Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy Dovepress
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HYPOTHESIS FORMATION

Comparison with ancestral diets suggests dense acellular carbohydrates promote an inflammatory microbiota, and may be the primary dietary cause of leptin resistance and obesity

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Abstract: A novel hypothesis of obesity is suggested by consideration of diet-related inflammation and evolutionary medicine. The obese homeostatically guard their elevated weight. In rodent models of high-fat diet-induced obesity, leptin resistance is seen initially at vagal afferents, blunting the actions of satiety mediators, then centrally, with gastrointestinal bacterial-triggered SOCS3 signaling implicated. In humans, dietary fat and fructose elevate systemic lipopolysaccharide, while dietary glucose also strongly activates SOCS3 signaling. Crucially however, in humans, low-carbohydrate diets spontaneously decrease weight in a way that low-fat diets do not. Furthermore, nutrition transition patterns and the health of those still eating diverse ancestral diets with abundant food suggest that neither glycemic index, altered fat, nor carbohydrate intake can be intrinsic causes of obesity, and that human energy homeostasis functions well without Westernized foods containing flours, sugar, and refined fats. Due to being made up of cells, virtually all "ancestral foods" have markedly lower carbohydrate densities than flour- and sugar-containing foods, a property quite independent of glycemic index. Thus the "forgotten organ" of the gastrointestinal microbiota is a prime candidate to be influenced by evolutionarily unprecedented postprandial luminal carbohydrate concentrations. The present hypothesis suggests that in parallel with the bacterial effects of sugars on dental and periodontal health, acellular flours, sugars, and processed foods produce an inflammatory microbiota via the upper gastrointestinal tract, with fat able to effect a "double hit" by increasing systemic absorption of lipopolysaccharide. This model is consistent with a broad spectrum of reported dietary phenomena. A diet of grain-free whole foods with carbohydrate from cellular tubers, leaves, and fruits may produce a gastrointestinal microbiota consistent with our evolutionary condition, potentially explaining the exceptional macronutrient-independent metabolic health of non-Westernized populations, and the apparent efficacy of the modern "Paleolithic" diet on satiety and metabolism.

Keywords: carbohydrate density, metabolic syndrome, nutrition transition, Paleolithic diet

Introduction

Due to the complexity of a phenomenon like obesity, it is inevitable that most study assumes a "bottom-up" approach, working to elucidate detailed knowledge of the systems believed to be involved. During the assembly of such detailed knowledge into a working whole, a measure of conformity to prevailing views is natural, as researchers work in detail on their part of the puzzle and seek to integrate that work into the network of existing knowledge. Bottom-up approaches do not lend themselves to rapid paradigm shifts in understanding, as each novel contribution is an incremental advancement.

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"Thus the "forgotten organ" of the gastrointestinal microbiota is a prime candidate to be in influenced by evolutionarily unprecedented postprandial luminal carbohydrate concentrations. **The present hypothesis suggests that in parallel with the bacterial effects of sugars on dental and periodontal health, acellular ours, sugars, and processed foods produce an inflammatory microbiota via the upper gastrointestinal tract, with fat able to effect a "double hit" by increasing systemic absorption of lipopolysaccharide."**

