#### **Health Strategies In Europe**

Lisbon, 12-13 July 2007

The Impact of Periodontal Health on General Health: Evidence of Association with Heart Diseases, Diabetes & Premature Birth



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## Periodontitis – Systemic Challenge

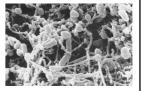
- **V** Pathogenesis of Periodontal Disease:
  - ü Intra-oral to Extra-oral pathways
- v Periodontal Disease as a Systemic Stressor:
  - ü Infectious
  - ü Inflammatory
- **V** Periodontal disease and systemic health:
  - ü Cardiovascular disease
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- v Conclusions & Implications for Health Care

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## **Periodontal Disease**

Chronic inflammatory disorder caused by bacterial plaque biofilm



# **Unique Features of Periodontal Infections**

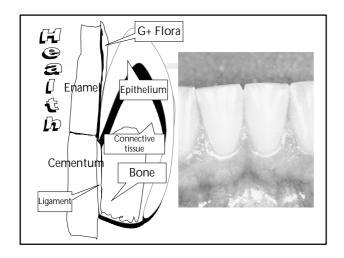
The tooth: mineralized structure, passing through the integument

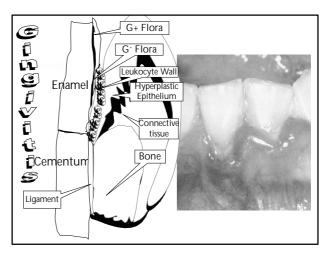
- v Non-shedding, stable surface:
  - facilitates bacterial colonization
- Bacterial location mainly outside the body:
   less accessible by host defense mechanisms
- v Exceptional bacterial complexity

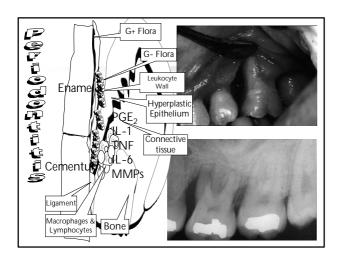
## The complexity of periodontal infections

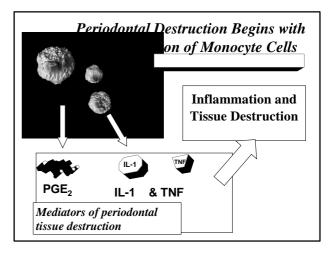


- v 400 500 different species are capable of colonizing the oral cavity
- v 150 species per mouth
- v 30 100 species in a single periodontal site
- v Healthy sulcus: 10<sup>3</sup>-10<sup>4</sup> bacteria
- v Deep periodontal pocket: 10<sup>8</sup>-10<sup>9</sup> bacteria









# Periodontitis - Systemic Health

# How is it Possible?

## Periodontal Disease & Systemic Health

- Association of tooth extraction to arthritis cure (Hippocrates 400 B.C.)
- V Oral sepsis: causal factor for systemic diseases (Miller 1890, Hunter 1900)
- V Theory of "focal infections": Extraction of teeth to prevent systemic diseases (Billings 1911)
- Rejection of "focal infection" theory (Editorial, *JAMA* 1952)
- Association of heart attacks to oral infections (Mattila et al, 1989, *BMJ*)

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Does the Periodontal Pocket Act as a Portal for Bacterial Entrance into the Circulation?

# Does the Periodontal Pocket Act as a Portal for Bacterial Entrance into the Circulation?

- v Total periodontal surface area = 70 76 cm<sup>2</sup>

  Gher & Vermino 1980, JAMA

  Klock et al, 1993, J Clin Periodontol
- V Dental Surgical manipulation has been linked to infective endocarditis in susceptible individuals

# Does Periodontitis Result in Repeated Episodes of Bacteraemia?

In a total of 2403 patients after dental extractions 937 had a positive blood culture

This rate of 40% was not significantly different from the 38% of positive cultures found after chewing!

