INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

*Research Article*

# EFFECT OF CALCIUM CHANNEL BLOCKERS ON GINGIVAL TISSUES IN HYPERTENSIVE PATIENTS VISITING AYDER REFERRAL HOSPITAL, MEKELLE, ETHIOPIA

**Bhumika Sehdev[1*], Haftom Zerihun[2], Rajeshwar Singh[3], Kashi Nataraj Vinay[4], P. Prasanna Kumar[5] and BS. Sridhar[6]**

[1]Department of Periodontics,
MekelleUniversity, Ayder Referral Hospital, Ethiopia.
[2]Intern Department of Dentistry,
Mekelle University, Ayder Referral Hospital, Ethiopia.
[3]Associate Professor, Department of Orthodontics and Dentofacial Orthopaedics, Mekelle University, Ayder Referral Hospital, Ethiopia.
[4]Department of oral and Maxillofacial Surgerym,
Mekelle University, Ayder Referral Hospital, Ethiopia.
[5]Department of Oral and Maxillofacial surgery,
CIDS, Virajpet, Karnataka, India.
[6]Department of Oral and Maxillofacial surgery,
Bangalore, Karnataka, India.

## ABSTRACT

**Background:** Long term treatment of common chronic cardiac conditions such as hypertension with Calcium channel blockers (CCBs) has been associated with gingival hyperplasia. This oral side effect may affect esthetics and function, yet often overlooked and therefore underreported among hypertensive patients visiting in Ayder Comprehensive Specialized Hospital, Mekelle, Ethiopia. **Aim:** this study aims to determine the association of CCBs with gingival overgrowth in hypertensive patients. **Methods and Materials**: this is hospital based cross sectional study conducted among 50 hypertensive patients (25 CCBs and 25 non-CCBs age matched controls) attending the medical outpatient clinic of Ayder Comprehensive Specialized hospital. Data collection tools included interviewer administered questionnaires and periodontal examination. Socio-demographic details, medical history and periodontal indices (plaque index, papillary bleeding index, grade of GO according to DIGO clinical index) were recorded. **Results**: the mean plaque index and mean papillary bleeding index for CCB users were 0.9±0.8 and 0.3±0.5 respectively, while mean plaque index and mean papillary bleeding index for non-CCB users were 1.4±0.8 and 0.8±1.3 mm respectively. Also, more females (44%) presented with DIGO compared to males (26%) in both the groups.Participants on CCBs had significantly increased probing depths than that of the non-CCB users (p= 0.001). **Discussion:** The higher prevalence of DIGO among CCB users compared with non-CCB users has been reported. Furthermore, there was an increased risk of GO nearly 3 folds in CCB users compared with non-CCB users.The slightly higher finding of DIGO among Nifedipine users in the current study may be related to the fact that more patients were placed on Nifedipine. . 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. **Conclusion:** The study reveals that the risk of GO is nearly three times higher in CCB than non-CCB users and 2 folds in nifedipine than amlodipine users in Mekelle. Further 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 Mekelle patients on CCB.

**Keywords**: Hypertension, Calcium channel blockers, Gingival overgrowth and Plaque index.

## INTRODUCTION

CCBs are classified according to their chemical structure into: dihydropyridines (nifedipine, amlodipine), diphenylalkylamines (verapamil), benzothiazipines (diltiazem), and diphenylpiperazines (flunarizine)[1]. They are used extensively for the management of cardiovascular disorders including hypertension, angina pectoris, cardiac arrhythmias, and coronary artery spasms[2,3,4].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 atrio-ventricularconduction[1].

Druginduced GO (DIGO) has been reported to be the most widespread unwanted effect of CCBs on periodontal tissues. Several reports have implicated nifedipine and amlodipine as the frequent causes of GO[5,3,6,7,8-12] though this unwanted effect has also been reported in patients taking verapamil[13] . Prevalence rates for GO induced by Nifedipine have been reported around 20% to 50%[4,14,15] while that induced by amlodipine have accounted for 3.3%[16]. However, these represent Caucasians' values.

