Understanding the Bi-directional Relationship Between Periodontal Disease and Diabetes

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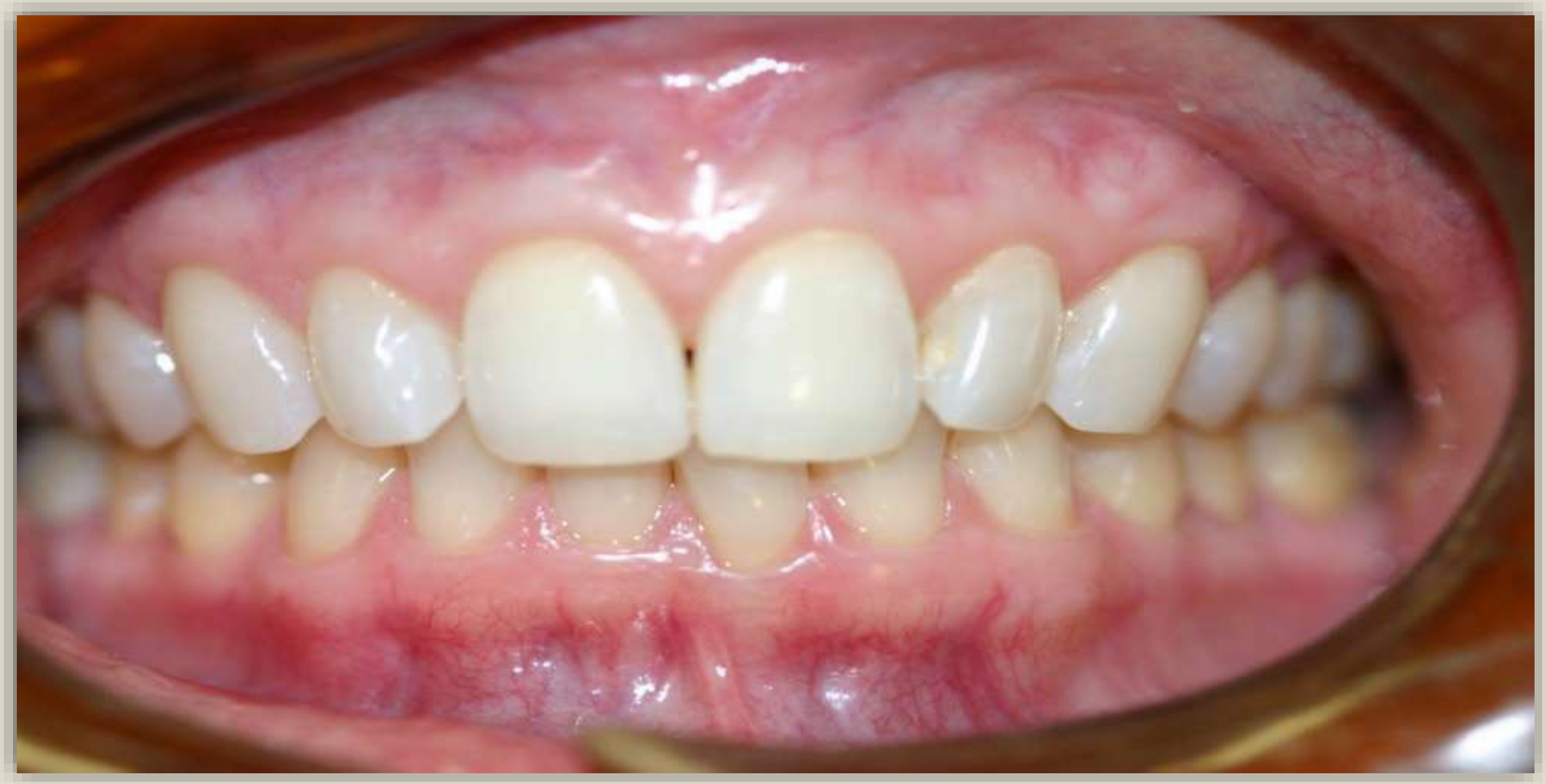
Objectives

- Describe periodontal (gum) disease
- Examine the bi-directional relationship between periodontal disease and diabetes
- Identify the pathways that relate periodontal disease to diabetes

Healthy gums

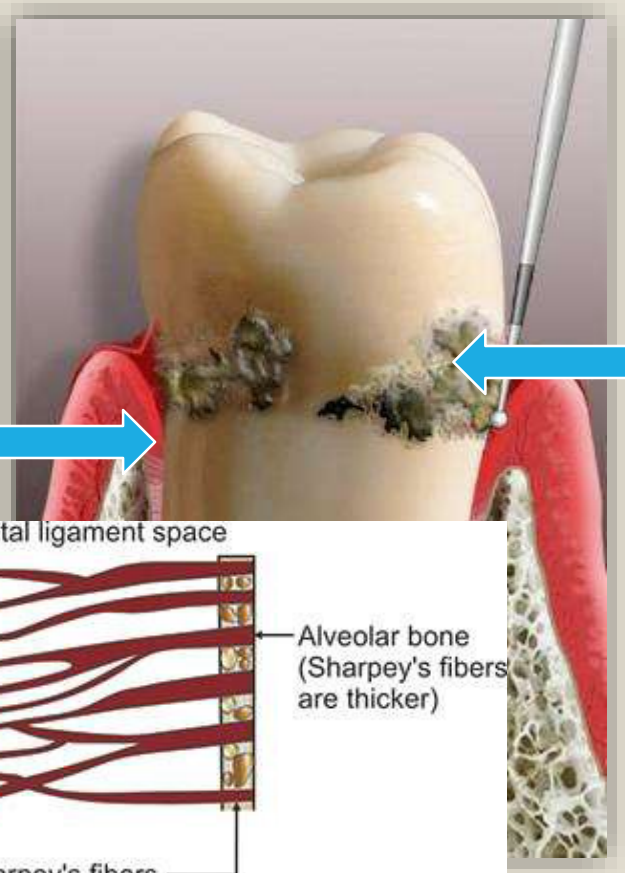


Periodontal Diseases

Gingivitis

Periodontitis

Periodontal Pocket Formation

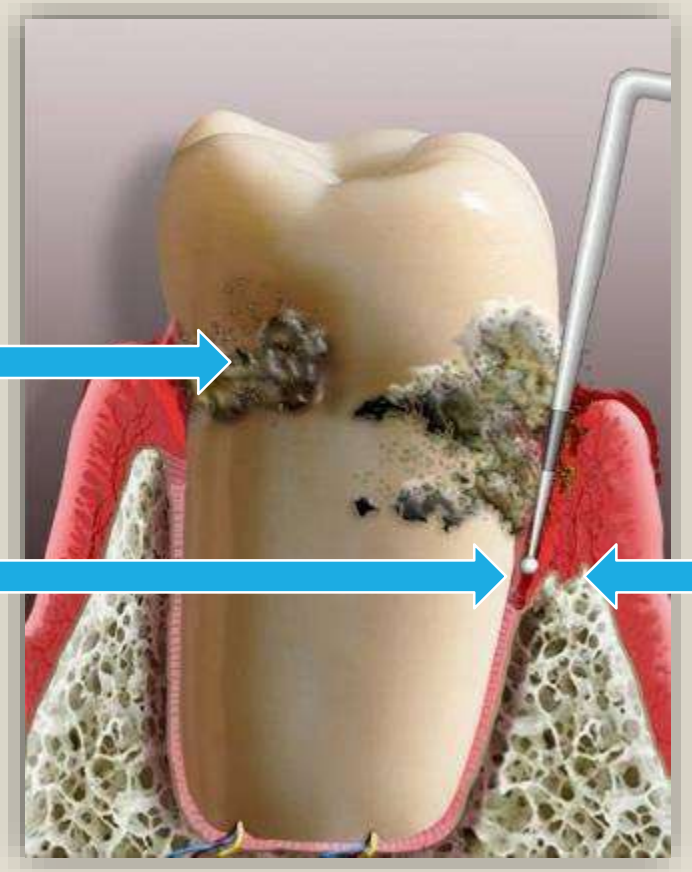


Connective Tissue Attachment

Gingivitis

Calculus

Ulcerated pocket mucosa



Bone Loss

Periodontitis

Illustrations by Dr. Tom Taylor

History of periodontitis, but healthy gums and stable bone levels

Prevalence of Periodontitis:

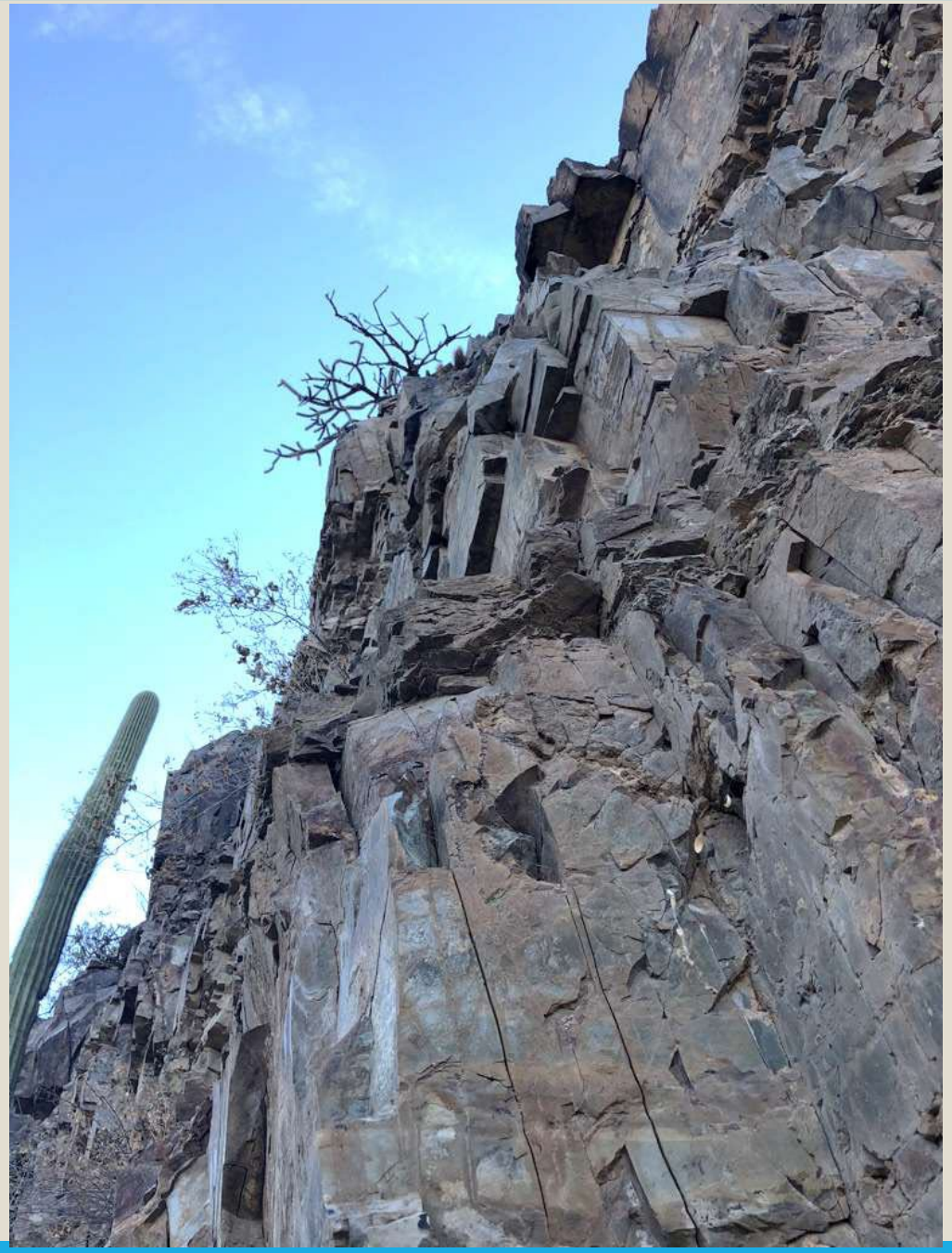
US adults over 30 with teeth:

- 8.7%- mild form
- 30.0%- moderate form
- 8.5%- severe form

Much higher prevalence than previously thought; almost 50% of adults have periodontitis. NHANES 2010, n=3742, Eke, JDR 2012

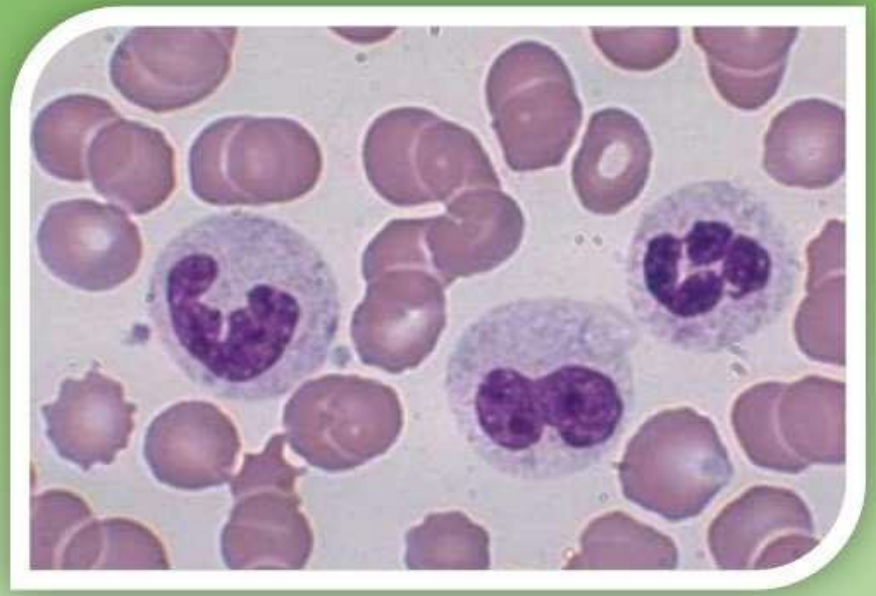
- 17% - severe form in- AI/AN age 35 and over

IHS 2015, Phipps and Ricks



Inflammation – Acute to Chronic

- Neutrophils = 1st line of defense



Initial Inflammatory Response

- Inflammation initially is protective
- Inflammatory chemicals released

Halt to Inflammation

- Neutrophils collaborate
- Change phenotype
- Secrete anti-inflammatory fatty acids

Chronic Inflammation

- In some who are susceptible, inflammation fails to resolve

Destruction

- Extracellular matrix and bone
- Scarring and Fibrosis
- ***Systemic Impact***

Periodontitis is a chronic inflammatory disease with a complex polymicrobial infection

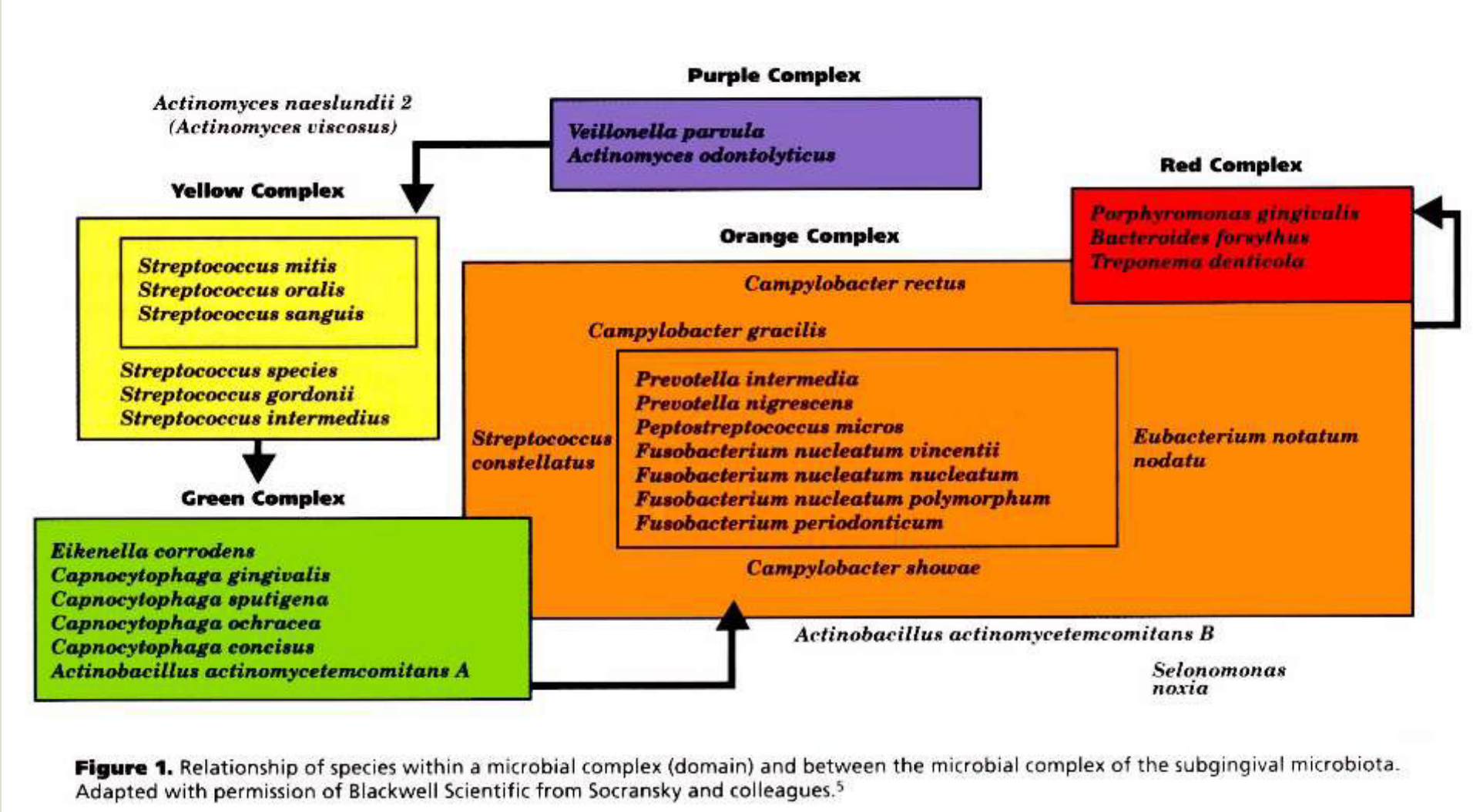


Figure 1. Relationship of species within a microbial complex (domain) and between the microbial complex of the subgingival microbiota. Adapted with permission of Blackwell Scientific from Socransky and colleagues.[5]

Viruses: EBV, HCMV, and HSV are immunosuppressive and support the overgrowth of the periopathogens.

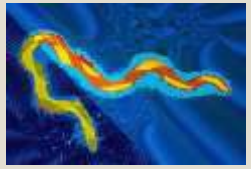
Virulence of Periodontal Pathogens:

- Not all oral bacteria are created equal.
- Some strains of oral bacteria can persist at extraoral sites:
  - Immune evasion
  - Selective virulence
  - Ability to disseminate

Offenbacher 2004

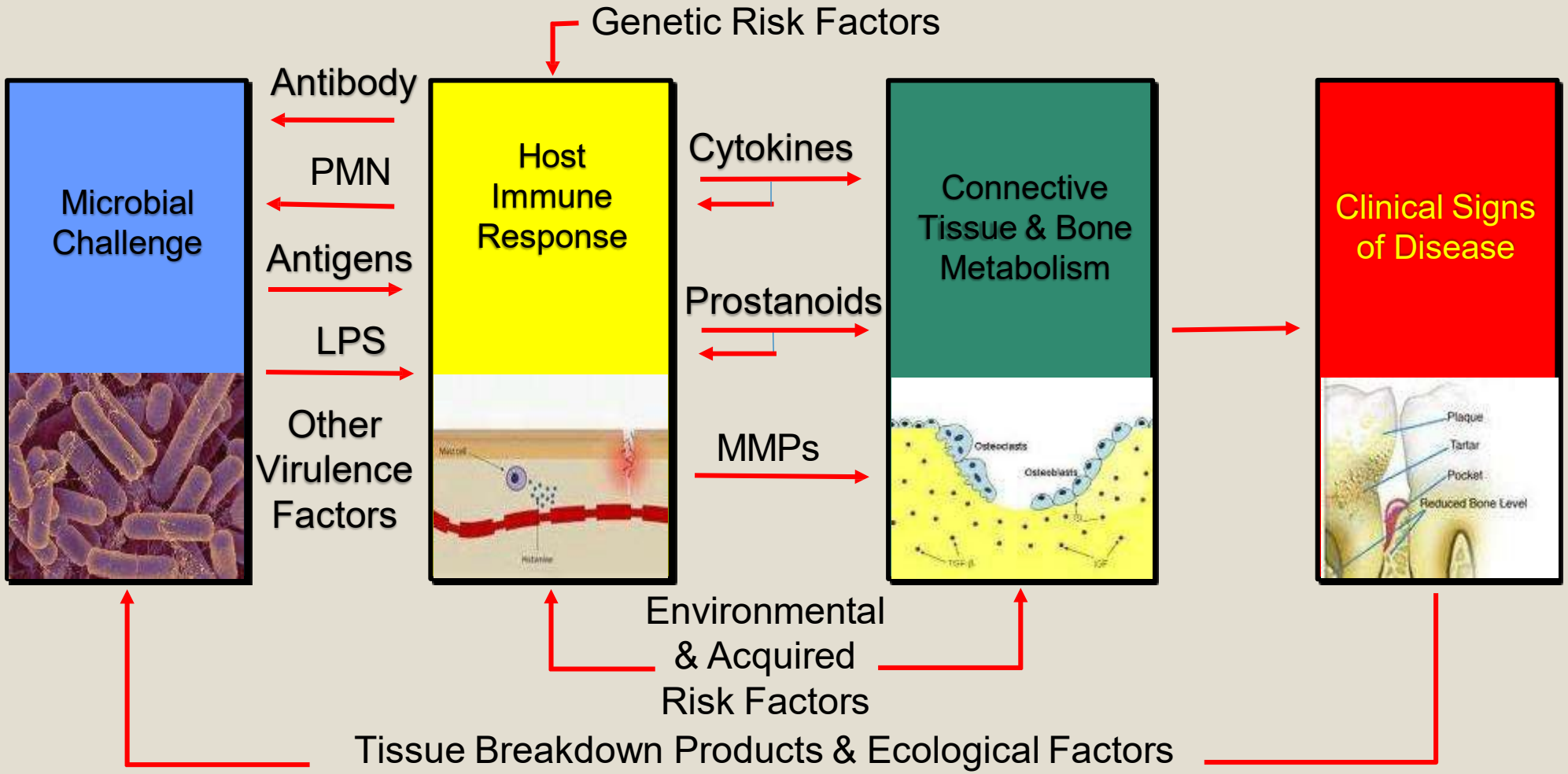
Porphyromonas gingivalis (Pg)
- Invades/survives in a variety of host cells, evades immune system
- Protease expression in atherosclerotic plaques, leading to plaque rupture
- Gingipains degrade host proteins

Fusobacterium nucleatum (Fn)
- Most prevalent oral species in extraoral infections
- Binds and invades cancerous cells and speeds tumor growth



Treponema denticola (Td) a.k.a. Spirochetes
- Attach to host cells and spread to distant sites through blood stream, lymphatics and along nerve fibers
- Alter gene expression leading to increased inflammation and atherosclerosis

Pathway to Periodontal Disease



Adapted from Kornman, 1997.

