Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/20679
DOI URL: http://dx.doi.org/10.21474/IJAR01/20679

RESEARCH ARTICLE

UNDERSTANDING DRUG-INFLUENCED GINGIVAL OVERGROWTH: MECHANISMS, MANAGEMENT, AND IMPLICATIONS

Sirsha Bhattacharjee, Ashish Kaur, Jinay Sathwara, Sona Sheth, Ankita Patel and Harjot Kaur

Manuscript Info

Manuscript History
Received: 25 January 2025
Final Accepted: 28 February 2025
Published: March 2025

Key words:-
Drug Induced Gingival Overgrowth, Gingival Enlargement, Anticonvulsants, Calcium Channel Blockers, Immunosuppressants

Abstract

Drug influenced gingival enlargement is the one of the most undesirable and adverse effects of systemic medication on the periodontal tissues affecting a patient's mastication, aesthetics, maintenance of oral hygiene, and the overall well-being of the patient. It is attributed mainly to three classes of drugs which comprise of anticonvulsants, calcium channel blockers and immunosuppressants. The pathophysiologic mechanisms responsible for drug influenced gingival overgrowth (DIGO) can be divided into biochemical and inflammatory pathways that alter the cation influx inhibiting folate absorption accompanied by the alteration in the production of inflammatory cytokines and interaction of chemotactic factors. Ultrastructural studies demonstrate that the increase in gingival tissue volume is primarily due to a connective tissue response rather than the epithelial cell layer involvement, wherein the main cell that is targeted is the gingival fibroblast, that is responsible for elevated levels of collagen synthesis and the decrease in its turnover rate. Comprehensive management of gingival enlargement is multi-disciplinary in nature and the dentist along with the physician, should emphasize on treatment that provides superlative functional and aesthetic outcome for the patient.

Introduction:-

Owing to the underlying pathology, gingival enlargement was previously termed as 'hypertrophic gingivitis' and/or 'gingival hyperplasia'; however, as these terms describe the histological features and require a microscopic analysis of the tissue, they are not accurate clinical descriptions of gingival enlargement and are thus, now obsolete. The term gingival enlargement, includes a perplexing array of clinical conditions in which gingival overgrowth (GO) may be confined to a few teeth in a localized and discrete manner or it may affect the entire dentition. While one of its most common etiological factors may be a result of plaque accumulation that culminates into inflammation like many other periodontal pathologies, it may also be an outcome of underlying systemic conditions, numerous drugs, nutritional deficiencies, trauma, neoplasms or even remain unexplained to the physician as an idiopathic condition [1].

Drug influenced enlargement is attributed mainly to three classes of drugs which comprise of anticonvulsants, calcium channel blockers and immunosuppressants (Table 1). In earlier literature, the term 'drug-induced gingival enlargement' (DIGE) was used frequently to denote the direct causal relationship between the drug and gingival

Corresponding Author:- Sirsha Bhattacharjee

enlargement. However, in the 2017 World Workshop, this term was revised to 'drug-influenced gingival enlargement' [2] highlighting the underlying fact that both plaque bacteria in conjunction with the drug are imperative to elicit such an exaggerated gingival response. Nonetheless, not all individuals who are prescribed these medications will necessarily develop enlargement of the gingival tissues, suggesting a susceptibility requiring specific genotypic and immunologic characteristics of the host, substantiating the complex pathogenesis of this condition. This article aims to shed light on one of the most frequently encountered hostile reactions of drugs on the periodontium i.e. drug induced gingival overgrowth.

Table 1:- Drugs that are documented to cause gingival enlargement.

CALCIUM CHANNEL BLOCKERS	Amlodipine, Felodipine, Nifedipine, Manidipine, Nitrendipine, Nimodipine, Diltiazem, Verapamil
ANTI-EPILEPTIC DRUGS	Phenytoin, Phenobarbitone, Methosuxinimide, Levitiracetam, Gabapentin, Sodium valproate, Ethotoin, Carbamezapine, Vigabatrin, Topiramate, Primidone
IMMUNOSUPPRESSIVE DRUGS	Cyclosporine, Sicrolimus, Tacrolimus, Mycophenolate mofetil
MISCELLANEOUS	Erythromycin, Estradiol, Lisinopril, Propanolol, Atenolol, Lynestrenol

Multifactorial Pathophysiology of DIGO

The pathophysiologic mechanisms responsible for DIGO can be divided into biochemical (non-inflammatory) and inflammatory pathways (Figure 1) [3].

