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Drug Induced Gingival Overgrowth : A review

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Review Article

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Abstract:

Pharmacological drug therapies are frequently associated with undesirable side effects. When considering the periodontal aspects, Drug Induced Gingival Overgrowth (DIGO) is a one such adverse effect. The first case of gingival overgrowth (previously known as hyperplasia) was reported by Kimball (1939) following chronic phenytoin therapy. Since then such proliferative lesions have been reported associated with several other groups of drugs namely Phenytoin (PHT) among the anti- epileptics, Cyclosporine (CsA) amongst immunosuppressants and various Calcium Channel Blockers (CCBs). The condition gradually leads to complications like pain, gingival disfigurement (aesthetic concerns) and difficulty in maintaining oral hygiene measures.

Management of this condition has been of a great challenge to the clinicians due to its relapse and persistence of risk factors (Age, periodontal factors, drug variables and genetic association). When considering the risk factors, their sensitivity and reliability are of utmost importance for determining the incidence of recurrence and formulation of patient specific therapy. Along with periodontal consultation, treatment should be multidisciplinary in approach discussed with the concerned physician. Initially non-surgical approach including elimination of local factors and drug substitution should be opted. The persistence of condition later necessitates the need for periodontal surgery in form of gingivectomy and flap surgery. Following surgery, maintenance by meticulous oral hygiene with chlorhexidine mouth rinses and periodic professional cleaning should be considered to prevent it from recurring and re-treatment.

Thus, for overall benefit of the patient it is fundamental to know the condition while considering its treatment. This review will briefly summarize the clinical aspects, pathogenesis, risk factors and management of DIGO.

Keywords: Gingival, Overgrowth, drug-induced

INTRODUCTION:

The terms "Gingival Enlargement"and/or "Gingival Overgrowth"areusually preferred for most of the drug - associated conditions as these terminologies avoid fallacious connotations of previously used terms, such as "Hypertrophic Gingivitis" or "gingival hyperplasia". Drug-induced gingival overgrowth had first been documented by Kimball et al in 1939, associatedwith prolonged use of Phenytoin which is an anti-epileptic medication. Numerous medications have now been specifically reported to cause this lesion, especially cyclosporine and specific calcium channel blockers including Dihydropyridines, verapamil and diltiazem.[1,2]Drug-induced gingival overgrowth typically occurs during the initial 3 months afterbeginningthe treatment and starts as an overgrowthin the interdental papilla.[3](Table 1 summarizes various drugs causing gingival overgrowth)

Gingival Enlargement is marked bythe collection of extracellular matrix in the gingival connective tissue.[4]Moreover, it has also been linked with various other factors comprising of systemic inflammation, unfavourable drug reactions and cardiovascular diseases.[5] As the gingival overgrowthprogresses, it begins to affect the daily oral hygiene procedures and might cause interference with masticatory function. It progressively becomes a source of pain and often leadstodisfiguration of gingival tissue.

Consideringmanagement point of view,the clinician should also be concernedwith other issues that arise with gingival enlargement as it may pose a problem in plaque control, mastication, might alter tooth eruption, interference with speech and raise aesthetic concerns.[6]This review briefly focuses on various drugs inducing gingival enlargement, proposed theories of pathogenesis, risk factors and its management.

Table 1. VARIOUS DRUGS KNOWN TO CAUSE GINGIVAL ENLARGEMENT

CATEGORY	DRUGS	PREVALENCE
ANTI- EPILEPTICS		**50%**
First Generation	Phenytoin Phenobarbital (Phenobarbitone)	
Second Generation	Carbamazepine Valproic acid (Sodium Valproate)	
Third Generation	Gabapentin Lamotrigine Vigabatrin	
CALCIUM CHANNEL BLOCKERS		
Dihydropyridines	Amlodipine, Nifedipine, Felodipine, Isradipine, Lacidipine, Lercanidipine	6-15%

Phenylalkalaminederivatives	Verapamil	< 5
Benzothiazine derivatives	Diltiazem	5-20%
IMMUNOSUPPRESSANTS	Cyclosporines	Adults: 25-30% Children: >70%
MISCELLANEOUS	Erythromycin Sertraline Azithromycin	

I. Anticonvulsants:

Phenytoin was clinically brought into use by Merritt &Putnam in 1938 and since then it has been used in patients with epilepsy.[7]PHT has been the drug of choice for management of grand mal, temporal lobe, as well as psychomotor epilepsy.[8]Reports relating phenytoin to gingival overgrowth received attention within one year of its initial clinical application.[9]

Phenytoin is concentrated in saliva. However, there is no evidence as to whether the extent of the overgrowth is linked to phenytoin concentrations in plasma or saliva. Number of tissue culture studiessuggest that phenytoin leads toproliferation offibroblast-like cells as well as theepithelium with increased production of GAGs (sulfated glycosaminoglycans) in vitro. PHT may cause a reduced collagen degradation.[10]The exactmechanism of PHTassociatedgingival overgrowthhas not beenidentified, but some evidences link it to a direct impact on particular, genetically predetermined sub populations of fibroblasts, collagenaseinactivation, and bacterial plaque associated inflammation.The clinical as well as histological features of three major drug groups are listed in table 2.

