The New Era of Wellness
The Science and Application of the “Mouth-Body” Connection
Inflammation and Interdisciplinary Care

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The Concept of Immunity

- Innate Immunity: Defenses against any pathogen
- Adaptive Immunity: Defenses against specific pathogens

1. Innate (Nonspecific)
   1st line of defense
   - Physical barriers: intact skin & mucous membranes
   - Chemical barriers
   - Genetic barriers
   - Phagocytic action
   - Fluids & secretions
   - Normal microflora (commensals)

2. Adaptive (Acquired)
   2nd line of defense
   - Antigen non-specific
   - No memory
   - PAMPs interact w/ PRR (TLRs)
   - Inflammation
   - Phagocytosis
   - Complement
   - Fever
   - Acute phase proteins & antimicrobial substances

3. 3rd line of defense
   - Natural & artificial
   - Specialized lymphocytes
   - T cells
   - B cells
   - Antibodies
   - Long-term = memory
   - Vaccination
   - Immune serum
   - Improves w/ exposures

Periodontal Biofilms
Bacteria, endotoxins and cytokines enter the general circulation through diseased gum tissue and become available to the rest of the body.

Portal of entry is diseased tissue stripped of protective epithelium barrier.

Red Complex Bacteria
1. Porphyromonas gingivalis
2. Tannerella forsythia
3. Treponema denticola

How Gram Negative Bacteria Affect Inflammation
Shedding of LPS remnants in-vivo upon death and lysis/phagocytosis of Gram-Negative Bacteria, and/or release from WBC

Porphyromonas gingivalis
http://www.pgingivalis.org/
**Phagocytosis**

1. Chemotaxis and adherence of microbe to phagocyte
2. Ingestion of microbe by phagocyte
3. Formation of a phagosome
4. Fusion of the phagosome with a vesicle to form a phagolysosome
5. Digestion of ingested microbe by enzymes
6. Formation of residual body containing indigestible material
7. Discharge of waste materials

**Innate Immunity Overview**

**PAMPs** - “Pathogen Associated Molecular Patterns”
- Provoke response from immune system
- Molecules common to all pathogens and distinguishable from host (“self”) molecules

**PRRs & TLRs**
- “Pattern Recognition Receptors”
- “Toll-Like Receptors”

TLRs bind PAMPs. When activated, TLRs upregulate (NF-κB) host cells to produce Cytokines.

Cytokines mediate the immediate responses which include vascular permeability, fever, phagocytosis, and further cytokine/chemokine production.
Inflammation & Damage
Upregulation
Cytokine Feedback Loops
Compliment Activation

**What Is Inflammation?**
- Systemic inflammation is the presence of proinflammatory proteins circulating in the bloodstream, exerting their effects on tissues of the body generally/systemically.

**Whole-Body Inflammatory Burden**
- **Non-Modifiable Risks**
  - Age & Gender
  - Genetic SNPs
  - Epigenetics
  - Ethnicity / Race
  - Family history / CVD, stroke, diabetes, cancer
- **Systemic Factors**
  - GI conditions
  - Respiratory conditions
  - Diabetes
  - Obesity
  - Rheumatoid arthritis
  - Pneumonia
  - Sepsis
  - Alzheimer’s
  - Cancer
  - Depression
  - Chronic infections
- **Environmental Factors**
  - Diet / Nutrition
  - Stress
  - Inactivity
  - Smoking
  - Excessive alcohol
- **Oral Factors**
  - Oral Biofilm (Red/Orange)
  - Xerostomia
  - Altered mouth chemistry
  - Faulty dentistry
  - Lack of dental care

**Clinical Predictive Value of Very Low as Well as Very High Levels of hsCRP**
  - Yeh ETH, Willerson JT. Circulation 2003;107:370.)

**The CRP Cascade**
- **Inflammatory Challenge**
  - Cellular & Vascular activation
  - Systemic Plasma-Humoral Immune activation
- **Liver**
  - Adhesion Molecules *Chemokines*
  - Inflammatory Proteins *Cytokines*
  - IL-1, TNFs
  - Interleukin-6
  - C-reactive protein
Periodontal Disease is Linked...

