Review Article

Calcium Channel Blockers Induced Gingival Overgrowth: A Comprehensive Review from a Dental Perspective

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ABSTRACT

Background: Gingival overgrowth (GO) as a manifestation of calcium channel blockers (CCBs) was first introduced in the literature by Ramon *et al.* in 1984. Since then, the use of CCBs as a treatment modality for hypertension has been recorded extensively in the literature for its association with GO. **Aim:** The aim of our study is to evaluate histopathology, treatment, and follow-up for the cases detailed in various studies and also to highlight the protocol mentioned to identify these presentations. **Materials and Methods:** A broad search was conducted from the period 1980 to 2021 using electronic databases PubMed Central, Scopus, Cochrane, and SciELO databases. About 293 articles were initially chosen. The articles further excluded did not fit the criteria for the study and eventually 50 articles which met the inclusion criteria were chosen as part of this literature review. **Results:** A comparative analysis was carried out regarding histopathology, treatment modalities, drug dosage, and duration to evaluate the differences in cases between 1980 and 2021. From the available studies, it was found that the histopathological and clinical findings were varied. Treatment strategies employed were different, though follow-ups in most cases were uniform. **Conclusion:** CCBs and their relationship with GO have been widely reported in the literature. Dentists should approach this condition by taking appropriate medical and dental history and follow evidence-based treatment guidelines to provide more relevant and judicious management of this condition. Inter-disciplinary treatment approaches would provide better outcomes.

Keywords: *Amlodipine, calcium channel blockers, drug-induced, gingival overgrowth, nifedipine*

Introduction

Gingival overgrowth (GO) is a manifestation of calcium channel blockers (CCBs), and it was first introduced in the literature by Ramon *et al.* in 1984.[1] Since then, numerous studies have been published in the literature on the association of drugs with GO [Tables 1-4], more specifically, cyclosporin, CCBs, and antiepileptics.[2,3] The use of CCBs for the treatment of hypertension has been recorded extensively in the literature. Drugs including nifedipine, amlodipine, diltiazem, and verapamil are all subclasses of CCBs and effectively control hypertensive patients.[4-8] Seymour *et al.*[9] identified sex, periodontal status, age, genetic predisposition, medications, and drug variables, increasing the risk for developing GO.

Epidemiology

In a 2017 systematic review, it was reported that the most common drug classes prescribed to hypertensive patients were CCBs; from the available CCBs,

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Table 1: Study characteristics of selected articles between 1980 and 1999

Author	Year	Type of study	Age	Sex	Medical history	Drug used	Dosage	Duration
Ramon *et al.**	1984	Case series	58	Male	History of myocardial infarctions and systemic vascular hypertension	Nifedipine	30 mg/day	5 years
Ramon *et al.**	1984	Case series	51	Female	Rheumatic heart disease	Nifedipine	60 mg/day	4 years
Ramon *et al.**	1984	Case series	65	Male	History of myocardial infarctions and systemic vascular hypertension	Nifedipine	30 mg/day	4 years
Ramon *et al.**	1984	Case series	69	Male	Angina pectoris	Nifedipine	60 mg/day	2 years
Ramon *et al.**	1984	Case series	61	Male	History of coronary bypass surgery and vascular hypertension	Nifedipine	60 mg/day	2 years
Shaftic *et al.**	1986	Case report	61	Male	Hypertension	Nifedipine	30 mg/day	2 months
Seymour *et al.**	1994	Case series	66	Female	Hypertension	Amlodipine	5 mg/day	4 months
Seymour *et al.**	1994	Case series	59	Female	Hypertension	Amlodipine	5 mg/day	6 months
Seymour *et al.**	1994	Case series	35	Male	Hypertension	Amlodipine	10 mg/day	8 months
Harel-Raviv *et al.**	1995	Case report	48	Female	Hypertension	Nifedipine	90 mg/day	Not mentioned
Santi *et al.**	1998	Case series	69	Male	Angina	Nifedipine	30 mg four times a day	18 month
Santi *et al.**	1998	Case series	34	Male	Kidney transplant	1. Cyclosporin 2. Nifedipine	1. 100 mg/day 2. 120 mg/day	Not mentioned

amlodipine was the most commonly prescribed CCB (37%).[10] CCBs have been extensively reported in the literature as being associated with GO [Tables 1-4]. The first report of CCBs associated with GOs was in 1984 by Ramon *et al.* A case series was published reporting five similar cases of patients taking nifedipine regularly and who developed GO [Table 1]. Ramon *et al.* reported the presence of an inflammatory reaction in the nifedipine-induced hyperplasia, which suggests that rigorous hygienic measures might retard its progress and diminish its extent.[1] Since then, many cases have been reported and published in the literature confirming Ramon's hypothesis on the association of nifedipine-induced gingival overgrowth (NIGO). Amlodipine-induced gingival overgrowth (AIGO) is less commonly reported and commonly present clinically several years after administering the drug. The first time it was reported in the literature was in 1994 by Seymour *et al.*[11] who published a case series on three patients receiving 5–10 mg of amlodipine daily [Table 2]. They report that in the three patients described, gingival changes can be observed as early as 3 months after dosage.

Prevalence

According to a randomized controlled trial in 1990, GO occurred in 20–83% of patients taking nifedipine.[8] In 1997, a study by Carty *et al.*[6] reported a 3.3% incidence rate of AIGO, which is significantly less than NIGO. Diltiazem, another CCB, was reported to be associated with GO and reported to have a 74% incidence rate.[12,13] A hospital-based study carried out in 2015 measured the prevalence of CCBs in association with DIGO, in which it was found that the frequency of GO was 75% for nifedipine, 31.4% for amlodipine, and 25% for amlodipine + metoprolol.[14,15] In a 2017 prospective clinical study assessing the prevalence of AIGO, they reported that 76% of the patients were found to have GO.[10] In a 2018 clinical study by Tejnani *et al.*, it was reported that the prevalence rate of amlodipine-induced gingival hyperplasia was 3.4%. These numbers show that the prevalence of DIGO is poorly defined, and more extensive clinical trials are needed. Like Seymour *et al.*[9] reported in 1993, Tejnani *et al.*[16] reported that the GOs were seen in patients taking amlodipine for a minimum of 3 months.

