# Periodontal Disease and Diabetes: Exploring New Paradigms

## Epidemiologic Perspectives on the Associations between Periodontal Disease, Glycemic Control and Complications of Diabetes

*Institute for Oral Health Conference*
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# *Diabetes and Oral Health*

- Periodontal diseases
- Tooth Loss
- Dental Caries
- Xerostomia
- Oral Candidiasis
- Oral Lichen Planus
- Burning Mouth Syndrome

# *Diabetes Mellitus and Periodontal Diseases*

# *Overview*

- Overview of periodontal diseases distribution
- Diabetes and periodontal health
- Inflammation, insulin resistance, and diabetes
- Periodontal infection and insulin resistance
- Periodontal infection and glycemic control
  - Observational studies
  - Treatment studies
- Periodontal disease and complications of diabetes
- Conclusions

# *Overview*

- Conceptual model for relationships between chronic inflammation, insulin resistance and diabetes
- Epidemiological evidence for inflammation associated with the occurrence of insulin resistance and diabetes
- Periodontitis and insulin resistance in the U.S. population
- Periodontitis and glycemic control in the U.S. population

# *Periodontal diseases*

- Chronic inflammatory disease
- Bacterial etiology
  - Gram negative anaerobes are prominent
- Destruction of periodontal tissues
  - Formation of pathologic pockets around teeth
  - Loss of connective tissue attachment
  - Loss of alveolar bone
- Can lead to tooth loss
- Chronic source of systemic challenge
  - Bacterial products (e.g. LPS)
  - Inflammatory mediators

## *Gingivitis*

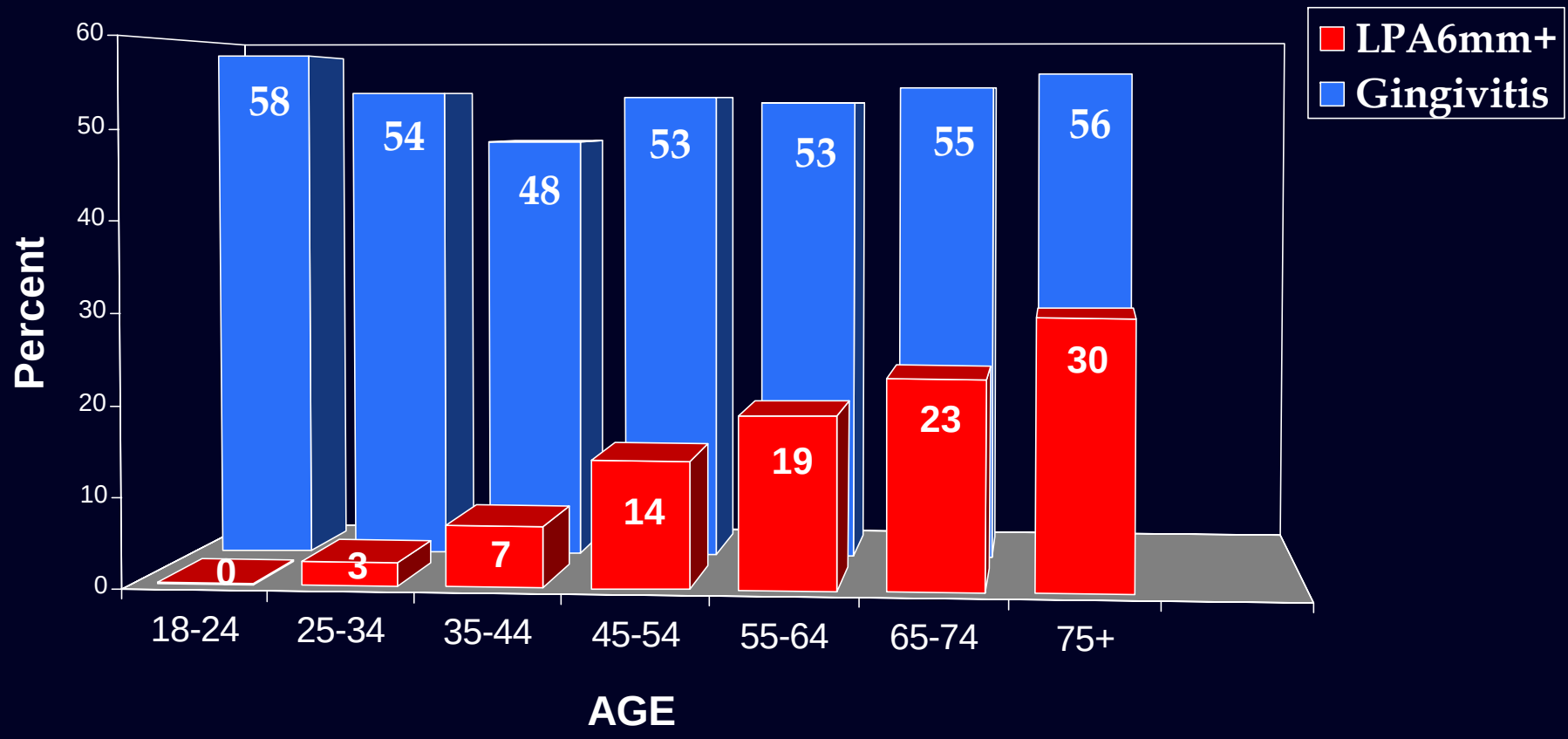
- Bacterial plaque
- Initial periodontal disease
- Inflamed gingiva
- Reversible
- Can progress if untreated

## *Periodontitis*

- Bacterial plaque
- Advanced periodontal disease
- Connective tissue loss
- Periodontal ligament loss
- Supporting bone loss

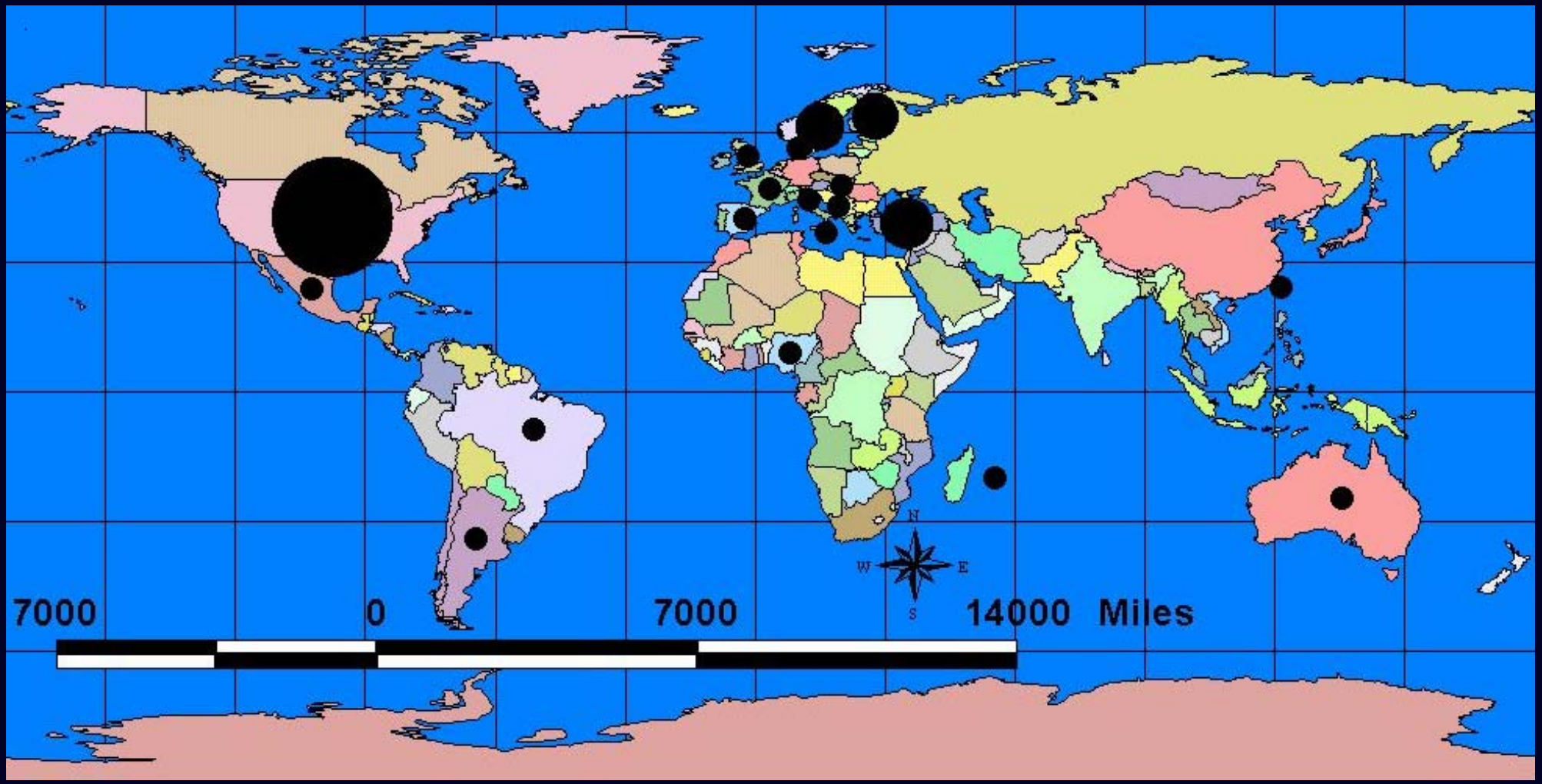
# *Periodontal Diseases in the U.S. Adult Population*

