RESEARCH ARTICLE

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Prevalence of Gingival Enlargement Induced by Antihypertensive Drugs

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ABSTRACT

Introduction: Drug-Induced Gingival Overgrowth (DIGO) is a pathological growth of the gingival tissue, which may occur as a side effect of certain drugs including some antihypertensive drugs, anti-epileptics and immunosuppressants. The literature reports a prevalence of gingival overgrowth among antihypertensive drug users, ranging from 13.5 to 83%. The aims of this study were to determine the prevalence of (DIGO) and the risk factors associated with it in a group of patients who were taking antihypertensive drugs attending. Erbil Cardiac Center in Erbil, Iraq.

Methods: This cross-sectional study evaluated 50 hypertensive patients treated with antihypertensive agents in Erbil Cardiac Center in Erbil region. Gingival overgrowth was clinically assessed using the gingival enlargement index (Miranda-Barent), gingival enlargement index (Miller & Dann) and (Silnes-Leo) Plaque index. Data on age, gender, smoking status, type/dose of antihypertensive medication, and duration of use were collected.

Results: Mean age was 58.3±12.9 years, and mean duration of antihypertensive medication uses was less than 5 years in (52%) of the patients, more than half were male (58.0%). The most commonly used antihypertensive agents were Amlodipine (48%), combination therapy contains Amlodipine 5mg (24%), and non-calcium channel blocker (28%). The prevalence of Gingival Overgrowth (GO) was 83%, in Calcium Channel Blockers (CCBs) group with the majority being grade I (42%). Gingival overgrowth was significantly associated with amlodipine dose, age and duration of drug use ($p<0.05$).

Conclusions: The prevalence of (DIGO) in patients taking (CCBs) among other antihypertensive medications was significant. Major risk factors were greater doses of Amlodipine, older age, longer duration of drug intake, and larger amount of plaque in the sulcus or pocket along the free gingival margin.

Keywords: Antihypertensives Agents, Calcium Channel Blocker, Drug-Induced Gingival Overgrowth, Gingival Overgrowth, Hypertension, Oral Hygiene.

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INTRODUCTION

(DIGO) is a pathological growth of the gingiva characterized by the accumulation of connective tissue that primarily affects the anterior regions of the maxilla and mandible [1-3]. It presents as gingival swelling and deformity, mostly affecting the interdental papilla and producing a nodule or lobule morphology [4-5]. This condition impairs oral hygiene practices, speech, mastication, and aesthetics, all of which contribute to more periodontal degradation[6].

(DIGO), it is also known as Drug-Induced Gingival Enlargement (DIGE), is a side-effect of some medications in which the gingival tissue is not the intended target organ. Calcium Channel Blockers (CCBs), immunosuppressants, and anticonvulsants are the primary pharmacological classes that cause offenses[7].

Compared to the most significant inflammatory gingival enlargements, the prevalence of drug-induced gingival enlargements is 3–20%. The (CCB) class of antihypertensive medications is widely used to elderly patients with peripheral vascular disease or angina. Gingival Overgrowth (GO) is an adverse effect of Amlodipine, a third-generation calcium channel blocker used to treat angina and hypertension. Amlodipine is an agent of dihydropyridine[8]. Clinical signs of the (DIGO) could be seen as soon as 1-3 months after the first (CCB) dosage. While edentulous areas do not appear to be affected by the overgrowth[9], the occurrence of (DIGO) is commonly reported in the literatures[10,11]. However, the data among local population is scarce although some cases have been documented[12-14]. Physicians may use information or scientific data regarding the incidence of (GO) and its related risk factors in the local community as justification for advice or early patient referrals to dentists. Moreover, identifying patients who are “at risk” would allow for the development of suitable treatment plans and the implementation of early care to stop this unfavorable pharmaceutical side effect[4]. Therefore, this study was carried out to evaluate the prevalence of (DIGO) among hypertensive patients to identify the risk factors associated with this condition.

PATIENTS & METHODS

Study design: This study design was cross sectional study included 50 hypertensive patients who were taking antihypertensive drugs, to evaluate the prevalence of (GO) among them.

