



The Oral/Systemic Relationship

Indian Health Service



Periodontal Treatment Initiative

Overall Health Begins With Periodontal Health





Purpose/Learning Objectives

- The purpose of this presentation is to provide dental and other health care professionals knowledge about the relationship between periodontal disease and systemic disease.
- By the end of this presentation, participants should be able to:
 - Broadly explain the relationship between periodontitis, chronic inflammation, and systemic inflammatory processes;
 - Describe the strength of association between periodontitis and: (1) diabetes; (2) cardiovascular disease; (3) adverse pregnancy outcomes; and (5) pulmonary disease; and
 - List 2-3 new relationships between periodontitis and systemic problems that are now being investigated.



News Headlines

- “By Gum, Your Life is in Danger”
- “Are My Bad Teeth Killing Me?”
- “Severe Gum Disease May Hasten Death”
- “The Checkup That Can Save Your Life”
- “Dental Calamities That Can Truly Hurt”
- “No Proof that Periodontitis Causes Heart Disease”

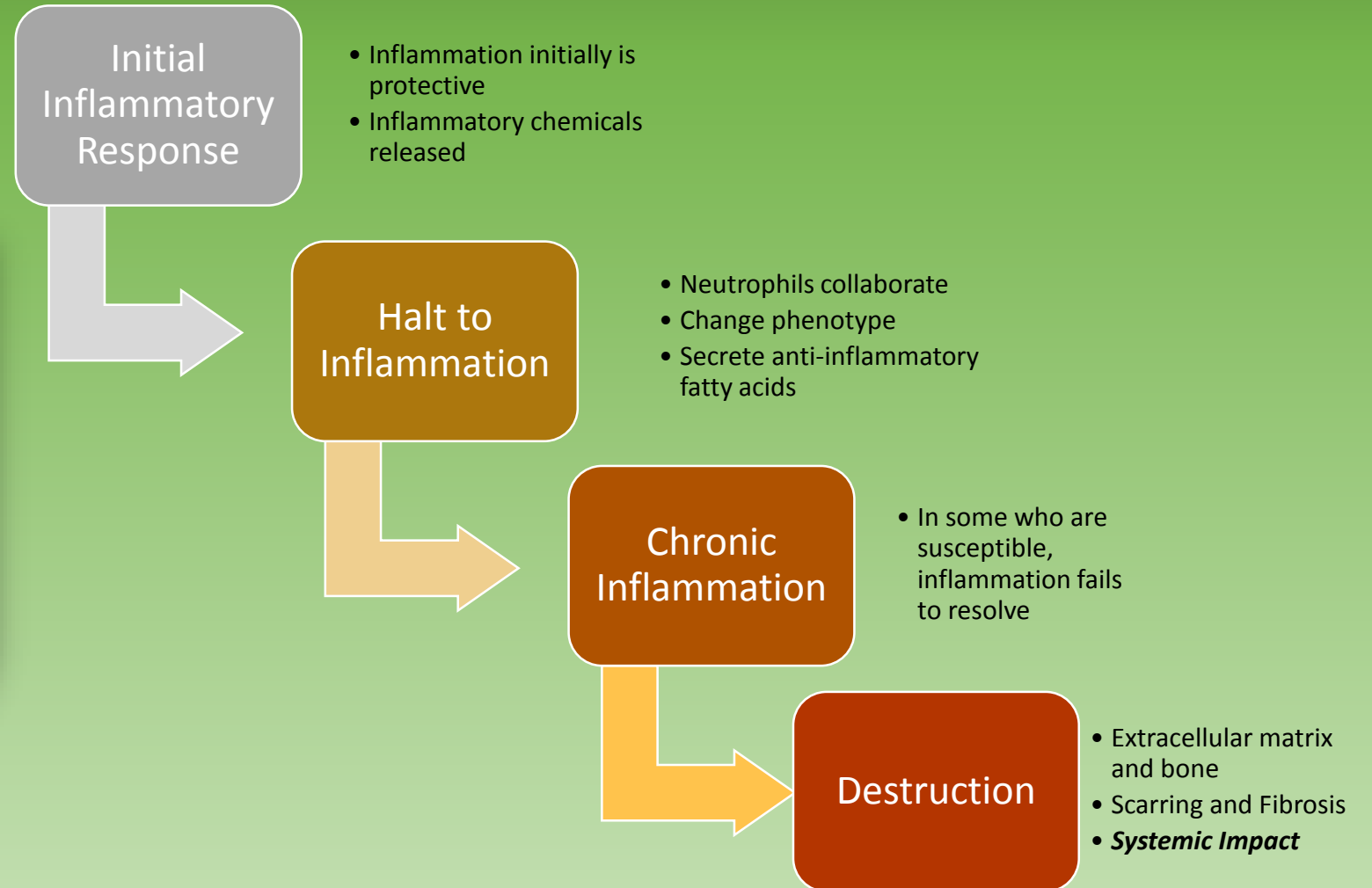
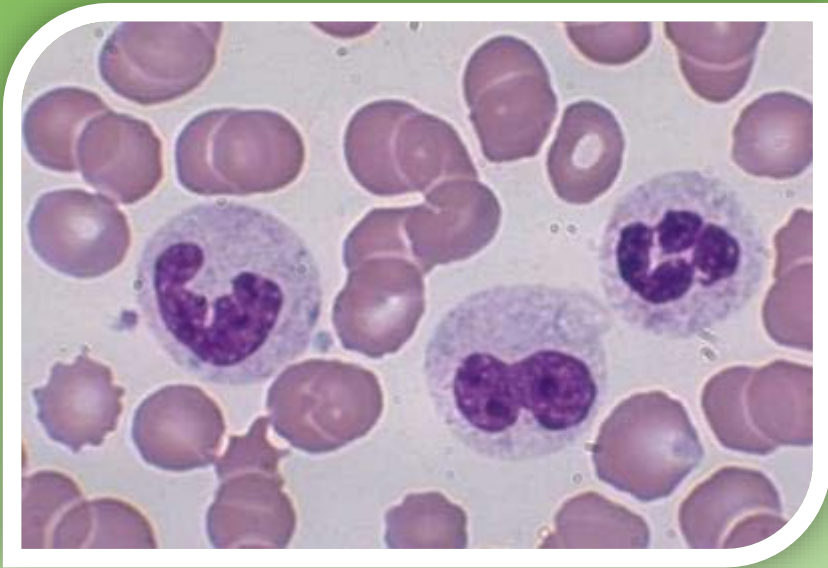