# *Gingivitis and severe periodontal disease prevalence (1+ sites with LPA 6+ mm)*




Source: NHANES 3 (1989-94), US Population

# *Diabetes and Periodontal Health*




Number of studies: smallest dot= 1 or 2; Middle sized dot= 4-5; Largest dot= 27

| Grade | Level | Type of Evidence |
|---|---|---|
| A | 1a | Systematic review (SR) of RCT's |
| | 1b | Individual RCT |
| | 1c | All or none |
| B | 2a | SR of cohort studies |
| | 2b | Individual cohort study |
| | 2c | "Outcomes" research |
| | 3a | SR of case-control studies |
| | 3b | Individual case-control study |
| C | 4 | Case series, cross sectional study |
| D | 5 | Expert opinion |

Source: Cochrane Collaboration, 1999

# *Diabetes adversely affects periodontal health: Status of the evidence, 2007*

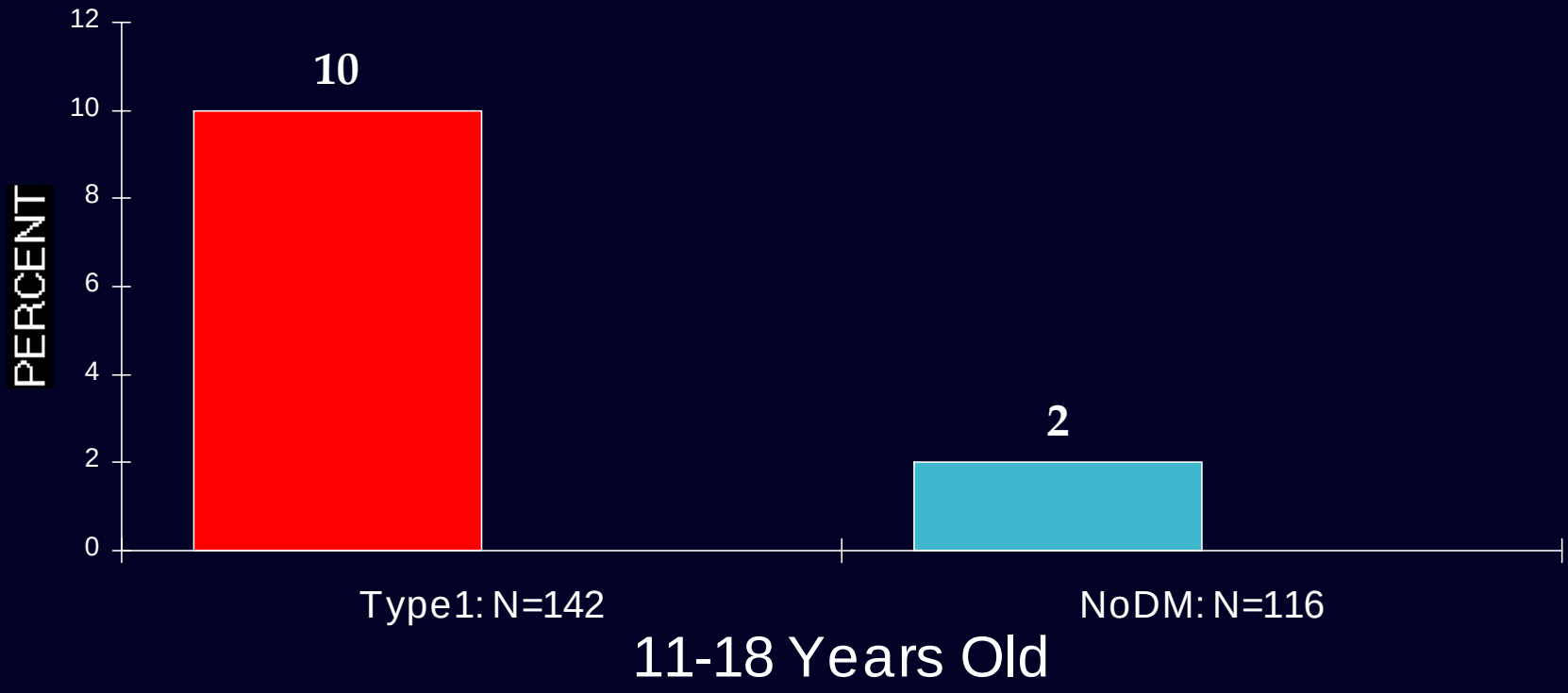
1a
1b
1c
2a
2b
2c
3a
3b
4
5

| Level of evidence | Type 1 | Type 2 | Type 1,2 | GDM | Type Unk | Total |
|---|---|---|---|---|---|---|
| 2b: cohort study | 3/3 | 5/5 | 0 | 0 | 0 | 8/8 |
| 4: x-sect, descr. | 17/18 | 7/10 | 10/13 | 2/2 | 8/9 | 44/52 |
| Total | 20/21 | 12/15 | 10/13 | 2/2 | 8/9 | 52/60 |

