Prevalence and Severity of Gingival Enlargement Among Antihypertensive Drug Users: A cross-sectional study

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ABSTRACT

Background

Drug-induced gingival enlargement is a well-known consequence of the administration of some antihypertensive drugs, including angiotensin-converting enzyme inhibitors, beta-blockers, and calcium channel blockers.

Objective

To determine the prevalence and severity of antihypertensive drug-induced gingival enlargement and to assess the probable risk factors associated with gingival enlargement.

Method

A hospital-based cross-sectional study was conducted in patients attending the Outpatient Department of Periodontology and Oral Implantology, Chitwan Medical College and Teaching Hospital, Bharatpur, Chitwan, Nepal, from July 2023 to May 2024. A total of 246 patients of both genders taking antihypertensive medications for a variable period and meeting all inclusion criteria were selected for the presence of gingival enlargement and classified by severity. Descriptive analysis was performed in the Statistical Package for the Social Sciences (SPSS, v.23.0.) using the chi-square test.

Result

A total of 210 (85.36%) subjects taking antihypertensive drugs appeared to have gingival enlargement. Among them, 86 (40.95%), 69 (32.86%) and 55 (26.19%) were taking calcium channel blockers, β-blockers and angiotensin-converting enzyme inhibitors, respectively. Regarding its severity, a marked severity was observed in patients taking calcium channel blockers followed by angiotensin converting enzyme inhibitors and beta-blockers accounting for 51 (56.0%), 19 (29.7%) and 13 (14.3%), respectively.

Conclusion

Patients taking antihypertensive medications are at high risk for gingival enlargement, and inflammation is considered an important cofactor for the expression of this effect.

KEY WORDS

Antihypertensive drugs, Drug-induced gingival enlargement, Prevalence, Severity

INTRODUCTION

Gingival enlargement is an overgrowth or increase in the size of the gingiva. Various types of gingival enlargement have been reported and are classified according to etiologic factors and pathologic changes, such as inflammatory enlargement, enlargements associated with systemic diseases or conditions, neoplastic enlargement, and drug-induced enlargement.[1]

The incidence of drug-induced gingival enlargement (DIGE) was first reported by Kimball in 1939 with chronic use of phenytoin, the antiepileptic drug.[2] Drugs related to gingival enlargement can be broadly categorized into three main groups, namely, anticonvulsants, immunosuppressants, and calcium channel blockers, according to their therapeutic actions.[3-5]

This study was carried out with the aim of evaluating the prevalence and severity of DIGE in patients treated with various antihypertensive drugs and to evaluate the probable risk factors associated with gingival enlargement.

METHODS

This was a hospital-based cross-sectional study conducted from July 2023 to May 2024 in 246 patients of both genders who were treated with antihypertensive drugs, in the Department of Periodontology and Oral Implantology, as well as referral patients from the Outpatient Department of Cardiology of Chitwan Medical College and Teaching Hospital, Bharatpur-10, Chitwan, Nepal, after obtaining ethical approval from the Institutional Review Committee (Reference No. 079/080-223) of the same institution while following the ethical guidelines outlined in the Declaration of Helsinki relating to biomedical research involving human subjects, which sets forth standards for research involving human subjects, including participant welfare, informed consent, and confidentiality. Participation was voluntary and the utmost confidentiality and personal identity of all participants were ensured. All patients were informed about the use of their records after their written consent.

Patients of all age groups except the peripubertal period taking antihypertensive drugs without interruption for a minimum period of at least three months at a variable dose, the presence of a minimum of 16 permanent teeth, with at least 10 anterior teeth, and patients who can follow verbal or written oral hygiene instructions were recruited for a study.

Patients who had undergone periodontal treatment within six months prior to the initiation of the study, peripubertal patients, pregnant women, patients under medications other than antihypertensive agents known to cause gingival enlargement, ie, phenytoin, mesantoin, ethosuximide, methosuximide, valproic acid, patients on the immunosuppressant drug cyclosporine, patients who discontinued therapy for more than four weeks, patients with concomitant systemic disorders known to affect the gums (such as diabetes, endocrine disorders, leukemia, or immunodeficiency states), patients known to have systemic diseases such as leukemia, granulomatous diseases such as wegener's granulomatosis and sarcoidosis, patients on orthodontic appliances or implants were excluded from a study.