Table 2: Site, nature, histopathology, treatment, and follow-up [continuation of Table 1]

Site of overgrowth	Nature of overgrowth	Histopathological findings	Treatment	Follow-up
Nodular type gingival hyperplasia-marked; site-lower anterior teeth and maxillary bicuspids and molars-buccal side. Ramon *et al.**	Tissues hard to touch, bleeding on probing	Lamina propria showing inflammatory reaction, epithelial hyperplasia and acanthosis	Drug discontinuation, gingivectomy	Recurrence after 2 weeks
Nodular type gingival hyperplasia-marked; site-lower anterior teeth and maxillary bicuspids and molars-buccal side. Ramon *et al.**	Tissues-firm and hard to touch, bleeding on probing	Lamina propria showing inflammatory reaction, epithelial hyperplasia, and acanthosis	Drug discontinuation, gingivectomy, periodontal therapy	No recurrence
Labial side of the lower anterior teeth and the maxillary molars. Ramon *et al.**	Gingiva—reddish and lobular	Lamina propria showing inflammatory reaction, epithelial hyperplasia, and acanthosis	Drug discontinuation	No recurrence
Enlargement diffuse-lower anterior teeth. Ramon *et al.**	Data unavailable	Lamina propria showing inflammatory reaction, epithelial hyperplasia, and acanthosis	Drug discontinuation	No recurrence
Lower and upper teeth-anterior region. Ramon *et al.**	Hyperplasia-nodular type	Inflammatory reaction in the lamina propria, epithelial hyperplasia, and acanthosis	Drug discontinuation	No recurrence
Edematous and bleeding gums Shaftic *et al.**	Bleeding gums and gingival hyperplasia	Data unavailable	Drug discontinuation	9 days (much of the pain and bleeding had resolved). 3 months follow-up no recurrence
Hyperplasia index of 46% and significant probing depth. Seymour *et al.**	Bleeding index of 11 and plaque index of 100%	The overlying epithelium showed acantholytic changes, loose collagen, abundance of matrix	Gingivectomy and maintenance regimen	3 month recall no recurrence
Hyperplasia index of 60% and significant probing depth Seymour *et al.**	Bleeding index of 59 and plaque index of 86%	The overlying epithelium showed acantholytic changes, loose collagen, abundance of matrix	Considerable improvement in gingival conditions after drug therapy changed to bendrofluazide	No recurrence
Hyperplasia index of 53% and significant probing depth. Seymour *et al.**	Bleeding index of 14, plaque index of 46	The overlying epithelium showed acantholytic changes, loose collagen, abundance of matrix	Gingivectomy and maintenance regimen	No recurrence
Labial surface of maxillary anteriors along with interdental papillae. Harel-Raviv *et al.**	False periodontal pockets and slight bleeding on probing	Data unavailable	Drug substitution, periodontal therapy, gingivoplasty, surgical gingivectomy	4 months no recurrence
Not mentioned Santi *et al.**	Data unavailable	Reduction in myxomatous changes, increased inflammatory cells, epithelial parakeratosis with acanthosis and dense collagen	Periodontal therapy, gingivectomy, and gingivoplasty	2, 9, 10, and 11 months follow-up no inflammation and no regrowth of gingiva
Nodular appearance-maxillary and mandibular sextants. Santi *et al.**	Generalized mild-to-moderate periodontitis with significant calculus subgingivally	Reduction in myxomatous changes, increased inflammatory cells, epithelial parakeratosis with acanthosis and dense collagen	Periodontal therapy, gingivectomy	2, 9, 10, and 11 months follow-up no inflammation and no regrowth of gingiva

Table 3: Study characteristics of selected articles between 2000-2021

Author	Year	Type of study	Age	Sex	Medical history	Drug used	Dosage	Duration
Missouris *et al.**	2000	Case report	49	Male	Hypertension and hypercholesterolemia	Nifedipine	60 mg/day	3 years
Routray *et al.**	2003	Case series	45	Male	Data unavailable	Amlodipine	5 mg/day	6 months
Routray *et al.**	2003	Case series	15	Male	Hypertensive	Amlodipine	5 mg/day	4 months
Sachdev *et al.**	2003	Case report	42	Male	Hypertensive	Amlodipine	5 mg/day	3 years
Yoon *et al.**	2006	Case report	63	Male	Hypertension and hypercholesterolemia	Amlodipine	Not mentioned	6 years
Taib *et al.**	2007	Case report	55	Female	Hypertensive	Amlodipine	5 mg daily	Not mentioned
Triveni *et al.**	2009	Case report	50	Female	Hypertensive	Amlodipine	5 mg/day	4 years
Srivastava *et al.**	2010	Case series	47	Female	Hypertensive	Amlodipine	5 mg once daily	7 years
Srivastava *et al.**	2010	Case series	50	Female	Hypertensive	Amlodipine	5 mg once daily	5 months
Srivastava *et al.**	2010	Case series	60	Female	Not mentioned	Amlodipine	5 mg once daily	10 years
Farias *et al.*	2010	Case report	75	Male	Hypertension and history of stroke	Nifedipine	40 mg/day	3 years
Smitha*	2011	Case report	60	Female	Diabetes mellitus type II, hypercholesterolemia, hypertension	Amlodipine	10 mg/day	3 years
Jose *et al.**	2011	Case report	47	Female	Hypertensive	Amlodipine	Data unavailable	7 months
Sharma and Sharma*	2012	Case report	55	Female	Hypertensive for the past 5 years	Amlodipine	5 mg/day	2 years
Fornaini and Rocca*	2012	Case report	75	Male	Hypertensive	Nifedipine	Data unavailable	Several years
Yoshihiro Shibukawa *et al.**	2012	Case report	47	Data unavailable	Diabetic, hypertensive	Nifedipine	Data unavailable	Not mentioned
Sunil *et al.**	2012	Case report	65	Male	Hypertensive	Nifedipine	60 mg daily	3 years
Joshi and Bansa*	2013	Case report	45	Male	Hypertensive	Amlodipine	5 mg daily	1.5 years
El Hawari *et al.**	2013	Case report	59	Male	Hypertension and chronic obstructive pulmonary disease	Nifedipine	Data unavailable	14 months
Sam and Sebastian*	2014	Case report	53	Male	Hypertensive	Amlodipine	20 mg/day	4 years
Tejnani *et al.**	2014	Case report	48	Female	Hypertensive	Amlodipine	10 mg/day	2 years
Vishnusdas *et al.**	2014	Case report	54	Female	Hypertensive	Amlodipine	10 mg/day	2 years
Vekaria *et al.**	2015	Case report	55	Male	Hypertensive	Nifedipine	40 mg/day	18 months
Aral *et al.**	2015	Case report	54	Male	History of kidney transplant, hypertension, for the prevention of thromboembolism as prosthetic heart valve-warfarin (5 mg/day)	Cyclosporin Nifedipine	500 mg/day 30 mg/day	4 years
Mathur *et al.**	2015	Case report	50	Female	Hypertensive	Amlodipine	20 mg/day	5 years