# Proposed explanatory mechanisms of the diabetes → periodontitis association

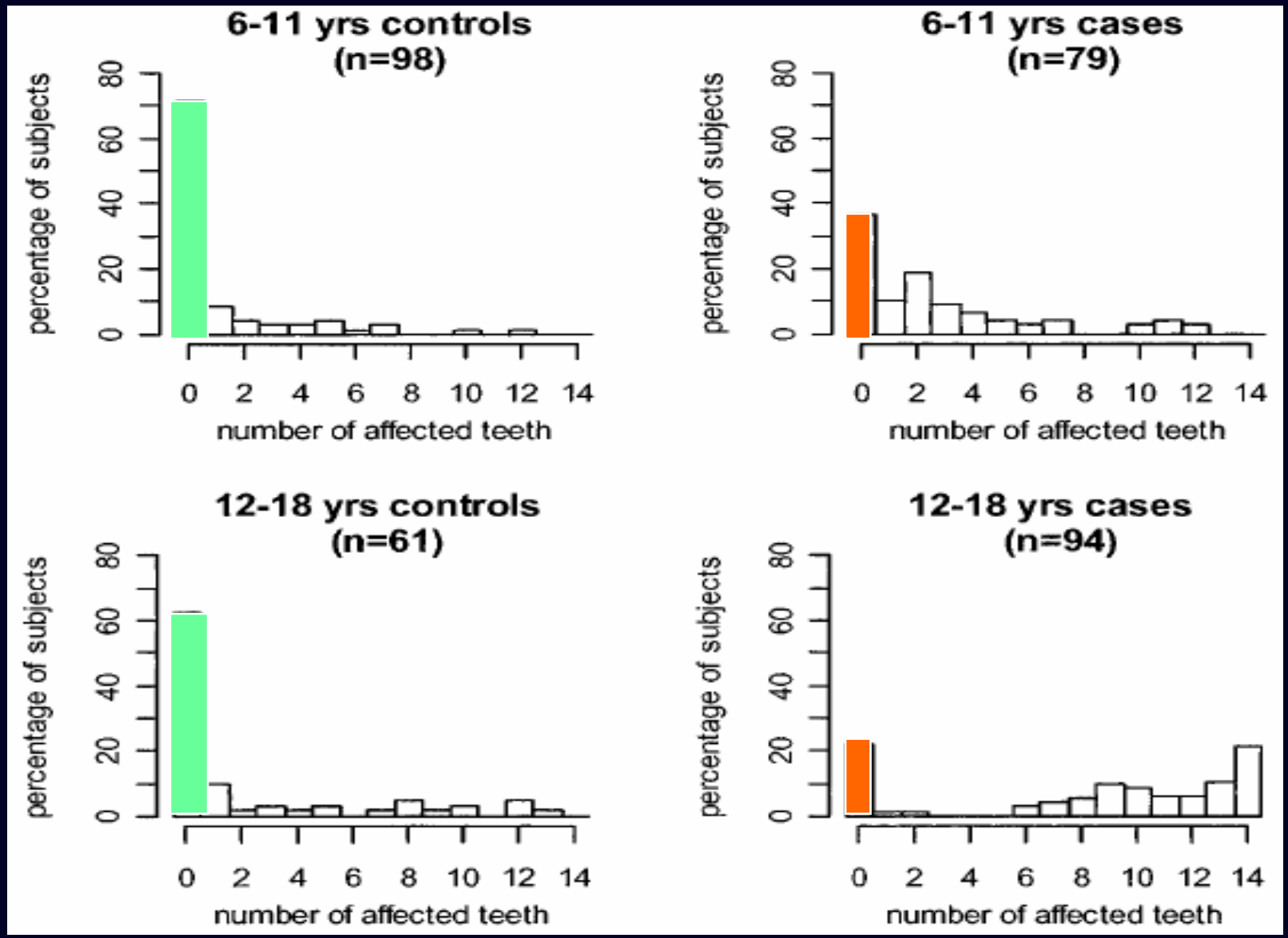
- Altered host response
- Alterations in connective tissue
- Microangiopathy
- Alterations in gingival crevicular fluid
- Altered subgingival microflora
- Hereditary predisposition

# *Prevalence of periodontal disease in children and adolescents: type 1 diabetes*

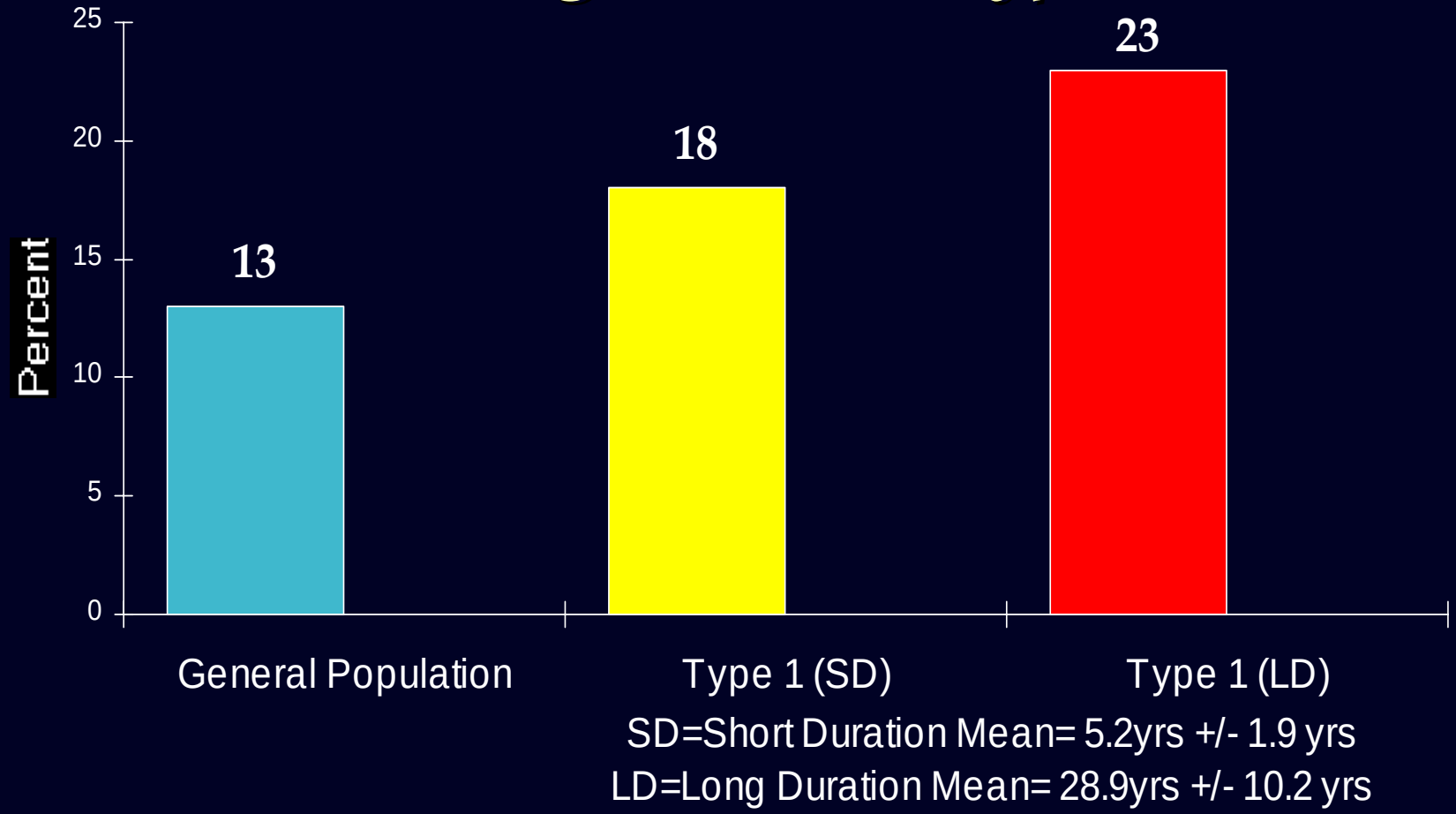



Source: Cianciola et. al., JADA, 1982.

*% Children and adolescents with 1+ sites with periodontal attachment loss ≥ 2mm. (Lalla E et al. 2006)*

