Early 1900’s: Connections between infected teeth and gums and multiple systemic diseases were wrong

Robert Koch, late 1800’s

WD Miller, late 1800’s

Koch’s Postulates
Evidence required to establish etiologic relationship between microorganisms and disease:
1. Microbe must be observed in every case of the disease
2. It must be isolated and grown in pure culture
3. The pure culture, when inoculated in animals, must reproduce the disease
4. The microorganism must be recovered from the diseased animal

WD Miller, 1891; The Human Mouth as a Focus of Infection. 
*Dental Cosmos* 33:689-706

WD Hunter, 1900; Oral sepsis as a cause of disease.
*British Medical Journal* 2:215-216

WD Hunter 1911; The role of sepsis and antisepsis in medicine and the importance of oral sepsis as its chief cause. *Lancet* 1:79-86; and *Dental Register* 44:579-611.
Periodontitis:
Bacterially-induced chronic inflammatory disease, that destroys connective tissue and bone that support the teeth

Approx 30% of adults have periodontitis
• 8-13% have severe generalized disease

Bacterial accumulations on the teeth initiate periodontal inflammation

Disease modifiers—e.g., diet, smoking, diabetes, genetics
Patients with periodontitis are on different paths

- 480 male Sri Lankan tea plantation workers
- 15 yr longitudinal monitoring q 3yrs
- No treatment

Loe et al. 1986

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>Number of Missing Teeth</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>35</td>
<td>20</td>
</tr>
<tr>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>45</td>
<td>30</td>
</tr>
</tbody>
</table>

8% 81%

Periodontitis progression and severity is primarily a function of host modifying factors

- Genetic risk factors
- Microbial Challenge
- Host immuno-inflammatory response
- Connective tissue and bone metabolism
- Environmental and acquired risk factors — i.e. smoking, diabetes, diet

Page and Kornman 1997
## Periodontitis, Inflammation, and the health of your patients

- The chronic diseases of aging are connected through common inflammatory mechanisms

- Inflammation levels differ among individuals and are mostly controllable

- Treatment of periodontitis reduces systemic inflammation—-and may improve diseases influenced by inflammation.

## Inflammation, your health, and the health of your patients

- The chronic diseases of aging are connected through common inflammatory mechanisms
Moderate to Severe periodontitis is associated with Rheumatoid arthritis

![Graph showing moderate to severe periodontitis](image)

% with mod-severe periodontitis

N= 69 RA; 35 OA

Rheumatoid arthritis: 51%

Osteoarthritis: 26%

$p=0.03$

Patients with recent acute myocardial infarction had worse dental problems than control subjects with no MI history

Mattila et al 1989

- 100 patients with acute MI
- 104 community controls; no history of MI
- Significant association between MI and severity of dental disease history

DeStefano et al. 1993

Offenbacher et al. 1996
Key Findings from Selected Observational Studies on Relationship of Periodontitis and Cardiovascular Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Country</th>
<th>Age</th>
<th>Outcome</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmlund et al. 2006</td>
<td>4,254</td>
<td>Sweden</td>
<td>20-70</td>
<td>CHD</td>
<td>2.69</td>
<td>1.12, 6.46</td>
</tr>
<tr>
<td>Dietrich et al. 2008</td>
<td>1,203</td>
<td>USA</td>
<td>21-59</td>
<td>CHD</td>
<td>2.12</td>
<td>1.26, 3.60</td>
</tr>
<tr>
<td>Senba et al. 2008</td>
<td>23,088</td>
<td>Japan</td>
<td>&lt;66</td>
<td>CHD</td>
<td>1.68</td>
<td>1.08, 2.61</td>
</tr>
<tr>
<td>You et al. 2009</td>
<td>22,862</td>
<td>USA</td>
<td>&gt;44</td>
<td>Stroke</td>
<td>1.27</td>
<td>1.09, 1.49</td>
</tr>
<tr>
<td>Choe et al. 2009</td>
<td>867,256</td>
<td>Korea</td>
<td>&gt;29</td>
<td>Stroke</td>
<td>1.3</td>
<td>1.2, 1.4</td>
</tr>
</tbody>
</table>

- Periodontitis effect is greater in young vs >60 yo;
- Effect on stroke is greater than effect on CHD.
- Effect also seen in multiple Asian studies and in never-smokers.

