Original Article

Effect of Calcium Channel Blockers on Gingival Tissues in Hypertensive Patients in Lagos, Nigeria: A Pilot Study

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Abstract

Background: Long-term treatment of common chronic cardiac conditions such as hypertension with calcium channel blockers (CCBs) has long been associated with gingival hyperplasia. This oral side effect may affect esthetics and function, yet often overlooked and therefore underreported among Nigerians. **Aim:** This study aimed to determine the association of CCBs with gingival overgrowth (GO) in hypertensive patients. **Methods:** This was a hospital-based, case–control study conducted among 116 hypertensive patients (58 CCB and 58 non-CCB age-matched controls) attending the medical outpatient clinic of a tertiary health institution in Lagos, Nigeria. Data collection tools included interviewer-administered questionnaires and periodontal examination. Sociodemographic details, medical history, and periodontal indices (gingival index, plaque index, class of GO according to drug-induced GO [DIGO] Clinical Index) were recorded. **Results:** The mean age was 59.4 ± 12.6 years, females representing 50.9%. In the CCB group, 39 (67.2%) participants were on amlodipine and 19 (32.8%) were on nifedipine. The mean duration of CCB use was 55.6 ± 53 months. DIGO was higher in CCB (36.2%) than that in non-CCB participants (17.2%) ($\chi^2 = 4.4$, $P = 0.036$). The risk of GO was higher in CCB users (odds ratio [OR] 2.7, [95% confidence interval (CI)]: 1.1–6.5). Amlodipine users had higher DIGO (37.5%) than that of nifedipine users (21.1%) (OR 2.3, [95% CI]: 1.0–5.3). The predominant class of DIGO among the CCB users was Class 2 DIGO Clinical Index (90.5%). **Conclusion:** The study reveals that the risk of GO is nearly three times in CCB than that of non-CCB users and twice higher in amlodipine than nifedipine users in Nigeria.

Keywords: *Calcium channel blockers, gingival overgrowth, Nigeria*

Introduction

Gingival overgrowth (GO) is an excessive enlargement of the gingival tissue that could occur as an unwanted side effect of systemic medications such as calcium channel blockers (CCBs) which is used in the treatment of hypertension. This group of antihypertensive drugs exhibit their pharmacologic effects on various primary target tissues, while acting secondarily on gingival connective tissues causing common oral clinicohistologic manifestations as unwanted side effects.[1,2] Drug-induced GO (DIGO) is reported to be the most widespread unwanted effect of CCBs on periodontal tissues and may interfere with esthetics, mastication, speech, and access for oral hygiene, resulting in increased vulnerability to bacterial infections including periodontal diseases and dental caries.[3,4]

Different prevalence rates (20% to 50%) have been reported for GO induced by CCB[5-7] for nifedipine-induced GO, while a prevalence rate of 3.3%[8] was reported for amlodipine-induced GO. These, however, represent Caucasians' values.

CCBs are classified according to their chemical structure into: dihydropyridines (nifedipine, amlodipine), diphenylalkylamines (verapamil), benzothiazipines (diltiazem), and diphenylpiperazines (flunarizine).[9] They are used extensively for the management of cardiovascular disorders including hypertension, angina pectoris, cardiac arrhythmias, and coronary artery spasms.[1,4,5] The effects of CCB are exerted by the inhibition of calcium ion influx in cardiac and smooth muscle cells resulting in coronary and peripheral arterial vasodilation, reduced heart rate, decreased myocardial contractibility and oxygen utilization by the myocardium, and slow atrioventricular conduction.[9,10]