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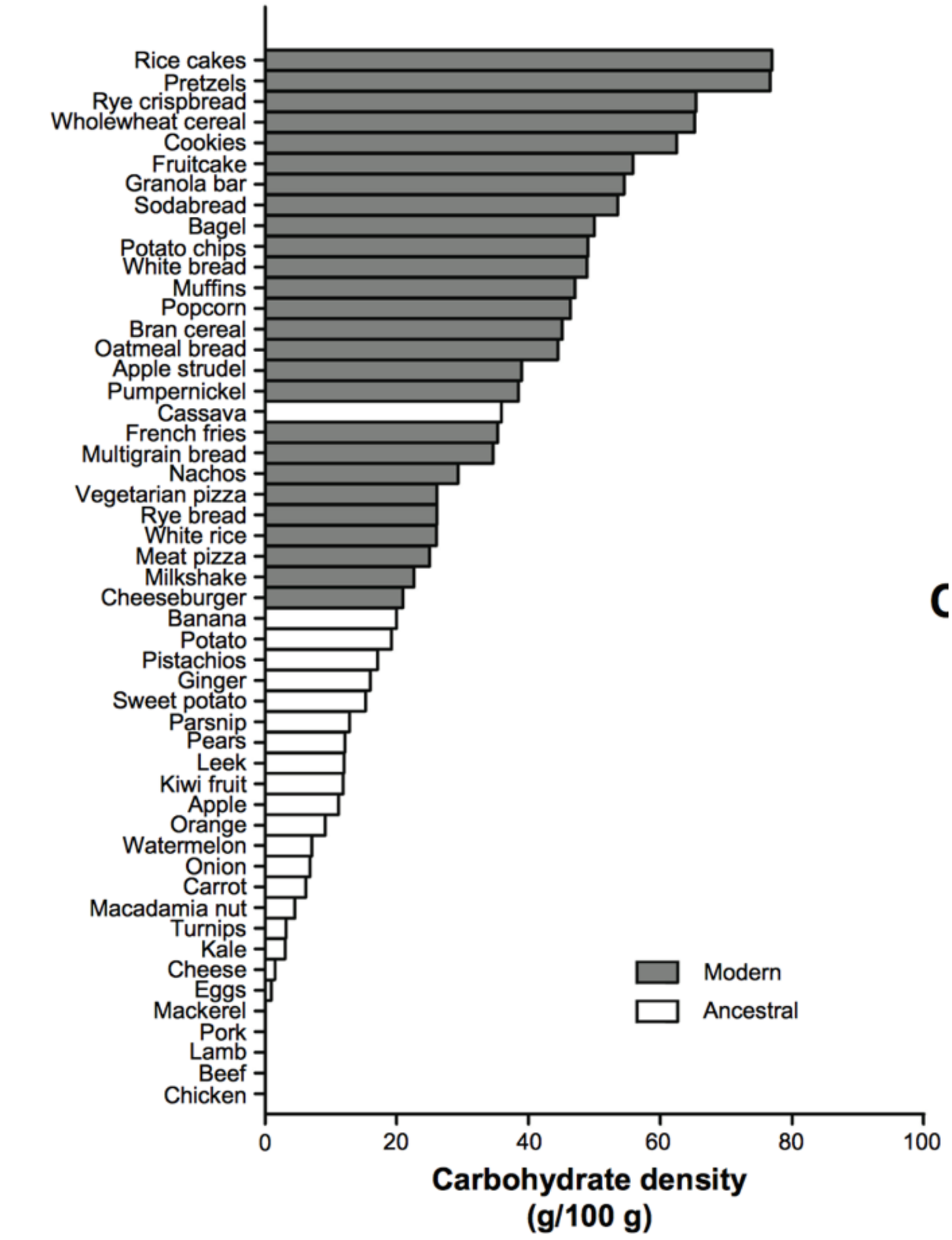
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Oatmeal bread
Apple strudel
Pumpernickel
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Vegetarian pizza
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Carbohydrate density
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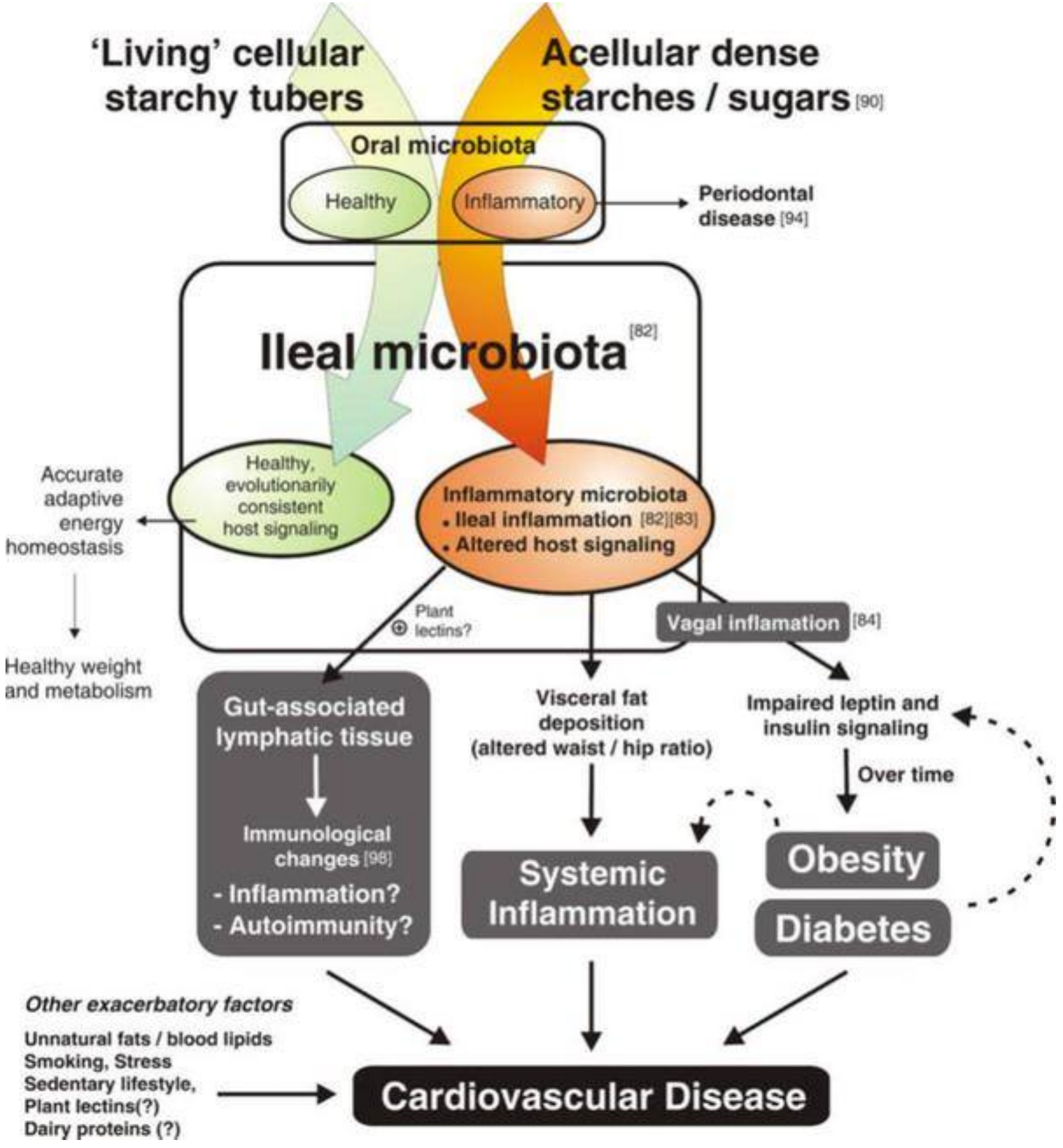
'Living' cellular starchy tubers
Acellular dense starches / sugars [90]
Oral microbiota
Healthy
Inflammatory
Periodontal disease [94]
Ileal microbiota [82]
Healthy, evolutionarily consistent host signaling
Inflammatory microbiota
• Ileal inflammation [82][83]
• Altered host signaling
Accurate adaptive energy homeostasis
Healthy weight and metabolism
Plant lectins?
Vagal inflamation [84]
Gut-associated lymphatic tissue
Immunological changes [98]
- Inflammation?
- Autoimmunity?
Visceral fat deposition (altered waist / hip ratio)
Impaired leptin and insulin signaling
Over time
Systemic Inflammation
Obesity
Diabetes
Other exacerbatory factors
Unnatural fats / blood lipids
Smoking, Stress
Sedentary lifestyle,
Plant lectins(?)
Dairy proteins (?)
Cardiovascular Disease