Study setting: The study conducted at Cardiac consultation clinic at Erbil Cardiac Center in Erbil-Kurdistan region of Iraq, starting in October 2022 and ending in October 2023.

Ethical considerations: This study was submitted to the Ethics and Scientific committee of Research Ethics at Kurdistan Higher Council of Medical Specialties for scientific and ethical approval. Each patient was informed about this study and given verbal assent, after which data anonymity and confidentiality were ensured.

Inclusion criteria:

- Every patient on one of the antihypertensive drugs;

1. Calcium channel blocker
2. Beta blocker,
3. ACE inhibiters
4. Combination therapy containing (Perindopril arginine 5mg, Indapamide 1.25mg, Amlodipine 5mg) included.

- Cases that have been using an antihypertensive medication for the past 6 months or more.
- Cases with existence of 10 or more anterior teeth and a minimum of 16 permanent teeth.

Exclusion criteria:

- Excluding pregnant ladies and patients during puberty, Leukemias, Granulomatous diseases and diabetes.
- Cases that are on drugs that may cause gingival enlargement such us (anticonvulsants and immunosuppressive agents.

Pilot study: A pilot study was carried out in November 2022, in the Oral and Maxillofacial Medicine department in Khanabad Teaching Center in Erbil -Kurdistan region of Iraq. Intra and inter calibration were performed to obtain the most critical consistency of data.

Inter and Intra calibrations were carried out among 10 patients that are taking antihypertensive drugs.

Examination included three measurements of (GO) methods: Gingival enlargement index (miller and damn)[15], Gingival enlargement index (miranda-burent)[16], Silness-Leo Plaque index[17].

Inter calibration carried out by examination of the patients twice, once by the researcher and the second by specialist.

Intra calibration carried out by the examination of the patients by the researcher with an interval period of two hours between two examinations.

RESULTS

No significant differences were detected between the specialist and the researcher regarding the parameters of plaque index ($p = 1.000$), Gingival enlargement index (by miranda-burent) ($p = 1.000$), Gingival enlargement index (miller and damn) ($p = 1.000$), and as presented in **Table 1.**

Clinical examination: Three measurement methods of (GO) were performed by William prob.

1- Gingival enlargement index (miller and damn); measure the height of gingival tissue from the cement enamel junction to the free gingival margin. Grades were scored in 6 points around each tooth as follows:

- Grade 0; Normal.
- Grade 1; Minimal enlargement (≤2 mm in size, with gingiva covering the cervical third or less of anatomic crown).
- Grade 2; Moderate enlargement (2–4 mm in size and/ or gingiva extending into middle third of anatomic crown).
- Grade 3; Severe enlargement (nodular gingiva >4 mm and/or gingiva covering more than two-thirds of tooth crown).

2- Gingival enlargement index (miranda-burent); measure the buccal-lingual direction in all interdental papilla, the increase in size of papilla was measured from the enamel surface, at interdental contact point to the outer papillary surface. Two scores will obtain, one for the buccal papilla and another for lingual/palatal papilla, according to the following criteria:

- Grade 0; Papillary thickness of <1 mm,
- Grade 1; Papillary thickness between 1 and 2 mm,
- Grade 2; Papillary thickness >2 mm.

Silness-Leo Plaque index under following criteria:

- Grade 0; Absence of microbial plaque,
- Grade 1; Thin film of microbial plaque along the free gingival margin,
- Grade 2; Moderate accumulation of soft deposits within the gingival margin or the tooth and gingival margin
- Grade 3; Abundance of soft matter within the gingival pocket and \ or on the tooth and gingival margin,

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 26). Chi square test of association was used to compare proportions of the study groups. Fisher's exact test was used when the expected frequency (value) was less than 5 of more than 20% of the cells of the table. Wilcoxon signed ranks test was used (in the pilot study) to compare the medians of the same sample but by two observers (the specialist and the researcher). A p value of ≤ 0.05 was considered as statistically significant.