Other hydantoins that are known to produceovergrowthof gingiva includeethotoin and mephenytoin. While, other anticonvulsants having same side effect are the succinimidesand valproic acid but the incidence is very low. Vigabatrin is a comparatively new antiepileptic drug that has reported to cause gingival enlargement.[11]In case of Valproic acid, overgrowth was noted 18 months after beginningthe therapy of *600 mg/day* and receded within 3 months of discontinuing the treatment.While evidence suggests that a minimal concentration or dosesof phenytoinare required for manifestation of gingivalovergrowth, its incidence and severity are notdirectly associated to the pharmacodynamic parameters of the therapeutic agent. Even the subtherapeutic concentrations ofPHT in serum have known to be relatedto gingival enlargement.[12]

II. Immunosuppressants:

Cyclosporine is aeffective immunosuppressive agent that is used in preventing rejection in organ transplant cases. Cyclosporin A has shownto repress humoral immunity (involving B lymphocytes); and to a larger extent, the cell-mediated immunity (involving T lymphocytes) thus used in cases ofrejection of allograft, delayed hypersensitivity reactions, graft-versus-hostdisease as well as autoimmune diseases.[13]

Gingival enlargement is more in individuals who are medicated with cyclosporine along withcalcium channel blockers.The microscopic analysis of several plasma cells shows the inclusion of an abundant extracellular amorphous material indicating that enlargement is a

hypersensitivity reaction to cyclosporine. Another immunosuppressive drug, tacrolimus, has been used successfully, where results are somewhat less extreme in terms of hypertension, hypertrichosis, and gingival overgrowth.

Cyclosporin A can bedeliveredorally or intravenously, and the doses *greater than 500 mg/day* have been noted to cause gingival enlargement.[7]While it seems that some individualshave increasedsusceptibility to gingival overgrowth, their relation to drug dosage as well as serum concentration is controversial. Whole salivary of Cs are greater in individuals taking the drug in liquid form relative to the tablet form, but the salivary levels are poorly associated with blood concentrations. Gingival enlargement is known to occurwithin 3 months inindividuals taking Cs.

III. Calcium Channel Blockers:

The extensive usage of calcium channel blockersstarted in the 1980s. these are the drugs formulated for treating cardiovascular conditions.The first report in scientific literature related to occurrence of calcium channel blocker associated (nefidipine) gingival overgrowthwas put forward by Ramon et al in 1984 and soon it was also identified with verapamil as well as diltiazem usage.Amongst the CCBs, Nifedipine has been most frequently involveddrug but Amlodipine appears to be accountablefor more severe GEs.[14]

GEs with treatment by CCB mostly appears after 2 to 15 months.[15]Nifedipine is known to be used along with cyclosporine in kidney transplant recipients, and the combination of both drugs results ininducing larger enlargements. Amlodipine induced overgrowthsgenerally occurs under the initial 3 months of beginning the drug therapy at a dose of 10 mg/day. Although handful of cases of overgrowth have been reported, with low doses of amlodipine (5 mg) regimefor a period of 6 months.

Table 2. CLINICAL AND HISTOLOGICAL FEATURES OF MAJOR DRUGS CAUSING GINGICAL OVERGROWTH (MARSHALL 2008)

DRUG	CLINICAL FEATURES	HISTOLOGICAL FEATURES
Anticonvulsants	Initially it begins asa diffuse swelling in theinterdental papillae thatlater enlarge and mergedisplaying a nodular presentation.	• The epithelium displaysvariablegrades of acanthosis along with elongated rete pegs that tend to possess divided ends. • There also appears to be decreased innervation density in overgrown gingiva. • Striking feature: Connective tissue component consisting of proliferated fibroblasts with increased amount of collagen.
Immunosuppressants	Clinically indistinguishable from that relatedto Phenytoin.	• The lesion is primarily connective tissue with a Para keratinized epithelium of variable thickness and deeply penetrating epithelial

	Common in anterior segment and labial surfaces of teeth. Generally confined toattached gingiva but may extend coronally causinginterreferencein occlusion, mastication as well as speech.	ridges. • The connective tissue is greatly vascularized with focal collection of inflammatory cells. • The fibroblasts of Cyclosporin overgrowth show ultrastructural features of protein synthesis and secretion and resemble Myofibroblasts. • Inflammatory infiltrates vary, and sometimes are dominated by plasma cells indicative of neoplastic process, however no such abnormalities are seen.
Calcium Channel Blockers	Similar to Cs and PHT overgrowth.	• Within lamina propria light inflammatory reaction is composed mostly of plasma cells, while fibroblasts are prominent with welldeveloped RER and contain membrane lined structures assumed to be secretory granules.