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The pathogenesis of CCB-induced GO is not clearly understood and is viewed as being multifactorial. Various risk factors including drug variables (dosage and duration), age, gender, oral hygiene status, and gingival inflammation have been associated with this condition.[1,6,7] Furthermore, Samudrala *et al*.[11] in a 2017 review suggested certain features to be generally more frequent in DIGOs. These include the initiation of GO within 3 months of drug use, frequent occurrence in the anterior gingiva in younger age groups, and a lack of association with attachment loss. Although the mechanism by which these drugs induce GO is still poorly understood, it has been postulated that CCB inhibit intracellular calcium uptake, thereby stimulating gingival fibroblast proliferation. According to Dongari *et al*.,[12] this negative effect on calcium ion influx across cell membranes interferes with the synthesis and function of collagenases. This occurs by the reduction of folic acid uptake leading to GO.[13] Not all patients on CCB develop GO, hence it has been suggested that the vulnerability of gingival tissues to the drugs may be due to the existence of a subset of gingival fibroblasts unique to each individual.[2,12,14] Furthermore, it has been proposed that gingival fibroblasts enhance collagenous protein synthesis when exposed to the simultaneous effects of nifedipine and pro-inflammatory cytokines such as interleukin-1 β (IL-1 β) that are elevated in gingival inflammation.[12]

Of the CCBs, GO is more common with the dihyropyridines (nifedipine and amlodipine). The clinical manifestation of GO may be seen within the first 1 to 3 months of treatment with CCB and begins from the interdental papillae. The DIGO is more frequently found adjacent to the labial surfaces of the anterior segments and is normally confined to the attached gingiva but may extend coronally, interfering with esthetics, speech, and mastication.[2,4,15]

Several reports have implicated nifedipine and amlodipine as the frequent causes of GO,[2,4,11,15-20] though this unwanted effect has also been reported in patients taking verapamil.[21] The recent case reports' review by Samudrala *et al*.[11] summarized the management of CCB-associated GO as follows; changing the drug, thorough scaling and root planing, and conscientious plaque control measures, followed by surgical intervention in the face of persistent DIGO. In their review, only one of the case reports of the CCB-induced DIGO needed surgical intervention despite changing the drug and performing nonsurgical professional therapy. The importance of histopathological examination of gingival tissues in the diagnosis and management of DIGO was also buttressed in their analysis.[11] This aims to clarify disparities that may sometimes occur between clinical and histopathological diagnoses such as that observed in the report by Vishnudas *et al*.,[11,22] in which a histopathological diagnosis of plasma cell granuloma was made following the initial amlodipine-associated gingival enlargement.

GO is reported to be an oral side effect associated with CCB use in hypertensive patients in other climes. However, there is a dearth of published literature in Nigeria on this reported effect which may be unknown to physicians managing hypertensive patients or if the effect is not prevalent. This, therefore, underscores the importance of documenting such clinically relevant side effects among the Nigerian population if present particularly as CCB is a commonly prescribed medication in the management of hypertensive patients in Nigeria. With the rising prevalence of hypertension in Nigeria, and the increasing use of CCB, it is important to investigate any associated CCB-associated gingival effects which may compromise periodontal health and possibly the overall systemic health.

This study aims to determine the association between CCBs and GO among a group of Nigerians on CCB.

Methods

This hospital-based, cross-sectional study was approved by the Health Research and Ethics Committee of the Lagos University Teaching Hospital. One hundred and sixteen hypertensive participants were recruited into the study. The cases comprised 58 participants who were defined as hypertensive patients, who were on CCB. The controls were from the same cohort and comprised 58 age-matched hypertensive patients on non-CCB medications attending the Medicine outpatient clinic of the Lagos University Teaching Hospital, Idi-Araba. The selection criteria included patients on antihypertensive medications for a minimum of 6 months, presence of at least 6–12 teeth in the anterior region of the upper and lower jaws, history of no periodontal therapy in the preceding 6 months, and nonuse of other groups of medications known to be associated with gingival hyperplasia such as cyclosporine. Participants with plaque-retentive factors such as orthodontic appliances, defective restorations, dentures, or anterior crowns, and those with other known systemic conditions that could modify their gingival condition such as pregnancy, diabetes mellitus, and leukemia were excluded from the study. After obtaining their written informed consent, participants' demographic information was obtained using interviewer-administered questionnaires. Two dentists carried out the periodontal examination, and the inter-examiner reliability was ensured between both examiners. The following periodontal indices were utilized – plaque index (Silness and Loe),[23] gingival index (Silness and Loe),[24] and probing depth. The presence of GO was assessed on the upper and lower teeth on the anterior and posterior segments by examining the lingual and facial interdental papillae. It was scored on a scale of 0–4 according to the Clinical Index for DIGO.[25]

The criteria are summarized as follows:

- Grade 0: No overgrowth, slight stippling, and no increase in density or size of the gingiva
- Grade 1: Early overgrowth, evidenced by increase

in density of the gingiva with marked stippling and granular appearance, tip of the papilla is rounded, and probing depth is ≤3 mm
- Grade 2: Moderate overgrowth, evidenced by increase in the size of the papilla, contour of gingival margin is concave or straight, gingival enlargement has a buccolingual dimension of up to 2 mm, papilla is somewhat retractable, and probing depth is ≤6 mm
- Grade 3: Marked overgrowth, with encroachment of the gingiva onto the clinical crown, gingival margin contour is convex rather than concave, gingival enlargement has a buccolingual dimension of approximately ≥3 mm, papilla is retractable, and probing depth is >6 mm
- Grade 4: Severe overgrowth, characterized by a profound thickening of the gingiva, large part of the clinical crown is covered, buccolingual dimension is approximately 3 mm, papilla is retractable, and probing depth is >6 mm.

The dose and duration of antihypertensive medications were obtained from participants' hospital records.

Data were analyzed using Epi Info-7.1.5.2 Statistical Software (CDC, Atlanta GA, 2015). Descriptive statistics were computed for categorical variables and presented as frequencies. Differences between groups (CCB vs. non-CCB; presence of DIGO vs. absence of DIGO) were compared using the Chi-square test of association and ANOVA for continuous variables. $P < 0.05$ was considered statistically significant.

Results

A total of 116 hypertensive participants (58 on CCBs and 58 age-matched controls on non-CCB) were enrolled into the study. Their mean age was 59.4 ± 12.6 years (range: 18–84 years). Females represented 50.9% ($n = 59$). The average duration of CCB use was 55.6 ± 53 months (range: 6–276 months). The mean plaque index and mean gingival index for the total study population were 1.1 ± 0.4, while mean probing depth was 2.3 ± 0.9. There were no significant differences in the mean plaque indices and gingival indices between the CCB and non-CCB groups [Table 1].

Among the CCB users, 39 (67.2%) participants were on amlodipine, while 19 (32.8%) were on nifedipine. Overall, the prevalence of GO among the hypertensive patients was 26.7%. The prevalence of DIGO among the CCB hypertensive participants was 36.2% [Figure 1]. There was a significant association between DIGO and type of antihypertensive medication used as participants on CCB had a higher prevalence of DIGO (36.2%) than that of non-CCB participants (17.2%) (Yates $\chi^2 = 4.4$, df = 1, $P = 0.036$) [Table 2]. The risk of GO was higher in CCB users (odds ratio [OR]: 2.7, [95% confidence interval (CI)]: 1.1–6.5) [Figure 2]. Amlodipine users had higher DIGO (37.5%) than that of nifedipine users (21.1%) (OR: 2.3, [95% CI]: 1.0–5.3).

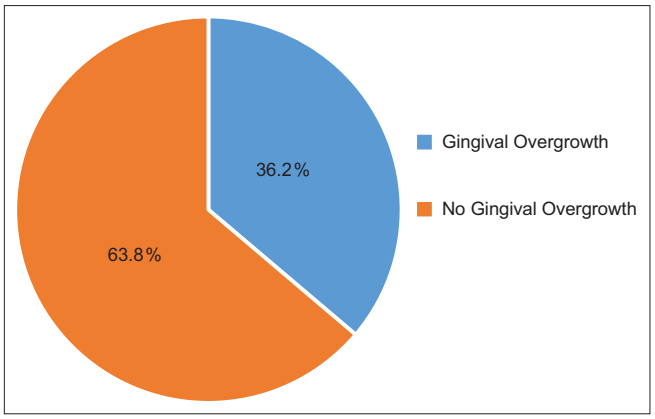

Figure 1: Prevalence of drug-induced gingival overgrowth among calcium channel blocker participants

Table 1: Demographic and clinical characteristics among calcium channel blocker and noncalcium channel blocker participants