Periodontitis & Systemic Inflammation

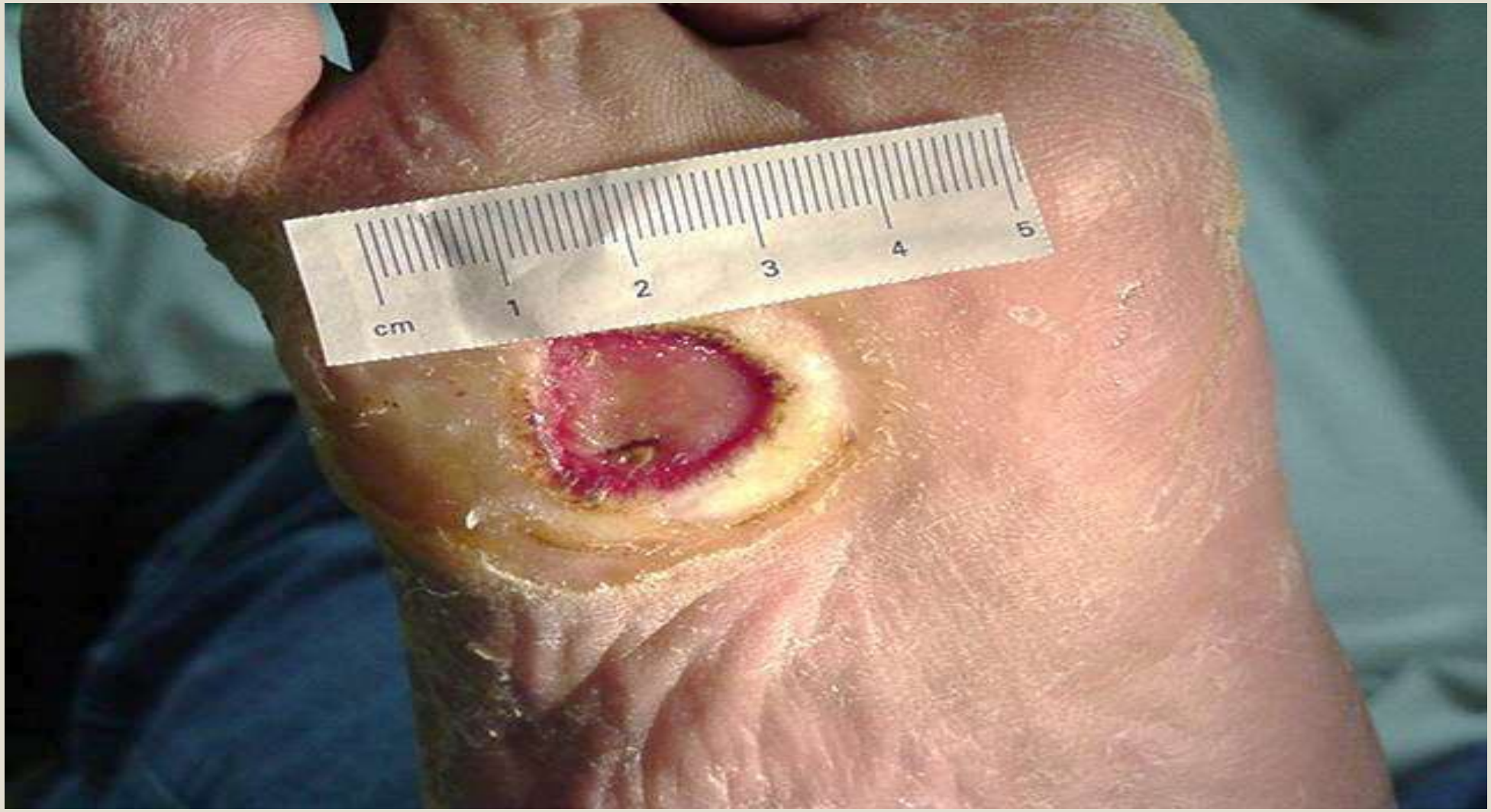
- Periodontitis is an anaerobic infection flooding the blood stream 24 hours a day with endotoxins and inflammatory mediators. Offenbacher, 1998
- Pro-inflammatory cytokines (IL-1, IL-6, TNF-α) and prostaglandins (PgE2) accumulate in the gum tissues in active periodontitis at extraordinary levels and can enter the circulation. Salvi 1997
- Periodontitis is asso. with increased systemic inflammation and oxidative stress. (hsCRP, IL-6, TNF- α, OHdG). Mattila 2002, Taylor 2006, Marcaccini 2009, Hendek 2015
- Perio treatment **decreases** systemic inflammation (CRP, IL-1B, IL-6, TNF- α, 8-OHdG, MIP 1B, Serum Amyloid A) Ide 2003, D'Aiuto 2004, Seinost 2005, Ortiz 2009, Hendek 2015, Giannopoulou 2016.

Moderate periodontitis with moderate to deep pockets and bone loss

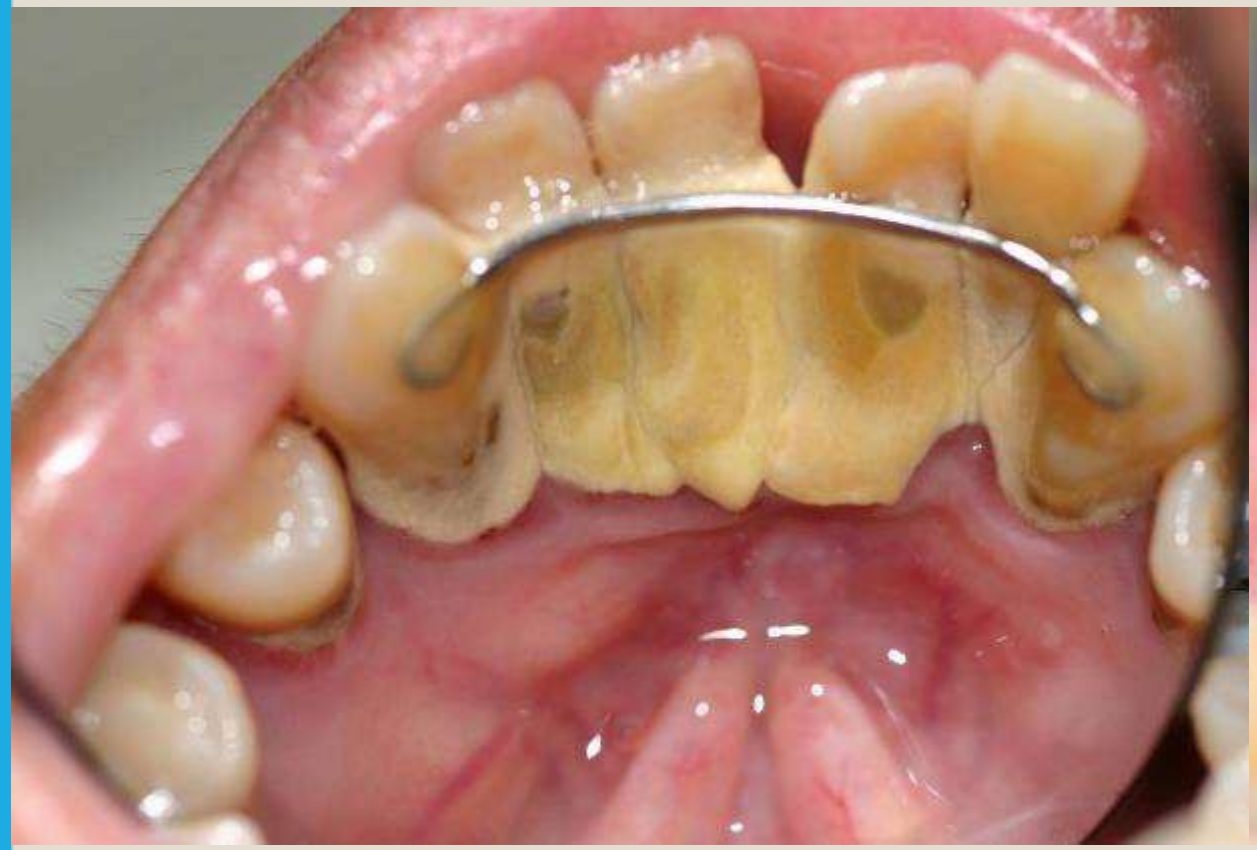
Estimated 8-20cm^2 ulcerated surface and area of tissue necrosis

