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ORIGINAL ARTICLE

Prevalence and Risk Factors of Drug-induced Gingival Overgrowth in Hypertensive Patients

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ABSTRACT

Gingival overgrowth (GO) or enlargement is an unwanted effect occurring on the gingiva that commonly associated with medications. Hypertension is a global burden systemic conditions and showed high prevalent and more patients are taking antihypertensive drugs. **Objective:** This study aimed to assess the prevalence of drug-induced gingival overgrowth (DIGO) and its associated risk factors among hypertensive patients attending Hospital Universiti Sains Malaysia, Kelantan, Malaysia. **Methods:** A total of 42 patients with the mean age of 57.1 (SD=9.3) years had participated in this cross-sectional study. They were recruited if they had consumed anti-hypertensive agents for at least 6 months. Demographic data and oral hygiene status were recorded and the presence of DIGO was assessed based on clinical index for gingival overgrowth. Data were analyzed using SPSS version 24.0 with $p< 0.05$ is considered statistically significant. **Results:** Majority of patients were taking calcium channel blockers (CCB) (81.0%) with amlodipine reported as the most common antihypertensive prescribed (47.6%). About 52% presented with DIGO and among them 55.9% were in those on CCB by which 9.5% presented with clinically significant enlargement. Except for gingivitis, oral hygiene status and demographic data were not significant risk factors for DIGO ($p > 0.05$). **Conclusion:** We found that DIGO is prevalent among hypertensive patients on CCB and its occurrence is coexists with gingivitis. Therefore, periodontal assessment is recommended among these patients for early detection and management of drug-induced gingival overgrowth.

Key words: Gingival overgrowth, drug-induced gingival enlargement, calcium channel blocker, anti-hypertensive agents

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INTRODUCTION

Gingival overgrowth (GO) or enlargement is an unwanted effect occurring on the gingiva that commonly associated with medications.[1] It appears as swelling and disfiguration of the gingiva usually affecting the interdental papilla and resulting in a lobulated or nodular morphology.[2,3] The gingiva may enlarge marginally, interdentally or diffusely affecting anterior and posterior teeth. This condition affects the aesthetic, mastication, speech and oral hygiene measures which lead further periodontal deterioration.[4]

The commonest drugs that have shown to induce GO includes anticonvulsants such as phenytoin; calcium channel blockers such as nifedipine and amlodipine; and immunosuppressive agents such as cyclosporin A and tacrolimus.[5] The onset is typically within the first three months of starting the medication, and it tends to occur mostly in the anterior gingivae. It is usually not associated with attachment loss or tooth mobility unless there is existing periodontal disease.[2,6,7] Nevertheless, this condition could be a major problem for the oral hygiene procedures thus it can elevate the risk for periodontal infection and inflammatory complications.[8]

Hypertension is a global burden systemic conditions and showed high prevalent in Malaysia.[9] Hence more patients are taking antihypertensive drugs particularly calcium channel blockers (CCB) such as nifedipine or amlodipine. However, patients are usually unaware of the possible side effects of those drugs in the oral cavity which affect their gingival health that may impair the mastication, aesthetic and their social life.[4] Furthermore, many people may not be aware of the health status of their gingival tissue unless it is symptomatic such as gum bleeding. As a result, they may have drug-induced gingival overgrowth (DIGO) which can only be clinically detected by the physician or dentist. It is therefore important for patients to undergo oral examination at the earlier stage to prevent this unwanted effect.

Calcium channel blockers-induced GO has been reported since 1984 by Lederman in patients taking nifedipine.[10] CCB is a calcium antagonist, category of medications commonly used in the treatment of hypertension. Over the past few years the overall number of prescriptions for this class of agents has continued to increase. These are the most common medicines used in management of hypertension[11] besides ACE inhibitors, angiotensin II receptor blockers, diuretics and B-blockers.[12] This drug is effective and has entertained extensive and widespread use throughout the world such as about 20% in United States and 6% in UK with amlodipine being the most prescribed drugs.[13,14] However, these drugs implicate the gingival condition as its promotes excessive growth possibly due to biochemical mechanism.[5] It was estimated that the prevalence of GO induced by CCBs were range from 6% to 83% in Caucasian population.[1,14,15]

The occurrence of DIGO is commonly reported in the literatures.[16,17] However the data among local population is scarce although some cases have been documented.[3,18,19] Information or scientific data in regard to prevalence of GO and its associated risk factors among local population may serve as a rationale for physician to give advice or early referral of their patients to dental practitioners. Moreover, by identifying patient 'at risk', appropriate treatment strategies could be developed, and early management could be carried out to prevent this unwanted side effect of their medications. Therefore, this study was conducted to determine the prevalence of DIGO among hypertensive patients particularly those on CCB and to identify the factors associated with this condition.

