

**Drug Induced Gingival Overgrowth- A Review Article**Dr. Beanish Bashir MDS<sup>1</sup>, Dr. Reyaz Ahmed Mir MDS<sup>2\*</sup>, Dr. Javeed Ahmed Parry DCP<sup>3</sup><sup>1</sup>Department of Periodontics, GDC, Srinagar, Jammu and Kashmir, India<sup>2</sup>Tutor, Department of Periodontics, GDC, Srinagar, Jammu and Kashmir, India<sup>3</sup>Department of Pathology, GMC, Jammu and Kashmir, India**Original Research Article****\*Corresponding author**

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**Abstract:** Drug-induced gingival overgrowth (DGO) is mainly associated with three types of drugs: phenytoin (PHT), cyclosporine A, and calcium channel blockers. The pathogenesis of drug-induced gingival overgrowth is uncertain, and there appears to be no unifying hypothesis that links together the 3 commonly implicated drugs. This review discusses the pathogenesis of DIGO and approaches to treatment based on the current knowledge and observations.

**Keywords:** Anticonvulsants, calcium channel blockers, immunosuppressant drug-induced gingival overgrowth.

**INTRODUCTION**

The gingiva and periodontium associated soft tissues may be enlarged in response to various host and the environment interactions. These enlargements mainly represent an inflammatory response to bacterial plaque, however increased susceptibility as a result of systemic factors or conditions should always be considered during the course of patient evaluation.

Systemically related gingival enlargements include, but are not limited to, scurvy, leukemia, puberty, pregnancy, multi-system syndromes and selected drugs and/or agents. Fibrotic gingival enlargement is believed to be the result of a genetic predisposition (such as hereditary or familial gingival enlargement); however, an idiopathic variant that has not been associated with genetic linkage has also been described.

Of the factors associated with disproportionate, disfiguring and functionally compromising overgrowth of gingival tissues, selected anticonvulsant drugs, calcium channel blockers and a potent immunosuppressant (cyclosporinA) have generated the most investigative attention in the scientific community. Unfortunately, the underlying pathogenic mechanism that mediates gingival overgrowth in affected individuals remains undefined despite intense clinical and laboratory investigation.

This review discusses the pathogenesis of DIGO and approaches to treatment based on the current knowledge and observations.

**Characteristics of drug-influenced gingival enlargement [1]**

- Variation in interpatient and inpatient pattern (ie genetic predisposition)
- Predilection for anterior gingiva
- Higher prevalence in children
- Onset within 3 months

- Change in gingival contour leading to modification of gingival size
- Enlargement first observed at the interdental papilla
- Change in gingival color
- Increased gingival exudate
- Bleeding upon provocation
- Found in gingiva with or without bone loss but is not associated with attachment loss
- Pronounced inflammatory response of gingiva in relation to the plaque present
- Reductions in dental plaque can limit the severity of lesion
- Must be using phenytoin, cyclosporine A or certain calcium channel blockers; the plasma concentrations to induce the lesion have not been clearly defined

**Measurements for gingival enlargement [2]**

- *Angelopoulos and Goaz Index (1972)*
- Angelopoulos & Goaz described an index to measure vertical enlargement,

- Grade 0- No gingival overgrowth
- Grade 1- Overgrowth covering the cervical one third of clinical crown
- Grade 2 -Overgrowth extending till the middle third of crown
- Grade 3- Overgrowth covering the two thirds of crown

#### **Bokenkamp classification (1994)**

- Grade 0- No sign of gingival enlargement
- Grade 1- Enlargement confined to interdental papilla
- Grade 2-Enlargement involving papilla and marginal gingiva
- Grade 3-Enlargement covering three quarter or more of crown

#### **Hyperplastic index [3]**

- In 1985, Seymour and colleagues described a gingival overgrowth index (GOi), based on a study on plaster casts, that included the registration of horizontal and vertical overgrowth, the overgrowth score being the sum of both *Vertical or apicocoronal*
- component
- Grade Criteria
- 0 no gingival hyperplasia
- 1 Blunting of gingival margin
- 2 Hyperplasia less than half of crown length
- 3 Hyperplasia more than half of crown length

#### **Horizontal or labio-lingual component**

- Normal width of free gingival margin
- Thickening from normal up to 2mm
- Thickening from normal >2mm