Various risk factors including drug variables (dosage and duration), age, gender, oral hygiene status, and gingival inflammation have been associated with this condition[2,14,15]. Furthermore, Samudrala et al.[6] 2017 suggested that certain features to be generally more frequent in DIGOs. 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[5,3,7].

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[17], 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[18]. 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[5,17,19]. 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-1β) that are elevated in gingival inflammation[17].

With the rising prevalence of hypertension in Mekelle, 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 the patients visiting Ayder Referral hospital, Mekelle on CCB.

## MATERIALS AND METHODS

This hospital-based, cross-sectional study was approved by Health Research and Ethics Committee of the ACSH, Mekelle University**.** The cases comprised 25 participants who were defined as hypertensive patients, who were on CCB. The controls were from the same cohort and comprised 25 age-matched hypertensive patients on non-CCB medications attending the Medicine outpatient clinic of the Ayder Hospital. The selection criteria included patients on antihypertensive medications for a minimum of 6 months, presence of at least 6 – 12 in the anterior region of the upper and lower jaws, history of no periodontal therapy in the preceding 6 months, and no use 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 consent, participant's demographic information was obtained using interviewer-administered questionnaires.

The following periodontal indices were utilized-plaque index (Silness and Loe)[20], papillary bleeding index (Mulhemann)[21], 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 the scale of 0-4 according to the Clinical Index for DIGO.

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 > 6mm.
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.
Also, dose and duration of antihypertensive medications were obtained from participant's hospital records.

**STATISTICAL ANALYSIS**

Data were analyzed using SPSS Version 20 for Windows. 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 ANNOVA for continuous variables. P< 0.05 was considered statistically significant.

**RESULTS**

A total of 50 hypertensive participants (25 on CCBs and 25 age-matched controls on non-CCB) were enrolled into the study. Their mean age was 58.3±14.7 years. The mean plaque index and mean papillary bleeding index for CCB users were 0.9±0.8 and 0.3±0.5 respectively. While mean plaque index and mean papillary bleeding index for non-CCB users were 1.4±0.8 and 0.8±1.3 mm respectively. There were significant differences in the mean plaque indices and papillary bleeding indices between the CCB and non-CCB groups. While mean Probing depth in CCB users was 3.4±1.6 mm and in non-CCB users was 2.4±0.7 mm. Participants on CCB had significantly increased probing depths than that of the non –CCB group (P= 0.001) (TABLE 1).Also, more females (56%) presented with DIGO comparedto males (44%) in CCB users and also in non –CCB users females presented with higher DIGO percentage (80%) compared to males (20%). (**Table 1: Demographic and Clinical Characteristics among Calcium Channel Blocker and Non Calcium Channel Blocker Participants).**

Table 2 shows the correlation between different dosages of CCBs (Amlodipine and Nifedipine) and gingival overgrowth. Among the CCB users, 10 (40%) participants were on amlodipine, while 15(60%) were on nifedipine.20 mg of Nifedipine users showed higher percentage of gingival overgrowth 86.7% whereas, 10 mg of Amlodipine users showed higher percentage of gingival overgrowth 54.5%. (**Table 2: Correlation between Dosage of CCBS and Gingival Overgrowth).**

Table 3 shows there was a significant association between DIGO and type of antihypertensive medication used as participants on CCB had a higher prevalence of DIGO (92%) than that of non-CCB participants (48%). 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 (10.6±7.6 years) than participants without DIGO (5.0±5.2 years). (**Table 3: Factors associated With Drug-Induced Gingival Overgrowth Among CCB And Non-CCB Participants)**

Table 4 shows the predominant grade of DIGO among CCB users was Grade 2 DIGO Clinical Index (60%) followed by Grade 1 DIGO Clinical Index (20%). (**Table 4: Grades of Gingival Hyperplasia in Study Population).**

**DISCUSSION**

Calcium channel blockers are 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[22], as well as the Joint National Committee Hypertension guidelines[23].
The higher prevalence of DIGO among CCB users (92%) compared with non-CCB users (48%) has been reported. Andrew et al[2] in a cross sectional study among kenyans patients 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[24]. It is important to stress the variations in criteria used for the clinical assessment of GO in different studies, which may influence the prevalence of DIGO reported. Both groups had similar demography; age, gender, and clinical characteristics and mean plaque and papillary bleeding 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[17]. 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 genetic tissues to these CCB drugs could be linked to the presence of a subset of gingival fibroblasts unique to each individual[5,17,19]. 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-1β) that are elevated in gingival inflammation[17].

