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

Marah Damdoum1, Sudhir R. Varma2,3,4, Manjusha Nambiar5, Adith Venugopal4,6

1Department of Periodontics, University of Buffalo, New York, USA, 2Department of Clinical Sciences, College of Dentistry, 3Centre of Medical and Biomedical Allied Health Sciences Research, Ajman University, Ajman, UAE, 4Saveetha Dental College and Hospitals, Chennai, Tamil Nadu, India, 5Department of Periodontics, Sr Rajiv Gandhi College of Dental Sciences and Hospital, Bengaluru, Karnataka, India, 6University of Puthisastra, Phnom Penh, Cambodia

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. Interdisciplinary treatment approaches would provide better outcomes.

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

Received: 25-02-22
Revised: 20-04-22
Accepted: 03-05-22
Published: 29-06-22

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. 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. 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. Seymour et al. 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,
amlodipine was the most commonly prescribed CCB (37%). 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. 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., 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. In 1997, a study by Carty et al. 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. 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. In a 2017 prospective clinical study assessing the prevalence of AIGO, they reported that 76% of the patients were found to have GO. 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. reported in 1993, Tejnani et al. reported that the GOs were seen in patients taking amlodipine for a minimum of 3 months.

| 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 | Not mentioned |
| Santi et al.*                   | 1998            | Case series     | 34      | Male    | Kidney transplant | 1. Cyclosporin 2. Nifedipine | 1. 100 mg/day 2. 120 mg/day | Not mentioned |
| 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/day daily       | Not       |
| 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,      | 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   |
| 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  |
| Tejmani * 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   | Cyclosporin         | 500 mg/day           | 4 years  |
|                         |      |               |     |      | prevention of thromboembolism as prosthetic heart    | Nifedipine         | 30 mg/day            |          |
|                         |      |               |     |      | valve-warfarin (5 mg/day)                             |                    |                      |          |
| Mathur * et al.         | 2015 | Case report   | 50  | Female| Hypertensive                                         | Amlodipine         | 20 mg/day            | 5 years  |
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. In an isolated case report on NIGO, they found marked epithelial hyperplasia, acanthosis, and moderate inflammatory reactions in the lamina propria. 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.