#### **Miranda and Brunet –20012**

- The MBI, also named the nodullary-papilla index, measures horizontal enlargement of the papilla from the enamel surface at the interdental point of contact to the most external enlarged buccal papillary surface.
- 0, papilla thickness < 1 mm;
- 1, papilla thickness 1–2 mm; and
- 2, papilla thickness > 2 mm

#### **Pathogenesis**

- The pathogenesis of drug-induced gingival overgrowth is uncertain, and there appears to be no unifying hypothesis that links together the 3 commonly implicated drugs.
- A multifactorial model was presented by Seymour *et al.* 1996 which expands on the
- Nteraction between drug and/or metabolite, with the gingival fibroblasts [3].
- Factors which impact upon this model include age, genetic predisposition, pharmacokinetic variables, plaque-induced inflammatory and immunological

changes and activation of growth factors. Of these, genetic factors which give rise to fibroblast heterogeneity, gingival inflammation, and pharmacokinetic variables appear to be significant in the expression of gingival overgrowth.

#### **Age**

- Clinical studies suggest that children and adolescents appear more susceptible to drug-induced gingival overgrowth than adults [17, 18].
- Fibroblasts obtained from both cyclosporin and phenytoin-induced gingival overgrowth cases failed to show an age-dependent decrease in protein synthesis and collagen production [19, 20].
- The failure of these cell culture investigations to confirm clinical findings may be related unique fibroblast phenotype or the influence of androgen metabolism.
- Monolayer cultures of gingival fibroblasts can readily metabolise labelled testosterone to the active metabolite 5 $\alpha$ -dihydrotestosterone (5 $\alpha$ -DHT).
- When phenytoin is added to such cultures there is an increase in metabolite formation [4].
- The active androgen metabolites could "target" sub-populations of gingival fibroblasts and cause either an increase in collagen synthesis and/or a decrease in collagenase activity. Such changes in androgen metabolism may account for the increased propensity of this unwanted effect in children and adolescents.

#### **Genetic Predisposition**

- Not all patients taking phenytoin, cyclosporine or a calcium channel blocker develop gingival overgrowth. Indeed the terms "responders and non-responders" have appeared in the literature to identify those who show or do not show drug induced gingival changes. Such inter-individual susceptibility to these gingival changes may be related to a genetic predisposition. Gingival fibroblasts exhibit functional heterogeneity in response to various stimuli [5].
- Phenytoin and its major metabolite (5-parahydroxyphenyl 1-5-phenyl hydantoin) could react with a phenotypically distinct subpopulation of gingival fibroblast and cause an increase in protein synthesis and cell proliferation rate [5]. Comparable results have also been shown for cyclosporine.
- Moreover these drugs namely phenytoin, cyclosporine and dihydropyridines (nifedipine) are metabolized by members of cytochrome p450 enzyme family.
- Cyt p450 genes exhibit considerable genetic polymorphism which results in interindividual variation in levels of enzymatic activity [21]. This inherited variation in metabolism of 3 drug groups may influence the patient's response to the drug in the form of overgrowth.

- Further evidence that genetic factors may relate to the expression of drug induced overgrowth has come from investigation of human leukocyte antigen (HLA) expression [21].
- One investigation done on patients taking cyclosporin and/or dihydropyridine has elucidated that HLA-DR1+ patients had significantly lower gingival overgrowth as compared HLA-DR2+ patients. So higher frequency of HLA-DR2 expression is associated with moderate to severe gingival overgrowth.

#### Pharmacokinetic Variables

- Certain threshold concentration of the drug or its metabolite is necessary to "activate" gingival fibroblasts. Such a threshold effect was postulated by Daley *et al.* who suggested that increasing the levels of the drug above this threshold did not increase the severity of the lesion [7].
- A direct relationship between the degree of salivary phenytoin and gingival overgrowth has been demonstrated in institutionalised epileptic patients [22]. Similar results have been shown between cyclosporin concentration in stimulated saliva and the extent of the gingival overgrowth [23, 18].
- A role for dental plaque as a reservoir for phenytoin in drug-induced gingival overgrowth has also been proposed [24], Cyclosporin dental plaque concentrations have been shown to be higher than those found in blood and other tissues.
- Thus Local concentrations of the various inducing drugs in GCF, plaque, or in the excised overgrown tissue may provide pertinent information for the expression and pathogenesis of gingival overgrowth.

