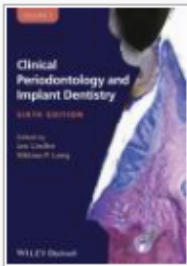


Periodontal Medicine

Dr Pradeep Koppolu, Associate Professor Leticia A Miranda

Reading Resources

▼ Clinical Periodontology and Implant Dentistry, 2 Volume Set



by Niklaus P. Lang, , Jan Lindhe, ,
and Niklaus P Lang

PUBLISHER

John Wiley & Sons, Incorporated

DATE

2015-03-25

CHAPTER 26

Impact of Periodontal Infection on Systemic Health

Brian L. Mealey | Perry R. Klokkevold | Yvonne L. Hernandez-Kapila



For online-only content on periodontal disease and pregnancy outcome, periodontal disease and chronic obstructive pulmonary disease, and periodontal disease and acute respiratory infections, please visit the companion website at eBooks.Health.Elsevier.com.

JDR Centennial Series

Periodontal Medicine: 100 Years of Progress

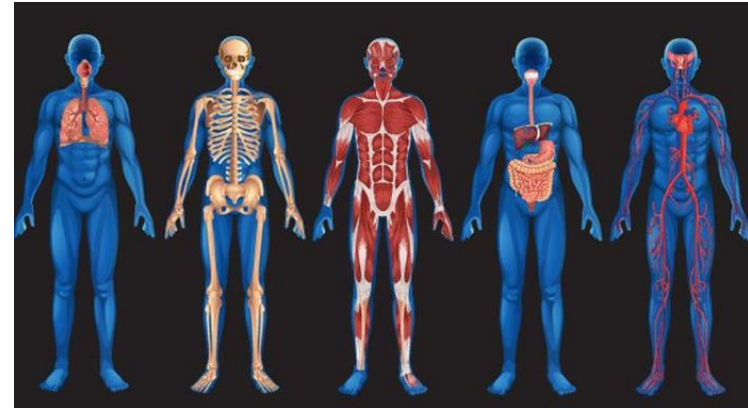


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J.D. Beck¹ , P.N. Papapanou², K.H. Philips³, and S. Offenbacher¹



Association of oral and general health – a new paradigm?



**“ You cannot have good general health
without good oral health”.**

Seymour 2007

“Our mouth is connected to our whole body !!!”

“The mouth is the window to general health”

Alpert 2017

**“Care of the mouth should be an integral part of overall
medical care”.**

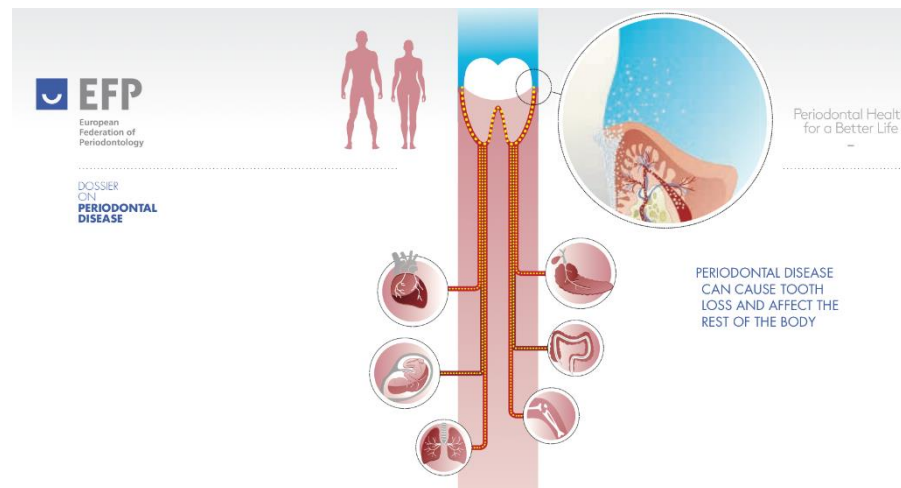
Migliorati & Madrid 2007

Association of oral and general health – a new paradigm?

SYSTEMIC DISEASES  PERIODONTITIS

More than a 100 systemic diseases and 500 medications have oral manifestations. Kane, 2017

SYSTEMIC DISEASES  PERIODONTITIS



Association of oral and general health – a new paradigm?

This is not new...

300 aC - **Hippocrates** reportedly cured systemic conditions by pulling out infected teeth.

1900 – **Dr Hunter and Dr Miller** – “*focal infection*” theory
Clinical experience and case reports
No systemic disease resolution after complete extractions

1989 - **Mattila and coworkers**
Evidence from well designed epidemiological studies began to emerge of possible linkages between poor oral health and atherosclerotic CVD

1997 – **Chapel Hill symposium** - Emergence of Periodontal Medicine

2012 - **EFP/AAP** – Periodontitis and Systemic diseases – EPF Manifesto

Periodontal Medicine

Periodontal medicine is a collective term commonly used to describe how periodontal infection/inflammation may affect extraoral health.

Association of oral and general health – a new paradigm?

Since then, an exponential rise in the number of studies investigating links between periodontal diseases and many diseases:

Cardiovascular diseases

Diabetes

Adverse pregnancy outcomes

Respiratory diseases

Kidney diseases

Rheumatoid arthritis and other
autoimmune diseases

Obesity

Cognitive impairments

Alzheimer

Cancer



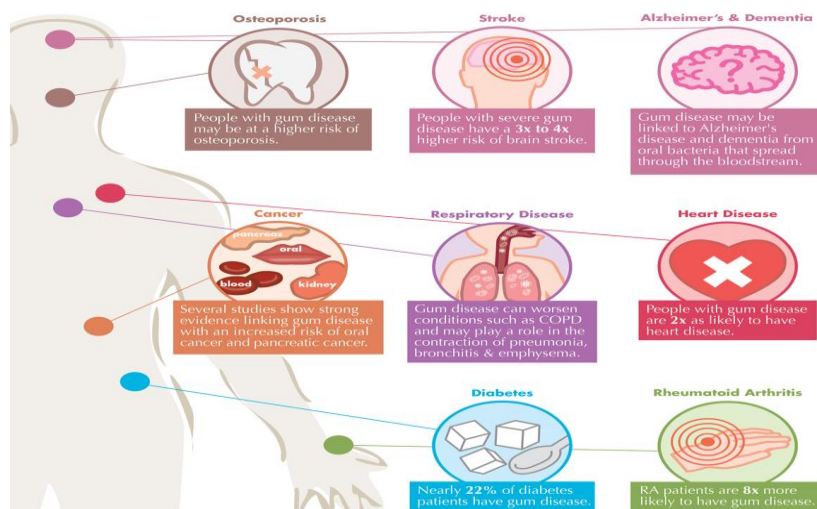
Fig. 1 Systemic diseases chronic periodontitis has been linked to.

Association of oral and general health – a new paradigm?



Gum Disease & Your Whole Body Health

Over 50% of adults in the U.S. have some degree of gum disease.
But did you know the impact goes far beyond your mouth...



MEN

Statistically, gum disease is higher in men (56.4%) than in women (38.4%).

Impotence
Men in their 30s with severe gum disease are 3x more likely to suffer from erectile dysfunction. Prolonged chronic inflammation associated with gum disease can damage blood vessels leading to impotence.

Prostate Health
Studies show that the prostate-specific antigen (PSA), an enzyme created in the prostate that is normally secreted in very small amounts, is secreted at higher levels in men with gum disease and prostate cancer.

