Chapter

Adverse Effects of Medications on Periodontal Tissues

Sukumaran Anil, Seham H.S.A. Alyafei, Annie Kitty George and Elna Paul Chalisserry

Abstract

Periodontal tissue is susceptible to a range of adverse effects of several medications used in daily medical practice. Phenytoin, cyclosporine, and calcium-channel blockers are the most commonly used drugs related to gingival disease. Several other medications can also have an adverse effect on the periodontium, especially in the presence of compromised oral hygiene. These medications act on periodontal tissues by triggering the inflammatory pathways involved in the pathogenesis of periodontal disease or by potentially compromising the management of patients with these conditions. Gingival overgrowth is probably the mostly widely recognized and investigated type of adverse drug reaction in the periodontal tissues. Since many patients are on such medications, dental practitioner should take a thorough medical history and be aware of medication-related problems and their potential effects on diagnosis and treatment planning. The chapter reviews the commonly prescribed medications that can affect the periodontium either in its healthy or inflamed condition.

Keywords: adverse effects, calcium channel blockers, gingival overgrowth, hypertension, anticonvulsants, immunosuppressants

1. Introduction

Medications are chemical substances used to treat, cure, prevent, or diagnose a disease or to promote well-being. An adverse drug reaction is defined by WHO as a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, therapy of diseases or for the modification of physiological function. Several medications can cause adverse effects in the periodontium. The most common are the gingival enlargement, inflammation, pigmentations, gingival bleeding and osteonecrosis [1]. Gingival overgrowth (GO) or enlargement is a condition is characterized by an increase in the size of gingiva subsequent to the increase in extracellular tissue volume. Gingival overgrowth is a side effect of several medications used by patients have the capability to cause adverse effects in the oral cavity and periodontal tissues [2]. Though many medications have marked effects on the periodontal tissues and these adverse reactions are well documented, many have been described only as isolated case series or reports [2]. It is important for the clinician to obtain a complete record of the medications the patient takes, including prescription drugs and over-the-counter drugs. This will help the clinician to diagnose and manage the adverse effects in the periodontal tissues.

2. Drug induced gingival overgrowth (DIGO)

The main drugs associated with GO can be divided into three categories such as anticonvulsants, calcium channel blockers, and immunosuppressants. Few isolated incidences of GO associated with antibiotics and sulphonamides were also reported. Though these drugs have different pharmacologic effect and targets, all of them seem to act similarly on the gingival connective tissue as a secondary target, leading to common clinical and histopathological changes. The gingival overgrowth (GO) is consequent to the alteration of the host tissue response, resulting in an increase in collagen synthesis and cellular changes within the connective tissue. The prevalence of gingival overgrowth varies with different medications, with a reported rate of 50% for phenytoin (anticonvulsant), 25–30% for cyclosporine (immunosuppressant), 5–20% for nifedipine and 3% for amlodipine (CCBs) [2]. The drug associated gingival overgrowth is three times more prevalent among men and can be attributed to the effect of testosterone on fibroblast proliferation and collagen stimulus [3].

The GO appears normally within 1–3 months after administration of these medications (**Table 1**). The gingival enlargement may appear inflamed or more fibrotic depending on the degree of inflammation. Normally the GO is confined to the attached gingiva which might occasionally extend coronally. The enlarged gingiva produces esthetic changes and its clinical symptoms include tenderness, bleeding, interference with speech, dental occlusion problems, and enhanced susceptibility to periodontal diseases [4–6].

Histologically, the drug-induced gingival overgrowth is indistinguishable from other types of gingival enlargement. The enlargement of the gingival tissue occurs as a result of accumulation of extracellular matrix (ECM), although the pathogenesis remains multifactorial. Age, genetic predisposition, pharmacokinetic variables, drug-induced alterations in gingival connective tissue homeostasis, inflammatory changes, drug-induced action on growth factors, etc. are some of the factors that influences the occurrence and severity of the gingival overgrowth.

Genetic factors are important in the pathogenesis of drug associated gingival overgrowth. The drugs are metabolized by cytochrome p450 enzymes, which are characterized by high genetic variability. Research on genes responsible for HLA leukocyte antigen coding confirmed the theory of HLA-DR2 antigen influence, which is found much more commonly in patients with moderate or severe drug-induced gingival overgrowth than HLA-DR1 [7]. The drug variables such as dosage, duration of therapy and concentration of drug in plasma and local fluids, like gingival crevicular fluid and saliva, play an important role in DIGO [8].

2.1 Pathogenesis of DIGO

The exact mechanism behind the pathogenesis of drug-induced gingival overgrowth is not yet fully understood. Each medication has got separate impacts on the range of cytokines and growth factors involved in connective tissue metabolism. Studies revealed that the molecular markers and clinical features of gingival overgrowth differ depending on the drugs. The cytokine and growth factor balances are altered in tissues with GO, including connective tissue growth factor (CTGF), a member of the interesting CCN (cysteine-rich angiogenic protein 61) family of factors [3, 9, 10].

Cytokine dependent alterations in extracellular matrix metabolism appear to be of functional importance to gingival overgrowth. Abnormal differentiation of cells, resulting in accumulation of fibroblasts with a pathologic range of proliferative

Drugs/groups	Incidence/prevalence	References
Anticonvulsants		
Phenytoin	13%	[17]
	50.3%	[18]
	57%	[19]
	40%	[20]
	50–60%	[21]
	53%	[22]
Sodium valproate	Rare	[22]
Vigabatrin	Rare	[23, 24]
Carbamazepine	None	[22]
Immunosuppressants		
Cyclosporines	10–85%	[25]
	30%	[26]
	8–70%	[27]
	25–81%	[8]
	22.4%	[28]
Tacrolimus	14.1%	[28]
Calcium channel blockers		
Nifedipine	6.3%	[29]
	50.8%	[30]
	83%	[31]
Diltiazem	20%	[31]
Verapamil	4–19%	[32, 33]
Amlodipine	3%	[34, 35]
Felodipine	Rare	[36]

Table 1.
Medications causing drug induced gingival overgrowth (DIGO).

and synthetic phenotypes, could result from deregulated cytokines. The unique metabolic aspects of gingival extracellular matrix metabolism; and a greater understanding of interactions between and among medications, the innate and acquired immune response, cytokines and growth factors, and gingival epithelial and connective tissue cells providing more detailed molecular and mechanistic information need to be elucidated [3, 11].

2.2 Histological features

Histologically, slight to moderate hyperkeratosis, thickening of the spinous layer, fibrosis of underlying connective tissue with fibroblastic proliferation, increase in the number of capillaries with slight chronic perivascular inflammation is seen. Excessive accumulation of extracellular matrix like collagen with varying amounts of inflammatory infiltrates, predominantly plasma cells are seen. Fibroblastic proliferation may not be evident. Plasma cells are the principal type of infiltrating

inflammatory cell. Parakeratinized epithelium of variable thickness covers the connective tissue stroma. The epithelial ridges may penetrate deep into the connective with columns of interspersed collagen fibers [12].

