

# DRUG-INDUCED GINGIVAL OVERGROWTH - A REVIEW

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### ABSTRACT

*Drug-induced gingival overgrowth is a side effect associated with 3 types of drugs: anticonvulsants (phenytoin), immunosuppressive agents (cyclosporine A), and various calcium channel blockers for cardiovascular diseases. Gingival overgrowth is characterized by the accumulation of extracellular matrix in gingival connective tissues, particularly collagenous components with various degrees of inflammation. Although the mechanisms of these disorders have not been elucidated, recent studies suggest that these disorders seem to be induced by the disruption of homeostasis of collagen synthesis and degradation in gingival connective tissue, predominantly through the inhibition of collagen phagocytosis of gingival fibroblasts. In this review, we focus on collagen metabolism in drug-induced gingival overgrowth, focusing on the regulation of collagen phagocytosis in fibroblasts.*

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### INTRODUCTION

Drug-induced gingival overgrowth is known as an adverse effect with three types of drug: phenytoin, an antiepileptic; cyclosporine A, an immunosuppressant; and calcium channel blockers, such as dihydropyridines (nifedipine), diltiazem, and verapamil, which are widely prescribed for the treatment of various cardiovascular diseases<sup>1</sup>. This is characterized by an accumulation of extracellular matrix within the gingival connective tissue, particularly the collagenous component, with various degrees of chronic inflammatory inflammation. An estimated 5% of elderly outpatients in the U.S.A. are taking these medications<sup>2</sup>. The prevalence rate of this disorder has been reported to vary: 10% to 50% for phenytoin; 8% to 70% for cyclosporine A; and 0.5% to 83% for nifedipine<sup>1,2,3</sup>. The accurate determination of the prevalence rate in each drug category is difficult. These differences in the reported prevalence may be due to the differing indices of gingival overgrowth<sup>3</sup>. Furthermore, the presence of various degrees of gingival inflammation is one reason for difficulty in the accurate assessment of drug-induced gingival overgrowth, because inflammation acts as an exacerbation factor of gingival overgrowth<sup>4</sup>. The most effective treatment for drug-induced gingival overgrowth is the withdrawal or substitution of medication<sup>5</sup>.

Since the first report of phenytoin-induced gingival overgrowth, many clinical and investigative approaches have been carried out to determine the pathogenesis of

this disorder. Although many studies yielded various pathogenetic data, it remains unknown why drugs with such different pharmacological actions induce similar gingival overgrowth<sup>6</sup>. The genetically determined capacity of the host to deal metabolically with chronically administered drugs, the responsiveness of gingival tissue to the drugs, and preexisting gingival condition, including inflammation may, differ among individuals. Moreover, calcium channel blockers are mainly prescribed for post-middle-aged patients for control of hypertension, whereas phenytoin and cyclosporin A are prescribed for a wide range of patients due to their wide spectrum of efficiency. These factors could make it difficult to elucidate the pathology of drug-induced gingival overgrowth. Although the pathology of drug-induced gingival overgrowth is not definitively known, these disorders seem to be induced through the disruption of the homeostasis of collagen synthesis and degradation in gingival connective tissues<sup>7</sup>. In this review, we focused on excess collagen fibers, especially type I collagen, the most abundant protein in mammals, in gingival connective tissue, and discussed the role of collagen phagocytosis of gingival fibroblasts for the induction of drug-induced gingival overgrowth.

### 1. ACCUMULATION OF TYPE I COLLAGEN IN GINGIVAL CONNECTIVE TISSUE

Although the pharmaceutical effect and primary target tissues of an antiepileptic, an immunosuppressant, and calcium channel blocker are different, they act similarly on gingival connective tissue, causing fibrous gingival overgrowth. Drug-induced gingival overgrowth is previously termed as gingival hypertrophy or gingival

hyperplasia by finding an increased number of fibroblasts in gingival connective tissue with histological analysis<sup>8</sup>. However, these earlier terms, "hypertrophy" or "hyperplasia" did not accurately reflect the histologic composition of enlarged gingiva. Not increase proliferation of gingival fibroblasts, but the severe accumulation of extracellular matrix within the gingival connective tissue, particularly collagenous components, was observed in human gingival overgrowth<sup>7,8</sup>. These discrepancies may be due to various degrees of gingival inflammation in human subjects because of the production of inflammatory cytokines, such as interleukin 1, which is known to stimulate the gingival fibroblast proliferation and has a potential influence on collagen metabolism of fibroblasts, and the situation of overgrown gingiva is complicated<sup>2,9</sup>.

