Vitamins in dental health

Vitamins

- Essential for normal functioning of the body- growth, vitality, well-being
- Vitamins occur in all organic material
- Cannot be synthesized internally (few exceptions) and assimilated without ingesting food
- They have no calories or energy value on their own
- They are not substitutes for protein or any other nutrients (mineral, fats, carbohydrates, water)- vitamins cannot replace food
- Vitamins themselves are not components of body structures
- Vitamins regulate metabolism through enzyme systems (coenzymes, cofactors)

Water soluble vitamins

- Inactive until they are transformed into their **coenzyme form**.
- Most water-soluble vitamins (C and all B vitamins) can act as coenzymes or are required for the synthesis of coenzymes that make enzymatic reactions possible
- Circulate freely in the blood, watery fluids between cells and inside cells
- Water-soluble vitamins are vulnerable to **losses** and **degradation** in **processing** and **cooking** (they can leach out into cooking water and are sensitive to heat)
- Excesses of water-soluble vitamins are eliminated by kidneys (except: folate, B_{12})
- **Water-soluble vitamins do not show toxicity** when consumed in food. Supplements are also not toxic in recommended amounts (except: B_3 in the form of niacin, vitamin C in the acidic form)

Vitamin	Functions	Deficiency signs	Oral signs of deficiency
C	• antioxidant • lowers cholesterol • supports the immune system • collagen synthesis	• poor collagen synthesis • weakening of the immune system, skin, muscles, heart, joints • iron deficiency • **Scurvy**	• bleeding gums • loosened teeth • Scorbutic gingivitis
B1 **Thiamin**	• active coenzyme form: thiamine pyrophosphate • sugars and aminoacids catabolism • promotes growth	• fatigue, lack of appetite, • changes in the nervous and cardiovascular systems • weight loss, muscular weakness, poor short-term memory, enlarged heart and cardiac failure • **Beri beri**	• hypersensitive dentine and oral mucosa • atypical neuralgias of the tongue, dentition, jaws and face
B2 **Riboflavin**	• works as a part of FAD and FMN coenzyme • metabolism of fats, protein, and carbohydrates into glucose • an antioxidant role • helps convert tryptophan to niacin,	• inflammatory changes on the skin, acne, dizziness, changes in the organ of vision • **Ariboflavinosis**-inflammation of the membranes of the eyes, the mouth, the skin, and the	• cracks on the side of the mouth (cheilosis) • sore throat with redness and swelling

	which activates vitamin B6 • necessary for normal development, lactation and reproduction • can help to prevent such diseases as anemia, cataracts, migraines, and thyroid dysfunction	gastrointestinal tract; also can cause sensitivity to light	of the mouth and throat mucosa • glossitis (inflammed red tongue with atrophy)
B3 **Niacin**	• two forms: niacin (nicotinic acid) and niacinamide (nicotinamide); • precursors of the NAD and NADP coenzymes • helps reduce cholesterol and triglicerides • aids in metabolizing fats and promotes a healthy digestive system • gives healthier looking skin • helps eliminate canker sores and bad breath • helps prevent and ease severity of migraine headaches • increases circulation and reduces high blood pressure	• disturbances in the process of glycolysis • disruption of the central and peripheral nervous system • digestive system dysfunctions. • **pelagra** - a disease whose symptoms are skin inflammation, diarrhea, nausea, changes in the tongue and mouth (inflammation of the mucosa, erosions, ulcers, inflammation of the mouth corner, tongue), and even paralysis of the limbs and dementia (4 Ds: diarrhea, dermatitis , dementia, death).	• tongue- swelling and burning, hypertrophic withpseudo-membranous furrows, erosions, ulcers • cheilitis, angular stomatitis, glossitis • dental caries • oral mucosa inflammation,
B9 **Folate** **Folacin** **Folic acid**	• primary coenzyme form: *TetraHydroFolate* (THF) – needed to transfer *one-carbon units* (methylation reactions) • essential for the formation of red blood cells and division of body cells • helps ward off anemia • important for the production of nucleic acids • needed for utilization of sugar and amino acids • lowers homocysteine levels, reducing the risk of heart disease • improves lactation • protects against intestinal parasites and food poisoning • promotes healthier looking skin and prevents canker sores • act as an analgesic for pain • protects against birth defects (neural tube defects)	• **neural tube defects** in an embryo • anemia and deterioration of the gastrointestinal tract • abnormal blood cell division (folate deficiency limits cell division) results in anemia, characterized by fewer and larger red blood cells (*megaloblastic anemia*) • weakness, headaches, heart palpitations, irritability and behavioral disorders	• impaired production and functioning of immune cells- high turnover of squamous • epithelium process which is essential for repair of periodontal tissues is damaged • absence of keratinization of gingival surface • early childhood caries • ulcerative glossitis and cheilitis • necrosis of gingiva, periodontal ligament, • and alveolar bone destruction
	• the largest and most complex vitamin in the human body, with a complex system of absorption • two active forms: methylcobalamin and adenosylcobalamin (most of the	• neurological effects (appear with mild cobalamin deficiencies) - ranging from milder symptoms (fatigue, paresthesia, tingling,	• appear in 50-60% of all patients with megaloblastic anemia) • “beefy” red and