2.3 Management of drug induced DIGO

The management of medication induced gingival overgrowth depends on the degree of progression of the disease. Withdrawal or substitution of medication is one of the methods that might resolve the gingival overgrowth. However, not all patients respond to this mode of treatment especially those with long standing gingival enlargement. Professional debridement with scaling and root planning as needed has been shown to offer some remission of the gingival overgrowth in patients. Since the anterior labial gingiva is frequently involved, surgery is commonly performed for esthetic reasons. The classical surgical approach has been the external bevel gingivectomy. However, a total or partial internal gingivectomy approach has been suggested as an alternative. This approach has the benefit of limiting the large denuded connective tissue wound and thereby minimizing postoperative pain and bleeding [13].

The surgical methods include traditional scalpel gingivectomy and periodontal flap surgery. Electrocautery may be used in difficult cases, children, or where the gingiva is fragile and likely to bleed. Excision using laser provides a superior incision margin and improved wound healing due to a coagulated layer along the incision, as well as a reduced incidence of scarring. CO_2 laser is very effective in surgery of soft tissues with high water content like the gingiva. Blood vessels up to a diameter of 0.5 mm can be sealed effectively and provides a dry field for better visibility of the surgical field. A laser is preferred over the scalpel as it has strong bactericidal and hemostatic effects [14, 15]. A combined non-surgical and surgical therapy with drug substitution is the most common treatment approach in the management of medication induced gingival overgrowth [16]. In most cases, conservative methods such as professional oral hygiene maintenance, topical anti-inflammatory and antibacterial drugs and a meticulous oral hygiene measures by the patient. Surgical excision is used in cases of where the gingival overgrowth interferes with food intake, causing difficulties in speech and maintaining oral hygiene. Surgical excision is more reliable as it eliminates the hyperplastic tissue and promotes plaque control as well as improves the esthetics.

2.4 Phenytoin

Phenytoin is an anticonvulsant prescribed for the control of epilepsy and neuralgias. In the present day, phenytoin is not usually prescribed as a first line drug for the management of epilepsy due to the availability of a wide range of newer, more effective anticonvulsant drugs with fewer side effects. The prevalence of drug-induced gingival overgrowth in patients taking phenytoin is reportedly between 15% and 60% [17]. Phenytoin, or its metabolites, probably acts directly on high activity fibroblasts leading to the high levels of production of collagen in the presence of inflammation. This results in gingival enlargement, characteristically originating principally from the interdental papillae (**Figure 1**). The amount or degree of severity of the overgrowth is not related to the dose of the drug. Presence of plaque and gingival inflammation, serum concentrations of the drug are factors which increases the risk of phenytoin-induced gingival overgrowth [37].

The management of this overgrowth is based on obtaining optimal control of plaque. Where the enlargement is unsightly and disfiguring, or even interfering

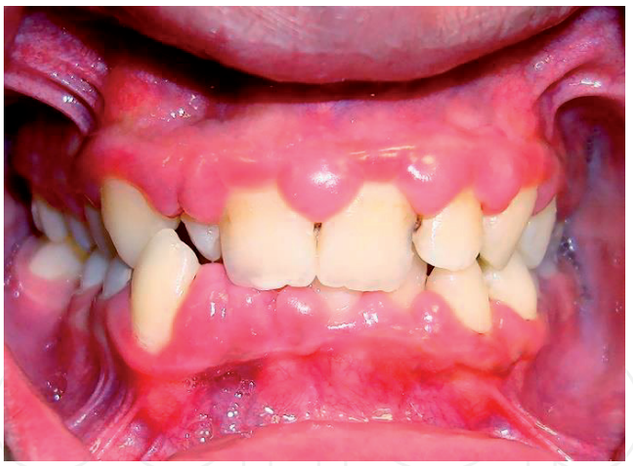

Figure 1.
A case of phenytoin induced gingival overgrowth.

with chewing, the over-growths should be removed. Gingivectomy appears to be the simplest and best way of achieving good gingival contour as a post-operative result. But optimal plaque control post-operatively is the most important determinant of success. Recent research work suggests that the use of chlorhexidine, especially brushing daily using the gel, can be of valuable assistance in controlling plaque and hence in controlling the overgrowths in the post-surgical phase.

2.5 Cyclosporin

Cyclosporin (CsA) is a cyclic polypeptide with potent immunosuppressive activity used widely to prevent organ transplant rejection and also in the treatment of autoimmune diseases [38, 39]. CsA selectively suppresses helper T-cell function and modulates the network of inflammatory cytokines. However, cyclosporin is associated with several untoward effects like nephrotoxicity, hepatotoxicity, hirsutism and gingival overgrowth [40, 41]. Gingival overgrowth is one of the common side effects of CsA treatment, observed in 13–81% of the patients [6, 39]. The prevalence of gingival overgrowth associated with CsA averages around 30%, with reported rates ranging from 10 to 85% [25]. Studies have shown certain degree of association between GO and potential risk factors, such as age, genetic susceptibility, pharmacokinetic variables, plaque-related inflammation and immunological changes [42–44]. Epidemiological studies have reported wide variation of its occurrence and it accounts for more than 70% of the transplant recipients [4, 45]. The severity of gingival overgrowth is often associated with its prolonged use and further influenced by bacterial plaque and local irritants (**Figure 2**) [46]. The use of other medication, such as calcium channel blockers along with CsA increases the prevalence of gingival overgrowth and subsequently the risks [11]. The condition can interfere with the mastication, speech and oral hygiene maintenance and has a psychological impact in the affected individual [5].

The most prominent pathologic manifestation of the gingival overgrowth is an excessive accumulation of extracellular matrix, predominantly type I collagen. Many studies have shown increased transcriptional and translational levels of type I collagen in both tissue and fibroblast cultures derived from CsA-induced gingival overgrowth [9, 10, 47]. Though the exact mechanism is not clearly understood, studies also have shown increased expression of specific cytokines, especially transforming growth factor-beta (TGF-β), in drug-induced gingival overgrowth. This suggests that TGF-β, an inflammatory mediator that regulates cell proliferation and differentiation, plays a role in enlarging the extracellular matrix in hyperplastic gingival tissue [48].

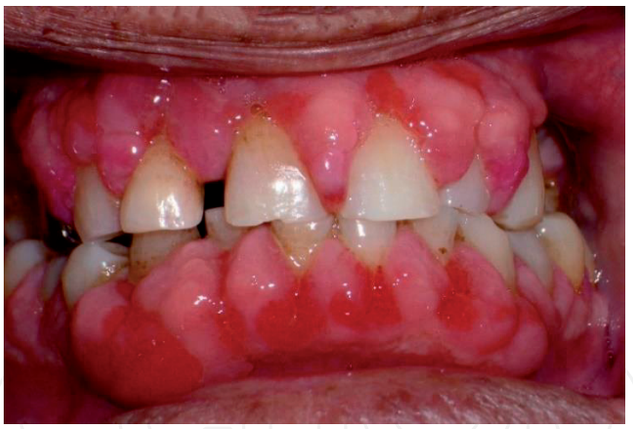

Figure 2.
A case of cyclosporin A induced gingival overgrowth.