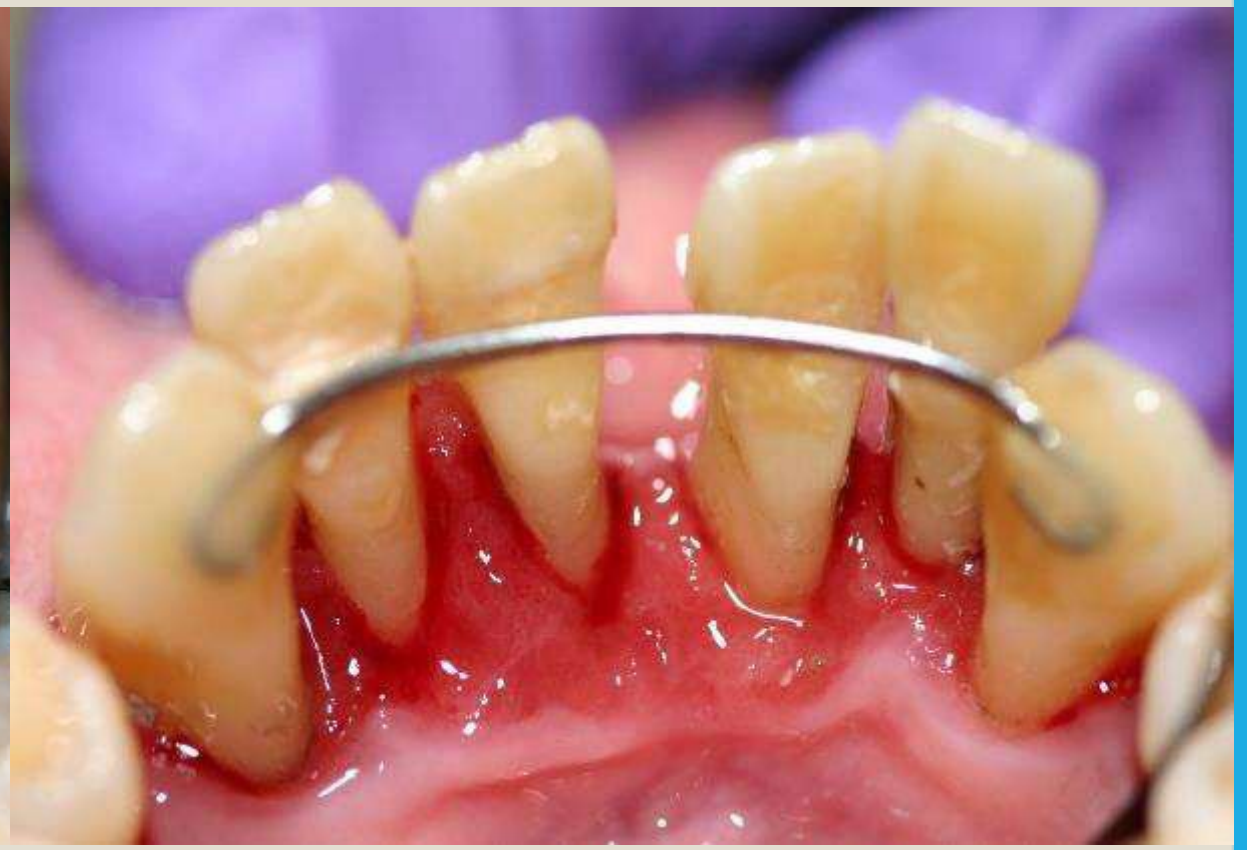
Hujoel 2001

Which is 3-5X larger than this 4cm^2 foot ulcer.



Heavy calculus after removal demonstrating inflammation and ulceration

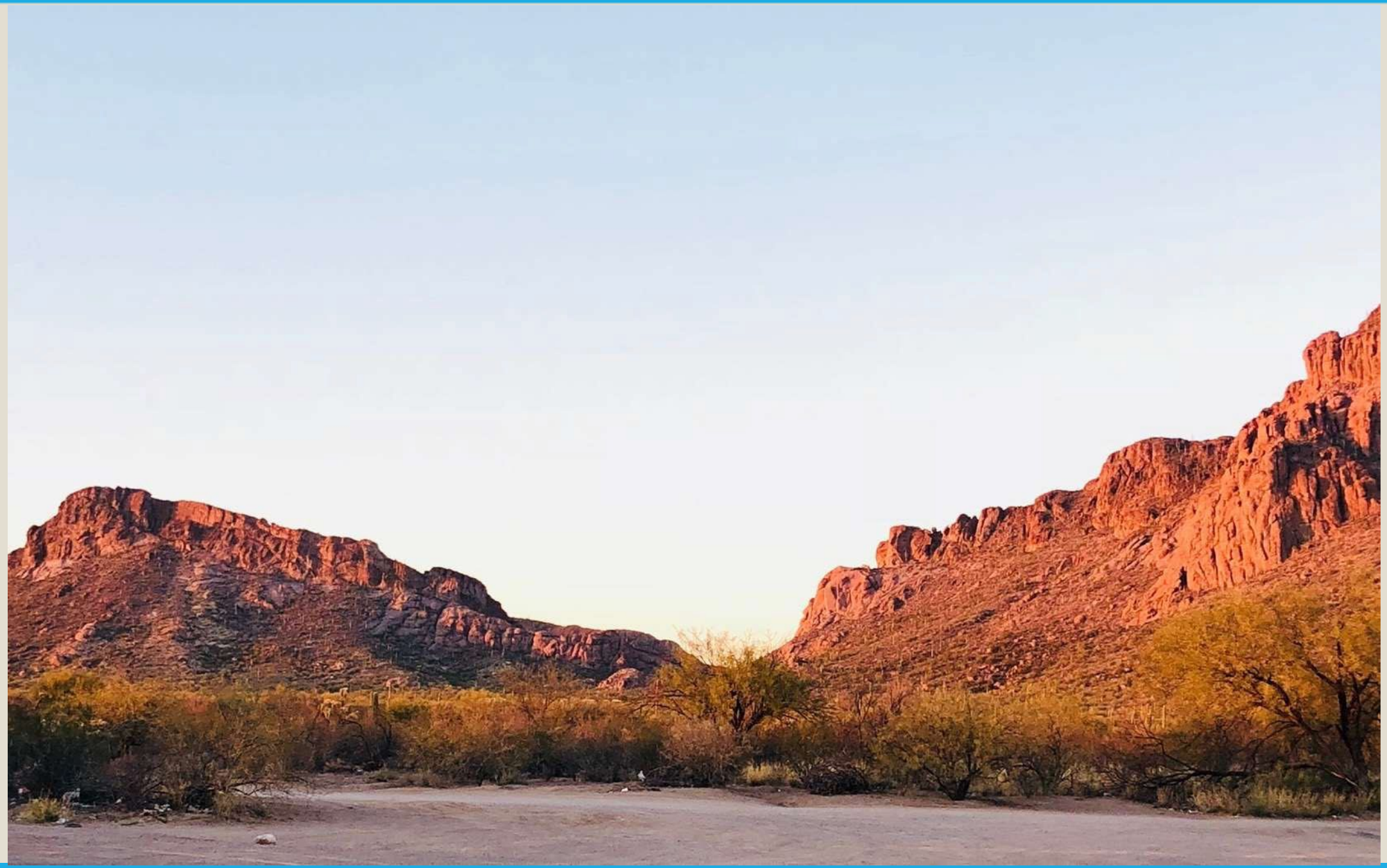




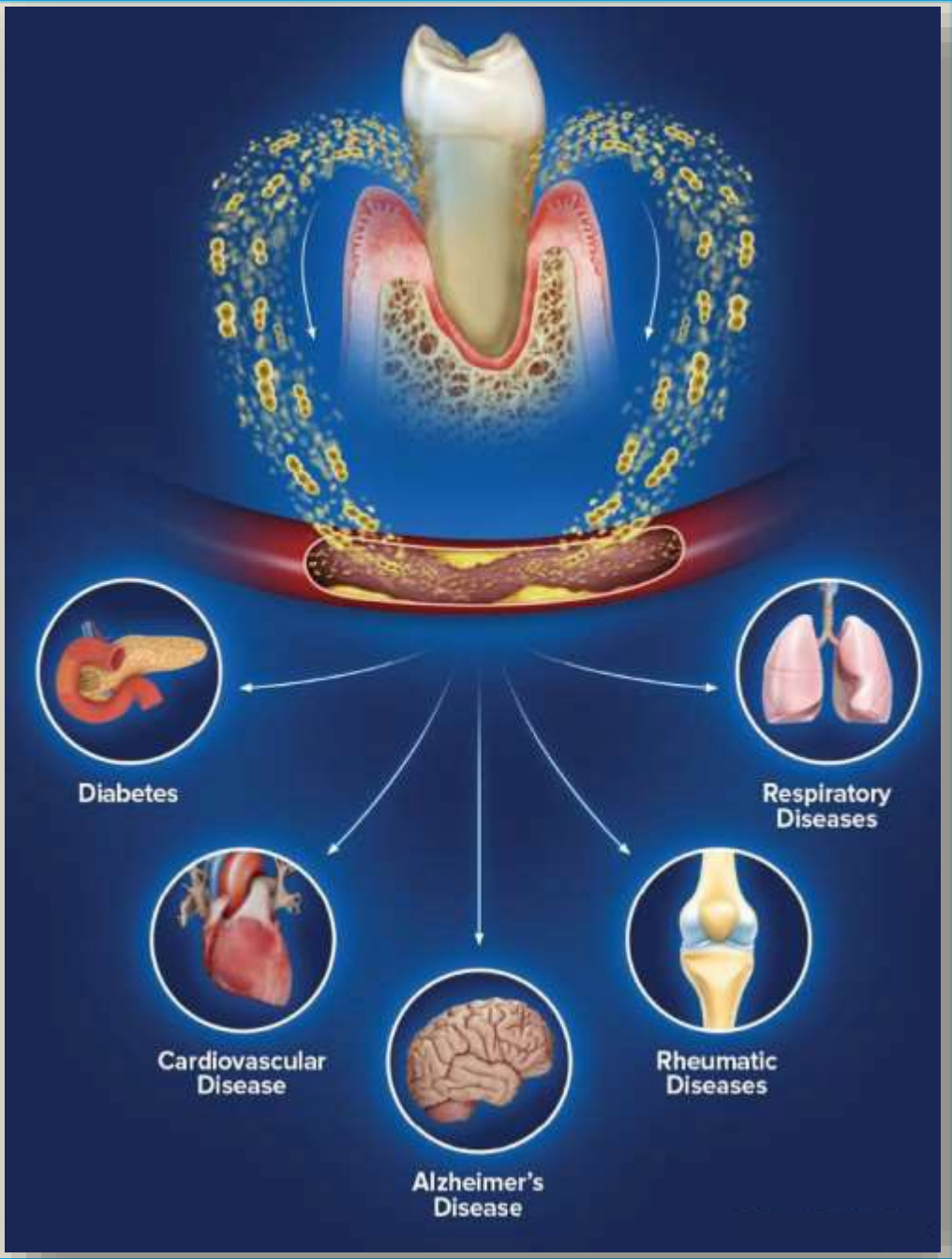
Summary – Periodontitis & Inflammation

- Periodontitis is an anaerobic infection flooding the blood stream 24 hours a day with endotoxins and inflammatory mediators.
- Associated with increased serum C-Reactive Protein (a measure of systemic inflammation).
- Periodontal treatment decreases CRP.
- Pro-inflammatory cytokines (IL-1, IL-6, TNF-a) and prostaglandins (PgE2) accumulate in gingival 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.