Variable	CCB group (*n*=58), *n* (%)	Non-CCB group (*n*=58), *n* (%)	*P*
Gender			
Male	30 (52.6)	27 (47.4)	0.710*
Female	28 (47.5)	31 (52.5)	
Mean age±SD (years)	60.1±13.1	58.7±12.2	0.564[ł]
Mean plaque index±SD	1.1±0.4	1.1±0.5	0.445[ł]
Mean gingival index±SD	1.1±0.3	1.1±0.4	0.971[ł]
Mean probing depth±SD	2.6±0.8	2.1±0.8	0.001[ł,]**
Mean number of teeth±SD	30.5±2.3	30.5±2.7	0.910[ł]

**Significant; [ł]χ^2; *ANOVA. SD: Standard deviation; CCB: Calcium channel blocker

The predominant class of DIGO among CCB users was Class 2 DIGO Clinical Index (90.5%). Figure 3 shows a patient with Class 2 DIGO followed by Class 3 DIGO Clinical Index (9.5%).

More males (33.3%) presented with DIGO compared to females (20.3%) in this study. Although there were more males, herbal users, and smokers with DIGO compared to participants without DIGO, the associations were not significant ($P > 0.05$) [Table 2]. Participants on CCB had significantly increased probing depths than that of the non-CCB group ($P = 0.001$). The duration of CCB use was not significantly associated with the occurrence of DIGO, although the mean duration of CCB use was higher among participants with DIGO (63.2 ± 69.2) than participants without DIGO (51.3 ± 41.2) [$P = 0.416$] [Table 2]. Among the non-CCB users, 11 (19%) had used CCB previously although this was more than 12 months prior to the study onset.

Discussion

DIGO has been reported in association with CCBs, developed for the treatment of cardiovascular conditions

Table 2: Factors associated with drug-induced gingival overgrowth among calcium channel blocker and noncalcium channel blocker participants

Variable	DIGO		OR (95% CI) Reference	*P*
	Present, *n* (%)	Absent, *n* (%)		
Gender				
Male	19 (33.3)	38 (66.7)	2.0 (0.8-4.5)	0.170*
Female	12 (20.3)	47 (79.7)		
Tobacco use				
Yes	2 (33.3)	4 (66.7)	1.4 (0.2-8.0)	0.510*
No	29 (26.4)	81 (73.6)		
Local herbs				
Yes	15 (29.4)	36 (70.6)	1.3 (0.6-2.9)	0.355*
No	16 (24.6)	49 (75.4)		
Drug type				
CCB	21 (36.2)	37 (63.8)	2.7 (1.1-6.5)	0.036**
Non-CCB	10 (17.2)	48 (82.8)		
Mean age±SD (years)	60±13.3	59.2±12.5	NA	0.755[ł]
Mean plaque index±SD	1.2±0.4	1.1±0.5	NA	0.536[ł]
Mean gingival index±SD	1.2±0.4	1.1±0.4	NA	0.525[ł]
Mean probing depth±SD	3.5±0.5	1.9±0.5	NA	0.000[ł].**
Mean duration of CCB±SD (months)	63.2±69.2	51.3±41.2	NA	0.416[ł]
Mean dose of amlodipine±SD (mg)	8.5±4.2	8±2.7	NA	0.664[ł]
Mean dose of nifedipine±SD (mg)	40±40.5	26.5±17.5	NA	0.537[ł]

*χ^2; [ł]ANOVA; **Significant. DIGO: Drug-induced gingival overgrowth; OR: Odds ratio; CI: Confidence interval; NA: Not applicable; SD: Standard deviation; CCB: Calcium channel blocker

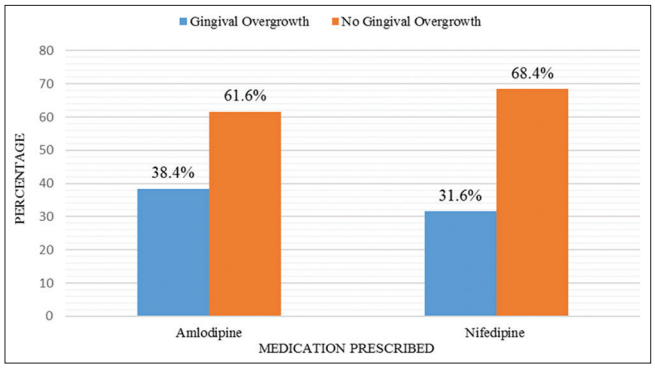

Figure 2: Comparison of gingival overgrowth between amlodipine and nifedipine users

