

eISSN: 2581-9615 CODEN (USA): WJARAI Cross Ref DOI: 10.30574/wjarr Journal homepage: https://wjarr.com/

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	World Journal of Advanced Research and Reviews								
		World Journal Series INDIA							
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(RESEARCH ARTICLE)



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World Journal of Advanced Research and Reviews, 2021, 12(03), 164-174

Publication history: Received on 01 November 2021; revised on 06 December 2021; accepted on 08 December 2021

Article DOI: https://doi.org/10.30574/wjarr.2021.12.3.0664

## Abstract

**Background:** Gingival overgrowth may be idiopathic or secondary. Drug Induced Gingival Overgrowth (DIGO) occurs within 3 months of treatment and is more prevalent in younger age group with predilection for the anterior gingival tissue and usually not associated with attachment loss or tooth mobility unless there is an existing periodontal disease.

**Methodology:** 170 hypertensive patients were recruited for the study; 85 calcium channel blocker (CCB) and 85 non-CCB users. Interviewer-administered questionnaires was used to obtain socio-demographic information as well as medical and drug history. GO was assessed using New Clinical Index for DIGO and data was analyzed with SPSS version 21 (Armonk, NY: IBM Corp). Continuous and nominal variables were described with means, standard deviations and frequencies. Statistical significance was set at P < 0.05.

**Results:** Amlodipine was the most commonly used CCB. The prevalence of DIGO in CCB and non-CCB was the same (49.5%). Gingival enlargement was found equally among both sexes in the CCB and non-CCB groups. A third of the participants with GO were 70 years and above while those without were majorly in the fifth and sixth decade of life. Two-third of those with DIGO had fair oral hygiene status, two-fifth had gingival bleeding and three-fifth had mild gingival inflammation. Those without DIGO in both groups had a slight female predominance and majorly good oral hygiene. Associated factors with DIGO were female sex, 60-69 age group, 10mg drug dosage, been on medication less than 10 years, mild gingival inflammation and generalized gingivitis.

**Conclusion:** There was no difference in the prevalence of DIGO between BBC and non-BBC users. However, there was mild gingival inflammation in all participants with DIGO and amlodipine users were three times more at risk of developing DIGO than nifedipine users. Thus, it is imperative to advise the hypertensives on the importance of maintaining adequate oral hygiene measures and incorporate periodontal care in their management so as to ameliorate the side effects of their medication.

Keywords: CCB; DIGO; Hypertensive patients; Gingival inflammation

## 1. Introduction

Gingival overgrowth (GO) or enlargement is an increase in the size of the gingiva as a result of the collagenous components of the extracellular matrix that accumulate within the gingival connective tissue [1]. It may be idiopathic or be associated with a variety of factors like congenital diseases, hormonal disturbances, long-term poor oral hygiene, inflammation, neoplastic conditions, and adverse drug reactions.<sup>1</sup> Some of the medications currently associated with gingival enlargement are anticonvulsants (phenytoin), antihypertensive drugs like calcium channel blockers (nifedipine and amlodipine) and immunosuppressive agents (cyclosporin A and tacrolimus) [1-3].

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Gingival overgrowth due to adverse drug reaction is designated Drug Induced Gingival Overgrowth (DIGO) and typically occurs within 3 months after commencement of treatment for hypertension.<sup>4</sup> DIGO appears to be more prevalent in younger age group with predilection for the anterior gingival tissue and is usually not associated with attachment loss or tooth mobility unless there is an existing periodontal disease. It starts as an overgrowth in the interdental papilla and gradually extends coronally [4,5].

As GO progresses it may cause interference with oral hygiene practice, mastication, and speech apart from the aesthetic problems from the disfiguring gingival appearance [3]. Interference with oral hygiene measures lead to further deterioration of periodontal health and increased risk of developing dental caries [4].

GO associated with calcium channel blockers was first described in 1984 by Lederman in patients treated with nifedipine [4,6]. Studies have reported that GO can reduce the quality of life for patients and cause indirect negative effects on systemic health [7-14].

The prevalence of hypertension, referred to as a silent killer, is increasing worldwide due to aging, stress as well as changes in behaviour and lifestyle. 25.4% of participants in a survey among adults aged 18 years and above in 7 communities in Kenya, Nigeria, Tanzania, and Uganda was found to have hypertension [15].