The convenience sampling method was used. The sample size of 246 was calculated using the following equation.

$n= Z^2 * (p) (q) / (d)^2$

Where, n = minimum sample size required; Z = 1.96 at 95% Confidence Interval(CI); p= prevalence, 81.2% i.e. 0.812; q = 1-p, 0.188; d = margin of error, 5%.[2]

Participants were interviewed to obtain demographic and medical information and further screened for periodontal examination. The oral hygiene status of paients was recorded using the simplified oral hygiene index (OHI-S). To investigate the plaque score and gingival inflammation in the study group, the plaque index (PI) of Silness and Loe; gingival index (GI) of Loe and Silness were utilized respectively.[6] All patients completed the questionnaires that included personal information, type, duration of drugs consumed, plaque and gingival indices coding, and oral hygiene preservation methods. The patients were divided into four groups according to the duration of drug consumption, ie, group I (0-1 year), group II (1-5years), group III (5-10 years), and group IV (> 10 years).[2]

The measurement of gingival enlargement was done from the cementoenamel junction to the free gingival margin. The gingival enlargement was classified according to the gingival overgrowth index described by McGaw et al. in 1987 as follows.[7]

0 = no overgrowth, feather-edged gingival margin

1 = blunting of the gingival margin

2 = moderate gingival overgrowth (1/3 of the crown length)

3 = marked gingival overgrowth (>2/3rd of crown length)

The data collected were entered into a spreadsheet (MS Excel 2018, Microsoft Corp., Redmond, WA, USA) and analyzed using statistical software (SPSS ver. 23.0; IBM Corp., Armonk, NY, USA). The means were calculated for all continuous variables. The mean of the quantitative variables was calculated and the difference for the mean was assessed using analysis of variance (ANOVA). The difference in proportions were calculated using the Chi-square test. Correlation analysis was done to account for confounders. The p-value < 0.001 was considered statistically highly significant; p-value < 0.01 was considered very significant; p-value < 0.05 was significant and the p-value > 0.05 as not significant.

RESULTS

A total of 246 participants were enrolled in the study, including 125 (50.81%) males and 121 (49.19%) females. The gender difference in gingival enlargement was found to be equal in both males and females, accounting for 42.68%. The mean age of the participants was 52 years and table 1 shows the age distribution of the study participants.

Table 1. Age-wise distribution of the study population according to the type of drugs consumed (n=246)

Antihpertensive Drugs	Minimum	Maximum	Mean±SD
ACE-Inhibitors	31	65	49.03±9.46
Beta Blockers	31	71	49.15±9.74
Calcium Channel Blockers	29	73	50.74±10.35

SD: Standard deviation

The prevalence of DIGE was 210 (85.36%) in the study population. Among them, 86 (40.95%), 69 (32.86%) and 55 (26.19%) were taking calcium channel blocker, β-blockers and ACE inhibitors, respectively. Regarding its severity, a marked severity was observed in the case of patients taking calcium channel blockers followed by ACE inhibitors and β-blockers that represent 51 (56.0%), 19 (29.7%), and 13 (14.3%), respectively, as illustrated in table 2.

Table 2. Severity of gingival enlargement according to the drugs consumed (n=246)

Antihpertensive Drugs	No overgrowth n (%)	Blunting n (%)	Moderate n (%)	Marked n (%)
ACE-Inhibitor	9 (14.1)	21 (32.8)	15 (23.4)	19 (29.7)
Beta Blockers	22 (24.2)	25 (27.5)	31 (34.1)	13 (14.3)
Calcium Channel Blockers	5 (5.5)	15 (16.5)	20 (22.0)	51 (56.0)

p-value=0.000 (highly signigicant); n (%); frequency (%)

Patients taking antihypertensive agents for more than 10 years showed marked gingival enlargement (Table 3).