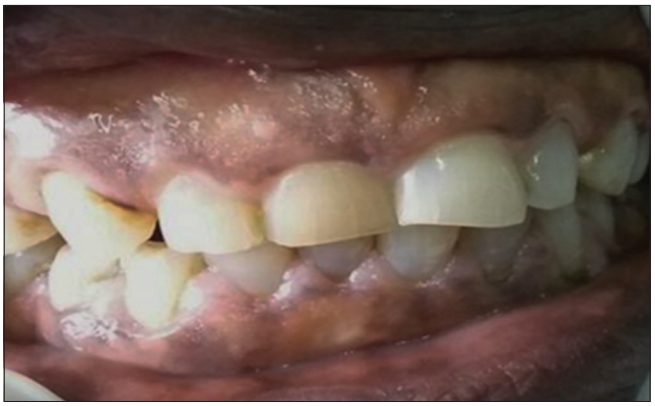

Figure 3: Drug-induced gingival overgrowth in a patient with Class 2 Clinical Index

such as hypertension and angina. The present study was designed to evaluate the association between CCBs and GO among a group of Nigerians on CCB. The Clinical Index for DIGO was utilized in assessing GO in the present study because it was considered to be a comprehensive index. CCBs is a commonly prescribed medication for hypertension in this clime which may be a reflection of physicians' preference for its use. This preference stems from the recommendation of the National Institute for Health and Clinical Excellence,[26] as well as the Joint National Committee Hypertension guidelines.[27] Moreover, the cost-effectiveness of CCB in controlling hypertension among patients in Nigeria has been highlighted and was observed to be the second best medication for moderate-to-high risk hypertension.[28] Amlodipine was the CCB drug of choice compared to nifedipine in our study and could be as a result of once-daily dosing of amlodipine compared to twice-daily dosing of nifedipine. Hence, this is likely to enhance compliance by patients. This is coupled with the better tolerability and longer plasma half-life of amlodipine, compared to nifedipine. Nifedipine is an older generation of CCB which may have other deleterious side effects, hence the preference of physicians in prescribing amlodipine.

The higher prevalence of DIGO among CCB users (36.2%) compared with non-CCB users (17.2%) has been reported. Andrew *et al*.[1] in a cross-sectional study among Kenyans attending a medical outpatient clinic found the prevalence

of DIGO to be 31.5% in CCB users compared to 7% in non-CCB users. Furthermore, there was an increased risk of GO, nearly 3 folds in CCB users compared with non-CCB users. This is similar to the findings in the study by Kaur *et al*. (2010)[29] The higher prevalence of DIGO among the non-CCB users in our study (17.5%) compared to the Kenyan study (7%) could be attributed to their previous use of CCB prior to our study commencement. This is supported by the fact that 19% of the non-CCB users in the present study had used CCB in the past. It is important to stress the variations in criteria used for the clinical assessment of GO in different studies, which may also influence the prevalence of the DIGO reported. Both groups had similar demography; age, gender, and clinical characteristics and mean plaque and gingival index scores. This, therefore, suggests that the significantly higher prevalence of DIGO among the CCB users was more likely due to their CCB usage. Although the mechanism by which these drugs induce GO is still poorly understood, it has been suggested that CCB inhibits the intracellular uptake of calcium across cell membranes, and may therefore interfere with the synthesis and function of collagenases, thus resulting in gingival fibroblast proliferation.[12] The fact that not all patients on CCB develop GO suggests that there may be a genetic predisposition. It has been postulated that the susceptibility of the gingival tissues to these CCB drugs could be linked to the presence of a subset of gingival fibroblasts unique to each individual.[2,12,14] Furthermore, it has been proposed that gingival fibroblasts enhance collagenous protein synthesis when exposed to the simultaneous effects of nifedipine and pro-inflammatory cytokines such as interleukin-1 β (IL-1 β) that are elevated in gingival inflammation.[12]