Periodontitis and Inflammation



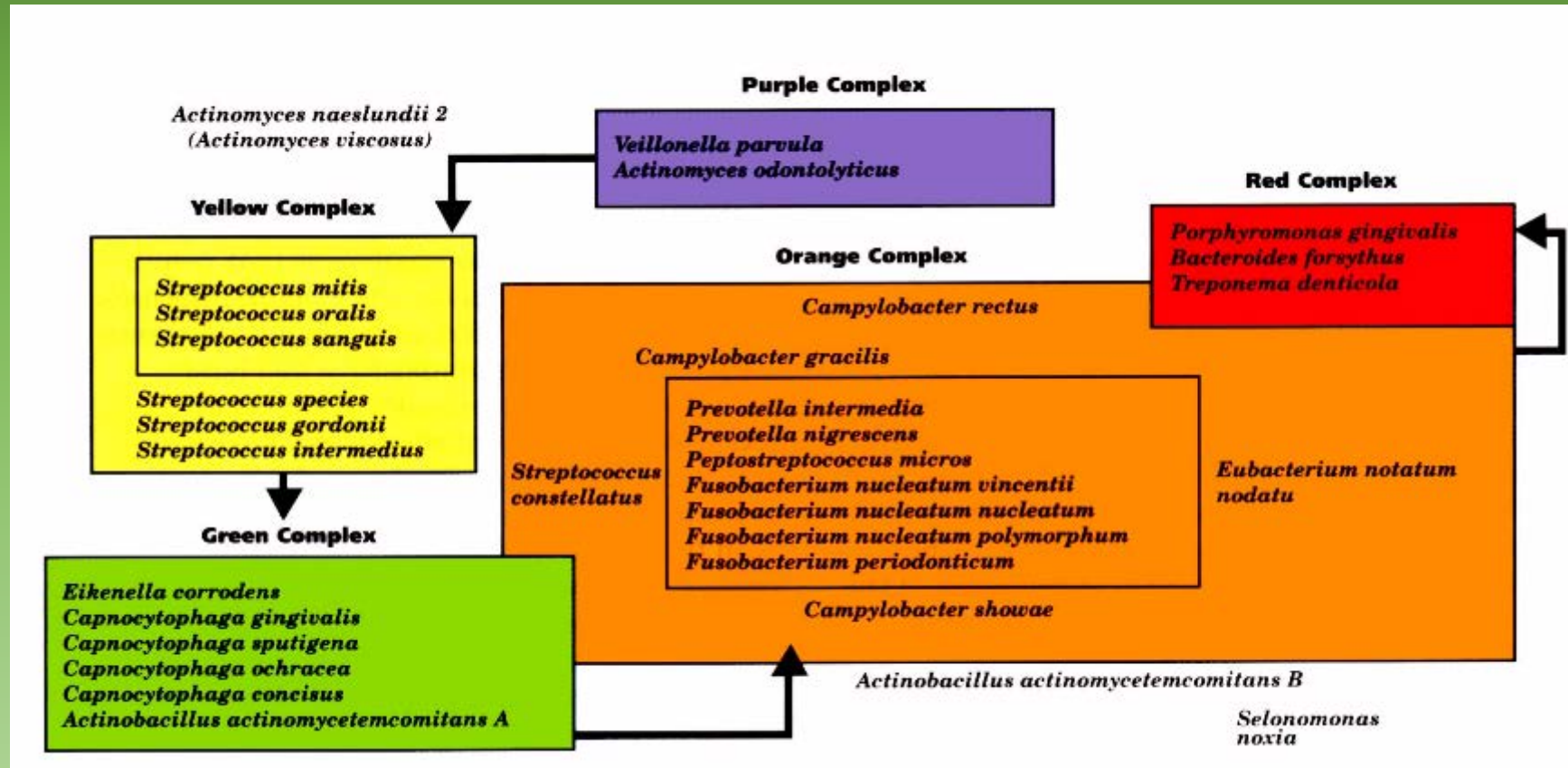
Inflammation: Acute to Chronic

- Neutrophils = 1st line of defense





Periodontitis is a chronic inflammatory disease with a complex poly-microbial infection



- 17 species of new perio pathogens. JDR 2014 meta analysis
- Viruses: EBV, HCMV, and HSV are immunosuppressive and support the overgrowth of the periopathogens.



Periodontal medicine- periodontal diseases have an effect on certain systemic conditions

- Not all oral bacteria are created equal.
- Stealth like properties enable oral organisms to persist at extraoral sites, even for years, through immune evasion, selective virulence, and the ability to disseminate (Offenbacher 2004).
- *S mutans* serotype e, f, and k, *Campylobacter concisus* Cluster I, *Fusobacterium nucleatum* sbsp *animalis*, oral *Treponema*, and certain *P. gingivalis* strains are more prevalent in extraoral infections (Han JDR 2013).



Porphyromonas gingivalis (Pg)

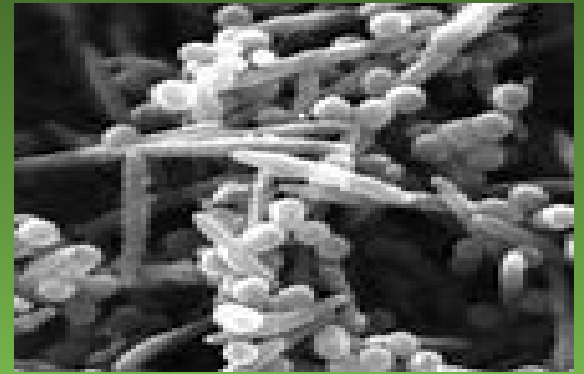


Highly virulent keystone pathogen influences other bacteria even at low numbers.

- Invades gingival epithelial cells to remain undetected by the immune system and becoming more resistant to perio therapy.
- Inhibits polymorphonuclear leukocytes' (PMNs) ability to phagocytose invading bacteria.
- One variation in the Lipid A outer coat is resistant to host bacterial killing, allowing access to the vasculature and distant tissues.
- Only bacteria with the enzyme PAD, which can induce ACPA's and trigger autoimmune inflammation in RA.
- Produces GroEL under stress, which reacts with human heat shock proteins and can lead to endothelial dysfunction and perhaps cardiovascular disease



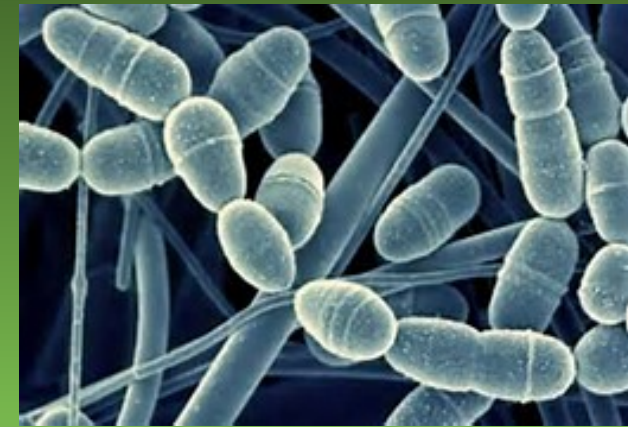
Fusobacterium nucleatum (Fn)



- Most prevalent oral species detected in extraoral infections.
- Adheres/invades host cells, evading host defense and spreading to deeper tissues through a unique surface adhesin FadA.
- Fad A allows direct cell invasion and loosens cell-cell junctions for other species to invade
- Fap2 protein protects tumors from immune cell attack.

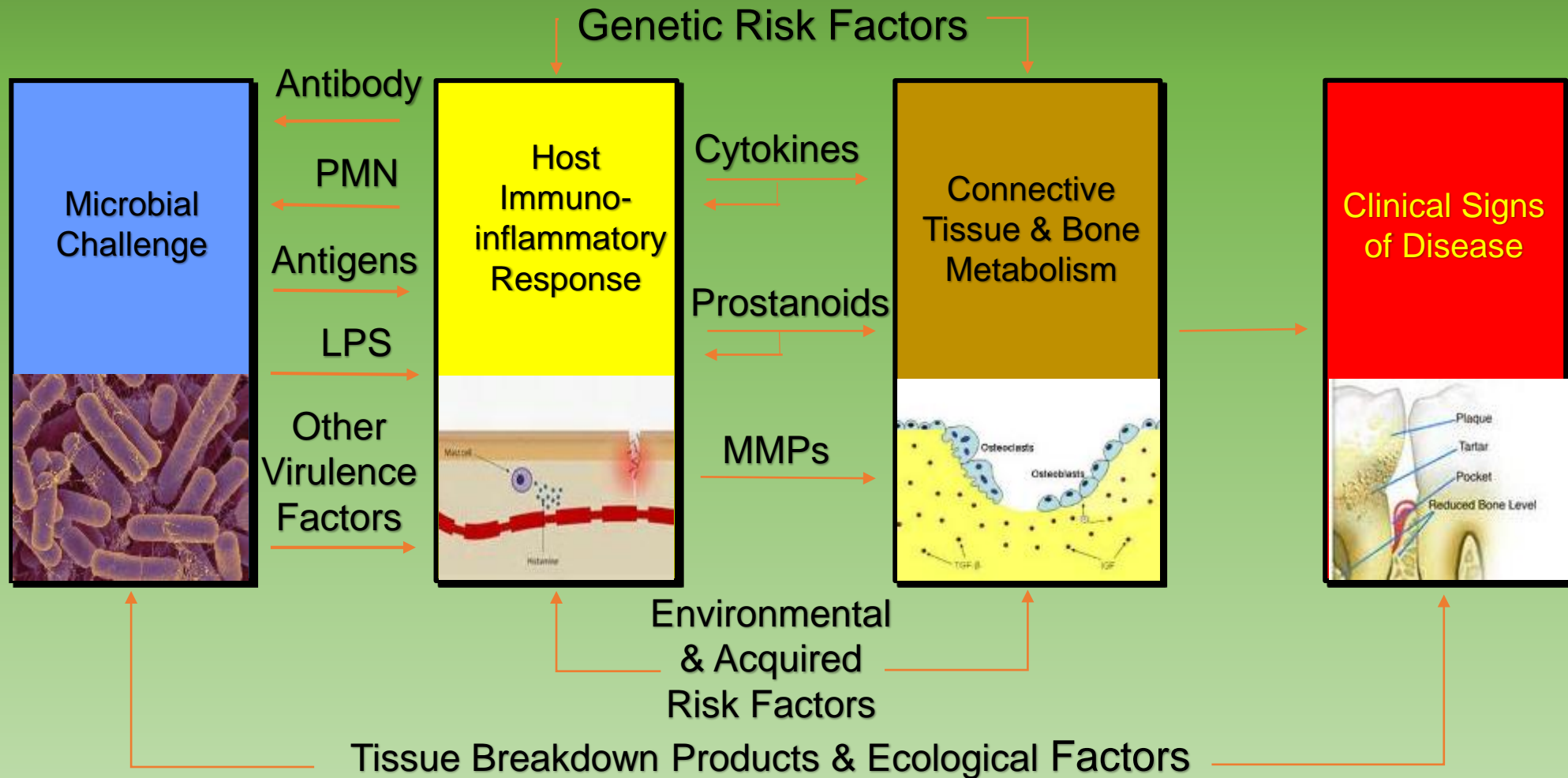


Treponema denticola (Td) *a.k.a. Spirochetes*



- Spirochetes attach to host cells through their collagen binding proteins and other surface components such as amyloids. They spread to distant sites through hematogenous, lymphatics and along nerve fibers. Found in trigeminal nerve and ganglia.
- Brain receptors specific for gram negative oral bacteria and treponemes found in the cortex of Alzheimer patient brains postmortem (14/16 vs 4/18 AD vs Healthy).
- Td found in 49% of atherosclerotic plaque samples and is associated with low HDL and high triglycerides, increasing risk for CVD.

