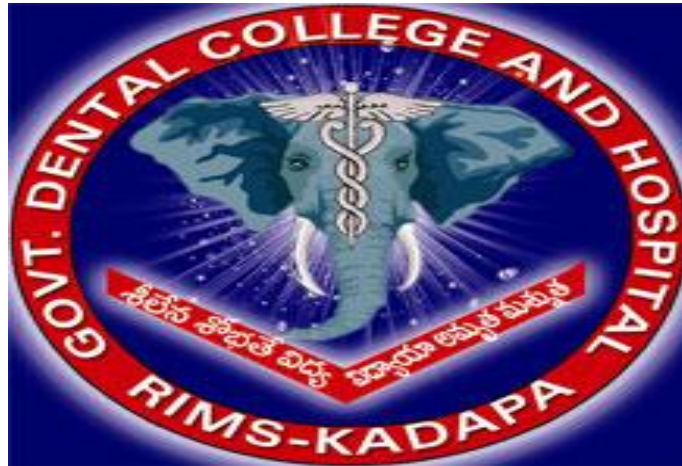


GOVERNMENT DENTAL COLLEGE & HOSPITAL, KADAPA.

DEPARTMENT OF PERIODONTICS



SEMINAR PRESENTATION ON “INFLUENCE OF SYSTEMIC DISEASES AND DISORDERS ON THE PERIODONTIUM.”

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INTRODUCTION

- Many systemic diseases, disorders have been implicated as risk indicators or risk factors in periodontal disease.
- Clinical and basic science research over the past several decades has led to an improved understanding of and appreciation for the complexity and pathogenesis of periodontal diseases.
- There is clear evidence for a bacterial etiology and there are specific bacteria (periodontal pathogens) associated with destructive periodontal disease, the presence of these pathogens does not invariably cause disease.
- Their absence, on the other hand, appears to be consistent with periodontal health.
- Systemic diseases, disorders, and conditions alter host tissues and physiology, which may impair the host's barrier function and immune defense against periodontal pathogens, thereby creating the opportunity for destructive periodontal disease to progress.

- Evidence also suggests that periodontal infections can adversely affect systemic health with manifestations such as coronary heart disease, stroke, diabetes, preterm labor, low-birth-weight delivery, and respiratory disease.

ENDOCRINE DISORDERS

- Endocrine diseases such as diabetes affect the condition of the periodontium.
- This affect the tissues directly, modify the tissue response to local factors, & produce anatomic changes in the gingiva that favours the plaque accumulation & disease progression.

DIABETES MELLITUS

- DM is a complex metabolic disorder of chronic hyperglycemia. Diminished insulin production, impaired insulin action, or a combination of both result in the inability of glucose to be transported from the bloodstream into the tissues, which in turn results in high blood glucose levels .
- Lipid and protein metabolism are altered in diabetes as well.

CLASSIFICATION OF DM:

- Type 1 DM
 - A. Immune mediated.
 - B. Idiopathic.
- Type 2 DM
 - Range from insulin resistance with relative deficiency to secretory defect with insulin resistance.
- Other specific types
 - Genetic defects in insulin action.
 - Diseases of exocrine pancreas.
 - Endocrinopathies.
 - Drug or Chemical induced.
 - Infections.
- Gestational
 - Occur during pregnancy.

- Type 1 diabetes mellitus, which was formerly known as insulin-dependent diabetes mellitus, is caused by a cell-mediated autoimmune destruction of the insulin producing beta cells of the islets of Langerhans in the pancreas, which results in insulin deficiency.
- Type 1 diabetes accounts for 5% to 10% of all cases of diabetes and most often occurs in children and young adults. This type of diabetes results from a lack of insulin production, and it is very unstable and difficult to control.
- It has a marked tendency toward ketosis and coma, it is not preceded by obesity, and it requires the injection of insulin to be controlled.
- Symptoms of type 1 DM are polyphagia, polydipsia, polyuria & predisposition to infections.
- Type 2 diabetes mellitus, formerly known as non– insulin-dependent diabetes mellitus, is caused by peripheral resistance to insulin action, impaired insulin secretion, and increased glucose production in the liver.
- Insulin-producing beta cells in the pancreas are not destroyed by cell-mediated autoimmune reaction. It typically begins as insulin resistance, which leads to the reduced pancreas production of insulin as the demand increases.
- Type 2 diabetes is the most common form of diabetes, and it accounts for 90-95% of all adult cases.
- Type 2 diabetes generally occurs in obese individuals, and it can often be controlled by diet and oral hypoglycemic agents.
- Ketosis and coma are uncommon. Type 2 diabetes can manifest with the same symptoms as type 1 diabetes but typically in a less severe form.
- Gestational diabetes develops in 2% to 10% of all pregnancies but disappears after delivery.
- Women who have had gestational diabetes are at increased risk of developing type 2 diabetes.
- Other specific types of diabetes are those associated with diseases that involve the pancreas, experimentally induced diabetes belongs to this group.
- Uncontrolled diabetes is associated with several long-term complications, including
 - Microvascular diseases (retinopathy, nephropathy, or neuropathy),
 - Macrovascular diseases (cardiovascular and cerebrovascular conditions),
 - Increased susceptibility to infections, and
 - Poor wound healing.

Oral manifestations:

- Numerous oral changes have been described in patients with diabetes, including cheilosis, mucosal drying and cracking, burning mouth and tongue, diminished salivary flow, and alterations in the flora of the oral cavity, with greater predominance of *Candida albicans*, hemolytic streptococci, and staphylococci.
- An increased rate of dental caries has also been observed in patients with poorly controlled diabetes.
- It is important to note that these changes are not always present, and that they are not pathognomonic for diabetes.
- These changes are less likely to be observed in patients with well controlled diabetes.
- Individuals with controlled diabetes have a normal tissue response, a normally developed dentition, a normal defense against infections, and no increase in the incidence of caries.
- The most striking changes in patients with uncontrolled diabetes are the reductions in the defense mechanisms and the increased susceptibility to infections, which lead to destructive periodontal disease.
- In fact, periodontal disease is considered to be the sixth complication of diabetes.
- Periodontitis in patients with type 1 diabetes appears to start after the age of 12 years, and it has a fivefold increased prevalence in teenagers.
- The prevalence of periodontitis has been reported as 9.8% in 13- to 18-year-old patients, and it increases to 39% in those who are 19 years old and older.
- Periodontal disease in patients with diabetes follows no consistent or distinct pattern.
- Severe gingival inflammation, deep periodontal pockets, rapid bone loss, and frequent periodontal abscesses often occur in patients with poorly controlled diabetes and poor oral hygiene.



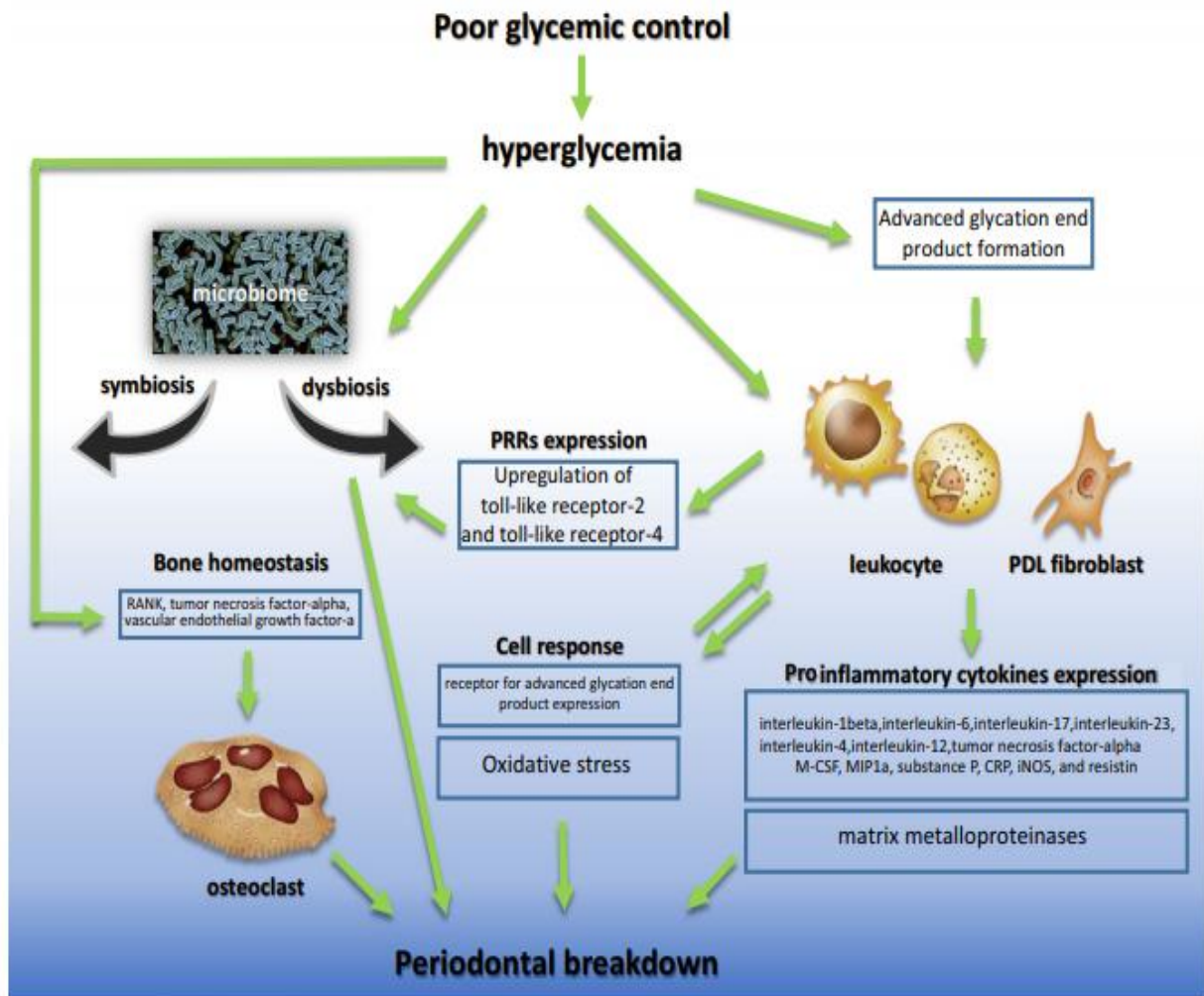
Bacterial Pathogens:

- The glucose content of GCF & blood is higher in individuals with diabetes than in those without diabetes with similar Plaque & Gingival Index scores.
- These increased levels of glucose could change the environment of microflora, including quantitative changes in the bacterial severity of periodontal diseases.
- In patients with type 1 DM & Periodontitis are reported to compose of subgingival flora like;
Capnocytophaga,
Anaerobic vibrios,
Actinomyces sps.
- In some studies they have stated that, P.g, P.i, A.a – common periodontopathogens in non-diabetics, but in diabetics they are low in number.

- Mandell RL et al conducted a study on a group of poorly controlled type 1 diabetics and found scarce Capnocytophaga & abundant A.a & black pigmented bacteroids like P.i, P.melanogenica, Camphylobacter rectus.
- The results suggest an altered flora in the periodontal pocket of the patients with diabetes.
- The exact role of these micro-organisms has not been determined.

Mechanism of Interactions:

- Changes in subgingival environment
 - Altered microbiota.
 - Change in GCF composition.
- Altered tissue homeostasis & wound healing
 - Decreased collagen production.
 - Increased MMP activity.
 - Accumulation of AGE's.
 - Decreased tissue turnover.
- Changes in host immuno – inflammatory response
 - Decreased PMNL's chemotaxis, adherence, phagocytosis.
 - Elevated pro-inflammatory cytokine response from macrophages.
 - Increased tissue oxidant stress.



Neutrophil Function:

- Increased susceptibility of diabetic patients to infections has been hypothesised as being caused by neutrophil deficiencies that cause
 - impaired chemotaxis,
 - defective phagocytosis
 - impaired adhesion
- In poorly controlled diabetics, the functions of neutrophils, monocytes & macrophages are impaired.
- It results in diminished primary defences mounted by neutrophils against periodontal pathogens.

Altered Collagen Metabolism:

- Chronic Hyperglycemia impairs the collagen structure & function.
- Decreased collagen synthesis, osteoporosis, reduction in alveolar bone height are demonstrated in diabetic animals.
- It adversely affects the synthesis, maturation of collagen & extracellular matrix.
- Numerous proteins & matrix molecules undergo a non-enzymatic glycosylation, and forms Advanced Glycation End- Products (AGEs).
- AGEs formation occurs at normal glucose level as well, in hyperglycemic environments it forms in excess.
- The collagen is cross-linked by AGE formation, which makes collagen less soluble & less likely to be repaired or replaced.
- Cellular migration through cross-linked collagen is impeded & more importantly tissue integrity is impaired as a result of damaged collagen that remains in tissue for longer periods.
- As a result, collagen in the tissues of patients with poorly controlled diabetes is older & more susceptible to pathogenic breakdown.
- AGE & Receptors of AGE's (RAGE'S) play central role in the classical complications of diabetes & also in progression of the periodontal disease.
- AGE's may exert their biological effects in tissues by receptor independent or receptor dependent pathways.
- In receptor independent pathways, AGE's may directly show impact on the structural integrity of the vessel wall & underlying basement membrane, in particular, excessive cross-linking of matrix molecules (i.e collagen) can lead to an alteration of matrix – matrix & matrix – cell interactions.
- In receptor dependent pathway, it is well established that AGE's may also exert their pathogenic effects by engagement of cellular binding sites/ receptors.
- To date, the most extensively studied is receptor for AGE (RAGE), but other binding proteins receptors include AGE receptors 1,2 and 3 and the ezrin, radixin & moesin family.
- These receptors are responsible for a range of functions in diabetic tissues, including modulation of cellular properties by receptor triggered signal transduction upon AGE engagement, as well as removal & detoxification of AGE's.

Diabetes & Periodontal Diseases:

- Gusberti et al conducted a study in a group of children with type 1 DM, before puberty – poorly controlled DM children had a higher incidence & severity of gingival inflammation than the well controlled children.
- During puberty, there is a general increase in gingivitis independent of glycemia.
- Cianciola et al confirmed that an increase in gingivitis in type 1 DM children after age of 11 when compared with non-diabetic controls.
- In a study of Pima Indians of Arizona, poor glycemic control of type 2 diabetics was associated with significantly increased risk of progressive bone loss compared to non diabetic subjects. These differences were most pronounced in younger individuals.
- Tervonen et al found a trend towards increasing prevalence of alveolar bone loss as glycemic control worsened. The mean percentage of sites with >15% bone loss went from 28% in well controlled type 1 diabetics to 44% in poorly controlled subjects. However, the difference did not reach statistical significance, due to the small size of the study population.
- The cumulative effects of altered cellular response to local factors, impaired tissue integrity & altered collagen metabolism undoubtedly play a significant role in the susceptibility of patients with diabetes to infections & destructive periodontal disease.

HORMONAL INFLUENCES

- Hormones are specific regulatory molecules that modulate reproduction, growth & development and the maintenance of internal environment as well as energy production, utilization & storage.
- Hormones are classified into four groups based on their chemical structure are steroids, glycoprotein's, polypeptides and amines.
- They also have potent effects on the nervous system & cardiovascular system & on major determinants of the development & integrity of skeletal & oral cavity including periodontal tissues.

ANDROGENS (TESTOSTERONE)

- Androgens are associated with normal spermatogenesis and development of secondary sexual characteristics in puberty.
- Two types:

Gonadal androgens – dihydrotestosterone(DHT)

Adrenal androgens – dehydroepiandrosterone.

- The former one is more active.
- Androgens play important role in:
- Maintenance of bone mass
- Inhibit osteoclastic function
- Inhibit prostaglandin synthesis
- Reduced IL-6 production during inflammation.
- Adrenal androgen & androstenedione are converted to testosterone & estrogen in the circulation & represent important source of estrogen in men & post menopausal women.
- Testosterone stimulates bone cell proliferation & differentiation & therefore has a positive effect on bone metabolism.
- Testosterone receptors are found in periodontal tissues & the number of receptors on fibroblasts tend to increase in inflamed or overgrown gingiva.
- Parker et al demonstrated that increasing DHT concentrations progressively reduced IL-6 production by gingival cells isolated from normal individuals & patients with gingival inflammation & gingival hyperplasia.
- Gornstein et al found the androgen receptors on both human gingival & pdl fibroblasts & androgens reduced IL-6 production by cells having these receptors. Testosterone has inhibitory effects in cyclo-oxygenase pathway of arachidonic acid metabolism in the gingiva.
- An effective way to analyze the effect of androgens on the bone metabolism is the evaluation of bone remodelling biochemical biomarkers.

OSTEOPROTEGERIN (OPG):

1. Implicated in pathogenesis & other metabolic bone diseases.
2. Inhibits osteoclast formation & activation of neutralizing factors of its co-ligand.
3. During disease progression, OPG action is associated with reduction in the loss of bone mineral density.
4. The serum concentration of OPG increases with age.

ESTROGEN & PROGESTERONE:

- Estradiol – principal premenopausal estrogen produced by the ovary.
- Placenta & peripheral tissue.

- Crucial role – many vital activities;
 - Development & maintenance of secondary sexual characters.
 - Uterine growth.
 - Pulsatile release of LH from anterior pituitary.
 - Development of peripheral skeleton.
- Progesterone – secreted by :
 - Corpus luteum,
 - Placenta,
 - Adrenal cortex.
- It is active in bone metabolism.
- Coupling – engaging osteoblast receptors.
- Receptors for both are demonstrated in the gingiva.
- Estrogen receptors – periosteal fibroblasts, scattered fibroblasts of the lamina propria & pdl fibroblasts & osteoblasts.

