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Is periodontal health a predictor of drug-induced gingival overgrowth? A cross-sectional study

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ABSTRACT

Background: Gingival overgrowth is a common side-effect of amlodipine regimen on the oral cavity. There is controversy regarding the cause and effect relationship of periodontal health and drug induced gingival overgrowth. Therefore, this study was conducted to investigate and to assess the relationship between the periodontal health and the onset and severity of gingival overgrowth in hypertensive patients receiving amlodipine.

Materials and Methods: A total of 99 known hypertensive patients on amlodipine regimen were included in this study. Probing pocket depth (PPD) and clinical attachment loss (CAL) were noted on four sites of maxillary and mandibular anterior teeth. Gingival enlargement scores were assessed for each patient by employing the hyperplastic index. Oral hygiene status was evaluated using the calculus index (CI). Patients were divided into H, E and L groups based on their periodontal status and responders and non-responders based on their hyperplastic index scores. Differences in means of different periodontal variables in different groups were tested for significance by using ANOVA and unpaired Student *t*-test. Pearson's correlation coefficient was calculated to assess the correlation between different variables. For all analyses, $P < 0.05$ was considered to be significant.

Results: All the periodontal parameters were statistically highly significant ($P = 0.00$) amongst H, E and L groups and between responders and non-responders. Statistically highly significant Pearson correlation coefficients were found between mean PPD and mean hyperplastic score, mean CAL and mean hyperplastic score and mean calculus and mean hyperplastic score.

Conclusion: The results of this study indicated a definite association between periodontal health and development and severity of amlodipine-induced gingival overgrowth

Key Words: Amlodipine, drug-induced gingival overgrowth, oral hygiene, periodontal disease

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INTRODUCTION

Calcium channel blockers are a group of drugs, which are widely used in the treatment of many cardiovascular disorders. It has been demonstrated that these drugs have an important side-effect on gingiva; principally gingival overgrowth (known as drug-induced gingival overgrowth [DIGO]).[1] Maximum prevalence of DIGO has been reported with nifedipine ranging from 20% to 83%.[2,3] Certain other calcium channel blockers such as verapamil and amlodipine have also been reported with this side-effect.[4,5] There are various factors, which affect the onset and severity of DIGO. Dosage, duration and blood level of drugs are the most important drug related factors. Patient related factors such as age, genetic predisposition and oral hygiene status are also considered to be aggravating factors for DIGO.[6] It is hypothesized that non-inflamed gingival fibroblasts are less active and do not respond to the drug molecules while the fibroblasts within inflamed tissue are in active state and can predispose the patient to

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gingival overgrowth.[7,8] A number of case reports and anecdotes have indicated the correlation between periodontal status and DIGO, but evidence based clinical studies relating the periodontal inflammation to drug induced gingival overgrowth are lacking. Hence, this study was conducted to investigate and to assess the relationship between periodontal health and the onset and severity of gingival hyperplasia in hypertensive patients receiving amlodipine.

MATERIALS AND METHODS

A cross-sectional study approved by institutional scientific committee was conducted in various hospitals and dental clinics of Indore city. A total of 99 hypertensive patients were included in this study.

Known hypertensive patients (both males and females, age range between 30 and 75 years) who were taking amlodipine regularly for at least 6 months,[9] had 12 permanent anterior teeth (full complement) and patients who agreed to take part in the study were included.

Patients with systemic disorders other than hypertension, who were taking amlodipine for less than 6 months, who had undergone periodontal treatment within 6 months prior to initiation of the study and taking drugs, which can cause gingival overgrowth such as anticonvulsant drugs like phenytoin and immune-suppressants like cyclosporine were excluded from the study.