Pathway to Periodontal Disease



After Kornman, 1997.

The Systemic Connection – Bacterial Access

- Ulcerated epithelium within infected periodontal pockets allows bacteria, toxins, and inflammatory mediators access to the blood stream.



Ulcerated
epithelium

Bone

How much access?

- A case of moderate periodontitis such as the one pictured may have 10-20 cm² of ulcerated surface area (the size of the palm of the hand)



Compared to...



- This diabetic foot ulcer may be 3-5 times smaller than the ulcerated epithelium within infected periodontal pockets

Healing of an Ulcerated Pocket

Pre-scaling and root planing



Recall at 6 months
No inflammation, local or systemic





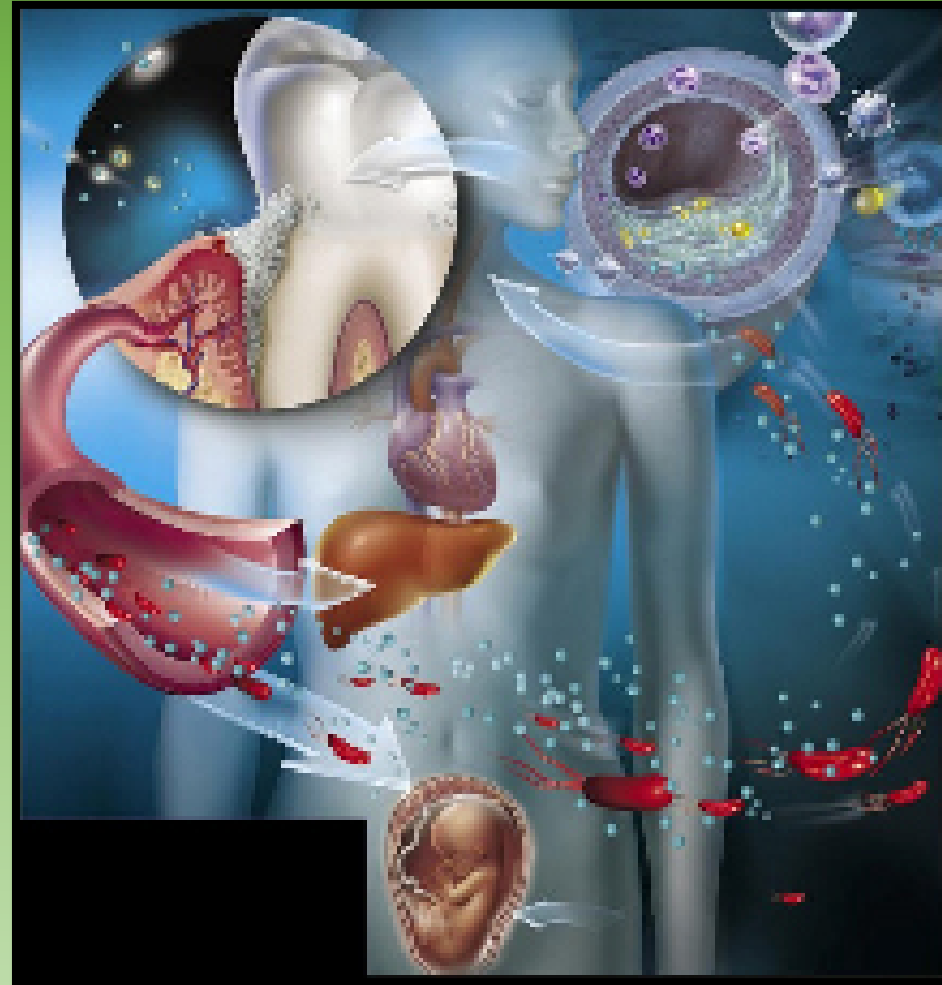
Summary – Periodontitis & Inflammation

- Periodontitis is an anaerobic infection flooding the blood stream 24 hours a day with endotoxins and inflammatory mediators.
- Periodontitis is associated with increased serum C-Reactive Protein (CRP, a measure of systemic inflammation), and periodontal treatment decreases CRP.
- Pro-inflammatory cytokines (IL-1, IL-6, TNF- α) and prostaglandins (PgE2) accumulate in the gum tissues in active periodontitis at extraordinary levels and can enter the circulation.
- Periodontitis, diabetes, cardiovascular disease, Alzheimer's, Parkinson's, and rheumatoid arthritis are all interrelated through inflammation.

Workshop on Inflammation 2008



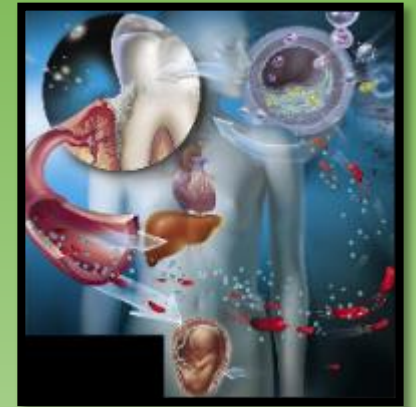
Periodontitis Associations with Systemic Disease





Periodontitis has an association with:

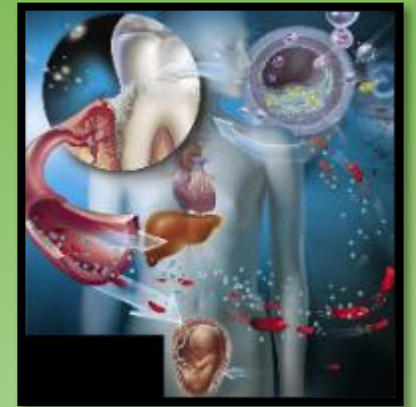
- Infective Endocarditis and Prosthetic Joint Infections
- Diabetes
- Atherosclerotic Cardiovascular Disease
- Adverse pregnancy outcomes
- Pulmonary Disease
- Others (RA, Cancer, Cognition/AD, ED, CKD)





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The Evidence/Association

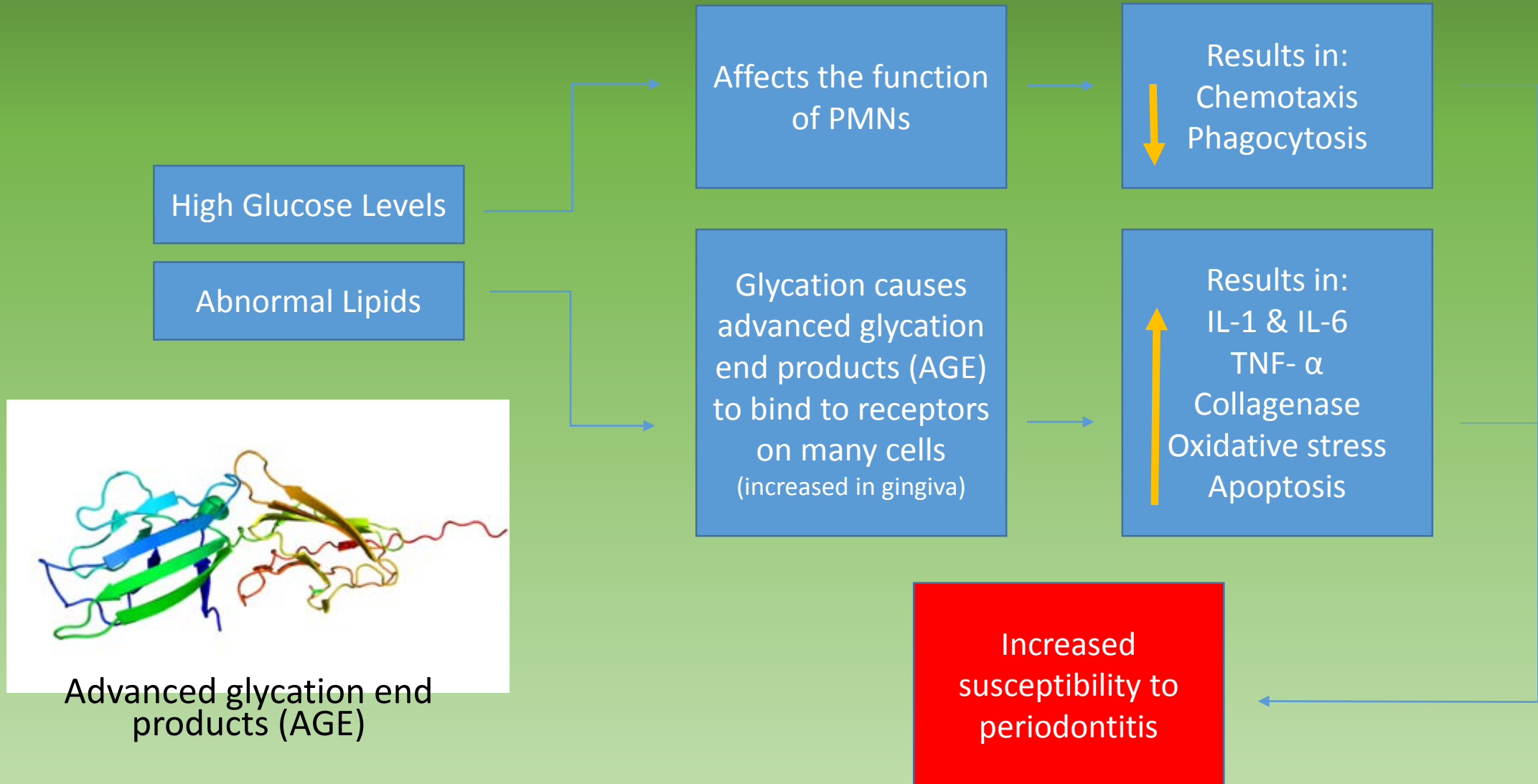
- A review of 55 studies involving subjects with diabetes found consistent evidence of increased:



- **Prevalence** of periodontitis
- **Incidence** of periodontitis
- **Severity** of periodontitis
- **Extent** of periodontitis
- **Progression** of periodontitis

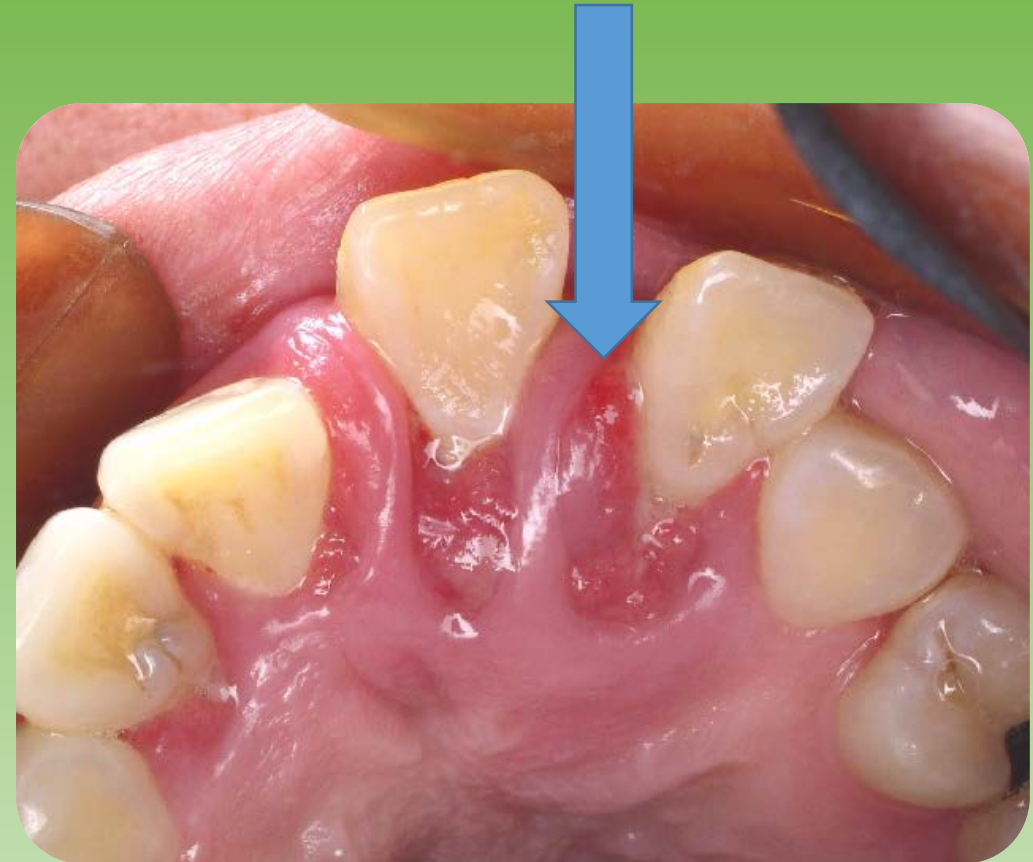
- **Periodontal Disease is considered to be the 6th complication of diabetes** – along with heart disease, stroke, diabetic retinopathy, kidney failure, and neuropathies.

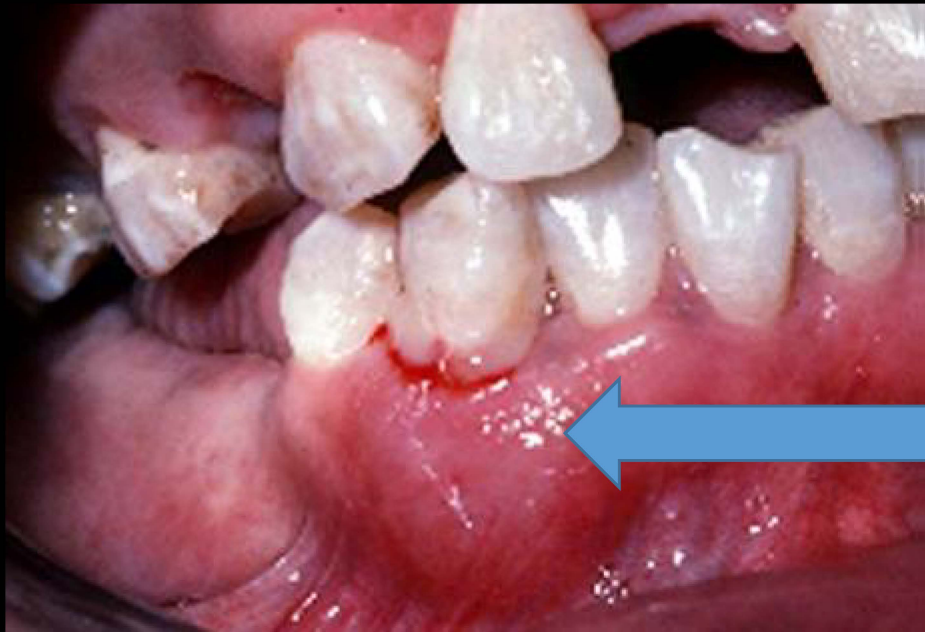
What causes the periodontal destruction in diabetes?



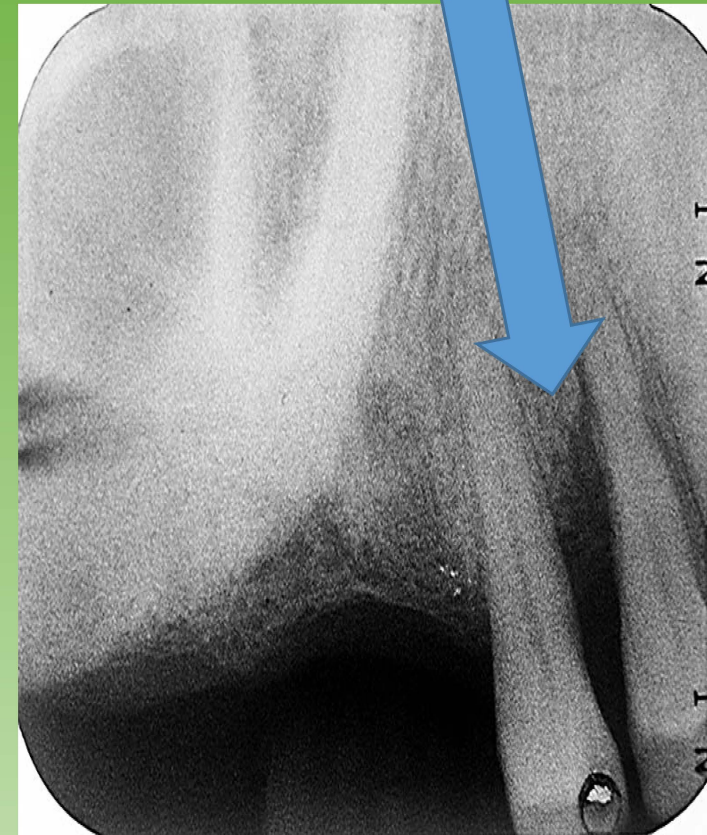
Oral Effects in Patients with Diabetes

- Increased gingivitis and periodontitis
- Caries
- Intraoral slow healing
- Xerostomia
- Burning mouth and tongue
- Cheilosis and moniliasis
- Multiple periodontal abscesses