METHODS

A cross-sectional study was conducted at the Outpatient Clinic, Hospital Universiti Sains Malaysia (USM), Kelantan, Malaysia involving hypertensive patients who were taking anti-hypertensive agents for at least 6 months. Patients were selected by convenient sampling on voluntary basis while they were at the waiting area during their follow-up visit at the clinic. We included all patients aged 18 years old and above with at least 6 teeth. Those who had undergone periodontal treatment within 6 months prior to the initiation of the study, taking other medications or having some systemic disorders known to affect the gingiva, and pregnant women were excluded.

Patients were briefed about the study procedures and the informed written consent were taken. Patient's background, medical and drug history were retrieved from patients' record followed by oral examination. Oral hygiene practice and smoking habit were noted during history taking. Patients were proposed to receive standard periodontal treatment, if they have any signs of GO as well as periodontal disease or other dental problem. This study protocol was approved by Human Research Ethics Committee USM (USM/JEPeM/19010019).

Plaque score (PS), Gingivitis score (GS) and Clinical Index for Drug-induced Gingival Overgrowth (CIGO) were recorded during oral examinations. All these parameters were measured by using standardized Michigan 'O' periodontal probe with Williams markings (Hu-Friedy, Chicago).

Plaque Score

PS was performed through the detection of plaque by visual assessment and also by running the probe along the gingival margin.[20] The plaque was assessed at buccal, lingual, mesial and distal surfaces of the teeth by recording as presence (yes) or absence (no) and was expressed as a percentage of the number of tooth surfaces examined in each patient. The oral hygiene is considered good if the PS was ≤30%, and as moderate to poor for PS >30%.

Gingivitis Score

GS was assessed through gentle probing of the gingival crevice to detect the presence of bleeding.[21] Similar to PS, GS was also recorded for four tooth surfaces. The bleeding is scored dichotomously as presence (yes) if occurs within 10 second upon probing, or absent (no). GS was expressed as a percentage of bleeding over a total number of tooth surfaces examined for each patient. GS ≤30% indicates localised gingivitis whereas generalised gingivitis for GS >30%.[22]

Clinical Index for Drug-induced Gingival Overgrowth

This index was used to assess and classify the presence of drug-induced gingival overgrowth.[23] It is easy to use and does not require diagnostic casts yet, provide some indications of the severity of the lesions as well as aiding in the selection of appropriate treatment intervention based on grading 0 to 4.

- Grade 0- No overgrowth, firm adaptation of the attached gingiva to the underlying alveolar bone, no or slight stippling, as well as no or only slightly granular appearance, and knife-edged papilla is present toward the occlusal surface. There is no increase in density or size of the gingiva.
- Grade 1- Early overgrowth, increase in density of the gingiva with marked stippling and granular appearance. The tip of interdental papilla is rounded.
- Grade 2- Moderate overgrowth manifested by an increase in the size of the papilla and/ or rolled margins. The contour of gingival margin is still concave or straight. The papilla is somewhat retractable. Gingival enlargement has a buccolingual dimension of up to 2 mm, measured from the tip of the papilla outward.
- Grade 3- Marked overgrowth, represented by encroachment of the gingiva onto clinical crown. The contour of the gingival margin is convex rather than concave. Gingival overgrowth has a buccolingual dimension of approximately 3 mm or more, measured from the tip of the papilla outward. The papilla is clearly retractable.
- Grade 4- Severe overgrowth, characterized by a profound thickening of the gingiva. A large percentage of the clinical crown is covered. As in grade 3, the papilla is retractable. The buccolingual dimension is approximately 3 mm.

Data Analysis

The data was analysed by using Statistical Programme for Social Sciences (SPSS) version 24. Data checking and cleaning were performed before analysis. Descriptive analysis was used to analyze mean (SD) and frequency (%). The factors associated was analysed by using Chi-square test or Fisher exact test where appropriate. The level of significance was set at p value<0.05.

RESULTS

A total of 42 patients with the mean age of 57.1 (SD 9.3) years old were recruited. The majority of patients were Malay (97.6%) and the number of female (57.1%) was slightly more than male (Table 1). More than two third (83.3%) of the patients had other systemic diseases such as diabetes mellitus and only 3 (7.1%) were smokers. About 55% of the patients were diagnosed with hypertension for more than 10 years and 81% were on CCB. Amlodipine was the most common anti-hypertensive prescribed (47.6%) followed by felodipine (31.0%) and nifedipine (2.4%).