#### Drug-induced alterations in gingival connective tissue homeostasis

- The essential feature of all drug-induced gingival overgrowth is an increase in the connective tissue matrix.
- Collagen production from gingival fibroblasts is controlled by the co-ordination of transcribed and post transplantation collagen regulatory mechanisms, the latter is controlled by synthesis and release of metalloproteinase and tissue inhibitors of metalloproteinase (TIMPs).
- Histometric analysis of phenytoin-induced gingival overgrowth has shown that the lesion is characterized by an increase in normal growth (i.e the ratio of cell to matrix remains same) as opposed to cellular hyperplasia/hypertrophy hence the accepted term gingival overgrowth [5].
- Overproduction of collagen by gingival fibroblasts in phenytoin-induced gingival enlargement involves an increased steady state level of collagen mRNA and not a decrease in collagen degradation.<sup>8</sup> Cell culture studies have shown that extracellular matrix produced by fibroblasts derived from

phenytoin induced gingival overgrowth facilitates fibroblast spreading. The latter is a prerequisite for growth [25] Cyclosporin-induced changes were related to a rise in the level of type I procollagen. The effects of the drug on the fibroblasts correlated well with an increase in type I *procollagen* mRNA indicating increased synthesis with increased secretion.

- At a molecular level, the effect of cyclosporin on gingival fibroblasts remains uncertain. The drug could act via a specific membrane receptor or via cyclophilin a cytosolic protein which has been identified as the cellular receptor for cyclosporin [26, 27]. Either mechanism could potentially result in an increase in procollagen gene expression.

#### Non-collagenous matrix

- Fibroblasts from a phenytoin induced gingival overgrowth show increased synthesis of sulphated glycosaminoglycans in vitro
- According to Dahloff- ferret- there is decreased degradation within the fibroblasts.

#### Histopathology,Ultrastructural Factors and Inflammatory Changes

- Electron microscopic examination of drug-induced gingival overgrowth has focused mainly on cyclosporin.
- Gingival fibroblasts in cyclosporin-induced overgrowth show characteristics of active protein synthesis and secretion, with reduced cytotoxic or degenerative changes.
- An increased proportion of cells containing microfilament bands with semiperiodic dense nodes, nuclear indentations, and basal lamina associated cell to stromal junctions has also been found [28].
- The term myofibroblast has been applied to such cells.
- Such "modified fibroblasts" have been found in various pathological conditions which are characterised by fibroplasia. Other findings from ultrastructural studies have suggested that cyclosporin induced gingival overgrowth is a consequence of individual hypersensitivity to the drug [29] as there is abundant amorphous substance when compared to fibrous material, and a marked plasma cell infiltrate in the gingival tissues
- There is considerable epidemiological evidence that plaque-induced gingival inflammation exacerbates the expression of drug-induced gingival overgrowth [7, 30].
- Furthermore, most studies suggest that improved oral hygiene measures inhibit the development and recurrence of gingival overgrowth [3].
- It can be argued that plaque-induced inflammatory changes within the gingival tissues enhance the

interaction between the drug and gingival fibroblasts.

- Putative mechanisms at either a cellular or molecular level have now been postulated to support the interactive component.
- Again, cyclosporin has generated renewed interest in this area because of its selective immunosuppressive properties, and ability to inhibit production of interleukins. The latter cytokines are potent stimulators of collagenase production from fibroblasts [31]. In a single case report [32], which documents the histopathology and immunohistopathology of cyclosporin-induced gingival overgrowth, it was shown that the tissue response was in concert with the pharmacodynamics of cyclosporin.
- The tissue contained a significant complement of immunocompetent cells that were dominated by large plasma cell aggregations, macrophages and helper Tcells.
- However, the latter were not expressing interleukin-2 membrane receptors, it was suggested that the drug-induced changes in T-cell function together with the elevated number of macrophages, may be instrumental in initiating a "fibrous hyperplastic response". The number of Langerhan cells also increase in gingival epithelium in patients on phenytoin [34].
- It was found that an increase in number of interleukin 1 is related to increase in langerhan cells in chronically inflammed gingiva [35] stimulating fibroblast proliferation in the presence of growth factors.