B12 Cobalamin	liver stores are in this form) - for enzymes involved in the synthesis of DNA, fatty acids and myelin
	• synthetic form - cyanocobalamin - the cheapest and most stable form, converted in the body into methyl- and hydroxocobalamin
	• required for the proper formation of red blood cells (along with iron and folic acid – it also helps in the absorption of folic acid)
	• necessary for the proper functioning of the nervous system and mental health (the synthesis of enzymes producing serotonin and dopamine in neurons depends on vitamin B12)
	• used in the treatment of sciatica, radicular pain and inflammation of the trigeminal nerve
	• B12 is naturally found in animal products, generally not present in plant foods, (but fortified breakfast cereals are a readily available source of vitamin B12 with high bioavailability) and it is also produced by healthy gut bacteria
	• B12 released from food quickly attaches to the cobalamin-binding protein (R-binder), found in saliva and gastric juice. In the stomach there is an intrinsic factor (Castle's) - IF (Intrinsic factor), which at the correct pH of gastric juice helps in the absorption of vitamin B12.
	• the liver stores 2-5 mg of cobalamin, which can last about 700-1500 days (in people with "full storage")
	• Interactions:
	  • about 30% of diabetics taking metformin have low B12 levels,
	  • PPIs, H2 blockers, antacids - lower the pH of gastric juice, which significantly reduces the absorption of B12
		numbness, problems with balance; psychological symptoms) to severe features (degeneration of the spinal cord)
		• **megaloblastic anemia** occurs when the body's cobalamin stores fall below 0.1mg (normal range- 4–5 mg stored in the liver)
		• macrocytosis due to cobalamin deficiency is a direct result of ineffective or dysplastic erythropoiesis
			inflamed tongue with
			
			erythematous macular lesions on the dorsal and border surfaces,
			• soreness of the tongue and generalized ulceration,
			• reduced taste sensitivity,
			• sore mouth or burning mouth,
			• candidiasis and angular cheilitis

Fat soluble vitamins

- Fat soluble vitamins are stored in adipose tissues (found in the liver and the fatty tissues of the body)
- These vitamins are not absorbed directly into the blood stream but are absorbed in the small intestine via chylomicrons, transported through the lymphatic system and then released into the blood stream
- **Require bile** in order to be absorbed into the lymph system from the intestines

- The fat-soluble vitamins are stored in the body for long periods of time and generally pose a greater risk for toxicity than water-soluble vitamins when consumed in excess
- While diseases caused by a lack of these vitamins are rather rare, symptoms of mild deficiency can develop.
- Some diseases, such as inflammatory bowel disease, chronic pancreatitis, and cystic fibrosis, may decrease the absorption of fat, and in turn, decrease the absorption of fat-soluble vitamins