42 year-old female with uncontrolled diabetes (FBG averages 300-400 mg/dl)

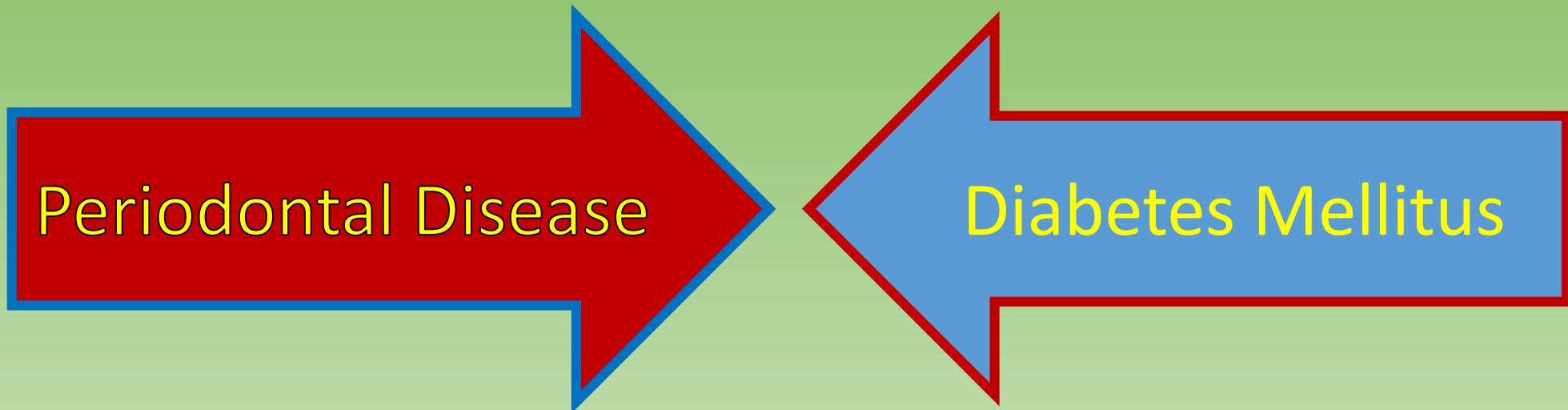


< 2 years later



The Two-Way Relationship

- Does periodontitis increase risk of:
 - Poorer glycemic control?
 - Increased risk of diabetes complications like heart attacks and kidney disease?
 - Mortality?





Glycemic Control, Diabetic Complications

- Diabetic subjects had a 6-fold increased risk of a worsening of HbA1c over 2-3 years when severe periodontitis was present at baseline.
- Patients with insulin-dependent DM had significantly higher prevalence of proteinuria and cardiovascular complications such as stroke, TIA, angina, and MI when severe perio was present at baseline.





Mortality

- Periodontal disease is a strong predictor of mortality from ischemic heart disease and diabetic nephropathy in Pimas with type 2 diabetes.
 - No/mild perio 0 deaths/1000 person-years
 - Moderate perio 4.8 deaths/1000 person-years
 - Severe perio 5.7 deaths/1000 person years
[2.3X higher risk of cardiac mortality]
- For deaths from diabetic nephropathy, there were 0, 0.5, and 5.3 deaths/1000 person-years for no, moderate, and severe periodontitis respectively ($p < 0.01$).
 - Severe perio 8.5X higher risk of renal mortality



Perio Therapy Improves Diabetic Control

- Scaling and root planing provides a significant improvement in glycemic control (average 0.40% decrease) in the majority of studies and meta-analyses.
- Perio treatment leads to improved glycemic control for at least 3 months
- It is not clear if and when antibiotics and antimicrobial irrigants improve the diabetes.





Medical Guideline for Health Care Workers on Oral Health for People with Diabetes

- Inquire about regular oral health check ups.
- Inquire at least annually for symptoms of gum disease, and to seek treatment if present.
- Remind that adequate daily home care is a normal part of diabetes self-management.
- Educate on the relationship between diabetes and gum disease.
- Resource Toolkit at www.cdc.gov/diabetes/ndep/ppod.htm

International Diabetes Federation 2009



Periodontitis has an association with:

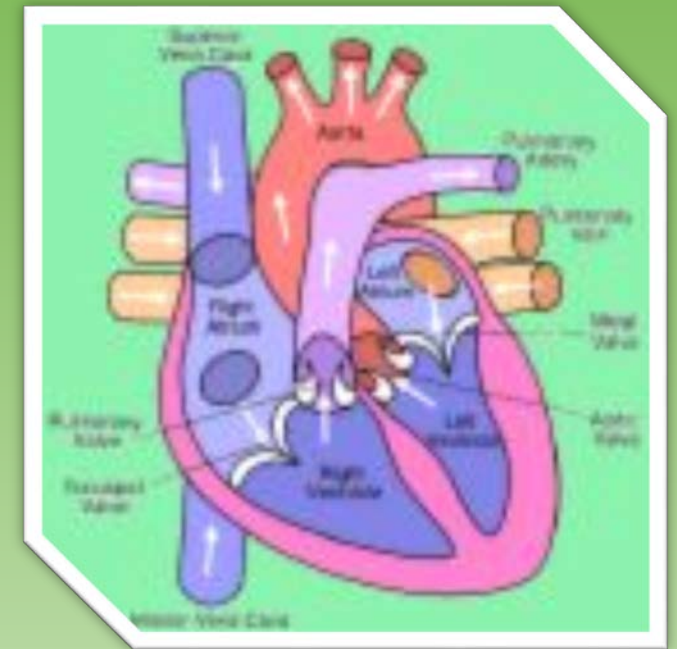
- ~~Infective Endocarditis and Prosthetic Joint Infections~~
- ~~Diabetes~~
- **Atherosclerotic Cardiovascular Disease**
- Adverse pregnancy outcomes
- Pulmonary Disease
- Others (RA, Cancer, Cognition/AD, ED, CKD)



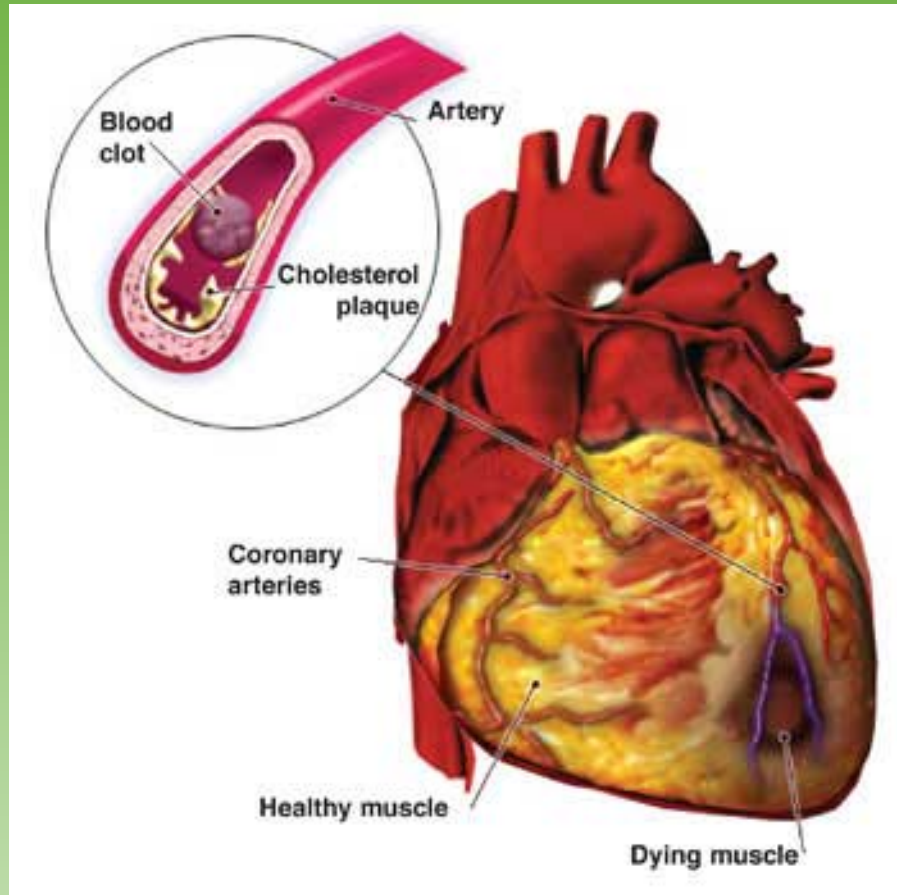


The Evidence in Animals

- In hypercholesterolemic mice infected with *Porphyromonas gingivalis*, *Pg* DNA was localized in aortic tissue and enhanced atherosclerosis.
- Pigs inoculated with *Pg* had elevated serum CRP and atheroma sizes compared with controls.
- Rabbits inoculated with *Pg* had platelet clumping, thrombus and emboli formation, and increased chance for MI and stroke.
- **Conclusion**: *Pg* accelerates early atherosclerosis, and its eradication may be beneficial in reducing the progression of atherosclerosis.