Endotoxemia, Immune Response to Periodontal Pathogens, and Systemic Inflammation Associate With Incident Cardiovascular Disease Events

Pirkko J. Pussinen, Karolina Tuomisto, Pekka Jousilahti, Aki S. Havulinna, Jouko Sundvall, Veikko Salomaa

Objective—In periodontitis, overgrowth of Gram-negative bacteria may cause endotoxemia and systemic inflammation leading to cardiovascular diseases (CVD). We investigated in a prospective study the associations of serum endotoxin, antibodies to periodontal pathogens, and inflammation markers with the risk of incident CVD.

Methods and Results—The FINRISK 1992 cohort of 6051 individuals was followed up for 10 years. We examined 185 incident CVD events and a control cohort of 320 individuals using a prospective case–cohort design. High antibody response to periodontal pathogens independently predicted incident CVD events with hazard ratios (HR, quartile 4 versus quartiles 1 to 3, 95% CI) of 1.87 (1.13 to 3.08). The subjects with a high antibody response and high CRP or interleukin (IL)-6 had multivariate-adjusted HRs of 3.01 (1.27 to 7.09) and 3.11 (1.42 to 6.83) compared with low-responders, respectively. The corresponding HRs for high endotoxin concentration were 1.82 (1.22 to 2.73, alone), 3.92 (1.99 to 7.74, with CRP), 3.54 (1.78 to 7.03, with IL-6), and 2.26 (1.13 to 4.52, with tumor necrosis factor (TNF)-α) after adjusting for age and gender. These associations were abolished after adjusting for serum lipids. High endotoxin/HDL ratio, however, had a multivariate-adjusted HR of 1.92 (1.19 to 3.08) for CVD events.

Conclusions—Our results suggest that the exposure to periodontal pathogens or endotoxin induces systemic inflammation leading to increased risk for CVD. (***Arterioscler Thromb Vasc Biol.*** **2007;27:1433-1439.**)

Key Words: infection ■ inflammation ■ lipopolysaccharide (LPS), serology ■ atherosclerosis

Periodontitis is a bacterial infection in the tooth-supporting tissues, which leads to chronic local inflammation, destruction of connective tissue and alveolar bone, and eventually loss of teeth. Mounting evidence[1–4] suggests that periodontitis is an independent risk factor for atherosclerosis and cardiovascular diseases (CVD). Data on the role of periodontal pathogens in atherogenesis are, however, more scarce. Several serological studies[5–10] and two studies based on detection of bacteria in subgingival plaque samples[11–12] support a direct relationship of pathogens etiologically linked to periodontal disease with increased risk for subclinical, prevalent, and future CVD.

Concerning atherosclerosis, the most widely studied periodontal pathogens are *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*, which both are Gram-negative, serologically heterogeneous species. DNA[13] of these species, as well as viable pathogens,[14] have been found in human atherosclerotic plaque. Bacteria or their parts may have an access to circulation via inflamed periodontal tissue during daily routines. Once in the circulation, bacterial components can induce and promote systemic inflammation and proatherogenic responses.

One potentially important bacterial source of inflammation is endotoxin (LPS), a unique glycolipid situated in the outer wall of Gram-negative bacteria. Endotoxin may trigger or accelerate atherosclerosis by multiple mechanisms, which include activation of inflammatory cells, increase in oxidative stress, and modification of lipoprotein metabolism.[15] Subclinical endotoxemia results in a 3-fold risk of incident atherosclerosis and CVD.[16–18] In the absence of quantitative methods to determine species-specific LPS concentrations, the sources of endotoxin activity measurable in the circulation may be various. Endotoxin can be found in the plasma of apparently healthy subjects,[19] because Gram-negative organisms may colonize the human gastrointestinal, respiratory, and genitourinary tracts. These bacteria produce endotoxin not only during acute infections, but also in common chronic and subclinical conditions, like periodontitis.

Despite of the widely accepted hypothesis that endotoxin is a key player in periodontitis-induced systemic

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Conclusions—Our results suggest that the exposure to periodontal pathogens or endotoxin induces systemic inflammation leading to increased risk for CVD.

MICROBIOTA

Ectopic colonization of oral bacteria in the intestine drives T_H1 cell induction and inflammation

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Intestinal colonization by bacteria of oral origin has been correlated with several negative health outcomes, including inflammatory bowel disease. However, a causal role of oral bacteria ectopically colonizing the intestine remains unclear. Using gnotobiotic techniques, we show that strains of *Klebsiella* spp. isolated from the salivary microbiota are strong inducers of T helper 1 (T_H1) cells when they colonize in the gut. These *Klebsiella* strains are resistant to multiple antibiotics, tend to colonize when the intestinal microbiota is dysbiotic, and elicit a severe gut inflammation in the context of a genetically susceptible host. Our findings suggest that the oral cavity may serve as a reservoir for potential intestinal pathobionts that can exacerbate intestinal disease.