Cancer in Men
Research has found that men with a history of gum disease are 14% more likely to develop cancer than men with healthy gums. Men with gum disease may be 43% more likely than women to develop kidney cancer, 24% more likely to develop pancreatic cancer, and 30% more likely to develop blood cancers.



WOMEN

Puberty & Menstruation
An increased level of sex hormones causes higher blood circulation to the gums, increasing the gum's sensitivity, susceptibility to irritation, and the growth of bacteria just beneath the gums.

These same hormones can cause menstruation gingivitis – red, swollen, tender or bleeding gums, and sores on the inside of the cheek – which typically occurs right before a woman's period and clears up once it has started.

Pregnancy & Preterm Births
Pregnant women with untreated gum disease may be more likely to have a preterm baby.

Menopause & Post-Menopause
Women may experience changes in their mouths, including discomfort in the mouth, dry mouth, pain and burning sensations in the gum tissue, and altered taste.

In addition, post-menopausal women with osteoporosis are 86% more likely to develop gum disease, while women with gum disease have a higher risk of having osteoporosis.

WHAT PROBLEMS COULD POOR DENTAL HEALTH CAUSE?





Cardiovascular and Cerebrovascular Systems

Atherosclerosis
Coronary heart disease
Angina
Myocardial infarction
Cerebrovascular accident (stroke)
Erectile dysfunction
Anemia

Endocrine System

Metabolic syndrome

Diabetes mellitus

Reproductive System

Preterm and low-birth-weight infants
Preeclampsia

Respiratory System

Chronic obstructive pulmonary disease
Acute bacterial pneumonia

Kidney Diseases

Renal insufficiency
Chronic kidney disease
End-stage kidney disease

Autoimmune Diseases

Rheumatoid arthritis
Ankylosing spondylitis

Cognitive Function

Dementia
Alzheimer disease

Cancers

Colorectal
Pancreatic
Hepatocellular
Others

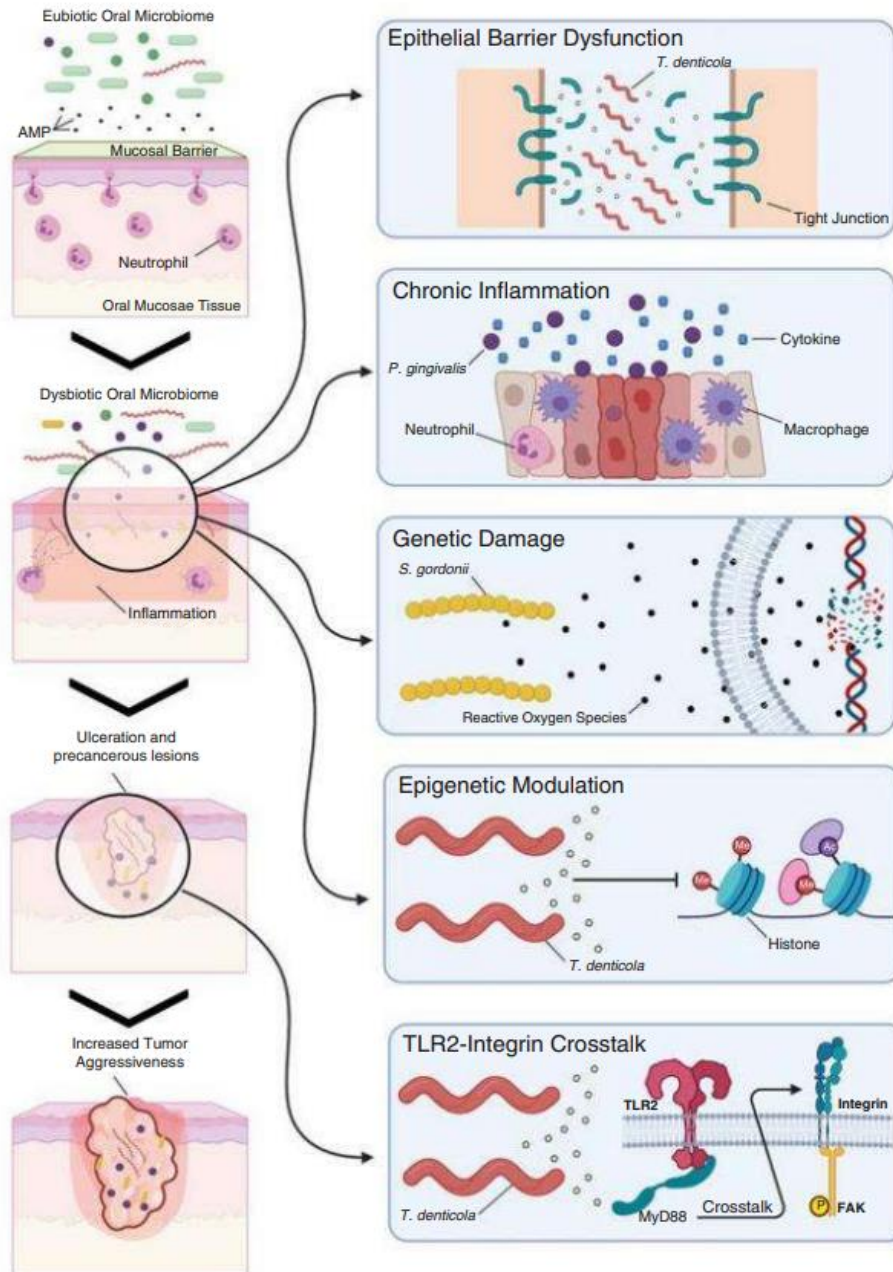


Fig. 26.1 Mechanisms of oral microbiome dysbiosis that promote carcinogenesis. Epithelial barrier disruption, bacterial invasion, chronic inflammation, genetic and epigenetic modulation, and altered tumor cell migration and signaling are mechanisms by which an oral microbiome dysbiosis can promote carcinogenesis.

Systematic Review

Clinical research activity in periodontal medicine: a systematic mapping of trial registers

Paul Monsarrat^{1,2}, Alessandra Blaizot³, Philippe Kémoun⁴, Philippe Ravaud^{5,6,7}, Cathy Nabet^{8,9}, Michel Sixou¹⁰ and Jean-Noël Vergnes^{10,11}

¹Dental Faculty, Department of Anatomical Sciences and Radiology, Paul Sabatier University, Toulouse University Hospital, Toulouse, France; ²CNRS 5273, UMR STROMALab, University of Toulouse UPS, INSERM U1031, EFS Pyrenees Mediterranean, Toulouse, France; ³University of Lille, Dental faculty, Place de Verdun, F-59000 Lille, France; ⁴Dental Faculty, Department of Biological Sciences, Paul

Conclusions: Periodontal medicine now constitutes an important part of clinical periodontal research.