Fifty patients participated in this study. Their mean age (SD) was 58.3 (12.9) years, the median was 58 years, and the age range was 38-83 years. Around one third (34%) of the patients were aged less than 50 years, and 24% aged ≥ 70 years. More than half (58%) were males. The duration of treatment was less than five years in 52% of the patients. Around half (48%) of the patients

Table 1. Results of Pilot Study.

	Specialist		Researcher		
	Mean	Median	Mean	Median	P value*
Plaque index	1.9	2	1.9	2	1
Gingival enlargement index (miranda-burent)	1.4	1	1.4	1	1
Gingival enlargement index (miller and damn)	1.4	1	1.4	1	1

*By Wilcoxon signed ranks test.

Table 2. Basic Characteristics.

	No.	%
Age		
< 50	17	34
50-59	8	16
60-69	13	26
≥ 70	12	24
Gender		
Male	29	58
Female	21	42
Duration of treatment (years)		
< 5	26	52
05-Sep	9	18
≥ 10	15	30
Drug type		
Calcium channel blockers	24	48
Combination containing amlodipine	12	24
Non-Calcium channel blocker	14	28
Smoking		
No	41	82
Yes	9	18
Total	50	100

were on (CCBs) only, while 24% were on combinations containing Amlodipine, and the rest (28%) were non (CCBs). Regarding smoking, only 18% of the patients were smokers **Table 2**.

It is evident in **Table 3** that the more the age, the more the prevalence of gingival enlargement, reaching 100% among patients aged ≥ 70 years (p = 0.005). The prevalence of gingival enlargement was 69% among males and 57% among females, but the difference was not significant (p = 0.390). Only one third (33.3%) of the smokers had gingival enlargement compared with 70.7% among non-smokers (p = 0.055). It was significant that the more the duration of treatment, the more the prevalence of gingival enlargement. It was 50% when the duration of treatment was less than five years, and 93.3% when the duration was ≥ 10 years (p = 0.017), as presented in **Table 3**.

The prevalence of gingival enlargement was 83.3% when the patients were on (CCBs) only, and it was 75% when they were on combinations containing amlodipine, while it was 21.4% when they were taking non (CCBs) (p< 0.001) as presented in **Table 4**.

Results showed that patients taking (CCBs) alone had more severe forms of gingival enlargement, where it is evident in **Table 5** that 16.7% had grade III and 29.2% had grade II, while none of the patients taking combinations containing (CCBs) or not taking (CCBs) had gingival enlargement of such grades (p< 0.001) as presented in **Table 5**.

Table 6 shows that the more the severity of plaque index, the more the prevalence of gingival enlargement, reaching 100% when there was abundance of plaque within the gingival pocket and\or the tooth and gingival margin (p< 0.001) as presented in **Table 6**.

Table 3. Prevalence of Gingival Enlargement by Sociodemographic Characteristics and Disease Duration.

	Prevalence of gingival enlargement			
	No	Yes	Total	
	No. (%)	No. (%)	No. (%)	P Value
Age (years)				
<50	10 (58.8)	7 (41.2)	17 (100.0)	
50-59	4 (50.0)	4 (50.0)	8 (100.0)	
60-69	4 (30.8)	9 (69.2)	13 (100.0)	
≥ 70	0 (0.0)	12 (100.0)	12 (100.0)	0.005**
Gender				
Male	9 (31.0)	20 (69.0)	29 (100.0)	
Female	9 (42.9)	12 (57.1)	21 (100.0)	
Smoking				
No	12 (29.3)	29 (70.7)	41 (100.0)	
Yes	6 (66.7)	3 (33.3)	9 (100.0)	0.055**
Duration (years)				
<5	13 (50.0)	13 (50.0)	26 (100.0)	
05-Sep	4 (44.4)	5 (55.6)	9 (100.0)	
≥ 10	1 (6.7)	14 (93.3)	15 (100.0)	0.017*
Total	18 (36.0)	32 (64.0)	50 (100.0)	

*By Chi square test. **By Fisher's exact test.