The average person generates and ingests ~1.5 liters of saliva per day, containing an enormous number of oral-resident bacteria (*1*, *2*). Ingested oral bacteria poorly colonize the healthy intestine (*3*); however, increased levels of microbes of oral origin have been reported in the gut microbiota of patients with several diseases, including inflammatory bowel disease (IBD) (*4*), HIV infection (*5*, *6*), liver cirrhosis (*7*, *8*), and colon cancer (*9*). For instance, the presence of oral bacteria such as Veillonellaceae and Fusobacteriaceae in the intestinal mucosal microbiota strongly correlates with disease status in Crohn's disease (CD) (*4*). Mining of our in-house data sets of 16*S* ribosomal RNA (rRNA) gene sequences revealed that several bacterial taxa—including species belonging to *Rothia*, *Streptococcus*, *Neisseria*, *Prevotella*, and *Gemella* (table S1A), all of which are aerotolerant and typically members of the oral microbiota—were significantly more abundant in the fecal microbiota of patients with ulcerative colitis (UC), primary sclerosing cholangitis (PSC), gastroesophageal reflux disease (GERD) being treated by long-term proton pump inhibitor therapy, and alcoholism, compared with that of healthy controls (Fig. 1A and table S1B). Thus, we hypothesized that a subset of oral microbiota may ectopically colonize and persist in the intestine under certain circumstances to aberrantly activate the intestinal immune system, resulting in chronic inflammatory diseases.

To search the human oral microbiota for bacterial strains showing strong immune-stimulatory activities upon intestinal colonization, we transplanted saliva samples from two patients with CD into C57BL/6 (B6) germ-free (GF) mice by gavage. Each group of mice was housed in separate gnotobiotic isolators for 6 weeks, at which time small intestinal and colonic lamina propria (LP) immune cells were examined. In mice receiving a saliva sample from CD patient #1 (GF+CD#1 mice), there were no significant changes in the intestinal T cells (Fig. 1B). In contrast, in the group that received a saliva sample from CD patient #2 (GF+CD#2 mice), we noticed a marked accumulation of interferon-γ^+ (IFN-γ^+) $CD4^+$ T cells [T helper 1 (T_H1) cells] in the intestinal LP (Fig. 1B). Using 16*S* rRNA gene sequencing, we compared the community composition of the saliva microbiota before administration into GF mice and the fecal microbiota of the colonized animals (Fig. 1C). Although the saliva samples of both patients contained similar microbial communities, the fecal microbiota compositions differed markedly between GF+CD#2 mice and GF+CD#1 mice (Fig. 1C). Importantly, most of the bacterial species observed in the fecal microbiota of the mice had been minor components of the salivary microbiota (Fig. 1C). These results indicate that bacterial species that constitute a small fraction of the oral microbiota can expand and colonize the gut, and a subset of these oral species can induce the accumulation of intestinal T_H1 cells.

To isolate T_H1 cell–inducing bacteria, we anaerobically cultured cecal contents from GF+CD#2 mice using several culture media and picked 224 colonies with different colony appearances. Sequencing of the 16*S* rRNA genes revealed that these colonies contained eight strains from diverse genera—including *Gemella*, *Bifidobacterium*, *Streptococcus*, *Escherichia*, *Fusobacterium*, *Veillonella*, *Anaerococcus*, and *Klebsiella*—and broadly represented the major members of the gut microbiota colonizing GF+CD#2 mice (Fig. 1C). To examine whether these isolated strains had T_H1 cell–inducing capability, we cultured all eight of them and introduced them as a mixture (8-mix) into GF mice. We observed efficient induction of T_H1 cells in the colonic LP of these mice, with a magnitude comparable to that observed in GF+CD#2 mice (compare Fig. 1, B and D). Because *Fusobacterium* and *Veillonella* have been implicated in IBD pathogenesis (*4*), we colonized mice with strains of these two genera (strain IDs Fu-21f and Ve-2E1, respectively); however, this resulted in only marginal elevation of T_H1 cell frequency (Fig. 1D). We tested *Klebsiella pneumoniae* 2H7 (Kp-2H7) because it was the most prominent component of the GF+CD#2 microbiota (Fig. 1C). Oral administration of Kp-2H7 alone significantly induced T_H1 cells, whereas a mixture of the remaining seven strains (7-mix) failed to do so (Fig. 1D), indicating that the Kp-2H7 strain was the major contributor to the accumulation of T_H1 cells observed in GF+CD#2 mice. The effect of Kp-2H7 was relatively specific for T_H1 cells (fig. S1A), which were negative for interleukin-17 (IL-17), RORγt, and Foxp3 but positive for T-bet and CD44 (fig. S1B). Kp-2H7 mainly colonized the colon and cecum (fig. S1C), reflecting greater T_H1 cell induction in the colon than in the small intestine (fig. S1D). There was no increase in the percentage of T_H1 cells in the oral tissues (palate and tongue) of B6 GF+Kp-2H7 mice (fig. S1E). The increase in T_H1 cells was observed in IQI/Jic mice and B6 mice, but not in BALB/c mice (fig. S1F), implying interplay between host genotype and Kp-2H7 for colonic T_H1 cell induction.