**Drug-induced Action on Growth Factors**

- Cytokines and growth factors found elevated in DIGO include IL-6, IL-1 $\beta$ , PDGF-B, FGF-2, TGF- $\beta$  and connective tissue growth factor (CTGF).
- The exact mechanism how these drugs cause cytokine imbalance is still being studied but

proposed mechanism indicate immunomodulatory effects of these drugs.

**Role of  $\alpha 2$  integrins**

- Integrins are heterodimeric transmembrane cellular receptors responsible for signalling mechanism from exterior to interior of cells and consisting of  $\alpha$  and  $\beta$  subunits.
- $\alpha 2\beta 1$  integrins have been shown to serve as specific receptors of collagen type I in fibroblasts[15]
- Initial binding step of collagen phagocytosis relies on adhesive interaction between fibroblasts and collagen.
- The  $\alpha 2$  integrin plays important role in phagocytic regulation of collagen internalization.
- Studies done on rats have shown significantly decreased collagen phagocytosis and suppressed  $\alpha 2$  integrin expression by fibroblasts isolated from overgrown gingiva as compared to controls [16].
- Thus inhibition of collagen phagocytosis due to reduced  $\alpha 2$  integrin expression leading to decreased fibroblast binding to collagen may be one of important factors in pathogenesis of GO.

**Role of folic acid / Na+/Ca++ ion flux in pathogenesis of GO**

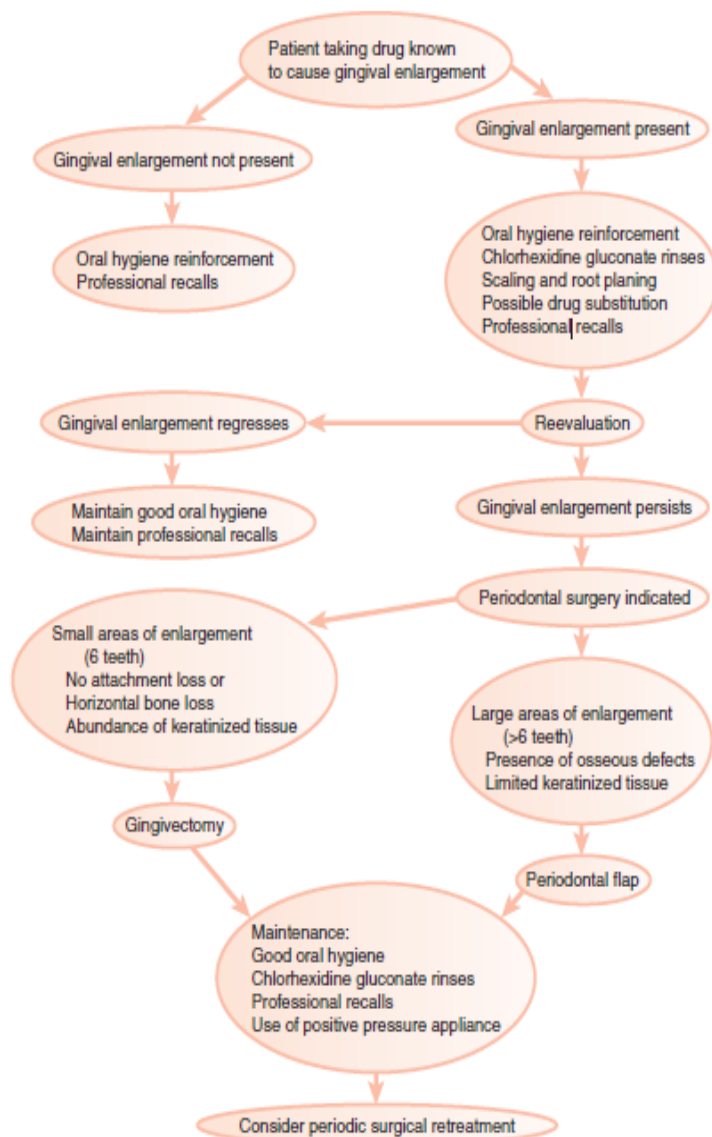
- Vogel proposed that DIGO may be secondary to a localized FA deficiency [9].
- Brown *et al.* [10] suggested that it is reasonable to assume that all the three drug categories of DIGO-inducing drugs (anti-seizure, CCBAs, and immunosuppressive drugs) possess a particular commonality with regard to an inhibitory influence upon cation channels , thus decreasing folate uptake which is dependent upon both active transport through cation channels and passive diffusion.