1. Inhibitory effect of sodium/calcium ion influx upon cation channel mechanisms
2. Defective collagenase activity due to decreased uptake of folic acid

The inflammatory pathways include:

1. Alteration in the production of inflammatory cytokines and interaction of chemotactic factors
2. Immunological changes and inflammatory process

In the complex pathophysiology of DIGO, mutual interactions between cellular and extracellular components are modulated by age, genetic predisposition, pharmacokinetic variables, alterations in gingival connective tissue homeostasis, pre-existing dental plaque and gingival inflammation, all of which determine the development of drug-induced lesion. The DIGO pathology is likely to be driven primarily by indirect effects of drugs that interact with innate and acquired immune responses mediated by a vast array of cytokines. Disturbed immune system functions associated with tissue specific responses of gingival cells can drive epithelial–mesenchymal transition (EMT) and extracellular matrix (ECM) remodeling, which result in the observed tissue abnormalities.

Role of Genetics

The availability of diagnostic aids has seen a quantum jump during the last decade in the identification of patients at risk to drug induced gingival overgrowth. In the forefront today, in fact leading the way, is genetics and genetic studies that have enabled the identification of gene mutations, which make patients susceptible to gingival overgrowth, secondary to drug use. A genetic factor that may relate to the expression of drug-induced gingival overgrowth is shown in studies of the human lymphocyte antigen (HLA). Pernu et al. found that patients who expressed HLA-DR1 appeared to have a protective role against gingival overgrowth from cyclosporin A, whereas those expressing HLA-DR2 showed an increased risk for overgrowth [4]. A recent study by Iacopino et al. revealed that platelet-derived growth factor B messenger RNA is significantly increased in cyclosporin A gingival overgrowth tissue relative to normal controls and independent of the inflammatory state [1]. It has been shown that patients with the genotype C 807 showed lower expression of integrins and those with GO had a higher frequency of the allele 807 C, suggesting that the integrin has a critical role in the induction of drug-induced GO [5]. Pharmacogenetic influences on drug metabolism have been widely reviewed and gene polymorphism of cytochrome P450 2C19 appeared to be responsible for much of the interindividual variability on drug elimination and therefore the half of the drug in the body[6].

Diagnosis and Evaluation

The diagnosis of drug-induced gingival overgrowth is made by extensive clinical examination along with the patient's past medical history, radiographic examination, and histopathological examination, if required [7]. Patients

with DIGO may report a past medical history of hypertension, angina, epilepsy, a recent organ transplant or even the combination of these comorbidities. The presence of other confounding systemic disorders apart from the primary condition for which the drug is taken, for instance, diabetes, should also be evaluated as they aid the clinician in evaluating the risk assessment of the patient.

There are numerous methods to assess and determine the severity of gingival overgrowth, out of which indices are the most frequently used simplistic measures. In order to tailor a comprehensive treatment plan, the operator must recognize the extent of the vertical and the horizontal components of the enlargement along with its etiopathogenesis. While earlier indices focused mainly on the vertical component of the enlargement, highlighting the percentage of crown covered by the overgrowth, novel indices emphasize both on the horizontal as well as vertical components of the overgrowth.