Pathophysiology

The exact mechanism behind DIGO has not yet been determined. However, there have been several theories and experimental hypotheses. Two main pathways have been proposed in the literature: an inflammatory and non-inflammatory mechanism. 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.
| 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 unavailable                   | 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                      | Drug discontinuation                                                                                                                                  | 2 months regression of the gingival hyperplasia | 1 month no recurrence, regression of GO |
| 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 | Drug substitution, periodontal therapy |
| 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 Irregular fibrous overgrowth with chronic inflammatory cell infiltrate and covered by an intact hyper-parakeratotic and acanthotic stratified squamous epithelium | 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, periodontal therapy, 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 parakeratized stratified squamous epithelium. Lymphocytes being the predominant cells | Periodontal therapy, drug substitution, surgical gingivectomy | No recurrence after 1 year          |
| 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  | Fibrous overgrowth, lobulated papillae, and rolled margins                            | Hyperkeratinized and proliferating stratified squamous epithelium.                       | Drug substitution,      | No recurrence after 3 months                        |
| pressure, and bleeding on probing was noted. Fornaini and Rocca*                 |                                                                                      | Chronic inflammatory infiltrate seen along with bundles of collagen fibers               | gingivectomy            |                                                     |
| Maxillary and mandibular arches, anterior and posterior areas present with gingival| Edema, bleeding, inflammation                                                       | Data unavailable                                                                       | CO₂ laser gingivectomy  | Several months no relapse                           |
| overgrowth. Shibukawa et al.*                                                    |                                                                                      |                                                                                          |                         |                                                     |
| Upper and lower anterior teeth overgrowth seen. Mohan et al.*                    | Bleeding on probing and PPD of more than 4 mm                                        | Data unavailable                                                                       | Drug substitution,      | 14-year follow-up no recurrence                     |
|                                                                                  |                                                                                      |                                                                                          | periodontal surgery     |                                                     |
|                                                                                  |                                                                                      |                                                                                          |                         |                                                     |
| Enlarged gingiva right side maxilla and mandible. Joshi and Bansa*               | Bulbous enlargement of the gingival mucosa. On palpation, it was non-tender and firm  | Increased plasma cells                                                                  | Data unavailable         | Data unavailable                                    |
|                                                                                  | in consistency                                                                       |                                                                                          |                         |                                                     |
|                                                                                  | Diffuse enlargement. Gingiva appears lobulated with scalloping absent, Local        | Inflammatory cell infiltrate and few areas of calcifications. Hyperplastic orthokeratinIZED | Drug substitution,      | Follow-up of 1.5 months showed reduction in         |
|                                                                                  | irritating factors present                                                           | and parakeratinized stratified squamous epithelium                                      | periodontal therapy,    | inflammatory component                              |
|                                                                                  |                                                                                      |                                                                                          | extractions             | Follow-up 6 months later showed partial resolution  |
|                                                                                  |                                                                                      |                                                                                          |                         |                                                     |
|                                                                                  |                                                                                      |                                                                                          |                         |                                                     |
| Severe gingival overgrowth that caused shifting of the right lower canine         | Data unavailable                                                                      | Data unavailable                                                                       | Drug substitution       | No recurrence after 2 months                        |
| downward and laterally. Sam and Sebastian*                                       | Lobulated surface with consistency firm and resilient                                 |                                                                                          |                         |                                                     |
|                                                                                  |                                                                                      |                                                                                          | Drug substitution,      | No recurrence after 2 months                        |
|                                                                                  | Ginval bleeding along with probing depth 5–7 mm, loss of scalloping, lobulated, and  | Acanthosis of overlying epithelium and connective tissue hyperplasia                     | periodontal therapy,    |                                                     |
|                                                                                  | erythematous                                                                         |                                                                                          | drug substitution,      | 6 months no recurrence                              |
|                                                                                  | All teeth mobile and non-tender and firm                                              |                                                                                          | surgical gingivectomy   |                                                     |
|                                                                                  |                                                                                      |                                                                                          |                         |                                                     |
|                                                                                  |                                                                                      |                                                                                          |                         |                                                     |
| Extensive gingival swelling in both maxillary and mandibular. Vishnusdas          | Sessile base, firm, and nodular in consistency                                        | Blood vessels filled with red blood cells, chronic inflammatory cells, and budding     | Drug substitution,      | 4-month follow-up showed a great significant        |
| et al.*                                                                          |                                                                                      | capillaries                                                                             | periodontal therapy,    | reduction in overgrowth                            |
|                                                                                  |                                                                                      |                                                                                          | internal bevel gingivectomy|                         |
|                                                                                  |                                                                                      |                                                                                          |                         |                                                     |
| 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.*                                                    |                                                                                      |                                                                                          |                         |                                                     |
|                                                                                  |                                                                                      |                                                                                          |                         |                                                     |
| Interdental papillae predominantly affected. Aral et al.*                         |                                                                                      |                                                                                          |                         |                                                     |

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 Attached gingiva erythematous, lobulated, and showed bleeding on probing | 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.*                      | Lobulated surface, firm and resilient and mulberry-shaped                            | Irregular connective tissue thickness and epithelial proliferation thickness increased       | Drug substitution, periodontal therapy                                        | Data unavailable |
| Overgrowth of overlying soft tissue in maxillary and mandibular arches. Madi et al.* | Attached gingiva erythematous, lobulated, and showed bleeding on probing              | Data unavailable                                                                        | Drug substitution, periodontal therapy                                        | Data unavailable |
| Pedunculated lump mesial to tooth 1–3 and maxillary anterior and mandible along the canine regions Carty et al.* | Spontaneous bleeding on touch, painful, and erythematous in appearance Attached gingiva erythematous, lobulated, and showed bleeding on probing | Data unavailable                                                                        | Drug substitution, periodontal therapy                                        | 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                | Data unavailable                                                                        | Drug substitution, periodontal therapy                                        | 6 months, no recurrence |
| Maxillary and mandibular residual alveolar ridges-labial. Asif et al.*            | Firm and nodular                                                                     | Data unavailable                                                                        | Drug substitution, periodontal therapy                                        | 7 days, 90 days, 180 days and 12 months recall. No recurrence after 1 year |
| 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 |
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.

---

**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 | 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 debrideament 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 |
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. 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.