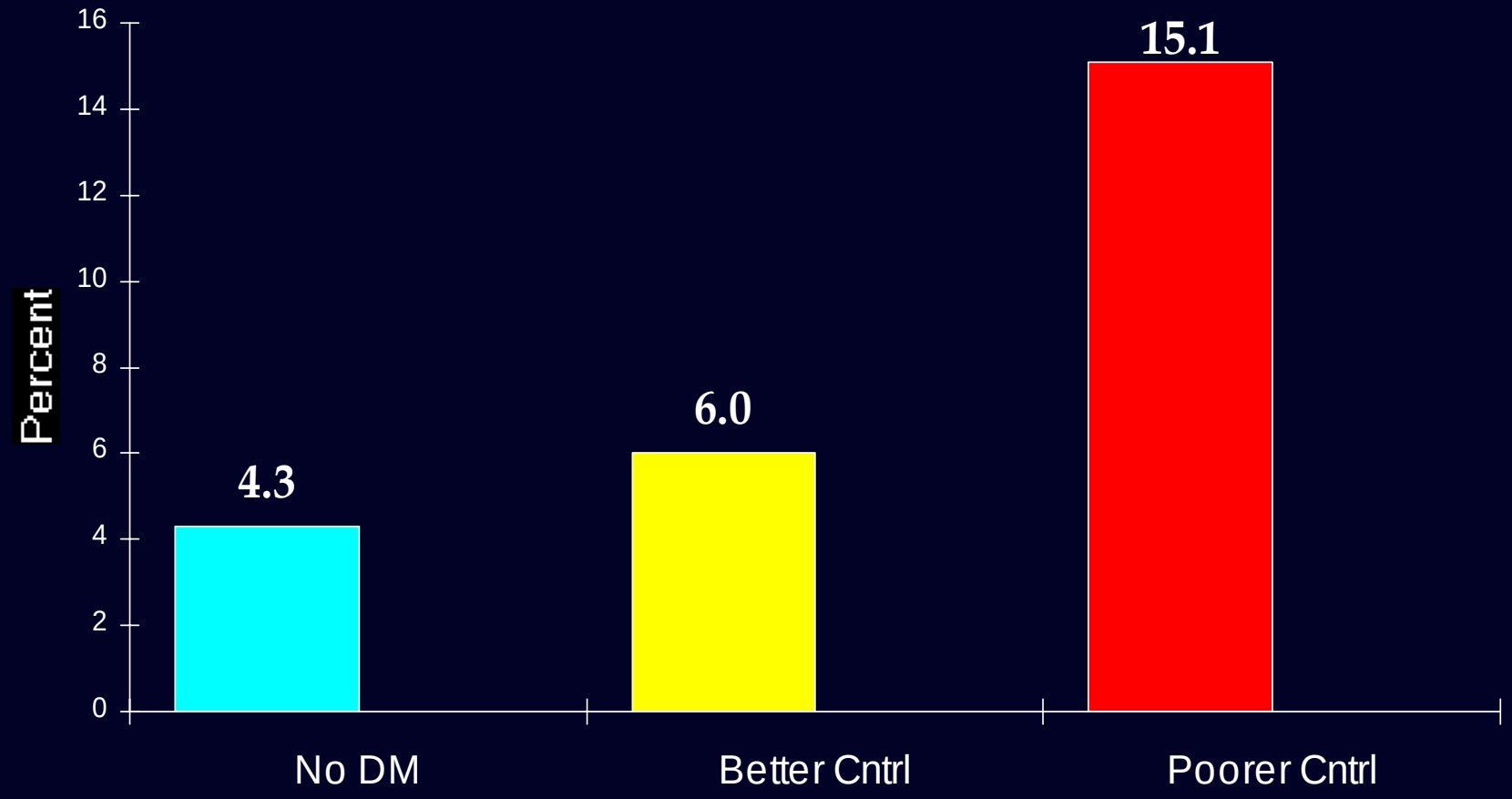


# *Severe periodontal disease prevalence: Swedish adults, ages 20-70, type 1 diabetes*



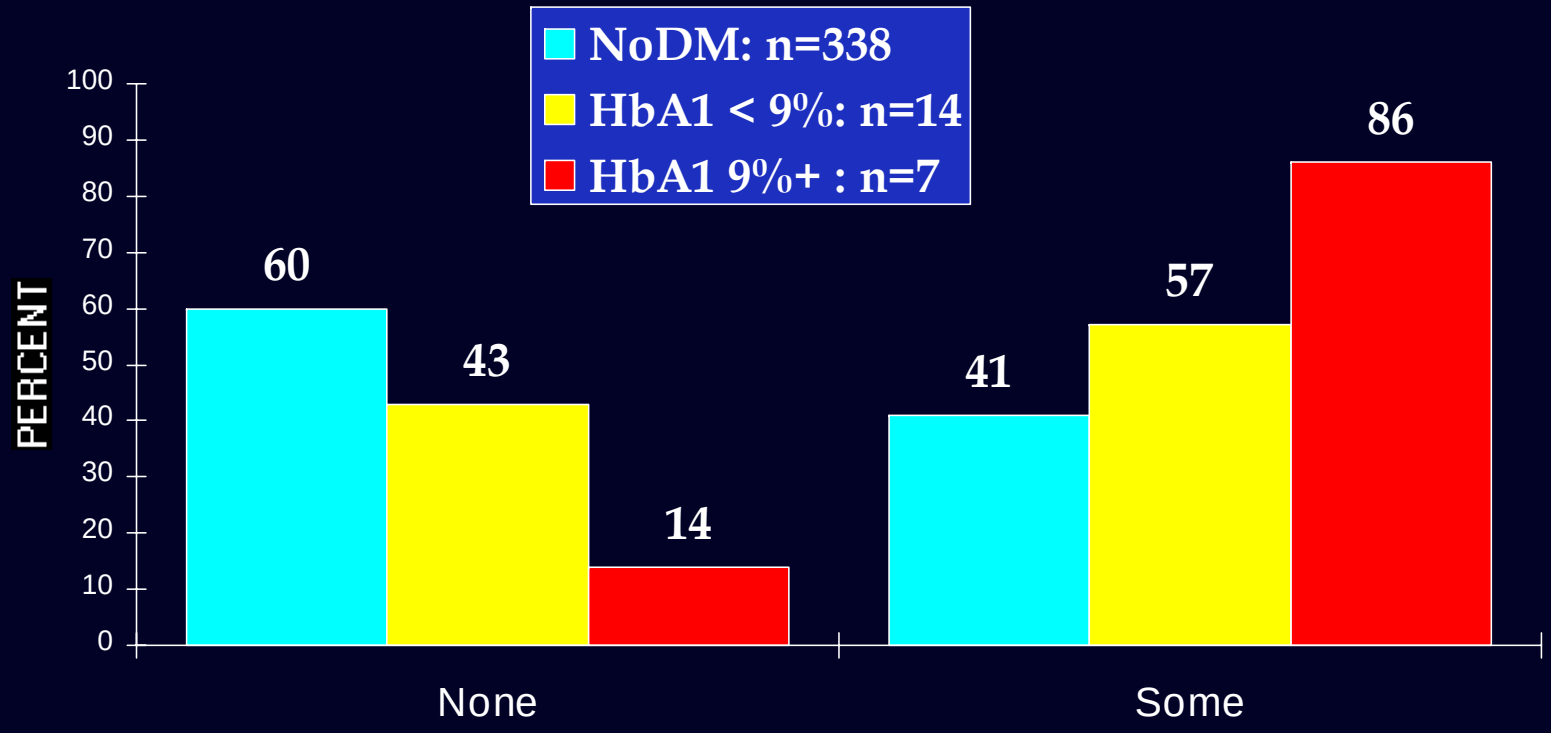

Source: Thorstensson, 1995

# *U.S adults, ages 45+, with severe, "active" periodontitis* by glycemic control status*




Source: NHANES III *1+ sites: LPA 6+ mm and gingival bleeding

# *Incidence of Alveolar Bone Loss after ~2 yrs Follow-up in the Pima Indians*




Source: Taylor et al., 1998

# *Inflammation, Insulin Resistance and Diabetes*

Chronic inflammation
Visceral obesity

Il-1
Il-6

TNFα

Proinflammatory state
Chronic overexpression of cytokines

Pancreatic beta cell damage

Liver

Insulin resistance

Acute Phase Response (CRP, Fibrinog., PAI-1)

Diabetes
CHD

Conceptual Model: Adapted from Richard Donahue, 2004

# *Supporting epidemiologic evidence*

- Inflammation and insulin resistance
- Insulin resistance and diabetes
- Inflammation and diabetes
- Periodontitis and sytemic inflammation/ acute-phase response
- Periodontitis and insulin resistance

# *Supporting epidemiologic evidence*

- Inflammation and insulin resistance
- Insulin resistance and diabetes
- Inflammation and diabetes
- Periodontitis and sytemic inflammation/ acute-phase response
- Periodontitis and insulin resistance

# *Supporting epidemiologic evidence*

- Cross sectional studies: associations in people without diabetes or with metabolic syndrome

  Subjects without diabetes, general population, or those with IGT/IFG

  - Correlation of acute-phase reactants and pro-inflammatory mediators (CRP, IL6 and TNFα) with:
    - Measures of insulin resistance/plasma insulin
    - Triglycerides and HDL cholesterol
    - Increasing number of components of the metabolic syndrome

# *Supporting epidemiologic evidence*

- Cross sectional studies: associations in people with diabetes
  - Subjects with newly diagnosed or established type 2 diabetes compared to controls without diabetes
    - Elevated acute-phase reactants (CRP, IL6 and TNFα
    - Correlation between HOMA and markers of inflammation:

      CRP, serum amyloid A, secretory phospholipaseA2, IL6, TNFα, and endothelial dysfunction (soluble cell adhesion molecules)

# *Supporting epidemiologic evidence*

- Inflammation and insulin resistance
- Insulin resistance and diabetes
- Inflammation and diabetes
- Periodontitis and sytemic inflammation/ acute-phase response
- Periodontitis and insulin resistance