**DIGO inducing drugs**

Drug category	Anti-convulsants	Anti-calcineurins (and immunosuppressants)	CCBAs
Drugs	PHT, carbamazepine, valproic acid	CsA, TAC (azathioprine, mycophenolate mofetil)	Amlodipine, nifedipine, felodipine, nitrendipine, verapamil, diltiazem
Therapies	Treatment of epilepsy	Immunosuppression	Anti-hypertensive
Incidence of DIGO	PHT – 10–83%	CsA – 7–80%	CCBAs – 30–50%
Mechanism	Blocking Na+ channels	Binding a protein in the cytosol (cyclophilin) through calmodulin	Blocking calcium channels
References	Daley <i>et al</i> (1986), Slavin and Taylor (1987), Brown <i>et al</i> (1991a), Somacarrera <i>et al</i> (1994), Kataoka <i>et al</i> (2005), Meisel <i>et al</i> (2005), Ciavarella <i>et al</i> (2007), Arya and Gulati (2012) and Jiang <i>et al</i> (2013)		

- A unifying hypothesis has been constructed which begins with cation flux inhibition induced by all three of these drug categories. Decreased cation influx of folic acid active transport within gingival fibroblasts leads to decreased cellular folate uptake, which in turn leads to changes in matrix metalloproteinases metabolism and the failure to

activate collagenase. Decreased availability of activated collagenase results in decreased degradation of accumulated connective tissue which presents as DIGO [10].



### Management

- Treatment of drug-induced gingival enlargement should be based on the medication being used and the clinical features of the case.
- Consider the possibility of changing or discontinuing the drug in consultation of the patient's physician.
- If any drug substitution is attempted, 6 to 12 month period of time should elapse between discontinuation of the offending drug and the possible resolution of gingival enlargement before a decision to implement surgical treatment is made.

### Drug substitution

#### CCB's

- Nifedipine with Isradipine ( 20 mg BD) [11]
- ACE Inhibitors like Captopril (12.5 to 50mgBD), Enalapril (2.5to20 mg OD) to control hypertension

### Anticonvulsants

- Phenytoin with Phenobarbital (60 mg TDS), Primidone (100mg TDS) Carbamazepine (200-400mg TDS) Valproic acid (200-500mg TDS)

### Immunosuppressants

Cyclosporin A with Tacrolimus (0.15 to 0.20/kg/d) Rapamycin

- A 3-day course of systemic azithromycin has been shown to significantly decrease gingival enlargement, and the effect was observed as early as 7 to 30 days after initiation of antibiotic therapy[12]
- Topical administration of azithromycin in the form of toothpaste also decreased the severity of cyclosporine-induced gingival enlargement. Argani H *et al.*

### Folic acid

- According to Drew *et al.* 1987 topical folate can be beneficial in phenytoin induced gingival overgrowth [13]. It may reduce inflammation by binding of plaque-derived endotoxin to folate [14]. This bond might prevent the endotoxin complement immune system from being stimulated and reduce local inflammatory hyperplastic changes in the gingival tissues. In addition, the topical dose may result in greater tissue concentration of the agent than if a systemically given one is administered and therefore may have a greater effect.
- The clinician should emphasize plaque control as the first step in the treatment of drug-induced gingival enlargement.
- Frequent professional removal of plaque decrease the degree of gingival enlargement and improve overall gingival health.
- The presence of drug-induced enlargement is associated with pseudopocket formation, frequently with abundant plaque accumulation leading to periodontitis. Therefore meticulous plaque control helps maintain attachment levels. Also, adequate plaque control may aid in preventing the recurrence of gingival enlargement in surgically treated cases.
- *In some patients, gingival enlargement persists even after careful consideration of the previous approaches. These patients may require surgery, either gingivectomy or the periodontal flap*

### CONCLUSION

As DIGO can favor plaque accumulation and can lead to periodontal diseases, dental practitioners will thus be tasked with the labor intensive management of this unwanted side effect until the medical community can provide alternative drug therapy with comparable efficacy that does not induce gingival overgrowth. Efforts to increase awareness about this condition within the medical community should continue, and early identification of patients susceptible to drug-induced gingival overgrowth will help minimize the treatment time needed to control this entity. Newer molecular appr information for the design of future preventive and therapeutic modalities.

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