The Role of Dental Plaque in Development of Drug-Induced Gingival Overgrowth [DGO]

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Abstract

Drug-induced gingival overgrowth (DGO) is an adverse effect of certain medicines: immunosuppressive agents, antiepileptics, and calcium (Ca 2+) channel blockers. The etiology of DGO is multifactorial and probably the dental plaque has the major role in it.

**Aim:** The aim of this study was to obtain the role of dental plaque in etiology of DGO.

**Material and methods:** 120 patients with renal transplants were included in this examination. The cohort was divided into four groups according to the daily dose of cyclosporine A (CsA) (100, 125, 150, 175 mg). The plaque index (PI), gingival index (GI), gingival overgrowth index (GOI), and cyclosporine dose, were recorded for various groups and a prospective longitudinal follow-up was conducted.

**Results:** There were no statistical differences of PI at examined groups (p>0.05). It was registered a significant difference among distribution of frequency for gingival overgrowth between the examined groups (x2 test=12.672; p<0.01). Statistically significant correlation were found between GOI and cyclosporine dose (p=0.3; p<0.01) and also with PI (p=0.6; p<0.01) and GI (p=0.3; p<0.01). Inter group comparison, showed the forth group (175mg) to significantly differ as compared to the first (100mg) and second (125mg) group; no statistically significant differences were found among the other groups (Chi-square test =13.222; p<0.01). Multiple regression correlation, showed that GOI is more affected of PI (Beta=0.507) than Cs dose (Beta=0.197).

**Conclusion:** Local factors are significant in the development of gingival overgrowth (GO).

INTRODUCTION

Drug-induced gingival overgrowth (DGO) is an adverse effect of certain medicines: immunosuppressive agents, antiepileptics, and calcium (Ca 2+) channel blockers.

The gingival overgrowth (GO) has been defined as abnormal growth of the gingiva as a part of the periodontal tissues. Histologically, DGO is associated with increased epithelial thickness, fibrosis in lamina and different degree of inflammation [1].

While the physiology behind drug-induced gingival enlargement has not been definitively elucidated, histopathologic studies have shown that the gingival tissue volume increase is due to an excessive accumulation of extracellular matrix proteins including collagen and ground substance with a predominance of plasma cells. Hence, the increase in tissue volume is primarily a connective tissue response and not epithelial [1].

CsA is known to increase the level of collagen in the gingival tissue by inducing collagen production and by inhibiting the degradation of collagen by gingival fibroblasts [2,3]. The association between CsA therapy and gingival fibroblasts seems to play role in its pathogenesis.

Also the review of the existing literature reveals clearly, that a cofactor is needed to induce gingival overgrowth. The role of dental plaque as a co-factor in the etiology of DGO was recognized in the latest periodontal disease classification system. In such classification system, the “drug-induced gingival diseases” were categorized into the major group “dental plaque-induced gingival diseases” and their development and severity were pointed as being influenced by the accumulation of dental plaque [4,5]. Despite this classification system, the literature is still controversial whether the oral biofilm is important to trigger or to worsen GO.

In fact, there are several observations [6], suggesting a modulation of inflammatory processes. The inflammatory changes in gingival tissues affect the interaction between Cs and fibroblasts and their subsequent activities.
Drug-induced gingival enlargements are characterized by a nodular lobulated spongy aspect and secondary inflammation that may partially or completely cover the teeth, induce edema, ulcerations, bleeding on brushing, ‘gummy smile’, mastication and speaking difficulties, pathological teeth migration, occlusal problems, caries and also periodontal disease. Severe forms can worsen the oral hygiene and can result in increased accumulation of microorganisms which subsequently lead to general health compromising [7].

For this reason, better understanding the pathogenesis of DGO is one of the important subjects in clinical periodontology. The aim of this article is to obtain the role of dental plaque in etiology of DGO.

**PATIENTS AND METHODS**

The research was conducted on 120 renal transplant recipients divided into 4 groups according to the daily dose of cyclosporine A (100 mg, 125mg, 150mg, 175mg), at Department of periodontology, Dental Clinical Center Ss „Pantelejmon”, Skopje. All patients underwent renal transplantation at least 6 months previously and were treated by standard triple protocol of maintenance immunosuppression: cyclosporine A (Neoral®; 6 to 8 mg/kg/day), prednisolone (1 mg/kg/day) and mycophenolate mofetil (Cellcept® 1.5- 2 g/day), Diltiazem® (2x90mg, Alkaloid), the last improving the absorption of CsA.

The medical history of all patients excluded use of any medicament, causing GO. All participants signed a standard informed consent form approved by the local institutional ethical committee in accordance with the Helsinki Declaration as revised in 2013.

Patient’s mean age at time of renal transplantation was 36,2 ± 9,5 years. The mean duration of therapy was 42,4 ± 36,2 months.