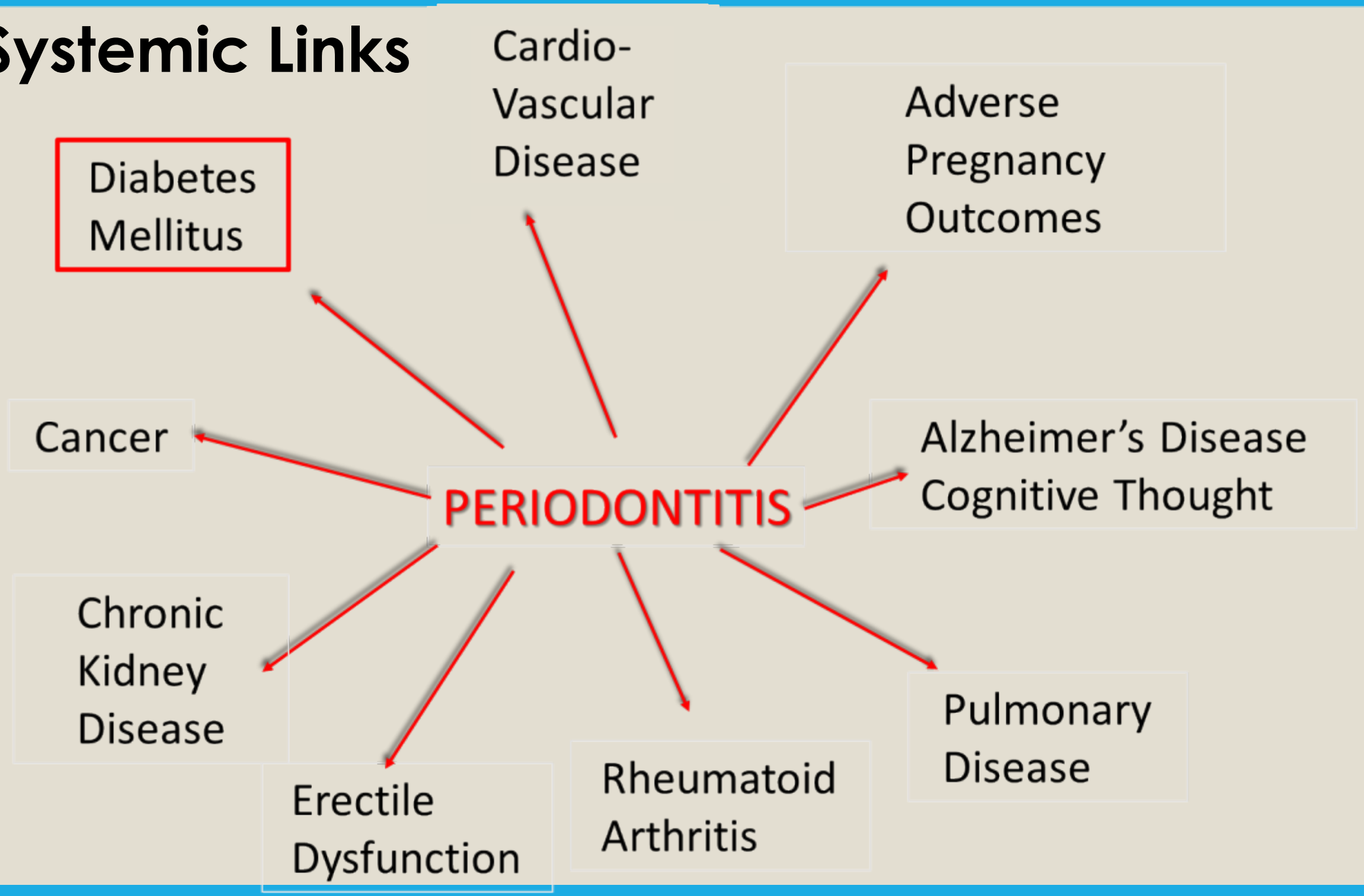
Workshop on Inflammation 2008



Oral infection can cause changes at distant body sites



Perio-Systemic Links



Diabetes and Periodontal Disease

Diabetes

Poor PMN Function
AGE binding/accumulation
Inflammatory State
Destructive Environment

↓ Periodontal Pathogens

Increased Periodontal Destruction

Chronic infection of periodontitis, with local and <u>systemic inflammation</u>

Further aggravated lipid metabolism & ↑ insulin resistance

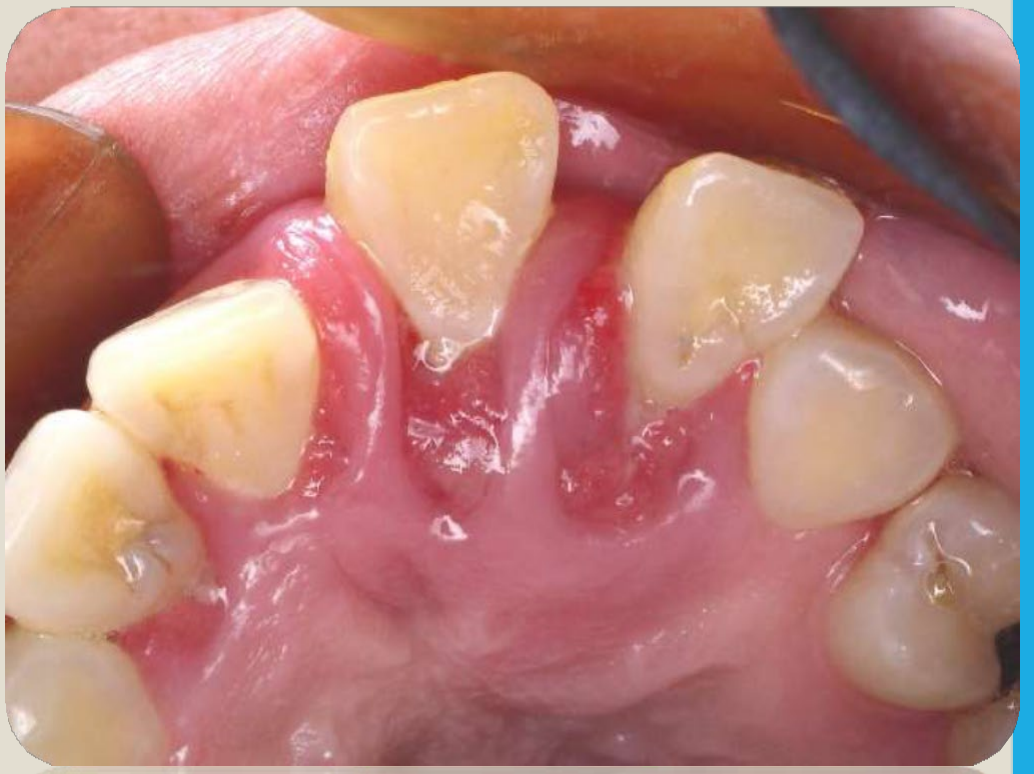
↑ serum lipids
↑ blood glucose

Periodontitis ⟷ Diabetes

Diabetes and Periodontal Disease

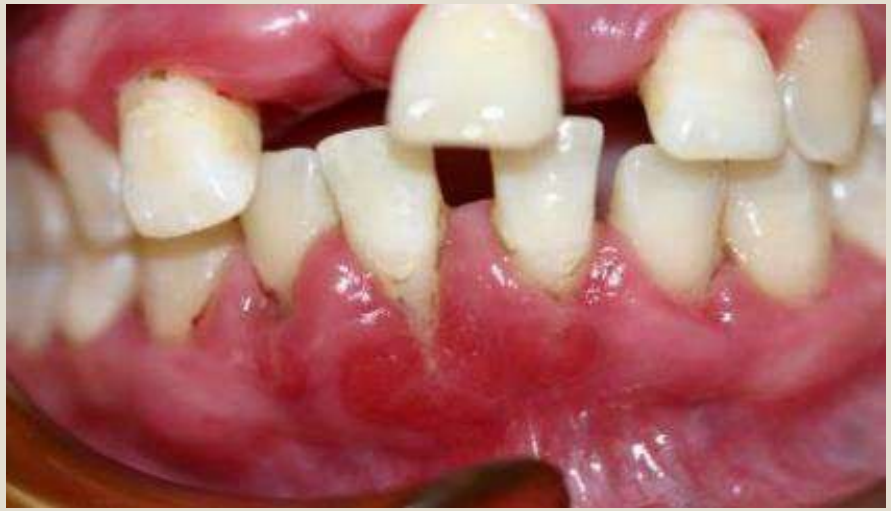
Oral Effects in Patients with Diabetes

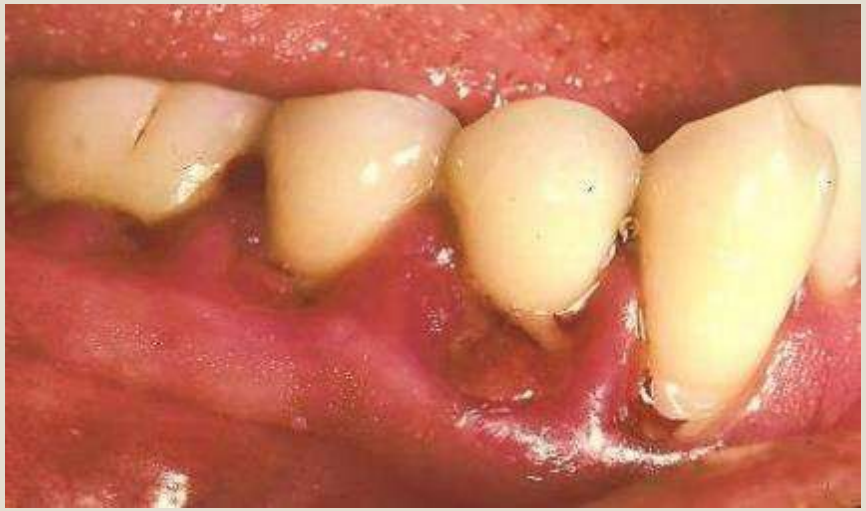
- Increased gingivitis and periodontitis
- Periodontal/odontogenic abscesses
- Impaired intraoral healing
- Dry mouth & Xerostomia
- Caries
- Cheilosis and candidiasis
- Burning mouth and tongue

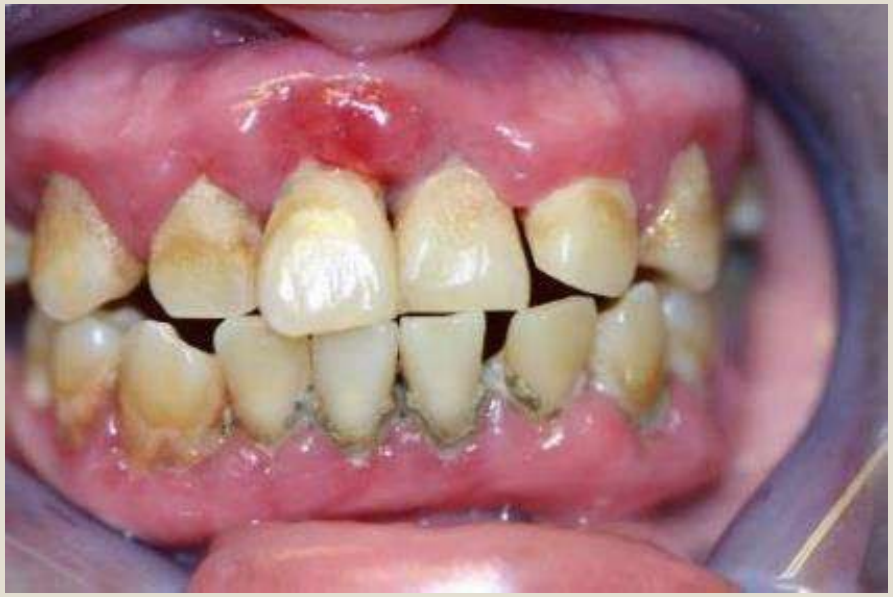


Borgnakke, Diabetes Res Clin Pract. 2019

Periodontal patients w/ undetected DM







Periodontal Destruction & DM

High Glucose Levels

Abnormal Lipids

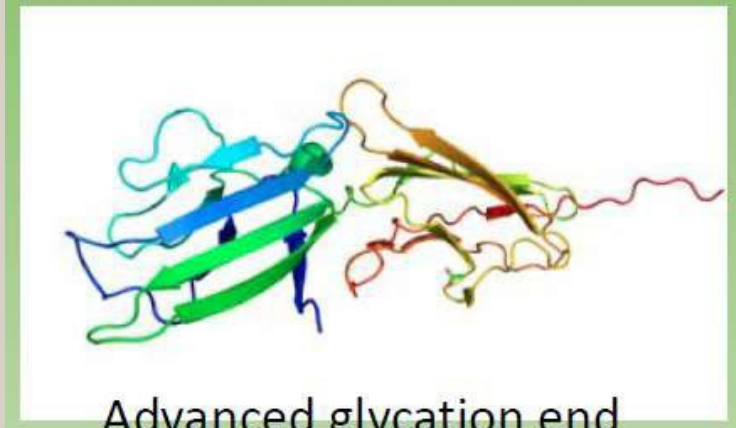
Affects the function of PMNs

Results in:
Chemotaxis
Phagocytosis

Glycation causes advanced glycation end products (AGE) to bind to receptors on many cells
(increased in gingiva)