The management of cyclosporin associated gingival overgrowth includes removal of local irritants and plaque and maintenance of adequate oral hygiene. Invasive procedures, such as gingivectomy is done in severe cases [49]. Currently the use of antibiotics has shown reduction in the GO associated with the drug usage. Azithromycin, a semi synthetic antibiotic, derived from the macrolide erythromycin has shown reduction in gingival overgrowth [50]. Roxithromycin, a macrolide antibiotic with similar characteristics of azithromycin, is also found to be effective in the reduction of gingival overgrowth in renal transplant recipients on CsA [25]. Gingival overgrowth can be prevented by intensive plaque-control practices including meticulous brushing, although critically ill patients receiving CsA may not be the ideal candidates for such intensive procedures. A combination of chlorhexidine or normal saline mouth rinses and mechanical cleaning was found to be effective in controlling the management of such patients [51, 52].

2.6 Calcium channel blockers

Drugs including diuretics, alpha and beta blockers, angiotensin converting enzyme inhibitors, angiotensin II type 1 receptor blockers and calcium channel blockers (CCBs) have been used to manage hypertension [53]. They are administered either alone or in combination, depending on the needs of the patient. The calcium channel blockers are the most frequently prescribed antihypertensive agents which is comprised of two subclasses, dihydropyridines and non-dihydropyridines. Although their mechanism of action is the same, they have varied pharmacological effects. While the dihydropyridines are potent vasodilators, the non-dihydropyridines produce more negative inotropic effects. The dihydropyridines such as nifedipine, amlodipine and felodipine are significantly associated with gingival overgrowth. The non-dihydropyridines such as diltiazem and verapamil are less commonly associated with gingival enlargement [54].

2.6.1 Nifedipine

Nifedipine, a drug that belongs to a pharmacological agent group known as calcium channel blocker was introduced in 1972 and has been used widely in the management of hypertension and angina pectoris. Lederman et al. [55] was the first to describe nifedipine-induced gingival overgrowth in patients treated with this drug. The prevalence of nifedipine-induced gingival overgrowth is between 30 and 50% and was found to be 3 times likely to develop in males [29]. The overgrowth

appears 1–9 months after administration of the drug and the most common sites affected included the labial anterior gingiva of both jaws [56, 57]. A multifactorial pathogenesis has been suggested including environmental, genetic, immunological and inflammatory factors [58]. The interdental papilla becomes more grossly enlarged followed by the marginal and the attached gingiva (**Figure 3**). Presence of gingival periodontal disease and dental plaque has been reported as significant risk factors in the development of gingival enlargement. Several hypotheses have been put forward to explain the phenomena of the gingival overgrowth. The interaction between nifedipine and gingival fibroblasts contain increased sulfated mucopolysaccharides which are precursors of ground substance, leading to the overproduction of collagen and extracellular ground substance [59]. A genetically specific predetermined subpopulations of fibroblasts are identified which are sensitive to nifedipine and cause an increase in the production of collagen [60]. The dose of nifedipine is important and it was found that its presence in gingival crevicular fluid is 15–316 times higher than plasma. The higher concentration of nifedipine in the gingival crevicular fluid could increase the severity of gingival enlargement.

2.6.2 Amlodipine

Amlodipine is a third-generation dihydropyridine calcium channel blockers (CCB) that is used in the management of both hypertension and angina. The prevalence of gingival overgrowth associated with amlodipine is between 1.7% and 3.3% [35]. Though the etiopathology of this adverse reaction is not clearly understood, mechanisms such as inflammatory and non-inflammatory pathways have already been hypothesized. The non-inflammatory mechanisms involves a defective collagenase activity due to decreased uptake of folic acid, blockage of aldosterone synthesis in the adrenal cortex and consequent increase in Adrenocorticotropic hormone level, and up-regulation of keratinocyte growth factor [61]. The inflammatory pathway develops as a result of direct toxic effects of concentrated drug in gingival crevicular fluid and bacterial plaques leading to the up-regulation of several cytokine factors such as transforming growth factor-beta (TGF-β) [62].

The gingival overgrowth normally begins at the interdental papillae and is more frequently found in the anterior segment of the labial surfaces. Subsequently gingival lobulations that develop might appear as inflamed or fibrotic in nature depending on the degree of contributing factors (**Figure 4**). Normally the fibrotic enlargement is confined to the attached gingiva which might advance coronally and

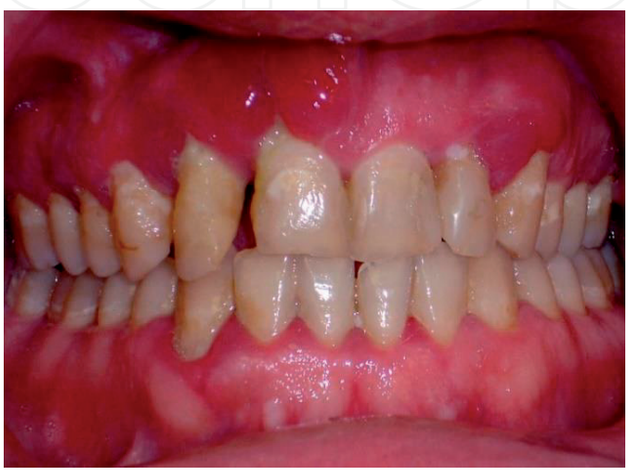

Figure 3.
A case of nifedipine induced gingival overgrowth.

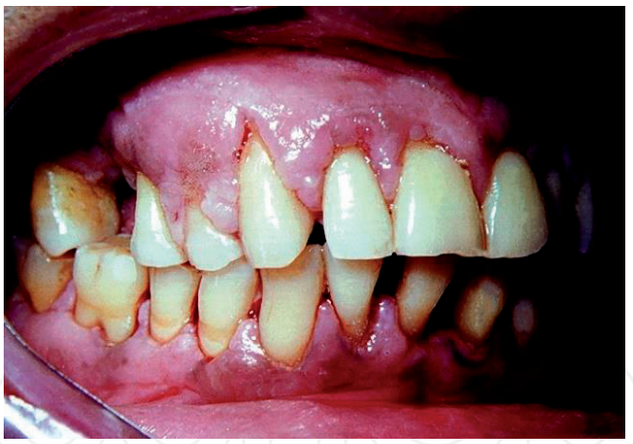

Figure 4.
A case of gingival overgrowth in a patient on amlodipine.

interfere with esthetics, mastication, or speech [63]. Management of amlodipine induced gingival overgrowth includes substitution of the drug and controlling the other risk factors with meticulous mechanical and chemical plaque control. Surgical management of the overgrowth is advised in cases to accomplish an esthetic and functional outcome [64].