Vitamin	Functions	Deficiency signs	Oral signs of deficiency

A	• two food forms: provitamin A carotenoids in plants, retinyl esters in animal products
	• forms of vitamin A:
	  • carotens
	  • retinyl esters
	  • retinol
	  • retinal
	  • retinoic acid
	  • retinyl palmitate
	• most of the vitamin A in the body is stored in the liver in the form of retinyl palmitate which is converted to retinol in the small intestine.
	• retinol is a storage form of the vitamin, supports healthy skin; can be converted to retinal- aldehyde form needed for vision (it is a part of rhodopsin)
	• antioxidant activity (beta-carotene)
	• counteracts night blindness, weak eyesights; aids in the treatment of many eye disorders
	• retinoic acid - growth factor for epithelial cells, exfoliating action but also inhibiting keratosis of the epidermis; applied externally helps treat acne, superficial wrinkles, age spots, impetigo (bacterial infection), boils (pimples), carbuncles (clusters of boils caused by bacterial infection) and open ulcers
	• builds resistance to respiratory infections
	• keeps the outer layers of tissues and organs healthy
	• aids in the treatment of emphysema and hyperthyroidism
	• promotes growth, strong bones, healthy skin, hair, teeth and gums
		• severe deficiency is one of the leading causes of blindness in children
		• multiple abnormalities in innate and adaptive immunity
		• all epithelial tissues are sensitive to a lack and excess of vitamin A; deficiency in skin appears as dryness
		
		Excess:
		• hyperactivity and irritability,
		• nausea, vomiting,
		• headaches, joint and muscle pain,
		• enlargement of the liver and disorders of its functions,
		• yellowish skin lesions,
		• Teratogenicity and birth defects in children of mothers who experienced hypervitaminosis during pregnancy,
			• efective formation of enamel →hypoplasia of teeth
			• dentin tubular structure may be disturbed
			• increased risk of caries
			• hyperplastic gingival epithelium
			• periodontal disease
			• salivary gland atrophy (reduces the defence of the oral cavity against infection and its ability to buffer the plaque acids)

Vitamin D Calciferol	• vitamin D is a prohormone – must be metabolized to a biologically active form that functions as a steroid hormone
	• vitamin D forms
	  • 7-Dehydrocholesterol - provitamin D3
	  • vitamin D3 - cholecalciferol, produced in the skin and taken in the form of supplements
	  • calcidiol - storage form
	  • vitamin D2 - ergocalciferol, is formed from ergosterol (found in fungi, e.g. yeast) under the influence of UV radiation
	  • calcitriol - the active form of vitamin D3
	• regulates calcium and phosphorus - increases the synthesis of calcium-binding protein and its absorption, releases calcium and phosphates - in hypocalcaemia and helps calcium reabsorption form kidneys- the correct amount of vitamin D in the body is an important factor in the prevention of osteoporosis, fractures, rickets and osteomalacia
	• plays a role in glucose metabolism - stimulates insulin secretion via the vitamin D receptor on pancreatic beta cells (relationship between low vitamin D levels and the occurrence of type 1 and type 2 diabetes)
	• aids the functioning of the immune system (taken with vitamins A and C can aid in preventing colds)
	• vitamin D receptors have been found in many tissues, including the cells that make up the cardiovascular system -vitamin D may be involved in the pathogenesis of cardiovascular diseases
	• necessary in the diet for people who get too little sun to synthesize it
		• Rickets, osteomalacia, senile osteoporosis
		• It becomes difficult to keep enough calcium in the bloodstream releasing calcium from bones
		• Severe deficiency in childhood: the bones fail to mineralize properly
		→ the arms and legs become bowed (rickets)
		• Very severe cases: low levels of blood calcium affect the nerves
		
		Deficiency risk factors:
		• the skin's ability to synthesize vitamin D declines with age
		• limited exposure to sunlight (office work, latitude)
		• UV filters (even SPF8 is able to reduce the skin synthesis of vitamin D by 97.5%)
		• dark complexion
		• impaired absorption of fats in the gut: inflammation of the intestines, liver disease
		• drugs: glucocorticoids, antiepileptic drugs
			• severe tooth decay
			• developmental abnormalities of dentine and enamel
			• higher risk of caries
			• enamel hypoplasia
			• pulp malformations