Table 3: Continued

Author	Year	Type of study	Age	Sex	Medical history	Drug used	Dosage	Duration
Madi *et al.**	2015	Case report	48	Male	Hypertensive	Amlodipine	5 mg/day	3 months
Walsh *et al.**	2015	Case report	63	Male	Hypertension, hyperlipidemia	Amlodipine	10 mg once daily	
Kato *et al.**	2015	Case report	88	Female	Hypertension and dementia	Nifedipine	Data unavailable	2 years
Gittaboyina *et al.**	2016	Case report	45	Female	Hypertensive	Amlodipine	5 mg once daily	Not mentioned
Asif *et al.**	2018	Case report	70	Male	Hypertensive	Nifedipine	10 mg/day	7 years
Quenel *et al.**	2018	Case report	56	Male	A monoclonal gammopathy of undetermined significance along with hepatitis C, type II diabetes, renal failure, and hypertension (MGUS)	Amlodipine	10 mg/day	3 years
Gulati *et al.**	2019	Case report	60	Female	Hypertension	Amlodipine	20 mg/day	20 years
Sun *et al.**	2019	Case report	48	Male	Diabetes mellitus type II, hypertension	Felodipine	Data unavailable	4 years ago
Quach and Ray-Chaudhuri*	2020	Case report	72	Female	Squamous cell carcinoma (SCC) of the right floor of mouth-T4 N0 M0 Hypertensive	Amlodipine	Data unavailable	Data unavailable
Uppal *et al.**	2020	Case report	45	Male	Hypertension-secondary, Stage 4 CKD and obstructive uropathy, recurrent renal stones, fibrosis, and hypertrophy	Nifedipine	Data unavailable	4 years
Yolcu *et al.**	2020	Case report	57	Male	Hypertension and diabetes mellitus type II	Amlodipine	10 mg/day	1 year
Morikawa *et al.**	2021	Case report	66	Male	Severe periodontitis along with type 2 diabetes and hypertension-enlargement covering almost the entire teeth	Nifedipine Amlodipine	40 mg/day 10 mg/day	5 years
Castelino *et al.**	2021	Case report	53	Female	Hypertensive	Nifedipine	20 mg/day	5 years

Histopathology

The histopathology for drug-induced GO (DIGO) is consistent, in which the epithelial layers showed elongated rete pegs, proliferation, acanthosis, and parakeratosis. The underlying connective tissue showed an abundance of ground substance, reduced myxomatous changes, pronounced inflammatory cells, and dense collagen bundles with active fibroblasts[5-7] [Table 1]. In an isolated case report on NIGO, they found marked epithelial hyperplasia, acanthosis, and moderate inflammatory reactions in the lamina propria.[1] In a study involving a 53-year-old hypertensive female on 20 mg of nifedipine daily, the patient presented with generalized GO covering almost all of the clinical crowns. The histopathological report presented stratified squamous epithelium with hyperplasia and acantholysis; the underlying fibrocollagenous connective tissue showed dense mixed inflammatory infiltrate with congested blood vessels. Histopathological observations were similar when comparing the first report of DIGO and the most recent report[10] [Tables 2 and 4].

Pathophysiology

The exact mechanism behind DIGO has not yet been determined. However, there have been several theories and experimental hypotheses.[13-17] Two main pathways have been proposed in the literature: an inflammatory and non-inflammatory mechanism[13,18] [Table 5]. According to the literature, the mechanism for GO caused by CCBs was first proposed by Nyska and co-workers in 1994. Nyska proposed that when CCBs are administered orally, their pharmacotherapeutic effect lowers the blood pressure and, in turn, signals the release of renin and angiotensin-converting enzyme.

Table 4: Site, nature, histopathology, treatment, and follow-up [continuation of Table 2A]