2.6.3 Verapamil

Verapamil is an effective preventive agent in both episodic and chronic cluster headache. Gingival overgrowth is an infrequent adverse effect of Verapamil and a prevalence rate of around 4.2% has been reported [33]. Histologically, verapamil induced gingival enlargement shows a highly vascular connective tissue, acanthotic and thickened epithelium with long rete pegs containing dyskeratotic pearls, and varying amounts of subepithelial inflammatory infiltrate which is similar to other group of drugs [65]. The histological appearance is similar to that caused by phenytoin, cyclosporin, and other calcium channel antagonists. Discontinuation of the drug usually results in complete regression of the gingival overgrowth.

3. Other effects of medications on periodontal tissues

3.1 Minocycline

Minocycline, a semi-synthetic broad-spectrum antimicrobial agent, is mainly used for the treatment of acne, chronic respiratory diseases, and rheumatoid arthritis. It is lipid soluble and therefore can easily penetrate into body fluids, such as saliva and gingival crevicular fluid, and into various body tissues including bone and soft tissues [66]. Minocycline-induced pigmentation of oral mucous membranes including the buccal mucosa, gingiva, palatal area, lips and tongue has been reported [67–69]. The pathophysiology of minocycline staining is not clearly understood. It has been suggested that either a minocycline-metabolite complex or melanin, iron and calcium-containing granules are the source of the pigment [70]. The pigmentation of oral soft tissues appears as distinctive blue-gray or brown in color and occurs as a result of pigmented black bone visible through the thin overlying mucosa without any actual involvement of the soft tissue itself (**Figure 5**) [71]. The pigmentation appears to be related to the duration of minocycline

therapy or the cumulative dose, and resolves once the drug is discontinued [69, 72]. Intraoral pigmentation can be managed with lasers [71].

3.2 Oral contraceptives

A higher prevalence of gingival inflammation, loss of attachment and gingival enlargement in woman taking hormone based oral contraceptives [73, 74]. The gingival inflammation seems to be associated to high concentrations of sex hormones present in oral contraceptives (**Figure 6**) [75]. Oral contraceptives (OCs) enhance periodontal breakdown by reducing the resistance to dental plaque and can induce gingival enlargement in otherwise healthy females [76, 77]. Oral contraceptives have pronounced effects on gingival microvasculature and it has been shown that human gingiva contains receptors for progesterone and estrogen. The dosage and duration of intake are the possible factors which influence the effect of oral contraceptives on the periodontal condition. A continued exposure of oral contraceptives for longer duration results in higher risk of periodontal disease development due to increased production of pro-inflammatory cytokines and prostaglandins as a result of elevated levels of the hormones [78, 79]. However, the currently used combined oral contraceptives showed little influence on the periodontal health, possibly related to their lower concentration of progesterone and estrogen compared to the earlier formulations [74, 80]. A critical review supports the conclusion that there is no impact of modern oral contraceptives on the periodontal and gingival tissues.

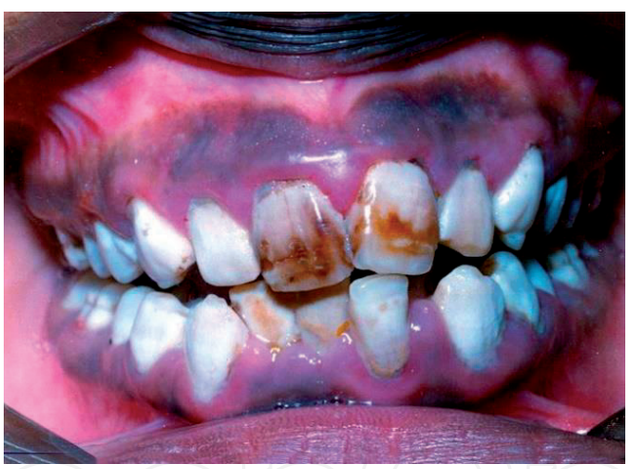

Figure 5.
Discoloration of the gingiva and teeth in a patient on minocycline therapy.

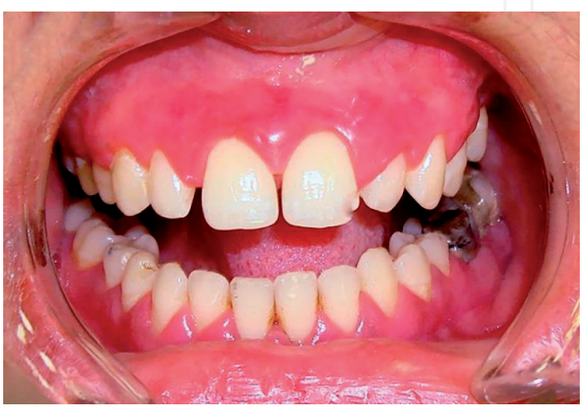

Figure 6.
Gingival changes in a patient on oral contraceptives.

Hence, it is concluded that oral contraceptives can no longer be considered to constitute a risk factor for gingivitis or periodontitis [81].

3.3 Bisphosphonates

Bisphosphonates are used widely in the management of primary and metastatic bone cancer, as well as osteoporosis. Bisphosphonates improve bone mineral density, reduce fracture risk, and reduce hypercalcemia of malignancy. Incidents of osteonecrosis of the jaw have been reported in people on bisphosphonates and undergoing invasive dental treatment procedures, including tooth extractions, dental implants, and surgical and nonsurgical periodontal treatment [82]. The risk for bisphosphonate-induced osteonecrosis may be influenced by the route of administration of the drug, the potency and the duration of use. Jaw osteonecrosis appears more associated with the intravenous use of bisphosphonates. A review showed that 94% of the published cases of osteonecrosis correlated with administration of intravenous, nitrogen-containing bisphosphonates [83].

Bisphosphonates inhibit bone resorption by acting on osteoclasts to reduce their activity or to increase the rate of apoptosis [84]. The inhibitory effect on osteoclast function, bone formation coupled with resorption results in an overall reduction in the rate of bone remodeling [85]. Moreover, bisphosphonates may antagonize the action of several matrix metalloproteinase involved in breakdown of structural components of periodontal connective tissue [86]. In view of the antiresorptive properties of bisphosphonates and the ability to inhibit cytokines of periodontal tissue destruction, there has been interest in the possible use of bisphosphonates as an adjunct to scaling and root planning in the management of periodontitis [87, 88]. Although bisphosphonates claim its effectiveness in controlling periodontal destruction, clinical use warrants further evidence. A systematic review concluded that bisphosphonates may be used topically as an adjunct to scaling and root planing [89].