Periodontitis is independently associated with atherosclerotic cardiovascular disease

- Periodontal disease is a risk factor for CHD that is independent of traditional CHD risk factor
  - Humphrey et al. 2008; meta-analysis
  - Risk 1.24 to 1.35

- Increased prevalence and incidence of CAD in patients with periodontitis, an independent risk factor for CAD
  - Babekar et al. 2007; meta-analysis
  - 5 prospective studies (86,092 patients) Periodontitis: 1.14 risk for CHD; p<0.001
  - Case –control studies (1,423 patients) Periodontitis: 2.22 risk for CHD; p<0.001
Potential explanations for periodontitis association with CHD

- Periodontal bacteria:
  - can be found in the blood
  - can be found in atheromas
  - Various microorganisms associated with CVD risk
  - Antibiotic studies show no benefit

- Periodontitis raises blood CRP
- Higher CRP associated with MI risk
- Periodontitis treatment reduces CRP levels

- Diabetes, smoking, may complicate statistical analysis
- Some studies adequately sized to properly adjust
- Common genetics

Chronic bacteremia
Periodontitis raises systemic inflammatory burden
Major risk factors are common to both diseases

Inflammation, your health, and the health of your patients

The chronic diseases of aging are connected through common inflammatory mechanisms

Inflammation levels differ among individuals and are mostly controllable
Inflammation levels differ among individuals

- NHANES 1999-2002; 8,335 adults
  - CRP mg/L
    - Male: 3.38 ± 0.12
    - Female: 4.88 ± 0.17
    - \( p < 0.01 \)

Ethnicity

- NHANES 1999-2002; 8,335 adults
  - Inflammation levels differ among individuals

Gender

- NHANES 1999-2002; 8,335 adults
  - Smoking
    - No: 3.90 ± 0.14
    - Yes: 4.47 ± 0.15
    - \( p < 0.01 \)

- NHANES 1999-2002; 8,335 adults
  - Body Fat
    - BMI
      | BMI | CRP mg/L | p-value |
      |-----|---------|---------|
      | <20 | 2.31 ± 0.30 | <0.01 |
      | 20-24.9 | 2.59 ± 0.13 | |
      | 25-29.9 | 3.80 ± 0.15 | |
      | >30 | 6.29 ± 0.24 | |

- NHANES 1999-2002; 8,335 adults
  - p-value
**Moderate to severe periodontitis increases systemic inflammation**

<table>
<thead>
<tr>
<th>Periodontitis patients have higher CRP</th>
<th>Generalized periodontitis raises systemic inflammation</th>
<th>Meta-analysis of periodontitis and blood CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>• N=40 adult periodontitis (AP); N=35 controls</td>
<td>• N=53 localized periodontitis; N=54 generalized; N=43 controls</td>
<td>• 18 suitable papers</td>
</tr>
<tr>
<td>• CRP higher in AP (p&lt;0.001)</td>
<td>• Median CRP p=0.030</td>
<td>• CRP higher in periodontitis than healthy</td>
</tr>
<tr>
<td>• Associated with number of active sites over 6 mos</td>
<td>• 1.45 mg/L generalized</td>
<td>• Often &gt;2.1 mg/L in periodontitis cases</td>
</tr>
<tr>
<td>• Ebersole et al. 1997</td>
<td>• 1.30 mg/L localized</td>
<td>• Weighted mean difference (WMD) between periodontitis and controls = 1.56 mg/L; p=0.00001</td>
</tr>
<tr>
<td></td>
<td>• 0.90 mg/L controls</td>
<td>• Paraskevas et al. 2008</td>
</tr>
<tr>
<td></td>
<td>• Leukocytes elevated in generalized vs. localized and controls (p=0.002)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Loos et al. 2000</td>
<td></td>
</tr>
</tbody>
</table>