Klebsiella spp. often acquire resistance to multiple antibiotics and can be a cause of health care–associated infection (*10*–*12*). Our isolate Kp-2H7 was resistant to multiple antibiotics, including ampicillin (Amp), tylosin (Tyl), spectinomycin

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"These Klebsiella strains are resistant to multiple antibiotics, tend to colonize when the intestinal microbiota is dysbiotic, and elicit a severe gut inflammation in the context of a genetically susceptible host. **Our findings suggest that the oral cavity may serve as a reservoir for potential intestinal pathobionts that can exacerbate intestinal disease.** "

REVIEW ARTICLE

COACTION

Rheumatoid arthritis and periodontitis – inflammatory and infectious connections. Review of the literature

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An association between oral disease/periodontitis and rheumatoid arthritis (RA) has been considered since the early 1820s. The early treatment was tooth eradication. Epidemiological studies suggest that the prevalence of RA and periodontitis may be similar and about 5% of the population are aged 50 years or older. RA is considered as an autoimmune disease whereas periodontitis has an infectious etiology with a complex inflammatory response. Both diseases are chronic and may present with bursts of disease activity. Association studies have suggested odds ratios of having RA and periodontitis varying from 1.8:1 (95% CI: 1.0–3.2, NS) to 8:1 (95% CI: 2.9–22.1, $p<0.001$). Genetic factors are driving the host responses in both RA and periodontitis. Tumor necrosis factor-α, a proinflammatory cytokine, regulates a cascade of inflammatory events in both RA and periodontitis. *Porphyromonas gingivalis* is a common pathogen in periodontal infection. *P. gingivalis* has also been identified in synovial fluid. The specific abilities of *P. gingivalis* to citrullinate host peptides by proteolytic cleavage at Arg-X peptide bonds by arginine gingipains can induce autoimmune responses in RA through development of anticyclic citrullinated peptide antibodies. In addition, *P. gingivalis* carries heat shock proteins (HSPs) that may also trigger autoimmune responses in subjects with RA. Data suggest that periodontal therapies combined with routine RA treatments further improve RA status.

Conclusions: Periodontal infection (*P. gingivalis*) carries a unique risk for development of autoimmune antibodies associated with RA. Patients with RA have either lost many teeth or usually have severe periodontitis. Additional research, both in regards to basic mechanisms as well as clinical studies, are necessary before it can be said that there are causative links between RA and periodontitis. Cross-disciplinary research in well-defined populations should be performed to further enhance knowledge and develop clinical strategies how to coordinate therapy and risk assessments of RA and periodontitis.

Keywords: *rheumatoid arthritis*; *periodontitis*; *bacteria*; *inflammation*; *Porphyromonas gingivalis*; *citrullination*; *genetics*; *review*

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During the last 200 years, a possible association between rheumatoid arthritis (RA) and oral disease (periodontitis) has been debated. Recent research with focus on inflammation in relation to infection by *Porphyromonas gingivalis* has identified an infection-immune response as one explanatory factor to why subjects with periodontitis may develop RA. Experiences from anti-inflammatory therapies in the management of RA may be useful also in the management of periodontitis. In the present review, studies on the associations, etiological co-factors, and effects of therapy in patients with RA and periodontitis will be discussed.

Approximately 1% of the total world population suffers from RA. The prevalence of RA increases with age and is three times more prevalent in women with 5% of women aged older than 55 years being affected (1, 2). RA is an autoimmune condition and diagnosed as chronic inflammatory polyarthritis when five or more joints are affected (3). The progression of RA can be (1) monocyclic (one single episode with or without therapy

Periodontal infection (P. gingivalis) carries a unique risk for development of autoimmune antibodies associated with RA. Patients with RA have either lost many teeth or usually have severe periodontitis. Additional research, both in regards to basic mechanisms as well as clinical studies, are necessary before it can be said that there are causative links between RA and periodontitis

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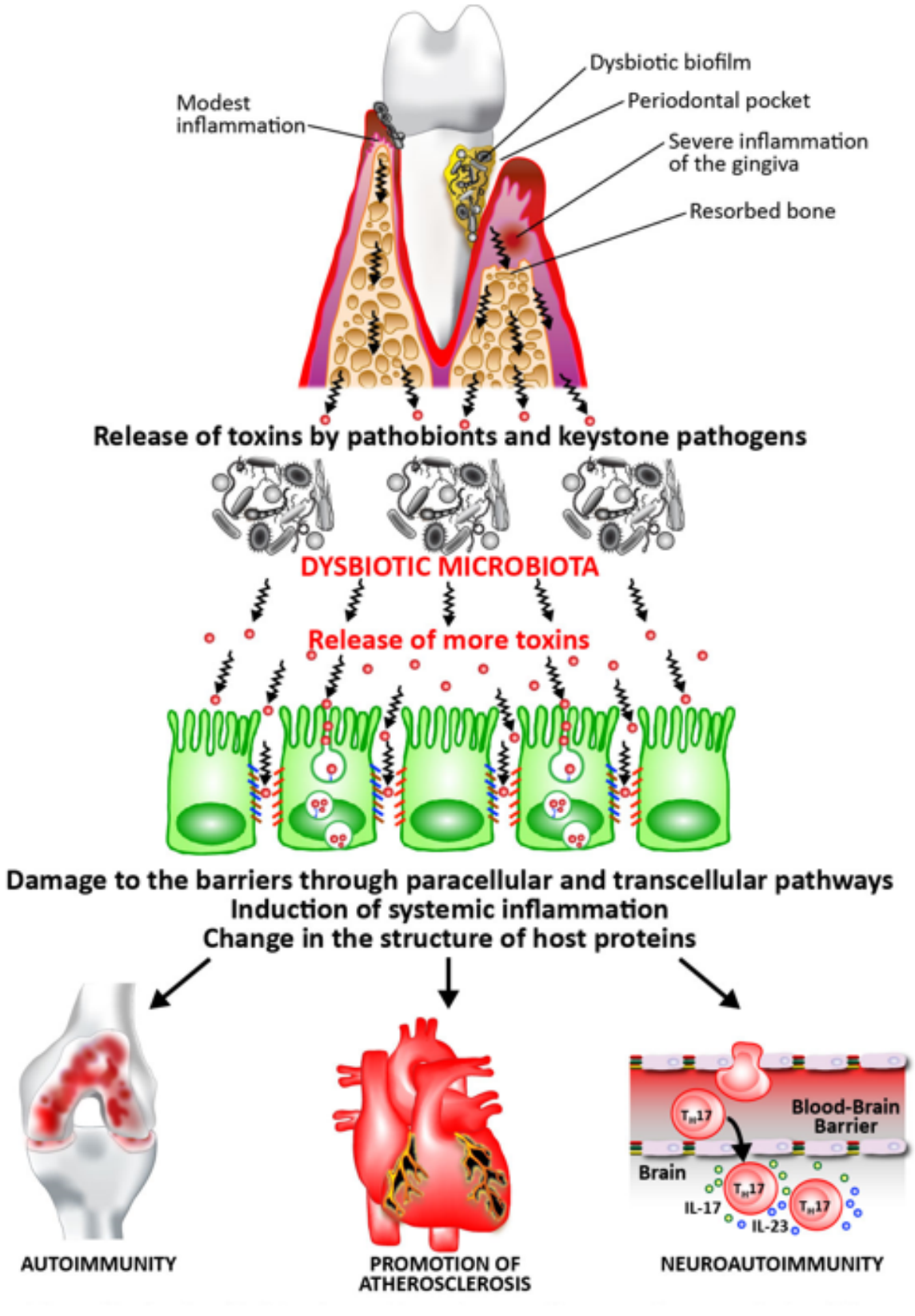