Clinical examination

Demographic data and patients' medical and drug history comprising of type, dosage and duration of drug administered were recorded. All patients were examined to assess the periodontal status of their maxillary and mandibular anterior teeth by plane mouth mirror and William's periodontal probe. Periodontal parameters included probing pocket depth (PPD) and clinical attachment loss (CAL) at four sites of each tooth, calculus index (CI)[10] (scores were given as 0 or 1 on the basis of absence or presence of calculus) and hyperplastic index [Table 1].[11] Patients were divided into three groups according to HEL scoring criteria [Table 2]. Gingival healthy group (H-Group) consisted of those scoring +2 (excellent) or +1 (good), equivocal group (E-Group) comprising of those patients scoring (0) and a less healthy group (L-Group) had scoring −2 (very poor) or −1 (poor).[12]

The degree of gingival enlargement was assessed by employing the hyperplastic index, which comprised of two components independently measuring the vertical and a horizontal extension of gingival enlargement.[11]

The vertical component of hyperplastic index measured the degree of gingival enlargement in an apico-coronal direction for a gingival unit by means of 4-point scale. Each unit extended from the buccal or lingual midpoint of a tooth to a midpoint of the adjacent tooth. The horizontal component of the hyperplastic index measured the degree of gingival thickening on both the labial and lingual aspects in a labio-lingual direction for a gingival unit. The vertical and horizontal scores were added, thereby giving a hyperplasia score for each gingival unit. The maximum obtainable score was five. As 20 gingival units were examined, the degree of hyperplasia around upper and lower teeth was expressed as a percentage.[11]

Patients were further divided into two subgroups-responders and non-responders according to their

Table 1: Hyperplastic index

Grade	Vertical component	Horizontal component
	Criteria	Criteria
0	No gingival hyperplasia	Normal width of free gingival margin
1	Blunting of gingival margins (mild hyperplasia)	Thickening from the normal up to 2 mm
2	Less than half of crown length (moderate hyperplasia)	Thickening from the normal >2 mm
3	Greater than half of crown length (marked hyperplasia)	

Table 2: HEL scoring criteria

Grade	Criteria
+2 (excellent)	Normal gingiva with no plaque or calculus
+1 (good)	Clean appearance, good oral hygiene and slight localized inflammatory changes
0 (equivocal)	Questionable appearance, difficult to assess a ± score
−1 (poor)	Poor appearance and oral hygiene, overt gingivitis
−2 (very poor)	Extremely poor appearance and oral hygiene, sever gingivitis

hyperplastic index score. Subjects with a score greater than 30% were regarded as responders while subjects with a score less than or equal to 30% were regarded as non-responders.[13]

All data were expressed as means. Differences in means of different periodontal variables in different groups were tested for significance by using ANOVA and unpaired Student *t*-test. Pearson's correlation coefficient was calculated to assess the correlation between different variables. For all analyses, $P < 0.05$ was considered to be significant. Multiple regression analysis was conducted to know the individual impact of factors including age, dose and duration, CAL, PPD and CI on gingival hyperplasia.

RESULTS

A total of 99 patients were enrolled in this study. The differences in mean drug dose and mean age of H, E and L groups were statistically not significant. The differences in mean treatment duration, mean calculus scores, mean PPD, mean CAL and mean hyperplastic scores were found to be statistically different amongst H, E and L groups ($P = 0.00$) [Table 3]. The differences of mean CAL, mean PPD and mean hyperplastic scores among responders and non-responders were found to be highly significant ($P = 0.00$) [Table 4].

Statistically significant Pearson correlation coefficients were found between mean PPD and mean hyperplastic score, mean CAL and mean hyperplastic score and mean calculus and mean hyperplastic score, which were 0.70, 0.90 and 0.83 respectively.

Multiple regression analysis was conducted to know the individual impact of factors including age, dose, duration, CAL, PPD, CI on gingival hyperplasia and none of factors could achieve significant odd's ratio at 95% confidence intervals [Table 5].

DISCUSSION

This cross-sectional study was carried out on 99 hypertensive patients who were taking amlodipine therapy. Patients were divided into H, E and L group based on HEL criteria. Though these criteria evaluate the patients subjectively, difference between mean CAL, mean PPD and mean calculus scores (as evaluated by ANOVA test) were found to be statistically significant. This proves the validity of HEL criteria for evaluating periodontal status of patients. Mean age and mean dose of drug were found to be similar in all the three groups. Difference in the duration of amlodipine therapy was found to be statistically significant in all three groups. This indicates that periodontal status worsened with the duration of disease (Hypertension) as most of these patients were taking amlodipine ever since

Table 3: Demographic, drug-related and periodontal parameters in H, E and L groups