In order to prevent complications of hypertension namely heart failure, heart attack, renal failure and stroke; antihypertensive therapy is used. The antihypertensives are used either as a monotherapy or in combination depending on patient's condition. Anti-hypertensive drugs are classified into seven different groups. They include diuretics, betablockers (BB), alpha-blockers (AB), calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARB) and central effect drugs [3, 16]. However, CCB are currently the most common antihypertensive prescribed throughout the world because of its effectiveness. In more than half of patients for the management of their hypertensive state [17,18].

CCBs are classified into: dihydropyridines (nifedipine, amlodipine), diphenylalkylamines (verapamil), benzothiazipines (diltiazem), and diphenylpiperazines (flunarizine) according to their chemical structure [19]. They act by inhibiting influx of calcium ion through cell membranes of cardiac and vascular smooth muscle. This results in vasodilation of the coronary and peripheral vessels, as well as reduction in heart rate and cardiac contractibility. Thus, the oxygen utilization by the myocardium is decreased and atrioventricular conduction is slow. [20-22]. These actions thus justify their widespread use in the management of hypertension, cardiac arrhythmias, angina pectoris, and coronary artery spasms. However, CCBs have been associated with DIGO as the most common unwanted effect on the periodontium.<sup>20</sup>

Prevalence rate of GO induced by nifedipine reported varied widely, ranging from 21% to 83% and 3.3% for that induced by amlodipine in Caucasians [20].

The pathogenesis underlying GO induced CCBs is not clearly understood but it is considered to be multifactorial.<sup>22</sup> Drug variables (dosage and duration), age, gender, oral hygiene status, genetics, and pre-existing gingival inflammation have been reported to influence DIGO [20]. It has been suggested that they influence the response of the gingiva to hypertensive medications [19,20, 23].

A steady increase from 11.2% to 28.9%.has been reported in the prevalence of hypertension in Nigeria over the years [24,25]. The resultant effect is increasing use of CCBs and increased exposure of patients to the risk of this disfiguring unwanted oral effect of these medications which may compromise periodontal health and possibly the overall systemic health. Also, there is paucity of published articles in Nigeria concerning this important condition which can ultimately affect the quality of life of affected individuals [7,9,10,12].

Thus, this study determined the association between CCBs and GO and evaluated the relationship between GO and associated factors among a group of Nigerian hypertensives attending the medical out-patient clinic of a Nigerian Tertiary Hospitals.

## 2. Material and methods

A cross-sectional study approved by the ethics committee of the University of Port-Harcourt Teaching Hospital (UPTH), Port-Harcourt, Nigeria was conducted at the Cardiology Outpatient Clinic.

The study population consisted of 170 hypertensive patients who have been taking antihypertensive medications for a minimum of six months prior to the commencement of this study; 85 cases on CCBs and 85 age-matched controls who are non-CCB antihypertensives.

For inclusion in the study participants needed to have at least 6 – 8 teeth in the anterior region of the upper and lower jaws and no history of periodontal therapy within 6 months prior to the commencement of the study. Those with systemic disorders known to affect the gingival condition (diabetes and connective tissue diseases), pregnant women, patients using partial denture prostheses or undergoing orthodontic therapy; as well as those who were taking other drugs that could potentially interfere with periodontal tissues (cyclosporine A, anticonvulsants, hormonal therapy) were excluded.

Sample size was determined using the formula:

$$S_{S} = \frac{r - 1(P^{*})(1 - P^{*})(Z_{\beta} + Z_{\frac{\alpha}{2}})^{2}}{r - (P_{1} - P_{2})^{2}}$$

*r* = Ratio of control to cases, 1 for equal number of cases and control.

 $P^*$  = Average proportion exposed =  $(P_1 + P_2)/2$ 

 $Z_{\beta}$  = Standard normal variate for power, for power 80% = 0.84

 $Z_{\alpha/2}$  = Standard normal variate for 95% level of significance = 1.96

 $P_1 - P_2 = Difference$  in proportion expected based on previous studies,  $P_1 = proportion$  in cases,  $P_2 = proportion$  in control.

The sample size for this study was calculated using the figures from the study of Umeizudike et al [26]. They reported prevalence of 36.2% and 17.2% of GO among CCB users (P<sub>1</sub>) and non-CCB users (P<sub>2</sub>) respectively and was 85.