3.4 Statins

Statins, or inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), are a group of drugs, used mainly to treat hyperlipidemia. In addition to their cholesterol lowering properties they also have strong anti-inflammatory properties and may stimulate bone growth [90]. Statins have anabolic effects on the bone by augmenting bone morphogenetic protein-2 expression and thereby contributing towards the differentiation and activity of osteoblasts [91]. Due to their activity on bone formation statins have been considered as potential agents in improving periodontal treatment outcomes [92]. Limited data is available on the impact of stains on periodontal tissues suggesting a reduction in periodontal destruction and tooth loss [93]. Experimental studies on rats support the potential protective effect of statins on periodontal bone loss. Although these basic data are interesting, further research could extrapolate the use of statins as a potential adjunctive therapeutic agent in periodontal disease and bone regeneration.

3.5 Anti-platelet drugs

Anti-platelet drugs are widely used for the treatment of established cardiovascular disease, the prevention of atherothrombotic events and the treatment of myocardial infarction. The most commonly prescribed antiplatelets drugs are aspirin

and clopidogrel which are often used in combination. Both of these drugs have been reported to cause increased gingival bleeding. Patients on these medications carry a risk of an increased tendency to bleeding during or following periodontal surgery and this risk is far greater when the drugs are used in combination [94].

4. Conclusion

Several systemic factors are known to contribute to periodontal diseases or conditions and among those are the intake of drugs. The gingival overgrowth associated with medications occur as a side effect of systemic medications. These medications include the anti-seizure drug phenytoin, the immune suppressor cyclosporin A, and certain anti-hypertensive dihydropyridine calcium-channel-blockers, most notably nifedipine. It is crucial that health professionals understand the complications that medications can have on the oral health of their patients. In order to properly diagnose and treat patients, a complete medical history including prescription medications, over the counter drugs and dietary supplements must be recorded which will enable the healthcare team to identify the causative agents.

Conflict of interest

None declared.

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References

[1] Bascones-Martinez A, Munoz-Corcuera M, Bascones-Ilundain C. Side effects of drugs on the oral cavity. Medicina Clínica (Barcelona). 2015;**144**:126-131. DOI: 10.1016/j.medcli.2014.01.025

[2] Heasman PA, Hughes FJ. Drugs, medications and periodontal disease. British Dental Journal. 2014;**217**:411-419. DOI: 10.1038/sj.bdj.2014.905

[3] Ramirez-Ramiz A, Brunet LL, Lahor-Soler E, Miranda-Rius J. On the cellular and molecular mechanisms of drug-induced gingival overgrowth. The Open Dentistry Journal. 2017;**11**:420-435. DOI: 10.2174/1874210601711010420

[4] Al Sayed AA, Al Sulaiman MH, Mishriky A, Anil S. The role of androgen receptor gene in cyclosporine induced gingival overgrowth. Journal of Periodontal Research. 2014;**49**:609-614. DOI: 10.1111/jre.12141

[5] Chabria D, Weintraub RG, Kilpatrick NM. Mechanisms and management of gingival overgrowth in paediatric transplant recipients: A review. International Journal of Paediatric Dentistry. 2003;**13**:220-229. DOI: 10.1046/j.1365-263x.2003.00465.x

[6] Marshall RI, Bartold PM. Medication induced gingival overgrowth. Oral Diseases. 1998;**4**:130-151. DOI: 10.1111/j.1601-0825.1998.tb00269.x

[7] Margiotta V, Pizzo I, Pizzo G, Barbaro A. Cyclosporin- and nifedipine-induced gingival overgrowth in renal transplant patients: Correlations with periodontal and pharmacological parameters, and HLA-antigens. Journal of Oral Pathology & Medicine. 1996;**25**:128-134. DOI: 10.1111/j.1600-0714.1996.tb00207.x

[8] Seymour RA, Ellis JS, Thomason JM. Risk factors for drug-induced gingival overgrowth. Journal of Clinical Periodontology. 2000;**27**:217-223. DOI: 10.1034/j.1600-051x.2000.027004217.x

[9] Dannewitz B, Edrich C, Tomakidi P, Kohl A, Gabbert O, Eickholz P, et al. Elevated gene expression of MMP-1, MMP-10, and TIMP-1 reveal changes of molecules involved in turn-over of extracellular matrix in cyclosporine-induced gingival overgrowth. Cell and Tissue Research. 2006;**325**:513-522. DOI: 10.1007/s00441-006-0200-x

[10] Gagliano N, Moscheni C, Dellavia C, Torri C, Stabellini G, Ferrario VF, et al. Effect of cyclosporin A on human gingival fibroblast collagen turnover in relation to the development of gingival overgrowth: An in vitro study. Biomedicine & Pharmacotherapy. 2004;**58**:231-238. DOI: 10.1016/j.biopha.2003.12.011

[11] O'Valle F, Mesa F, Aneiros J, Gomez-Morales M, Lucena MA, Ramirez C, et al. Gingival overgrowth induced by nifedipine and cyclosporin A. clinical and morphometric study with image analysis. Journal of Clinical Periodontology. 1995;**22**:591-597. DOI: 10.1111/j.1600-051x.1995.tb00810.x

[12] Dongari-Bagtzoglou A, Research, Science and Therapy Committee, American Academy of Periodontology. Drug-associated gingival enlargement. Journal of Periodontology. 2004;**75**:1424-1431. DOI: 10.1902/jop.2004.75.10.1424

[13] Camargo PM, Melnick PR, Pirih FQ, Lagos R, Takei HH. Treatment of drug-induced gingival enlargement: Aesthetic and functional considerations. Periodontology 2000. 2001;**27**:131-138. DOI: 10.1034/j.1600-0757.2001.027001131.x

[14] Muralikrishna T, Kalakonda B, Gunupati S, Koppolu P. Laser-assisted

periodontal management of drug-induced gingival overgrowth under general anesthesia: A viable option. Case Reports in Dentistry. 2013;**2013**:387453. DOI: 10.1155/2013/387453

[15] Fornaini C, Rocca JP. CO_2 laser treatment of drug-induced gingival overgrowth—Case report. Laser Therapy. 2012;**21**:39-42. DOI: 10.5978/islsm.12-CR-01

[16] Tejnani A, Gandevivala A, Bhanushali D, Gourkhede S. Combined treatment for a combined enlargement. Journal of Indian Society of Periodontology. 2014;**18**:516-519. DOI: 10.4103/0972-124X.138747

[17] Thomason JM, Seymour RA, Rawlins MD. Incidence and severity of phenytoin-induced gingival overgrowth in epileptic patients in general medical practice. Community Dentistry and Oral Epidemiology. 1992;**20**:288-291. DOI: 10.1111/j.1600-0528.1992.tb01701.x

[18] Angelopoulos AP, Goaz PW. Incidence of diphenylhydantoin gingival hyperplasia. Oral Surgery, Oral Medicine, and Oral Pathology. 1972;**34**:898-906. DOI: 10.1016/0030-4220(72)90228-9