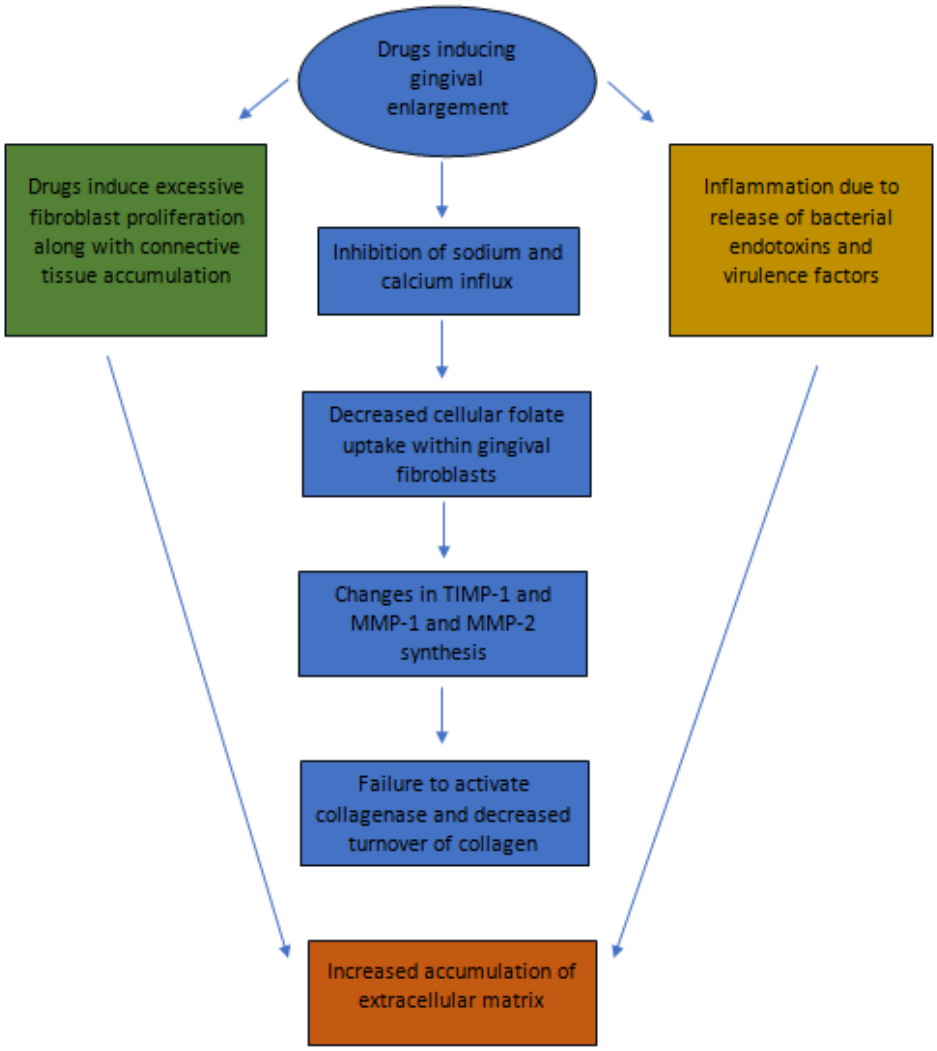


Fig 1:- Pathophysiologic mechanisms of DIGO.

Differential Diagnosis

A thorough evaluation of the patient allows the operator to eliminate differential diagnoses of enlargement which could clinically resemble DIGO including familial or hereditary conditions like familial fibromatosis, idiopathic enlargement, pseudo enlargement due to underlying osseous involvement, conditioned enlargement due to systemic diseases like leukemia, and other physiologic conditions like puberty and pregnancy [8].

Clinical features

Clinical manifestation of gingival enlargement frequently appears within 1 to 3 months after initiation of treatment with the associated medications[9]. Gingival overgrowth in drug induced enlargement begins as a painless beadlike enlargement of the interdental papillae and extends to the facial and lingual margins. As the condition progresses, the marginal and papillary enlargements unite; they may develop into a massive tissue fold covering a considerable portion of the crowns causing interference with occlusion and masticatory functions [10]. The enlargement is usually generalized throughout the mouth but is more severe in the maxillary and mandibular anterior regions [11]. Furthermore, the growth can be appreciated more on the labial surface of the dentition and in the interdental areas.The clinical observation that DIGO usually begins in the interdental papillae can be explained by the theory that the interdental papillae provide a more suitable nidus for GO to develop [12]. Hyperplasia of the mucosa in edentulous mouth has been reported but is comparatively rare [13].

When uncomplicated by inflammation, the lesion is mulberry shaped, firm, pale pink and resilient, with a minutely lobulated surface and no tendency to bleed [14]. The enlargement is limited to the keratinized portions of the gingiva, and characteristically appears to project from beneath the gingival margin, from which it is separated by a linear groove. In severe cases, when the enlargement extends to attached gingiva, a loss of scalloping is observed [10]. Typically, however, the condition is described to cause 'pseudo' pockets due to enlargement of gingiva from beneath the gingival margin with an increase in the probing depths and little or no clinical attachment loss [15].

Drug influenced enlargement may occur in mouths with little or no plaque and may be absent in mouths with abundant deposits indicating the possibility of a genotypic influence on the host underlying the pathophysiology of the condition. However, the presence of the enlargement complicates plaque control often resulting in a secondary inflammatory process that synergistically acts on the gingival overgrowth caused by the drug. Inflammatory changes not only add to the size of the lesion but also produce a red or bluish-red discoloration of gingiva, obliterate the lobulated surface demarcations, and result in an increased tendency towards bleeding [16].Ikawa et al. described the lesion as being shiny and erythematous in areas where greater accumulation of dental plaque was observed [17]. Cases complicated by inflammation present with spontaneous gingival bleeding, clinical attachment loss, bone loss as well as mobility in advanced cases[18].

Immune-inflammatory features associated with DIGO include increased macrophage reparative/proliferative phenotype, up-regulation of essential GF, IL-1β, and IL-6 cytokines, and variable lymphocyte proportions. Histologically speaking, it is important to note the proportions of fibrosis and inflammation with respect to the drug used: phenytoin causes moderate inflammation and high fibrosis, nifedipine produces moderate inflammation and fibrosis, whilst cyclosporine leads to intense inflammation and low fibrosis. It is possible that gingival enlargement produced by cyclosporine presents a very pronounced immune response with some moderate antifibrotic effects in the synthesis and deposition of collagen.