Research activity in periodontal medicine has grown continuously since the early 2000s, and exploration of registers gives a useful up-to-date snapshot of this constantly evolving field of research

Periodontal medicine in trial registers 395

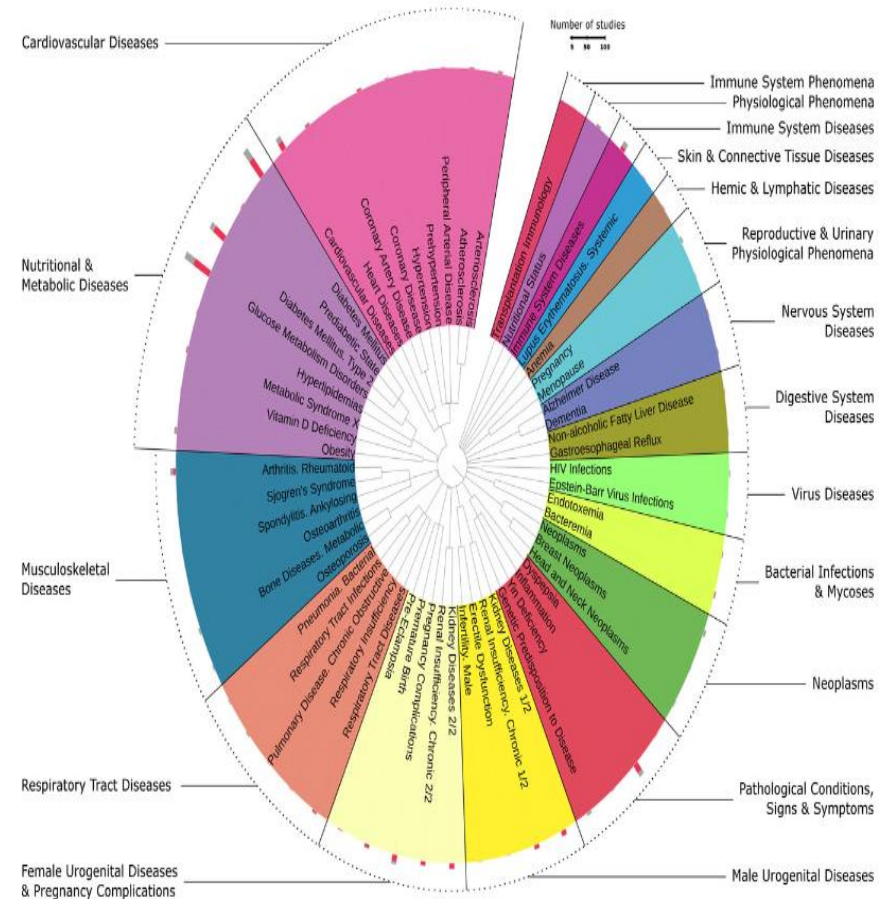


Fig. 2. Phylogenetic-like tree of systemic conditions that have been hypothesized in the registers to be related to periodontal diseases. Lines from the centre to the periphery of the circle represent the hierarchical tree structure of the MeSH classification. At the end of each taxon, a two-coloured rectangular bar has been added, with length proportional to the relative number of registration records in the A (red) and B1+B2 (grey) categories respectively. *Abbreviations:* trials concerning periodontal intervention to improve (or prevent) a systemic condition are classified as A; trials concerning intervention for a better understanding of the links between oral and overall health are classified B1 and observational studies of the link between periodontal disease and a systemic condition are classified B2.

The EFP MANIFESTO: Perio and General Health

The EFP MANIFESTO – Perio and General Health – is a call to action in terms of prevention, early detection and treatment of periodontitis. It is the first formal declaration in international dentistry to condense years of research into the links between periodontal disease and systemic illnesses into an acknowledgement of periodontitis as a major public health issue.



EFP Manifesto

This MANIFESTO calls upon all dental and health professionals to act in the prevention, early diagnosis, and effective treatment of periodontal disease in order to combat the devastating oral and general health effects for the individual and society.

The views and intentions herein expressed are informed by the rigorous scientific analysis of the evidence base for reported links between periodontal and systemic diseases, as carried out at the 9th European Workshop in Periodontology, an event jointly organised by the European Federation of Periodontology and the American Academy of Periodontology, and held at La Granja de San Ildefonso, Segovia, Spain.

Consensus was reached by the experts at this meeting (in November 2012) that periodontal disease should be acknowledged as a major public health issue, that all dental and medical professionals should be provided with relevant treatment guidelines, and that recommendations be given for future research to help clarify these associations and their consequences in terms of primary prevention.



How periodontitis and peri-implantitis can systemically affect individuals?!?

Possible pathways

Direct mechanism

- Direct infection by periodontal bacteria through ulcerated pocket epithelium and bloodstream

Indirect mechanism

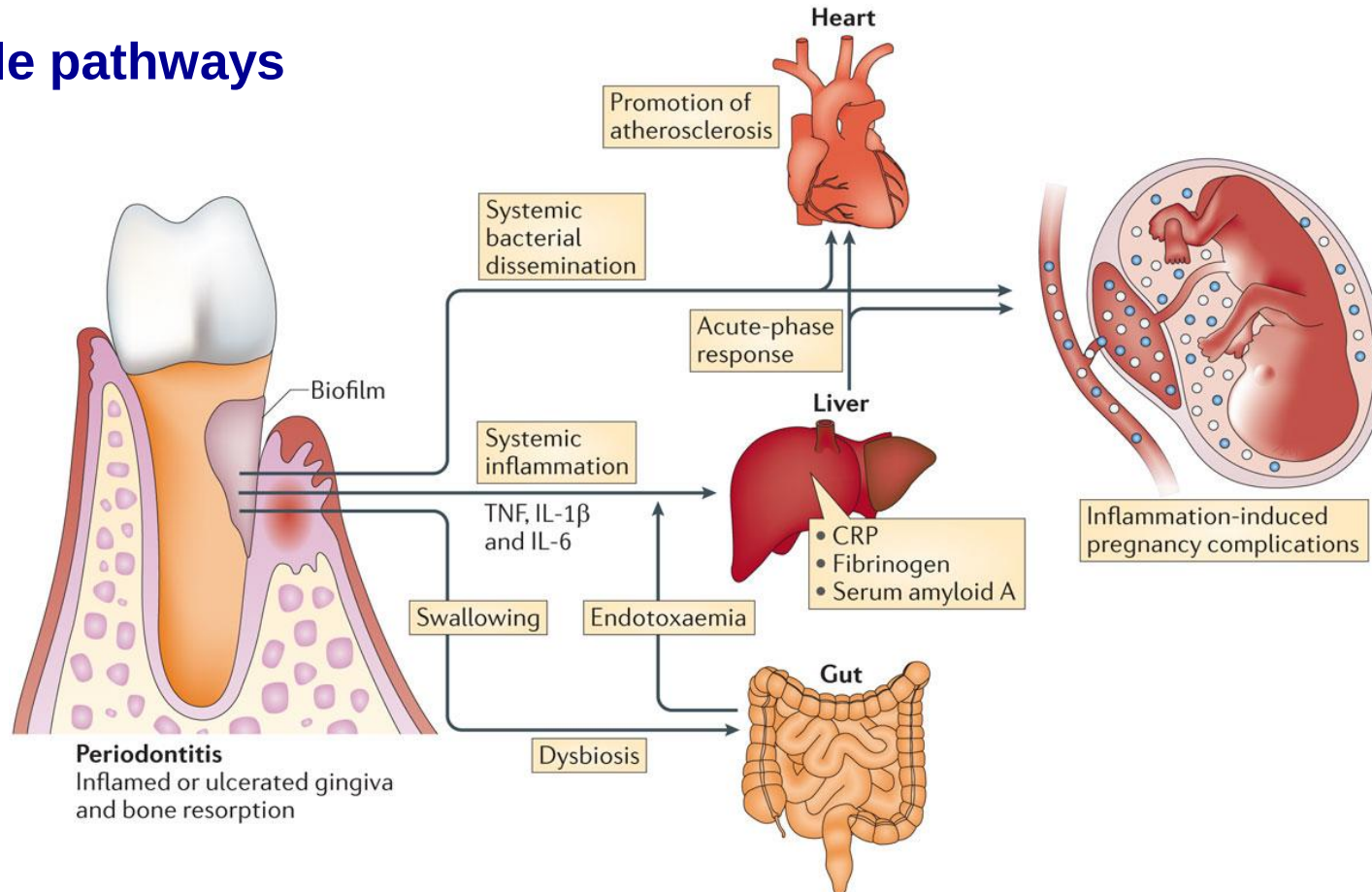
- Systemic inflammation model

Inflammatory response to periodontal infection has systemic effects
Inflammation itself is involved in the pathogenesis of many chronic illnesses

Seymour 2007; Linden 2015, Falcao & Bullon 2019

How periodontitis and peri-implantitis can systemically affect individuals?!?