The observation of more males (33.3%) with DIGO compared to females (20.3%) in this study has been attributed to the effect of androgens.[13] Ellis *et al*.[30] found that males were three times more likely than females to have DIGO. Similar male preponderance of DIGO has been reported by Seymour *et al*.[31] and Livida *et al*.[13] The slightly higher finding of DIGO among amlodipine users in the current study may be related to the fact that more patients were placed on amlodipine. Amlodipine users had higher DIGO (37.5%) than that of nifedipine users (21.1%) (OR: 2.3, [95% CI]: 1.0–5.3). This finding is interesting and contrasts with previous studies in which nifedipine was more associated with GO.[29] Interestingly, the review by Samudrala *et al*.[11] highlighted a changing pattern of CCB-associated DIGO in the last two decades, with more cases of GO reported following amlodipine use compared with nifedipine. The prevalence of nifedipine-associated GO in the present study falls within the reported range of 6.3%–83% in the literature.[29,30] This large range in prevalence can be explained by the differences in the populations that have been studied, differences in drug dosages or oral hygiene practice, and differences in case ascertainment. We did not observe a significant association between the duration and dose of CCB with the prevalence of DIGO. This is similar to the reports in other similar studies.[1,5,32,33] It has been suggested that drug dosage may be a poor predictor of gingival changes, being influenced largely by pharmacokinetics and pharmacodynamics.[1] The significant association between increased probing depth and DIGO in our study was not unexpected owing to the formation of false pocketing in relation to GO. The clinical relevance, however, lies in the increased potential for further plaque retention, which could set in an unwanted chain of persistent chronic inflammation which may aggravate systemic inflammation. This may potentially place hypertensive patients using CCB at an increased risk of cardiovascular complications. This is buttressed by recent evidence supporting the effect of periodontal inflammation with an increased risk of cardiovascular complications.[32] CCBs are commonly prescribed antihypertensive drugs in this clime and the control group had some participants who had a history of previous use but had stopped in the preceding 12 months. This was a potential confounder, but this factor did not contribute much to the results as the current CCB users still had significantly higher DIGO. Future studies intend to conduct multicenter studies with larger sample sizes to further elucidate the effect of the dose and duration of CCB on DIGO and also consider genetic studies for DIGO among Nigerians on CCB.

Conclusion

The study reveals that the risk of GO is nearly three times higher in CCB than non-CCB users and 2 folds in amlodipine than nifedipine users in Nigeria. Physicians who are involved in the management of these patients may need to perform oral examinations, albeit brief during their patients' appointment. They should also educate their patients on the likelihood of its occurrence among them and emphasize good oral hygiene care and refer them to dentists for proper clinical assessment and possible professional oral prophylaxis.

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Conflicts of interest

There are no conflicts of interest.

References

1. Andrew W, Evelyn W, Francis M, Mark J, Mark C. Pattern of gingival overgrowth among patients on antihypertensive pharmacotherapy at a Nairobi hospital in Kenya. OJST 2014;4:169-73.
2. Grover V, Kapoor A, Marya CM. Amlodipine induced gingival hyperplasia. J Oral Health Commun Dent 2007;1:19-22.
3. Amit B, Shalu BV. Gingival enlargements induced by anticonvulsants, calcium channel blockers and immunosuppressants: A review. IRJP 2012;3:116-9.
4. Shinha A, Oswal S, Shivamurthy R. Amlodipine induced gingival overgrowth: A case report. Int J Case Rep Images 2014;5:509-12.
5. Barclay S, Thomason JM, Idle JR, Seymour RA. The incidence