Results in:
IL-1 & IL-6
TNF- α
Collagenase
Oxidative stress
Apoptosis

Increased susceptibility to periodontitis



Advanced glycation end products (AGE)

Diabetes Worsens Periodontal Disease

- Reviews of dozens of studies involving subjects with diabetes found strong evidence of increased:
  - Prevalence and incidence of periodontitis
  - Severity of periodontitis
  - Extent of periodontitis
  - Progression of periodontitis

- Periodontitis may be the 1st clinical manifestation of DM
- Periodontitis is more prevalent and severe in those with poorer glycemic control.

  Taylor, Oral Dis 2008; Garcia, JOP 2015

- Diabetic retinopathy, nephropathy, neuropathy are risk factors for severity of periodontitis

  Nitta, JDI 2017

- Poorly controlled DM significantly increases risk of severe perio
- "Better" controlled DM slightly increased risk, but NOT statistically significant

  Tsai, Community Dent Oral Epidemiol 2002

- Those with good glycemic control are not at greater risk.

  Nitta, JDI 2017

Perio Increases DM Complications & Mortality

Periodontitis is a risk for poor glycemic control

- Pima Indians – from NIDDK study
- Subjects w/ severe perio more likely to have poor glycemic control (HbA1c > 9.0%)

Taylor, JOP 1996

Periodontal disease is a strong predictor of mortality from ischemic heart disease and diabetic nephropathy in Pima Indians with type 2 DM.

- Study on the effect of periodontitis on cardiovascular and renal mortality.
- Severe perio at baseline associated w/ 8.5 X higher risk of renal mortality
  2.3 X higher risk of cardiac mortality.

Saremi et al, Diabetes Care 2005

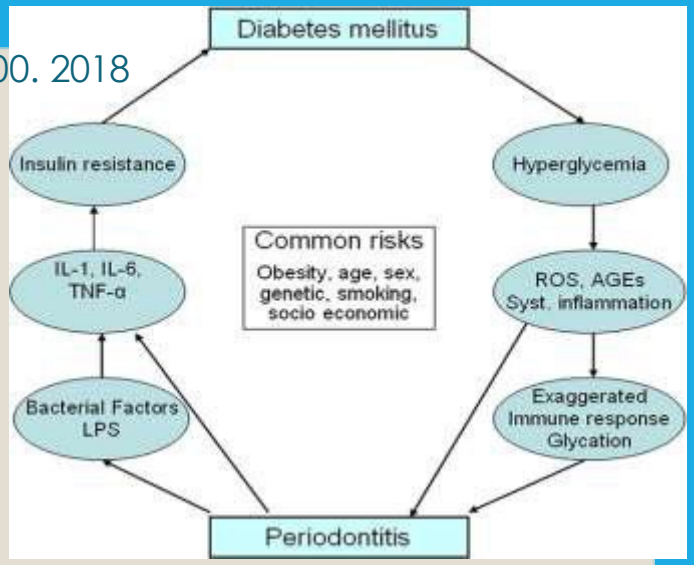
Effect of periodontitis on overt nephropathy and ESRD in type 2 diabetics:

- Incidence of kidney and ESRD increased with severity of periodontitis.
- After adjusting for confounding factors, compared to those periodontally healthy:
  - Moderate perio: 2.3 X higher risk of ESRD
  - Severe perio: 3.5 X higher risk of ESRD
- Periodontitis predicts development of overt nephropathy and ESRD in a dose dependent manner in individuals with type 2 DM.

Shultis et al, Diabetes Care 2007 n=529

Biologic Mechanisms

Kocher, Periodontology 2000. 2018



- Hyperglycemia can result in the activation of pathways that increase inflammation, oxidative stress and apoptosis Brownlee, 2005 Diabetes

- Serum levels of IL-6, CRP elevated in periodontitis
- IL-6 levels correlate with the severity/extent of periodontitis Loos, JOP 2005; Paraskevas, JCP 2008

- Serum levels of IL-6, CRP predict future occurrence of type 2 diabetes
- CRP is associated with insulin resistance Schmidt et al. Lancet 1999

- Defective PMN activity in diabetic pts: impaired chemotaxis, phagocytosis and microbicidal functions Alba-Loureiro, Braz J Med Biol Res 2007

- Diabetic subjects w/ periodontitis have higher levels of P. *gingivalis*, P. *intermedia*

Thorstensson, JCP 1995; Takahashi, J Int Acad Perio 2001

Periodontal therapy and diabetic control
Recent reviews and meta analyses :

- Teeuw et al Diabetes Care 2010

Perio tx leads to an improvement of glycemic control in Type 2 DM for at least 3 months.

- Simpson. Cochran Library 2015

0.3% improvement in HbA1c with perio tx for up to 4 months. No difference between non-surgical, surgical perio tx.

- Darre et al Diabetes Metab 2008

SRP provided a small but significant improvement in glycemic control (mean 0.46% decrease).

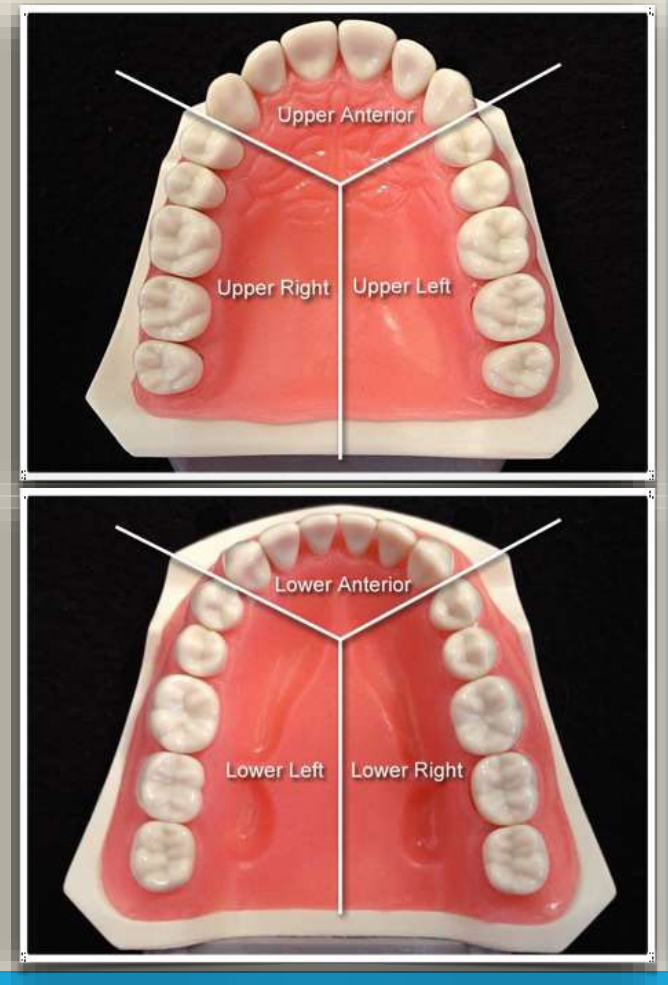
- Engebretson JCP/JOP 2013

0.36% decrease in HbA1c from periodontal tx vs. no treatment. Study published in JAMA 2013 showed no change in HbA1c.

Periodontal Disease Treatment Protocol

The Community Periodontal Index

- What is meant by an INDEX? → Screening only
- Does not replace the need for a comprehensive periodontal examination when indicated
- A periodontal examination should be completed on any patient where periodontal therapy such as scaling and root planning (SRP) is planned



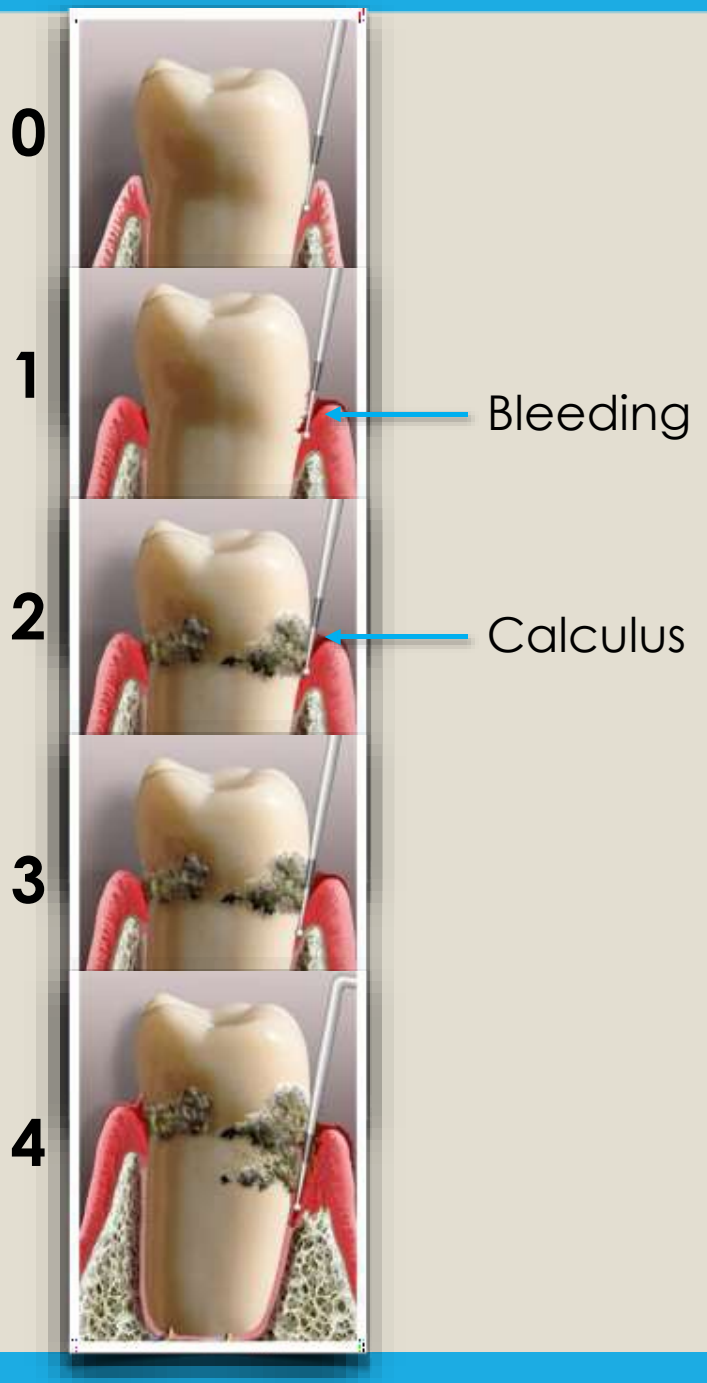
CODE 0 = SHALLOW POCKET DEPTH
HEALTHY GUMS