Possible pathways



Nature Reviews | Immunology

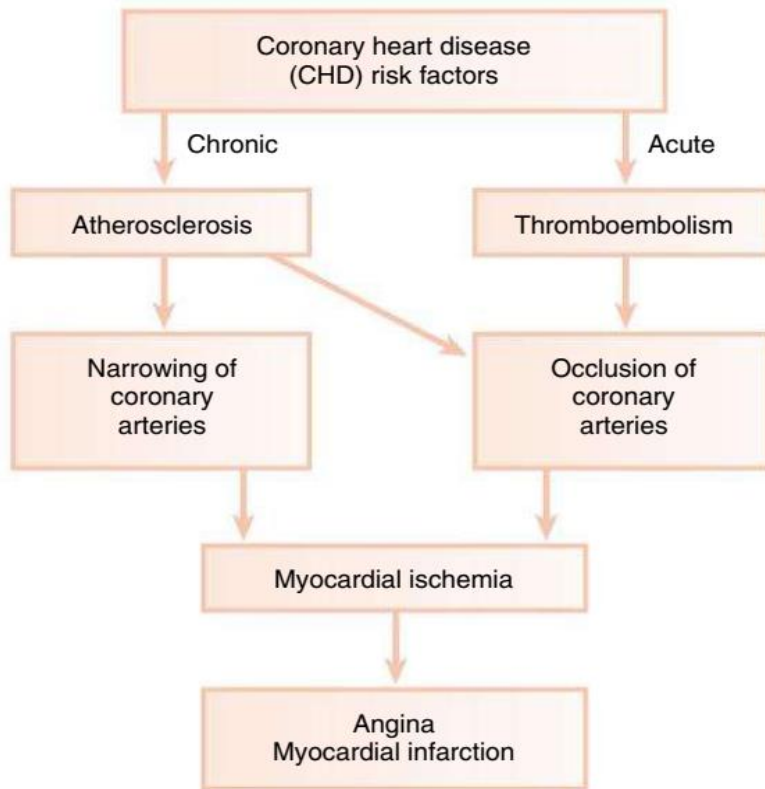


Fig. 26.2 Acute and chronic pathways to ischemic heart disease. Coronary heart disease–related events, such as angina and myocardial infarction, may be precipitated by either pathway or both pathways.

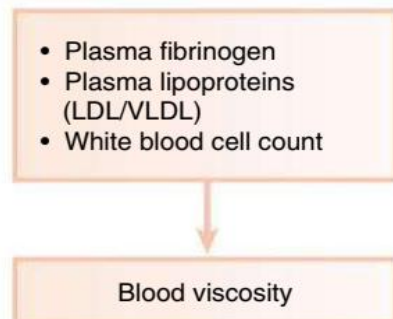


Fig. 26.3 Factors that affect blood viscosity in health. *LDL*, Low-density lipoprotein; *VLDL*, very-low-density lipoprotein.

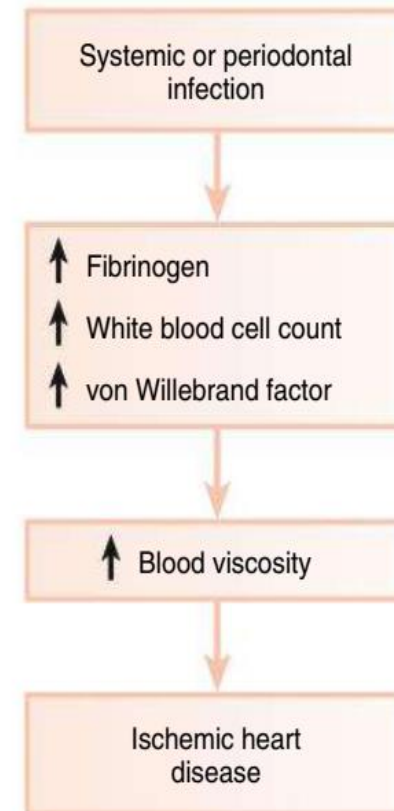


Fig. 26.4 The effect of infection on blood viscosity. Increased plasma fibrinogen and von Willebrand factor cause hypercoagulability. When they are combined with an increased white blood cell count, the blood viscosity increases, thereby increasing the risk of coronary ischemia.

Direct mechanism

- Direct infection by periodontal bacteria through ulcerated pocket epithelium and bloodstream
- Ulcerated pocket epithelium allows bacteria entrance
- Bacteremia is common after periodontal examination (Daly et al 2001)
- Bacterial byproducts, such as LPS, also disseminate in the bloodstream (Gentx 2002)

Indirect mechanism

- Systemic inflammation model
- Blood and tissue cells where these antigens relocate produce inflammatory mediators
- Excessive production of inflammatory mediators in periodontal lesions/sites enter bloodstream and affect distant organs
- Liver = acute phase response

Systemic inflammation model - Periodontitis

Increase
circulating levels
of pro-
inflammatory
cytokines

IL-1/IL-6/TNF- α

Diminish
circulating levels
of anti-
inflammatory
cytokines

IL-4/IL-10

Alter blood counts:

+ Leukocytes
+ PMN
+ Platelets

- Lymphocyte
- Erythrocytes



Increase circulating
levels of acute
phase response:
non-specific
systemic markers of
inflammation

C-reactive protein
and fibrinogen
(ESR)

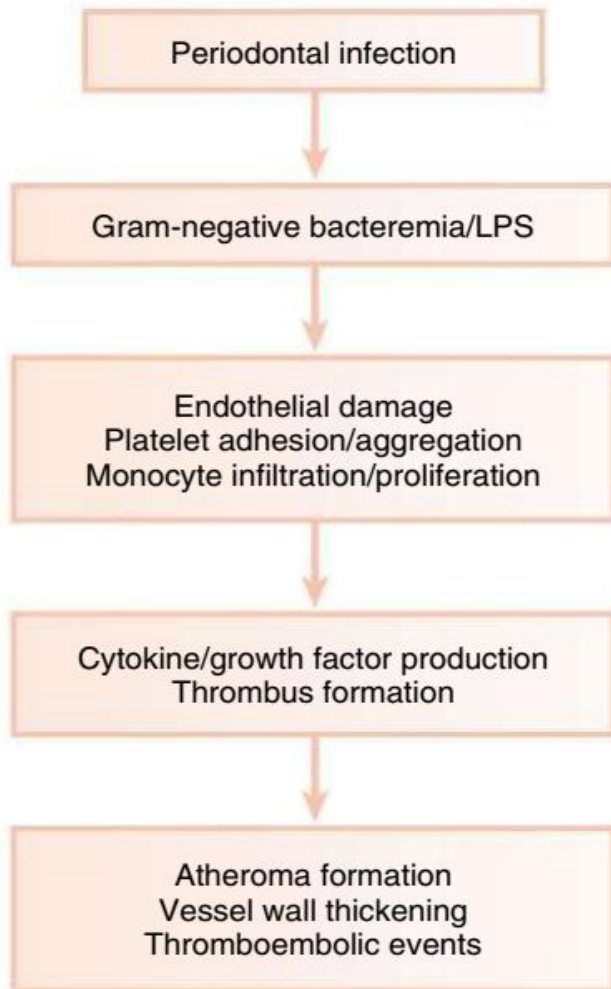


Fig. 26.6 The influence of periodontal infection on atherosclerosis. Periodontal pathogens and their products result in damage to the vascular endothelium. Monocytes and macrophages enter the vessel wall and produce cytokines that further increase the inflammatory response and propagate the atheromatous lesion. Growth factor production leads to smooth muscle proliferation in the vessel wall. Damaged endothelium also activates platelets, thereby resulting in platelet aggregation and potentiating thromboembolic events. *LPS*, Lipopolysaccharide.