Histopathology

The histological picture of DIGO includes cellular as well as extracellular changes which account for the marked increase in size and morphological changes in gingiva. It is characterized by hyperplasia in the junctional epithelium and hypertrophy of keratinized epithelium. The classic feature of DIGO includes elongation of epithelial rete pegs deep into the connective tissues underlying the epithelial layer. The lamina propria shows fibrosis with variable fibroblasts, infiltration of inflammatory cells, increased vascularity, and an amorphous ground substance with elevated levels of glycosaminoglycans (GAGs) [19,20]. Although the histological features of all drug-associated gingival overgrowth are comparable to a certain extent, variations in the histology of enlargement induced by different classes of drugs are attributed to their diverse chemical structures and properties.

DIGO is a pathology which is characterized by increased deposition of extracellular matrix components particularly interstitial collagen accompanied by an alteration in the collagen turnover rate. The enlargement begins as a hyperplasia of the connective tissue core of the marginal gingiva and increases by its proliferation and expansion beyond the crest of the gingival margin. The connective tissue consists of excess collagen, but has relatively few fibroblasts and blood vessels.

Kantor and Hassell (1983) reported an increased accumulation of sulfated GAGs and noted that this finding could be related either to increased synthesis or decreased catabolism [21]. Enlarged fibroblasts appear to alternate with thin and thick collagen fibrils.Furthermore, major differences in gingival fibroblasts subpopulations was noted

confirming the heterogeneity of gingival fibroblasts in which they termed responders as fibroblasts that were altered to the effect of the drug administration and non-responders which remained unaltered in the presence of the drug. McKevitt et al. used fibroblasts from responders and non-responders to study the effect of phenotypic differences in growth, matrix synthesis and response to nifedipine [22]. The responder cells presented increased growth potential and produced greater levels of protein and collagen than did non-responder cells.

Complications associated with DIGO

Apart from the routine clinical findings, the patient may also present with various complications that can manifest with drug-induced gingival overgrowth. In the early stages, the gingival enlargement appears to be painless; however, in more advanced cases, it can cause considerable discomfort during mastication as well as in the routine maintenance of oral hygiene resulting in increased incidence of caries and halitosis. Due to the increased bulk of the connective tissue that continuously applies force on the teeth, pathologic migration of teeth is a commonly encountered intraoral finding in such patients which simultaneously poses esthetics concerns.

A Non-Surgical Approach to DIGO

The first phase of any periodontal treatment plan is to reduce and control identifiable risk factors combined with scaling and root planing as this isimperative in the management of drug influenced gingival enlargement given the heightened response to dental biofilm found in these patients [23]. It has been substantiated in numerous studies that the addition of an inflammatory component exacerbates the pathology as well as complicates the management of DIGO. Intraoral features that increase the challenge of maintaining optimal plaque control should be modified or eliminated which may include the replacement of over contoured restorations and the modification of prostheses or appliances to minimize gingival irritation. Mild to moderate cases of gingival enlargement may even regress with frequent professional mechanical plaque removal and rigorous home care regimen without the need for further surgical intervention. Therefore, it is imperative to emphasize on preventive approaches that call for routine dental visits, frequent oral prophylaxis alongwith oral hygiene reinforcement from the time of commencement of the medication[24].

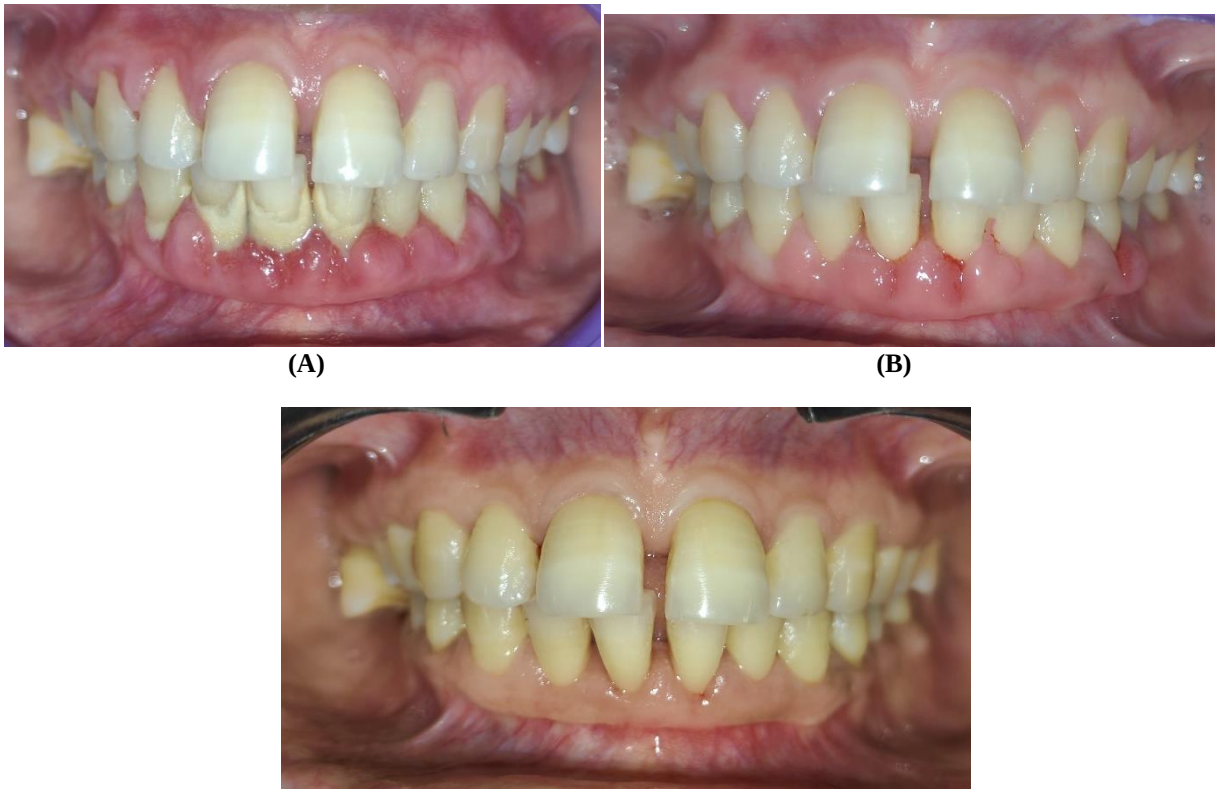
Reducing the dose or providing suitable drug substitution often brings about partial or complete regression of the lesion, but should be considered only after a physician's consultation. It may not be not practically possible to completely discontinue the offending drug, but alternate substitution of the drug may be a possibility with the advent of newer generations of drugs (Table 2). If any drug substitution is attempted, a time period of 6- to 12-month should be stalled between discontinuation of the offending drug and substitution with an alternative drug.