Guntheroth WG 1984, Am J Cardiol

Procedure	Incidence of bacteraemia (%
Extractions	
single	51
multiple	68–100
Periodontal surgery	
flap procedure	36–88
gingivectomy	83
Scaling and root planing	8–80
Toothbrushing	24–26
Dental flossing	20–58
Interproximal cleaning toot	hpicks 20-40
Chewing	17–51
	Roberts GJ 1999, Pediatr Cardio

## Incidence of Bacteraemia after Periodontal Procedures

Analysed by PCR:

toothbrushing 13.3% periodontal probing 10.8% cavitron scaling 20.0%

Kinane et al, 2005, J Clin Periodontol

#### **Incidence of Bacteremia**

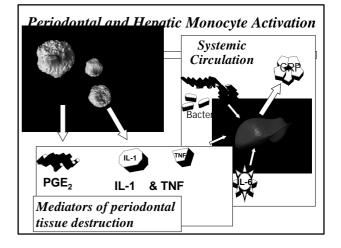
	Chewing	Brushing	Scaling
Periodontitis	20%	10%	<b>75%</b>
Gingivitis	0%	0%	20%
Healthy controls	0%	0%	10%

Forner et al, 2006 J Clin Periodontol

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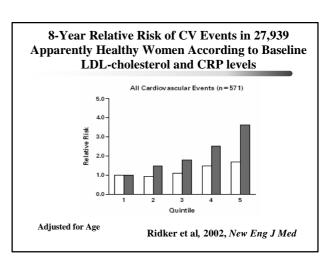
Does Periodontal Disease Contribute to an elevated Systemic Inflammatory Status?



# Systemic Inflammation and Heart Disease

v In 1,043 apparently healthy men, it was found that baseline plasma concentrations (in the high normal range) of C-reactive protein predicts the risk of future MI and stroke.

Ridker et al, 1997, New Eng J Med



## **Periodontitis and Acute Phase Proteins**

v Adult periodontitis patients had higher levels of C-reactive protein (CRP) and haptoglobin(Hp) than normal subjects

Ebersole et al. 1997, Clin Ex Immunol

## NHANES III: CRP levels according to Percent of Sites with PD 4+ mm in Persons Aged 18+ Years

% of Sites with PD 4+ mm	N	Age- standardized Mean CRP (μg/dl)	
0%	9145	0.29 (0.01)	
1-9%	2253	0.31 (0.02)	
10+ %	1550	0.41 (0.04)*	
All Persons	12948	0.30 (0.01)	

\* P<0.01

Slade et al, 2000, J Dent Res

## Case-Control studies on CRP and Periodontitis

Study	N	CRP		P value
		m	g/l	
Ebersole et al 1997	P:40	9.12	1.61	P < 0.001
	C:35	2.17	0.41	
Fredriksson et al	P:17	2.62	2.90	P = 0.04
1998	C:17	0.87	1.73	
Fredriksson et al	P:37	2.	0*	P = 0.012
1999	C:38	0.	0*	
Loos et al 2000	P:107	2.64	3.48	P = 0.017
	C:43	1.21	1.34	
Noack et al 2001	P:50	4.06	5.55	P = 0.011
	C:65	1.70	1.91	

## Case-Control studies on IL-6 and Periodontitis

Study	N	IL-6 pg/ml	P value
Loos et al 2000	P: 28 C: 11	0.46 0.20	P = 0.015
Buhlin et al 2003	P:50 C:46	3.66 9.74 1.57 2.10	P < 0.05
Yamazaki et al 2004	P: 24 C: 21	0.70 (pg/ml)* 0.56 (pg/ml)*	P = ns

\*median value

# Case-Control studies on Fibrinogen and Periodontitis

Study	N	Fibrinogen g/l	P value
Kweider et al 1993	P:50 C:50	3.00 0.59 2.32 0.44	P < 0.001
Sahingur et al 2003	P: 79 C: 75	2.50 0.10 2.25 0.12	P = 0.004
Bizzaro et al 2005	P: 91 C: 39	3.26 0.68 2.90 0.63	P = 0.158

\*median value

Effect of Periodontal Therapy on CRP & IL-6						
Study	N	Therapy	△ -CRP	P-value	-IL-6	P-value
			mg/l		ng/l	
D'Aiuto et	T <sub>1</sub> = 20	T <sub>1</sub> = SRP	+0.3 (6m)	P = ns	-0.5	P = ns
al 2006	$\mathbf{T}_2 = 20$	T <sub>2</sub> = SRP+ local AB	-0.7 (6m)	P < 0.05	-0.5	P < 0.05
Yamazaki et al 2005	T = 24	SRP + Surg+AB	-0.056	P = 0.087	-0.01	P = ns
D'Aiuto et al 2004	T = 94	SRP	-0.1 (2m) -0.5 (6m)	P = ns P < 0.001	-0.18 -0.22	P = 0.02 P < 0.01
Pussinen et al 2004	T = 30	SRP + metronid	+0.15	P = 0.308		
Iwamoto et al 2003	T = 15	SRP + local AB	-0.734	P < 0.01		
Mattila et al 2002	T = 30	SRP	-0.34	P = 0.05		