In our group of patients, GO was more prevalent among females in both the groups (44%)for the test group and (24%) for the control group. This finding was in correlation with the study done by Portela et al[25]. However, the Spearman test did not reveal a correlation between patients gender and the occurrence of GO. According to Umeizudike et al[26] Guncu et al[27] there are evidences that male patients under treatment with nifedipine specifically are more prone to a greater prevalence and severity of GO than female patients. Since the medication may alter androgen metabolism, reaching the gingival fibroblasts, with a consequent increase in propensity to GO. However, the relation between GO and patient gender acting as a hormonal cofactor has not been completely clarified by this study neither in the literature correlated[28].

The slightly higher finding of DIGO among nifedipine users in the current study may be related to the fact that more patients were placed on nifedipine. Nifedipinie users had higher DIGO (60%) than that of Amlodipine users (40%). This finding is interesting and correlates with previous mentioned studies in which nifedipine was more associated with GO[4,14,15]. Interestingly, the review by Samudrala et al. highlighted a changing patterns of CCB-associated DIGO in the last two decades, with more cases of GO reported following amlodipine users compared with nifedipine[6]. The prevalence of nifedipine-associated GO in the present study falls within the reported range of 6.3%-83% in the literature [24,29]. 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. It has been suggested that drug dosage may be a poor predictor of gingival changes, being influences largely by pharmacokinetics and pharmacodynamics[2].

In addition, the severity of gingival enlargement is well correlated with poor oral hygiene. 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[30].

The importance of the microbial plaque as a cofactor in the etiology of drug-associated gingival enlargement has been recognized in a recent classification system of periodontal diseases by the American Academy of Periodontology[31].

## CONCLUSION

The study reveals that the risk of GO is nearly three times higher in CCB than non-CCB users and 2 folds in nifedipine than amlodipine users in Mekelle. Further 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 Mekelle patients on CCB.

## RECOMMENDATION OF THE STUDY

Physicians who are involved in the management of hypertensive patients may need to perform oral examinations, albeit brief during their patient's 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.

Drug cessation and a substitution to the other class of antihypertensive medications is the best treatment options. Otherwise, these lesions could be managed by non-surgical or surgical techniques that only provide a short-time relief, as reoccurrence is to be expected if the offending drug is continued.

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

| Variable | CCB GROUP (n= 25), n (%) | NON CCB GROUP (n= 25) n (%) | P |
|---|---|---|---|
| Gender | | | |
| Male | 11 (44%) | 5 (20%) | 0.612* |
| Female | 14 (56 %) | 20 (80%) | |
| Mean age ± SD (years) | 58.3±14.7 | 58.3±13.6 | 0.586 |
| Mean PI± SD | 0.9±0.8 | 1.4±0.8 | 0.449 |
| Mean PBI±SD | 0.3±0.5 | 0.8±1.3 | 0.940 |
| Mean PPD±SD | 3.4±1.6 | 2.4±0.7 | 0.001 |

**Table 2: Correlation between dosage of CCBS and gingival overgrowth**

| CCB Users | DOASE OF CCB | Study Population | Gender with DIGO | | Percentage |
|---|---|---|---|---|---|
| | | | M | F | |
| Amlodipine | 5 MG | 3 | 2 | 1 | 27.3% |
| | 10 MG | 5 | 3 | 2 | 54.5% |
| | 20 MG | 1 | 1 | 0 | 9.1% |
| | 25 MG | 1 | 0 | 1 | 9.1% |
| Nifidipine | 5 MG | 0 | 0 | 0 | 0% |
| | 10 MG | 1 | 0 | 1 | 6.7% |
| | 20 MG | 13 | 6 | 7 | 86.7% |
| | 25 MG | 1 | 0 | 1 | 6.7% |