Vitamin E α-tocopherol	• main role: antioxidant neutralizing free radicals in cell membranes, in mitochondrial membranes and LDL
	• protects the lungs from air pollution, along with vitamin A (also increases the activity of vitamin A)
	• important in the production of red blood cells **-** involved in the protection of red blood cells, gene expression
	• dilates blood vessels and maintains the proper level of blood clotting.
		• occurs rarely, virtually never as a result of dietary deficiency:
		  • genetic defect in α-tocopherol transfer protein
		  • genetic defect in lipoprotein synthesis
		  • fat malabsorption syndromes
		  • the primary manifestations of human vitamin E
			• loss of pigmentation
			• atrophic degenerative changes in enamel

	• lowers the risk of ischemic heart disease and stroke • affects the proper muscle performance and the production of sperm in men • co-responsible for the maintenance of pregnancy and proper development of the fetus • supports the body in the effective use of vitamin K • when applied to the skin, it can penetrate the epidermis and build up into intercellular • cement, improving skin elasticity and accelerating its healing • decreases risk of Alzheimer's disease and helps to prevent various forms of cancer	deficiency include spinocerebellar ataxia, skeletal myopathy, and pigmented retinopathy • earliest observed symptom is hypo- or a-reflexia	

Vitamin K	• vitamin K - compounds with biological activity: phylloquinone (vitamin K1), menaquinone (vitamin K2), menadione (vitamin K3) - synthetic form
	• The demand for vitamin K in healthy adults is covered by food (vitamin K1 - plant foods- amount of vitamin K in plant leaves is proportional to the chlorophyll content) and its synthesis by the jejunum and ileum microbiome (vitamin K2).
	• has an antihaemorrhagic effect, it is needed for the production of prothrombin in the liver, which is essential for blood clotting
	  • serving vit. K is one way of treating bleeding caused by an overdose of warfarin, an anticoagulant medicine
	  • vitamin K is given by injection to newborns to prevent bleeding from deficiency
	• Takes part in the formation of bone tissue; control of calcium binding in bones and other tissues (in the case of deficiency, the risk of osteoporosis and calcification of arteries and other soft tissues increases).
	• Characterized by antibacterial, antifungal, anti-inflammatory and analgesic properties
		• deficiency can occur in newborns because the bacteria that produce vitamin K are not yet in their intestines
		• deficiency is not a common occurrence with a balanced diet, but it can occur in people with bulimia and following a strict diet.
		• people suffering from liver diseases and damage (including alcoholism), cystic fibrosis, inflammatory bowel diseases, and who have recently undergone abdominal surgery are also susceptible.
		• drugs associated with vitamin K deficiency include anticoagulants, salicylates, barbiturates, and cefamandol.
		• K1 deficiency symptoms include anemia, bruising, nose and gum bleeding in both sexes, and heavy menstrual bleeding in women. Osteoporosis and ischemic heart disease are strongly associated with lower K2 levels.
			• gingival erythema and bleeding
			• petechia
			• ecchymoses
			• hematomas of oral mucosa

Probiotics

- According to the FAO / WHO definition, the term "probiotic" refers to live microorganisms which, when administered in appropriate amounts, exert beneficial health effects.
- The probiotic microorganisms include mainly lactic acid-producing bacteria of the following types:
  - **Lactobacillus** (e.g. L. acidophilus, L. casei, L. reuteri, L. rhamnosus)
  - **Bifidobacterium** (e.g. B. animalis)
  - Other microbes traditionally classified as probiotics are the yeast Saccharomyces boulardii.

- Probiotics are a kind of bacteriotherapy, which may provide a decrease in CFU (colony forming units) counts of cariogenic pathogens (i.a.***Streptococcus mutans, Streptococcus sobrinus***)
- Probiotic bacteria are able to modulate the inflammatory response (humoral and cellular) and produce substances such as **lactic acid**, **hydrogen peroxide** and **bacteriocins** (antimicrobial agents produced by lactic acid bacteria, whose action provides the probiotic effect).
- Most of the studies mention its ability to compete with pathogens for adhesion surfaces and nutrients – beneficial bacteria can displace the pathogenic ones

Probiotic species used in clinical trials to target oral diseases/conditions:

Species	Condition	Number of subjects	Vehicle of administration	Reference
L. rhamnosus	Caries prevention	261	milk	Rodriguez et al. 2016
L. reuteri	Early carious lesions	36	tablet	Keller at al. 2014
B. lactis	Caries prevention	106	tablet	Taipale et al. 2012
L. rhamnosus	Root caries	160	milk	Petersson et al. 2011
L. reuteri	Chronic periodontitis	40	lozenge	Tekce et al. 2015
L. reuteri	Gingivitis	40	tablet	Iniesta et al. 2012
L. salivarius	Halitosis	20	tablet	Iwamoto et al. 2010
L.salivarius	Prevention of periodontitis	66	tablet	Shimauchi et al. 2008
B. longum, S. thermophilus, L. bulgaricus	Candida-associated stomatitis	65	mixture	Li et al. 2014
L. rhamnosus	Candida prevention	276	cheese	Hatakka et al. 2007
L. brevis	Halitosis	20	lozenge	Marchetti et al. 2015
L. reuteri	Halitosis	25	chewing gum	Keller et al. 2012
L. reuteri	Alteration to oral microbiotia	44	lozenge	Romani Vestman et al. 2015

On the market:

- *Lactobacillus plantarum CETC 7481, Lactobacillus brevis CETC7480, Pediococcus acidilacti CETC 8633* + vitamin D
- *Lactobacillus salivarius HM6 Paradens* + xylitol + vitamin D, C + coenzyme Q10

Adverse drug effects - stomatological complications

- Certain **prescription drugs** may cause specific changes to the periodontal tissues and influence the clinical presentation or progression of periodontal diseases:
  - **gingival overgrowth**
  - **gingival bleeding**
  - **inflammatory process**
  - **periodontal disease progression**
- The case in aging populations in which widespread long-term use of drugs for therapeutic use is seen, resulting in the phenomenon of "**polypharmacy**" (taking regularly 5 or more different medications)
- Central registries of adverse drug interactions tend to severely underrepresent adverse drug reactions affecting the periodontal tissues –
  - they are frequently not recognized by prescribing clinicians
  - go unreported because they are not considered of sufficient seriousness
  - it is difficult to assign a specific periodontal phenotype with a particular medication

Adverse drug effects:

Drug-induced Gingival Overgrowth (DIGO)

Gingival overgrowth (GO)

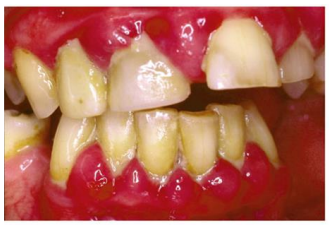
- characterized by an inflammatory hyperplasia and/or hypertrophy of the soft tissue between the teeth
- gingival tissue develops a characteristic of thickened and lobulated appearance that gradually extends along the labial, lingual, and coronal aspects
- may be associated with pain, tenderness, and bleeding of the gums
- it may increase the risk of oral infection, caries and predispose the affected individuals to periodontal diseases
- in advanced cases may interfere with speech, chewing, nutrition, and cause tooth eruption

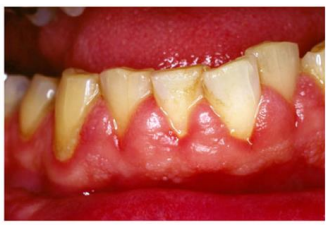
GO caused by: **Calcium channel blocker (CCBs)**

Calcium channel blockers classification:

- dihydropyridines (such as nifedipine, amlodipine and felodipine)
  - treatment of hypertension (smooth muscle relaxation and vasodilation)
- nondihydropyridines consisting of phenylalkylamines (verapamil)
  - anti-hypertensive, anti-anginal, anti-arrhytmic
- benzothiazepines (diltiazem)
  - anti-hypertensive, anti-anginal, anti-arrhytmic