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# Periodontal Disease & Cardiovascular Disease

- **V** Epidemiological Studies
- **V** Role of Periodontal Pathogens
- **V** Experimental Studies
- **V** Clinical Intervention Studies

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## **Initial Epidemiological Studies**

- V Case-control study of 100 hospital patients with AMI and 102 community controls in Helsinki (Mattila KJ et al. *BMJ* 1989)
  - Clinical and radiographic dental index of caries, periodontitis, periapical lesions and pericoronitis
  - v 10 traditional risk factors for CHD assessed
  - v Higher dental index significantly increased odds of AMI after controlling for traditional risk factors (odds ratio=1.2 per unit increase in index, P=0.004)

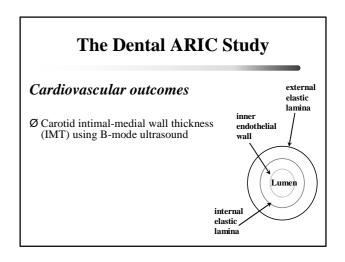
## Summary of Associations: Case-Control Studies

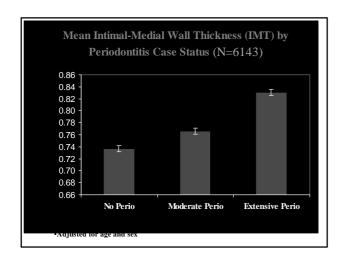
- v 18 published studies
- Associations between oral disease and CVD were adjusted for multiple known risk factors for CVD
- v people with periodontal disease are more likely to have heart disease than people without periodontal disease (14/18)

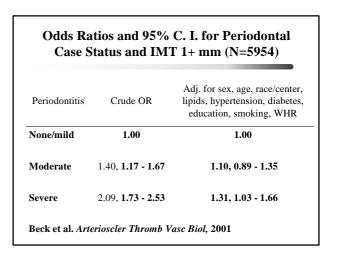
# Associations Between Oral Conditions and Atherosclerosis/CHD in 5 Longitudinal Studies

Study	Exposure	Outcome	Risk
De Stefano et al 1993/USA/14yrs	Periodontal Index	Admits/death CHD (men < age 50)	20% Excess 70% Excess
Mattila et al 1995/Finland/7yrs	Total Dental Index	New MI or death	20% Excess
Joshipura et al 1996/USA/ 6 yrs	Tooth loss in men with Perio	New CHD	70% Excess
Beck et al 1996/USA/18yrs	Bone level	New CHD Fatal CHD Stroke	50% Excess 90% Excess 180% Excess
Jansson et al 2001/Sweden/26 yrs	Bone level	Fatal CHD	100% Excess

#### **Associations Between Oral Conditions and** Atherosclerosis/CHD in 5 Longitudinal Studies Study Adjusted For Smoking, hypertension, age, sex, triglycerides, Mattila et al social class, diabetes, serum lipids, BMI, 1995/ Finland previous myocardial infarctions. Age, sex, race, education, poverty, marital state, De Stefano et al SBP, cholesterol, diabetes, BMI, physical activity, 1993/ USA alcohol and smoking Joshipura et al Age, BMI, exercise, smoking, alcohol, vit. E, 1996/ USA family hx. MI before age 60 Beck et al Age, BMI, Cholesterol, smoking, diabetes, blood 1996/ USA pressure, family hx., education Jansson et al Age, Gender, smoking, previous CVD 2001/ Sweden



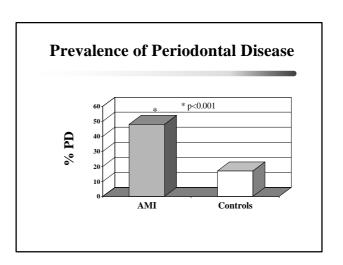


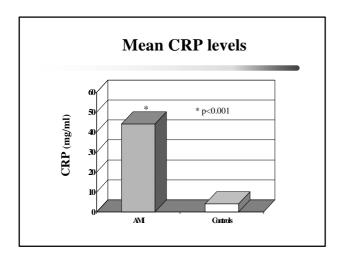


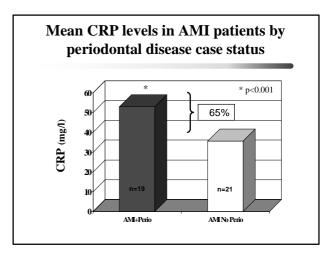
# **Periodontal Disease in Acute Myocardial Infarction Patients**