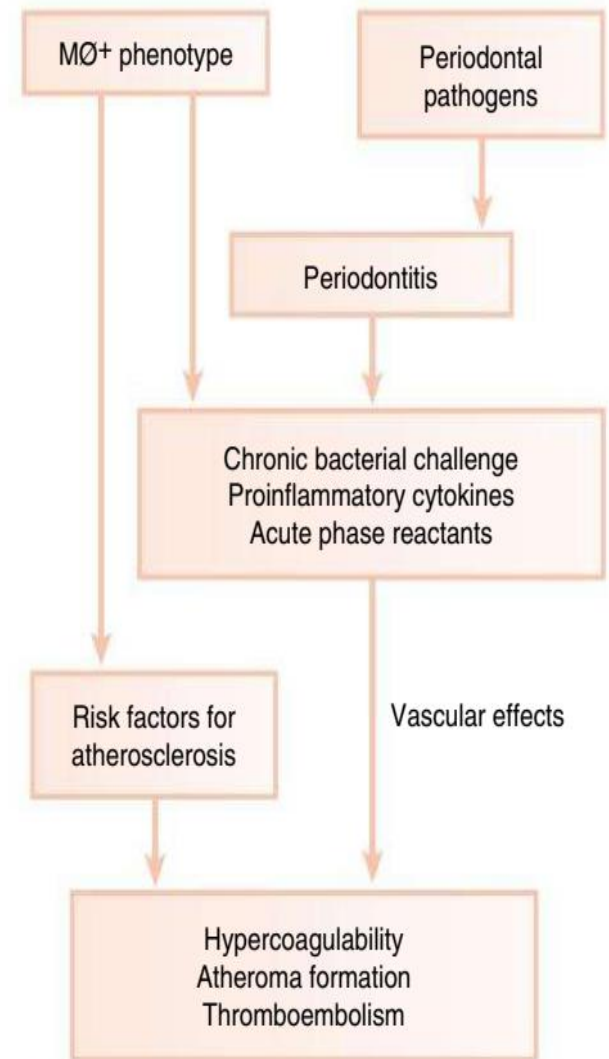


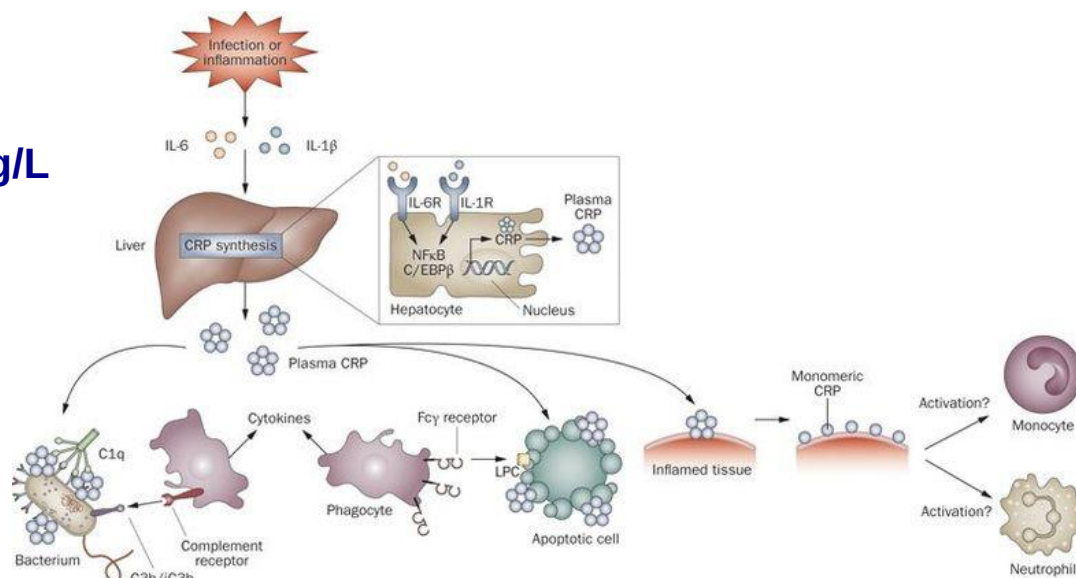
Fig. 26.7 The cardiovascular and periodontal consequences of the hyper-responsive monocyte/macrophage phenotype (MØ⁺). In combination with other risk factors, the MØ⁺ phenotype predisposes individuals to both atherosclerosis and periodontitis. Bacterial products and inflammatory mediators associated with periodontitis affect vascular endothelium, monocytes and macrophages, platelets, and smooth muscle and may increase blood coagulability. This may further increase atherosclerosis and may result in thromboembolism and ischemic events.

Acute phase response = CRP and ESR

Non specific systemic inflammation markers

C-Reactive Protein

- Chronic infections: **> 3.0 mg/L**
(*H. pylori*, *Chlamydia*)



Inflammation Markers | C-Reactive Protein (CRP), Cardiac

CRP Clinical Levels: 0.00 - 3.00 mg/L

The clinical levels here are the standard lab ranges. your goal is to move into the low and moderate ranges.

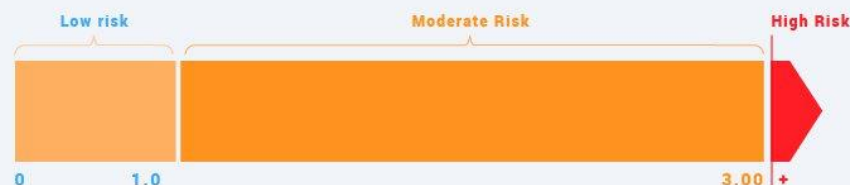


Table 3.

Overview of Case-Control Studies Reporting on C-Reactive Protein (CRP) Plasma Levels (mg/l) in Periodontitis Patients and Healthy Controls

Reference	Patients			Controls			p*
	N	Mean $\pm$ SD	Median	N	Mean $\pm$ SD	Median	
Ebersole et al. 1997 ⁴⁴	40	9.12 $\pm$ 1.61	†	35	2.17 $\pm$ 0.41	†	<0.001
Fredriksson et al. 1998 ¹⁵	17	2.62 $\pm$ 2.90	†	17	0.87 $\pm$ 1.73	†	0.04
Fredriksson et al. 1999 ¹⁶	37	†	2.0	38	†	0	0.012
Loos et al. 2000 ¹²	107	2.64 $\pm$ 3.48	1.4	43	1.21 $\pm$ 1.34	0.9	0.017 ^{‡§}
Noack et al. 2001 ⁴⁵	50	4.06 $\pm$ 5.55	†	65	1.70 $\pm$ 1.91	†	0.011 [†]
Glurich et al. 2002 ⁴⁶	26	2.40 $\pm$ 1.89	†	20	1.68 $\pm$ 1.42	†	>0.05
Craig et al. 2003 ⁴⁷	44	5.78 $\pm$ 1.07	†	25	2.46 $\pm$ 1.44	†	>0.05
Buhlin et al. 2003 ⁴²	50	3.28 $\pm$ 4.64	†	46	1.74 $\pm$ 1.68	†	<0.05
Bizzarro et al. 2005 ¹⁸	91	3.12 $\pm$ 3.81	1.9	39	1.88 $\pm$ 2.04	0.9	0.074

* Indicates strength of the observed differences between patients and controls.