- Heart disease & Stroke
- Diabetes
- Alzheimer’s
- Rheumatoid arthritis
- Cancer
- Pregnancy complications
- Lung disease
- Osteoporosis
- Obesity
- High blood pressure
- Kidney disease

What is Cardiovascular Disease?

- Heart disease
- Stroke
- Diabetes
- Alzheimer’s
- Rheumatoid arthritis
- Cancer
- Pregnancy complications
- Lung disease
- Osteoporosis
- Obesity
- High blood pressure
- Kidney disease

The “Old” View

- Not designed to look for atherosclerosis

Risk Factors for Future Cardiovascular Event

- Lipoprotein (a)
- Homocysteine
- IL-6
- Total Cholesterol
- LDLC
- SAA
- Apo B
- TC : HDLC
- hs-CRP
- hs-CRP+TC:HDLC

Consequences of Periodontal Disease

1. Chronic Bacterial Insult
   - Bacteria and endotoxins in blood spread through body
   - Tissues Break Down
2. Systemic Disease
   - Periodontal Disease

What is Periodontal Disease?

Periodontal Disease is...
The New View

Inflammation is now recognized as the key process in atherosclerosis.

“Arterologist” vs “Lumenologist”

The progressions of atherosclerosis involve various inflammatory factors that can be easily measured to determine an individual’s risk for heart disease and cardiac events.

Conclusion: Bacteria believed to be important contributors to clinical periodontal disease are positively associated with novel inflammatory markers [Lp-PLA2] recently shown to have prognostic value for incident coronary artery disease.


With permission, courtesy Cleveland HeartLab
How “hot” are your arteries?

Panoramic Carotid Calcification

What is Periodontal Disease?

What comes first?

The periodontal pocket or the microbial profile?

Which is worse?

Shallow pockets or deep pockets?

What is Periodontal Disease

Can a person have periodontal disease before there is bleeding or tissue breakdown – or any other clinical signs or symptoms?
Three Studies

1. Changes in Clinical and Microbiological Periodontal Profiles Relate to Progression of Carotid Intima-Media Thickness; Desvarieux
2. Evaluating Clinical Periodontal Measures as Surrogates for Bacterial Exposure; Demmer
3. Bacterial Signatures in Thrombus Aspirates of Patients with Myocardial Infarction; Pessi

Discussion / Conclusions

- Etiologic Bacteria = “Red Complex” bacteria
- First evidence – improvement in periodontal status (clinical & microbiological) associated with less progression in atherosclerosis.
- Longitudinal (temporal) change in periodontal status is concurrent with longitudinal carotid artery IMT progression.
- Dose-response relationship between IMT progression and peri pocket changes and presence of etiologic bacteria.
- Improvement in peri status (clinical and biological) realized slower IMT progression.
- Etiologic bacteria considered “causal” (peri), most closely linked to atherosclerotic progression
**Discussion / Conclusions**

- “Pre-clinical” — low threshold periodontal measures (≤3mm) strongly correlate with etiologic pathogen bacteria, inflammation and atherosclerotic progression.
- Systemic translation of local infection is more related to bacterial levels than overt clinical disease.
- 3 mm pocket depth should not be assumed to be healthy.
- “Pre-clinical” periodontal disease cannot be ignored.
- Avg 0.03mm/yr difference in IMT score with deteriorating vs improving periodontal status.

  - Thresholds of clinical significance: reference:
    - 0.03mm/yr increase in IMT associated with 230% increase risk for coronary events (Hodis et al; progression study).
    - 0.0082mm/yr (Crouse et al; statin study).

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**Discussion / Conclusions**

- Study supports the role of high risk bacteria and atherosclerotic vascular disease (ASVD).
- ASVD is improved with effective periodontal therapy.
- B.O.P. is harmful to health — regardless of pocket depth, if there are high risk bacteria present.
- Judging perio health based on probing depths is now obsolete due to a scientific point of view.

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**Discussion / Conclusions**

- Perio - etiologic bacteria burden = “Red complex” (Ag, Pg, Td, Tt).
- B.O.P. strongly associated with bacterial burden and is more pronounced in shallow than deep periodontal pockets.
- Low-severity thresholds have strongest correlations with etiologic bacteria.