Effects of Estrogen on the Periodontium

- Decreases keratinisation
- Increases cellular proliferation.
- Stimulates neutrophil phagocytosis.
- Inhibits neutrophil chemotaxis.
- Suppress leukocyte production.
- Inhibits pro-inflammatory cytokines.
- Reduces T-cell mediated inflammation.
- Stimulates proliferation of the gingival fibroblasts.
- Stimulates synthesis & maturation of gingival CT.
- Increases the amount of gingival inflammation with no increase in plaque.

Effects of Progesterone on the Periodontium:

- Increase vasodilation & permeability.
- Increases the production of prostaglandins.
- Increases neutrophil & prostaglandin E2 in the GCF.
- Reduces glucocorticoids anti-inflammatory effect.
- Inhibits collagen & non-collagen synthesis in pdl fibroblast.
- Inhibits proliferation of human gingival fibroblasts.
- Alters rate & pattern of collagen production in the gingiva.
- Increases metabolic breakdown of folate.

PERIODONTAL MANIFESTATIONS OF VARIOUS STAGES:

PUBERTY:

- It marks the initiation of changes from maturation into adulthood.
- It is associated with a major increase in the secretion of the sex steroid hormones:

Testosterone

Estradiol

- Several cross – sectional & longitudinal studies have demonstrated an increase in gingival inflammation without increase in plaque levels.
- Increased gingival inflammation- positively correlated with an increase in serum estradiol & progesterone.
- A higher incidence of black-pigmented bacteroids & higher populations of other gram –ve rods in sub-gingival microflora compared to healthy sites.



MENSTRUATION

- The onset of increased production & secretion of estrogen & progesterone in a cyclic manner accompanies the onset of puberty & is referred to as the reproductive or menstrual cycle.
- Normal reproductive cycle – 28 days.
- Reproductive cycle – four phases.
- Follicular phase –
 - FSH & estrogen levels are increased.
 - Estrogen peaks around 2 days before ovulation.
- Secretory phase –
 - begins on day 14 of the cycle
 - synthesis & release of estrogen & progesterone by follicular cells.

PREGNANCY

- Gingival changes in pregnancy – late 1800's.
- Pregnancy itself does not cause gingivitis, it is caused by bacterial plaque.
- The hormonal changes in pregnancy accentuate the gingival response to plaque & modify the clinical presentation.
- Incidence of gingivitis in pregnancy – 50-100%.
- Tooth mobility, pocket depth & gingival fluids are increased during pregnancy.

- It affects the severity of the previously inflamed areas, but does not effect healthy gingiva.
- Severity increases – 2nd & 3rd trimesters.
- More severe in 8th mon & decreases during 9th mon.
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HORMONAL CONTRACEPTIVES:

- The agents are based on the effects of gestational hormones that stimulate a state of pregnancy to prevent ovulation.
- Oral contraceptives (OC's) are one of the most commonly used classes of drugs.
- Current OC's consists of low doses of estrogens (0.05 mg/day) & progestins (1.5 mg/day).
- Gingival tissues may have an exaggerated response to local irritants.
- Inflammation – ranges from mild to severe.
- There may be spotty melanotic pigmentation of the skin with the use of OC's.
- A 50% increase in gc volume is reported in women using OC's for a period of 12 yrs compared with women who do not use them.
- Kalkwarf reported that the response might be due to alterations of microvasculature, increased gingival permeability and increased synthesis of prostaglandins.
- There are no significant differences in PI & GI scores & attachment level between OC group & Control group.
- A 16x increase in bacteroides sps has been noted in the OC user group versus control group.
- Women taking OC's experience a two fold increase in the incidence of localised osteitis following extraction of man 3rd molar.
- The estrogen in OC causes a variation in the coagulation & fibrinolytic factors in women taking them leading greater incidence of clot lysis.

MENOPAUSE OR POST MENOPAUSE:

- During menopause the usual rhythmic hormonal fluctuations of the female cycle are ended as estradiol ceases to be the major circulating estrogen.
- 45-55 yrs of age.
- The levels of estrogen begin to drop mainly during the late follicular & luteal phase of the menstrual cycle when women approach menopause.
- Katz & Epstein suggested that peripheral conversion of androgens to estrogens might be the main factor for protecting bone.
- Women can develop gingivostomatitis during menopause or post-menopausal period.
- Oral disturbances are not a common feature of menopause.

- The gingiva & remaining oral mucosa are dry & shiny, they may vary in color from abnormal paleness to redness & they may bleed easily.
- Fissuring in mucobuccal fold in some women & comparable changes may be seen in vaginal mucosa.
- Microscopically, gingiva exhibits atrophy of the germinal & prickle cell layers of the epithelium & in some patients, area of ulcerative.
- Dry, burning sensations & extreme sensitivity to thermal changes in the oral mucosa.
- Taste disturbances.
- Post menopausal period – increased risk for osteoporotic factors & others.

HYPERPARATHYROIDISM

- PTH hypersecretion – generalised demineralization of the skeleton, increased osteoclasts with proliferation of the connective tissue in the enlarged marrow spaces & the formation of bone cysts & giant cell tumours.
- This disease is called as osteitis fibrosa cystica or Von Recklinghausen bone disease.
- Loss of lamina dura,

Giant cell tumour in jaws – late signs of hyperparathyroid bone disease.

- Reports suggest – 25-50% of patients with hyperparathyroidism have associated with oral changes like:

malocclusion, tooth mobility, radiographic evidence of alveolar osteoporosis with closely meshed trabeculae, widening of pdl space, absence of lamina dura, radiolucent cyst like spaces.

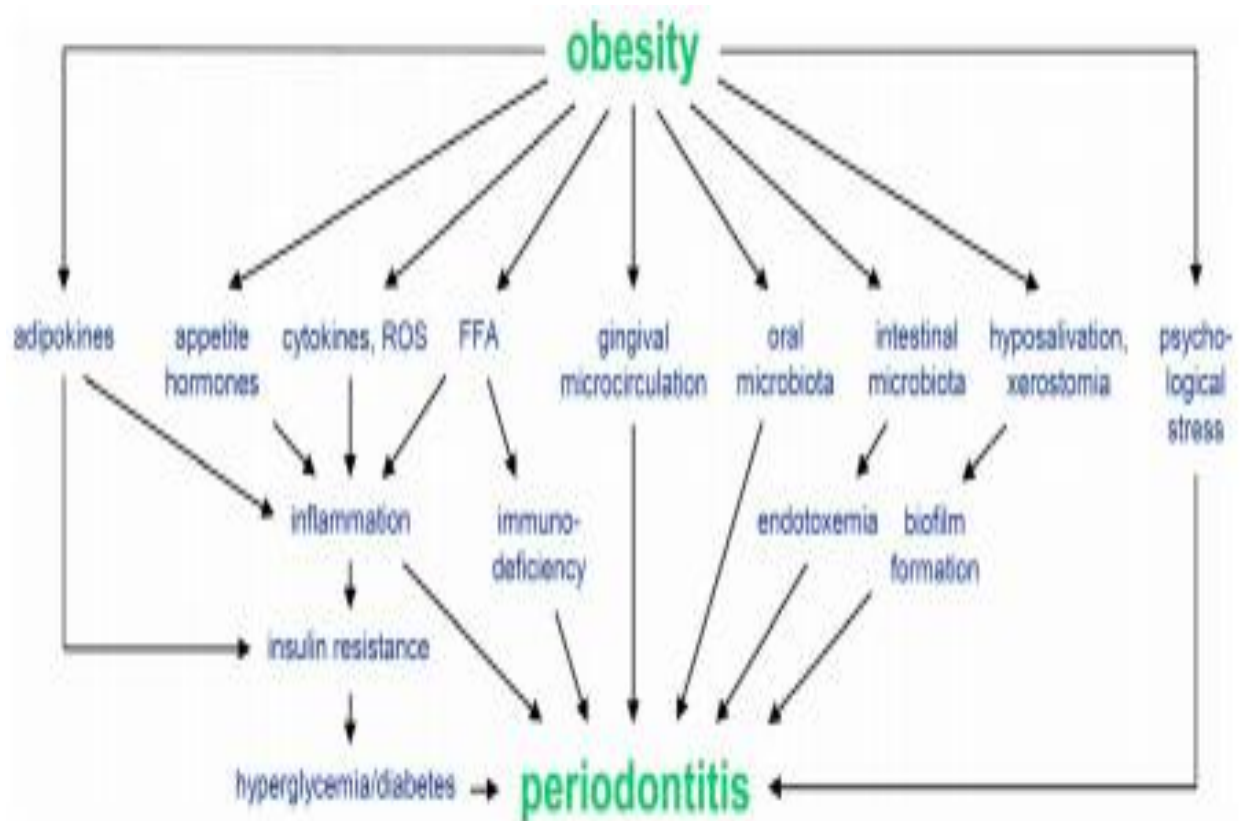
- Bone cyst may be filled with fibrous tissue with abundant hemosiderin – laden macrophages & giant cells. These cysts are called Brown tumours, but they are not tumours.