Table 3. Relation between the duration of drug consumption and the severity of gingival enlargement (n=246)

Duration (years)	No overgrowth n (%)	Blunting n (%)	Moderate n (%)	Marked n (%)
0-1	14 (70.0)	6 (30.0)	0 (0.0)	0 (0.0)
1-5	10 (14.3)	36 (51.4)	12 (17.1)	12 (17.1)
5-10	9 (11.0)	16 (19.5)	25 (30.5)	32 (39.0)
>10 years	3 (4.1)	3 (4.1)	29 (39.2)	39 (52.7)

p-value=0.000 (highly signigicant); n (%); frequency (%)

All patients with a poor plaque index were found to have DIGE. Among patients with poor oral hygiene, blunted gingiva was observed in 10 (16.7%), moderate gingival enlargement was observed in 31 (51.7%) and 19 (31.7%) had severe gingival enlargement (p-value <0.001) as tabulated in table 4.

Table 4. Relation between plaque index and severity (n=246)

Plaque Index Score	No overgrowth n (%)	Blunting n (%)	Moderate n (%)	Marked n (%)
Good (0.1-.9)	16 (34.0)	18 (38.3)	7 (14.9)	6 (12.8)
Fair (1.0-1.9)	20 (14.4)	33 (23.7)	28 (20.1)	58 (41.7)
Poor (2.-3.0)	0 (0.0)	10 (16.7)	31 (51.7)	19 (31.7)

p-value=0.000 (highly significant); n (%); frequency (%)

A poor plaque index was observed among 28 (46.7%) using CCBs, 20 (33.3%) using β- blockers and 12 (20%) using ACE inhibitors as tabulated (Table 5).

Table 5. Relation between plaque index and drugs (n=246)

Plaque Index Score	ACE-Inhibitors n (%)	Beta-blockers n (%)	Calcium Channel Blockers n (%)
Good (0.1-0.9)	9 (19.1)	28 (59.6)	10 (21.3)
Fair (1.0-1.9)	43 (30.9)	43 (30.9)	53 (38.1)
Poor (2.0-3.0)	12 (20.0)	20 (33.3)	28 (46.7)

p-value=0.003 (very significant); n (%); frequency (%)

Marked gingival enlargement was observed in a patient with severe gingival inflammation and was found to be statistically highly significant (p-value < 0.001) as summarized (Table 6).

Table 6. Relation between gingival index and severity (n=246)

Gingival Index Score	No overgrowth n (%)	Blunting n (%)	Moderate n (%)	Marked n (%)
Mild gingivitis (0.1-1.0)	30 (32.6)	61 (66.3)	1 (1.1)	0 (0.0)
Moderate gingivitis (1.1-2.0)	6 (2.4)	0 (0.0)	60 (24.4)	3 (1.2)
Severe gingivitis (2.1-3.0)	0 (0.0)	0 (0.0)	5 (5.9)	80(94.1)

p-value=0.000 (highly significant); n (%); frequency (%)

The relationship between gingival index and drugs is as shown in table 7.

Table 7. Relation between gingival index and drugs (n=246)

Gingival Index Score	ACE-Inhibitor n (%)	Beta Blockers n (%)	Calcium Channel Blockers n (%)
Mild	30 (30.6)	48 (49.0)	20 (20.40)
Moderate	15 (23.8)	30 (47.6)	18 (28.6)
Severe	19 (22.35)	13 (15.3)	53 (62.35)

p-value=0.000 (highly significant); n (%); frequency (%)

DISCUSSION

Gingival enlargement is a condition in which the size of the gingiva increases, and can be caused by inflammation, systemic diseases, or certain medications.[4] Various factors including age, genetic predisposition, pharmacokinetic variables, alteration of gingival connective tissue

homeostasis, histopathology, ultrastructural factors, inflammatory changes, and drug action on growth factors affect gingival tissues.[8] Patients medicated with certain drugs may be involved in this adverse effects of drug-induced gingival enlargement. Three classes of drugs responsible for gingival enlargement are anticonvulsants, antihypertensives (specifically calcium channel blockers), and immunosuppressants.[9,10] This study was conducted with the aim of assessing gingival enlargement in patients taking antihypertensive drugs.