Parameters	H	E	L	ANOVA	*P* value
Number of patients	31	31	37		
Mean age (years)	54.13±8.99	51.68±9.40	54.76±9.64	0.98	0.38 (NS)
Mean drug dose (mg)	7.42±2.54	8.87±2.12	8.11±2.46	2.87	0.06 (NS)
Mean treatment duration (months)	23.26±15.26	35.39±20.72	52.14±27.23	14.79	0.00 (HS)
Mean calculus index score	0.10±0.07	0.32±0.06	0.91±0.08	1.17	0.00 (HS)
Mean probing pocket depth (mm)	2.41±0.23	2.53±0.15	6.50±0.21	4.75	0.00 (HS)
Mean clinical attachment loss (mm)	0.01±0.04	1.45±0.11	3.47±0.23	4.09	0.00 (HS)
Mean hyperplastic index scores	0.09±0.06	0.36±0.01	0.44±0.01	995.11	0.00 (HS)

ANOVA: Analysis of variance; NS: Non significant; HS: Highly significant; H: Healthy; E: Equivocal; L: Low; $P < 0.05$ was considered significant

Table 4: Demographic, drug-related and periodontal parameters in responders and non-responders

Parameters	Responders	Non-responders	*t*-test	*P* value
Number	68	31		
Mean age (years)	53.35±9.58	54.13±8.99	0.38	0.70 (NS)
Mean drug dose (mg)	8.46±2.33	7.42±2.54	−2.0	−0.05 (NS)
Mean treatment duration (months)	44.50±25.71	23.26±15.26	−4.26	0.00 (HS)
Mean calculus index score	0.64±0.31	0.10±0.07	−9.76	0.00 (HS)
Mean probing pocket depth (mm)	4.68±2.0	2.41±0.23	−6.30	0.00 (HS)
Mean clinical attachment loss (mm)	2.54±1.02	0.01±0.04	−13.70	0.00 (HS)
Mean hyperplastic index score	0.40±0.041	0.09±0.06	−31.3	0.00 (HS)

NS: Non significant; HS: Highly significant; $P < 0.05$ was considered significant

Table 5: Multiple logistic regression analysis showing odd's ratio at 95% confidence interval

Parameters	Sig	Exp (B)
Sex	1.00	0.34
Age	1.00	1.02
Duration	1.00	1.03
Dose	1.00	1.31
Mean probing pocket depth	0.99	0.00
Mean clinical attachment loss	0.99	1.40
Mean calculus index	1.00	8.77

Sig: Significant; $P < 0.05$ was considered significant

the diagnosis of their disease. Seymour *et al*. have concluded in their study that the gingival overgrowth began 2-3 months after starting the medication at 5-10 mg/day and these authors attributed these changes to be compounded by the patients' existing periodontal condition.[14] In our study, we have included patients with more than 6 months of amlodipine use.

Differences in mean hyperplastic score were found to be statistically significant between all three groups. This indicates that as periodontal health worsens, degree of gingival overgrowth increases. This increased tendency of overgrowth might be a result of a combination of DIGO overlapped with secondary inflammatory component as it is difficult for patients to maintain oral hygiene in areas of gingival enlargement.

Patients were also divided into responders and non-responders based on their mean percentage hyperplastic score. Subjects having a score of ≥30% were designated as responders and those with a score <30% were designated as non-responders. In our study, 68% were responders and 32% were non-responders. Similar rate of prevalence were found by Kazi *et al*. in patients taking verapamil. This prevalence has to be considered in the light of small sample size as in Kazi *et al*. study, only 30 patients were evaluated out of which, 20 were responders and 10 belonged to non-responder group.[13] The prevalence of amlodipine induced gingival over growth reported by Jorgensen[5] and Ellis *et al*. was 3.3% and 1.7% respectively.[15]

In our study, the difference in mean CAL, PPD and CI between responders and non-responders were found to be significant. This indicates that patients with gingival overgrowth had poorer periodontal health and compromised oral hygiene. This can indirectly indicate an association between compromised periodontal health and presence and degree of gingival enlargement.