- Higher CRP levels in patients with a recent heart attack (AMI) are associated with future events
- We investigated whether the presence of periodontal disease was associated with an elevated inflammatory response in 40 AMI patients and 40 community volunteers

Deliargyris, Madianos, et al, 2005 Am Heart J



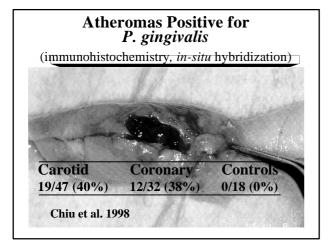




# Periodontal Disease & Cardiovascular Disease

- **V** Epidemiological Studies
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Do Periodontal Pathogens
Disseminate Systemically & Localize
in Distant Sites/Organs?



## Periodontal Pathogens in Carotid Endarterectomy Specimens

(PCR, Southern hybridization with oligo-probes)

 P. gingivalis
 13/50
 26%

 B. forsythus
 15/50
 30%

 P. intermedia
 7/50
 14%

 A. actinom.
 9/50
 18%

44% positive for at least one periodontal pathogen

Haraszthy et al, 2000, J Periodontol

# Viable Periodontal Pathogens in Atheromas

Cell Culture Invasion assay & Fluorescent Microscopy







ECV-304 cells Infected with A.a.

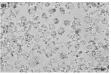
Kozarov et al, 2005, Arterioscler Thromb Vasc Biol

## New Virulence Properties for Oral Bacteria

#### Atherogenic

P. gingivalis promotes foam cell formation





Mingshan et al, 2003, Microbiol Pathog Lala et al, 2004, FEMS Microbiol Letters

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# Atheroma formation in the aortas, 6 weeks after *P. gingivalis* oral challenge of ApoE-/- Mice

Unchallenged



Invasive

Non-Invasive





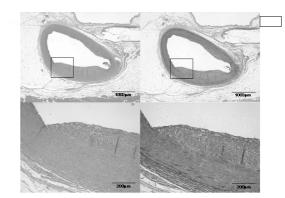
Gibson et al. 2004, Circulation

## Porcine Model of Recurrent Bacteremia

#### Aim

To determine whether recurrent, low-dose intravenous (i.v.) challenges with *P. gingivalis* mimicking periodontitis-associated bacteremia promotes atherogenesis in pigs

## Coronary artery atherosclerosis in challenged pigs



# Periodontal Disease & Cardiovascular Disease

- **V** Epidemiological Studies
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# Periodontal Therapy, Endothelial Function & Systemic Inflammation 22 pts with severe PD, no known CAD Baseline 4 weeks 9 weeks Control PD Treatment CRP, IL-6, CRP, IL-6, FMD Elter et al, 2006, Am Heart J

## Vascular reactivity, CRP & IL-6 Before & After Periodontal Therapy (N=22)

Visit	FMD (%)	IL-6 (pg/ml)	CRP (mg/ml)	
Baseline	8.6 (4.7)	1.7 (1.5)	2.4 (3.3)	
Post-treatment	10.2 (3.9)	1.1 (1.3)	1.4 (2.8)	
		Elter et al, 2006, Am Heart J		

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# Categories of Pregnancy Outcomes: Definitions

- v Low Birth Weight (PLBW): <2500 g
- v Preterm Birth (PB): <37 weeks
- v Very Low Birth Weight (VLBW): <1500g (usually <32 weeks)

## **Importance of PLBW**

- v Last decades decline in infant mortality, but not in PLBW births
- V Overall 10% PLBW incidence rate in the U.S. annually: 250,000 LBW (<2500g) 40,000 VLBW (<1500g)
- v PLBW infants:
  - Ø7x more likely to die prior to 1st birthday
  - Øat increased risk for: neuro-developmental, respiratory disorders, learning disabilities, delayed development