**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.

**Inclusion Criteria**

Case reports and case series which highlighted overgrowth/enlargement and hyperplasia were selected for the study. Cases 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.\[11\] 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.[\textsuperscript{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.[\textsuperscript{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.[\textsuperscript{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.[\textsuperscript{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\[\textsuperscript{31}\] 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.[\textsuperscript{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.[\textsuperscript{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\textsubscript{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\textsubscript{2} laser was introduced in the literature as a DIGO treatment in 1988 by Barak and Kaplan.\[34\] They reported that with CO\textsubscript{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[\textsuperscript{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 epithelium, a patchy distribution of chronic inflammatory cells characterized predominantly by mature plasma cells,
suggested 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, they reported a secondary reaction of myeloid sarcoma with concurrent AIGO. They reported 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 AIGO. 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. Biopsies must be taken to rule out secondary reactions or lesions that mimic other lesions.

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.
severe chronic periodontitis and nifedipine-induced gingival overgrowth. Bull Tokyo Deni Coll 2012;53:91-9.

9. Seymour RA, Ellis JS, Thomason JM. Risk factors for drug-induced gingival overgrowth. J Clin Periodontol 2000;27:217-23.

10. Wang AL, Iadeola C, Wang G. New generations of dihydropyridines for treatment of hypertension. J Geriatr Cardiol 2017;14:67-72.

11. Seymour RA, Ellis JS, Thomason JM, Monkmann S, Idle JR. Amlodipine-induced gingival overgrowth. J Clin Periodontol 1994;21:281-3.

12. Brown RS, Sein P, Corio R, Bottomley WK. Nifedipine-induced gingival hyperplasia. First case report. Oral Surg Oral Med Oral Pathol 1990;70:593-6.

13. Klar LA. Gingival hyperplasia during Dilantin therapy: A survey of 312 patients. J Publ Health Dent 1973;33:180-5.

14. Gopal S, Joseph R, Santhosh VC, Kumar VV, Joseph S, Shete AR. Prevalence of gingival overgrowth induced by antihypertensive drugs: A hospital-based study. J Indian Soc Periodontol 2015;19:308-11.

15. Jayanthi R, Kalifa AM, Archana BM, Jayachandran S, Varghese F. Prevalence and severity of amlodipine induced gingival overgrowth. Int J Contemp Med Res 2017;4:377-9.

16. Tejnani A, Gandevivala A, Bhanushali D, Gourkhede S. Combined treatment for a combined enlargement. J Indian Soc Periodontol 2018;18:516-9.

17. Conlin PR, Williams GH. Use of calcium channel blockers in hypertension. Adv Intern Med 1998;43:533-62.

18. Border WA, Noble NA. Transforming growth factor beta in tissue fibrosis. N Engl J Med 1994;331:1286-92.

19. van der Vleuten CJ, Trijbels-Smeulders MA, van de Kerkhof PC. Hypotheses 1994;43:115-8.

20. Border WA, Noble NA. Transforming growth factor beta in tissue fibrosis. N Engl J Med 1994;331:1286-92.

21. Brown RS, Beaver WT, Bottomley WK. On the mechanism of drug-induced gingival hyperplasia. J Oral Pathol Med 1991;20:201-9.

22. Border WA, Noble NA. Transforming growth factor beta in tissue fibrosis. N Engl J Med 1994;331:1286-92.

23. Asif SM, Shaik N, Barthunia B, Kaleem SM, Zakirulla M, Das SJ, Olsen I. Keratinocyte growth factor is upregulated by the hyperplasia-inducing drug nifedipine. Cytokine 2000;12:1566-9.

24. Damdoum, et al.: Calcium blockers induced GO

25. Bökenkamp A, Bohnhorst B, Beier C, Albers N, Offner G, Brodehl J. Nifedipine aggravates cyclosporine A-induced gingival hyperplasia. Pediatr Nephrol 1994;8:181-5.

26. Ingle E, Rossmann JA, Caffesse RG. New clinical index for drug-induced gingival overgrowth. Quintessence Int 1999;30:467-73.

27. Shafic AA, Widup LL, Abate MA, Jacknowitz AI. Nifedipine-induced gingival hyperplasia. Drug Intell Clin Pharm 1986;20:602-5.