**Table 3: Factors Associated With Drug-Induced Gingival overgrowth Among CCB And NON-CCB Participants**

| VARIABLE | DIGO | | OR (95% CI) REFERENCE | P |
|---|---|---|---|---|
| | Present, n(%) | Absent, n (%) | | |
| Gender | | | | |
| Male | 13 (26%) | 3 (6%) | 0.186 | 0.036* |
| Female | 22 (44%) | 12 (24%) | 0.247 | 0.171* |
| Tobacco use | 1 (2%) | 0 (0%) | 0.012 | 0.174 |
| Drug Type | | | | |
| CCB | 23 (92%) | 2 (8%) | N.A. | 0.002** |
| Non-CCB | 12 (48%) | 13 (52%) | N.A. | 0.172 |
| Mean Duration of CCB±SD (years) | 10.6±7.9 years | 5.0±5.2 years | N.A. | 0.342* |
| Mean Age±S.D | 64.39±23 | 64.31±25 | 0.006 | 0.937 |
| Mean PI±SD | 1.7±0.3 | 1.2±0.5 | N,A. | 0.039 |
| Mean PBI±SD | 0.4±0.3 | 1.3±0.5 | N.A. | 0.062 |
| Mean PPD±SD | 4.06±1.6 | 2.72±0.4 | N.A. | 0.007 |

$x_2$; ANNOVA; Significant DIGO; Drug-induced gingival overgrowth; OR: Odds ratio; CI: Confidence Interval; SD: Standard Deviation; CCB: calcium channel blockers.

**Table 4: Grades of Gingival Hyperplasia in Study Population**

| GRADES OF HYPERTROPHY | NUMBER OF POPULATION (N) | PERCENTAGE OF POPULATION (%) |
|---|---|---|
| Grade 0 | 3 | 12% |
| Grade 1 | 5 | 20% |
| Grade 2 | 15 | 60% |
| Grade 3 | 2 | 8% |