PATHOGENESIS:

Three very diverse groups of pharmacological agents are linkedto the manifestation of gingival enlargement in the susceptible population. These agents being anticonvulsants, immunosuppressants and calcium channel blockers. Various mechanisms pertaining to their pathogenesis have been proposed but the exact mechanism has still not been figured out. Various proposed mechanisms are summarized in the table 3.

Table 3. PATHOGENESIS OF DRUG INDUCED GINGIVAL OVERGROWTH (BROWN 1991)

HYPOTHESIS	**CONCLUSIONS**
Inflammation from bacterial plaque	Aninflammatory bacterial component is essential for appearance of the adverse effects of the drugs. Oral prophylaxis and "good" oral hygiene can aid inreduction and prevention of the expression of DIGH
Increased production of gags	Increase in accumulation of GAGs (sulfatedglycosaminoglycans) have been investigated from PHT-induced hyperplastic humangingival fibroblasts. However, as aprimary rationale for DIGO this hypothesis is conflicting due to the heterogeneity among the gingival fibroblast.
Immunoglobulins	Immunoglobulins might be anindicator rather than a causativein local cellular immune responsestaking place within the gingival

	tissuethrough the course of periodontal disease.
Phenotypical differences Within gingival fibroblasts	Genetic heterogeneity may exist along several parameters. Differences in receptor binding affinity, cellular ion flux, cellular turnover rate, and cellular GAG, protein, collagenase and collagen production capacity are all possibilities in inducing gingival hyperplasia.
Epidermal growth factor (EGF)	It EGF stimulates collagen synthesis in gingival fibroblasts
Pharmacokinetics and tissue-binding	Anincreased concentrationof PHT in the salivaryglands was reported. CONRAD *et al.* affirmed a significant correlation between PHT content ofsaliva and the manifestation of GH.
Collagenase activation	HASSELL observed that PHT induced overgrowth was associatedwithdecreased collagenase activity. There is a substantial correlation among production of inactive collagenase and the responding fibroblasts (fibroblasts producing more connective tissue than normal after exposure to PHT).
Disruption of fibroblast cellular Na^+ / Ca^{2+} flux	There is asimilarity in the actions of PHT, CsA and calcium channel blocking drugs. It was proposed that these drugs may influence Ca^2+/Na+ flux. Concluding that there is anassociationamong PHT changes in calcium ions in gingival fibroblasts and that this relationrequited with theclinical manifestation of DIGO.
Folate acid uptake	It was Proposedthat DIGO might be secondary to localized Folic Acid deficiency. Arya et al (2011) determined systemic Folic Acid administration at the beginning of PHT treatment on adolescent individuals and identified that Folic Acid was greatlyrelatedwith the preclusion of gingival overgrowth.
Matrix metalloproteinases	Kato et al (2005) concluded that PHT causes impairment in collagen degradation by MMPs/TIMP-1 during a particular cellular signalling pathwaysand nuclear factor kappaB, perhaps leading to collectionof collagen, resulting subsequently in Gingival Overgrowth.
A combination hypothesis/ Unifying hypothesis/ Biochemical Pathway	In this particular hypothesis, inflammatory bacterial component (plaque), FA (folic acid), Na+/Ca^{2+} flux, along withactivation of collagenase is involved: In justification, these 3elements are needed for drug-associatedgingival overgrowth: A. Drug (including phenytoin/ cyclosporine/ nifedipine etc) B. Bacterial inflammatory component(dental plaque) C. Teeth (sulcular epithelium).