Site of overgrowth	Nature of overgrowth	Histopathological findings	Treatment	Follow-up
Generalized enlargements-mandible. Missouris *et al.**	Lobulated/nodular appearance	Gingival fibroblasts contain sulfated mucopolysaccharides secretory granules along with gingival acanthosis, rete peg proliferation	Data uavailable	Data unavailable
Hyperplasia-anterior segment-upper/lower arch. Routray *et al.**	Gingiva was red, glazed, and no bleeding seen	Data unavailable	Data unavailable	Data unavailable
Overgrowth in the maxillary and mandibular arch. Routray *et al.**	Data unavailable	Data unavailable	Drug discontinuation	2 months regression of the gingival hyperplasia
Generalized enlargement-maxillary and mandibular teeth-labial. Sachdev *et al.**	Stippling absent, interdental papillae lobulated and erythematous-firm and resilient gingiva	Data unavailable	Drug substitution, periodontal therapy	1 month no recurrence, regression of GO
Diffuse enlargement labial/buccal surfaces-maxillary and mandibular arches. Yoon *et al.**	Gingiva erythematous and firm	In the underlying tissues, inflammatory cells, lymphocytes, and plasma cells combined with medium-sized atypical cells	Chemotherapy	Death 4 months after diagnosis
Labial/palatal of the maxillary/mandibular arches overgrowth. Taib *et al.**	Bleeding on probing—generalized, poor oral hygiene. Interdental papillae lobulated and inflamed at lower anterior teeth	Irregular fibrous overgrowth with chronic inflammatory cell infiltrate and covered by an intact hyper-parakeratotic and acanthotic stratified squamous epithelium	Periodontal therapy, drug substitution, laser gingivectomy, surgical gingivectomy	Follow-up was done 1–3 months, 2 years after completion of treatment
One-third of maxillary and mandibular anterior teeth-enlargement covering interdental and marginal gingiva. Triveni *et al.**	Gingiva firm and resilient. Margins rolled with loss of scalloping. Color pink and lobulated surface	Few areas of calcifications in the stroma along with inflammatory cell infiltrate	Drug substitution, periodontal therapy, gingivectomy/ gingivoplasty	No recurrence after 3 months
Labial side of the teeth-generalized nodular enlargement. Srivastava *et al.**	Gingiva-consistency-soft and edematous	Dysplasia absent. Hyperplastic squamous epithelium present	Drug substitution, periodontal therapy, surgical gingivectomy	Significant improvement after 12 months
Enlargement covering to middle third of the tooth surface and diffuse. Srivastava *et al.**	Generalized abrasion, staining of teeth, and spontaneous bleeding	Dysplasia absent. Hyperplastic squamous epithelium present	Drug substitution, surgical gingivectomy	Follow-up of 10 weeks showed reduction in inflammation
Generalized gingival enlargement in the maxillary left canine-premolar region. Srivastava *et al.**	Fibrous, pedunculated, 2 × 3 cm soft tissue mass and enlargement generalized	Data unavailable	Drug substitution, periodontal therapy	Follow-up of 2 months showed reduction in enlargement
Interdental papillae predominantly affected and edematous tissues generalized. Farias *et al.**	Probing pocket depths of >6 mm generalized, BOP severe	Data unavailable	Drug substitution, periodontal therapy	11 weeks, marked reduction in GO
Anterior teeth in both maxillary and mandibular teeth-GO on lingual and labial. Smitha*	Mandibular anterior teeth-interdental papillae fibrous, enlarged, and lobulated	The underlying connective tissue dense with numerous collagen bundles interspersed with fibroblasts. Hyperplastic parakeratinized stratified squamous epithelium. Lymphocytes being the predominant cells	Periodontal therapy, drug substitution, surgical gingivectomy	No recurrence after 1 year

Table 4: Continued

Site of overgrowth	Nature of overgrowth	Histopathological findings	Treatment	Follow-up
Generalized overgrowths of the upper and lower jaw. Sharma and Sharma*	Massive inflammation and bleeding of the gums	Data unavailable	Drug substitution	2 weeks symptoms reduced
Generalized deep pockets, fibrous overgrowth exudation on application of digital pressure, and bleeding on probing was noted. Fornaini and Rocca*	Fibrous overgrowth, lobulated papillae, and rolled margins	Hyperkeratinized and proliferating stratified squamous epithelium. Chronic inflammatory infiltrate seen along with bundles of collagen fibers	Drug substitution, gingivectomy	No recurrence after 3 months
Maxillary and mandibular arches, anterior and posterior areas present with gingival overgrowth. Shibukawa *et al.**	Edema, bleeding, inflammation	Data unavailable	CO_2 laser gingivectomy	Several months no relapse
Upper and lower anterior teeth overgrowth seen. Mohan *et al.**	Bleeding on probing and PPD of more than 4 mm	Data unavailable	Drug substitution, periodontal surgery	14-year follow-up no recurrence
Enlarged gingiva right side maxilla and mandible. Joshi and Bansa*	Bulbous enlargement of the gingival mucosa. On palpation, it was non-tender and firm in consistency	Increased plasma cells	Data unavailable	Data unavailable
Mobile teeth in maxillary and mandibular anterior region with swollen and bleeding gums. El-Hawari *et al.**	Diffuse enlargement. Gingiva appears lobulated with scalloping absent. Local irritating factors present	Inflammatory cell infiltrate and few areas of calcifications. Hyperplastic orthokeratinized and parakeratinized stratified squamous epithelium	Drug substitution, periodontal therapy, extractions	Follow-up of 1.5 months showed reduction in inflammatory component
Severe gingival overgrowth that caused shifting of the right lower canine downward and laterally. Sam and Sebastian*	Data unavailable	Data unavailable	Drug substitution	Follow-up 6 months later showed partial resolution
Right side of upper arch-nodular and enlargement generalized in the lower arch. Tejnani *et al.**	Lobulated surface with consistency firm and resilient	Data unavailable	Drug substitution, periodontal therapy	No recurrence after 2 months
Extensive gingival swelling in both maxillary and mandibular. Vishnusdas *et al.**	Gingival bleeding along with probing depth 5–7 mm, loss of scalloping, lobulated, and erythematous	Acanthosis of overlying epithelium and connective tissue hyperplasia	Periodontal therapy, drug substitution, surgical gingivectomy	6 months no recurrence
Distal surface of the upper right canine to the distal surface of upper left central incisor-exophytic sessile circumscribed spherical mass of 1.5 in along with erythema. Vekaria *et al.**	All teeth mobile and non-tender and firm	Dutcher bodies were seen overlying the plasma cell nuclei occasionally and uniform distribution of plasma cells	Extraction of hopeless teeth, surgical excision	5 months no recurrence
Interdental papillae predominantly affected. Aral *et al.**	Sessile base, firm, and nodular in consistency	Blood vessels filled with red blood cells, chronic inflammatory cells, and budding capillaries	Drug substitution, periodontal therapy, internal bevel gingivectomy	4-month follow-up showed a great significant reduction in overgrowth