Effect of Bacteria in CVD

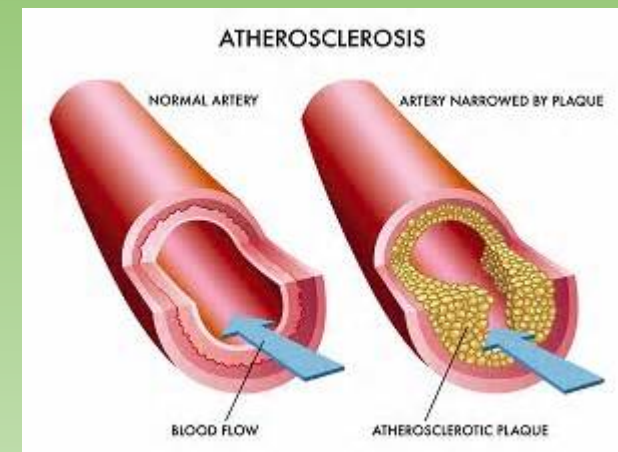


- Bacteria/endotoxins negatively affect platelet function, coagulability, endothelial cell function, smooth muscle cell function, and integrity of the blood vessel wall.
- Artery walls can thicken and become occluded with plaques or atheromas.
- The worse the periodontitis, the higher the markers of platelet activation and procoagulant state.



Effect of Bacteria in CVD Theories:

- Bacteria or viruses from the mouth directly infect blood vessel walls and contribute to development of plaques and atherosclerosis.
- Bacteria or viruses interact with white blood cells or platelets and trigger platelet clumping and release of pro-inflammatory cytokines, prostaglandins, and TNF- α .
- Bacterial products in the blood stimulate liver production of pro-inflammatory or pro-coagulant as C-reactive protein (CRP) and fibrinogen, exacerbating other ongoing inflammatory processes and increasing risk of atherosclerosis.
- Immune cross reactivity (molecular mimicry) between peptides and host peptides.





Periodontitis and Myocardial Infarction (MI)

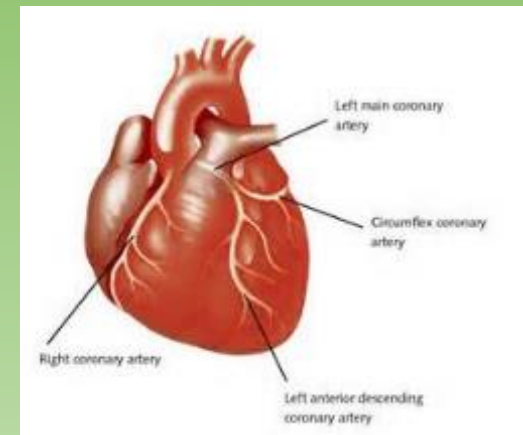
- Periodontitis was associated with a 1.72 odds ratio of a fatal MI (72% more likely to die)
- Over an 18-year study period, veterans were 1.9 X more likely to develop fatal heart disease and 3 X more likely to have a stroke
- Patients with a recent acute MI had worse oral health compared to controls (bleeding gums, deep pockets, decreased number of teeth) and increased levels of *P. gingivalis* immunoglobulins
- Greater extent and severity of periodontitis was asso with greater infarct size in patients experiencing MI





Periodontitis and Coronary Heart Disease (CHD)

- Those with periodontitis had a significant 1.14 to 1.59 increased risk of developing CHD compared to those without periodontitis, after adjusting for DM, smoking, alcohol, obesity, and HTN.
- In men <60, the rate of CHD increased by 39% for each 20% increase in mean periodontal bone loss, and the rate of CHD increased with increasing pocket depth
- Periodontitis is associated with recurrence of CV events mortality
- Periodontal disease is an independent risk factor for CHD





Perio Therapy Improved Early CVD

- Periodontal therapy can improve vascular endothelial function, enhancing blood flow
- Treating periodontal disease can reverse the process of early atherosclerosis
- Periodontal therapy was effective in improving endothelial dysfunction and reducing carotid intima media thickness
- Frequent cleanings reduced incidence rate and risk of acute MIs





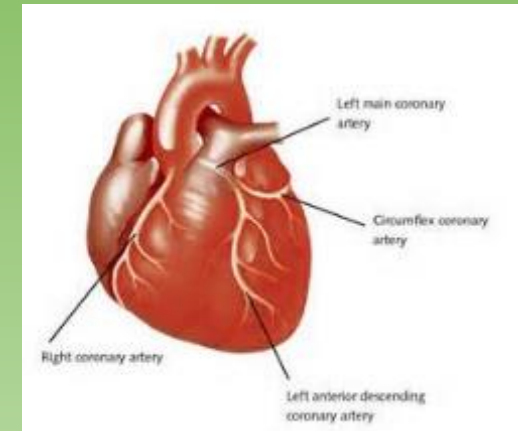
Epidemiological Evidence - Cerebrovascular Ischemia

- Periodontitis is a significant risk factor for non-hemorrhagic stroke (OR 2.11), fatal non-hemorrhagic stroke (OR 2.90), and those edentulous (OR 1.41) NHANES I to II (21 years) - Wu 1999
- In men <60, subjects with severe periodontitis had a 4.3 fold higher risk for TIA or stroke than subjects with mild or no periodontitis.
- Stroke strongly associated with severe CAL especially in adults < 60 and normal BP Adjusted Odds Ratio = 4.8
- There is an independent association between severe periodontitis and recurrent vascular events in stroke/TIA patients - Sen. J Stroke Cerebrovasc Dis 2013
- Dental prophylaxis and periodontal treatment reduces the incidence of ischemic stroke. – Lee, Stroke 2013



Management of Patients with CVD and/or Periodontal Disease

- **Patients with CVD with or without a periodontal diagnosis:**
 - Dentists and physicians should closely collaborate.
 - Perio evaluation should be considered in pts with CVD who have signs or symptoms of perio and unexplained elevations in hsCRP or other inflammatory biomarkers.
- **Patients with periodontitis:**
 - Should be informed there may increased risk for CVD associated with periodontitis.
 - With >1 known CVD risk factor, medical evaluation is recommended.



Amer J. Cardiology and J. of Periodontology Editors' Consensus, 2009



Conclusions on Periodontitis and CVD:

- The association between periodontal disease and CVD is real and independent of shared risk factors. Patients and healthcare providers should not ignore the risk of heart disease associated with gum disease just because we do not have all the answers yet.
- There is no scientific evidence of a cause-and-effect relationship between periodontal disease and CVD. - AHA Circulation 2012, JCP/JOP 2013
- There is consistent and strong epidemiological evidence that periodontitis imparts increased risk for future ACVD. - JCP/JOP 2013
- CVD is multifactorial and periodontitis contributes to a certain number of cases along with other exposures or influences (smoking, diabetes, BMI, stress, HTN, and hypercholesterolemia).