# *Supporting epidemiologic evidence*

- Longitudinal studies: markers of inflammation predicting type 2 diabetes:
  - ARIC : WBC, low serum albumin, α1-acid glycoprotein, fibrinogen, sialic acid
  - US Women's Health Study: CRP, IL-6
  - US Cardiovascular Health Study: CRP
  - Pima Indians: WBC, adiponectin
  - US Insulin Resistance and Atherosclerosis Study: CRP, fibrinogen, PAI-1
  - West of Scotland Coronary Prevention Study: CRP

# *Supporting epidemiologic evidence*

- Longitudinal studies: markers of inflammation predicting type 2 diabetes (con't.):
  - NHANES: WBC
  - Hoorn Study in the Netherlands:CRP
  - European Prospective Investigation into Cancer and Nutrition-Postdam Study: IL-6, IL-1β
  - MONICA Augsburg Study: CRP
  - Mexico City Diabetes Study: CRP (signif. in men only)

# *Supporting epidemiologic evidence*

- Inflammation and insulin resistance
- Insulin resistance and diabetes
- Inflammation and diabetes
- Periodontitis and systemic inflammation
- Periodontitis and insulin resistance

# *Periodontal therapy: effects on systemic inflammation*

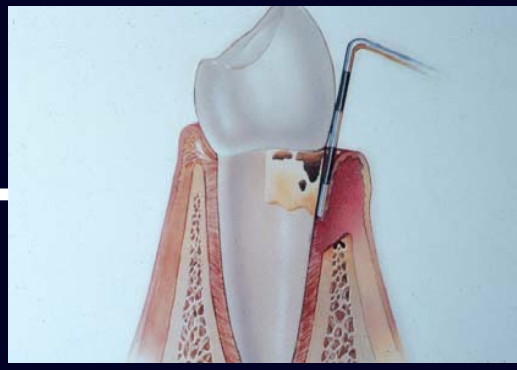
- Improved endothelial function
  - Seinhost et al., 2005
  - Elter et al., 2006
  - Tonetti et al., 2007
- CRP level reduced
  - Seinost et al., 2005
  - D'Aiuto et al., 2005
  - Ebersole et al., 1997
- IL-6 levels reduced
  - D'Aiuto et al., 2005
  - Iwamoto et al., 2003
- TNFα levels reduced
  - Iwamoto et al., 2003

# *Supporting epidemiologic evidence*

- Inflammation and insulin resistance
- Insulin resistance and diabetes
- Inflammation and diabetes
- Periodontitis and sytemic inflammation/ acute-phase response
- Periodontitis and insulin resistance

*Why do we think periodontal disease is linked to insulin resistance and glycemic control?*

Chronic inflammation
Visceral obesity



Il-6

TNFα

Proinflammatory state
Chronic overexpression of cytokines

Pancreatic beta cell damage

Liver

Insulin resistance

Acute Phase Response (CRP, Fibrinog., PAI-1)

Glycemic Control

Conceptual Model: From Richard Donahue, 2004

# *Periodontitis and Insulin Resistance: Epidemiologic Evidence of an Association*

# *Periodontitis and Insulin Resistance in U. S. Adults, NHANES III, Preliminary Results*

- To evaluate the association between severe periodontitis and insulin resistance in a representative sample of U.S. adults, ages 17-90 years old.

## STUDY POPULATION

- Participants of the Third National Health and Nutrition Examination Survey (NHANES III)
- Data collected between 1988-1991 and 1992-1994 to provide national estimates in studying oral and systemic health.
- Non-smokers, [no diabetes] or [diabetes and no meds for diabetes].

## DATA SOURCES

- Face-to-face interview
- Comprehensive oral exam
- Medical exam
- Laboratory assays

## MAJOR EXPOSURE

- Severe periodontitis
  - At least 1 site with 6 mm or more of attachment loss

    &

  - Gingival bleeding at the teeth with 6+ mm of attachment loss

## OUTCOME

- Insulin Resistance

  HOMA formula

  Fasting insulin (FI)

  Fasting glucose (FG)

$$\frac{FI \times FG}{22.5}$$

Dichotomous variable using the 80$^{th}$ percentile as the cutpoint

# *Association between severe periodontitis and insulin resistance (HOMA 80$^{th}$ ): crude odds ratio*

- N= 5313
- Severe periodontitis (sPD+): n=281 (5.3%)
- sPD- /HOMA80+: n=1474 (24.6%)
- sPD+ /HOMA80+: n=100 (38.7%)
- Crude Odds Ratio: 2.3 (1.58, 3.39)

# *Logistic regression model*
# *Response: HOMA 80$^{th}$ (n=1574/5313)*

| COVARIATE | OR | 95% CI |
|---|---|---|
| Severe perio. | 1.74 | 1.01, 3.0 |
| BMI (>27) | 4.77 | 4.1, 5.6 |
| HDL (≤40) | 2.2 | 1.7, 2.9 |
| TRIG (>200) | 2.7 | 2.0, 3.6 |
| CRP | 1.3 | 1.1, 1.5 |
| Diabetes | 4.72 | 2.6, 8.4 |

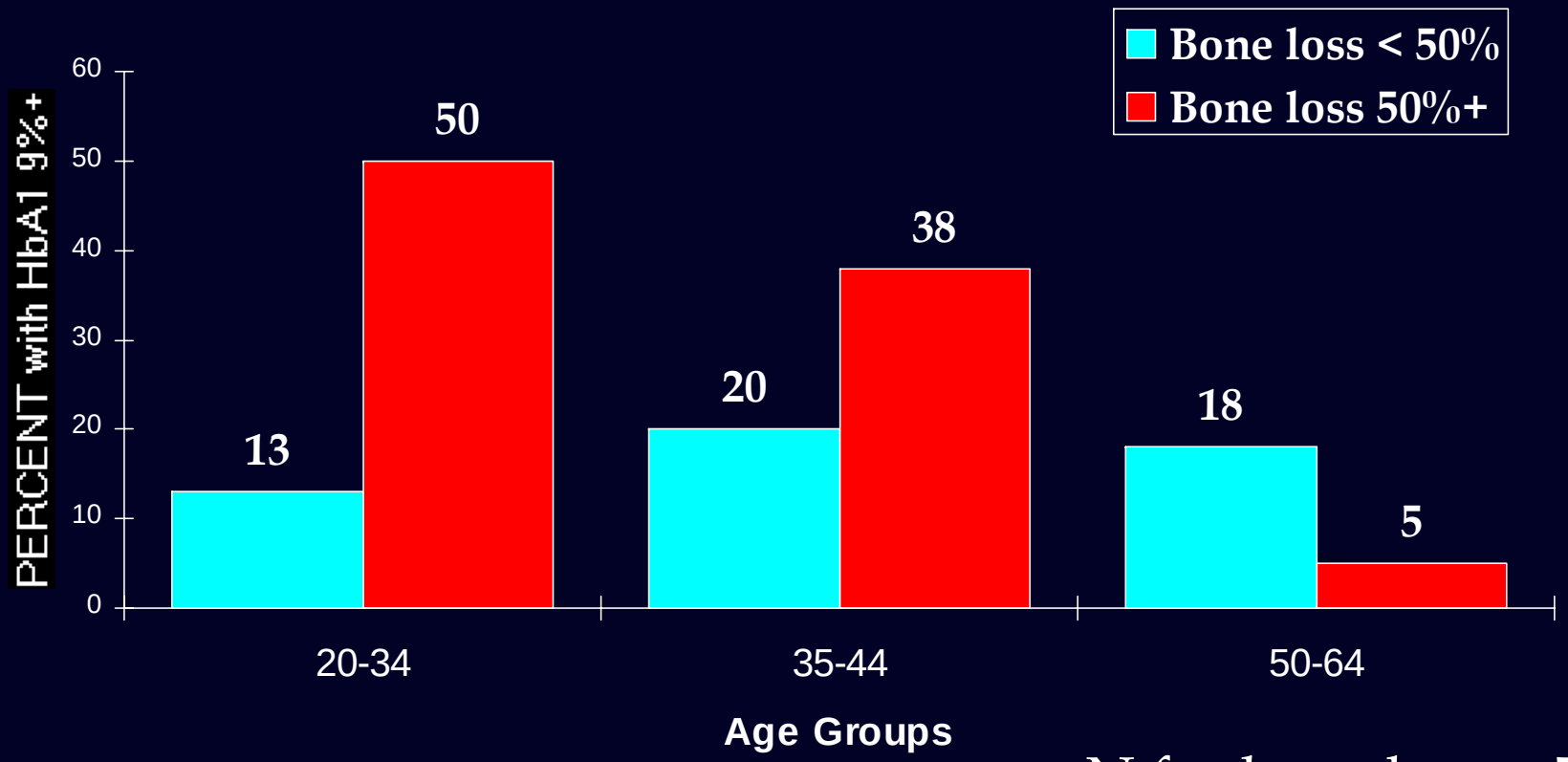
Other covariates controlled in model were age, race/ethnicity, exercise, white blood cell count, fibrinogen.