Table 4: Continued

Site of overgrowth	Nature of overgrowth	Histopathological findings	Treatment	Follow-up
Gingival lesions extended from edentulous maxillary ridge and from mucogingival junction of mandibular arch. Mathur *et al.**	Lobulated surface, firm and resilient and mulberry-shaped	Irregular connective tissue thickness and epithelial proliferation thickness increased	Drug substitution, periodontally weakened teeth were extracted, periodontal therapy, and diode laser-assisted gingivectomy	18 months recall, no relapse
Overgrowth of overlying soft tissue in maxillary and mandibular arches. Madi *et al.**	Spontaneous bleeding on touch, painful, and erythematous in appearance	Inflammatory cell infiltration in connective tissue, and presence of parakeratinized epithelium with acanthosis	Non-surgical periodontal therapy, drug substitution	1 month no relapse
Upper and the lower jaws-diffuse enlargement. Walsh *et al.**	Attached gingiva erythematous, lobulated, and showed bleeding on probing	Data unavailable	Professional debridement with scaling and root planning followed by surgical periodontal treatment for aesthetic and functional reasons	Data unavailable
Pedunculated lump mesial to tooth 1–3 and maxillary anterior and mandible along the canine regions Carty *et al.**	Mucosa overlying intact, mobile, and firm to touch	Marked fibroepithelial overgrowth	Non-surgical periodontal therapy, surgical removal	Data unavailable
Maxillary and mandibular anterior teeth-gingival overgrowth seen. Kato *et al.**	Bleeding on probing, sites of suppuration	Data unavailable	Drug substitution, periodontal therapy	No relapse
Enlarged gums in the lower anterior. Gittaboyina *et al.**	Bleeding on probing and mobility seen. Nodular enlargement of the gums	Thick collagenized bundles with a few blood vessels and focal chronic inflammatory cell aggregations	Periodontal therapy, extraction of hopeless teeth, drug substitution	6 months, no recurrence
Maxillary and mandibular residual alveolar ridges-labial. Asif *et al.**	Firm and nodular	Focal areas of fibrosis with hyperplasia and acantholysis seen in epithelium extending into connective tissue	No drug alteration, external bevel gingivectomy	7 days, 90 days, 180 days and 12 months recall. No recurrence
Enlargements affecting predominant on anterior teeth. Quenel *et al.**	Data unavailable	Epithelial hyperplasia. No dysplastic changes seen. Lymphocytic infiltration predominant with fibrosis seen in chorion	Drug substitution, extraction of mobile teeth	No recurrence after 1 year
Buccal and palatal aspects of maxillary right canine to distal of left lateral-overgrowth. Gulati *et al.**	Nodular, polypoidal mass	Fibrocellular with bundles of collagens in the underlying stroma	Surgical gingivectomy, drug substitution, antibiotic coverage, extraction of hopeless teeth	15 months no recurrence
Gingival overgrowth generalized. Chengxin *et al.**	Bleeding on probing	Data unavailable	Drug substitution	The gingival overgrowth reduced marginally with oral hygiene status improvement visible after 3 months

Table 4: Continued

Site of overgrowth	Nature of overgrowth	Histopathological findings	Treatment	Follow-up
Gingival enlargement in the floor of the mouth. Quach *et al.**	Firm, nodular	Neutrophil polymorphs seen in the underlying stroma	Drug substitution, external bevel gingivectomy	No recurrence
Diffuse swelling involving all the gums. Uppal *et al.**	Mulberry-shaped generalized gingival enlargement nodular papillae-firm-fibrotic consistency	Data unavailable	Drug substitution, periodontal therapy, external bevel gingivectomy, antibiotics regimen	No recurrence 6 months later
Generalized enlargement in both arches. Yolcu *et al.**	Bleeding	Data unavailable	Drug substitution	No recurrence after 2 months
Maxillary and mandibular arches covering all the teeth. Morikawa *et al.**	Hard fibrous swellings	Data unavailable	Drug substitution, periodontal management, external bevel gingivectomy, drug was resumed during periodontal treatment	Significant improvement, periodontal scores improved
Generalized edema of gingival tissues, predominantly involving the interdental papillae. Lorina *et al.**	The enlarged gingiva was firm, non-tender, and pale pink in color	Professional debridement with scaling and root debridement along with surgical periodontal treatment for aesthetic and functional reasons	Extraction of hopeless teeth, periodontal therapy, surgical gingivectomy, drug substitution	6 months no recurrence

Table 5: Proposed mechanisms for the pathogenesis of DIGO

Author	Year	Pathway	Proposed mechanism
Brown *et al.*	1990	Non-inflammatory	Decrease in sodium flux by the drug causes a decrease in cellular folate uptake, which causes collagenase deficiency. The result is connective tissue catabolism, thus DIGH presents clinically
Nyska *et al.*	1994	Non-inflammatory	Increase in ACTH level due to blocking of synthesis in adrenal cortex
Border *et al.*	1994	Non-inflammatory	Upregulation of transforming growth factor-beta 1 (TGF-beta 1) due to inflammation in the gingival crevicular fluid
Van der Vleuten *et al.*	1999	Inflammatory	Presence of concentrated drug in crevicular gingival fluid results in inflammatory effects
Das *et al.*	2000	Inflammatory	Upregulation of keratinocyte growth factor

The angiotensin, which generally would produce aldosterone, is blocked by the calcium ions of the drug, which causes a diversion into another unblocked metabolic pathway. This pathway leads to the overproduction of androgens and adrenocorticotropic hormone (ACTH), which induces hypertrophy of the kidneys. This overproduction in androgens is suggested to act on the gingival tissue and stimulate fibroblast proliferation and collagen production, resulting in GO.[19-23]