Another such method of non-surgical approach includes full mouth disinfection (FMD). The aim of full-mouth disinfection approach is to eradicate, or at least suppress, all periodontal pathogens in a very short time span, not only from the periodontal pockets but also from the entire oropharyngeal cavity (mucous membranes, tongue, tonsils, and saliva) [25] as well to reduce the intraoral translocation of periodontopathogens. In a study conducted by Pundir et al. applying the FMD regime in patients with drug-induced GO resulted in a statistically significant reduction of the GO and concomitantly the pocket probing depths [26].

Table 2:- Alternative drugs for drug substitution therapy to treat DIGO.

DRUG	ALTERNATIVE DRUGS
Phenytoin	Vigabatrin, Lomatrigine, Gabapentin, Topiramate, Sulthiame
Nifedipine, Amlodipine	Verapamil, Diltiazem, Isradipine, Captopril, Monoxdine
Cyclosporine	Tacrolimus, Mycophenolate mofetil, Rapamycin, Azathioprine

Local or systemic antibiotics may be effective in reducing or eliminating drug–associated gingival alterations when plaque–associated inflammation is present due to the reduction in the bacterial load in the gingival sulcus, consequently diminishing the inflammatory component in individuals with gingival enlargement. Several case reports have indicated that by blocking cyclosporine A-induced cell proliferation and collagen synthesis and by activating MMP-2 in gingival fibroblasts, azithromycin reduced gingival overgrowth of patients with cyclosporine A-induced gingival overgrowth whereas metronidazole significantly reduced the anaerobic bacterial load. However, potential side effects associated with long–term or extended use of antibiotics should be taken into consideration.



(A) **(B)**

(C)

Fig 2:- (A) Amlodipine influenced gingival enlargement complicated by secondary inflammation due to poor plaque control **(B)** After Phase I periodontal therapy **(C)** Resolution of gingival enlargement after scaling and root planing combined with drug substitution 6 months postoperatively.

A patient centric approach in DIGO

In the holistic management of DIGO, it is crucial for medical practitioners, being the primary healthcare givers, to be aware and thorough regarding the effects of their prescribed medications on the periodontium. Patients should be informed of the periodontal implications of the drug in the long run and emphasis should be placed on the importance of a dental checkup at least twice in the first 3 months after drug therapy is initiated. Patients should be counselled by the dentists regarding the treatment modalities in DIGO including a possibility for drug cessation or substitution, as deemed necessary by the physician and surgical intervention if needed. Moreover, the importance of meticulous oral hygiene and routine recall visits should be accentuated to patients to improve the overall periodontal prognosis.

