *vs* 25%)[22]. Furthermore, the use of CCBs in tacrolimus-treated patients results in higher severity of gingival changes[27]. These findings indicate the synergistic effect of CCBs and calcineurin inhibitors. On the contrary, azathioprine has a protective effect in patients on cyclosporin or tacrolimus and lowers the risk for DIGO[27,51]. Although tacrolimus provides a better safety profile regarding DIGO and could be a treatment option in patients with cyclosporin-induced gingival overgrowth, it is important to point out that in some cases, changes persist even after the switching of therapy, especially with concomitant use of CCBs[27].

**TREATMENT OPTIONS**

Management of DIGO can be conservative or surgical, with the aim to provide a satisfactory cosmetic outcome and minimize discomfort and pain[1]. Non-surgical methods are the treatment of choice, including proper oral hygiene and mechanical removal of dental plaque, together with the mandatory exclusion of the offending drug[14]. Periodontal treatment reduces inflammation and prevents the need for surgical treatment in cyclosporin-treated patients[52]. A rigorous oral hygiene regime has been recommended for patients with DIGO resulting from CCBs use[32]. Since a worse periodontal state has been associated with a higher risk for DIGO[15,27], preventive measures targeting oral health could be valuable. Reduction of drug dose or switching to that of a lower potential for side-effects should always be considered, if possible. In that case, complete improvement can be expected in 1-8 wk[53] (Figure 1).

Stopping the use of CCBs or switching to non-CCB antihypertensives provides satisfactory results, but it is not always possible, as some patients may have problems controlling their hypertension[54]. In an attempt to treat gingival overgrowth caused by cyclosporin, replacing this medication with tacrolimus or everolimus remains an option[55,56] (Figure 2).

Flutamide, an androgen receptor antagonist, inhibits gingival cells' response to nifedipine and could be used to prevent or treat nifedipine associated DIGO[28]. Non-surgical methods are often not sufficient if the drug cannot be withdrawn for other reasons[54]. Persistent DIGO requires surgical treatment, which could either involve gingivectomy or periodontal flap[57]. The use of carbon dioxide lasers is a solid choice that provides adequate postoperative hemostasis[23]. Recurrence of DIGO after surgical treatment was reported in about 40% of the patients still treated with the offending drug[58]. In conclusion, the prognosis of DIGO is good, as it can be successfully managed and resolved with discontinuation of the inducing drugs[1].

**CONCLUSION**

Since CCBs and immunosuppressants are widely used medications in patients with hypertension or after heart transplantation[9,10], health professionals should be aware of gingival overgrowth as an unpleasant side-effect that can result from the use of these drugs[23,55]. Although it might not be life-threatening, it poses a significant problem for the patients, not only because of the cosmetic effect but also due to the impairment of speech, eating, and maintaining oral hygiene[12,13]. Furthermore, infections resulting from the lack of proper oral hygiene could enhance the risk for cardiovascular diseases[59]. Recognizing the importance of DIGO and its effect on the patients' health is crucial for providing better health outcomes and satisfactory quality of life. If possible, treatment of choice should be changing of a drug and conservative periodontal treatment, whereas surgical treatment is reasonable only in resistant cases. Since it is multifactorial and reoccurs if the drug must be continued, efforts need to be made to find each patient's optimal treatment. An interdisciplinary approach and cooperation of medical and dental professionals are necessary to reach this goal.