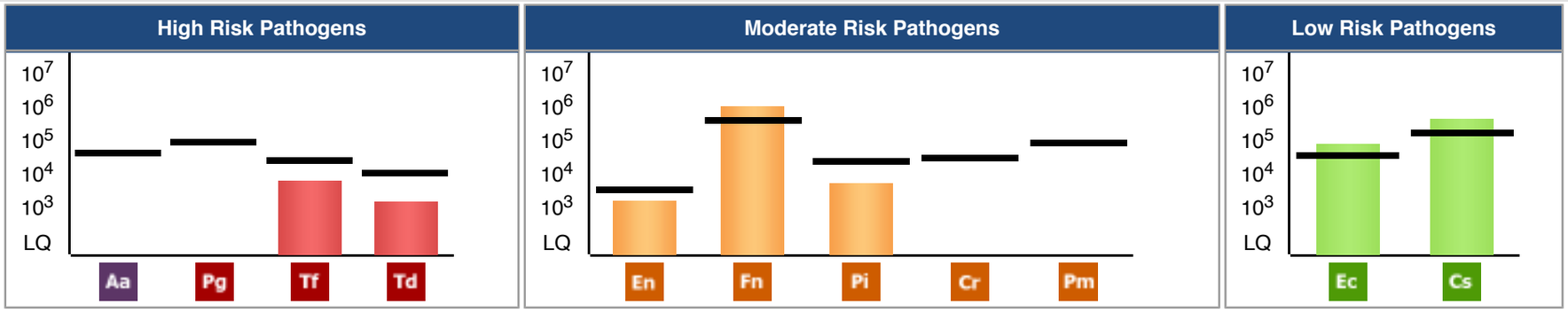
Figure 13. Mechanism of Oral Pathogens in Autoimmunity. *Keystone and pathobionts such as P. gingivalis and S. mutans can trigger periodontitis, which alters microbiota, which leads to dysbiosis, opening of intestinal tight junctions, systemic inflammation and autoimmunity.*

Diagram courtesy of Cyrex Labs

Oral Bacterial DNA test

MYPERIOPATH MOLECULAR ANALYSIS OF PERIODONTAL AND SYSTEMIC PATHOGENS

Results



Legend: The result graphic (above) shows the bacterial level for each of the assayed species. The vertical axis displays bacterial genome copies/milliliter in log10. The limit of quantification (LQ) is the lowest bacteria level that can be repeatedly measured. The black lines across each colored bar are the Therapeutic Threshold.

Interpretation of Results

- This result shows a combination of 2 high risk (Tf, Td) below, and 1 moderate risk (Fn) pathogens above, the therapeutic threshold. High levels of Ec, Cs are frequently part of this complex bacterial profile.
- The bacterial species Tf and/or Td are strongly associated with chronic periodontitis, are transmissible and tissue invasive even at low amounts of these organisms. Moreover, Td is present in 20-40% of cases of periodontitis where because it possesses proteins needed for adherence and invasion of host cells, it can cause destruction of periodontal tissue.
- The detected pathogens are also risk factors for various systemic diseases, including atherosclerosis, type 2 diabetes, arthritis, dementia and several types of cancer. Periodontal infections involving Ec have been associated with widespread and tissue invasive diseases of the lung, pancreas, heart, and bone. The spread of Ec infections is direct and often associated with abscess formation.

Treatment Considerations: to be determined by the healthcare professional

- **Mechanical/Debridement:** Scaling and root planing (SRP) is a mainstay of therapy to disrupt biofilm, remove plaque and debride compromised tissue. This patient harbors a series of pathogens (Tf, Pi) that may be refractory to this treatment.
- **Local Antibiotics and Chemical Hygiene:** As an adjunct to SRP, sub-antimicrobial doses of doxycycline hyclate lower collagenase activity and reduce periodontal pocket depth. Alternatively, locally delivered antimicrobial agents (LDA) including minocycline microspheres, doxycycline hyclate in an absorbable polymer, or chlorhexidine in a gelatin matrix have been shown to decrease pocket depth modestly.
- **Pocket or Field Decontamination:** Laser decontamination as an adjunct therapy to SRP may be beneficial in reducing probing depth and bacterial loads. The consideration of using lasers as an adjunct to SRP is dependent on type of laser used and the particular protocol.
- **Chemical and Gaseous antiseptics:** Chlorhexidine or Povidine iodine rinses can reduce periodontal pocket depth. Prescription tray application of peroxide gel, as an adjunct to frequent periodontal maintenance appointments for refractory patients, demonstrated significant reductions in bleeding on probing. Ozone is a volatile antiseptic that can disrupt microbial membranes.
- **Probiotics and Prebiotics:** Probiotics are live, beneficial bacteria, typically administered as a food or dietary supplement. Prebiotics are non-digestible ingredients that promote growth of commensal bacteria. Research shows that prebiotics and probiotics control the growth of pathogens and reverse tissue destruction caused by periodontitis.
- **Periodontal Surgery:** For severe and/or refractory periodontitis - surgical approaches such as gum flap repairs, procedures to reduce pocket depth, or other restorative procedures may be indicated.