Athough the pharmacological effects of each of these drugs are different and directed at various primary target tissues, all of these drugs seem to act similarly in gingival connective tissue considered as secondary target tissue, leading to common clinical and histopathological findings.[11]

The underlying mechanism remains to be fully understood. However, the two main inflammatory and non-inflammatory pathways have already been proposed. The suggested non-inflammatory mechanisms include defective collagenase activity secondary to decreased folic acid uptake, blockage of aldosterone synthesis in the adrenal cortex, and consequent feedback increase in adrenocorticotropic hormone level, and up-regulation of keratinocyte growth factor. Alternatively, inflammation may develop due to direct harmful effects of concentrated drug in GCF and/ or bacterial plaque. This inflammation could lead to up-regulation of several cytokine factors, such as transforming growth factor beta-1.[12] Furthermore, not all patients receiving the same drug develop gingival enlargement, as susceptibility to pharmacologically induced gingival enlargement can be governed by the existence of differential proportions of fibroblast subsets in each that exhibit a fibrogenic response to these medications. Functional heterogenicity has also been observed in gingival fibroblasts in response to various stimuli.[13] Similarly, the two main genes and their associated proteins involved in DIGE include permeability glycoprotein (P-gp) and human leukocyte antigen.[14]

In our study, of 246 patients taking antihypertensive drugs, 85.36% were clinically diagnosed with gingival enlargement. Previous estimates ranged from 20% to 83%.[5,15-17] Among them, 40.95%, 32.86%, and 26.19% were taking CCBs, β-blockers and ACE inhibitors, respectively. According to a study conducted by Pradhan et al., the findings of our study also showed a higher prevalence of gingival enlargement in patients taking CCB, representing 40.95% followed by 32.86% and 26.19% in patients taking β-blockers and ACE inhibitors, respectively, similar to the prevalence rate of our study, which could be attributed to the greater tendency of physicians to prescribe calcium channel blockers.[2]

Regarding severity, marked severity was observed in the case of patients taking CCB followed by ACE inhibitors and β-blockers accounting for 56.0%, 29.7%, and 14.3%, respectively. The results of the present study showed statistically significant significance (p-value < 0.001) between the duration of drug use and the severity of gingival enlargement, as individuals who consuming antihypertensive drugs for more than ten years were found to have marked gingival enlargement compared to individuals who consuming for a shorter period.

Clinical manifestations of gingival enlargement often appear 1-3 months after starting treatment with associated medications.[17,21] It usually begins in the interdental papillae and is found more frequently in the anterior segment of the labial surfaces. Gradually, gingival lobulations form that may appear inflamed or fibrotic in nature depending on the degree of local factor-induced inflammation. However, the fibrotic enlargement is normally confined to the attached gingiva, but may extend coronally and interfere with esthetics, mastication, or speech. The disfiguring gingival enlargement caused by these medications is not only aesthetically disconcerting, but often impairs the evaluation of nutrition and oral hygiene, resulting in increased susceptibility to oral infection, caries, and periodontal diseases.[18] It has multifactorial etiologies.[19] Several factors are involved in the pathogenesis and can increase risk, such as younger age, preexisting periodontal inflammation, and concomitant use of other DIGE-inducing medications. Another factor that affects the occurrence of gingival enlargement may include gender, with men three times as likely to develop enlargement.[20] In contrast, our study showed the similar rate of occurrence in both genders, covering 42.68% and illustrating no statistically significant correlation between gender and gingival enlargement as the findings of other studies.[17,21]

The present study showed highly significant association between gingival enlargement and duration of drug consumption, which can be explained by the pharmacokinetics of the inducing drugs and the gingival binding affinities of these drugs. The self-manifestation of gingival enlargement can be importantly determined by the drug concentrations in whole blood and saliva.[22]

Most studies had shown an association between oral hygiene status and the severity of DIGE suggesting the role of plaque in the development and expression of gingival changes.[15] The significance of plaque as a cofactor in the etiopathogenesis of drug-associated gingival enlargement has been lately recognized in the most recent classification system for periodontal disease.[23]