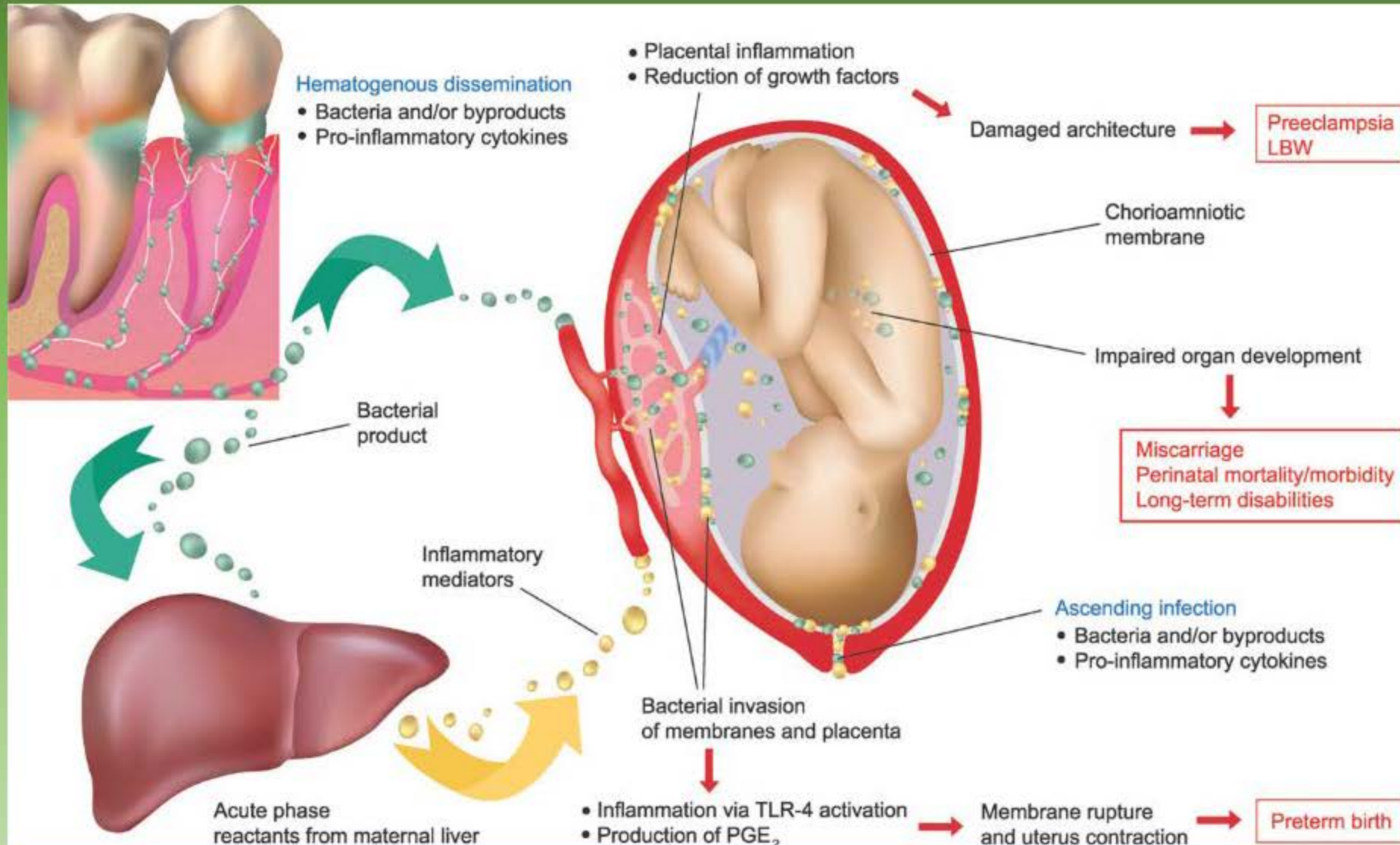


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- ~~Diabetes~~
- ~~Atherosclerotic Cardiovascular Disease~~
- **Adverse pregnancy outcomes**
- Pulmonary Disease
- Others (RA, Cancer, Cognition/AD, ED, CKD)



Adverse Pregnancy Outcomes and Periodontitis





Biologic Mechanism- Immune Response

- Fetal exposure to oral pathogens and asso inflammation is asso with PTB:

IgM	OR 6.0
PgE2	OR 4.1
CRP	OR 4.3
TNF- α	OR 7.6



640 human umbilical specimens. - Boggess J Ob & Gyn 2005

- *Pg* invasion of the amniotic cavity was detected in 30% of pregnant women with threatened premature labor.
- Fetal exposure to oral pathogens increased risk for neonatal intensive care admissions and extended lengths of stay.



Term stillbirth caused by oral bacteria

- Fusobacterium spread through the blood from the mothers mouth to the uterus when the immune system was weakened.
- Baby died from septic infection and inflammation.
- *Fn* prevalent in intrauterine infections and PTB.
- Mother had pregnancy associated gingivitis and a respiratory infection just prior to stillbirth.

Han et al. Case Report. Obstet and Gynecol 2010



Pre-Term Birth and/or Low Birth Weight?

- The risk for preterm labor requiring medical intervention or premature rupture of membranes (<36 weeks), or low birth weight infants (<2500 grams), was greater if the mother had periodontitis:
 - Pre-term birth: **Odds Ratio = 7.9**
 - Low birth weight: **Odds Ratio = 7.5**
- Maternal periodontitis is signif asso with PTB and LBW-2013 syst review.



- **1 million pre-term babies die annually (15 million, or 1/10 are born each year)**
- **Each PTLBW costs on average at least \$50K extra in hospital costs**



The Evidence/Association for Preeclampsia

- Women with severe periodontitis during pregnancy had increased risk of developing preeclampsia compared to those with gingival health:
 - Perio healthy at delivery- 3% developed preeclampsia
 - Mild periodontitis at delivery- 5%
 - Severe periodontitis at delivery- 10% (Odds ratio = 2.4)
- Periodontitis and urinary tract infections are with increased risk of preeclampsia
- A 2013 Systematic Review found maternal periodontitis was associated with preeclampsia.





Perio Therapy May or May Not Improve PTLBW Incidence

- Periodontal treatment is often ineffective in controlling gingival inflammation in pregnant patients.
- Many studies suggest that non-surgical periodontal therapy does NOT alter rates of PTB and LBW deliveries.
- In one study use of a mouthrinse and OHI reduced the risk of PTB by more than 2/3 in women with periodontitis.
- Periodontal therapy in the second trimester is safe.





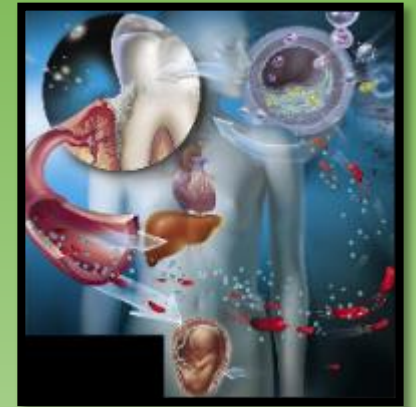
Medical/Dental Considerations

- Preventive oral care services should be provided as early in pregnancy as possible.
- If exam indicates a need for periodontal therapy, these procedures should be scheduled early in the 2nd trimester.
- The presence of acute infection, abscess, or other potentially disseminating sources of sepsis may warrant prompt intervention, irrespective of the stage of pregnancy. - American Academy of Periodontology Report 2004
- Pregnant women are encouraged to sustain their oral health and get regular cleanings during pregnancy. - Am College of Ob and Gyn, AAP, EFP 2013
- **Expectant mothers should be counseled in the importance of oral health.**



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The Evidence/Association

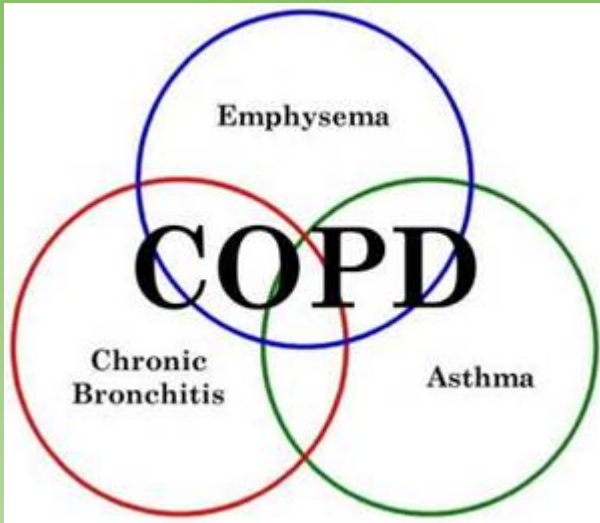
- Poor OH and denture plaque is associated with increased levels of respiratory pathogens and aspiration pneumonia.
- Poor perio health, infrequent cleanings, and poorer oral hygiene knowledge were associated with increased risk of chronic obstructive pulmonary disease.
- Patients with a history of moderate to severe perio were at higher risk of developing COPD than those without periodontitis.





Further Evidence of an Association

- The elderly were 4X more likely to die from pneumonia when many periodontal pockets were present.
- Poor perio health (bleeding gums, deeper pockets, and attachment loss) was associated with COPD and increased risk for being hospitalized for acute respiratory disease.
- Moderate to severe perio increased the risk for community acquired pneumonia over 4 times compared to healthy gums.





Perio Therapy Reduced Pulmonary Disease

- Oral hygiene practices may prevent death from bacterial pneumonia and respiratory tract infection in about 1 in 10 elderly residents of nursing homes.
- Strong evidence OH interventions prevent nosocomial pneumonias.
- ICU patients receiving toothbrushing, tongue scraping, cleanings, extractions, interim restorations and chlorhexidine 4-5X/week had significantly fewer respiratory infections.