## 2. SYNTHESIS AND DEGRADATION OF TYPE I COLLAGEN IN DRUG INDUCED GINGIVAL OVERGROWTH.

The metabolism of collagen, the most abundant protein in mammals, is precisely balanced by collagen synthesis and degradation to maintain tissue volume<sup>2</sup>. Generally, fibrosis is caused by the loss of homeostasis of the synthesis and degradation of collagen fibers, especially type I collagen, resulting in the excess accumulation of collagen fibers<sup>10</sup>. The cell proliferation and collagen synthesis rates of gingival fibroblasts isolated from human drug-induced overgrown gingiva tended to be greater than those of gingival fibroblasts isolated from non-responder exposed to nifedipine or phenytoin in vitro<sup>11</sup>. Furthermore, the stimulating effect of cyclosporin A on type I collagen synthesis in human gingival fibroblasts has been reported; however, there are conflicting results of these drugs on cell proliferation and or collagen synthesis in vitro study. Cell proliferation is not affected by nifedipine or phenytoin treatment, but collagen synthesis is inhibited by these drugs<sup>7</sup>. Some researchers have shown that collagen synthesis in human gingival fibroblasts is not affected or inhibited by cyclosporine A treatment. It has been proposed that the decreased collagen degradation caused by phenytoin may contribute to the appearance of gingival overgrowth<sup>9</sup>. Collagen may be degraded via an extracellular pathway involving the secretion of collagenase and via an intracellular pathway involving phagocytosis by fibroblasts. The collagenase-mediated route is accompanied by a loss of tissue architecture e.g. inflammation, while the collagenase-independent intracellular route is important during normal turnover. The physiological conditions, collagen fibers in gingival connective tissue, undergo rapid collagen turnover to maintain homeostasis<sup>12</sup>. Due to morphological studies of human cyclosporin A-induced gingival overgrowth, the decrease of phagocytosed collagen by fibroblasts has been reported. Recent studies has shown that drug-

induced gingival overgrowth is not due to the increased synthesis of type I collagen but the decreased degradation of type I collagen in gingival connective tissue through the reduction of collagen phagocytosis of fibroblasts<sup>13</sup>.



**Fig-1:** *Gingival Overgrowth in an Adult Undergoing Treatment with a Calcium Channel Blocker for Hypertension in the Anterior Facial Area*

## 3. ROLE OF CALCIUM IN COLLAGEN PHAGOCYTOSIS.

Although the pharmacological actions and primary target tissues of calcium channel blockers, phenytoin, and cyclosporin A are quite different, these drug are known as calcium antagonists. Calcium channel blockers are able to block the influx of calcium ions into cells and to reduce oxygen consumption<sup>14</sup>. Phenytoin is known to act as a calcium channel antagonist and inhibit calcium ion flux. Cyclosporin A is reported to inhibit the release of calcium from intracellular stores, including endoplasmic reticulum and mitochondria. Actin is the most abundant protein in various types of eukaryotic cells and is involved in a variety of processes, including cell locomotion, contraction and phagocytosis. In phagocytosis, particle internalization is initiated by the interaction of receptors with ligands, and this leads to the polymerization of actin at the ingestion site, and internalization of the particle via an actin-based mechanism. After internalization, actin shed from the phagosome. McCulloch CA, have shown the implication of the actin filament in the regulation of collagen phagocytosis<sup>15</sup>. By treating fibroblasts with latrunculin B (actin monomer sequester), increased collagen binding, and enhancement of collagen receptor mobility are observed. Furthermore, the apparently enhancement of collagen phagocytosis is shown by the disengagement of actin from collagen receptors on fibroblasts. Actin rearrangements depend on actin-serving and capping proteins<sup>16</sup>.

## CONCLUSION

Drug-induced gingival overgrowth is induced by reduced collagen phagocytosis in gingival fibroblasts

on cell surface. These drugs are known to act as calcium antagonists. Furthermore, actin binding protein is considered an important factor for this disorder because of the maintenance of normal tissue integrity by regulating collagen phagocytosis. Further studies of the overgrown gingiva should provide more insight into the molecular pathogenesis of drug-induced gingival overgrowth.

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