Based on PS, 59.5% of patients have moderate to poor oral hygiene (PS>30%) and mostly presented with localised gingivitis (78.6%). There was no significant different in oral hygiene (p=0.69) and gingival health status (p=0.66) between CCB and non-CCB users (Table 2). It was found that 22 (52.4%) patients presented with DIGO whereby more than half were among those taking CCB (55.9%; 95% CI: 38%, 73%). Although there is no significant association between GO and types of antihypentensive drugs (p=0.44) but odds of taking CCB among those with GO is two times (95% CI: 0.4, 10.3) higher than those without GO (Table 3). As amlodipine is the most CCB taken, among them 12 (60%) have GO and mostly presented with clinical index of GO grade 1 (mild in severity). Nevertheless, in overall, the result shows 4 (9.5%) patients have moderate to marked GO from those taking amlodipine (1 patient grade 3), felodipine (2 patients grade 2) and nifedipine (1 patient grade 2) as shown in Table 4. Meanwhile GO grade 1 was also noted in 3 (7.1%) patients taking non-CCBs.

Table 1. Demographic characteristic of the study subjects (n=42)

Variables	Frequency, n(%)
Age, years (Mean, SD)	57.1 (9.34)
Gender	
Male	18 (42.9)
Female	24 (57.1)
Ethnicity	
Malay	41 (97.6)
Chinese	1 (2.4)
Duration on HPT medication (years)	
<5 years	6 (14.3)
5-10 years	14 (33.3)
>10 years	22 (55.4)
Type of antihypertensive	
[a]CCB	34 (81.0)
Non-CCB	8 (19.0)
Other systemic diseases	
Yes	35 (83.3)
No	7 (16.7)
Smoking habit	
Non-smokers	34 (81.0)
Smokers	3 (7.1)
Ex-smoker	5 (11.9)

HPT= hypertension CCB= calcium channel blockers
[a]47.6% Amlodipine

Further analysis showed that age, gender, smoking status, duration on medication and oral hygiene status were not significant risk factors for GO (Table 5). However, GO was significantly associated with generalised gingivitis (OR=10.9, 95% CI: 1.22, 97.06, p=0.02).

DISCUSSION

We found that the majority of the patients were taking CCB (81%) with amlodipine as the most frequently

Table 2. Oral hygiene and gingival health status among hypertensive patients (n=42)

Variables		Antihypertensive drugs		p-value[a]
		CCB n (%)	Non-CCB n (%)	
Oral hygiene				
	Good	13 (76.5)	4 (23.5)	0.69
	Moderate to poor	21 (84.0)	4 (16.0)	
Gingivitis Score				
	Localised gingivitis	26 (78.8)	7 (21.2)	0.66
	Generalised gingivitis	8 (88.9)	1 (11.1)	

[a]Fisher's exact test; CCB=calcium channel blockers

Table 3. The prevalence of gingival overgrowth among hypertensive patients (n=42)

Variables		n (%)	CCB n (%)	Non-CCB n (%)	OR (95% CI)	p-value[b]
Gingival overgrowth						
	Present	22 (52.4)	19 (55.9)[a]	3 (37.5)	2.1 (0.4, 10.3)	0.44
	Absent	20 (47.6)	15 (44.1)	5 (62.5)		

[a]95%CI (38%, 73%); [b]Fisher's exact test; CCB=calcium channel blockers

Table 4. Severity of gingival overgrowth based on Clinical Index of Gingival Overgrowth among different antihypertensive drugs (n=42)

Antihypertensive drugs	n (%)	Severity of gingival overgrowth			
		Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)
	42				
CCB					
Amlodipine	20 (47.6)	8 (40.0)	11 (55.0)	0	1 (5.0)
Felodipine	13 (31.0)	7 (53.8)	4 (30.8)	2 (15.4)	0
Nifedipine	1 (2.4)	0	0	1 (100.0)	0
Non-CCB	8 (19.1)	5 (62.5)	3 (37.5)	0	0

CCB=calcium channel blockers

Table 5. Factors associated with gingival overgrowth among antihypertensive patients (n=42)

Variables		n (%)	Gingival overgrowth		OR (95% CI)	p-value[a]
			Present n (%)	Absent n (%)		
Age (years)						
	> 50	32 (76.2)	18 (56.3)	14 (43.8)	1.93 (0.45, 8.18)	0.48
	≤ 50	10 (23.8)	4 (40.0)	6 (60.0)		
Gender						
	Male	18 (42.9)	9 (50.0)	9 (50.0)	0.85 (0.25, 2.88)	0.79
	Female	24 (57.1)	13 (54.2)	11 (45.8)		
Duration medication						
	≥ 5 years	36 (85.7)	17 (47.2)	19 (52.8)	0.18 (0.02, 1.69)	0.19
	< 5 years	6 (14.3)	5 (83.3)	1 (16.7)		
Smoking status						
	Smoker	5 (11.9)	3 (60.0)	2 (40.0)	1.42 (0.21, 9.52)	>0.9[a]
	Non-smoker	37 (88.1)	19 (51.4)	18 (48.6)		
Oral hygiene						
	Moderate to poor	25 (59.5)	15 (60.0)	10 (40.0)	2.14 (0.61, 7.51)	0.23
	Good	17 (40.5)	7 (41.2)	10 (58.8)		
Gingival status						
	Generalised gingivitis	9 (21.4)	8 (88.9)	1 (11.1)	10.9 (1.22, 97.06)	0.02[a]
	Localised gingivitis	33 (78.6)	14 (42.4)	19 (57.6)		