[19] Prasad VN, Chawla HS, Goyal A, Gauba K, Singhi P. Incidence of phenytoin induced gingival overgrowth in epileptic children: A six month evaluation. Journal of the Indian Society of Pedodontics and Preventive Dentistry. 2002;**20**:73-80

[20] Casetta I, Granieri E, Desidera M, Monetti VC, Tola MR, Paolino E, et al. Phenytoin-induced gingival overgrowth: A community-based cross-sectional study in Ferrara, Italy. Neuroepidemiology. 1997;**16**:296-303. DOI: 10.1159/000109700

[21] Pick L, Bauer J. Dentistry and epilepsy. Nervenarzt. 2001;**72**:946-949. DOI: 10.1007/s001150170008

[22] Suneja B, Chopra S, Thomas AM, Pandian J. A clinical evaluation of gingival overgrowth in children on antiepileptic drug therapy. Journal of Clinical and Diagnostic Research. 2016;**10**:ZC32-ZC36. DOI: 10.7860/JCDR/2016/16443.7069

[23] Katz J, Givol N, Chaushu G, Taicher S, Shemer J. Vigabatrin-induced gingival overgrowth. Journal of Clinical Periodontology. 1997;**24**:180-182. DOI: 10.1111/j.1600-051x.1997.tb00488.x

[24] Mesa F, Aguilar M, Gonzalez-Moles MA, Guerrero A, Sanchez-Alvarez JC, Del Moral RG, et al. Vigabatrin-induced modification of Ki-67 expression in gingival epithelium: Immunohistochemical study of a short series. Journal of Periodontal Research. 2004;**39**:66-71. DOI: 10.1111/j.1600-0765.2004.00711.x

[25] Conde SA, Aarestrup FM, Vieira BJ, Bastos MG. Roxithromycin reduces cyclosporine-induced gingival hyperplasia in renal transplant patients. Transplantation Proceedings. 2008;**40**:1435-1438. DOI: 10.1016/j.transproceed.2008.04.012

[26] Cebeci I, Kantarci A, Firatli E, Aygun S, Tanyeri H, Aydin AE, et al. Evaluation of the frequency of HLA determinants in patients with gingival overgrowth induced by cyclosporine-A. Journal of Clinical Periodontology. 1996;**23**:737-742. DOI: 10.1111/j.1600-051x.1996.tb00603.x

[27] Kataoka M, Kido J, Shinohara Y, Nagata T. Drug-induced gingival overgrowth—A review. Biological and Pharmaceutical Bulletin. 2005;**28**:1817-1821. DOI: 10.1248/bpb.28.1817

[28] Ellis JS, Seymour RA, Taylor JJ, Thomason JM. Prevalence of

gingival overgrowth in transplant patients immunosuppressed with tacrolimus. Journal of Clinical Periodontology. 2004;**31**:126-131. DOI: 10.1111/j.0303-6979.2004.00459.x

[29] Ellis JS, Seymour RA, Steele JG, Robertson P, Butler TJ, Thomason JM. Prevalence of gingival overgrowth induced by calcium channel blockers: A community-based study. Journal of Periodontology. 1999;**70**:63-67. DOI: 10.1902/jop.1999.70.1.63

[30] Miranda J, Brunet L, Roset P, Berini L, Farre M, Mendieta C. Prevalence and risk of gingival enlargement in patients treated with nifedipine. Journal of Periodontology. 2001;**72**:605-611. DOI: 10.1902/jop.2001.72.5.605

[31] Fattore L, Stablein M, Bredfeldt G, Semla T, Moran M, Doherty-Greenberg JM. Gingival hyperplasia: A side effect of nifedipine and diltiazem. Special Care in Dentistry. 1991;**11**:107-109. DOI: 10.1111/j.1754-4505.1991.tb00828.x

[32] Steele RM, Schuna AA, Schreiber RT. Calcium antagonist-induced gingival hyperplasia. Annals of Internal Medicine. 1994;**120**:663-664. DOI: 10.7326/0003-4819-120-8-199404150-00006

[33] Miller CS, Damm DD. Incidence of verapamil-induced gingival hyperplasia in a dental population. Journal of Periodontology. 1992;**63**:453-456. DOI: 10.1902/jop.1992.63.5.453

[34] Jorgensen MG. Prevalence of amlodipine-related gingival hyperplasia. Journal of Periodontology. 1997;**68**:676-678. DOI: 10.1902/jop.1997.68.7.676

[35] Sucu M, Yuce M, Davutoglu V. Amlodipine-induced massive gingival hypertrophy Canadian family physician. Medecin de Famille Canadien. 2011;**57**:436-437

[36] Lombardi T, Fiore-Donno G, Belser U, Di Felice R. Felodipine-induced gingival hyperplasia: A clinical and histologic study. Journal of Oral Pathology & Medicine. 1991;**20**:89-92. DOI: 10.1111/j.1600-0714.1991.tb00896.x

[37] Majola MP, McFadyen ML, Connolly C, Nair YP, Govender M, LaherMH. Factorsinfluencingphenytoin-induced gingival enlargement. Journal of Clinical Periodontology. 2000;**27**:506-512. DOI: 10.1034/j.1600-051x.2000.027007506.x

[38] Faulds D, Goa KL, Benfield P. Cyclosporin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in immunoregulatory disorders. Drugs. 1993;**45**:953-1040. DOI: 10.2165/00003495-199345060-00007

[39] Ting LS, Villeneuve E, Ensom MH. Beyond cyclosporine: A systematic review of limited sampling strategies for other immunosuppressants. Therapeutic Drug Monitoring. 2006;**28**:419-430. DOI: 10.1097/01.ftd.0000211810.19935.44

[40] Seymour RA, Jacobs DJ. Cyclosporin and the gingival tissues. Journal of Clinical Periodontology. 1992;**19**:1-11. DOI: 10.1111/j.1600-051x.1992.tb01140.x

[41] Fahr A. Cyclosporin clinical pharmacokinetics. Clinical Pharmacokinetics. 1993;**24**:472-495. DOI: 10.2165/00003088-199324060-00004

[42] de Oliveira Costa F, Diniz Ferreira S, de Miranda Cota LO, da Costa JE, Aguiar MA. Prevalence, severity, and risk variables associated with gingival overgrowth in renal transplant subjects treated under tacrolimus or cyclosporin regimens. Journal of Periodontology. 2006;**77**:969-975. DOI: 10.1902/jop.2006.050327

[43] Oliveira Costa F, Ferreira SD, Lages EJ, Costa JE, Oliveira AM, Cota LO. Demographic, pharmacologic, and periodontal variables for gingival overgrowth in subjects medicated with cyclosporin in the absence of calcium channel blockers. Journal of Periodontology. 2007;**78**:254-261. DOI: 10.1902/jop.2007.050445