Surgical approach

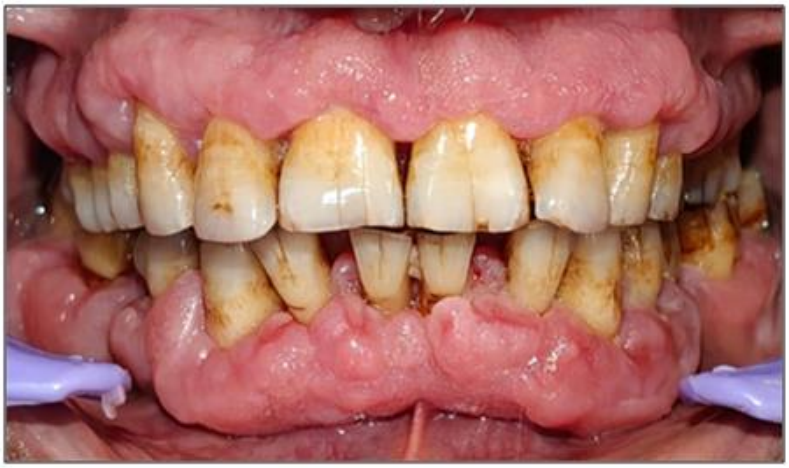
Surgical intervention is one of the most common treatment approaches for management of drug induced gingival overgrowth. Unfortunately, these patients are medically compromised and spend considerable time within medical units monitoring whilst treating their primary condition. To avoid repeated surgical procedures and decrease the chances of recurrence a precise surgical approach should be opted by the clinician. This is dictated by the extent of the area to be operated, the presence of periodontitis and osseous defects, and the location of the base of the pockets in relation to the mucogingival junction. Additionally, an important consideration is the amount of keratinized tissue that is present wherein at least 2-3 mm of keratinized gingiva apicocoronally should remain after the surgery is completed.

In general, small areas (up to six teeth) of DIGO with no evidence of attachment loss can effectively be treated with the gingivectomy. Gingivectomy can be performed using the conventional scalpel technique, laser, electrosurgery

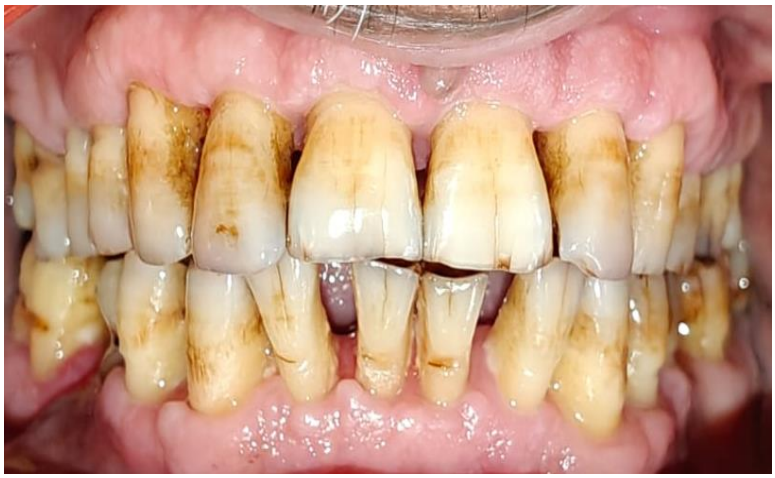
and chemo cautery. Perioperative hemorrhage and healing by secondary intention are the main disadvantages of scalpel excision and this can be significant in highly vascularized and inflamed overgrown gingival tissues.

In cases of gingival enlargement characterized by gingiva that is thick, fibrous, and difficult to cut, electrosurgery has the added benefit of debulking large areas of hyperplastic tissue with minimal hemorrhage. Use of several different wavelengths of laser have also been used to treat gingival overgrowth, such Argon, Nd:YAG, Diode, Er,Cr:YSGG, Er:YAG and CO_2. Specifically the usage of diode lasers is advantageous because of potentially lower pain and inflammation, and improved wound healing due to its selective affinity for soft tissue, sparing both bone and enamel.

Larger areas of gingival enlargement (involving more than six teeth) or areas where attachment loss and osseous defects are present should be treated by periodontal flap surgery, as should any situation in which the gingivectomy technique may create a mucogingival problem. The treatment of drug-induced gingival enlargement by the periodontal flap offers potential advantages due to healing by primary intention unlike gingivectomy.



(A)



(B)

Fig 3:- (A) A 62-year-old man taking nifedipine since the last 3 years presented reported to the department with the chief complaint of masticatory dysfunction. **(B)** Postoperative photograph at 4 months after periodontal flap surgery had been conducted following Phase I therapy.

Recurrence

Several studies have been conducted to correlate the rate of recurrence with the choice of surgical approach to treat DIGO. Although insignificant differences were observed when gingivectomy and periodontal flap surgery were compared, what was appreciable is the faster recurrence of DIGO in cases treated with gingivectomy. This suggests that cellular activity is high during healing by secondary intention as observed following gingivectomy compared to the activity present in the primary intention type of healing associated with the periodontal flap. It could be also be speculated that the faster recurrence observed in the gingivectomy group is attributed to the immediate effects of the offending drug on the surface of a more extensive open healing area (the gingivectomy external bevel) as compared to a narrow incision line present in the periodontal flap group. Cellular mitotic activity starts from within the connective tissue following periodontal flaps and, therefore, more time is necessary for gingival enlargement to manifest itself clinically as compared to gingivectomies.