Written informed consent was obtained from each participant after the study was explained to them. Intervieweradministered questionnaires was used to obtain socio-demographic information as well as medical and drug history which was confirmed from patients' case records. All participant thereafter underwent periodontal examination by dentists with assured inter-examiner reliability. The indices used were Simplified Oral Hygiene index of Green & Vermillion, Gingival index of Silness and Loe and presence or absence of gingival bleeding [27-28]. Scores were recorded in accordance with WHO Oral Health Survey Basic Methods [29]. The subjects were grouped into clinical oral hygiene levels (good: OHI-S score 0.0 to 1.2, fair: 1.3 to 3.0 and poor: 3.1 to 6.0), gingival status (GI score 0.1-1, Mild gingivitis; 1.1-2, Moderate gingivitis and 2.1-3, Severe gingivitis) and extent of gingival inflammation (GBI score < 10% = Healthy, 10 – 30% = Localized gingivitis, >30% = Generalized gingivitis)

GO was assessed using New Clinical Index for Drug-Induced Gingival Overgrowth (DIGO) [30]. The vestibular and lingual papillae were evaluated for signs of GO and scored on a scale of 0 to 4 as follows: 0: no overgrowth or inflammation, 1: no overgrowth but inflammation present, 2: mild overgrowth (thickening of marginal gingiva not requiring treatment), 3: moderate overgrowth (covering gingiva not more than one-third of any of the crowns, but requiring treatment; and 4 severe overgrowths extending onto the coronal two thirds of one or more crowns. GO was regarded to be absent in participants with score of 0- 2 and present in those with score of 3 or 4.

Data was analyzed using SPSS version 21 (Armonk, NY: IBM Corp). Continuous variables were described with mean and standard deviation while nominal variables were described with frequency. CCB-users were compared with non-CCB, using the Chi-square ( $\chi$ 2) test or Fisher's exact test for category variables. The influence of associated risk factors on GO was explored by the  $\chi$ 2 test. Statistical significance was set at P < 0.05.

## 3. Results

One hundred and seventy patients participated in this study with age ranging from 22 – 83years and a mean of 54.34±14.25years. There was a slight female predominance; 82 males and 88 females with M: F of 1:1.07. The participants consisted of age-matched equal number of cases (85 CCB group) and control (85 non-CCB group) with mean age 56.49±12.38yrs and 52.18±15.69yrs respectively. Table 1.

Variables	ССВ		Non-CCB		Т	P-value	
Range:	26-8	1 years	22-83 years		22-8		
Mean	54.34±1	4.25years	56.49±1	56.49±12.38yrs		15.69yrs	
	Freq	%	Freq	%	Freq	%	
Gender							0.539
Male	39	45.9	43	50.6	82	48.2	
Female	46	54.1	42	49.4	88	51.8	
Age group (years)							0.006*
20-29	1	1.2	4	4.7	5	2.9	
30-39	4	4.7	18	21.2	22	12.9	
40-49	19	22.4	20	23.5	39	23.0	
50-59	27	31.7	15	17.6	42	24.7	
60-69	19	22.4	11	12.9	30	17.7	
≥70	15	17.6	17	20.0	32 18.8		
Marital status							
Single	8	9.4	5	5.9	13	7.7	0.245
Married	67	78.8	75	88.2	142	83.5	
Widower	10	11.8	5	5.9	15	8.8	
Tribe							0.001*
Yoruba	24	28.3	8	9.4	32	18.8	
South-South	58	68.2	77	90.6	135	79.4	
Hausa	3	3.5	0	0.0	3	1.8	
Educational status							0.611
No Formal	5	5.9	6	7.1	11	6.5	
Primary	12	14.1	17	20.0	29	17.1	
Secondary	23	27.1	25	29.4	48	28.2	
Tertiary	45	52.9	37	43.5	82	48.2	
Occupation							0.126
Civil servants	36	42.4	40	47.1	76	44.7	
Farmer	3	3.5	7	8.2	10	5.9	
Self-employed	28	32.9	30	35.3	58	34.1	
Retiree	18	21.1	8	9.4	26	15.3	
Duration of diagnosis of Hy	pertensio	on (years)					
1-10	58	68.2	44	51.7	102	60.0	0.218
11-20	20	23.5	32	37.6	52	30.5	
21-30	4	4.7	6	7.1	10	5.9	