# Periodontal Infection
# Its Effect on Glycemic Control:
# Summarizing the Empirical Evidence

# Periodontal Infection
# Its Effect on Glycemic Control:

## Observational Studies

# *Observational Evidence: Incidence of poorer glycemic control at ~2-yrs. follow-up in Pima Indians*



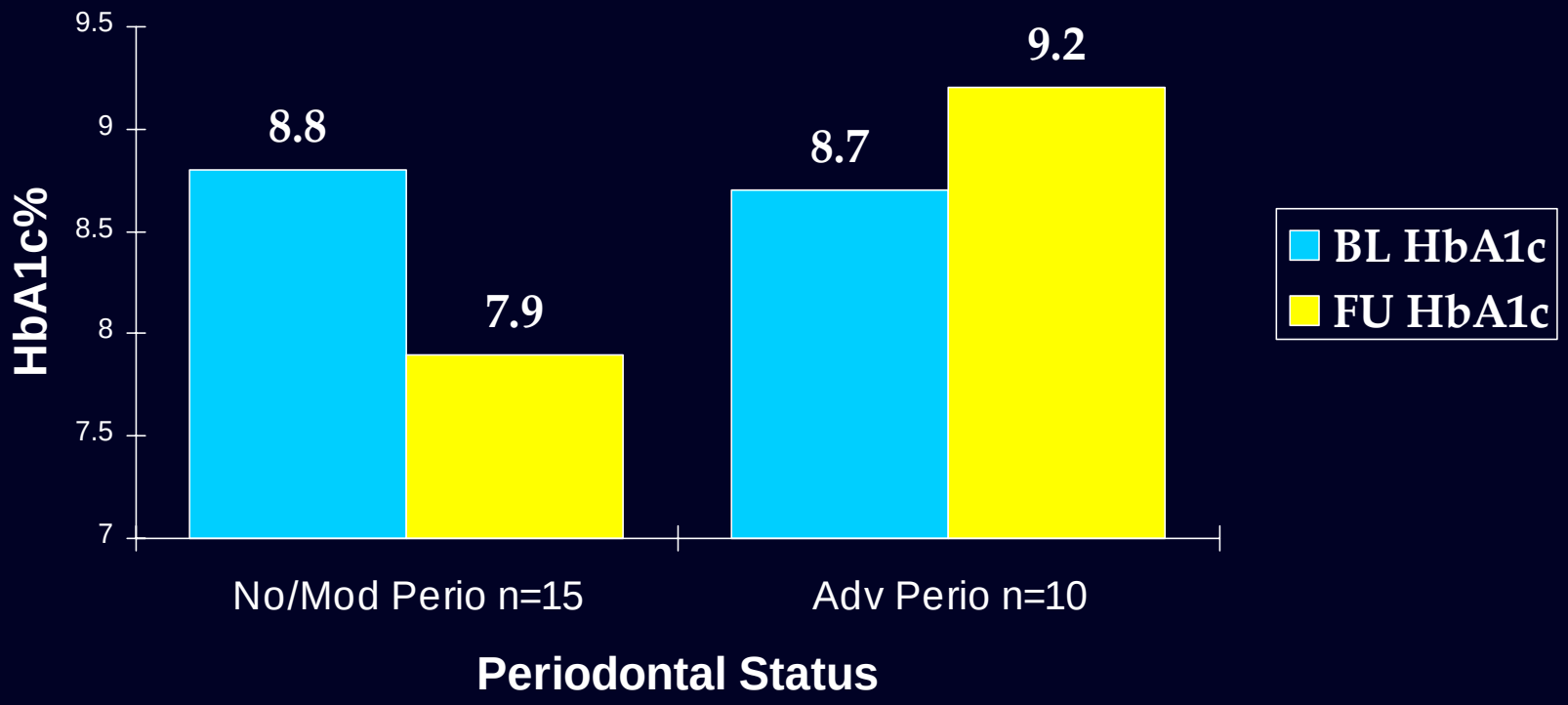

N for bone loss < 50% = 56
N for bone loss 50%+ =49

Source: Taylor et al., 1996

# Effect of severe bone loss on follow-up HbA1 at 9%+

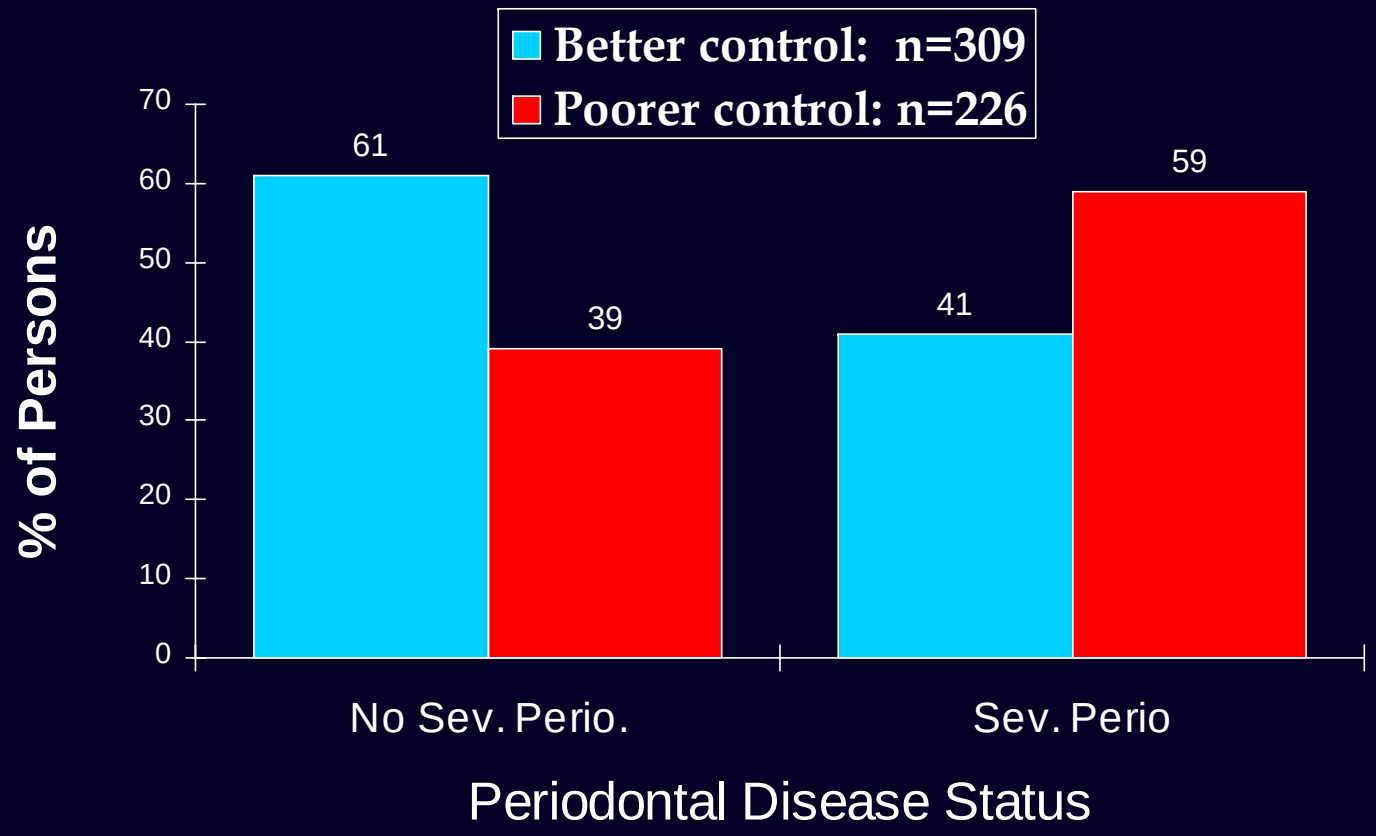
| PREDICTOR | ODDS RATIO (95% CI) |
|---|---|
| Bone loss | |
| 25 year old | 13.6 (1.7, 106.0) |
| 35 year old | 4.2 (1.2, 14.9) |
| 50 year old | 0.71 (0.2, 2.9) |
| HbA1 (baseline) | 1.9 (1.1, 3.5) |