[44] Cota LO, Aquino DR, Franco GC, Cortelli JR, Cortelli SC, Costa FO. Gingival overgrowth in subjects under immunosuppressive regimens based on cyclosporine, tacrolimus, or sirolimus. Journal of Clinical Periodontology. 2010;**37**:894-902. DOI: 10.1111/j.1600-051X.2010.01601.x

[45] Daley TD, Wysocki GP, Day C. Clinical and pharmacologic correlations in cyclosporine-induced gingival hyperplasia. Oral Surgery, Oral Medicine, and Oral Pathology. 1986;**62**:417-421. DOI: 10.1016/0030-4220(86)90291-4

[46] Pernu HE, Pernu LM, Huttunen KR, Nieminen PA, Knuuttila ML. Gingival overgrowth among renal transplant recipients related to immunosuppressive medication and possible local background factors. Journal of Periodontology. 1992;**63**:548-553. DOI: 10.1902/jop.1992.63.6.548

[47] Schincaglia GP, Forniti F, Cavallini R, Piva R, Calura G, del Senno L. Cyclosporin-A increases type I procollagen production and mRNA level in human gingival fibroblasts in vitro. Journal of Oral Pathology & Medicine. 1992;**21**:181-185. DOI: 10.1111/j.1600-0714.1992.tb00098.x

[48] Fu MM, Chin YT, Fu E, Chiu HC, Wang LY, Chiang CY, et al. Role of transforming growth factor-beta1 in cyclosporine-induced epithelial-to-mesenchymal transition in gingival epithelium. Journal of Periodontology. 2015;**86**:120-128. DOI: 10.1902/jop.2014.130285

[49] Malek R, El Houari B, Kissa J. Periodontal management of cyclosporin A-induced gingival overgrowth: A nonsurgical approach. Case Reports in Dentistry. 2019;**2019**:8609547. DOI: 10.1155/2019/8609547

[50] Ramalho VL, Ramalho HJ, Cipullo JP, Azoubel R, Burdmann EA. Comparison of azithromycin and oral hygiene program in the treatment of cyclosporine-induced gingival hyperplasia. Renal Failure. 2007;**29**:265-270. DOI: 10.1080/08860220701263580

[51] Gau CH, Tu HP, Chin YT, Chen RY, Fu MM, Fu E. Can chlorhexidine mouthwash twice daily ameliorate cyclosporine-induced gingival overgrowth? Journal of the Formosan Medical Association = Taiwan yi zhi. 2013;**112**:131-137. DOI: 10.1016/j.jfma.2011.12.004

[52] Pilatti GL, Sampaio JE. The influence of chlorhexidine on the severity of cyclosporin A-induced gingival overgrowth. Journal of Periodontology. 1997;**68**:900-904. DOI: 10.1902/jop.1997.68.9.900

[53] Morgan TO, Anderson AI, MacInnis RJ. ACE inhibitors, beta-blockers, calcium blockers, and diuretics for the control of systolic hypertension. American Journal of Hypertension. 2001;**14**:241-247. DOI: 10.1016/s0895-7061(00)01266-8

[54] Seymour RA. Effects of medications on the periodontal tissues in health and disease. Periodontology 2000. 2006;**40**:120-129. DOI: 10.1111/j.1600-0757.2005.00137.x

[55] Lederman D, Lumerman H, Reuben S, Freedman PD. Gingival hyperplasia associated with nifedipine therapy. Report of a case. Oral Surgery, Oral Medicine, and Oral Pathology. 1984;**57**:620-622. DOI: 10.1016/0030-4220(84)90283-4

[56] Ramon Y, Behar S, Kishon Y, Engelberg IS. Gingival hyperplasia caused by nifedipine—A preliminary report. International Journal of Cardiology. 1984;**5**:195-206. DOI: 10.1016/0167-5273(84)90145-1

[57] Lucas RM, Howell LP, Wall BA. Nifedipine-induced gingival hyperplasia. A histochemical and ultrastructural study. Journal of Periodontology. 1985;**56**:211-215. DOI: 10.1902/jop.1985.56.4.211

[58] Trackman PC, Kantarci A. Molecular and clinical aspects of drug-induced gingival overgrowth. Journal of Dental Research. 2015;**94**:540-546. DOI: 10.1177/0022034515571265

[59] Mishra MB, Khan ZY, Mishra S. Gingival overgrowth and drug association: A review. Indian Journal of Medical Science. 2011;**65**:73-82. DOI: 10.4103/0019-5359.103971

[60] Barak S, Engelberg IS, Hiss J. Gingival hyperplasia caused by nifedipine. Histopathologic findings. Journal of Periodontology. 1987;**58**:639-642. DOI: 10.1902/jop.1987.58.9.639

[61] Lauritano D, Lucchese A, Di Stasio D, Della Vella F, Cura F, Palmieri A, et al. Molecular aspects of drug-induced gingival overgrowth: An in vitro study on amlodipine and gingival fibroblasts. International Journal of Molecular Sciences. 2019;**20**:2047. DOI: 10.3390/ijms20082047

[62] Lafzi A, Farahani RM, Shoja MA. Amlodipine-induced gingival hyperplasia. Medicina Oral, Patologia Oral y Cirugia Bucal. 2006;**11**:E480-E482

[63] Gaur S, Agnihotri R. Is dental plaque the only etiological factor in amlodipine induced gingival overgrowth? A systematic review of evidence. Journal of Clinical and Experimental Dentistry. 2018;**10**:e610-e6e9. DOI: 10.4317/jced.54715

[64] Nanda T, Singh B, Sharma P, Arora KS. Cyclosporine A and amlodipine induced gingival overgrowth in a kidney transplant recipient: Case presentation with literature review. BMJ Case Report. 2019;**12**. DOI: 10.1136/bcr-2019-229587

[65] Pernu HE, Oikarinen K, Hietanen J, Knuuttila M. Verapamil-induced gingival overgrowth: A clinical, histologic, and biochemic approach. Journal of Oral Pathology & Medicine. 1989;**18**:422-425. DOI: 10.1111/j.1600-0714.1989.tb01576.x

[66] Saivin S, Houin G. Clinical pharmacokinetics of doxycycline and minocycline. Clinical Pharmacokinetics. 1988;**15**:355-366. DOI: 10.2165/00003088-198815060-00001

[67] Berger RS, Mandel EB, Hayes TJ, Grimwood RR. Minocycline staining of the oral cavity. Journal of the American Academy of Dermatology. 1989;**21**:1300-1301. DOI: 10.1016/s0190-9622(89)80309-3

[68] Noonan VL, Kabani S, Wu J. Minocycline-induced staining of the oral cavity. Journal of the Massachusetts Dental Society. 2009;**57**:42

[69] LaPorta VN, Nikitakis NG, Sindler AJ, Reynolds MA. Minocycline-associated intra-oral soft-tissue pigmentation: Clinicopathologic correlations and review. Journal of Clinical Periodontology. 2005;**32**: 119-122. DOI: 10.1111/j.1600-051X.2005.00646.x

[70] Siller GM, Tod MA, Savage NW. Minocycline-induced oral pigmentation. Journal of the American Academy of Dermatology.