28. Sun L, Wang C, Xi S, Zhou T, Wang G, Gang X. Felodipine-associated gingival overgrowth in a type 2 diabetic patient: A case report and literature review. Exp Ther Med 2019;17:3399-402.

29. Routray SN, Mishra TK, Pattanaik UK, Satapathy C, Mishra CK, Behera M. Amlodipine-induced gingival hyperplasia. J Assoc Physicians India 2003;51:818-9.

30. Madi M, Shetty SR, Babu SG, Achalli S. Amlodipine-induced gingival hyperplasia—A case report and review. West Indian Med J 2015;64:279-82.

31. Sam G, Sebastian SC. Nonsurgical management of nifedipine induced gingival overgrowth. Case Rep Dent 2014;2014:741402.

32. Srivastava AK, Kundu D, Bandyopadhyay P, Pal AK. Management of amlodipine-induced gingival enlargement: Series of three cases. J Indian Soc Periodontol 2010;14:279-81.

33. Taib H, Ali TBT, Kamin S. Amlodipine-induced gingival overgrowth: A case report. Arch Otorhinolaryngol 2007;2:61-4.

34. Barak S, Kaplan I. The CO2 laser in the excision of gingival hyperplasia caused by nifedipine. J Clin Periodontol 1988;15:633-5.

35. Santi E, Bral M. Effect of treatment on cyclosporine- and nifedipine-induced gingival enlargement: Clinical and histologic results. Int J Periodont Restorative Dent 1998;18:1424-31.

36. Vekaria A, Sheth T, Shah S, Shah M. Nifedipine-induced gingival enlargement—A systematic treatment approach: A case report. J Adv Oral Res 2015;6:49-52.

37. Quelen L, Kerbin P, Giran G, Tessier MH, Lesclous P. Amlodipine-induced gingival enlargement: A case report. J Stomatol Oral Maxillofac Surg 2020;121:308-11.

38. Mathur S, Khatri RK, Mathur R, Srivastav, R. Nag BP. Drug-induced gingival overgrowth: A rare case report. J Clin Diagn Res 2015;9:ZD31.

39. Missouri GG, Kalaitzidis RG, Cappuccio FP, MacGregor GA. Gingival hyperplasia caused by calcium channel blockers. J Hum Hypertens 2000;14:155-6.

40. Smitha K. Amlodipine-induced gingival overgrowth in a patient with uncontrolled type 2 diabetes mellitus with hypercholesterolemia: A case report. Clin Adv Periodontol 2012;2:115-22.

41. Sharma S, Sharma A. Amlodipine-induced gingival enlargement—A clinical report. Compend Contin Educ Dent 2012;33:e78-82.

42. Gittaboyina S, Mana TK, Koduguri RR, Reddy PVN. Amlodipine induced gingival enlargement. J Oral Res Rev 2016;8:23.

43. Vishnudas B, Sameer Z, Shriram B, Rekha K. Amlodipine induced plasma cell granuloma of the gingiva: A novel case report. J Nat Sci Biol Med 2014;5:472-6.

44. Gulati R, Ratre MS, Khetarpal S, Varma M. A case report of a gingival plasma cell granuloma in a patient on antihypertensive therapy: Diagnostic enigma. Front Dent 2019;16:144-8.

45. Yolcu A, Aydogdu I. Amlodipine-induced gingival hypertrophy. Eur J Intern Med 2020;78:127-8.

46. Ramesh R, Sadasivan A. Oral squamous cell carcinoma masquerading as gingival overgrowth. Eur J Dent 2017;11:390-4.

47. Sunil PM, Nalluswami JS, Sanghar SJ, Joseph I. Nifedipine-induced gingival enlargement: Correlation with dose and oral hygiene. J Pharm Bioallied Sci 2012;4:S191-3.

48. Uppal J, Trivedi H, Gupta ND, Bey A. Periodontal management of severe periodontitis and generalized gingival enlargement in a patient with chronic renal failure. J Indian Soc Periodontol 2020;24:284-8.

49. El Hawari M, Alameddine S, Gill T, Hussain M. Medication-induced gingival overgrowth. Kansas J Med 2013;6:80-1.

50. Jose J, Santhosh YL, Naveen MR, Kumar V. Case report of amlodipine induced gingival hyperplasia—Late onset at a low dose. Asian J Pharm Clin Res 2011;4:65-6.