# *Observational Evidence: Change in HbA1c by periodontal disease status in adults with type 2 diabetes, ages 58-76*




Source: Collin et al., 1998

# Prevalence of poorer glycemic control in U.S. adults, ages 45+, by periodontal status*




* Sev. Perio=1+ site w LPA 6 mm+, gingival bleeding

Source: NHANES III (1989-94), US Population

# *Association between severe periodontitis and glycemic control: N=535*

Crude Odds Ratio: 3.20 (1.47, 6.98)

| | **Glycemic Control** | |
|---|---|---|
| **Periodontal Status** | **Better** HbA1c < 8% | **Poorer** HbA1c ≥ 8% |
| Sev. Perio: NO | 270 (61%) | 170 (39%) |
| Sev. Perio: YES | 39 (41%) | 56 (59%) |

## *Logistic regression model: poor glycemic control in U.S. adults, ages 45+, non-smoking, NHANES III*

| COVARIATE | OR | 95% CI |
|---|---|---|
| Severe perio. | 4.9 | 2.0, 11.9 |
| Taking Diab med | 3.4 | 1.7, 5.8 |
| BMI (≥ 27) | 2.6 | 1.2, 5.4 |
| TRIG (>200) | 2.7 | 2.0, 3.6 |
| CRP (>1.0) | 2.6 | 0.5, 13.8 |
| Exercise | 1.0 | 0.99, 1.01 |

Other covariates controlled in model were age, race/ethnicity, sex, education, poverty income ratio, and MD and DDS visits.

# Periodontal Infection: Effect on Glycemic Control

## Beyond observational studies

| Grade | Level | Type of Evidence |
|---|---|---|
| A | 1a | Systematic review (SR) of RCT's |
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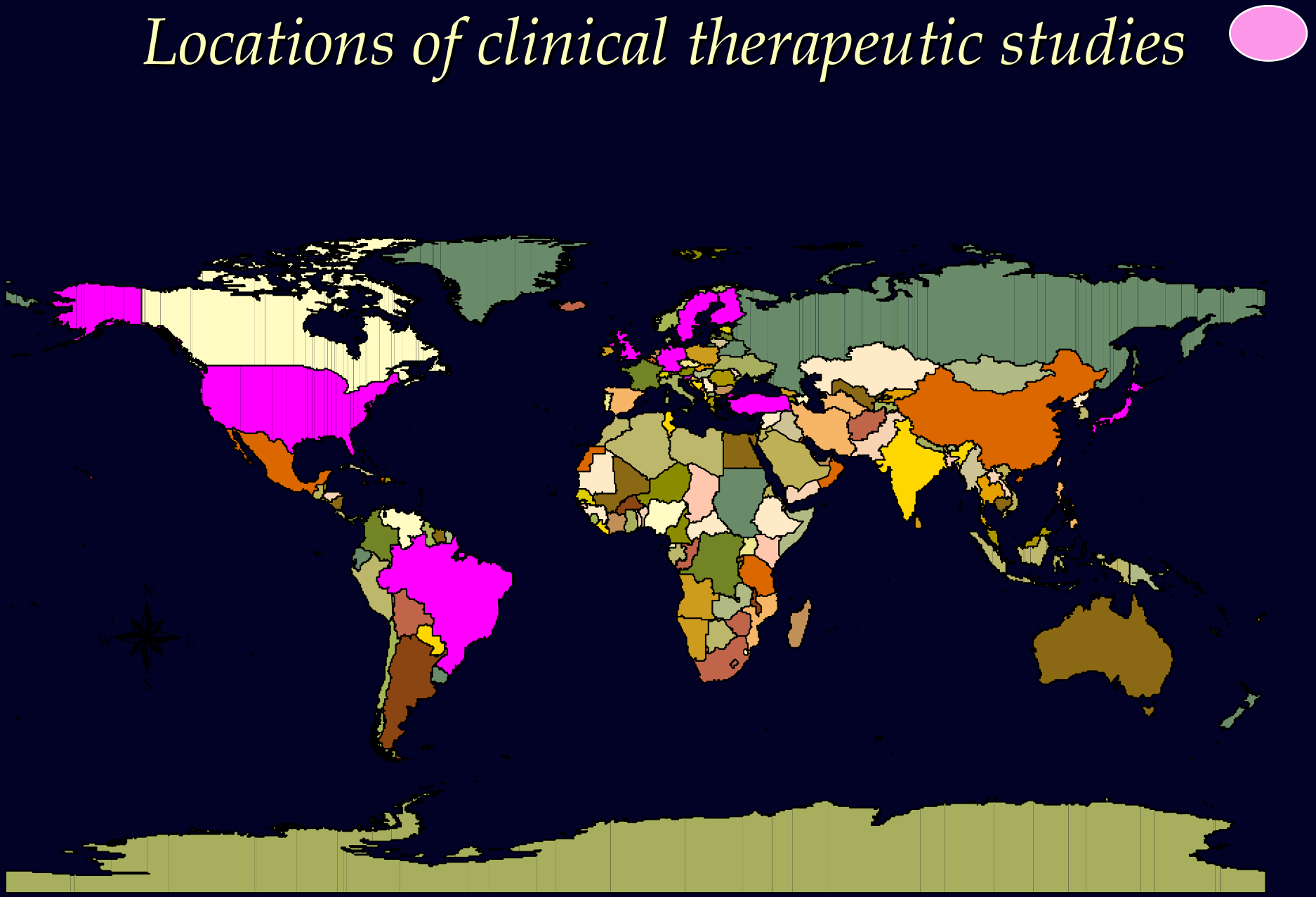
Source: Cochrane Collaboration, 1999

# Periodontal Infection
# Its Effect on Glycemic Control:

## Non-surgical Periodontal Treatment Studies

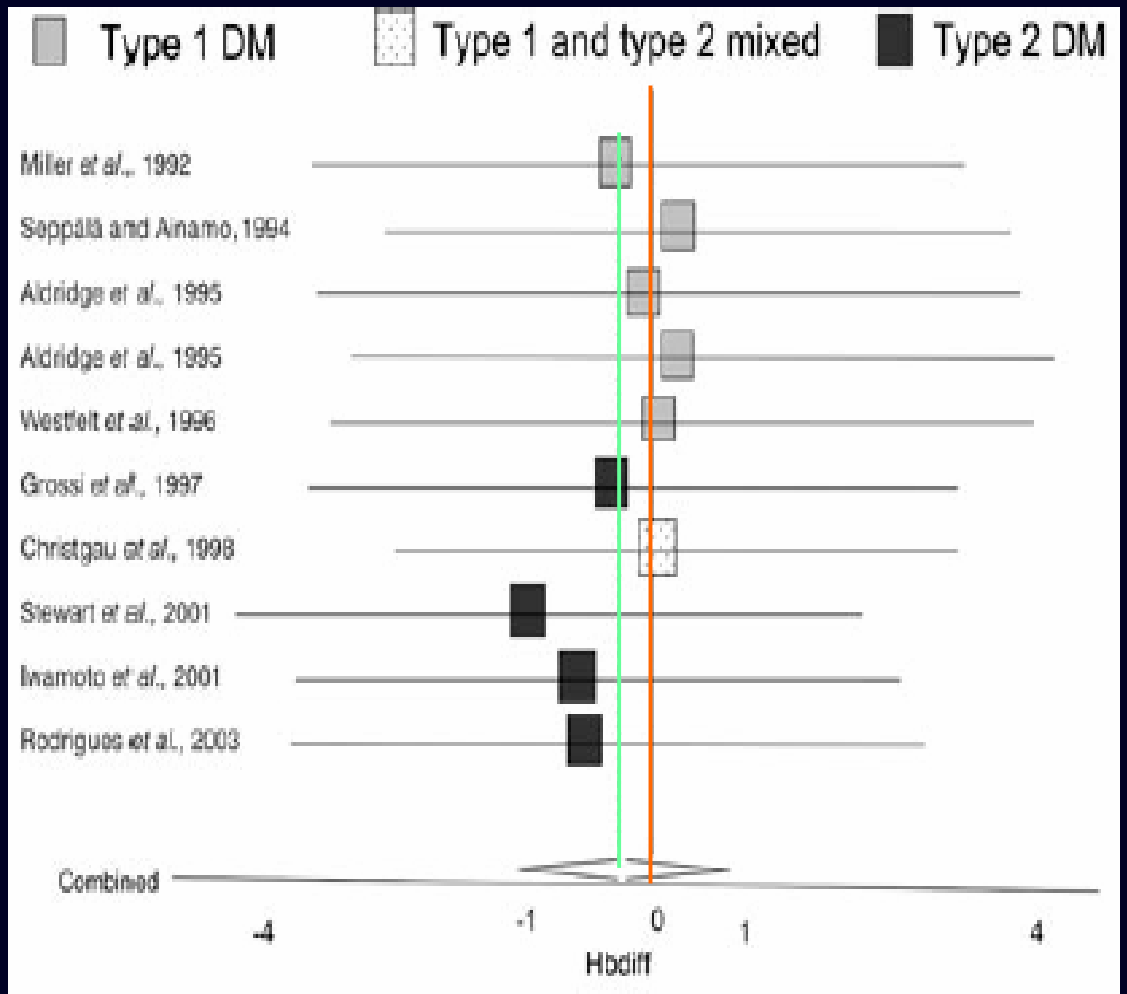
# *Locations of clinical therapeutic studies*