METABOLIC SYNDROME & OBESITY

- Metabolic syndrome is a term used to describe a condition of abnormal obesity combined with two or more of the following metabolic disturbances:
 - ☐ Hypertension
 - ☐ Dyslipidemia
 - ☐ Hyperglycemia
- Metabolic syndrome leads to an increased risk of diabetes & cardiovascular disease.

- A bidirectional relationship between periodontal disease & metabolic syndrome/obesity has been suggested.
- Obesity is defined as abnormal or excessive fat accumulation that presents a risk to health.
- It is also considered to be a complex multi-factorial chronic disease.

Mechanism by which obesity poses a risk for periodontitis:



Inflammation

- Obesity – excess of adipose tissue, i.e adipocytes are increased in number & volume.
- Adipose tissue – also source for several pro-inflammatory mediators like adipokines.
- Adipokines – cytokines which are produced by adipocyte fraction, also by non-adipocyte fraction as well.
- Besides insulin sensitivity & energy expenditure, they also regulate inflammatory & wound healing process.
- Adiponectin – anti-inflammatory

- Visfatin, leptin & resistin – pro-inflammatory effects.
- Obesity – imbalance between pro & anti-inflammatory adipokines.
- Example:

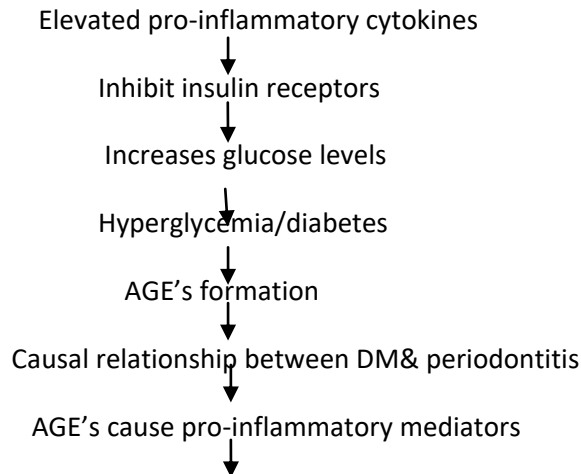
Zuza et al found higher serum levels of IL-1 β , IL-6 & TNF- α in obese subjects compared to individuals with normal weight.

These cytokines promote recruitment of immuno-inflammatory cells & production of proteases & bone resorption.

Adipokines like visfatin enhances inflammation through cc-chemokine ligand 2 & MMP-1.

- Ghrelin – an appetite hormone, anti-inflammatory in nature that stimulate appetite.
- It is originally identified as a hormone secreted mainly by gastrointestinal cells, plays critical role in physiological process like food intake, energy balance, as well as sleep & memory.
- It was found in gcf & saliva as well as in several cells & tissues like IEE, mesenchymal cells, ameloblasts, odontoblasts & HERS.
- It mediates its action by binding to the growth hormone secretagogue receptors present in hypothalamus, pituitary, pancreas, heart, salivary glands, stomach & many other organs.
- Recently, it is found that growth hormone secretagogue receptor is also expressed & regulated in periodontal cells.
- Serum levels of ghrelin is reduced in obesity resulting in enhanced periodontal inflammation & destruction in obese individuals.
- Obesity causes production of ROS & reduce the antioxidant capacity.
- Obesity associated oxidative stress might be another potential mechanism for periodontal inflammatory progression.
- Free Fatty Acid either derived from adipose tissue or diet also increased in obese individuals & exert pro-inflammatory effects.
- An increase in FFA levels in obesity might also promote periodontal inflammation & destruction.

Obesity also increases the risk of periodontal inflammation through DM:



Cross – linking of collagen & degradation & resorption of periodontal tissues.

Immunodeficiency:

- The immune response to periodontal bacteria is disrupted in obesity.
- Bacteria activate the immuno-inflammatory cells of the host by binding to TLR.
- In a chronic exposure of these receptors to bacteria, a constant stimulation occurs causing the development of tolerance.
- FFA may also bind to TLR in obesity & promote tolerance & result in no appropriate response to microbial attack, facilitating periodontal destruction.
- Huang et al concluded from a preclinical study that obesity may paralyze the innate immune response of periodontium via attenuating infiltration & activation of macrophages.

Impairment of microcirculation:

- A study by Lin et al suggests that obesity may also contribute to periodontitis by affecting the gingival vascular supply & microcirculation.
- Gingival biopsy – in obese & normal subjects, showed that the basement membrane thickness of terminal arterioles was increased in obesity.
- Elevated levels of plasminogen activator inhibitor-1 is seen – prevents fibrinolysis, in the serum of obese individuals.

Overgrowth of microbial pathogens:

- In the subgingival biofilms of periodontally healthy or gingivitis individuals, *Tannerella forsythia* is found in greater proportions in obese subjects.

- Al-Rawi & Al-Marzooq found *Tannerella forsythia* as well as *Fusobacterium* spp & *P.gingivalis* in significantly higher quantities in obese subjects than non-obese.

HYPOSALIVATION/ XEROSTOMIA:

- Another mechanism
- Prevalent in obesity
- Promotes plaque accumulation thereby cause periodontal inflammation.

Hematological disorders & Immune deficiencies:

- Blood cells - maintenance of periodontium.
- WBC – cellular defence against microbes,
release pro-inflammatory cytokines.
- RBC – gaseous exchange & nutrient supply to tissue.
- Platelets – normal haemostasis,

recruitment of cells during inflammation & wound healing.

- Disorders of any blood cells or blood forming organs – profound effect on periodontium.
- Hemorrhagic tendencies – normal mechanism are disturbed.
- Abnormal bleeding from gingiva or other areas of the mucosa is difficult to control is a important clinical sign.
- Petechiae, ecchymosis of soft palate – signs of bleeding disorders.
- Diagnose.
- Deficiencies in host immune response lead to destructive periodontal lesions.
- They are:
 - Primary – inherited
 - Secondary – acquired
 - Immunosuppressive drugs
 - Pathologic destruction of lymphoid system.
- Leukemia

- Hodgkins disease
- Lymphomas
- Multiple myeloma
- All the above are secondary immunodeficiency disorders.

Leukocyte (neutrophil) disorders:

- It affects the production or function of leukocytes & may result in severe periodontal destruction.
- Neutrophils – first line of defence.
- Quantitative deficiency (neutropenia, agranulocytosis)– more generalised periodontal destruction.

Neutropenia

- Low level of circulating neutrophils.
- Causes:
 - Diseases
 - Medications
 - Chemicals
 - Infections
 - Idiopathic conditions
 - Hereditary conditions.
- Can be Chronic or Cyclic & Severe or Benign.
- Affects one in three patients receiving chemotherapy for cancer.
- Absolute Neutrophil Count(ANC) of 1000 – 1500 cells/ μ l → mild

500 – 1000 cells/ μ l → moderate

< 500 cells/ μ l → severe neutropenia

- Severe neutropenia – it is difficult to manage infections & may be life threatening.

Agranulocytosis

- It is more severe neutropenia that involves deficient in basophils & eosinophils.
- Agranulocytosis is defined as a ANC of < 100 cells/ μ l.
- Characterized by a reduction in circulating granulocytes & results in severe infections including ulcerative necrotizing lesions of oral mucosa, the skin & gastrointestinal or genitourinary tracts.
- Less severe form of the disease are neutropenia or agranulocytopenia.
- Drug idiosyncrasy – most common cause.
- Drugs like
 - Aminopyrine
 - Barbiturates
 - Benzene derivatives
 - Sulfonamides
 - Gold salts
 - Arsenical agents cause agranulocytosis.
- It may occur as acute or chronic or periodic.
- The onset of disease is accompanied by
 - Fever,
 - Malaise,
 - Generalised weakness,
 - Sore throat.
- Ulcerations of oral mucosa, oropharynx & throat.
- The mucosa exhibits isolated necrotic patches that are black & gray & demarcated from adjacent area.
- Absence of a notable inflammatory reaction caused by lack of granulocytes.
- Clinical features – gingival hemorrhage, necrosis, increased salivation, fetid odor.
- In cyclic neutropenia, gingival changes recur with recurrent exacerbation of disease.

- Generalized aggressive periodontitis.

Leukemia

- It is a malignant neoplasm of WBC precursors characterized by
 - Diffuse replacement of the bone marrow with proliferative leukemic cells.
 - Abnormal number & form of immature WBCs in the circulating blood.
 - Widespread infiltrations in the liver, spleen, lymph nodes & other body sites.
- Acc to cell type
 1. lymphocytic
 2. myelogenous.
- Monocytic leukemia is a sub-group of myelogenous.
- Lymphocytic means that the malignant changes in the cells that form lymphocytes.
- Myelogenous – malignant changes in cells normally form RBC, some WBC & platelets.
- Leukemias can be:
 - Acute
 - Sub acute
 - Chronic
- Acute form:

primitive blast cells released into peripheral circulation are immature & non functional.