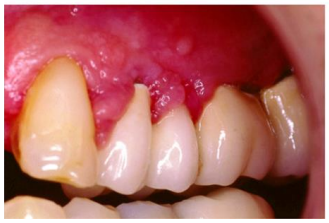
Nifedipine

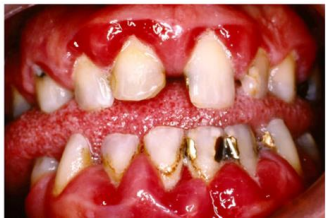




Felodopine

Amlodipine





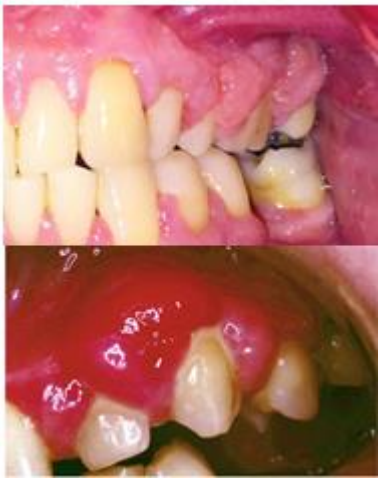
Verapamil

- The most widespread unwanted effect of CCBs on periodontal tissues
- Detected clinically as early as 1-3 months following the initial dose of CCB
- Reported to occur with all calcium channel blockers - very wide variations (5% up to 80%) in the prevalence, resulting from the design of studies, diagnostic criteria, actual drugs taken and drug dosages
- Characterized by an increase of the gingival mass and volume
- Can range from mild increase of the interproximal gingival papillae to severe enlargement of both marginal and papillary tissues

Mechanisms

- CCBs alter transmembrane calcium flux in gingival fibroblasts, producing an inactive form of collagenase enzyme reducing the degradation of collagen. This effect is compounded by increased production of collagen associated with growth factors (the basic fibroblast growth factor and transforming growth factor-β).
- The role of the bacterial biofilm in gingival inflammation, production of interleukin-1β and interleukin-6 and gingival enlargement- proinflammatory cytokines seem to have a synergistic effect in the enhancement of collagen synthesis
- Genetic predispositions of different fibroblasts phenotypes to CCB, or predispositions influencing the metabolism of CCBs by cytochrome P450 enzymes.

GO caused by: **Cyclosporine**



- **Cyclosporine** -an immunosuppressant medication of natural origin. Taken for rheumatoid arthritis, psoriasis, Crohn's disease, nephrotic syndrome, and to prevent rejection in organ transplants.
- The prevalence 40%-60%
- Patients who have had renal or cardiac transplantation are frequently prescribed a CCB in addition to cyclosporine. The combination of cyclosporine with a dihydropyridine-type CCB results in both increased prevalence and severity of gingival overgrowth.

Mechanisms- multifactorial pathogenesis:

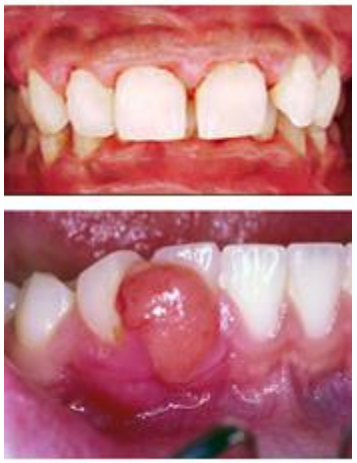
- the age at the time of transplant,
- gender of the patient (men being three times more susceptible),
- duration of treatment and dosage prescribed (directly proportional relationship),
- drug concentration in serum and saliva,
- combination with other drugs,
- genetic predisposition and oral hygiene.

- The **level of inflammatory cytokines is elevated** in inflamed gingival tissues causing fibrotic gingival enlargement (interleukin-6 enhances proliferation, **collagen and glycosaminoglycan synthesis**)
- Fibroblasts show reduced phagocytical activity in inflamed tissue which result in **increased connective tissue**.

Treatment

- Discontinuation and substitution of the drug causing gingival enlargement with a drug reportedly not causing GO
- Prophylactic antibiotic coverage due to increased susceptibility to possible bacteraemia along with folic acid and vitamin C supplementation
- Surgical treatment - risk (~50%) of recurrence of GO in the patients after 3 to 6 months of surgical treatment approach, mostly associated with poor oral hygiene and cumulative effects of plaque and calculus with the drug

Gingival bleeding - hormonal gingivitis



- Can be caused by oral contraceptives (both progesterone-only and combined) and hormone replacement therapy (for postmenopausal women)
- Also present in patients receiving ovulation-inducing medication for infertility treatment
- Granuloma formation following ingestion of the contraceptive pill has also been observed