## **Importance of PLBW**

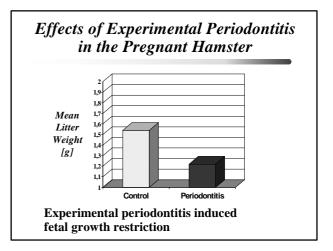
- v Significant disparities by race and ethnicity
- v Prenatal care intervention strategies over last 40 years have failed to diminish PLBW rate
- v USA NICU costs in excess of 5.5 billion dollars a year as consequence of preterm births

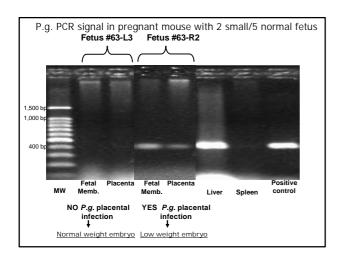
## Known Risk Factors for PLBW

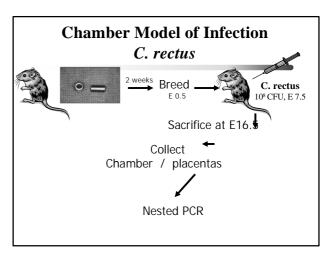
- v Maternal age
- v Drug, alcohol and tobacco usage
- v Genitourinary tract infection, bacterial vaginitis
- v 25-50% occur without any known etiology

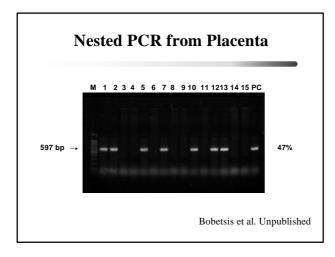
Evidence on the Potential of Periodontal Disease to Affect Pregnancy Outcome

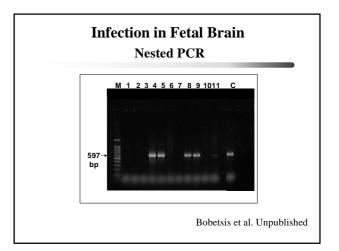
**Experimental Studies** 











## Evidence on the Potential of Periodontal Disease to Affect Pregnancy Outcome

## **Human Studies**

## **Case-control studies**

- v 17 published studies
- v 12 studies show that mothers with preterm and/or low birth weight delivery have significantly worse periodontal condition in comparison to mothers with a normal delivery

## **European Case-Control Studies**

- v 8 published studies
- v UK: Davenport et al. 2002, Moore et al. 2005
- v Hungary: Radnai et al. 2004, 2006
- v Germany: Noack et al. 2005
- v Turkey: Canakci et al. 2004, Buduneli et al. 2005
- v Croatia: Bosnjak et al. 2006
- v 4 of 8 studies found no association between periodontal disease and adverse pregnancy outcome. Three studies found significant association with PTB and one with preeclampsia

# Do maternal periodontal bacteria reach the fetus?

#### Aim:

v To investigate the presence of fetal IgM in cord blood directed against periodontal organisms, as direct evidence of fetal exposure *in utero* to these organisms or their products.

Madianos et al, 2001, Annals Periodontol

#### Prevalence of Fetal IgM responses against periodontal organisms among 271 Term & 80 Preterm Neonates

<u>Organism</u>	<u>Term</u>	Preterm	
	(n=271)	(n=80)	
C. rectus	6.3	20.0	P=0.0002
F. nucleatum	2.2	7.5	P=0.02
P. micros	1.1	8.8	NS
P. nigrescens	1.5	6.3	0.018
P. intermedia	1.1	8.8	0.0003
P. gingivalis	16.2	16.3	NS
B. forsythus	10.7	20.0	P=0.03
T. denticola	8.1	17.5	P=0.015

Madianos et al, 2001, Annals Periodontol

## **Cohort Studies**

- v 9 published studies
- 6 studies show that mothers with periodontal disease have an increased risk to deliver a preterm and/or low birth weight baby

## **European Cohort Studies**

- v 3 published studies
- v UK: Moore et al. 2004
- v Iceland: Holbrook et al. 2004
- v Austria: Dortbudak et al. 2005
- v 2 of 3 studies found no association between periodontal disease and adverse pregnancy outcome. One study found an increased host response in the chorioamnion leading to PTB

# Effect of Periodontal Therapy on Rate of Prematurity

- v 850 pregnant women ≤20 weeks
- v 400 women with periodontal disease (≥4 teeth with 1 or more sites with PD≥4mm and ≥3mm attachment loss)
- Random assignment to 2 groups;
   periodontal scaling & root planing vs
   delayed treatment (post-partum)