- Chronic form:

abnormal cells tend to be more mature & to have normal morphologic characteristics & functional when released into circulation.

- All leukemias tend to displace normal components of bone marrow elements with leukemic cells, resulting in decrease in RBC production & WBC & platelet, resulting in anemia, leucopenia, thrombocytopenia.
- Anemia – poor tissue oxygenation, making tissue more friable & susceptible to breakdown.
- Decrease in WBCs in circulation leads to poor cellular defense & increased susceptibility to infections.

- Thrombocytopenia – bleeding tendency, occurs in any tissue but in particular affects the oral cavity, especially gingival sulcus.
- Aleukemic leukemia – normal blood counts while leukemic cells reside primarily in the bone marrow.

The periodontium in leukemic patients:

- Oral & periodontal manifestations of leukemia may include leukemic infiltration, bleeding, oral ulcerations & infections.
- Expression of these signs is more common with acute & sub acute forms of leukemia than in chronic forms.

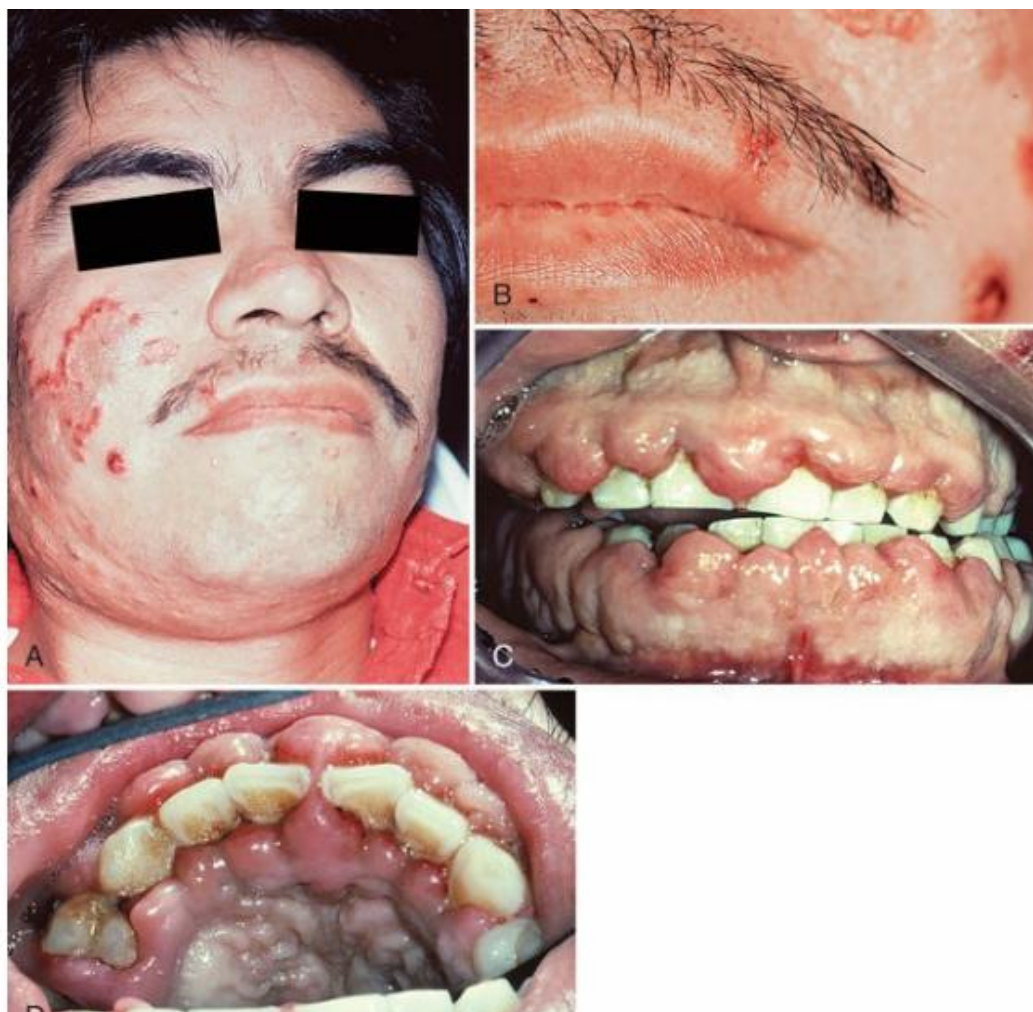
Leukemic Infiltration:

- Leukemic cells infiltrate the gingiva & less frequently alveolar bone.
- Gingival infiltration often results in leukemic gingival enlargement.
- A study of 1076 adult patients with leukemia showed 3.6% of patients with teeth had leukemic gingival proliferation.
- Highest incidence – acute monocytic (66.7%).

Acute myelocytic-monocytic leukemia (18.7%)

Acute myelocytic leukemia (3.7%).

- Monocytic leukemia – extremely rare.
- Leukemic gingival enlargement- basic infiltration of gingival corium by leukemic cells that increases gingival thickness & creates gingival pockets with plaque accumulations at late stage, initiating secondary inflammation & cause enlargement of gingiva.
- It may be localised to interdental papilla area or may include marginal gingiva & partially cover the crown of the teeth.
- Clinically, gingiva appears bluish red & cyanotic with rounding & tenseness of gingival margin.
- Leukemic cells in dermal & subcutaneous connective tissue – leukemic cutis, it forms elevated & flat macules & papules.



- Microscopically, gingiva exhibits a dense, diffuse infiltration of predominantly immature leukocytes in attached & marginal gingiva.
- Connective tissue components are displaced by leukemic cells.
- Reticular layer – dense cellular accumulations.
- Papillary layer – few leukocytes.
- Blood vessels – distended & predominantly leukemic cells & reduced RBC.
- Epithelium – thinned & hyperplastic.
- Common findings are degeneration associated intercellular & intracellular edema & leukocytic infiltration with decreased surface keratinization.

Bleeding

- Gingival haemorrhage is common finding in leukemic patients, even in the absence of clinically detectable gingivitis.
- Bleeding gingiva is common finding in leukemic patients.
- It is caused by thrombocytopenia result of replacement of marrow cells with leukemic cells & their products.
- Bleeding tendency can also occur in skin & throughout the oral mucosa, petechiae are found



with or without leukemic infiltrates.



- Diffuse submucosal bleeding manifests as echymosis.
- Oral bleeding reported in 17.7% acute leukemic patients & 4.4% chronic leukemic patients.
- Bleeding may also be side effect of the chemotherapeutic agents used to treat leukemia.

Antibody Deficiency Disorder:

- Agammaglobulinemia or Hypogammaglobulinemia is an immune deficiency caused by a deficiency that results from inadequate antibody production of B cells.
- Congenital – X linked or Burton agammaglobulinemia.
- Acquired – common variable immunodeficiency.

Congenital agammaglobulinemia:

- X linked recessive gene(Burton tyrosine kinase).
- 1 in 1 lakh.
- Only males are affected.
- The gene is responsible for B cell development.
- Absence of mature B cells – lack lymphoid tissue & fail to develop plasma cells.
- Thus, production of antibodies is deficient.
- Germinal centres (for B cells) are poorly developed in all lymphoid tissues.
- Tonsils, adenoids & peripheral lymph nodes are small or absent.

Acquired or Late onset Agammaglobulinemia:

- Is most often known as common variable immunodeficiency disease(CVID).
- Onset of recurrent bacterial infections during second & third decades due to decrease in antibodies.
- Basic defect is the failure of B-lymphocyte differentiation into plasma cells.
- Enlargement of spleen & swollen glands or lymph nodes is seen.
- Both male & female are susceptible.

STRESS & PSYCHOSOMATIC DISORDERS:

- Risk factor
- Stress affects health through different pathways, resulting in biological impact on the auto-immune & endocrine systems & on metabolism.
- It can also affect the change in behaviour such as smoking, excessive alcohol consumption.
- Unhealthy habits as coping mechanism, increases risk for periodontal diseases, dental caries & oral cancer.

Role of stress in the complex determinants of periodontal disease:

- Psychological stressors – role in periodontitis.
- Stressors have impact on the body.

- Types of stress:

Based on duration of exposure - chronic or acute.

- Stressors – external stimuli that causes stress in an individual & they are 3 types.
- Disasters or Crises:
 - An unpredictable event which is completely out of control of the individual.
 - Devastating natural disasters.
- Major life events:

These are rare events that can be either positive or negative & include marital separation etc.

- Micro stressors:

Accumulation of micro stressors or daily hassles can have the same negative impact on our health as experiencing a major stressful event.

They occur in every individuals life, they are different for each individual.