CODE 1 = SHALLOW POCKET DEPTH
BLEEDING ON PROBING

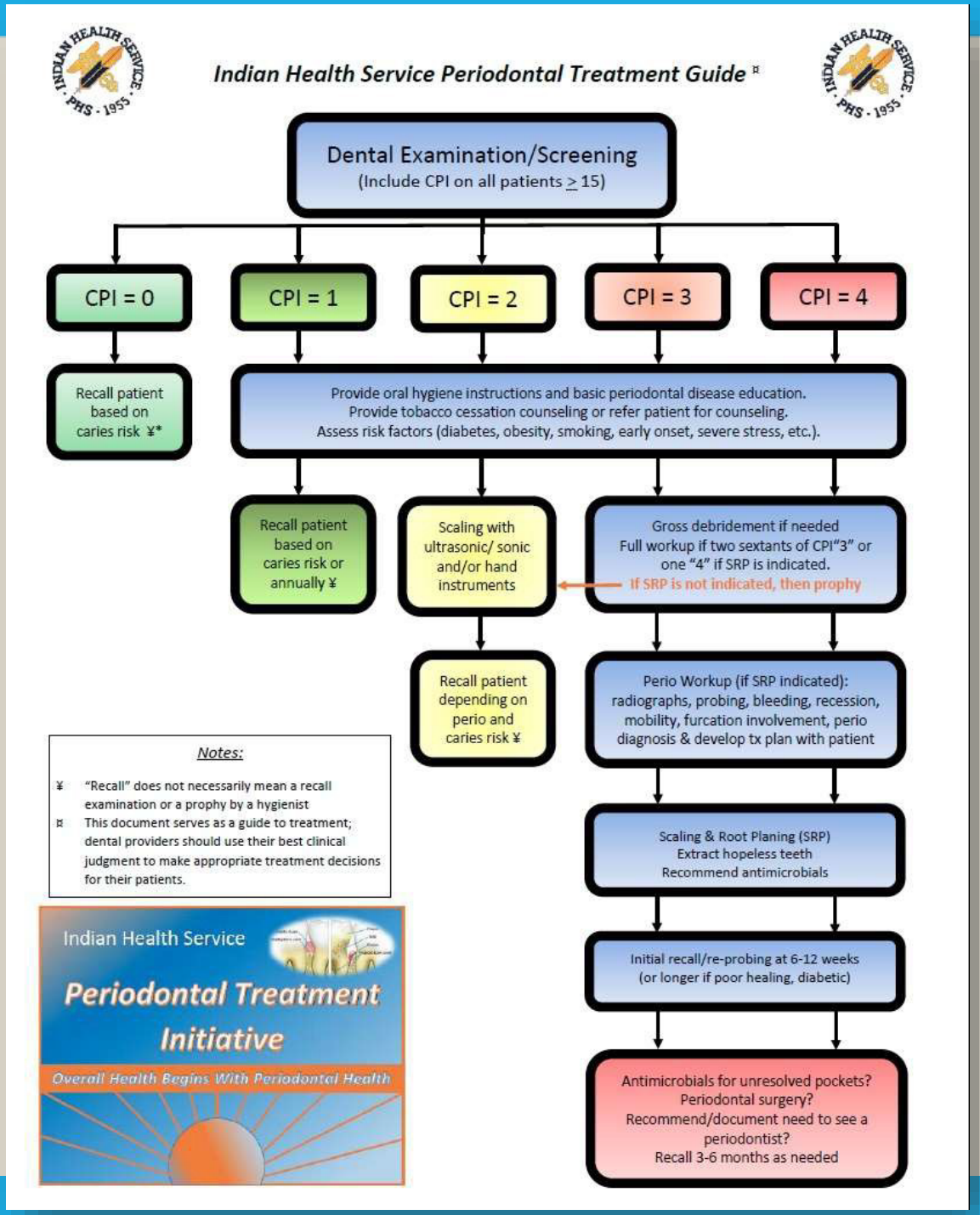
CODE 2 = SHALLOW POCKET DEPTH
SUPRA OR SUBGINGIVAL CALCULUS
AND/OR DEFECTIVE MARGINS

CODE 3 = MODERATELY DEEP POCKET DEPTH
CALCULUS AND BLEEDING MAY OR MAY NOT BE PRESENT
PD ≥ 3.5 mm, but < 5.5 mm

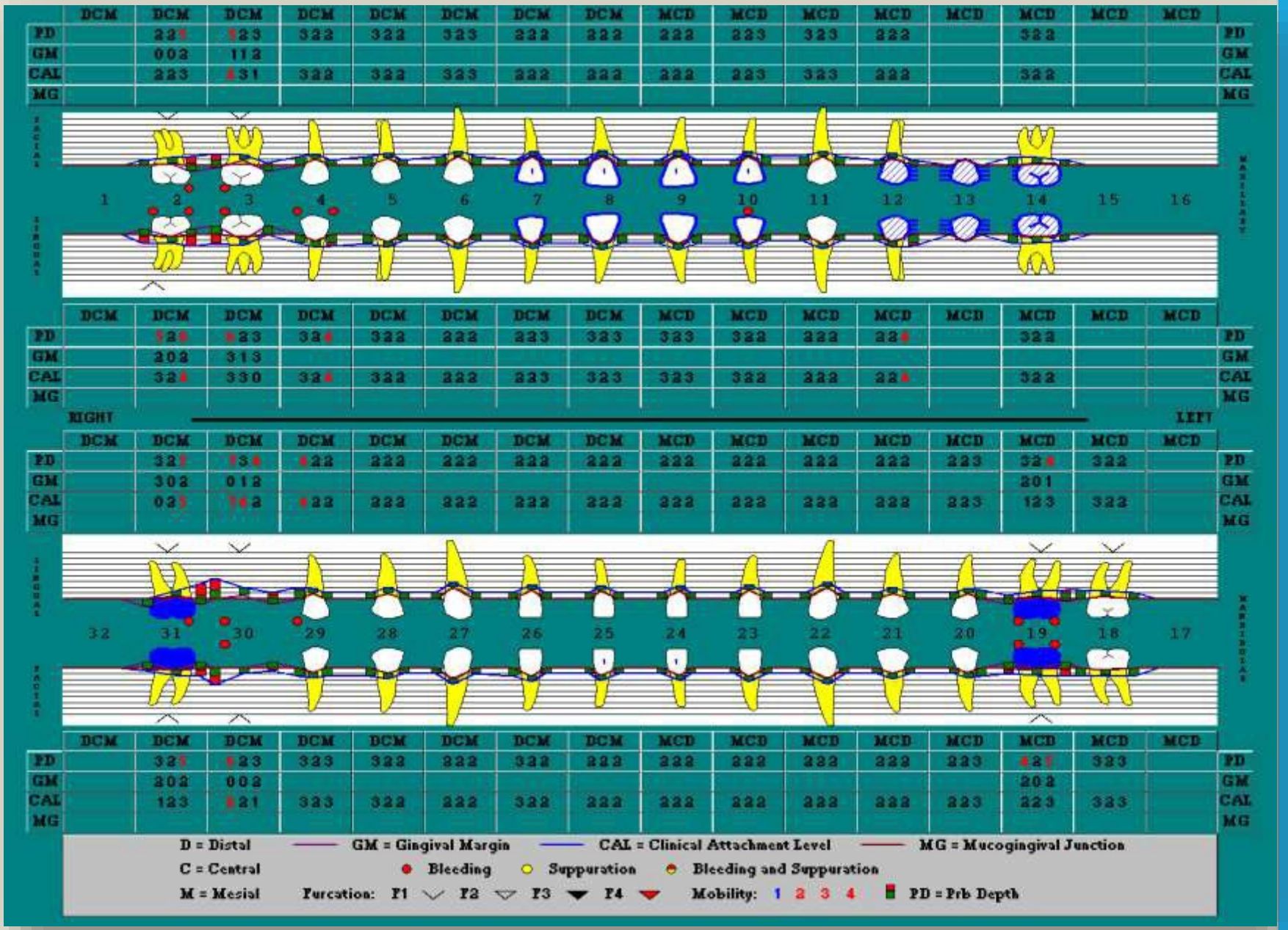
CODE 4 = DEEP POCKET DEPTH
CALCULUS AND BLEEDING MAY OR MAY NOT BE PRESENT
PD ≥ 5.5 mm



Periodontal Treatment Guide



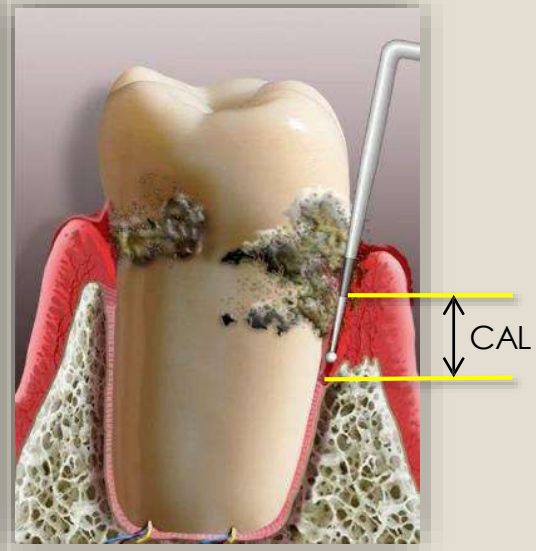
Comprehensive Periodontal Exam



2017 World Workshop On The Classification Of Periodontal And Peri-implant Diseases And Conditions

Periodontitis stage		Stage I	Stage II	Stage III	Stage IV
Severity	Interdental CAL at site of greatest loss	1 to 2 mm	3 to 4 mm	≥5 mm	≥5 mm
	Radiographic bone loss (site of greatest loss)	Coronal third (<15%)	Coronal third (15% to 33%)	Extending to mid-third of root and beyond	Extending to mid-third of root and beyond
	Tooth loss (due to periodontitis)	No tooth loss due to periodontitis		Tooth loss due to periodontitis of ≤4 teeth	Tooth loss due to periodontitis of ≥5 teeth
Complexity	Local	Maximum probing depth ≤4 mm Mostly horizontal bone loss	Maximum probing depth ≤5 mm Mostly horizontal bone loss	In addition to stage II complexity: Probing depth ≥6 mm Vertical bone loss ≥3 mm Furcation involvement Class II or III Moderate ridge defect	In addition to stage III complexity: Need for complex rehabilitation due to: Masticatory dysfunction Secondary occlusal trauma (tooth mobility degree ≥2) Severe ridge defect Bite collapse, drifting, flaring Less than 20 remaining teeth (10 opposing pairs)
				Still able to save most of the teeth	Entire dentition in jeopardy
Extent and distribution	Add to stage as descriptor	For each stage, describe extent as localized (<30% of teeth involved), generalized, or molar/incisor pattern			