Classifications

The classification of GO has been defined in the literature several times over the last century. The most commonly known classifications are Angelopoulos and Goaz Index (1972), hyperplastic index (1985), Bokenkamp classification (1994), and Ingle classification (1999). These classifications vary in their definitions, whether in the nature of the GO or in the direction of overgrowth. Angelopoulos and Goaz[24] described an index that measured the vertical relationship of gingival tissue on the clinical crown: Grade 0: no GO, Grade 1: overgrowth covering cervical third of clinical crown, Grade 2: overgrowth extending to the middle of the clinical crown, Grade 3: overgrowth covering two-thirds of the clinical crown. As defined by Seymour *et al.*[11] in 1994, the hyperplastic index assesses GOs based on their vertical and horizontal relationship with the clinical crown: Grade 0: absent gingival hyperplasia, Grade 1: blunting of margin, Grade 2: hyperplasia less than two-thirds of the clinical crown, Grade 3: hyperplasia more than two-thirds of the clinical

crown. The disadvantage with this index is that it is non-specific and vague. Classifying GOs in this index may be confusing. Bokenkamp's 1994 classification is similar to Seymour's hyperplastic index; however, it is more specific and defined: Grade 0: no sign of gingival enlargement, Grade 1: enlargement confined to the interdental papilla, Grade 2: enlargement involving marginal and papillary gingiva, and Grade 3: enlargement diffused and covering almost the entire crown.[25] The most updated and commonly used index in 2021 is Ingle's 1999 classification, which defined GO in a cohesive and precise manner: Grade 0: no overgrowth, slight stippling, and knife-edge papilla; Grade 1: increase in the density with marked stippling, papilla is rounded, and probing depth is equal to or less than 3 mm; Grade 2: moderate overgrowth, size of the papilla is increased and/or rolled margins, gingival enlargement has a buccolingual dimension of up to 2 mm, probing depth is equal to or less than 6 mm; Grade 3: marked overgrowth, the contour of the margin is convex, enlargement has a buccolingual dimension of approximately 3 mm or more, probing depth is greater than 6 mm, the papilla is retractable; Grade 4: severe overgrowth, thickening of the gingiva, large percentage of the crown is covered, the papilla is retractable, probing depth is greater than 6 mm, and buccolingual dimensions are approximately 3 mm.[26]

Materials and Methods

A broad search of literature published between the years 1980 and 2021 from electronic databases through PubMed Central, Scopus, Cochrane, and SciELO databases was conducted using keywords: Calcium Channel Blockers, Gingival overgrowth, Gingival enlargement, Gingival Hyperplasia. This literature review *includes* case reports and case series. Fifty articles were chosen to be screened further for drug dosage, duration, site, and nature of overgrowth, treatment, and follow-up [Tables 1-4]. The age group of the patients seen in the studies was from 20 to 65 years and comprised both genders.

The search was carried out using the following keywords: Calcium Channel Blockers, Gingival overgrowth, Gingival enlargement, Gingival Hyperplasia. Advanced search incorporating Boolean operators Calcium Channel Blockers AND Gingival overgrowth AND Gingival enlargement AND Gingival Hyperplasia was performed. The data generated were reviewed and any disagreement was resolved through discussion. A flowchart for this review which emphasized the article selection is shown in Figure 1.

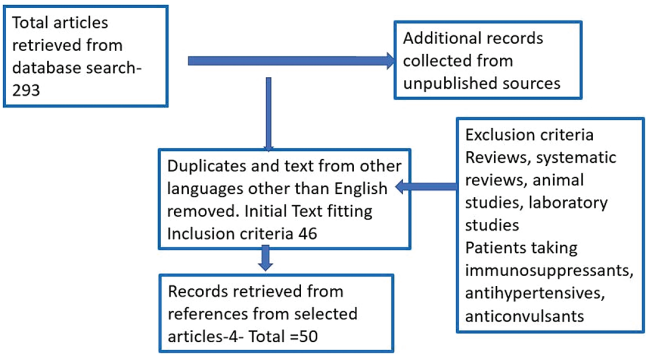

Figure 1: Flowchart for article selection

Inclusion criteria

Case reports and case series which highlighted overgrowth/enlargement and hyperplasia were selected for the study. Studies in which patients had taken any other medications but did not contribute to the overgrowth of the tissue were also considered.

Exclusion criteria

Reviews, systematic reviews, animal studies, *ex-vivo* studies, and other laboratory-based studies were excluded. Studies in which patients were taking immunosuppressants, antihypertensives, and anticonvulsants were discarded.

Results

Approximately 293 publications were found to be related. Further screening identified 46 articles that fulfilled the inclusion criteria. Full texts were evaluated for these articles, and their references were screened for any relevant article. This led to identifying another four articles. Thus, 50 articles met the final inclusion criteria and were considered for this review. Tables 1-4 summarize the study characteristics of case reports and case series of GO caused by CCBs published between 1984 and 2021. A comparative analysis was done regarding histopathology, treatment modalities, drug dosage, and duration to evaluate the differences between cases in 1984–2000 and 2000–2021. The selected studies detailed the clinical presentation and drug history and also performed elaborate follow-ups, but the proposed mechanism for the pathogenesis of drug-induced gingival growth was not adequately proposed.

Discussion

In 1984, Ramon published a series of five cases of NIGO. This was the first reported case of NIGO in the literature. It included five patients between the ages of 51 and 69 with systemic vascular hypertension. The dosage prescribed varied between 30 and 60 mg of nifedipine daily for a duration of 2–5 years. Ramon

reported the nature of the gingival tissues to be firm and relatively hard to touch but bled rather easily on probing and brushing. The histopathological findings of all five cases revealed marked epithelial hyperplasia, acanthosis, and moderate inflammatory reaction in the lamina propria.[1] Since then, there have been many reported cases of NIGO in the literature. It is essential to note the duration of drug consumption and how that affects the outcome of GO. In 1986, Shaftic *et al.*[27] published a case report of a 61-year-old male patient with hypertension who had been using nifedipine 30 mg/day for only 2 months and developed NIGO. Drug discontinuation was the proposed treatment plan, and 9 days later, the bleeding and pain were eliminated. A 3-month recall visit showed no signs of recurrence as well. In 1993, Seymour *et al.*[11] published a case series of three hypertensive patients ranging between 35 and 65 years who took 5–10 mg of amlodipine daily for 4–8 months. They reported that it takes an average minimum of 3 months of drug consumption before gingival changes can be noted.