- Acute stressors – short term & time limited events.
- Chronic stressors – long lasting & may not attribute to the discrete events.
- Organizational model of stress process is categorized into 3 stages:
 - Exposure to environmental demands or negative life events or stressors.
 - Self-evaluation & appraisal of the stressors, which could elicit negative responses in the absence of coping skills
 - Activation of the biological systems in response to environmental & psychological demand.

Stress assessment:

- They are subjective, objective & physiological/biomedical measures to measure stress response.
- In the absence of a gold standard for measurement of stress, selection of tool depends on the stressor in the study.
- Questionnaires & interviews are the main tools used to assess environmental & self-percieved stress, while biomarkers or endocrine measures help to quantify physiological or chronic stress.

Self reported measures:

Perceived stress scale:

- Most validated tool.
- Strong psychometric properties.
- 14 items – for rating stress based on the frequency of difficult events in a period of 1 month.
- Two short versions:
 - Perceived stress scale – 4
 - Perceived stress scale – 10

Stress appraisal measure:

- 28 items – based on the different aspects of 6 dimensions of:
 - Primary – threat, challenge, centrality.
 - Secondary – controlled by self,
controlled by others,
uncontrolled by anyone.

Each of this item is rated on a 4 point scale & overall mean rating is obtained.

Impact of event scale:

- It consist of 22 items.
- Assesses the degree to which a distressful traumatic events impacts an individual.
- An individual should identify a difficult situation in the past week.
- Indicate the difficulty score on a 5 point scale, ranging from “not at all” to “extremely”, a total score of up to 88 is obtained.

Life experiences survey:

- 60-item self reported structured interview, includes events that typically would be percieved as negative or positive.
- The experiences are indicated on a 7 point scale.
- The range spans score from extremely negative to no influence to extremely positive.

Clinical – biochemical measures:

Neuro-endocrine biomarkers:

- Stressors induces chronic physiological stress, there are some systemic level alterations, as well as an increase in the energy production.
- Neuro-endocrine system is first to be triggered & will initiate the release of endocrine markers which can be detected effectively.
- Various neuro-endocrine markers are:

Cortisol,

dehydroepiandrosterone,

epinephrine,

norepinephrine

dopamine.

Cortisol & dehydroepiandrosterone:

- Cortisol levels- most frequently used.
- It captures the status of hypothalamic-pituitary-adrenal axis function.
- Blood & saliva.
- Dehydroepiandrosterone – chronic stress & HPA axis antagonist.
- Diurnal variations.
- Recently – hair samples.
- Level of cortisol in hair – reflect both acute & chronic stress.

Epinephrine, Dopamine, aldosterone & Norepinephrine.

- These levels increase in response to stress, regardless of type of stress.
- Norepinephrine – sympathetic nervous system.
- Dopamine – cardiovascular system.
- Aldosterone – useful to measure the function of the adrenal gland when used in conjugation with others.

Immunological biomarkers:

- Others – circulating levels of IL-6, TNF- α , CRP & IGF.

- Secretion of immunological biomarkers is altered by chronic exposure to stress.
- IL-6 functions synergistically with TNF- α & IL-1, indirectly captures the dysfunction of HPA axis mediated by glucocorticoid signalling.
- Levels of CRP - as one the inflammatory responses to chronic stress.
- Not primary indicators.

Metabolic biomarkers:

- Changes in the metabolism have been used as a secondary & tertiary marker of stress.
- Cholesterol levels, albumin, waist-hip ratio, glycosylated HB – biomarkers.
- Less reliable & less valid.

Allostatic load:

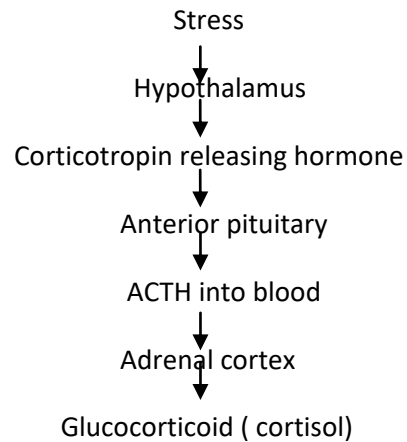
- A compendium of biomarkers released from different body systems, known as allostatic load.
- Defined as “ the price the body pays for being forced to adapt to adverse psychological or physical situations & it represents either the presence of too much stress, or the inefficient operation of stress hormone response system.
- Acute stress response – critical for survival
- Chronic exposure – deleterious effects.
- Chronic exposure hinders the physiological regulatory system.

Stress & Immune system:

- Biondi(2001) showed the impact of psychosomatic condition on immune system.
- Down regulation of immune system through – HPA & Sympathetic Adrenal Medullary Axis.
- HPA & its end product, cortisol – mediators of its relationship between stressful life experience & health outcome.
- Cortisol – decrease the Ig A & Ig G secretion.
- The systemic reaction produces an interrelated non-specific tissue change resulting from continued exposure to stress is termed as general adaptation syndrome (GAS).
- Three stages of syndrome:
 - The initial response

- The adaptation of stress
- The final stage – inability to maintain adaptation to stress.

Mechanism:

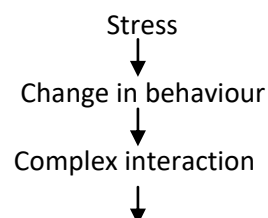


Sympathetic nervous system:

- 2nd pathway.
- Stress acts on ANS by activating fibers to innervate tissues of immune system.
- Role in regulatory immune cell activation.
- Protective
- Provides energy.
- All these immune responses are critical for normal immuno-inflammatory responses to “periodontal pathogens”.

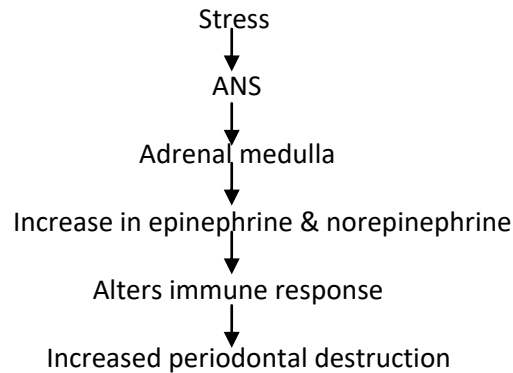
Role of stress in periodontal disease:

- Decreases the salivary flow & increases the plaque formation.
- Studies have shown that psychological factors are predisposing factors for necrotizing periodontitis.

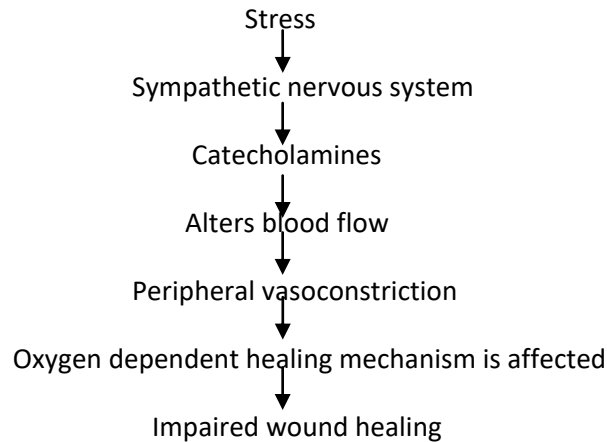


Impact on periodontal health

Effect of pro-inflammatory cytokines & glucocorticoids in stress:



Effect of stress on wound healing:



Nutritional influences:

- Majority of opinions & research findings regarding the effects of nutrition on oral & periodontal tissue point follows:
 1. No nutritional deficiencies can cause gingivitis & periodontitis. They affect the condition of the periodontium.
 2. Nutritional deficiencies produce changes in the oral cavity, like tissues of lips, oral mucosa, gingiva & bone.
- A 2009 review of literature evaluating the effect of nutritional factors on inflammation demonstrated a subtle shifts in nutritional status – prevalence of periodontitis.
- Evidence suggest that effect of nutrition on inflammation is significant. It suggests that diet containing antioxidants are beneficial, high levels refined food.

Effects of vitamin deficiencies on periodontium:

- Fat soluble vitamin deficiency:

Vitamins A, D, E & K.

VITAMIN A DEFICIENCY:

- Epithelial cells of the skin & mucous membrane.
- Dermatological, mucosal & ocular manifestations.
- Epithelial changes.
- Protection against microbes.
- No evidence.
- Experimental studies in animals results in:

hyperkeratosis, hyperplasia of gingiva & increased pocket formation.

VITAMIN D DEFICIENCY:

- Ca absorption from GIT & maintenance of Ca-P balance.
- Deficiency results in:
 - Rickets – in children
 - Osteomalacia – in adults.
- No studies have demonstrated a relationship between vitamin D deficiency & periodontal disease.

VITAMIN E DEFICIENCY:

- Anti-oxidant.
- Cell membranes – site of damage.
- No relationship.

Water soluble vitamins:

- Vitamin B & C.

B-COMPLEX DEFICIENCY:

- Common oral changes – glossitis, gingivitis, glossodynia, angular cheilitis & inflammation of mucosa.
- Gingivitis – non specific.