All subjects underwent the scheduled clinical examinations:

**Clinical examinations**

The clinical examinations were made by applying a few indexes:

- Plaque Index (PI) according to Silness - Løe [8]: Each of the four surfaces of the teeth (buccal, lingual, mesial and distal) is given a score from 0-3. The scores from the four areas of the tooth are added and divided by four in order to give the plaque index for the tooth with the following scores and criteria: 0-No plaque; 1-A film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque may be seen in situ only after application of disclosing solution or by using the probe on the tooth surface; 2-Moderate accumulation of soft deposits within the gingival pocket, or the tooth and gingival margin which can be seen with the naked eye; 3-Abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin.

- Gingival Inflammation Index (GI) according to Løe-Silnes [9]: 0-normal; 1-mild inflammation, slight color change and edema, no bleeding; 2-moderate inflammation, redness, edema, bleeds on probing; 3-severe inflammation, marked redness and edema, ulceration, spontaneous bleeding.

- Gingival overgrowth index (GOI) according to MacGaw et al. [10]. The vertical component measures the degree of gingival enlargement in an apico-coronal direction for every gingival unit graded by means of a 4 point scale (0-no gingival hyperplasia; 1-blunting of gingival margin; 2-less than 1/2 crown length; 3-more than 1/2 crown length).

Statistical Analysis: Data were analyzed by using One-way ANOVA test along with Student’s independent t-test. Statistical significance was considered when p<0.05. Findings were further confirmed using SPSS program by one-way ANOVA and Post hoc test. The results obtained from the clinical and histochemical researches were Statistical program 7.

**RESULTS**

There was registered a significant difference among distribution of frequency for gingival overgrowth between the examined groups (χ² test=12,672; p<0,01) (Figure 1). Furthermore, with Mann-Whitney U test, the forth group (175mg) was presented to have much higher gingival overgrowth when compared to the first (100mg) and second (125mg) group. Other significant intergroup differences were not established.

There was no statistical differences of PI at examined groups (The Kruskal–Wallis test=0,827; p>0,05) (Figure 2). There was registered a high value of PI at all patients PI 3 was registered at 14 cases in first group; PI 3 at 17 cases in second group; PI 3 at 15 patients in third group and the same index in the forth group was registered at 14 patients.

In addition, statistically significant correlation were found between GOI and cyclosporine dose (p =0,3; p<0,01) (Figure 3). And also with PI (p= 0,6; p<0,01) (Figure 4).

The correlation between gingival index (GI) scores and daily doses of cyclosporine was evaluated in all groups (Figure 5). The dose of cyclosporine positively correlated with the gingival index (ρ =0,3; p<0,01). Inter group comparison, showed the forth group (175mg) to significantly differ as compared to the first (100mg) and second (125mg) group; no statistically significant differences were found among the other groups (Chi-squared test =13,222; p<0,01). Multiple regression correlation, shows that GOI is more affected of PI (Beta=0,507) than Cs dose (Beta=0,197).

**DISCUSSION**

The concept which generally prevails in theories of DGO is...
multi causal ethiology with individual sensitiveness to CsA or its metabolites, different gingival susceptibility to invasion of microorganisms from dental plaque, or an interference of CsA with the T-cell immunity. Literary data are still controversial and this side effect is not completely elucidated.

According to the relevant data [5,11,15] the incidence of CsA-induced GO, varies in each study and generally ranges from 25%-50%. These differences may relate to drug dosage, serum concentration, method of assessing and duration of therapy.

In our observation there was a significant difference of GOI between the examined groups, the groups with higher doses (150mg and 175mg) were presented to have much higher gingival overgrowth when compared to the lowest doses (100mg and 125mg) (Figure 1). The pharmacokinetic variables are related with developing of the gingival lesions [18], supported our results of statistically significant correlation between GOI and cyclosporine doses ($p =0.3; p<0.01$) (Figure 3). The study of other authors [19,22], confirm that the development of CsA-induced gingival overgrowth, was positively related to the total dose of the drug administered to the children during the first 6 post transplant months, and also it was significantly higher in the children with gingival overgrowth than in those without.

In contrast, results of other authors [16,17], do not support a role of dose dependency of the drug, explaining that the dose is just a trigger factor which initiates the gingival changes, but that it is developed in time of the restricted sensitivity of the fibroblast in correlation with their response to the medicament. The prevalence of this side effect tends to be increased when multiple inducing drugs such as cyclosporine and nifedipine are combined within patients’ drug therapies, like prednisone in our study. In particular, transplant patients treated with CsA additionally take calcium channel blockers because of the CsA side effects and also to improve the bioavailability of CsA. A combination of CsA and calcium channel blockers can increase the prevalence of gingival overgrowth, but the severity does not appear to be influenced by the combination.

The interaction between dental plaque and the host response to it, probably has a great role in the etiology of PGO. The bacterial components in dental plaque can be recognized by host cell Toll-like receptors (TLRs), which are sensors of pathogen-associated molecular patterns. An in vitro study [11], using hamster cells treated with phenytoin and CsA, showed opposite results for these two substances. While cyclosporine increased signaling by TLR2 and TLR4, phenytoin decreased this signaling with lower expression of adhesion molecules such as CD54. Recognition of the cell-wall components peptidoglycan and lipoproteins by TLR2 and recognition of the outer membrane component lipopolysaccharide (LPS) by TLR4 lead to a series of events, including nuclear factor (NF)-κB activation, that results in cytokine production and expression of adhesion molecules in fibroblasts. Changing the cell signaling induced by phenytoin and CsA, may alter the inflammatory response in gingival tissues, favoring bacterial invasion and proliferation and, therefore, may be an important factor in the pathogenesis of DGO.