Table 4. Prevalence of Gingival Enlargement by Type of Antihypertensive Drug.

	Prevalence of Gingival Enlargement			
	No	Yes	Total	P Value*
Type of drug	No. (%)	No. (%)	No. (%)	
Calcium channel blocker	4 (16.7)	20 (83.3)	24 (100.0)	
Combination containing Amlodipine	3 (25.0)	9 (75.0)	12 (100.0)	
Non-Calcium channel blocker	11 (76.6)	3 (21.4)	14 (100.0)	< 0.001
Total	18 (36.0)	32 (64.0)	50 9100.0)	

*By Chi square test.

Table 5. Severity of Gingival Enlargement by Type of Drug.

	Normal	Grade I	Grade II	Grade III	
	No. (%)	No. (%)	No. (%)	No. (%)	p value
Calcium channel blockers	4 (16.7)	9 (37.5)	7 (29.2)	4 (16.7)	
Combination containing Amlodipine	3 (25.0)	9 (75.0)	0 (0.0)	0 (0.0)	
Non-Calcium channel blocker	11 (76.6)	3 (21.4)	0 (0.0)	0 (0.0)	< 0.001
Total	18 (36.0)	21 (42.0)	7 (14.0)	4 (8.0)	

Table 6. Prevalence of Gingival Enlargement by Plaque Index Categories.

	Prevalence of Gingival Enlargement			
	No	Yes	Total	P Value*
Plaque index	No. (%)	No. (%)	No. (%)	
Thin film of plaque along the free gingival margin	14 (70.0)	6 (30.0)	20 (100.0)	
Moderate accumulation with plaque in the sulcus	4 (17.4)	19 (82.6)	23 (100.0)	
Abundance of plaque in the gingival pocket and\or the tooth.	0 (0.0)	7 (100.0)	7 (100.0)	< 0.001
Total	18 (36.0)	32 (64.0)	50 (100.0)	

*By Fisher's exact test.

DISCUSSION

This cross-sectional study demonstrates that patients with hypertension treated with calcium channel blockers are more susceptible to have gingival enlargement, than others who are taking other antihypertensive drugs.

The average patient age was 58.3 years, other studies of antihypertensive drug-induced gingival enlargement have reported a similar average age of 40-60 years[18,19]. Results in **Table 3** showing that the higher the age, the more the prevalence of gingival enlargement, reaching100% among patients aged ≥ 70 years (p= 0.005). According to the age (GO) is most frequently seen in men in their fourth or fifth decade of life. Because of the skewed data, it is challenging to conclude with certainty that this age group is more likely to experience this problem. Since most hypertensive patients begin taking amlodipine in middle age, the increased incidence of Amlodipine Induced Gingival Overgrowth (AIGO) in middle-aged patients may simply be a result of these patients' higher usage of antihypertensive drugs[20]. Age may alter collagen turnover and wound healing response, whereas long-term drug exposure increases metabolism as active drugs[21].

Duration of use was also significantly different between the groups (p=0.017), Longer duration of use has also been highlighted as a risk factor in other studies, with longer duration of use being associated with an increased incidence of enlargement[22,23]. The age and duration of antihypertensive medication are associated with (GO), consistent with accepted risk factors in other studies[22,24].

In the current study, there were 29 (58%) male participants who presented with (GO), and there were 21 (42%), female participants. Despite the fact that there are more men than women, the difference is not statistically significant (P>0.05). According to the studies, men were more likely than women to develop (GO)[25_27]. Men are 3.3 times more likely than women to have (GO)[28,29]. Studies indicate that since men are more prone to (AIGO) than women, sex may have an impact on the disease's development. By transforming testosterone into an active metabolite, (CCBs) have the ability to affect androgen metabolism. This metabolite appears to stimulate collagen synthesis or inhibit its breakdown by focusing on specific fibroblast populations[30].

Table 4 results show that the frequency of gingival enlargement in the current study was 83% in patients receiving (CCBs) (amlodipine 5 mg, 10 mg), and 73% in patients receiving combination therapy that included Amlodipine. (CCBs) are frequently recommended drugs for hypertension in this region, which would indicate that doctors favor their use. This preference is based on the National Institute for (Health and Clinical Excellence's) suggestion[31] as well as the (Joint National Committee's guidelines for hypertension)[32].