Correlation coefficient is the measurement of the degree of relationship between two variables. It indicates direction as well as closeness of relationship between two variables. It is usually denoted by r which lies between +1 and −1. If r is +1, it indicates a strong positive association, i.e., when one variable increases, the other variable also increases. A value of −1 indicates a strong negative association, i.e., when one variable increases, the other decreases. If $r = 0$, there is absolutely no correlation. Between 0 and +1 and 0 and −1 partial positive and partial negative correlation exits (moderate correlation).[16]

In this study, statistically significant Pearson correlation coefficients were found between mean PPD and mean hyperplastic score, mean CAL and mean hyperplastic score and mean calculus and mean hyperplastic score, which were 0.70, 0.90, 0.83 and respectively. Similar findings were reported by Kazi *et al*. who found significant correlation between plaque index and hyperplastic index in patients on Verapamil.[13] The findings of present study correlating oral hygiene status associated with gingival overgrowth are also in accordance with Morisaki *et al*.[17] and Barclay *et al*.[2]

The role of plaque has not been clearly defined in most medication-induced gingival overgrowths. There is no doubt that the resulting gingival inflammation can contribute to an additional level of enlargement due to edema, regardless of any initiating or contributing effect it may have on gingival overgrowth.[18] Though, no cause and effect relationship has been established, following mechanisms have been suggested to explain the link between gingival inflammation and occurrence and severity of DIGO:

1. Charles *et al*. have concluded that the presence of dental plaque may provide a reservoir for accumulation of drugs causing gingival enlargement such as amlodipine.[19] The crevicular fluid concentrations of the drugs were found to be up to 292 times of those found in plasma.[14]
2. Amlodipine inhibits intracellular uptake of calcium ions. This inhibitory effect may affect the secretory properties of gingival fibroblasts or the production of collagenases such as matrix metallo-proteinase (MMP)-1 and MMP-3 leading to accumulation of extracellular matrix.[20,21]
3. Gingival inflammation and plaque induces a proliferative response in keratinocytes and provides a reservoir for the accumulation of drugs, thereby providing local source for gingival epithelial deposition of the drug.[22]

4. Pro-inflammatory cytokines that are released during the initial stages of inflammation influence the migration of mast cells. Mast cells containing chymase and tryptase are directly involved in gingival fibrosis.[23,24] Mast cells produce mediators such as histamine, heparin and tumor necrosis factor-α, which can influence fibroblast proliferation, extra cellular matrix synthesis and degradation.[25] The gingiva provides all the essential components for a functional rennin angiotensin system (RAS).[26-28] Angiotensin-2 (Ang-2) is effector peptide of RAS, which acts as a major role in regulation of collagen synthesis and growth modulating effects on fibroblasts.[29-31]
5. A recent study shows a possible association between gingival overgrowth and epithelial mesenchymal transition (EMT). EMT is a process in which epithelial cells trans-differentiate into fibroblast-like cells. transforming growth factor-β1 (TGF-β1) is a potent inducer of EMT in a variety of tissues and connective tissue growth factor (CTGF) expression is increased in cells undergoing EMT.[32]

Some cytokines and growth factors were found in higher levels in gingival overgrown tissues, including interleukin (IL-6), IL-1, platelet derived growth factor-β, fibroblast growth factor-2 (FGF-2), TGF-β and CTGF.[33-35] Inflammation causes upregulation of TGF-β1, which is responsible for the production of fibrous scaffold that may be essential for the vertical growth of gingiva (pseudopocket development).[36] These drugs may stimulate the production of IL-2 by T-cells causing fibrosis.[37] FGF-β and heparin sulfate glycosaminoglycans may also play a role in DIGO.[37]

Limitations

1. Smaller sample size can be one of limiting factors as large samples are recommended in cross-sectional studies.
2. Smokers were not excluded which might have affected the results.
3. Though an association can be established in cross-sectional studies but these studies lack the power to predict a cause and effect relationship.

CONCLUSION

Based on these limitations, it can conclude that oral hygiene plays a decisive role in the development of gingival hyperplasia. The statistically significant difference found in mean CI scores, mean PPD and mean CAL between responder and non-responder groups in the present study suggests an association between compromised oral hygiene, poor periodontal status and presence and severity of gingival overgrowth, though it is not possible to establish a cause and effect relationship in cross-sectional studies. Great emphasis should be given to oral health maintenance and regular dental checkups in patients on calcium channel blockers to improve the quality-of-life in such patients and to save them from adverse drug effects.

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