Lopez et al. J Periodontol, 2002

## **Results**

	Untreated	Treated	P Value
Mean birth weight	3344(598)	3501 (429)	0.0047
Incident GA<37*	10.1%(19/188)	1.8%(3/163)	0.001

\*Univariate RR = 5.49, 95%CI = 1.65-18.22

Lopez et al. J Periodontol, 2002

# Multivariate logistic regression model of prematurity

Variable	Relative Risk	95% CI	P Value
No periodontal Tx	4.70	1.29-17.1	0.018
Previous GA < 37	3.98	1.11-14.2	0.033
Low # Prenatal visits	3.70	1.46-9.38	0.005
Mother underweight			
	3.42	1.16-10.0	0.024

Also controlled for age, parity, smoking, vaginosis,

## **Effect of Periodontal Therapy on Rate of Prematurity**

- v 366 pregnant women ≤25 weeks with periodontal disease (>4 sites with attachment loss > 3mm)
- v Randomization
  - ØControl group (prophylaxis + placebo)
  - ØTherapy group 1 (scaling and root planing + placebo)
  - ØTherapy group 2 (scaling and root planing + Metronidazole 250 mg, TID)

Jeffcoat et al. J Periodontol 2003

#### **Results**

Therapy 1 Therapy 2 Reference Prematurity Control (<35 εβδ.) 4,9% (6/123) 0,8% (1/123) 3,3% (4/120) 6,3% (45/723)

Risk Ratio = 5,00 95% CI = 0,71 - 50,0

Jeffcoat et al. J Periodontol 2003

## Pregnancy-gingivitis: Effect of Periodontal Therapy on Rate of Prematurity

- 870 pregnant women with gingivitis <20
- v Random assignment to 2 groups
- v 580 received periodontal therapy (scaling + daily 0.12% clorhexidine rinsing)
- 290 received periodontal therapy postpartum

Lopez et al. J Periodontol, 2005

#### **Results**

Untreated Treated P Value Incident  $PT/LBW\!<\!37^{\star}$ 6.71% (19/283) 2.14%(12/560) 0.009

OR = 3.26, 95%CI = 1.56 - 6.83

Multivariate OR = 2.76, 95%CI= 1.29 - 5.88

Lopez et al. J Periodontol, 2005

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#### **Diabetes melitus**

- v Type I
- v Type II
- v Other specific types:

-Genetic defects of β-cell function -Genetic defects in insulin function -Diseases of the exocrine pancreas -Endocrinopathies -Drug or chemical induced -Genetic syndromes -Immune mediated -infection

v Gestational diabetes

American Diabetes Association (ADA) 2006

## Type II diabetes melitus

- V 5η cause of death in the USA ADA 2003
- $\vee$  12.1 mill. diabetics in the USA ADA 2003
- $\vee$  90-95% of total diabetics in the USA  $_{\rm A.D.A~2006}$

#### P.D. and D.M II association

- ∨ Periodontal disease is the 6<sup>th</sup> complication of diabetes melitus. Löe 1993
- ∨ Strong corellation between P.D. and D.M. Finestone 1967, Collin 1998, Grossi 1998
- ∨ Increased incidence of D.M. in patients with P.D. (12,5% vs. 6,3%) Soskolne 2001

#### P.D. and D.M II association

- v 2,8 times increased risk for periodontal disease regardless of age and plaque accumulation Emrich 1993
- v 2,32 fold risk for further CAL for patients with DM II Grossi 1994

#### P.D. and D.M II association

- ∨ Correlation between P.D. severity and glycemic control Taylor 2001, Tsai 2002
- V Increased PPD and CAL in poorly controlled diabetics Tervonen 1993, Novaes 1996, Collin 1998
- v Exaggerated collagenase activity in poorly controlled diabetics Iacopino 1985, Cutler 1999

#### P.D. and D.M II association

Periodontal disease and mortality in type 2 diabetes

Prospective longitudinal study of 628 subjects (Pima Indians) with 11year followup

Saremi, Nelson, Reid, Hanson, Sievers, Taylor, Shlossman, Bennet, Genco, Knowler 2005

	Pe	riodontal disease	
	No or mild	moderate	severe
HbA1C	7,5 ± 2,4	8,1 ± 4,6	$8,9 \pm 2,5$

Patients with sever periodontal disease had 3,2 times the risk of cardiorenal mortality (ischemic heart disease and diabetic nephropathy combined) compared with the reference group (no or mild and moderate periodontal disease)

#### P.D. and D.M II association

Is it a two-way Relationship?