Mechanism**:**

- mechanisms are diverse, and based on the observations that female sex hormones are capable of altering the gingival vascular system, depressing cell-mediated immune responses and modulating the subgingival flora
- human gingiva have receptors for estrogen and progesterone (elevated levels of these hormones during puberty and pregnancy have all been associated with periodontal pathology)
- estrogens can influence the cytodifferentiation of stratified squamous epithelium, and the synthesis and maintenance of fibrous collagen

Gingival bleeding- **anti-platelet drugs**

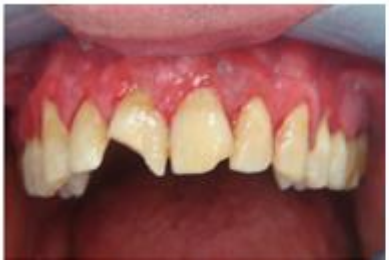
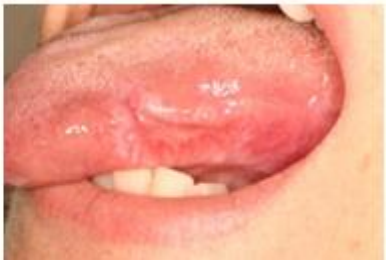
- Anti-platelet drugs, principally **aspirin** and **clopidogrel**, are widely used for prophylaxis of thrombotic events, particularly in high-risk subjects (myocardial infraction, cerebral ischaemia and peripheral arterial insufficiency)
- Severe, spontaneous, hard to control gingival bleeding can be the result of thrombocytopenia, a rare but dangerous adverse effect of clopidogrel
- Patients using anti-platelet drugs are susceptible to gingival bleeding, especially when undergoing surgical periodontal treatment but also during scaling or probing

Fig. 1. Notable bleeding presented immediately after scaling and root planing of the upper teeth. The oral tissues are covered with a thick layer of bloody saliva. Origin of bleeding is from the gingiva of the molars.

Fig. 2. A large clot covers the lower incisors immediately after scaling and root planing of the lower teeth. The clot is soft and breaks easily. Gingival bleeding from adjacent teeth is present.

(Elad et al., 2008)

Inflammatory process - **nonsteroidal antiinflammatory drugs**

- **Ibuprofen, aspirin, naproxen** and **indomethacin**
- Disturbances in blood clotting - act by inhibiting cyclooxygenase enzymes (COX-1, COX-2 and COX-3), which are rate-limiting enzymes responsible for synthesis of the prostanoid group of inflammatory mediators and thromboxanes involved in blood clotting
- Nonspecific drug-induced lichenoid reactions and xerostomia (dry mouht) have been observed following ingestion of nonsteroidal anti-inflammatory drugs

Periodontal disease progression – **Bisphosphonates**

- A group of widely prescribed drugs that inhibit bone resorption.
- Oral preparations (alendronate and risedronate) are used widely for the management of metabolic bone disease, notably osteoporosis.
- Intravenous bisphosphonates, such as pamidronate and zoledronate, are used for anti-resorptive applications, such as management of bony metastases in advanced malignancy.
- Increased in risk of osteonecrosis of the jaw (ONJ) in patients receiving intravenous bisphosphonates (the risk with oral preparations seems to be much less), especially after tooth extraction.
    - Osteonecrosis of the jaw- risk factors:
        - immunosuppression and altered wound healing
        - osteonecrotic lesions are initiated by trauma to the oral mucosa and inflammation derived from infection (e.g during dental extraction)
        - BPs sequestered in the jaw bones inhibit wound closure
        - age, corticosteroid therapy, diabetes, tobacco use
        - microbial environment of the oral cavity

Periodontal disease progression – **Statins**

- Statins (HMG-CoA reductase inhibitors), some of the most commonly prescribed regular medications, used to lower cholesterol levels and are taken by people considered to be at increased risk of cardiovascular disease, particularly in older cohorts.
- A number of recent studies have described significant enhancement of periodontal healing following application of adjunctive topical statins
    - Statins act through several pathways to modulate inflammation, immune response, bone metabolism, and bacterial clearance.
    - They prevent inflammation-mediated bone resorption and promote bone formation
    - They control periodontal inflammation through inhibition of proinflammatory cytokines and promotion of anti-inflammatory and/or proresolution molecule release.

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