**Severe periodontitis is associated with increase in “high” CRP levels**

<table>
<thead>
<tr>
<th>Severe periodontitis is associated with CRP≥3mg/L</th>
<th>Generalized Severe periodontitis is associated with CRP≥3mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>• N=59 moderate periodontitis</td>
<td>• Thai population</td>
</tr>
<tr>
<td>• N=50 severe periodontitis</td>
<td>• N=62 localized chronic periodontitis</td>
</tr>
<tr>
<td>• N=65 healthy</td>
<td>• N=21 generalized severe periodontitis</td>
</tr>
<tr>
<td></td>
<td>• N=38 healthy</td>
</tr>
<tr>
<td></td>
<td>• Lower CRP than Caucasians</td>
</tr>
<tr>
<td>Subjects with CRP ≥ 3mg/L</td>
<td>Subjects with CRP ≥ 3mg/L</td>
</tr>
<tr>
<td>• Severe: 38%</td>
<td>Generalized: 28.6%</td>
</tr>
<tr>
<td>• Moderate: 23.7%</td>
<td>Localized: 17.7%</td>
</tr>
<tr>
<td>• Healthy: 16.9%</td>
<td>Healthy: 2.6%</td>
</tr>
<tr>
<td>• Noack, Genco, et al. 2001</td>
<td>• Pitiphat et al. 2008</td>
</tr>
</tbody>
</table>
Inflammation, your health, and the health of your patients

The chronic diseases of aging are connected through common inflammatory mechanisms.

Inflammation levels differ among individuals and are mostly controllable.

Treatment of periodontitis reduces systemic inflammation—and may improve diseases influenced by inflammation.

Treatment of moderate to severe periodontitis decreases systemic inflammation—with time.

**Meta-analysis of periodontitis treatment and blood CRP**
- 6 tx studies
- Weighted mean difference = 0.5 mg/L; p=0.02
- Paraskevas et al. 2008

**Acute periodontal treatment increases systemic inflammatory mediators**
- Aggressive non-surgical treatment increases systemic inflammatory mediators for up to 1 month; then lower mediators after 6 mos
  - D’Aiuto et al. 2004; 2007
  - Graziani et al. 2010
- 14 severe chronic periodontitis cases
- Scaling & root planing
- 24 hrs post-treatment increased CRP to mean > 12mg/L
Periodontal treatment reduces signs and symptoms of rheumatoid arthritis

- Patients with periodontitis AND rheumatoid arthritis (RA)

- Periodontal treatment significantly reduced inflammation in periodontal tissues
  - Decreased probing depths
  - Decreased bleeding on probing
  - Decreased Gingival Index

- Periodontal treatment decreased RA parameters
  - Decreased erythrocyte sedimentation rate
  - Decreased number of swollen and tender joints
  - Decreased patient’s assessment of pain (VAS)


Patients with moderate to severe periodontitis should be informed there may be an increased risk of atherosclerotic CVD

Patients with periodontitis and atherosclerotic CVD should be informed that periodontitis may raise inflammatory biomarkers associated with increased risk for CVD events.

Patients with periodontitis should assess their risk for future CVD events and coronary artery disease using Reynold’s Risk Score or National Cholesterol Education Program Risk Calculator.

Periodontal evaluation should be considered in patients with atherosclerotic CVD who have:
- Sign/symptoms of gingival disease;
- Significant tooth loss,
- Unexplained elevation of hs-CRP.

Periodontal treatment to reduce CVD risk should be focused on reducing and controlling the bacterial accumulations and eliminating inflammation.
Where periodontitis appears to fit into risk for other diseases

1. Inflammation modifiers: smoking, diabetes, genetics,
2. Local sources of inflammatory mediators: visceral fat, chronic infections
3. Moderate-severe periodontitis increases systemic inflammation
4. Systemic inflammation may modify the course of chronic diseases of aging

Periodontal Disease and Cardiovascular Health: What we know and how it applies to your patients

Ken Kornman DDS, PhD
Interleukin Genetics
Waltham, MA

Sunset's Inflammation of the Rocks
2005 Chen Feng

Sixth Annual Women's Cardiac Health Conference
Massachusetts Medical Society
February 4, 2011