† Values not reported.

‡ P value adjusted for background variables and potential confounding factors reported in original paper.

§ P value calculated for the purpose of this review; in original article, the adjusted P value is 0.030 for a difference between three groups: healthy controls, patients with localized periodontitis, and patients with generalized periodontitis, with the generalized periodontitis group having the highest value and the control group having the lowest value (also see Figure 3).

|| P value calculated for the purpose of this review; in original article, the adjusted P value is 0.197 for a difference between three groups: healthy controls, patients with moderate periodontitis, and patients with severe periodontitis, with the severe periodontitis group having the highest value and the control group having the lowest value.

Acute phase response = CRP and ESR

Non specific systemic inflammation markers

Erythrocyte sedimentation rate

Increased fibrinogen production

Increased pro coagulation state

Table 1. Reference values for ESR.

Age	Male	Female
0-50	<15 mm/h	<20 mm/h
51-85	<20 mm/h	<30 mm/h
>85	<30 mm/h	<42 mm/h

Source: Sox H.C., Liang M.H. The erythrocyte sedimentation rate: guidelines for rational use. Ann Int Med 1986;104:515-23.

ESR measures the rate at which RBC settle in one hour at the bottom of a tube that contains a blood sample

1
img

The faster the blood cells sink, the more inflammation you have in your body



1 hr



E
S
R

The distance, in mm, the RBC fall in 1 hour

Clumps of Red Blood Cells

High ESR can be seen in:

- Inflammatory diseases
- Infections
- Autoimmune diseases
- Chronic kidney diseases
- Viral infections
- Pregnancy
- Cancer

Erythrocyte Sedimentation Rate Test

► [Int J Health Sci \(Qassim\)](#). 2016 Apr;10(2):293–307.

Periodontal Systemic Connections-Novel Associations-A Review of the Evidence with Implications for Medical Practitioners

[Butchibabu Kalakonda](#) ^{a,✉}, [Pradeep Koppolu](#) ^a, [Kusai Baroudi](#) ^a, [Ashank Mishra](#) ^b

► [Author information](#) ► [Copyright and License information](#)

PMCID: PMC4825901 PMID: [27103910](#)

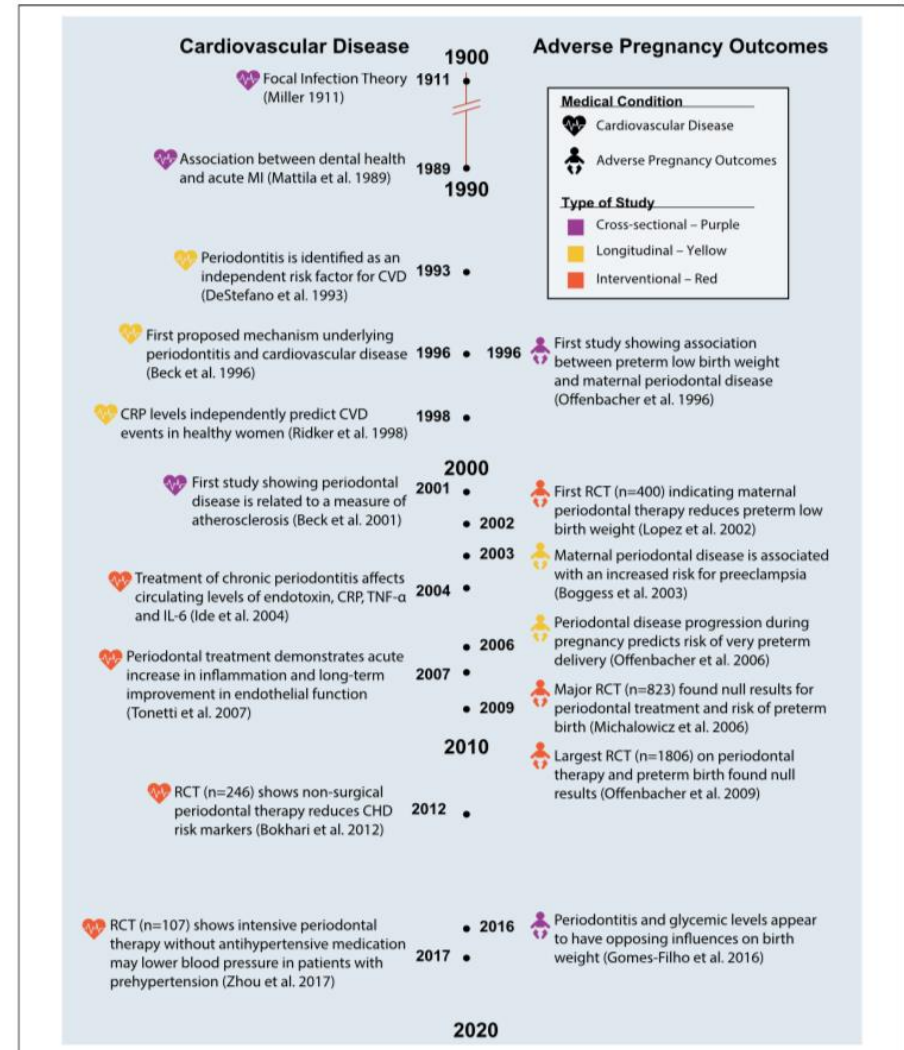
Electronic databases such as PubMed, Google Scholar and Cochrane databases were used as source of the data for relevant studies published from 2005 up to 2015 with the following keywords, “Periodontal disease”, “systemic conditions”, “periodontal disease and Alzheimer’s”, “Periodontal disease and Schizophrenia”, “Periodontal disease and Psoriasis” and “Periodontal disease and erectile dysfunction”.

The evidence presented ascertains that a reasonable and modest association does exist between Periodontal disease and Alzheimer’s, Schizophrenia, Erectile dysfunction, as well as Psoriasis and thus establishes periodontal disease as a potential risk factor.

Main association findings

Cardiovascular disease

Adverse pregnancy outcomes



Beck et al 2019

Figure 2. Shared periodontal medicine timelines for cardiovascular disease and adverse pregnancy outcome studies. Timeline overview from 1900 to 2020 showing 10 milestone studies for periodontal medicine and cardiovascular disease and 7 milestone studies for periodontal medicine and adverse pregnancy outcomes, organized by medical condition and type of study with descriptors. CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; IL-6, interleukin-6; MI, myocardial infarction; RCT, randomized controlled trial; TNF- α , tumor necrosis factor α .