The sustained lower post-operative gingival re-growth in the laser treated surfaces may suggest a specific response towards this treatment modality which may be attributable to decreased collagen production by gingival fibroblasts along with a laser-induced action on the enzymatic reactions controlling the synthesis and breakdown of collagen [8].

Recurrence of DIGO after surgical treatment was reported in about 34% of the patients still treated with the offending drug [2]. Ilgenli reported 43% recurrence 18 months after periodontal therapy in nifedipine-associated GO and overall 34% recurrence of GO in patients who were on cyclosporine or nifedipine[27]. Poor attendance at recall appointments was associated with increased risk of recurrence. Therefore, a vigorous supportive periodontal maintenance program with regular recall appointments for follow up is recommended following active periodontal therapy to monitor oral health, reinforce home care instructions, and perform in-office plaque control measures. Moreover, according to their study, coefficients generated from regression analysis showed that recurrence of severe DIGO is inversely correlated with age which further concluded that age, gingival inflammation, and attendance at recall appointments could be important determinants for the recurrence of severe DIGO following surgical therapy.

Conclusion:-

Drug induced gingival overgrowth is one of the most widespread unwanted effects of systemic medication on the periodontal tissues. When all the evidence is considered, there appears to be three significant factors which are important in the expression of these gingival changes, notably drug variables, plaque-induced inflammatory changes in the gingival tissues and genetic factors that influence drug metabolism, pharmacokinetics and pharmacodynamics. All these factors can impact the turnover of the collagen matrix by affecting its synthesis and release of matrix metalloproteinases and tissue inhibitors of metalloproteinase. Comprehensive treatment of these cases is multidisciplinary in nature, and dentists and physicians should first consider the nonsurgical approach, including the effective control of local inflammatory factors and possible drug substitution followed by surgical intervention if required. Use of newer molecular approaches such as reverse transcription-polymerase chain reaction (RT-PCR), quantitative real-time PCR, and DNA microarray technologies are needed to clearly establish the pathogenesis of gingival overgrowth and to provide novel information for the design of future preventive and therapeutic modalities.

References:-

1. Ozgoz M. Chronic Inflammatory Gingival Enlargement and Treatment: A Case Report. Advances in Dentistry & Oral Health. 2018;9(4). doi:https://doi.org/10.19080/adoh.2018.09.555766
2. Beaumont J, Chesterman J, Kellett M, Durey K. Gingival overgrowth: Part 1: aetiology and clinical diagnosis. British Dental Journal. 2017;222(2):85-91. doi:https://doi.org/10.1038/sj.bdj.2017.71
3. Brown R, Arany P. Mechanism of drug-induced gingival overgrowth revisited: a unifying hypothesis. Oral Diseases. 2014;21(1):e51-e61. doi:https://doi.org/10.1111/odi.12264
4. Savage N, Daly C. Gingival enlargements and localized gingival overgrowths. Australian Dental Journal. 2010;55:55-60. doi:https://doi.org/10.1111/j.1834-7819.2010.01199.x
5. Dogan A, Tunca Y, Özdemir A, Sengül A, Imirzalioglu N. The effects of folic acid application on IL-1.BETA. levels of human gingival fibroblasts stimulated by phenytoin and TNF.ALPHA. in vitro: A preliminary study. Journal of Oral Science. 2001;43(4):255-260. doi:https://doi.org/10.2334/josnusd.43.255
6. Lin K, Guilhoto LMFF, Yacubian EMT. Drug-induced gingival enlargement - Part II. Antiepileptic drugs: not only phenytoin is involved. Journal of Epilepsy and Clinical Neurophysiology. 2007;13(2):83-88. doi:https://doi.org/10.1590/s1676-26492007000200009