THIAMINE DEFICIENCY:

- Beri – beri.
- Paralysis, cardiovascular symptoms, edema, loss of appetite.
- Oral – hypersensitivity of oral mucosa, vesicles, erosion of oral mucosa.
- Riboflavin deficiency – glossitis, angular chielitis, seborrheic dermatitis & superficial vascularising keratitis.
 - Glossitis – magenta colored & atrophy of papillae.
 - Severe deficiency – dorsum is flat, dry & often fissured.
 - Angular cheilitis.
- NIACIN DEFICIENCY:
 - Pellagra
 - Rare
 - Earliest signs – glossitis & stomatitis.
- FOLIC ACID DEFICIENCY:
 - Macrocytic anemia.
 - Oral changes.
 - Gastrointestinal lesions
 - Diarrhoea
 - Intestinal malabsorption
 - In a series of human studies, Vogel & colleagues a significant reduction in gingival inflammation after systemic or local use of folic acid compared to placebo.

VITAMIN C DEFICIENCY:

- Scurvy
- Hemorrhagic diathesis,
- Delayed wound healing.
- Infants
- Effects collagen.
- Bone

Clinical manifestations:

- Haemorrhagic lesions
- Petechae
- Infections
- Impaired wound healing
- Swollen gums

Possible etiological factors:

- Vit C may play a role in periodontal disease through one or more of the following mechanism:
 - Low levels of vit C – metabolism of collagen of the periodontium, thereby affects the tissues regenerative & reparative capacity. No evidence.
 - Bone formation.
 - Increases permeability of oral mucosa.
 - Effects on leukocytes.
 - Microvasculature.
 - Ecological equilibrium.

Epidemiological studies:

Gingivitis:

- Enlarged, hemorrhagic, bluish red gingiva. Gingivitis is not caused by vit C deficiency.

- Increases severity.
- Correcting the deficiency may reduce the severity.

Periodontitis:

- Documented in experimental animals.
- Acute vit C deficiency – edema & hemorrhage in pdl, osteoporosis of alveolar bone, tooth mobility, edema & degeneration of collagen fibers in the gingiva.
- Impairs gingival healing.
- Periodontal fibers are least by vit C deficiency.
- A case report by Charbeneau & Hurt showed worsening of a pre-existing moderate periodontitis with development of scurvy.
- In a retrospective study of 12,419 adults studied in the Third National Health & Nutrition Examination Survey (NHANES III), Nishida & Colleagues found that there was a weak but statistically significant dose- response relationship between dietary vit C intake & periodontal disease in current & former smokers as measured by clinical attachment.

PROTEIN DEFICIENCY:

- Results in hypoproteinemia with many pathologic changes like:
 - Muscular atrophy,
 - Weakness
 - Weight loss
 - Leukopenia,
 - Edema
 - Impaired lactation
 - Decreased resistance to infections,
 - Slow wound healing,
 - Reduced ability to form certain hormones & enzymes.
- It causes changes in the periodontium in experimental animals.

- Protein deficiency – destructive effects in bacterial plaque & occlusal trauma on periodontium, but initiation of gingival inflammation & its severity depends on the plaque.

MEDICATIONS

- Medications are prescribed for various diseases.
- Bisphosphonates are a class of drugs – widely used to treat osteoporosis & various types of cancers.
- It is implicated in osteonecrosis of jaw (ONJ) – A serious condition characterised by non-healing & often painful exposure of non-vital & often sequestering bone in the jaws.
- Corticosteroids have long been used to suppress the immune system for control & management of auto-immune diseases, during cancer treatment & anti-rejection medication after organ transplantation.

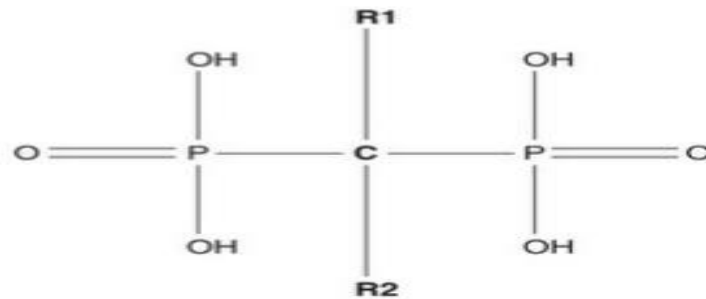
BISPHOSPHONATES

- Cancer & Osteoporosis.
- Act by inhibiting osteoclastic activity, leading to:
 - Less bone resorption
 - Less bone remodelling &
 - Less bone turnover.
- In cancer treatment, it is aimed at preventing the lethal imbalance of osteoclastic activity.
- In osteoporosis, the goal is to harness osteoclastic activity to minimize or prevent bone loss & in many cases to increase the bone mass by creating an advantage to osteoblasts.
- Major differences between the bisphosphonates for cancer & osteoporosis is:
 - Potency &
 - Route of administration.
- First synthesised during 1950's.
- Ability to increase the bone mass was discovered in 1966, their advantage for humans with low bone mass was not appreciated until 1984.
- FDA approved the use of alendronate for osteoporosis in 1995.

- The chemical structure of bisphosphonate consist of:
 - Two phosphate groups covalently bonded to a central carbon.
 - The central carbon also has two side chains – R1 & R2.
 - The long R2 chain also influences the mode of action & determines the strength & potency of the medication.

Structure

Generic bisphosphonate



R1 Enhances binding to hydroxyapatite
 -C- Enhances chemical stability
 R2 Determines antiresorptive potency

- Bisphosphonates inhibit osteoclasts by two mechanisms that depends on whether the R2 side chain contain nitrogen.
- Nonaminobisphosphonates – metabolised by osteoblasts to form an ATP analouge that interferes with energy production & cause osteoclast apoptosis.
- Aminobisphosphonates are more potent & have multiple effects on osteoclasts, include the following:
 - Inactivation of ATP
 - Osteoclast cytoskeleton disruption
 - Impairment of osteoclast recruitment
 - Induction of osteoblasts to produce osteoclast inhibiting factor.
- Anti-angiogenesis
- Growing evidence – affect on soft tissues.
- An in vitro study by Kim & colleagues suggested that bisphosphonates may act on oral keratinocytes to impair wound healing by inhibiting epithelial migration & wound closure.

- Bisphosphonates – affinity for hydroxyapatite.
- Rapidly absorbed in the bone, especially in areas of high activity, which may explain why bisphosphonate induced osteonecrosis is found only in the jaws.
- Bisphosphonate – incorporated into bone without being metabolized or modified.
- During resorption of the bone, the trapped bisphosphonate is released & able to affect osteoclasts again.
- Half-life – 10 years or longer.

Osteonecrosis Of Jaw:

- It is associated with bisphosphonates was first described in 2003 by Marx in a report of 36 patients with avascular necrosis of the jaw who had been treated with IV bisphosphonates for malignant tumours.
- Terms used to describe this type ONJ:
 - Avascular necrosis,
 - Bisphosphonate associated ONJ,
 - Bisphosphonate induced ONJ,
 - Bisphosphonate related ONJ (BRONJ).
- The necrotic bone exposure of the jaw (ONJ) is a condition with multiple possible etiopathogenesis, including
 - systemic medications,
 - radiation,
 - infection,
 - trauma,
 - direct chemical toxicity,
 - other idiopathic mechanisms.
- Diagnosis of BRONJ should be carefully be made.
- BRONJ has been **defined** as the exposure & necrosis of portions of the jaw bone in patients who have been exposed to bisphosphonates that has persisted for longer than 8 weeks with no history of radiation therapy of the jaws.

Stages of osteonecrosis:

- **Stage 0:** patient at risk, who have been treated with IV bisphosphonates but who have no apparent exposed or necrotic bone.
- **Stage 1:** involves exposed or necrotic bone in patients who are asymptomatic with no infection.
- **Stage 2:** involves exposed or necrotic bone in patients with pain & clinical evidence of infection.
- **Stage 3:** involves exposed or necrotic bone in patients with pain, infection & one or more of the following: pathologic fracture, extra-oral fistula or osteolysis that extends to the inferior border.

Clinical manifestations

- Exposed alveolar bone occurs spontaneously or after a traumatic events.
- The site may be painful, with surrounding soft tissue indurations & inflammation.
- Infection with drainage may be present.





Radiographically

- Lesion appears radiolucent, with sclerosis of lamina dura, or a widening of the pdl area where teeth are present.

Histologically

Bone appears necrotic, with empty lacunae demonstrating a lack of living osteocytes.

In advanced cases, pathologic fractures may be present through the area of exposed or necrotic bone.

Incidence

- High potency of nitrogen containing bisphosphonates, like zoledronate IV for cancer treatment may explain the high incidence of BRONJ compared to osteoporotic patients taking oral bisphosphonates.
- Incidence among cancer patients may range from 2.5 – 5.4% or from 1 – 10%.
- Estimation of incidence among patients who are taking oral bisphosphonates for osteoporosis is more difficult due to large number of patients taking oral bisphosphonates (appears to be low) & lack of good reporting or documentation.