1994;**30**:350-354. DOI: 10.1016/s0190-9622(94)70038-9

[71] Friedman IS, Shelton RM, Phelps RG. Minocycline-induced hyperpigmentation of the tongue: Successful treatment with the Q-switched ruby laser. Dermatologic Surgery. 2002;**28**:205-209. DOI: 10.1046/j.1524-4725.2002.01083.x

[72] Eisen D, Hakim MD. Minocycline-induced pigmentation. Incidence, prevention and management. Drug Safety. 1998;**18**:431-440. DOI: 10.2165/00002018-199818060-00004

[73] Domingues R S, Ferraz B F, Greghi SL, Rezende M L, Passanezi E, Sant'Ana AC. Influence of combined oral contraceptives on the periodontal condition. Journal of Applied Oral Science: Revista FOB 2012;**20:**253-259. DOI: 10.1590/s1678-77572012000200022

[74] Mullally BH, Coulter WA, Hutchinson JD, Clarke HA. Current oral contraceptive status and periodontitis in young adults. Journal of Periodontology. 2007;**78**:1031-1036. DOI: 10.1902/jop.2007.060163

[75] Pankhurst CL, Waite IM, Hicks KA, Allen Y, Harkness RD. The influence of oral contraceptive therapy on the periodontium—Duration of drug therapy. Journal of Periodontology. 1981;**52**:617-620. DOI: 10.1902/jop.1981.52.10.617

[76] Mariotti A. Sex steroid hormones and cell dynamics in the periodontium. Critical Reviews in Oral Biology & Medicine. 1994;**5**:27-53. DOI: 10.1177/10454411940050010201

[77] Prachi S, Jitender S, Rahul C, Jitendra K, Priyanka M, Disha S. Impact of oral contraceptives on periodontal health. African Health Sciences. 2019;**19**:1795-1800. DOI: 10.4314/ahs.v19i1.56

[78] Mealey BL, Moritz AJ. Hormonal influences: Effects of diabetes mellitus and endogenous female sex steroid hormones on the periodontium. Periodontology 2000. 2003;**32**:59-81. DOI: 10.1046/j.0906-6713.2002.03206.x

[79] Mistry S, Bhowmick D. Oral contraceptive pill induced periodontal endocrinopathies and its management: A case report. European Journal of Dentistry. 2012;**6**:324-329

[80] Haerian-Ardakani A, Moeintaghavi A, Talebi-Ardakani MR, Sohrabi K, Bahmani S, Dargahi M. The association between current low-dose oral contraceptive pills and periodontal health: A matched-case-control study. The Journal of Contemporary Dental Practice. 2010;**11**:033-040

[81] Preshaw PM. Oral contraceptives and the periodontium. Periodontology 2000. 2013;**61**:125-159. DOI: 10.1111/j.1600-0757.2011.00399.x

[82] Anil S, Preethanath RS, Al Moharib HS, Kamath KP, Anand PS. Impact of osteoporosis and its treatment on oral health. American Journal of Medical Science. 2013;**346**:396-401. DOI: 10.1097/MAJ.0b013e31828983da

[83] Mucke T, Krestan CR, Mitchell DA, Kirschke JS, Wutzl A. Bisphosphonate and medication-related osteonecrosis of the jaw: A review. Seminars in Musculoskeletal Radiology. 2016;**20**:305-314. DOI: 10.1055/s-0036-1592367

[84] Rogers MJ. From molds and macrophages to mevalonate: A decade of progress in understanding the molecular mode of action of bisphosphonates. Calcified Tissue International. 2004;**75**:451-461. DOI: 10.1007/s00223-004-0024-1

[85] Bellido T, Plotkin LI. Novel actions of bisphosphonates in bone: Preservation of osteoblast and osteocyte

viability. Bone. 2011;**49**:50-55. DOI: 10.1016/j.bone.2010.08.008

[86] Franco C, Patricia HR, Timo S, Claudia B, Marcela H. Matrix metalloproteinases as regulators of periodontal inflammation. International Journal of Molecular Science. 2017;**18**:440. DOI: 10.3390/ijms18020440

[87] Pradeep AR, Kumari M, Rao NS, Naik SB. 1% alendronate gel as local drug delivery in the treatment of Class II furcation defects: A randomized controlled clinical trial. Journal of Periodontology. 2013;**84**:307-315. DOI: 10.1902/jop.2012.110729

[88] Bhavsar NV, Trivedi SR, Dulani K, Brahmbhatt N, Shah S, Chaudhri D. Clinical and radiographic evaluation of effect of risedronate 5 mg as an adjunct to treatment of chronic periodontitis in postmenopausal women (12-month study). Osteoporosis International. 2016;**27**:2611-2619. DOI: 10.1007/s00198-016-3577-8

[89] Akram Z, Abduljabbar T, Kellesarian SV, Abu Hassan MI, Javed F, Vohra F. Efficacy of bisphosphonate as an adjunct to nonsurgical periodontal therapy in the management of periodontal disease: A systematic review. British Journal of Clinical Pharmacology. 2017;**83**:444-454. DOI: 10.1111/bcp.13147

[90] Lindy O, Suomalainen K, Makela M, Lindy S. Statin use is associated with fewer periodontal lesions: A retrospective study. BMC Oral Health. 2008;**8**:16. DOI: 10.1186/1472-6831-8-16

[91] Zhou H, Xie Y, Baloch Z, Shi Q, Huo Q, Ma T. The effect of atorvastatin, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (HMG-CoA), on the prevention of osteoporosis in ovariectomized rabbits. Journal of Bone and Mineral Metabolism. 2017;**35**:245-254. DOI: 10.1007/s00774-016-0750-2

[92] Pradeep AR, Garg V, Kanoriya D, Singhal S. 1.2% rosuvastatin versus 1.2% atorvastatin gel local drug delivery and redelivery in treatment of intrabony defects in chronic periodontitis: A randomized placebo-controlled clinical trial. Journal of Periodontology. 2016;**87**:756-762. DOI: 10.1902/jop.2016.150706

[93] Santos BF, Souza EQ, Brigagao MR, Lima DC, Fernandes LA. Local application of statins in the treatment of experimental periodontal disease in rats. Journal of Applied Oral Science: Revista FOB. 2017;**25**:168-176. DOI: 10.1590/1678-77572016-0149

[94] Graziani F, Cei S, Guerrero A, La Ferla F, Vano M, Tonetti M, et al. Lack of short-term adjunctive effect of systemic neridronate in non-surgical periodontal therapy of advanced generalized chronic periodontitis: An open label-randomized clinical trial. Journal of Clinical Periodontology. 2009;**36**:419-427. DOI: 10.1111/j.1600-051X.2009.01388.x