# *Non-surgical periodontal therapy studies: Organizing the evidence*

- Randomized clinical trials (RCT)
  - Non-treated control group: 1 positive/3 studies
  - Positive control group: 3 positive/3 studies
  - Usual source of care 0 positive/1 study
- Non-randomized clinical treatment studies (non-RCT)
  - Non-treated control group: 1 positive/2 studies
  - No control group: 7 positive/10 studies

# *Non-surgical periodontal therapy: a meta-analysis. Janket et al. J Dent Res, 2005*




| | Weighted Average Change in HbA1c | 95% Confidence Interval |
|---|---|---|
| All intervention studies | - 0.4% | - 1.5, 0.7 |
| Studies of type 2 DM only | - 0.7% | - 2.2, 0.9 |
| Non-surgical debridement only | - 0.4% | - 2.1, 1.3 |
| Antimicrobial intervention in type 2 diabetic patients | - 0.7% | - 2.3, 0.9 |

| Clinical Study | DM | Effect | N |
|---|---|---|---|
| RCT: non-tx controls | | | |
| Aldridge et al. (1995) | 1 | N | 31 |
| Aldridge et al. (1995) | 1 | N | 22 |
| Kiran et al. (2005) | 2 | Y | 44 |
| RCT: usual care controls | | | |
| Jones et al. (2007) [2,7] | 2 | N | 165 |
| RCT: positive controls | | | |
| Grossi et al. [2] (1996) | 2 | Y | 104 |
| Rodrigues et al. [4] (2003) | 2 | Y * | 30 |
| Skaleric et al. [3] (2004) | 1 | Y | 20 |

1=Penicillin; 2=Systemic doxycycline; 3=Minocycline, locally delivered
4=Amoxicillin and augmentin; 5=Systemic doxycycline: non-antimicrobial

# *Significance of improving of glycemic control*

- Any sustained lowering of blood glucose helps delay the onset and progression of microvascular complications of diabetes
- Prevalence of complications in people with diabetes
  - Neuropathy – 50%
  - Any cardiovascular disease – 38%
  - Coronary heart disease – 22%
  - Stroke – 21%
  - Visual Impairment – 23%
  - Kidney disease – 40% of new cases of renal failure due to diabetes

# *Landmark clinical trials demonstrating the significance of improving of glycemic control*

- Diabetes Control and Complications Trial (DCCT)
  - Intensive blood glucose control in type 1 diabetes
  - 35% to 70% reduction in risk of retinopathy, nephropathy and neuropathy
- UK Prospective Diabetes Study (UKPDS)
  - Intensive blood glucose control in type 2 diabetes
  - 12% to 33% reduction in risk of retinopathy and nephropathy

# *Periodontal infection and complications of diabetes*

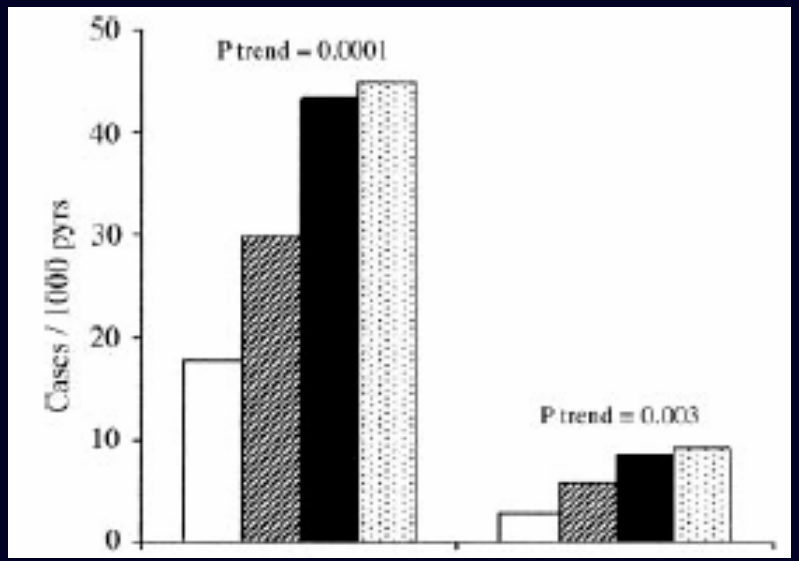
- Thorstensson et al., 1996; J Clin Periodontol.
  - 39 case-control pairs, type 1 and type 2 diabetes
  - Cases (severe periodontal disease) had greater risk for
    - Proteinuria
    - Cardiovascular complications: stroke, TIA, angina, myocardial infarction, and intermittent claudication

# *Periodontal infection and complications of diabetes*

- Saremi et al., 2005; Diabetes Care.
  - Prospective cohort study of n=628, type 2 diabetes
  - Severe periodontal disease: 3.2x greater risk for cardiorenal mortality (ischemic heart disease and nephropathy)
  - Controlled for established risk factors: age, sex, duration, BMI, hypertension, blood glucose, cholesterol, ECG abnormalities, macroalbuminuria, and smoking

# *Periodontal infection and complications of diabetes: Overt nephropathy and ESRD*

- Shultis et al., 2007; Diabetes Care.
  - Prospective cohort study of n=529, type 2 diabetes
  - Severe periodontal disease associated with incidence of macroalbuminuria and ESRD adjusted for age and sex




(n = 529). □, *none/mild periodontitis;* ▨, *moderate periodontitis;* ■, *severe periodontitis;* ▩, *edentulous.*

# *Periodontal infection and complications of diabetes: Overt nephropathy and ESRD Shultis et al., 2007; Diabetes Care*

**Macroalbuminuria**

| | HRR |
|---|---|
| Mod Perio: | 2.0 (1.2-3.5) |
| Sev Perio: | 2.1. (1.2-3.8) |
| Edent: | 2.6 (1.4-4.6) |

n=193/529

**ESRD**

| | HRR |
|---|---|
| Mod Perio: | 2.3 (0.6-8.1) |
| Sev Perio: | 3.5 (0.96-12.4) |
| Edent: | 4.9 (1.4-17.4) |

n=68/529

Proportional Hazards Model: Adjusted for Age, Sex, Diabetes Duration, BMI, and Smoking

# *Conclusions*

- Consistent, world-wide evidence that diabetes adversely affects periodontal health
- Evidence that chronic periodontitis may potentiate insulin resistance
- Evidence that treating periodontal infection can:
  - Lead to improved glycemic control
  - Possibly prevent, delay, or reduce severity of complications
  - Possibly prevent the development of diabetes itself

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# *Thank you for your attention*

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