(CCB)s have been extensively reported in the literatures as being associated with (GO)[33]. The pathogenesis of (CCBs) induced (GO) remains uncertain. However, it is believed that they all share the capacity to alter calcium metabolism at the cellular level. Reduction in membrane permeability is expected to cause a decrease in the influx of calcium ions across the cell membrane. Increased fibroblastic proliferation and collagen synthesis result from lower calcium inflow because it also reduces or inhibits the secretory activity of the fibroblastic cells or collagenase production[34,35]. Inflammatory changes within the tissue may enhance the interaction between calcium and fibroblast[34,36].

The first report regarding (AIGO) was published in 1994[37-39]. (AIGO) has an unclear underlying mechanism, although two primary inflammatory and non-inflammatory mechanisms have been proposed[40,41]. A pathophysiological hypothesis for (AIGO) involves changes in collagenase activity resulting from reduced folic acid absorption, obstruction of aldosterone synthesis in the adrenal cortex, and subsequent elevation of adrenocorticotropic hormone levels and keratinocyte growth factor. Furthermore, toxic impact of Amlodipine in periodontal pockets associated with periodontal pathogens may result in inflammation by up regulating many cytokine factors, including transforming growth factor-beta 1 (TGF-β1)[40,42,43].

Table 5 demonstrates that patients receiving (CCBs) alone had more severe GO, 16.7% had grade III and 29.2% had grad II which is higher compared to previous studies ranged from 1.3% to 3.4%[44-46] and 9.5%[4]. Additional periodontal therapy, including as complete mouth scrubbing, supervision of oral hygiene, and maybe surgical correction of the (GO), is necessary for this condition[47].

Table 6 shows that the prevalence of (GO) increases with the severity of the plaque index, the more the prevalence of gingival enlargement, reaching 100% when there was abundance of plaque within the gingival pocket and\ or the tooth and gingival margin. Many studies have demonstrated that dental plaque is essential for the growth and manifestation of (DEGO)[48-52]. Bacterial plaque in Gingival Crevicular Fluid (GCF) increases the production

of both cytokines that promote inflammation such as interleukins IL-1[48] ,IL-2[52] ,1L-6[53] and anti-inflammatory cytokines and mitogens, such as TGF-beta 1[54]. Platelet-Derived Growth Factor (PDGF) and Insulin-like Growth Factor (IGF)[55]. It has been proposed that stimulation of gingival fibroblasts occurs when they are exposed to (CCBs) and pro-inflammatory cytokines, such as IL-1[48,53]. Kasasa et al. reported that IL-1 cause an increase in production of 5DHT from labeled testosterone in human gingiva and periodontal ligament (PDL)[56].

Poor plaque control was identified as a risk factor in almost all the studies[57]. This concurs with previous studies which proposed that (GO) hampered routine oral hygiene measures. The oral bacterial biofilm exacerbates gingival enlargement caused by (CCB) and is a frequent risk factor for all types of inflammatory periodontal disorders. There is a strong correlation between gingival enlargement severity and inadequate dental hygiene. The American Academy of Periodontology has updated its classification system for periodontal diseases that recognizes the role of the microbial plaque as a cofactor in the etiology of drug-associated gingival enlargement[58].The role of plaque in contributing to (GO) cannot be ruled out as the PI by Silness and Leo has no qualitative measure of the pathogenicity of plaque[27] Instead, the PI is only a quantitative assessment of plaque and lacks the sensitivity to identify the precise function that microorganisms play in causing gingival inflammation. Plaque microbiological examination is necessary to elucidate the link between plaque and GO[11.]

LIMITATIONS

One of the limitations was this study has been carried out only in one center in the Erbil city, while a community- or population-based study would have achieved more precise results. As this was only a cross-sectional analysis the causal relation of (GO) and plaque cannot be definitively determined.

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