21 40	1							
31-40	1	1.2	2	2.4	3 1.8			
41-50	2	2.4	1	1.2	3	1.8		
Mean	11.20±	:8.16yrs	10.31±	8.90yrs	Mean 10.			
Gingival Overgrowth (GO)							0.01*	
Yes (GOI score 3-4)	39	45.9	39	45.9	78	45.9		
No (GOI score 0-2)	46	54.1	46	54.1	92 54.1			
Duration of CCB use (years	)							
<2 years	12	14.1	0	0.0	12	14.1		
2-5 years	26	30.6	0	0.0	26 30.6			
>5 years	47	55.3	0	0.0	47	55.3		
CCB Dosage (millimeters)								
5	15	17.6	0	0.0	15	17.6		
10	63	74.1	0	0.0	63	74.1		
20	6	7.1	0	0.0	6	7.1		
30	1	1.2	0	0.0	1	1.2		
Total	85	100.0	0	0.0	85	100.0		

Mean age =54.34±14.25 years, Mean period of use= 8.12±6.72 years, Mean drug dosage =10.06±4.05mg

Highest proportion of participants had tertiary education (82; 48.2%) and are from South-South (135; 79.4%). Twofifth (68;40%) have been diagnosed with hypertension for over a decade. Of those who use CCB, more than half (48;56.5%) have been doing so for over five years and about 4 out of 5 (70;82.4%) of them are on more than 10mg dosage. Table 1.



Figure 1 Participants' CCB distribution

Amlodipine was the most commonly used CCB among the participants (67 of 85; 78.8%). Figure 1.

About half of the participants (50.6 % CCB and 55.3% non-CCB) had fair oral hygiene. Prevalence of gingival bleeding is 41.2% and 24.7% among CCB and non-BBC respectively. Though more of participants who use CCB have generalized gingivitis compared to non-CCB, half of the participants have localized gingivitis especially the non-CCB group. The severity of inflammation is mild majorly in the two groups. Statistical analysis of the presence of gingival bleeding and extent of inflammation showed significance (p = 0.022; 0.009). Table 2.

Variables	ССВ		Non-CCB		Total		P-value
	Freq	%	Freq	%	Freq	%	
OHI Status							0.048
Good (OHI score 0.1-1.2)	37	43.5	25	29.4	62	36.5	
Fair (OHI score 1.3-3.0)	43	50.6	47	55.3	90	52.9	
Poor (OHI score 3.1-6.0)	5	5.9	13	15.3	18	10.6	
Gingival bleeding							0.022*
Yes	35	41.2	21	24.7	56	32.9	
No	50	58.8	64	75.3	114	67.1	
Extent of gingival inflammation							0.009*
Healthy gingiva (GBI<10%)	16	18.8	21	24.7	37	21.8	
Localized gingivitis (GBI 10-30%)	36	42.2	49	57.7	85	50.0	
Generalized gingivitis (GBI >30%)	33	38.8	15	17.6	48	28.2	
Severity of gingival inflammation	l						0.558
Healthy (GI score 0)	14	16.5	21	24.7	35	20.6	
Mild (GI score 0.1-1.0)	54	63.5	46	54.1	100	58.8	
Moderate (GI score 1.1-2.0)	15	17.6	16	18.8	31	18.2	
Severe (GI score 2.1-3.0)	2	2.4	2	2.4	4	2.4	
Total	85	100.0	85	100.0	170	100.0	

Table 2 Oral hygiene and gingival health status among hypertensive patients (CCB/Non-CCB)

Comparing factors associated with GO between the participants with GO in both the CCB and non-CCB groups, gingival enlargement was found among equal number of both male and female, a third of the participants with GO were 70 years and above, two-third had fair oral hygiene status, two-fifth had gingival bleeding, about half had localized gingivitis and three-fifth had mild gingival inflammation. Table 3.