RISK FACTORS (SEYMOUR ET AL 2000):

The occurrence of this undesirable effect differsamong drugs, and a wide range of risk factors have been determinedrelated to the manifestation of drug related gingival overgrowth (DIGO). Some of the identifiable elements can be deemed under the subsequententities: age

along with other demographicalvariables; drug variables; use of concomitant medication; the periodontal variables and the genetic factors.[16]

1. **Age and other demographic variables:**

- Age isdeemedto be a risk factor for the cyclosporin-relatedovergrowth of gingiva.[17,18]
- It isproposedthat variations in the occurrence of the enlargementstriggered by these diverse drugs reveal the distincttargetage categories,[19]phenytoin generallytargeting the young individuals, CCBstargeting post middle-agedpopulation andCsAdistributed over a wideage group.
- One probableclarification for such association with age may dwellinaconnectionbetween the androgens and the gingival fibroblasts.
- There is scarce evidence on whether or not gender acts as a risk factor for drug initiated gingival Enlargements. It was stated that race and gender are not substantial risk factors formanifestation of gingival enlargements.[20]

2. **Drug variables:**

- Drug dosage are poor predictors of the gingival changes.[21,22]
- It is more suitable to associatethe dose to individual's body weightfor a greaterunderstanding of dosesand theirrelationto the gingival enlargement.
- Serum concentrations, protein bindingdegree,bioavailability, volume of distribution along with overall evaluation of drug levels in relation to time are some more pertinent pharmacokinetic measures. These measuresrequire recurrent sampling which is usually impractical when consideringlarger epidemiological studies
- In case of phenytoin, few studies have marked that the salivary levels are certainlyassociated with the gingival enlargements[23]while others have failed to do so.[24]

3. **Concomitatnt medication:**

- These 3 major categories of drugsrelated to gingival enlargementare rarely the only medications that are prescribed to theseindividuals. The effects of "polypharmacy"have been researchedregarding both CsAas well asPHT-triggered gingival enlargements.
- Currently, substantial body of evidence is availableindicating combination therapy of nifedipine with cyclosporin in patients oforgan transplant leads togreater gingival overgrowths than when the drug is used individually.[25,26]
- It is proposed that the combination therapy may increase the occurrencewith no effect on severity of the related disease.[27]

4. **Periodontal variables:**

- Plaque scores andgingival inflammationmayaggravate the manifestation of DIGO, regardless of the triggering drug.[28]

- Such findings suggest that oral hygiene as asubstantial risk factor in manifestation of drug-related gingival enlargements.[29, 30]

5. Genetic factor:

- Heterogenicity amongst fibroblast remains one of the major factors that is used to clarify the diverse patterns inreaction of the gingiva to various triggering drugs.
- Expression ofHuman lymphocyte antigen (HLA) is one such genetic indicator that is greatly studiedrelatedto drug related gingival overgrowth in patients with organ transplant asin them HLA phenotype is usually determined preliminary to the transplant. Multiple evidences have been reported associatedwith relationbetween expression of HLA and occurrenceof DIGO. While, the exact mechanism is still unclear concept of molecular mimicry and itseffect on the lymphocyte functionhave been postulated.[31]

DECISION MAKING AND MANAGEMENT:

In severe cases gingival overgrowth often leads to disfigurementwhile interfering with both speech as well as masticatory function. Adequate information related to drug safety and its adverse effects should be addressed to vulnerable individualswhile prescribing specific drugs causing DIGO.[32]Despite our betterknowledgeregarding pathogenesis of drug induced enlargement, its treatment continues to challenge the Periodontists. The condition is complicated by the higher rate of relapsethat arisesdue tolong term usage of the triggeringdrugs and persistent risk factors. When treating the cases with gingival enlargement both non- surgical and surgical therapies should be considered. (for decision tree refer figure 1)

The nonsurgical therapy involves drug substitution and plaque control by oral hygiene maintenance. It is an established fact that scaling along with root planing (SRP) are considered as anti-infective procedures that aid insupragingival and subgingival reduction in load of pathogenic bacteria.[33]Whenever,attempting a drug substitution, a period of 6–12 months is crucial between thetermination of causative drug and the potential regression of the gingival overgrowthprior to a final judgement regarding implementation of surgical therapy is made.[34]Various drug substitutes are mentioned in table 4.

Generally, small regions (involving upto 6 teeth) of drugtriggered gingival overgrowth with no sign of attachment loss (thus no estimated requirement to undergo an osseous surgery) should be managedefficientlyusing gingivectomy.[6] The amount of keratinized tissue presents as an essential element in the selection of gingivectomy as a surgical technique for treating drug-induced gingival overgrowth.It is suggested that minimum 3 mm width of keratinized tissue should remain in apico coronal direction post-surgey. Thus, if the preliminary incision for gingivectomy is to be positioned in close vicinity to or at mucogingival junction, the approach is contraindicated. Larger sites with gingival overgrowth (involving more than 6 teeth) or sites where there is a loss of attachment along with presence of osseous defects may be considered to be managed a periodontal flap. In addition, any condition wherein gingivectomy can lead to loss of all keratinized tissue and, subsequently lead to mucogingival problems, can be managed using periodontal flap.