**REFERENCES**


1. Toyo-Oka T and Nayler WG. Third generation calcium entry blockers. Blood Press. 1996;5:206-8.
2. Andrew W, Evelyn W, Francis M, Mark J and Mark C. Pattern of gingival overgrowth among patients on antihypertensive pharmacotherapy at a Narobi Hospital at Kenya. OJST. 2014;4:169-73.
3. Shinha A, Oswal S and Shivamurthy R. Amlodipine induced gingival overgrowth: A case report. Int J Case Rep Images. 2014;5:509-12.
4. Barclay S, Thomason JM, Idle JR and Seymour RA. The incidence and severity of nifedipine-induced gingival overgrowth. J ClinPeriodontol. 1992;19:311-4.
5. Grover V, Kapoor A and Marya CM. Amlodipine induced gingival hyperplasia. J Oral Health Commun Dent. 2007;1:19-22.
6. Samudrala P, Chava VK, Chandana TS and Suresh R. Drug-Induced gingival overgrowth: A clinical insight into case reports from over two decades. J Indian Soc Periodontol. 2016;20:496-502.
7. Missouris GG, Kalaitzidis RG, Cappuccio FP and MacGregor GA. Gingival hyperplasia caused by calcium channel blockers. J Hum Hypertens. 2000;14:155-6
8. Taib H, Ali TB and Kamin S. Amlodipine-induced gingival overgrowth; a case report. Arch OrofacSci. 2007;2:61-4.
9. Firkova EI, Panchovska SM and Daskalov H. Amlodipine induced gingival overgrowth and application of Er:YAG laser in the treatment protocol. J IMAB. 2013;19:295-7.
10. Ramon Y, Behar S, Kishon Y and Engelberg IS. Gingival hyperplasia caused by nifedipine- A preliminary report. Int J Cardiol. 1984;5:195-206.
11. Nishikawa S, Tada H, Hamasaki A, Kasahara S, Kido J and Nagata T. Nifedipine-induced gingival hyperplasia: A clinical and in vitro study. J Periodontol. 1991;62:30-5.
12. Lafzi A, Farahani RM and Shoja MA. Amlodipine-induced gingival hyperplasia. Med Oral Patol Oral Cir Bucal. 2006;11:E480-2.
13. Miller CS and Damm DD. Incidence of verapamil-induced gingival hyperplasia in a dental population. J Periodontol 1992;63(5):453-6.
14. Nery EB, Edson RG, Lee KK, Pruthi VK and Watson J. Prevalence of nifedipine-induced gingival hyperplasia. J Periodontol. 1995;66:572-8.
15. Guncu GN, Caglayan F, Dincel A, Bozkurt A, Ozmen S and Karabulut E. Clinical and pharmacological variables as a risk factor for nifedipine-induced gingival overgrowth. Aust Dent J. 2007;52:295-9.
16. Jorgensen MG. Prevalence of amlodipine-related gingival hyperplasia. J Periodontol. 1997;68:676-8.
17. Dongari-Bagtzoglou A. Research, Science and Therapy Committee, American Academy of Periodontology. Drug-associated gingival enlargement. J Periodontol. 2004;75:1424-31.
18. Joshi S and Bansal S. A rare case report of amlodipine-induced gingival enlargement and review of its pathogenesis. Case Rep Dent 2013;2013:138248.
19. Taib H, Ali TB and Kamin S. Amlodipine-induced gingival overgrowth; a case report. Arch OrofacSci. 2007;2:61-4.
20. Sillness J and Loe H. Periodontal disease in poor oral hygiene patients. II. Correlation between oral hygiene and periodontal condition. ActaOdontolScand. 1964;22:121-35.
21. Mulhemann HR. Psychological and chemical mediators of gingival health. J Prevo Dent. 1977;4:6.
22. National Clinical Guideline Centre. The Clinical Management of Primary Hypertension in Adults. Clinical Guideline 127,2011. Available from: https://www.nice.org.uk.
23. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C and Handler J. 2014 vidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eight joint national committee (JNC 8). JAMA. 2014;311:507-20.
24. Kaur G, Verhamme KM, Dieleman JP, Vanrolleghem A, van Soest EM and Stricker BH. Association between calcium channel blockers and gingival hyperplasia. J ClinPeriodontol. 2010;37:625-30.
25. KehindeAdesolaUmeizudike, Adetokunbo B Olawuyi, Theophilus I Umeizudike, Akinsanya D Olusegun-Joseph and Babawale T Bello. Effect of Calcium Channel Blockers on Gingival Tissues in Hypertensive Patients in Lagos, Nigeria: A Pilot Study. 2017;8(4):565-570.

26. Guncu GN, Caglayan F, Dincel A, Bozkurt A, Ozmen S and Karabulut E. Clinical and pharmacological variables as a risk factor for nifedipine-induced gingival overgrowth. Australian Dental Journal. 2007;52(4):295-299.
27. Sooriyamoorty M, Gower DB and Eley BM. Androgen metabolism in gingival hyperplasia induced by nifedipine and cyclosporine. Journal of Periodontal Research. 1990;25(1):25-30.
28. Ellis JS, Seymoue RA, Steele JG, Robertson P, Butler TJ and Thomason JM. Prevalence of gingival overgrowth induced by calcium channel blockers: A community-based study: J Periodontol. 2000;27:217-23.
29. Ellis JS, Seymoue RA, Steele JG, Robertson P, Butler TJ and Thomason JM. Prevalence of gingival overgrowth induced by calcium channel blockers: A community-based study: J Periodontol. 2000;27:217-23.
30. Bahekar AA, Singh S, Saha S, Molnar J and 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.
31. Romito GA, Pustiglioni FE and Saraiva L. Relationship of subgingival and salivary microbiota to gingival overgrowth in heart transplant patients following cyclosporine A therapy. J Periodontol. 2004;75:918-924.