## P.D. and D.M II association

inflamed periodontal tissue seems to act like a reservoir or an "endocrine gland" producing of inflammation like TNF-α and IL-1, which in turn interfere with lipid metabolism and contribute to tissue resistance to insulin

Grossi & Genco 1998

## P.D. and D.M II association

Patients with D.M. and severe P.D. exhibit more complications resulting from D.M. than subjects with mild or moderate or no periodontal disease

Thorstensson 1996

#### P.D. and D.M II association

patients with D.M. and severe P.D have a 6-times higher probability to present with difficulty achieving glycemic control than patients with no or mild or moderate P.D.

Taylor 1996

	TYPE OF STUDY	TYP E OF D.M.	NUMBER OF PATIENTS	TYPE OF PERIODONTAL THERAPY	PERIODONTAL PARAMETERS MEASURED	GLYCEMIC CONTROL	HbA1C RESULTS
GROSSI 1997	RCT 6 MONTHS	11	113	ULTRASONIC, CHX, P.I., DOX SYST. DOX	PPD CAL	HbA1c	IMPROVEMEN AT 3 MTHS 11 NO DIF IN 6
GROSSI 1996	RCT 12 MONTHS	ıı	85	ULTRASONIC, CHX, P.I., SYST. DOX	PPD CAL	HbA1c	IMPROVEMEN 1% AT 3 MTH NO DIF IN 12
PROMSUDTHI 2005	RCT 3 MONTHS	ıı	52	SRP, SYST. DOX	PPD CAL BOP	ньа1С	NO DIFFERENCI
KIRAN 2005	RCT 3 MONTHS	II	44	SRP	PI, GI, PPD, CAL, BOP	HbA1c	IMPROVEMEN (0,8%)
RODRIGUES 2003	RCT 3 MONTHS	11	30	ONE STAGE SRP, AMOXYCILLIN/CLAVUL ANIC ACID	PPD, CAL, BOP	HbA1c	IMPROVEMEN
STEWART 2001	NRCT 9 MONTHS	II	72	SRP	PPD, CAL, GI	HbA1c	IMPROVEMEN
WESTFELT 1996	NRCT 5 YEARS	1&11	40	SRP, SURGICAL THERAPY	PPD, CAL. B.O.P.	HbA1c	NO DIFFERENCI
CHRISTGAU 1998	NRCT 2 MONTHS	1811	40	SRP. CHX	PPD, CAL B.O.P,. P.B.I	HbA1c	NO DIFFERENCI

## Periodontitis – Systemic Challenge

- **V** Pathogenesis of Periodontal Disease:
  - ü Intra-oral to Extra-oral pathways
- v Periodontal Disease as a Systemic Stressor:
  - ü Infectious
  - ü Inflammatory
- v Periodontal disease and systemic health:
  - ü Cardiovascular disease
  - ü Pregnancy complications
  - ü Diabetes
- **v** Conclusions & Implications for Health Care

## **Summary & Conclusions**

- v There is enough evidence to support the notion that periodontitis acts as a systemic stressor
- Periodontitis increases the incidence of transient bacteremias
- v Periodontal bacteria are capable of hematogenous dissemination
- v Dissemination appears to target major blood vessels, liver, placenta, and fetal compartments

# **Summary & Conclusions**

- v New virulence properties for plaque bacteria suggest their potential role in systemic disease
- Periodontal disease is associated with an increased systemic inflammatory response
- v Epidemiological data link periodontal disease to cardiovascular disease, prematurity and diabetes
- v Association with preterm birth is not confirmed in certain populations

# **Summary & Conclusions**

- v There is currently not enough evidence to prove causality of the observed associations
- v Intervention studies suggest that periodontal therapy may reduce systemic inflammation and the risk for prematurity, while it may improve endothelial function and glycemic control
- v Randomized controlled trials with large population size are needed in order to confirm the above

## **Implications for Health Care**

- v Periodontitis is both preventable and treatable
- v We need to educate the public, our patients and health care professionals to promote the need for good oral health as an important part of a healthy lifestyle
- Home care strategies, employing brushing, flossing and adjunctive antiseptic rinsing may be helpful in preventing local and systemic problems associated with periodontal infections