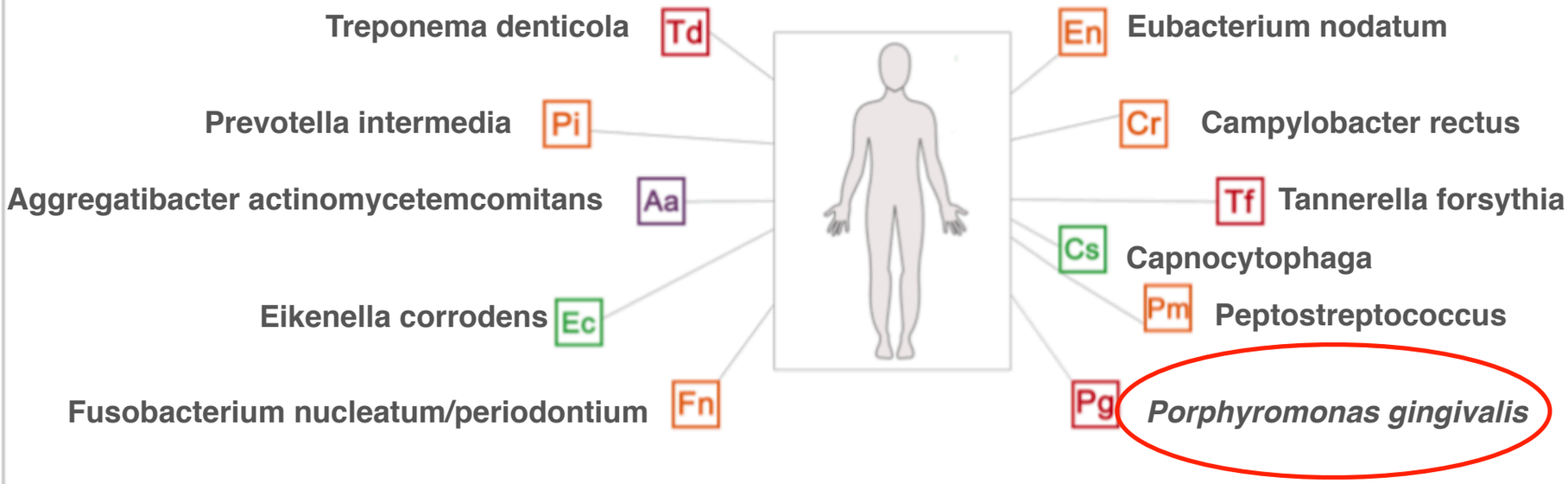
Follow up Recommendations

- ☑ Good periodontal health depends on compliance of a home care regimen as detailed by your healthcare provider. Daily brushing, flossing, as well as attention to nutrition, proper rest and cessation of smoking are essential.
- ☑ Follow-up testing between 6-12 weeks with MyPerioPath is recommended. Persistence of bleeding on probing is often indicative of unresolved infection. Retesting will identify residual or refractory bacteria. Currently there is not a cure for periodontal disease, only periods of remission.
- ☑ Assessment of a patient's level of inflammation with Celsus One is valuable in deciding the frequency of patient recall and treatment.

Clinical Considerations

Reason for Testing	Clinical	Diagnostic	Medical History
☑ Not Provided	☑ Not Provided	☑ Periodontal Classification: Not Provided ☑ Tooth Numbers Pocket Depths(mm)	☑ Not Provided

Systemic Effects of Oral Pathogens



Cancer	Cardiovascular Health	Joint and Musculoskeletal Health	Dementia and Brain Health	Metabolic Health	Healthy Pregnancy
Chronic gum disease, involving Aa, Pg, Td, Tf, & Fn is a risk factor for the development of certain cancers including ones involving the pancreas, esophagus, colon, lungs, and the head and neck. Additionally, untreated gum disease is a cause of ongoing inflammation, which may promote the advancing growth of tumors.	Select bacteria such as Aa, Td, Tf, Pg, Pi, & Fn can leak from blood vessels in the gums and travel to the heart, where cholesterol and other lipids deposit. These bacteria can incite inflammation in arteries, and if occluded, cause a heart attack. A goal of treatment is to minimize the levels of these bacteria as much and as long as possible.	The periodontal bacteria Pg, Fn & Ec are a cause of arthritis. The oral inflammation caused by these bacteria also leads to total body inflammation which, combined with changes in a person's immunity, may result in chronic joint diseases like rheumatoid arthritis.	Recent medical studies point to poor oral health, and high levels of the bacteria Pg, Cr, Cs in our gums, increasing the risk of developing dementias such as Alzheimer's.	Obesity, lack of exercise and chronic gum disease involving the bacteria Aa, Td, Tf, Pg, & Fn cause chronic inflammation. Inflammation can damage the pancreas where insulin is produced, possibly leading to diabetes. Also, diabetes worsens oral health by increasing the level of harmful bacteria in the gums.	Bacteria associated with gum disease, especially Aa, Tf, Pg, Fn, and Ec, are known to put a pregnancy at risk for pre-term birth, decreased birth weight and even blood infection in the placenta or newborn. Every pregnant woman should be tested for these harmful bacteria.