CAL – Clinical attachment loss (loss of connective tissue attachment)



J Periodontol. 2018;89(Suppl 1):S159–S172

2017 World Workshop On The Classification Of Periodontal And Peri-implant Diseases And Conditions

Periodontitis grade			Grade A: Slow rate of progression	Grade B: Moderate rate of progression	Grade C: Rapid rate of progression
Primary criteria	Direct evidence of progression	Longitudinal data (radiographic bone loss or CAL)	Evidence of no loss over 5 years	<2 mm over 5 years	≥2 mm over 5 years
	Indirect evidence of progression	% bone loss/age	<0.25	0.25 to 1.0	>1.0
		Case phenotype	Heavy biofilm deposits with low levels of destruction	Destruction commensurate with biofilm deposits	Destruction exceeds expectation given biofilm deposits; specific clinical patterns suggestive of periods of rapid progression and/or early onset disease (e.g., molar/incisor pattern; lack of expected response to standard bacterial control therapies)
Grade modifiers	Risk factors	Smoking	Non-smoker	Smoker <10 cigarettes/day	Smoker ≥10 cigarettes/day
		Diabetes	Normoglycemic/ no diagnosis of diabetes	HbA1c <7.0% in patients with diabetes	HbA1c ≥7.0% in patients with diabetes

Likely to respond better to treatment

Likely to respond worse to treatment

J Periodontol. 2018;89(Suppl 1):S159–S172

5 Steps in Periodontal Disease Management

1. Assess periodontal risk and risk factors that may affect the outcome of periodontal therapy.
2. Eliminate/Mitigate risk factors.
3. Eliminate the periodontal infection.
4. Modulate the host response and inflammation.
5. Select an appropriate recall interval.

1. Assessing Risk

Medical History

- Diabetes – does the patient have DM? How well controlled is it? What medications is the patient taking?
- Tobacco use – is the patient a current or former smoker? Smokeless tobacco?
- Immunosuppression – does the patient have HIV, an organ transplant, or other conditions that suppress their immune system?
- Systemic Inflammation – Obesity, chronic kidney disease, rheumatoid arthritis

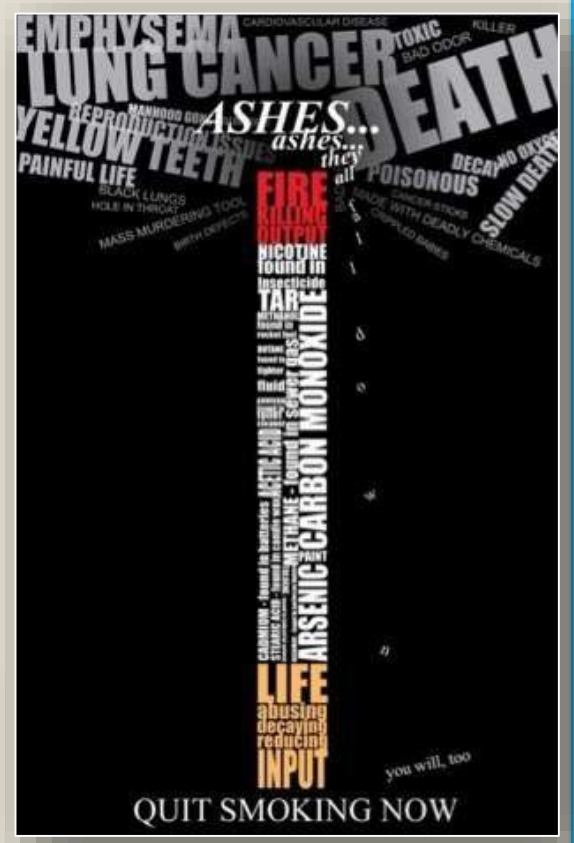
1. Assessing Risk

Medications

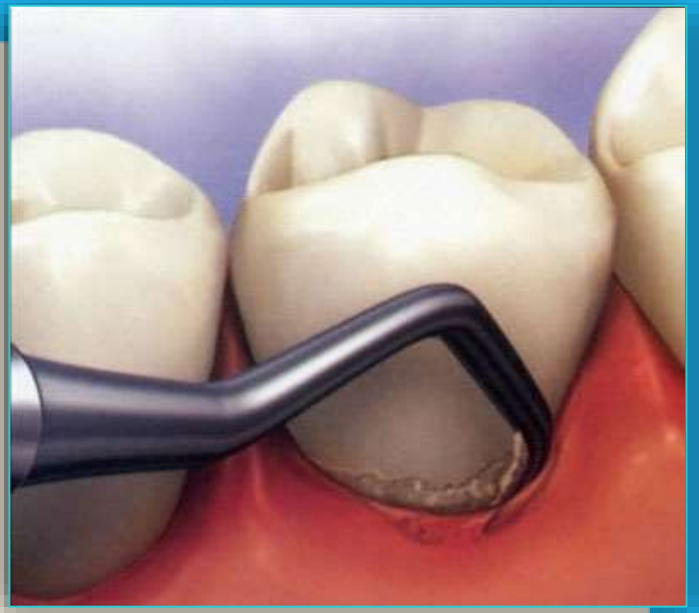
- Dry mouth – does the patient take medications that may cause dry mouth (blood pressure medications, antihistamines, antidepressants, diuretics, etc.)?
- Anticoagulants/Antithrombotics – is the patient on an anti-coagulant or antithrombotic (warfarin, DOACs, Plavix®, etc.)?
- Gingival hyperplasia – is the patient taking medications that may cause hyperplasia (anticonvulsants, calcium channel blockers, cyclosporine, etc.)?

2. Eliminate/Mitigate risks

- Smoking/tobacco cessation counseling
- Promote/educate about blood sugar control
- Provide oral hygiene instructions
- Introduce oral hygiene aids



3. Eliminate the Infection



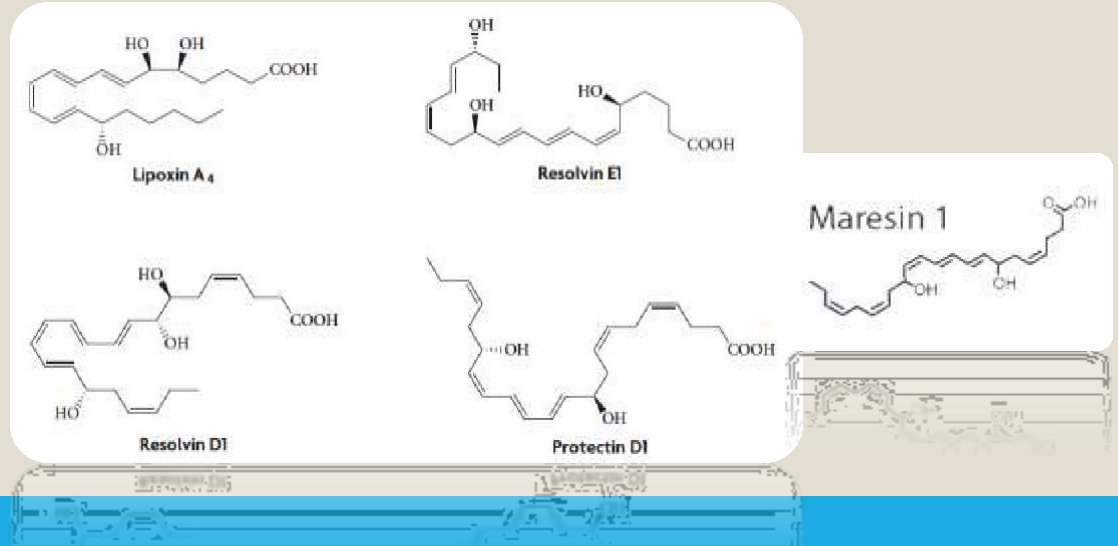
- Non-surgically – ultrasonics and hand instruments
  - Re-evaluation at 6-8 weeks
- Surgically – following non-surgical tx & re-evaluation
- Topical antimicrobials (toothpastes, mouthrinses)
- Local antimicrobials such as gels, chips, etc.
  - Placed in pockets
- Systemic antimicrobials such as antibiotics

IHS Treatment Protocol – diabetic pts with mod-severe periodontitis

- Intensive OHI and motivation
- 1/2 mouth ultrasonic SRP with LA
  - Aggressive periodontal pocket debridement in deep pockets.
- Extract hopeless teeth
- Antibiotic
  - Doxy 100mg bid X 14 or 21 days
- Antimicrobial mouthrinse
- Recall 3-6 months

4. Modulate host response/inflammation

- Enzyme suppressors (Low dose doxycycline)
  - 20mg doxycycline, sub-antimicrobial dose
- Antioxidants/Vitamins (leaf and berry products, Vitamin D)
- Specialized Pro-resolving Mediators (SPMs): Lipoxins, Resolvins, Protectins, Maresins



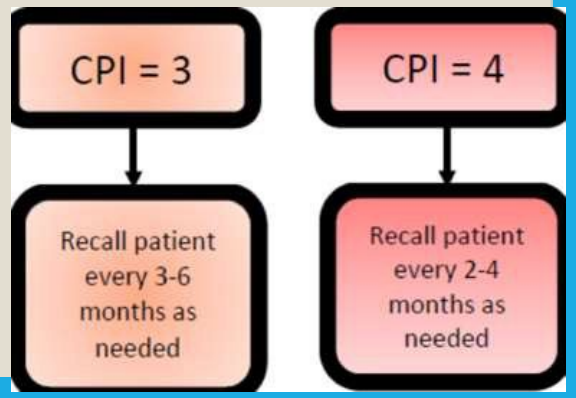
Adapted from Van Dyke, J Periodontol. 2020

5. Select an appropriate recall interval

- Re-evaluation should occur 6-12 weeks after initial treatment (diabetics and poor healers, wait up to 16 weeks)
- Depends on response to initial therapy
- Recalls decrease tooth loss
- Patients who didn't comply with recalls were 5X more likely to have tooth loss

  Checci 2002
- Recall intervals can be extended beyond 6 months for low risk patients

  Mettes 2005, Giannobile 2013



Interprofessional Collaboration

- Screening for diabetes in the dental office
- Including oral health in diabetes management
- Routine referral to dental
- Educate on the relationship between diabetes & gum disease
  - Remind that daily oral hygiene is part of diabetes self management.

Periodontal treatment and maintenance reduces medical visits and costs:

- For diabetes patients:
  - 33% reduction in hospitalizations
  - 13% reduction in physician visits
  - $1814 annual reduction in overall medical costs
-

Reported 11/2012 on 1.7 million United Concordia dental and Highmark medical coverage individuals.

In Summary

- Chronic inflammation is the link between many illnesses, and periodontal pathogens can be causative in the initiation and progression of them.
- Oral health is important to general health (Surgeon General's Report). It is also one of the more easily modifiable risk factors for many diseases of chronic inflammation.
- Periodontal treatment reduces the cumulative systemic pathogen and inflammatory burden throughout the body.

Thank you!

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