Several studies attempted drug discontinuation and/or non-surgical periodontal therapy and reported successful results in terms of management.[28] A case series published by Routray *et al*.[29] in 2003 reported a 15-year-old male taking 5 mg of amlodipine daily for hypertension induced by aortoarteritis. The patient reported GOs in the upper and lower arch. It was reported that 4 months after periodontal therapy, there were no signs of inflammation, and 2 months after drug discontinuation, the GOs completely subsided. In 1998, Madi *et al.*[30] reported that the ideal treatment for DIGO is the discontinuation of the drug. However, since then, numerous studies have been reported which took different approaches to regressing GO. A study by Sam and Sebastian[31] reported AIGO in a 42-year-old patient who was taking amlodipine 10 mg daily for hypertension for the past 8–9 years. This patient presented with massive generalized GO, of which the interdental papilla was lobulated, and erythematous. The gingiva was firm and resilient to the touch. Their treatment strategy included periodontal therapy and drug discontinuation, which ultimately led to the subside of the GO. It was reported that surgical intervention would have been necessary if there was a delay in the periodontal management. Another treatment modality introduced in 1973 included the use of an extraoral appliance to regress GO. Srivastava *et al.*[32] created articulated models of silicone and polyethylene, which were placed on the gingiva and teeth at night only. They believed the positive pressure exerted by the appliance could shrink and regress the gingival tissue. Although the model was successful in some patients, there lacks evidence regarding the acceptability of this treatment modality.

Among the reviewed articles, several studies reported drug discontinuation and periodontal therapy as an acceptable method of treatment for DIGO.[3,32] A study reports a 75-year-old male with hypertension and a history of ischemic stroke taking 40 mg of nifedipine daily. In this case report, a conservative treatment plan was made, including oral hygiene instructions, scaling and root surface debridement, and suspension of nifedipine. They reported that at 11 weeks, the GO completely subsided.[3] It is unclear which mode of treatment is considered the gold standard since some articles claim the non-surgical conservative approach to be effective, and others claim that surgical intervention is a necessity in the treatment method. A 2007 case report by Taib *et al.*[33] reported a 55-year-old hypertensive female taking 5 mg of amlodipine daily who presented with massive GO and inflamed/lobulated interdental papillae. Their study reports that periodontal therapy alone without drug intervention can yield satisfactory results. Surgical and CO_2 laser gingivectomies were done to the upper and lower arches without substituting or discontinuing amlodipine. At a 2-year recall visit, the periodontal status was deemed satisfactory, and the patient was sent to a prosthodontist to fabricate an upper and lower removable partial denture. The first time CO_2 laser was introduced in the literature as a DIGO treatment in 1988 by Barak and Kaplan.[34] They reported that with CO_2 laser gingivectomy, post-operative pain and discomfort are significantly reduced, and bleeding is controlled more efficiently. This is especially important with cardiac patients taking CCBs.

According to the literature, DIGO can occur in patients taking any amount of CCBs. No significant difference in GO severity was noted with different doses of CCBs, although a decrease in GO can appear after dose reduction.[34] It is important to note that DIGO cases reported between 1900 and 1999 mainly consisted of patients taking a higher dose of CCBs when compared with the reported cases between 2000 and 2021 [Tables 1-4]. Santi and Bral[35] reported a case of a 34-year-old male patient who had recently undergone a kidney transplant. The patient was on 120 mg of nifedipine and 100 mg of cyclosporin daily. Both these drugs are known to cause GO, so it was very likely that the patient would suffer from DIGO. However, the dosage of both drugs is relatively high, and it is unclear whether the dosage may have contributed to the amount of GO that the patient presented with. In other studies, a dosage of 5 mg of CCBs daily was enough to cause

massive GOs. A 1994 case series by Seymour *et al.*[11] reported three cases taking 5–10 mg of amlodipine daily who presented with significant probing depth and exhibited a gingival hyperplasia index of 46.60%. In all three cases, amlodipine was substituted, and no recurrence was reported in a 3-month recall visit. It can be observed that most of the studies between 2000 and 2021 report massive GOs in patients taking 5–10 mg of CCBs daily [Tables 3 and 4]. In a 2015 case report by Madi *et al.*,[30] a 48-year-old hypertensive male who developed GOs after taking amlodipine 5 mg daily for only 3 months was reported.

Within the literature, histopathology is consistent and similar. A 2015 case report by Vekaria *et al.*[36] reported a 55-year-old hypertensive male patient who had been on 40 mg of nifedipine daily. The histopathology report presented stratified squamous epithelium with hyperplasia and acantholysis, and the underlying fibrocollagenous connective tissue showed congested blood vessels. Similarly, in a 2018 case report of AIGO by Asif *et al.*,[23] they report hyperplastic and acantholytic stratified squamous epithelium with elongated rete peg ridges extending into connective tissue, which was fibrocollagenous and showed focal areas of fibrosis. Infiltration of chronic inflammatory cells and acanthosis was seen, suggesting gingival hyperplasia. Dysplastic changes were not reported in any of the studies. A case series by Srivastava *et al.*[32] reported three cases of AIGO, and in all three cases, they report hyperplastic stratified squamous epithelium without dysplasia. The underlying connective tissue contained scanty inflammatory cells.