Methodology: Genomic DNA is extracted from the submitted sample and tested for 10 species-specific bacteria [Aa: Aggregatibacter actinomycetemcomitans, Pg: Porphyromonas gingivalis, Tf: Tannerella forsythia, Td: Treponema denticola, En: Eubacterium nodatum, Fn: Fusobacterium nucleatum/periodontium, Pi: Prevotella intermedia, Cr: Campylobacter rectus, Pm: Peptostreptococcus (Micromonas) micros, Ec: Eikenella corrodens] and 1 genus of bacteria [Cs: Capnocytophaga species (gingavalis, ochracea, sputigena)] known to cause periodontal disease. The bacteria are assayed by real-time quantitative polymerase chain reaction (qPCR). Bacterial levels are reported in log 10 copies per mL of sample (e.g. 1x10^3 = 1000 bacteria copies per mL of collection). Cross-reactivity is possible with Leptotrichia buccalis, Fusobacterium hwasooki, Capnocytophaga granulosa and Capnocytophaga leadbetteri. This test was developed, and its performance characteristics determined by OralDNA Labs pursuant to CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

70yo female with diagnosis of frontal lobe dementia/Alzheimer's

MYPERIOPATH MOLECULAR ANALYSIS OF PERIODONTAL AND SYSTEMIC PATHOGENS

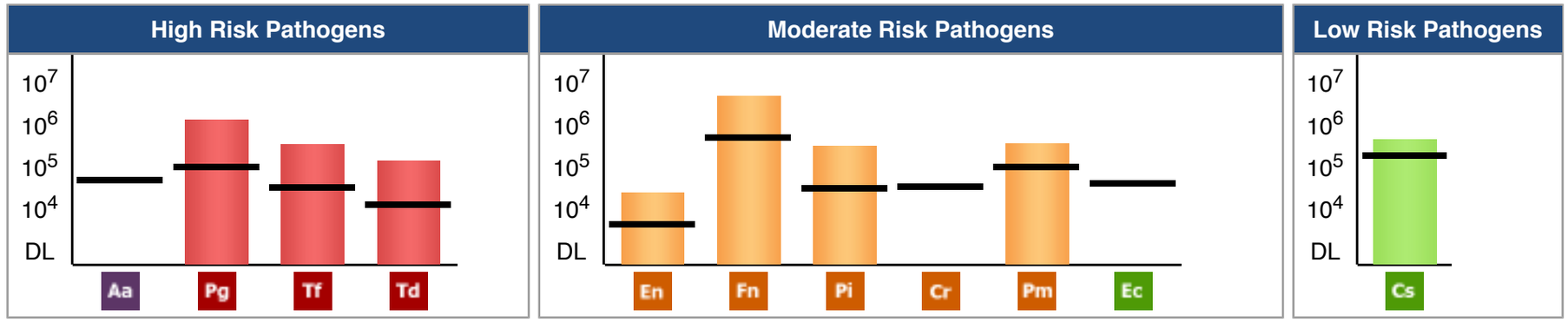
Result: PATHOGENIC BACTERIA DETECTED, 8 ABOVE THERAPEUTIC THRESHOLD

Pg Tf Td En Fn Pi Pm Cs

Bacterial Risk: HIGH - Very strong evidence of increased risk for attachment loss

Legend
▬ = Therapeutic Threshold*
DL = Detection Limit

Result Interpretation: Periodontal disease is caused by specific, or groups of specific bacteria. Threshold levels represent the concentration above which patients are generally at increased risk for attachment loss. Bacterial levels should be considered collectively and in context with clinical signs and other risk factors.



Pathogen	Result	Clinical Significance
Pg **Porphyromonas gingivalis**	**High**	Very strong association with PD: Transmittable, tissue invasive, and pathogenic at relatively low bacterial counts. Associated with aggressive forms of disease.
Tf **Tannerella forsythia**	**High**	Very strong association with PD: common pathogen associated with refractory periodontitis. Strongly related to increasing pocket depths.
Td **Treponema denticola**	**High**	Very strong association with PD: invasive in cooperation with other bacteria. Usually seen in combination with other bacteria.
En **Eubacterium nodatum**	**High**	Strong association with PD: specific role uncertain. Often seen in refractory disease.
Fn **Fusobacterium nucleatum/periodonticum**	**High**	Strong association with PD: adherence properties to several oral pathogens; often seen in refractory disease.
Pi **Prevotella intermedia**	**High**	Strong association with PD: virulent properties similar to Pg; often seen in refractory disease.
Pm **Peptostreptococcus (Micromonas) micros**	**High**	Moderate association with PD: detected in higher numbers at sites of active disease.
Cs **Capnocytophaga species (gingavalis,ochracea,sputigena)**	**High**	Some association with PD: Frequently found in gingivitis. Often found in association with other periodontal pathogens. May increase temporarily following active therapy.

Not Detected: (Aa) Aggregatibacter actinomycetemcomitans, (Cr) Campylobacter rectus, (Ec) Eikenella corrodens

Additional information is available from OralDNA.com

Methodology: Genomic DNA is extracted from the submitted sample and tested for 10 species-specific bacteria and 1 genus of bacteria known to cause periodontal disease. The bacteria are assayed by real-time quantitative polymerase chain reaction (qPCR). Bacterial loads are reported in log copies per mL of sample (e.g. 1x10^3 = 1000 bacteria copies per mL of collection). *Modified from: Microbiological goals of periodontal therapy; Periodontology 2000, Vol. 42, 2006, 180-218. This test was developed, and its performance characteristics determined by OralDNA Labs pursuant to CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.