**Table 3** Relationship of some factors with gingival overgrowth among hypertensive patients

Variables	Gingival Enlargement						
	Present (GOI sco	ore 3-4)	Absent (GOI so	Absent (GOI score 0-2) Tota			
	Freq	%	Freq	%	Freq	%	
Gender							
Male	39	50%	43	46.7	82	48.2	
Female	39	50%	49	53.3	88	51.8	
Age group (years)							
20-29	2.6	40.0	3	3.3	5	2.9	
30-39	9	11.5	13	14.1	22	12.9	
40-49	10	12.8	29	31.5	39	23.0	
50-59	13	16.7	29	31.5	42	24.7	
60-69	17	21.8	13	14.1	30	17.7	

≥70yrs	27	34.6	5	5.4	32	18.8		
OH status							< 0.0001*	
Good (OHI score 0.1-1.2	15	19.2	47	51.1	62	36.5		
Fair (OHI score 1.3-3.0)	47	60.3	43	46.7	90	52.9		
Poor (OHI score 3.0-6.0)	16	20.5	2	2.2	18	10.6		
Extent of gingival inflammation	on						< 0.0001*	
Healthy gingiva (GBI<10%)	8	10.3	29	31.5	37	21.8		
Localized gingivitis (GBI10- 30%)	36	46.2	49	53.3	85	50.0		
Generalized gingivitis (GBI>30%)	34	43.6	14	15.2	48	28.2		
Severity of gingival inflammat	tion						< 0.0001*	
Healthy (GI Score = 0)	6	7.7	29	31.5	35	20.6		
Mild (GI Score 0.1-1.0)	47	60.3	53	57.6	100	58.8		
Moderate (GI Score 1.1-2.0)	22	28.2	9	9.8	31	18.2		
Severe (GI Score 2.1-3.0)	3	3.8	1	1.1	4	2.4		
Gingival bleeding								
Yes	33	42.3	23	25.0	56	32.9		
No	45	57.7	69	75.0	114	67.1		
Total	78	100.0	92	100.0	170	100.0		

Considering factors within participants with no GO in both the CCB and non-CCB groups; there is a slight female predominance with M: F of 1:1.4, more participants within the fifth and sixth decade of age, more than half had good oral hygiene status and localized gingivitis. Table 4.

Table 4 Relationship of some factors with gingival overgrowth among CCB group

Variables	Gingival Enlargement						
	Present (GOI sco	ore 3-4)	Absent (GOI sc	Total			
	Freq	%	Freq	%	Freq	%	
Gender							0.963
Male	18	46.2	21	45.7	39	45.9	
Female	21	53.8	25	54.3	46	54.1	
Age group (years)							
20-29	0	0.0	1	2.2	1	1.2	
30-39	1	2.6	3	6.5	4	4.7	
40-49	5	12.8	14	30.4	19	22.4	
50-59	9	23.1	18	39.1	27	31.8	
60-69	13	33.3	6	13.0	19	22.4	
≥70yrs	11	28.2	4	8.7	15	17.6	

Type of Calcium Channel Blocker (CCB)									
Nifedipine	8	20.5	10	21.7	18	21.2			
Amlodipine	31	79.5	36	78.3	67	78.8			
CCB Dosage							0.088		
5mg	4	10.3	11	23.9	15	17.6			
10mg	30	76.9	33	71.7	63	74.1			
20mg	5	12.8	1	2.2	6	7.1			
30mg	0	0.0	1	2.2	1	1.2			
Duration of diagnosis (years)							0.444		
1-10	23	59.0	35	76.1	58	68.2			
11-20	12	30.8	8	17.4	20	23.5			
21-30	2	5.1	2	4.3	4	4.7			
31-40	1	2.6	0	0.0	1	1.2			
41-50	1	2.6	1	2.2	2	2.4			
OH status							0.002*		
Good (OHI score 0.1-1.2	9	23.1	28	60.9	37	43.5			
Fair (OHI score 1.3-3.0)	27	69.2	16	34.8	43	50.6			
Poor (OHI score 3.0-6.0)	3	7.7	2	4.3	5	5.9			
Extent of gingival inflammation	l						0.083		
Healthy gingiva (GBI<10%)	5	12.8	11	23.9	16	18.8			
Localized gingivitis (GBI10- 30%)	14	35.9	22	47.8	36	42.4			
Generalized gingivitis (GBI>30%)	20	51.3	13	28.3	33	38.8			
Severity of gingival inflammation							0.014*		
Healthy (GI score 0.1-1.0)	3	7.7	11	23.9	14	16.5			
Mild (GI score 0.1-1.0)	23	59.0	31	67.4	54	63.5			
Moderate (GI score 1.1-2.0)	12	30.8	3	6.5	15	17.6			
Severe (GI score 2.1-3.0)	1	2.6	1	2.2	2	2.4			
Total	39	100.0	46	100.0	85	100.0			

# 4. Discussion

This study determined the association between CCBs and GO, and the relationship between GO and associated factors among a group of Nigerian hypertensives.