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**Footnotes**

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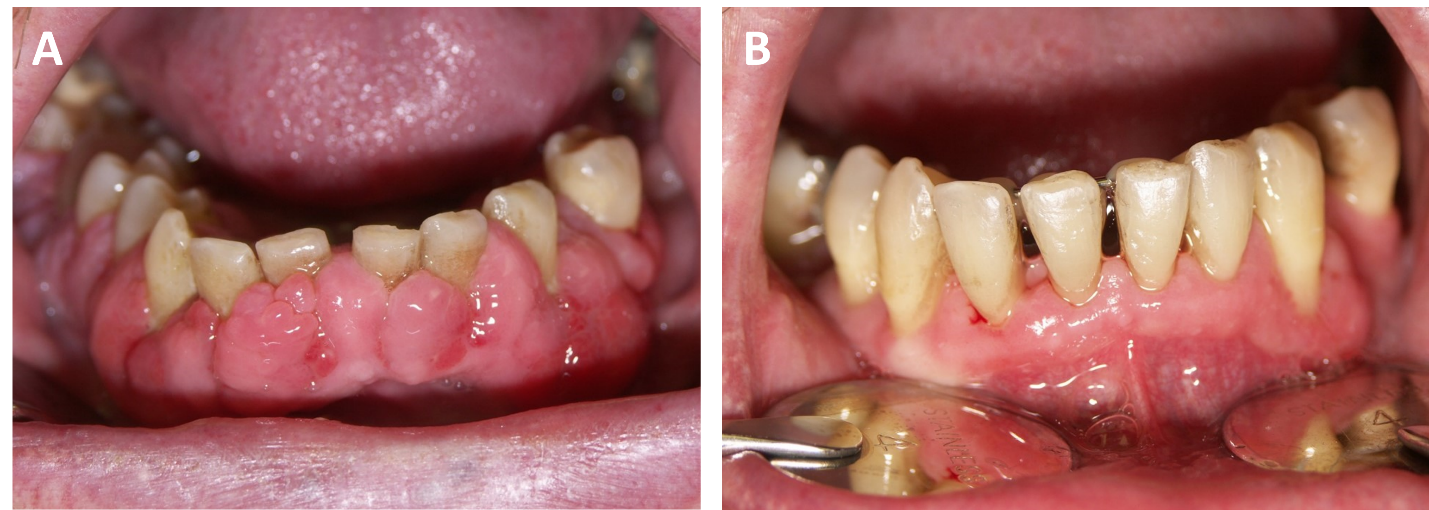
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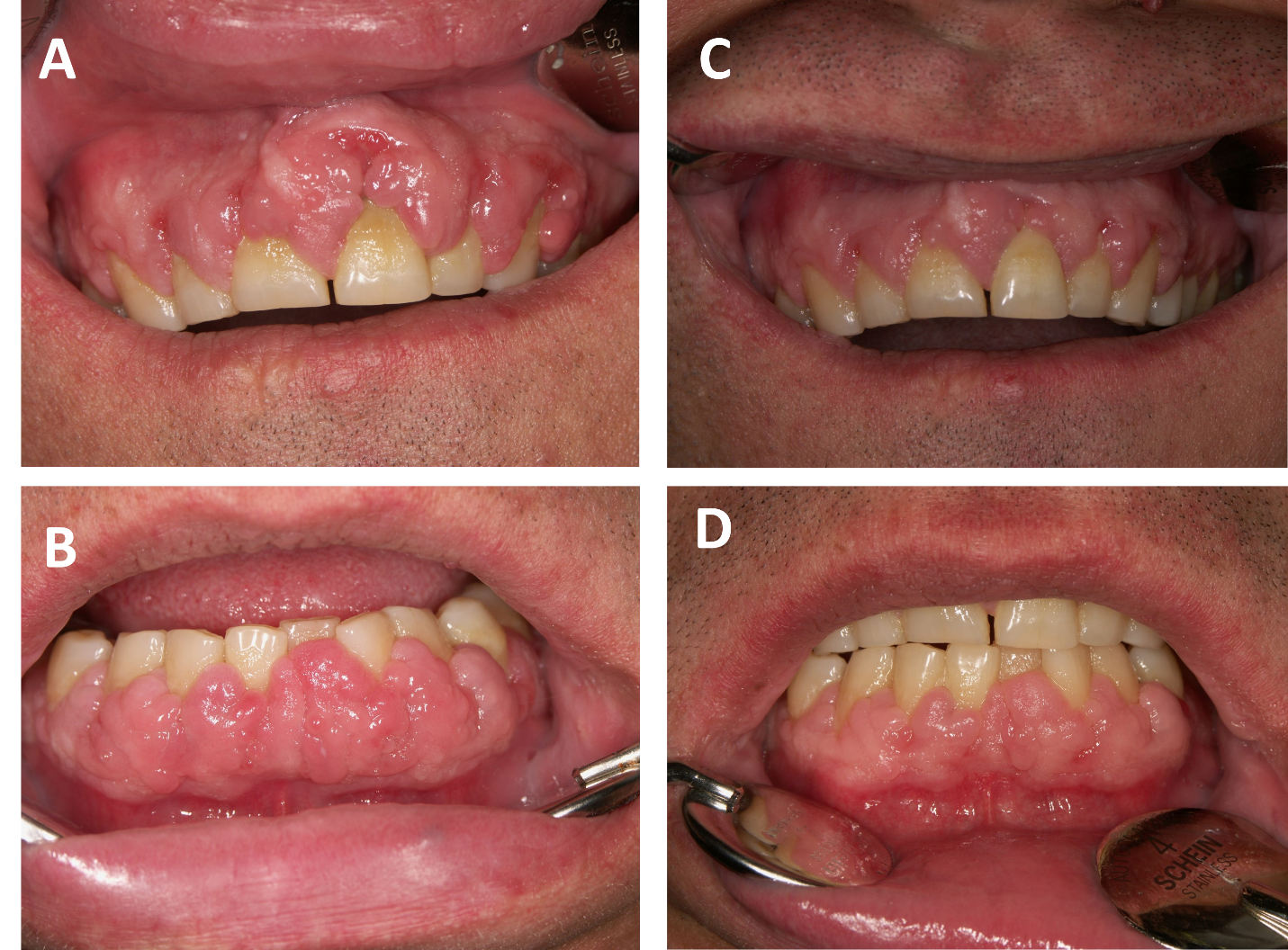
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**Figure Legends**



**Figure 1 A complete response of a severe drug-induced gingival overgrowth case following seven weeks after amlodipine removal and six consecutive tooth scaling and cleaning treatments.** A: Amlodipine induced gingival overgrowth successfully treated by vigorous weekly plaque control; B: Calculus removal during seven weeks following the drug withdrawal and substitution by angiotensin-converting enzyme inhibitor (courtesy of Prof. Vlaho Brailo).



**Figure 2 An improvement in a heart transplant patient, whose medication included both cyclosporin and amlodipine, four weeks following professional teeth cleaning and switching to tacrolimus and alternative antihypertensive drug.** A and B: Gingival overgrowth in a heart transplant patient receiving both cyclosporin and amlodipine; C and D: An improvement is observed following conservative periodontal treatment and four weeks of switching to tacrolimus and angiotensin-converting enzyme inhibitor.



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