[a]Fisher's Exact Test; OR= Odd Ratio

used drug, reflects that CCB is the commonest antihypertensive prescribed.[9,24] Most of them (55%) were taking medication for more than 10 years. However patients' compliance on medication was not investigated further in this study. Of the 42 patients, 22 (52.4%) were diagnosed clinically as having DIGO. The frequency of occurrence of DIGO mainly focus on CCBs (56%) and could be considered as quite prevalent although most of them were in mild severity (grade 1). This result is almost similar with previous study by Andrew et al. although their sample size was larger[1] and also consistent with other reports.[5,14] DIGO is observed more prevalent in patients taking antihypertensive medication more than 5 years (77.3%) while Karnik et al. had detected GO as early as 24 months (62.5%) of their patients.[25] This present study is cross-sectional design thus we are unable to determine the possible existing of GO prior to taking medications.

The pathogenesis of DIGO was reported to be due to the inhibitory effect of drugs on intracellular calcium and sodium ion influx upon cation channel at cellular level.[26] This may leads to decrease in folate cellular uptake by gingival fibroblast, thus affecting the synthesis and activation of matrix metalloproteinases. As a consequences, there is insufficient amount of active collagenase for breakdown of the excess gingival connective tissues resulting in DIGO.[5]

Those patients taking CCB appeared to be more at risk for developing clinically significant overgrowth (9.5% with grade 2 to 3), which is higher compared to previous studies ranged from 1.3% to 3.4%.[15,27,28] This condition requires further periodontal intervention such as full mouth scaling, oral hygiene control and possible surgical correction of the GO.[26] Nevertheless, the surgically treated DIGO showed common recurrent rates which could be as early as 3-6 months.[29] It is recommended that by implementing meticulous oral hygiene home care and professional cleaning may help to reduce the degree of recurrence.[30] Consultation or referral to physician may also be required in severe GO cases for conceivable withdrawal or substitution of medication.[31]

The severity of DIGO in patients taking CCB have been reported to correlate with poor plaque control and also other factors such sex, age, smoking status and duration of medication.[25,32,33] Other identifiable risk factors have been proposed that include genetic predisposition, periodontal parameters, pharmacokinetic/drugs variables, and combination of medications.[10,33,34] However, those factors were not proven significant in our study yet also stated in previous studies.[35,36] The development of GO could be related to patients' susceptibility towards the effect of drug on gingival tissues. Nevertheless, this current study showed significant association between DIGO and gingivitis ($p=0.02$) by which the odds of having generalised gingivitis in those with GO is 10.9 times of that among those without GO (95% CI: 1.22, 97.06).

This can be explained that the occurrence of gingivitis could be the synergistic effect due to changes of the gingival architecture in GO that provide suitable niche for bacterial growth thus enhanced gingival inflammation.[17] On the other hand the gingival inflammation became the significant cofactor in the expression of DIGO.[37] However, our cross-sectional study design could not determine the sequence of event on such relationship. Even though it is believed that the presence of plaque biofilm that induced gingival inflammation may play a role in the severity of DIGO[38], such finding was not clear in this current study. This could be attributed by the quantitative measure of plaque score that may lack of sensitivity in determining gingival infection and DIGO,[39] which we consider as study limitations. Further investigation on the development of GO is remain necessary.

Almost all patients in this study were Malay, the main ethnic population in Kelantan, Malaysia, thus our findings may not apply for the whole population. Nevertheless, the detection of DIGO in this selected group warrants further studies in larger scale for more conclusive evidence.

CONCLUSION

We conclude that DIGO is prevalent (55.9%) among hypertensive patients and mainly induced by CCB. The occurrence of DIGO is not significantly associated with oral hygiene status and demographic data, but rather prone to synergistically occur with generalised gingivitis. Hypertensive patients particularly those on CCB should be advised for regular dental examination to prevent and/ or provide appropriate management of this unwanted condition. Collaboration with medical counterparts is also beneficial to increase the awareness among patients.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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