In our study, the prevalence of DIGO in CCB and non-CCB was the same (49.5%) and this compared with a study done in Turkey among hypertensives attending a medical outpatient clinic that found no difference in the prevalence of DIGO among their participants [31]. However, the prevalence found in this study is comparable to another study done among patients diagnosed with refractory hypertension in an Institute of Cardiology in Rio de Janeiro, Brazil that reported a prevalence of 45.4% among BBC users [13]. A study done in Kenya, found a prevalence of 31.5% among their BBC users [20]. These differences may be attributed to the grading and clinical parameters used for classifying and assessing the

related factors to DIGO. This study assessed GO using New Clinical Index for Drug-Induced Gingival Overgrowth (DIGO) [29].

Amlodipine was the most commonly used CCB among the participants (67 of 85; 78.8%) in this study. This is similar to other studies done in India and Nigeria that reported that 76.7% and 67.2% of their participants respectively used amlodipine [14]. These studies were hospital based and the preference for prescribing Amlodipine to their patients maybe as a result of its less frequency of use and ease of compliance by patients (its substantivity is 24 hours) compared to Nifedipine. However, other studies reported Nifedipine as the most commonly used CCB [13, 14, 32].

Though, Gopal et al, Umezuidike et al, Lividia et al and Seymour et al reported a male preponderance of DIGO among their participants, our study reported no difference in the occurrence of DIGO between males and females [9,14,26,33]. The result from our study compared to studies reported by Jorgensen et al and Karnik et al [33,34].

The mechanism of action by which CCB induces GO is not well understood, however, it has been postulated that there could be a genetic predisposition to the proliferation of gingival fibroblasts. Our study contrasted with several studies that reported a higher prevalence of DIGO among nifedipine users than amlodipine, but is similar to that reported by Umeizudike et al [26, 35-38].

The prevalence of DIGO among nifedipine and amlodipine users in our study were 44.4% and 46.3% respectively. However, only a quarter of those with DIGO were on nifedipine while the remaining three quarters were on amlodipine. Thus, this study showed that amlodipine users are three times at risk of developing DIGO than nifedipine users. Not surprising since many studies have reported a reversal in the presenting pattern of CCB-associated DIGO where more cases are seen in those on amlodipine rather than nifedipine in the last two decades; but what is responsible for this is not yet clear [33, 39]. Could it be as a result of increased prescription by physicians of amlodipine compared to nifedipine based on recommendations from the Joint National Committee Hypertension guidelines or is there a genetic predliction? [40]. Genetic studies may reveal more information as regards this.

Factors associated with DIGO in our study were the female gender 21(53.8%), age group 60-69, 13(33.3%), more amlodipine users 31(79.5%), those on 10mg dosage of drug 30(76.9%), those who have been on medication less than 10 years 23(59.0%), those with fair OH 27(96.2%), mild inflammation 23(59.0%) and generalized gingivitis 20(51.3%). The age group, oral hygiene status, extent and severity of inflammation were all significantly associated with the occurrence of DIGO. Similar to the reports from similar studies, drug dosage was not identified as a significant risk indicator in this study [9, 41]. This is because drug dosage has been reported to be a poor predictor of gingival changes because it is influenced by pharmacokinetics and pharmacodynamics [20].

# 5. Conclusion

In conclusion, the prevalence of DIGO between CCB and non-BBC users were the same. However, DIGO was found to be three times more among amlodipine users than nifedipine users. Since gingival inflammation was associated with this finding, it is needful that periodontal care be included in the management of the hypertensives.

## Limitation

Study was hospital based and not community based.

## **Compliance with ethical standards**

#### Acknowledgments

All who consented to participate in the study.

Disclosure of conflict of interest

N0 conflict of interest

Statement of informed consent

Informed consent was obtained from all participants included in the study.

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