- Some reports estimate the incidence of BRONJ from oral bisphosphonates range from 0.007 – 0.04%, other reports suggest a slightly higher incidence range from 0.004 – 0.11%.

Location or site:

- BRONJ lesions occur most often in areas with dense bone & thin overlying mucosa, such as tori, bony exostoses & mylohyoid ridge.
- Mandible than maxilla → 2:1
- Work by Schaudinn & colleagues suggests that there may be a toxic threshold of accumulated bisphosphonates in the bone that leads to the induction of BRONJ lesions & measuring or calculating the concentration in the bone may be a means of assessing an individual's risk for the development of BRONJ.

Other factors:

- In addition to bisphosphonates therapy, other factors are thought to increase individual susceptibility to BRONJ.
- Potential risk factors are:
 - Systemic corticosteroid therapy,
 - Smoking,
 - Alcohol,
 - Poor oral hygiene,
 - Chemotherapy,
 - Radiotherapy,
 - Diabetes,
 - Hematologic factors.
- Precipitating Factors:
 - Extractions,
 - Root canal treatments,
 - Periodontal infections,
 - Periodontal surgery,
 - Dental implant surgery,

- Idiopathic.

BISPHOSPHONATES & PERIODONTAL BONE LOSS:

- Bone – preserving action → periodontal disease.
- Topical or systemic use – reduce alveolar bone loss.
- Bone regeneration.
- Bone preservation – low doses.
- In a 2-3 yrs follow up report of four female patients with periodontitis treated with etidronate, the potential of this agent to prevent periodontal bone loss was reported.
- Alendronate.

CORTICOSTEROIDS:

- Systemic – cortisone & adrenocorticotrophic hormone appears to have no effect on the incidence or severity of gingival or periodontal disease.
- Patients receiving immuno-suppressive therapy have significantly less gingival inflammation than control subjects with similar amounts of plaque.
- Exogenous cortisone – adverse effect on bone quality & physiology.
- Systemic administration – experimental animals resulted in osteoporosis of alveolar bone.

OSTEOPOROSIS:

- Osteoporosis is a disease characterised by low bone mass & structural deterioration leading to an increased risk of bone fracture.
- Females > males.
- Bone loss greater in women – peri-menopausal period.
- BMD test – to measure an individuals bone mass.
- DEXA score or T-score – comparison of patients BMD with healthy 30 yr old adult with peak bone mass.
- WHO defines osteoporosis & osteopenia by measures of standard deviation rather than comparison with a normal healthy, young adult.
- T – score → +1 to -1 → normal,
- 2 to - 2.5 → low bone density or osteopenia.

< - 2.5 → osteoporosis.

- All bone affected by osteoporosis are susceptible to fracture.
- Pelvis & Vertebrae.
- There may be a relationship between osteoporosis & periodontitis.
- Both are chronic, multi-factorial diseases that result in bone loss & in each condition it is exacerbated by local & systemic factors.
- Gender,
- Genetic predisposition,
- Inactivity,
- Deficient diet,
- Alcohol,
- Smoking,
- Hormones &
- Medications put individuals at risk for osteoporosis, some of these act as risk factors for periodontitis as well.
- A study by elder & colleagues failed to show a correlation between lumbar BMD & clinical parameters periodontitis in dentate group of 286 females between age of 46 & 55 yrs. They used intra-oral periodontal examinations & bitewing radiographs to assess clinical parameters of periodontitis & interproximal alveolar bone loss.
- This study included edentulous & dentate subjects, suggesting that neither periodontitis nor tooth loss was related to osteoporosis.
- Most studies citing a positive correlation between osteoporosis & periodontitis are cross-sectional studies of post-menopausal females.
- Klemetti & colleagues evaluated 227 healthy post menopausal women between the ages of 48 & 56 yrs & found that women with higher skeletal BMD were more likely to retain their teeth in the presence of periodontitis.
- Tezal & colleagues concluded that skeletal BMD is related to alveolar bone loss, & to a lesser extent to clinical attachment loss, thereby implicating postmenopausal osteopenia as risk indicator for periodontal disease.

CONGENITAL HEART DISEASE:

- 1% of live births.
- 40% of individuals born with heart defects – die without treatment.
- Cardiac defects may involve the heart, the adjacent vessels, or a combination of both.
- Most striking feature – cyanosis.
- In severe cases, cyanosis is obvious at birth, particularly in cases of Tetralogy of Fallot.
- Chronic hypoxia causes impaired development, compensatory polycythemia & clubbing edema of toes & fingers.
- Patients with congenital heart diseases are at risk for infective endocarditis.
- The need for prophylactic antibiotics should be evaluated before dental therapy.

TETRALOGY OF FALLOT:

- Characterised by four cardiac defects:
 - Ventricular septal defect
 - Pulmonary stenosis
 - Malposition of the aorta to the right
 - Compensatory right ventricular enlargement.
- Clinical features:
 - Severe cyanosis
 - Audible heart murmurs
 - Breathlessness.
 - Cerebral anoxia & syncope may occur.
- Oral manifestations:
 - Purplish red discoloration of lips & the gingiva.
 - Severe marginal gingivitis

- Periodontal destruction.
- The discoloration of the lips & the gingiva corresponds to cyanosis & it returns to normal after corrective heart surgery.
- Tongue appears coated, fissured & edematous & there is extreme reddening of fungiform & filiform papillae.

EISENMENGER SYNDROME:

- In patients with ventricular septal defects, about half of those with large defects (i.e >1.5 cm in diameter) develop Eisenmenger Syndrome.
- It is distinguished by a greater blood flow from the stronger left ventricle to right ventricle (backward flow), through the septal defects.
- This causes increased pulmonary blood flow, which leads to pulmonary fibrosis, small vessel occlusion & high pulmonary vascular resistance.
- With increasing pulmonary resistance, the right ventricle hypertrophies, the shunt becomes bidirectional, & ultimately blood flow is reversed.
- In untreated patients a gradual increase in cyanosis over many years that eventually leads to cardiac failure.
- Cyanosis of lips, cheeks & buccal mucosa is observed, but it is much less severe than in those with Tetralogy of Fallot.
- Severe, generalised periodontitis has been reported in patients with Eissenmenger Syndrome.

HYPOPHOSPHATASIA:

- It is a rare familial skeletal disease characterised by rickets, poor clinical bone formation, craniostenosis & the premature loss of the primary teeth, particularly the incisors.
- The patients have a low level of serum alkaline phosphatase, & phosphoethanolamine is present in serum & urine.
- Teeth are lost with no clinical evidence of inflammation, they show reduced cementum formation.
- In patients with minimal bone abnormalities, the premature loss of deciduous teeth may be the only symptom of hypophosphatasia.
- In adolescents, this disease resembles localised aggressive periodontitis.

METAL INTOXICATIONS:

- Ingestion of metals like mercury, lead & bismuth in medicinal compounds & through industrial contact may result in oral manifestations caused either by intoxication or absorption without evidence of toxicity.

BISMUTH INTOXICATION:

- Gastrointestinal disturbances, nausea, vomiting, jaundice as well as ulcerative gingivostomatitis.
- Pigmentation & metallic taste & burning sensation of oral mucosa.
- Tongue – sore & inflamed.
- Urticaria, exanthematous eruptions, bullous & pruritic lesions, herpes zoster like eruptions.
- Acute condition – less frequent, accompanied by methemoglobin formation, cyanosis & dyspnoea.

Oral manifestations:

- Narrow, bluish-black discoloration of gingival margin in areas of pre existing gingival inflammation.
- Bismuth pigmentation – linear form if the marginal gingiva is inflamed.

LEAD INTOXICATION:

- It is slowly absorbed, toxic symptoms are not definitive.
- Pallor of the face & lip & gastrointestinal symptoms that consists of nausea, vomiting, loss of appetite & abdominal colic.
- Peripheral neuritis, psychologic disorders, encephalitis are reported.

Oral signs:

- Salivation, coated tongue, a peculiar sweetish taste, gingival pigmentation & ulceration.
- Gingival pigmentation is linear (burtonian line), steel gray & associated with local inflammation.

MERCURY INTOXICATION:

- Headache, insomnia, cardiovascular symptoms, pronounced salivation (ptyalism) & metallic taste.
- Gingival pigmentation.

- Metal sulfide – act as irritant, accentuate the pre-existing inflammation, leading to notable gingival ulceration & also the mucosa & may cause destruction of underlying bone.

OTHER CHEMICALS:

- Others like – phosphorous, arsenic, chromium, cause necrosis of the alveolar bone, with loosening & exfoliation of the teeth.
- Inflammation & ulceration of gingiva are usually associated with destruction of the underlying tissues.
- Benzene intoxication is accompanied by gingival bleeding & ulceration with destruction of the underlying bone.

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