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Periodontitis and Rheumatoid Arthritis (RA)

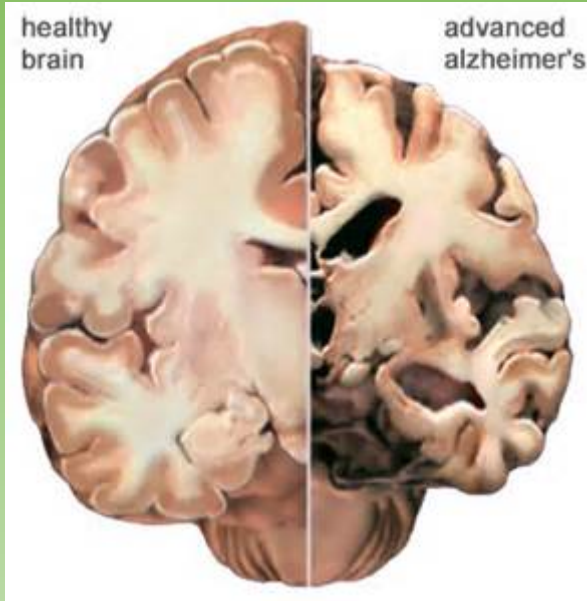
- Of those with RA, 63% had advanced forms of periodontitis
- Individuals with RA had more missing teeth and deep pocketing
- Perio bone loss was associated with RA severity including swollen joints and high CRP levels
- Individuals with mod to severe periodontitis are at higher risk of severe RA and vice versa- another 2 way relationship
- *F nucleatum* and *P gingivalis* in synovial fluid of failing joints and patients with refractory RA.
- Periodontal treatment can reduce swelling and pain in the joints.





Periodontitis, Cognitive Impairment, and AD

- Gingival inflammation is independently associated with cognitive impairment (controlling for education, race, CVD, and depression)
 - Periodontitis was associated with accumulation of amyloid plaques in normal humans, a central feature of Alzheimer's Disease (AD)
 - Tooth loss before age 35 is strongly associated with AD
 - Subjects with few teeth and irregular dental visits are at risk for developing dementia
 - Perio pathogen *Treponema* spirochetes can invade and persist in the brain and are strongly associated with dementia.





Periodontitis and Cancer

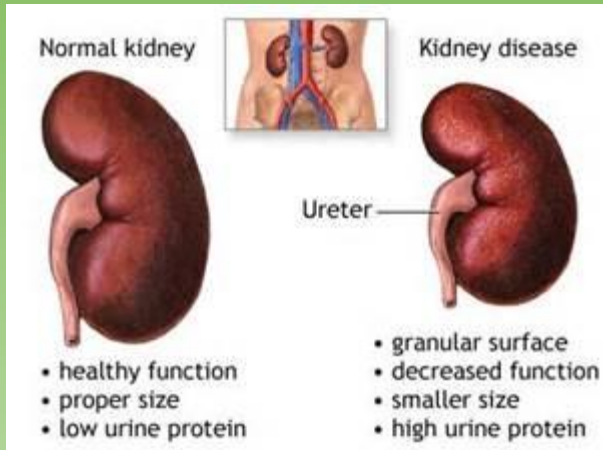
- Periodontitis was associated with increased risk for precancerous lesions (OR 1.55) and **oral tumors** (OR 4.57).
- Periodontitis is a risk factor for head and neck **squamous cell carcinoma**. Over a 4-fold increase when advanced alveolar bone loss after adjusting for smoking, alcohol, etc.
- Periodontitis was associated with increased risk developing **pancreatic cancer**.
- Men with periodontitis were 49% more likely to **cancer** and 30% more likely to
- Periodontal bacteria (*Fn* and *C. concissus*) are associated with **inflammatory bowel disease and cancer**.





Periodontitis and Chronic Kidney Disease

- Adults with periodontitis and those edentulous may be twice as likely to have CKD, adjusting for risk factors.



- Individuals with high perio pathogen antibodies may be more likely to have reduced renal function.
- Periodontitis is more advanced in patients with renal failure compared with the general population and may become more severe when CKD progresses.
- **Severe perio is associated with mortality in hemodialysis patients.**

Periodontitis: New Systemic Relationships





Relationships being investigated

Periodontitis may:

1. Worsen prostatitis
2. Lead to anemia
3. Potentiate the development of amyloidosis
4. Increase the risk of age-related macular degeneration
5. Increase the time it takes to become pregnant



Relationships being investigated

Periodontitis may:

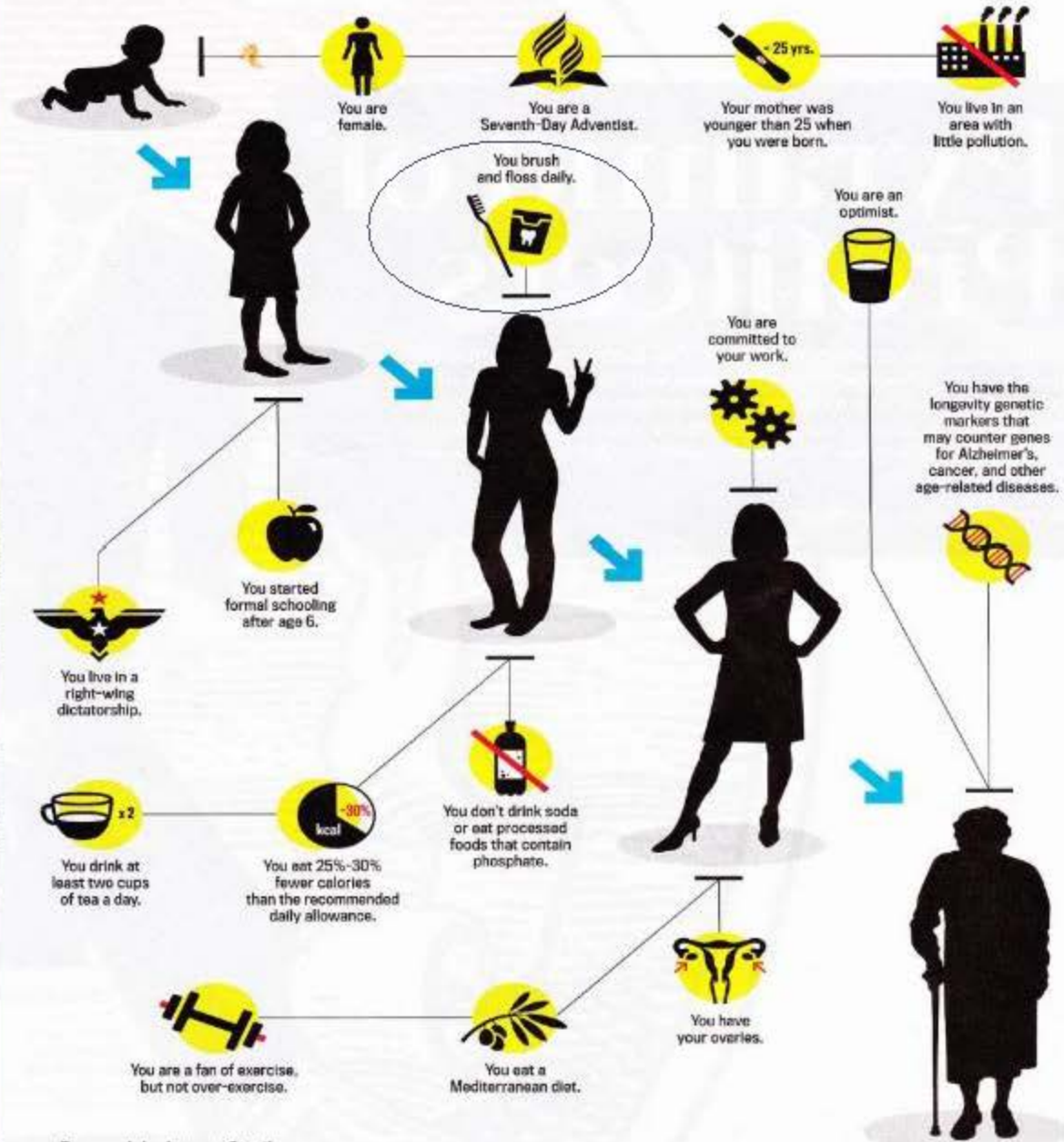
6. Increase risk for developing psoriasis
7. Increase seizure frequency in epilepsy
8. Increase risk of erectile dysfunction
9. Reduce quality of life (pain, disability)





How to Live Forever

Plucked from scientific research, here's what it takes to lengthen your days.



Research by Lauren Strelb

From Newsweek
18 Apr 2011

Summary





Summary

- Chronic inflammation can speed the aging process and significantly reduce healthspan
- Chronic inflammation is the link between many illnesses.
- Periodontal treatment reduces the cumulative systemic pathogen and inflammatory burden throughout the body.

The consequences of undertreating periodontitis could be more than the loss of a few teeth.