Main association findings

Diabetes

Beck et al 2019

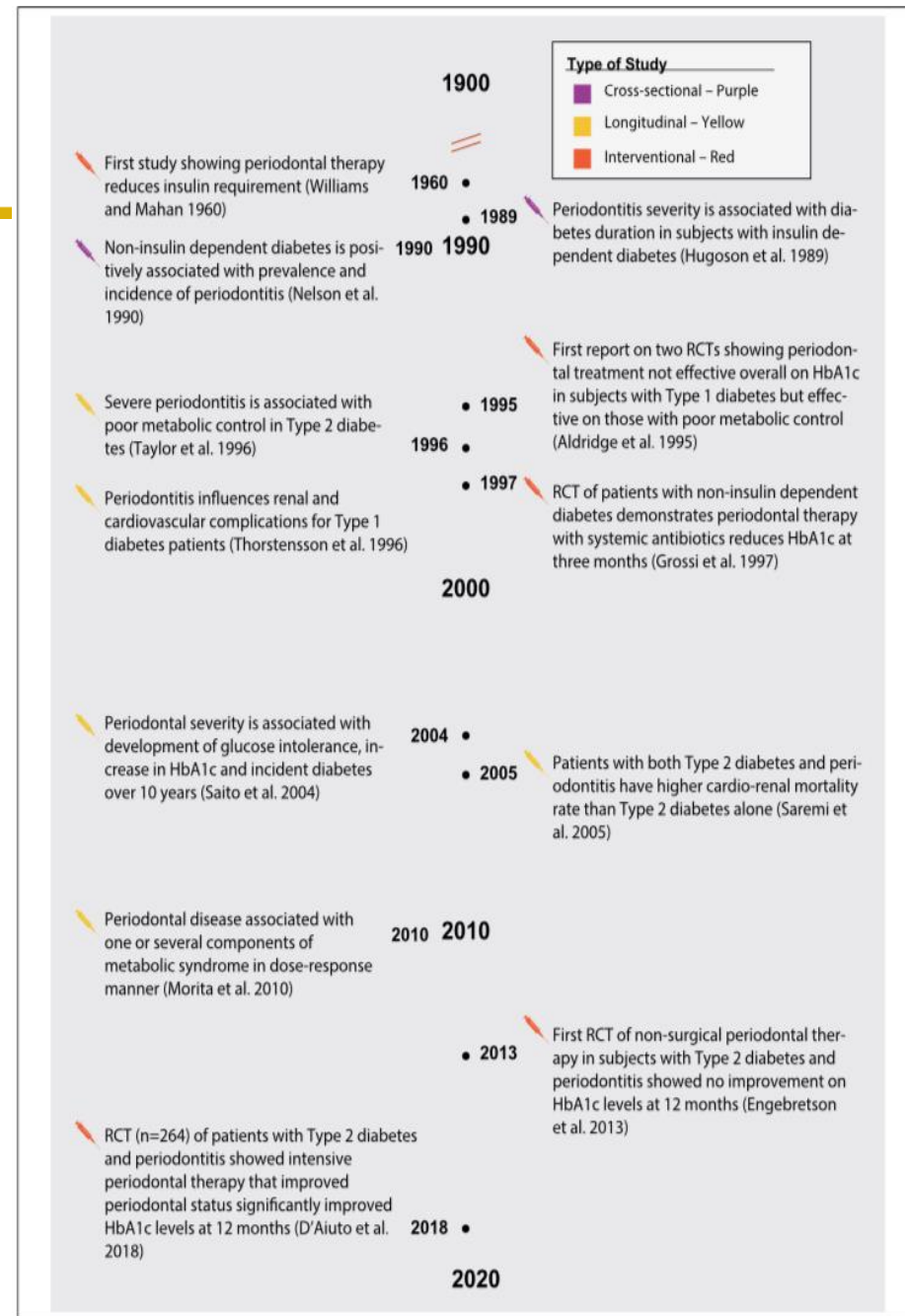


Figure 3. Periodontal medicine timeline for diabetes mellitus studies. Timeline overview from 1900 to 2020 showing 12 milestone studies for periodontal medicine and diabetes mellitus, organized by type of study with descriptors. HbA1c, hemoglobin A1c or glycosylated hemoglobin; RCT, randomized controlled trial.

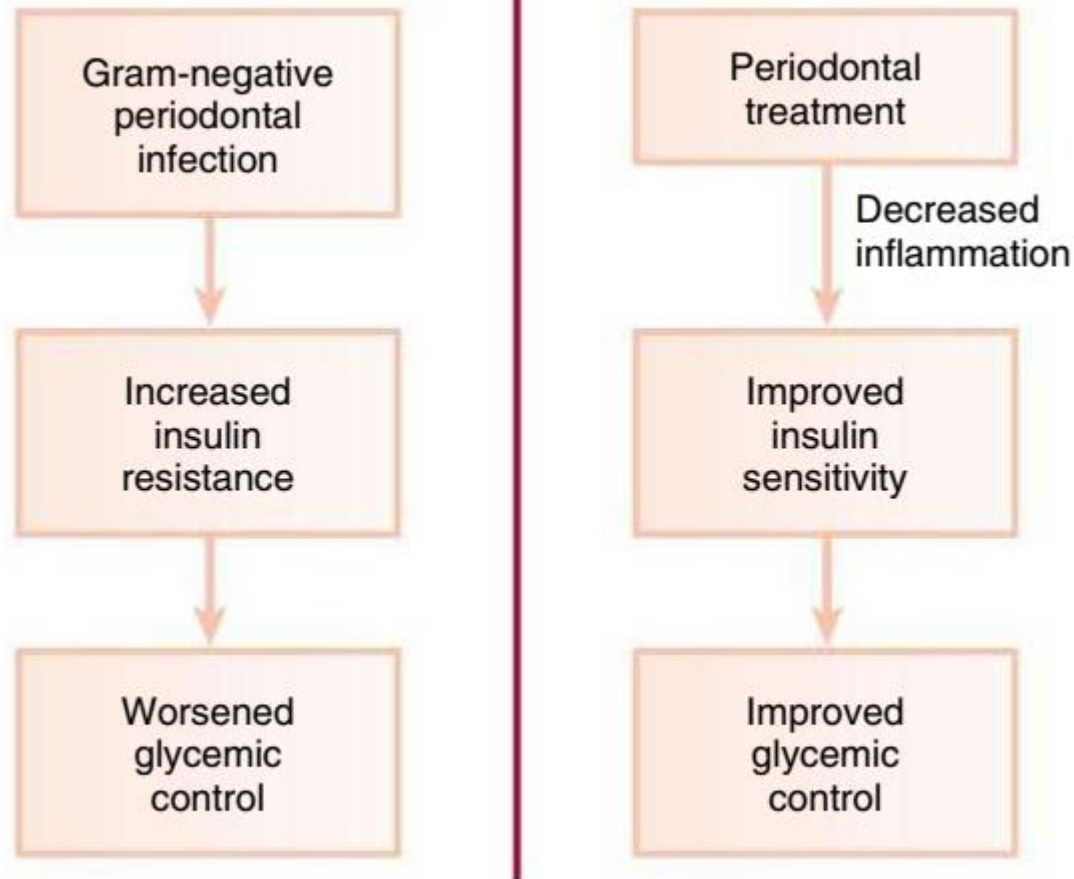
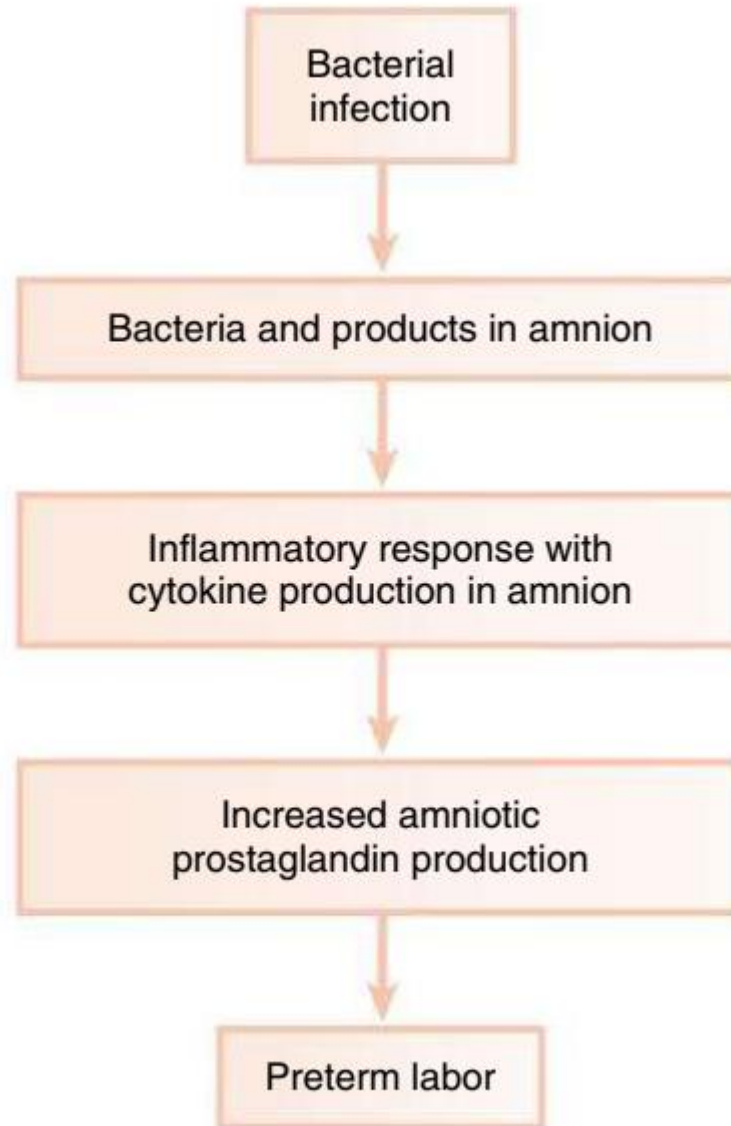