and severity of nifedipine-induced gingival overgrowth. J Clin Periodontol 1992;19:311-4.
6. Nery EB, Edson RG, Lee KK, Pruthi VK, Watson J. Prevalence of nifedipine-induced gingival hyperplasia. J Periodontol 1995;66:572-8.
7. Güncü GN, Cağlayan F, Dinçel A, Bozkurt A, Ozmen S, Karabulut E, *et al.* Clinical and pharmacological variables as a risk factor for nifedipine-induced gingival overgrowth. Aust Dent J 2007;52:295-9.
8. Jorgensen MG. Prevalence of amlodipine-related gingival hyperplasia. J Periodontol 1997;68:676-8.
9. Toyo-Oka T, Nayler WG. Third generation calcium entry blockers. Blood Press 1996;5:206-8.
10. Silverstein LH, Koch JP, Lefkove MD, Garnick JJ, Singh B, Steflik DE, *et al.* Nifedipine-induced gingival enlargement around dental implants: A clinical report. J Oral Implantol 1995;21:116-20.
11. Samudrala P, Chava VK, Chandana TS, Suresh R. Drug-induced gingival overgrowth: A critical insight into case reports from over two decades. J Indian Soc Periodontol 2016;20:496-502.
12. Dongari-Bagtzoglou A, Research, Science and Therapy Committee, American Academy of Periodontology. Drug-associated gingival enlargement. J Periodontol 2004;75:1424-31.
13. Livada R, Shiloah J. Calcium channel blocker-induced gingival enlargement. J Hum Hypertens 2014;28:10-4.
14. Joshi S, Bansal S. A rare case report of amlodipine-induced gingival enlargement and review of its pathogenesis. Case Rep Dent 2013;2013:138248.
15. Missouris GG, Kalaitzidis RG, Cappuccio FP, MacGregor GA. Gingival hyperplasia caused by calcium channel blockers. J Hum Hypertens 2000;14:155-6.
16. Taib H, Ali TB, Kamin S. Amlodipine-induced gingival overgrowth; a case report. Arch Orofac Sci 2007;2:61-4.
17. Firkova EI, Panchovska SM, Daskalov H. Amlodipine induced gingival overgrowth and application of Er:YAG laser in the treatment protocol. J IMAB 2013;19:295-7.
18. Ramon Y, Behar S, Kishon Y, Engelberg IS. Gingival hyperplasia caused by nifedipine – A preliminary report. Int J Cardiol 1984;5:195-206.
19. Nishikawa S, Tada H, Hamasaki A, Kasahara S, Kido J, Nagata T, *et al.* Nifedipine-induced gingival hyperplasia: A clinical and *in vitro* study. J Periodontol 1991;62:30-5.
20. Lafzi A, Farahani RM, Shoja MA. Amlodipine-induced gingival hyperplasia. Med Oral Patol Oral Cir Bucal 2006;11:E480-2.
21. Cucchi G, Giustiniani S, Robustelli, F. Gingival hyperplasia caused by verapamil. Italian J Cardiol 1985;15:556-7.
22. Vishnudas B, Sameer Z, Shriram B, Rekha K. Amlodipine induced plasma cell granuloma of the gingiva: A novel case report. J Nat Sci Biol Med 2014;5:472-6.
23. Silness J, Loe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. Acta Odontol Scand 1964;22:121-35.
24. Löe H. The gingival index, the plaque index and the retention index systems. J Periodontol 1967;38:610-6.
25. Inglés E, Rossmann JA, Caffesse RG. New clinical index for drug-induced gingival overgrowth. Quintessence Int 1999;30:467-73.
26. National Clinical Guideline Centre. The Clinical Management of Primary Hypertension in Adults. Clinical Guideline 127; 2011. Available from: https://www.nice.org.uk. [Last accessed on 2016 Oct 13].
27. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, *et al.* 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eighth joint national committee (JNC 8). JAMA 2014;311:507-20.
28. Ekwunife OI, Okafor CE, Ezenduka CC, Udeogaranya PO. Cost-utility analysis of antihypertensive medications in Nigeria: A decision analysis. Cost Eff Resour Alloc 2013;11:2.
29. Kaur G, Verhamme KM, Dieleman JP, Vanrolleghem A, van Soest EM, Stricker BH, *et al.* Association between calcium channel blockers and gingival hyperplasia. J Clin Periodontol 2010;37:625-30.
30. Ellis JS, Seymour RA, Steele JG, Robertson P, Butler TJ, Thomason JM, *et al.* Prevalence of gingival overgrowth induced by calcium channel blockers: A community-based study. J Periodontol 1999;70:63-7.
31. Seymour RA, Ellis JS, Thomason JM. Risk factors for drug-induced gingival overgrowth. J Clin Periodontol 2000;27:217-23.
32. Bahekar AA, Singh S, Saha S, Molnar J, Arora R. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: A meta-analysis. Am Heart J 2007;154:830-7.
33. Tam IM, Wandres DL. Calcium-channel blockers and gingival hyperplasia. Ann Pharmacother 1992;26:213-4.