In the current study, positive association was seen between

gingival enlargement with plaque and gingival indices alike various other studies conducted by Gopal et al., Taib et al. and Tejnani et al. and, possibly explained by the presence of local environmental factors, such as poor plaque control at the initial presentation, which can act as a risk factor that had contributed to the worsening of existing gingival enlargement, thus further, complicating of oral hygiene measures.[17,18,24] But the results of a study by Kothari et al. was contradictory to our findings.[25]

High plaque scores and gingival inflammation are fundamental etiologic factors in exacerbating drug-induced gingival enlargement regardless of the causative medication. Patients with significant gingival enlargement were found to have higher plaque scores and papillary bleeding indices. Patients on antihypertensive therapy tend to have generalized heavy deposits of calculus, considerable plaque, and unmanaged periodontal disease. A positive correlation was seen between severity of DIGE with poor plaque control and was proportional to the degree of plaque-induced inflammation. Good plaque control and regular periodontal maintenance are crucial in the treatment of patients taking these medications.[21,26]

Gingival enlargement, irrespective of its etiology, can be problematic and contribute to an increased risk of dental caries and periodontal disease. It also produces an alteration in the aesthetic profile, and clinical symptoms such as pain, tenderness, bleeding, abnormal tooth movement, and dental occlusion problems may be produced.[8]

Although it may not be life-threatening, it poses a significant problem for patients, not only due to cosmetic implications, but also due to impaired maintenance of mastication, phonetics, eating, and oral hygiene.[27,28]

Furthermore, infections resulting from lack of proper oral hygiene could increase the risk of cardiovascular disease.[29] The interdisciplinary approach and cooperation with dental care experts are imperative for patient management. Treatment includes discontinuation of the drug and substitution with a better profile, improvement of oral hygiene, and surgical removal of enlarged tissue. An early detection and adequate management of this complication may be possible by acknowledging the potential of commonly used medications to cause DIGE and its effect on patient' health. The condition is multifactorial and depends primarily on the potential of the drug consumed drug to cause changes in the gingiva and the state of oral hygiene. Preventive and curative measures must be implemented as part of a care plan for patients at risk with the aim of improving quality of life.[30]

In some conditions, the causative drug regimen cannot sometimes be altered as it is essential to maintain patient health, special care and maintenance are required in such conditions. Medication-related gingival enlargement generally requires intervention. Surgical treatment is often the major treatment option for patients with severe enlargement. Physicians and dentists need to be made aware of these medications, which helps in identifying early gingival changes once the medication has started.

Patients under the regular supervision of a dentist may benefit from early detection of changes in gingival tissue, when non-surgical therapy can be used to reduce the extent of plaque-induced gingival inflammation and limit the occurrence, or minimize the rate of recurrence, of this unwanted side effect and devastating tooth loss.[31]

Finally, it should be noted that one question remains cryptic, that is, why some drug receptors become affected by gingival enlargement and others do not, despite the fact that there are similar conditions with respect to the dosage of amlodipine and the amount of plaque accumulation. This can probably be attributed to biological differences between humans, for example, the existence of different subgroups of gingival fibroblasts. Therefore, investigating the interactions between factors such as gingival fibroblast subgroup metabolism, hormonal effects, and growth agents can be a guide to find such differences.[24]

In the current study, there are few limitations, including a small sample size and lack of long-term evaluation. Additionally, longitudinal studies can be conducted recruiting a larger sample size in the future and a biochemical evaluation of the hormonal level can be performed to find the corelation between hormonal changes and oral health status. Only a clinical evaluation was performed, although radiographs are widely considered a reliable tool for assessing bony alveolar changes.

CONCLUSION

Patients consuming antihypertensive medications are at high risk for gingival enlargement, and inflammation is considered an important cofactor for the expression of this effect. It is of paramount importance for physicians and dentists to be aware of the etiologic medications that can cause gingival enlargement and to be able to identify changes in the oral cavity in those patients to prevent, diagnose quickly, and successfully manage them. Supportive follow-up and periodic professional periodontal care are crucial to prevent the recurrence of gingival enlargement.

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