The results from this study showed that in all patients, regardless of the applied CsA dose (100, 125, 150 or 175mg),
there was a low level of oral hygiene, and the highest plaque values were noted in the group taking the highest dose of CsA (Figure 2). The patients were not motivated to practise a good oral hygiene, probably because of the primary disease.

Statistically significant correlation were found between GOI and PI ($p = 0.6, p<0.01$) (Figure 4). Results confirm the hypothesis that there is a presents of local irritative factors being important etiological factors, besides medical variables in the development of the GO. The results from multiple regression correlation, has shown that GOI, was more affected of PI than Cs dose (Table 1).

McGaw et al. [10]. Found that “responder”(subjects manifesting clinically obvious overgrowth) also had significantly more severe gingival inflammation and plaque scores than “non responders” (PI= 2.34 vs 1.36).

Despite the fact that dental plaque is a predisposing factor for development of the GO, Somacarrera [11]. believed it is not a vital one, since they have registered high dental plaque and gingival inflammation indexes, as well as a high values of serum CsA concentration in patients with no gingival changes were observed.

The observation of other authors [12], suggests that CsA might accumulate locally in saliva or in bacterial plaque, in higher than it that can be measured systemically, which can be supported by clinical observation that gingival enlargements always start in the inter dental space, in other words where the greatest buildup of plaque can be seen.

Contrary to this, Schulz et al. [13]. In their study of 80 renal transplant patients detected no significant correlation between plaque score and gingival overgrowth occurrence, nor between severity of gingival inflammation and overgrowth. In 100 subjects, the presence of plaque was related to the presence of overgrowth, but no correlation was detected between abundance of plaque accumulation and overgrowth severity [14].

Although Seymour [15], believed that plaque control does not prevent the development of the GO in sensitive patients yet, the elimination of the inflammatory component leads to a reduction of the GO. They also considered that plaque control and the removal of plaque retention factors is necessary for the gingival health of renal-transplant patients, but these measures themselves do not prevent the development of GO or recurrence following surgical intervention.

McGaw [10], consider the dental plaque as a local depot of CsA, which leads to suppression of immune response in gingival epithel. The epithelial cells, especially the keratinocytes and Langerhan’s cells (antigen-presenting cells), come in direct contact with dental plaque, which as “local source” of CsA, makes immune suppression of gingival epithel. On the other hand, this increased immunosuppressant might inhibit the immunity of the periodontal - tissue complex of the plaque products, which will in turn affect periodontal status.

Gingival inflammation could be very important in the pathogenesis of gingival overgrowth. In our study, there was registered positive correlation between cyclosoprine dose and GI (Figure 5). It has been shown by several cross-sectional studies a strong association between dental plaque, gingival inflammation and gingival lesions, but it is not yet clear if plaque accumulation is a causal factor or a consequence of the morphological gums changes. It would seem that the morphological alterations, in drug-induced gingival overgrowth, could be started by the plaque induced inflammation, and this would lead to a hyperemic and edematous gingival tissue. Maintained of oral hygiene is more difficult in cases of GO and represents an irritation factor, that wors the gingival lesion [18]. Yahia et al. [19]. demonstrated that a rigorous oral hygiene before development of CsA gingival lesions, was effective in reducing the clinical manifestations of gingival inflammation, but was totally without effect in terms of reducing the magnitude of gingival mass.

Despite these reservations, there is no doubt that improving individual oral hygiene and reducing gingival inflammation can have a pronounced effect in terms of preventing and treating this condition.

Aimet [20], Dannewitz [21], Pundir [22] have all reported beneficial results in the treatment and prevention of DGO with respect to dental plaque control/oral hygiene protocols, adjunctive chlorhexidine anti-plaque therapeutics. Full-mouth desinfection might be a beneficial treatment concept in patients with DGO, thus decreasing the need for surgical therapy.

**CONCLUSION**

The results confirm the hypothesis that local factors are significant in the development of gingival overgrowth. Although we can not claim precise whether the GO has been primarily caused by the inflammatory component, or by the drug, we can confirm that it makes plaque elimination difficult and it leads to severe gingival overgrowth.

Dentist should be able to recognize this side effect from CsA therapy, and to provide oral hygiene instructions, together with scaling and root planning. Whenever is possible, CsA should be replace with another drug without this side effect. Successful treatment will be realized with joined collaboration with a periodontist and the patient’s physician, especially with the patients being treated with larger doses of Cy, over 175 mg, thus preventing the oral infections which can compromise oral health, and basic human health at patients having reduced immunity.

**REFERENCES**


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**Table 1: Multiple regression correlation of GO, PI, GI and Cs dose.**

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