Table 4. DRUG SUBSTITUTES FOR DIGO	
DRUGS CAUSING GINGIVAL OVERGROWTH	**DRUG SUBSTITUTES**
PHENYTOIN	Bamazepine Phenobarbital Primidone Carbamazepine valproic acid Lamotrigine Gabapentin Sulthiame Topiramate
NIFEDIPINE	Isradipine **ACE Inhibitors:** Captopril and Enalapril
AMLODIPINE	Diltiazem Verapamil Angiotensin receptor blockers like losartan
CYCLOSPORIN A	Tacrolimus

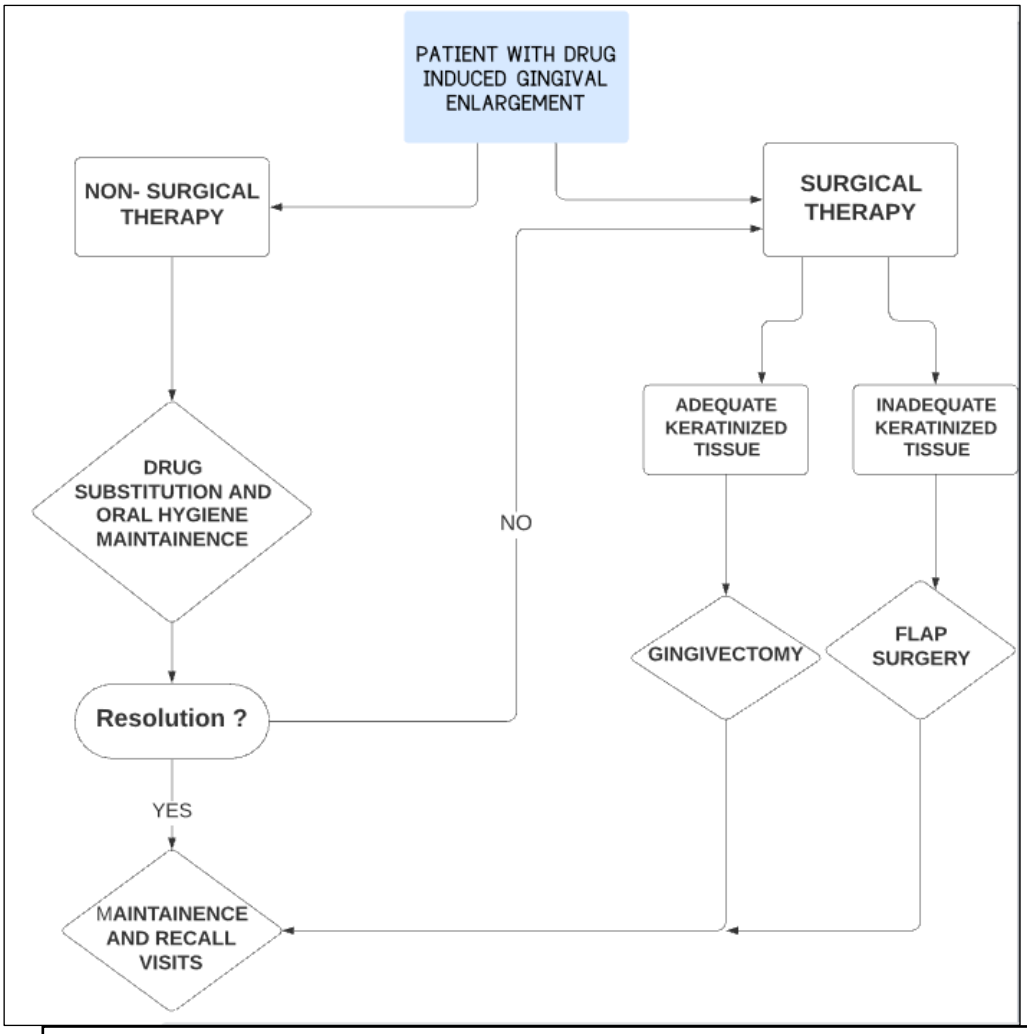

Figure 1. Decision tree showing treatment protocol in cases of DIGO.

CONCLUSION:

In conclusion, drug induced gingival overgrowth has been studied and extensively researched over the years. It is the most undesirable side effect of the concerned drugs. When treating a patient with DIGO its pathological and clinical understanding is essential for effective management. Thus, this review has briefly tried to simplify the concepts of DIGO related to its clinical presentation, pathogenesis, risk factors and management. Along with the drug substitution implementation of good oral hygiene should be stressed upon. DIGO has good prognosis and is often reversible with appropriate patient education and treatment approach.

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