7. Tungare S, Paranjpe AG. Drug Induced Gingival Overgrowth (DIGO). PubMed. Published 2020. https://www.ncbi.nlm.nih.gov/books/NBK538518/
8. Agrawal AA. Gingival enlargements: Differential diagnosis and review of literature. World Journal of Clinical Cases. 2015;3(9):779. doi:https://doi.org/10.12998/wjcc.v3.i9.779
9. Nakib N, Ashrafi SS. Drug-Induced Gingival Overgrowth. Disease-a-Month. 2011;57(4):225-230. doi:https://doi.org/10.1016/j.disamonth.2011.03.010
10. Tejnani A, Gandevivala A, Bhanushali D, Gourkhede S. Combined treatment for a combined enlargement. Journal of Indian Society of Periodontology. 2014;18(4):516. doi:https://doi.org/10.4103/0972-124x.138747
11. Seymour RA, Ellis JS, Thomason JM, Monkman S, Idle JR. Amlodipine-induced gingival overgrowth. Journal of Clinical Periodontology. 1994;21(4):281-283. doi:https://doi.org/10.1111/j.1600-051x.1994.tb00318.x
12. Ramírez-Rámiz A, Brunet-LLobet L, Lahor-Soler E, Miranda-Rius J. On the Cellular and Molecular Mechanisms of Drug-Induced Gingival Overgrowth. The Open Dentistry Journal. 2017;11(1):420-435. doi:https://doi.org/10.2174/1874210601711010420
13. Sun S, Pan Y, Zhang J, Jiang Y. Nifedipine-Influenced Enlargement of the Masticatory Mucosa in an Elderly Edentulous Patient: A Rare Case Report with a Two-Year Follow-Up. Case Reports in Dentistry/Case reports in dentistry. 2024;2024:1-6. doi:https://doi.org/10.1155/2024/6889574
14. Bharti V, Bansal C. Drug-induced gingival overgrowth: The nemesis of gingiva unravelled. Journal of Indian Society of Periodontology. 2013;17(2):182-187. doi:https://doi.org/10.4103/0972-124X.113066
15. Samudrala P, Chava V, Chandana T, Suresh R. Drug-induced gingival overgrowth: A critical insight into case reports from over two decades. Journal of Indian Society of Periodontology. 2016;20(5):496. doi:https://doi.org/10.4103/jisp.jisp_265_15
16. Newman MG, Takei HH, Klokkevold PR, Carranza FA. Newman and Carranza's Clinical Periodontology. Elsevier; 2019
17. Ikawa K, Ikawa M, Shimauchi H, Iwakura M, Sakamoto S. Treatment of Gingival Overgrowth Induced by Manidipine Administration. A Case Report. Journal of Periodontology. 2002;73(1):115-122. doi:https://doi.org/10.1902/jop.2002.73.1.115.
18. MohanKumar Pasupuleti, SvvsMusalaiah, M. Nagasree, Kumar Pa. Combination of inflammatory and amlodipine induced gingival overgrowth in a patient with cardiovascular disease. Avicenna journal of medicine. 2013;03(03):68-72. doi:https://doi.org/10.4103/2231-0770.118462
19. Dill RE, Iacopino AM. Myofibroblasts in Phenytoin-Induced Hyperplastic Connective Tissue in the Rat and in Human Gingival Overgrowth. Journal of Periodontology. 1997;68(4):375-380. doi:https://doi.org/10.1902/jop.1997.68.4.375
20. Castro LA, Larissa, Oton-Leite AF, et al. Long-term effects of nifedipine on human gingival epithelium: a histopathological and immunohistochemical study. Journal of Oral Science. 2010;52(1):55-62. doi:https://doi.org/10.2334/josnusd.52.55
21. Kantor ML, Hassell TM. Increased Accumulation of Sulfated Glycosaminoglycans in Cultures of Human Fibroblasts from Phenytoin-induced Gingival Overgrowth. Journal of Dental Research. 1983;62(3):383-387. doi:https://doi.org/10.1177/00220345830620031601
22. McKevitt KM, Irwin CR. Phenotypic differences in growth, matrix synthesis and response to nifedipine between fibroblasts derived from clinically healthy and overgrown gingival tissue. Journal of oral pathology & medicine : official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology. 1995;24(2):66-71. doi:https://doi.org/10.1111/j.1600-0714.1995.tb01141.x
23. BSP. BSP Implementation of European S3 - Level evidence-based Treatment Guidelines for Stage I-III Periodontitis in UK Clinical Practice. Journal of Dentistry. 2021;106(103562):103562. doi:https://doi.org/10.1016/j.jdent.2020.103562
24. Pihlstrom BL, Carlson JF, Smith QT, Bastien SA, Keenan KM. Prevention of Phenytoin Associated Gingival Enlargement—A 15-Month Longitudinal Study. Journal of Periodontology. 1980;51(6):311-317. doi:https://doi.org/10.1902/jop.1980.51.6.311.
25. Schulz A, Lange DE, Hassell TM, Stone CE, Lison AE. Cyclosporine-induced gingival hyperplasia in renal transplant patients. Deutsche zahnarztlicheZeitschrift. 1990;45(7):414-416. https://pubmed.ncbi.nlm.nih.gov/2269137/
26. Pundir A, Pundir S, Yeltiwar RK, Farista S, Gopinath V, Srinivas TS. Treatment of drug-induced gingival overgrowth by full-mouth disinfection: A non-surgical approach. Journal of Indian Society of Periodontology. 2014;18(3):311. doi:https://doi.org/10.4103/0972-124x.134567

27. Ilgenli T, Atilla G, Baylas H. Effectiveness of Periodontal Therapy in Patients With Drug-Induced Gingival Overgrowth. Long-Term Results. Journal of Periodontology. 1999;70(9):967-972. doi:https://doi.org/10.1902/jop.1999.70.9.967.