  - This does not imply that high-severity sites are not pathologic. (Note: high severity thresholds skewed due to lower prevalence, access to care issues with affected study population, & severe sites more predisposed to treatment/removal).

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**Discussion / Conclusions**

- Low threshold definitions of clinical periodontal disease tend to optimize associations with cardiovascular disease biomarkers.
- Highlights importance of subclinical periodontal infection (i.e. “low-severity”) in the context of periodontal infection and cardiovascular disease risk.
- Shallow pockets → gingivitis/periodontitis PLUS subclinical pathological processes with systemic effects.
- Shallow sites might be considered as “nascent” disease; (i.e beginning, starting, developing, emerging).

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**Discussion / Conclusions**

- “The finding that pocket depth and bleeding on probing definitions performed as well as, and often better than, attachment loss definitions might have been anticipated when considering that pocket depth and bleeding tend to be better markers of current infection while attachment loss better reflects historical disease.”
Discussion / Conclusions

While the relative risk for bacterial colonization in deep vs. shallow periodontal pockets is high, the prevalence of deep pockets is often low in epidemiological settings. Therefore, in absolute terms, much of the attributable risk from exposure to pathogenic bacteria would likely occur in relatively shallow periodontal pockets. Specifically, our findings highlight the potential importance of using clinical definitions that include less severe periodontal disease when such disease is viewed as a model of infection in studies of systemic disease risk.

www.biomedcentral.com/1471-2288/10/2

What does this mean?

• Gingivitis & subclinical perio disease should not be trivialized, normalized, or “watched”.
  – No more “bloody prophyl”.
• B.O.P. is disease; is assoc with high levels of etiologic bacterial burden
• Shallow pockets are associated with systemic pathology.
  – Low threshold perio tends to optimize associations with cardiovascular disease biomarkers.

www.biomedcentral.com/1471-2288/10/2

101 people with heart attack – evaluation of thrombus

• 78% had DNA evidence of bacteria oral step virulans
• 35% had DNA evidence of bacteria that cause gum disease
• All 9 thrombi evaluated by electron microscopy showed bacterial parts
• Whole bacteria were found in 3 of the 9.
Hippocrates
Father Of Western Medicine And Dentistry
Suggested pulling teeth could cure arthritis

Citrullination
Citrulline – an amino acid first isolated from watermelon in 1914. Citrullus is Latin word for watermelon.

Citrullination
Citrullination or deimination is the conversion of the amino acid arginine in a protein into the amino acid citrulline. Enzymes called peptidylarginine deiminases (PADs) replace the amino group (NH₂) by a keto group (–CO–).

Citrullination
PADD enzymes lead to post-translational modification.

Citrullination is important because it controls the expression of genes, particularly in the developing embryo, and because the immune system often attacks citrullinated proteins, leading to autoimmune diseases such as rheumatoid arthritis and multiple sclerosis.

Citrullination
Citrulline is not one of the 20 standard amino acids encoded by DNA in the genetic code. Instead, it is a post-translational modification.

http://en.wikipedia.org/wiki/Citrullination

http://autoimmunityblog.kim.wordpress.com/2011/03/30/citrullinierungen2.jpg


CONCLUSIONS: Dental infection and oral bacteria, especially variants streptococci, may be associated with the development of acute coronary thrombosis.
Antibodies Against Citrullinated Peptides

Citrullination is an enzymatic process that results in a post-translational modification of arginine residues found in protein molecules. This process is mediated by peptidyl arginine demethylase (PAD). In the presence of calcium, a positively charged arginine residue is deminated by the enzyme, ultimately releasing ammonia and forming a neutral amino acid referred to as citrulline. It has been demonstrated by numerous groups that the antibodies originally characterized as anti-peptidyl arginine antibodies and anti-id antibodies are all specific to the citrulline-derived form of a variety of proteins.


Periodontal disease is worse in rheumatoid arthritis patients!


The Science of Inflammation

Medical Problem – Dental Solution

The Oral-Systemic Connection

This is what makes periodontal disease a medical problem, and why physicians and dentists MUST work together to co-manage their patients.