Similarly, a 2018 case report by Quenel *et al.*[37] presents a case of AIGO in which their histopathological reports presented epithelial hyperplasia with hyperkeratosis without dysplasia. Several studies reported acanthosis in the epithelial layer with epithelial hyperplasia/parakeratosis. A case series by Santi and Bral[35] reported epithelial parakeratosis with irregular acanthosis, dense collagen, pronounced inflammatory cell infiltrate, reduction in myxomatous changes, and vascularity. Inflammatory cells were present in both their patients. A 2015 case report by Mathur *et al.*[38] reported similar findings of the presence of parakeratinized epithelium with elongated rete pegs and acanthosis and scattered giant cells indicating a superimposed inflammation. The majority of studies also reported the proliferation of fibroblasts and capillaries [Tables 1-4]. Missouris *et al.*[39] reported gingival acanthosis, parakeratosis, rete pegs, proliferation, varying densities of fibroblastic and capillary proliferation, and mononuclear cell aggregations.

Regarding gingival fibroblasts, they reported strongly sulfated mucopolysaccharides in the fibroblasts and numerous secretory granules. Lymphocytic infiltration is also a common feature in the literature. Smitha[40] reported the inflammatory component observed more toward the epithelium, with lymphocytes being the predominant cells.[41] Similarly, Quenel *et al.*[37] also reported fibrosis and lymphocytic infiltration predominant around blood vessels. An abundance of dense collagen fibers interspersed between the blood vessels is also a common feature among DIGO. Taib *et al.*[33] reported irregular fibrous overgrowth composed of collagenous connective tissues with a diffuse chronic inflammatory cell infiltrate and covered by an intact hyperparakeratotic and acanthotic stratified squamous epithelium. Smitha[40] also reported the underlying connective tissue as dense with numerous collagen bundles arranged in a haphazard manner interspersed with fibroblasts. Sharma and Sharma reported that the underlying connective tissue presented bundles of collagen fibers with an admixture of mild chronic inflammatory infiltrate and a small number of blood vessels.[41] Gittaboyina *et al.*[42] also noted thick collagenized bundles with a few blood vessels and a few areas of focal chronic inflammatory cell aggregations in the connective tissue.

There have been a few cases of secondary reactions that were formed after DIGO. A 2014 case report by Vishnudas *et al.*[43] presented a 54-year-old hypertensive female who was on 10 mg of amlodipine daily. She presented with non-tender and firm GOs. All teeth were mobile. The histopathology reports presented parakeratinized stratified squamous epithelium, connective tissue with sheets of plasma cells. The plasma cells were reasonably uniform in appearance, with scattered nucleoli. Occasional Dutcher bodies were seen overlying the plasma cell nuclei. The inflammatory infiltrates also contained varying numbers of neutrophils, lymphocytes, and macrophages. The diagnosis of amlodipine-induced plasma cell granuloma was made, and the gingiva was excised surgically. No recurrence was reported 5 months after treatment. In a similar case, Gulati *et al.*[44] reported a 60-year-old hypertensive female who was on 20 mg of amlodipine daily. She presented with GO as nodular, polypoid masses with a smooth surface. GO was non-tender and non-fluctuant. The histopathological report presented proliferative stratified squamous epithelium. Areas of ulceration were seen. The underlying stroma was fibrocellular with bundles of collagen intersecting, a patchy distribution of chronic inflammatory cells characterized predominantly by mature plasma cells,

suggesting a plasma cell lesion. A diagnosis of AIGO with a secondary reaction of plasma cell granuloma was made, and the lesions were excised surgically, and drug substitution was done. The patient was also put on antibiotics coverage. Fifteen months after treatment, the patient presented with no signs of recurrence. In another case report by Yolcu and Aydogdu,[45] they reported a secondary reaction of myeloid sarcoma with concurrent AIGO. They report a 63-year-old hypertensive male on amlodipine for 6 years. Diffuse, erythematous, and firm lesions were noted on the maxillary and mandibular arches. Histopathological reports presented benign-appearing stratified squamous epithelium, with rete pegs elongated. There were dense aggregates of atypical medium-sized cells combined with smaller numbers of inflammatory cells in the underlying fibrous tissue, including plasma cells and lymphocytes. In a 2017 case report by Ramesh and Sadasivan, they reported a case of oral squamous cell carcinoma masquerading as GO. They reported a 49-year-old male patient who had been on nifedipine for the past 5 years. Palpable, firm, mobile, and nodular submandibular lymph nodes on the left side were observed on extraoral examination. The patient was initially advised to take an intraoral periapical radiograph. Radiographic evaluation showed an extensive bone loss. Histopathological reports showed hyperplastic hyper-parakeratinized stratified squamous epithelium with features of dysplasia. A breach in the continuity of the basement membrane was observed. The underlying connective tissue was densely collagenous and showed abundant keratin pearl formation and neoplastic epithelial cells. Chronic inflammatory infiltrate composed of lymphocytes, plasma cells, and neutrophils was also seen. A well-differentiated squamous cell carcinoma diagnosis was made based on these histopathological findings.[46] Biopsies must be taken to rule out secondary reactions or lesions that mimic other lesions.[47-50]

Some of the limitations in our review was providing treatment guidelines, and associating the required treatment along with histopathological and clinical interpretation seen from most case reports has been a challenge. Secondly, oral hygiene status could not be considered as a variable in our review, due to an element of bias. Clinical studies could have provided more detailed interpretation but again, requirement of a large sample size is needed, which was not seen from the available repositories.

Conclusion

GO caused by the consumption of CCBs has been widely reported in the literature. The management of DIGO varies. However, most studies support drug substitution as the primary form of treatment. The exact pathogenesis of DIGO remains poorly defined by the literature, and more research is required to understand the specific correlation of drugs to GO. Dentists need to take a detailed medical and dental history. This circumvents the possibility of any unwanted outcomes and allows the dentist to provide judicious and evidence-based treatment to the patient.

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Conflicts of interest

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Authors contributions

SRV, MD, MN, AV—Conceptualization, methodology, study design; analysis—interpretation of data and critical revision, manuscript editing, reviewing and final draft, methodology, study design.

Ethical policy and institutional review board statement

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Patient declaration of consent

Not applicable.

Data availability statement

Data of literature are available on appropriate request.

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