Fig. 26.8 Potential effects of periodontal infection and periodontal therapy on glycemia in patients with diabetes.



eFig. 26.1 Mechanisms by which infection may induce preterm labor.



► Pan Afr Med J. 2013 Jul 10;15:92. doi: [10.11604/pamj.2013.15.92.2326](https://doi.org/10.11604/pamj.2013.15.92.2326) [↗](#)

Estimate of CRP and TNF-alpha level before and after periodontal therapy in cardiovascular disease patients

[Pradeep Koppolu](#)^{1,&}, [Satyanarayana Durvasula](#)², [Rajababu Palaparthi](#)², [Mukhesh Rao](#)³, [Vidya Sagar](#)², [Sunil Kumar Reddy](#)², [Swapna Lingam](#)⁴

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PMCID: PMC3810246 PMID: [24198887](https://pubmed.ncbi.nlm.nih.gov/24198887/)

Conclusion

It can be concluded from the study that there can be a possible causal relationship between pathogenesis of periodontal disease and CVD as inferred from the statistical significant outcome in the form of decreased inflammatory biomarkers after the periodontal treatment.



► [Int J Appl Basic Med Res.](#) 2017 Apr-Jun;7(2):121–124. doi: [10.4103/2229-516X.205814](#) 

Evaluation of Serum C-reactive Protein Levels in Subjects with Aggressive and Chronic Periodontitis in Comparison with Healthy Controls: A Clinico-biochemical Study

[Vijayalakshmi Bolla](#) ^{1,✉}, [P Santha Kumari](#) ¹, [Surendra Reddy Munnangi](#) ², [D Sunil Kumar](#) ¹, [Y Durgabai](#) ¹, [Pradeep Koppolu](#) ³

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PMCID: PMC5441260 PMID: [28584744](#)

Conclusion:

The mean CRP levels were found to be greater in CP compared to GAP subjects, but there was no statistically significant difference.

CASE SCENARIO 26.1

Patient: A 38-year-old female

Chief Complaint: “I have swelling and pain in my gums.”

Background Information

Patient is a nonsmoker with poorly controlled diabetes mellitus (HbA1c = 8.4). Patient is overweight. She indicates brushing one to two times per day but does not floss. She reports infrequent dental visits. Her last professional dental cleaning was at least 3 years ago.

Current Findings: Probing depths were generally in the range of 2 to 4 mm with localized 5 to 7 mm, BOP was 43%.



CASE-BASED QUESTIONS

1. Does the patient's diabetes pose an increased risk for periodontitis?
 - A. Yes
 - B. No
2. This patient requires nonsurgical periodontal therapy. Could periodontal therapy improve glycemic control?
 - A. Yes
 - B. No
3. Which of the following are complications of diabetes mellitus?
 - A. Retinopathy
 - B. Nephropathy
 - C. Periodontal disease
 - D. All of the above
 - E. A and B

SOLUTION AND EXPLANATION

Answer: A

Explanation: There is increased prevalence of periodontitis in patients with diabetes mellitus, especially if poorly controlled.

Answer: A

Explanation: Although there are conflicting results from different studies, numerous systematic reviews and meta-analyses have consistently shown that periodontal therapy is associated with statistically significant and clinically relevant improvement in glycemic control in patients with diabetes and periodontitis.

Answer: D

Explanation: Complications of diabetes mellitus include **retinopathy**, **nephropathy**, neuropathy, macrovascular disease, altered wound healing, and periodontal disease.

CASE SCENARIO 26.2

Patient: A 49-year-old African-American female.

Chief Complaint: “I am feeling discomfort in my gums. They bleed a lot when I brush, and they are always sore.”

Background Information

Patient is a smoker with controlled hypertension and uncontrolled type 2 diabetes mellitus with an HbA1c of 9.8. She is currently taking metoprolol and metformin to treat these inflammatory diseases. She reports brushing twice daily but often skips flossing or other dental aids because it hurts her gums.

Clinical Findings: Generalized probing depths ranging from 2 to 7 mm. **Bleeding on probing** was 52% and patient exhibits poor oral hygiene (biofilm control). Gingival tissues are erythematous, edematous, and tender.

CASE-BASED QUESTIONS

- Which of the following diseases have been linked to (adversely affected by) periodontal disease?
 - Coronary heart disease
 - Diabetes
 - Myocardial infarction
 - All of the above
- Periodontal disease is one of the six complications of diabetes mellitus.
 - True
 - False
- Periodontal therapy has a beneficial effect on glycemic control.
 - True
 - False

SOLUTION AND EXPLANATION

Answer: D

Explanation: Periodontal disease has been associated with each of these disease processes. However, causal studies still need to be performed. It is difficult because these disease processes share many of the same risk factors. Thus, the association may be among the risk factors rather than the diseases themselves.

Answer: A

Explanation: Yes, along with retinopathy, nephropathy, neuropathy, macrovascular disease, and altered wound healing, periodontal disease is officially recognized by the American Diabetes Association as a common complication among patients with poorly controlled diabetes mellitus.

Answer: A

Explanation: This may be true for patients with poor glycemic control and more advanced periodontal destruction. Patients who improved periodontal health with treatment also experienced improvements in glycemic control.

Thank you!!!



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