

Periodontitis and premature death: a 16-year longitudinal study in a Swedish urban population

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Background and Objective: Growing experimental evidence implicates chronic inflammation/infection due to periodontal diseases as a risk factor for death. The objective was to evaluate the role of periodontitis in premature death in a prospective study.

Methods: The causes of death in 3273 randomly-selected subjects, aged 30–40 years, from 1985 to 2001 were registered. At baseline, 1676 individuals underwent a clinical oral examination (Group A) and 1597 did not (Group B). Mortality and causes of death from 1985 to 2001 were recorded according to ICD-9-10.

Results: In Groups A (clinically examined group) and B, a total of 110 subjects had died: 40 subjects in Group A, and 70 in Group B. In Group A significant differences were present at baseline between survivors and persons who later died, with respect to dental plaque, calculus, gingival inflammation and number of missing molars in subjects with periodontitis ($p < 0.001$). The multiple logistic regression analysis results of the relationship between being dead (dependent variable) and several independent variables identified periodontitis with any missing molars as a principal independent predictor of death.

Conclusions: Young individuals with periodontitis and missing molars seem to be at increased risk for premature death by life-threatening diseases, such as neoplasms, and diseases of the circulatory and digestive systems.

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Epidemiological studies suggest a link among severe chronic periodontitis, atherosclerosis, and mortality (1–5). Reports describing an association between periodontal diseases and cardiovascular disease, and postulating possible causative pathways, have recently been published by Buhlin *et al.* (6) and Söder *et al.* (7).

Periodontal disease is characterized by chronic infection and inflammation in periodontal tissue, leading to destruction of bone surrounding the

teeth and, ultimately, to tooth loss (8,9). An estimated 15–35% of the adult population in industrialized countries suffers from this multifactorial disease (10–12). Periodontal disease is initiated by a biofilm of bacteria on the teeth, which triggers an immuno-inflammatory response in the adjacent host tissues (8,9,13). Tobacco smoking is an important risk factor for development of periodontitis and increases the severity of periodontal diseases (9,14–16).

Although bacterial pathogens are required to initiate the disease process, their presence alone is insufficient to cause the tissue destruction that occurs in periodontitis (17,18). In some individuals, the reaction to bacteria may lead to an excessive host response, producing a general inflammatory response.

Most of the epidemiological studies evaluated in meta-analysis reports and systematic reviews are retrospective, and results regarding periodontal

disease and mortality are inconsistent (3,19–24).

The presence of gingivitis and periodontitis in young adults may reflect an underlying weakness of the host defense system. The chronic inflammatory and microbial burden of periodontitis in these subjects may predispose them to future infectious diseases. To investigate the relationship between periodontitis and general diseases, longitudinal studies spanning several years are recommended to ensure that the time period in which periodontitis develops is taken into account.

Epidemiological data from prospective studies regarding the risk for premature death in subjects who have periodontitis early in life are lacking.

Our hypothesis here is that the presence of gingivitis and periodontitis in young adults increases the risk for future life-threatening diseases.

Our aim was therefore to evaluate the role of periodontitis in premature death in a prospective study.

Material and methods

Study population

In 1985, we undertook a study comprising a random sample of 3273 individuals aged 30–40 years. The subjects were selected from a registry file of all inhabitants ($n = 105,798$) of Stockholm County born on the 20th of any month from 1945 to 1954. They were informed about the purpose of the study and offered an oral clinical examination. In total, 1676 individuals (51.2%; 838 men and 838 women), underwent a detailed oral clinical examination and answered a questionnaire (Group A). The remaining 1597 subjects (849 men and 748 women), constituted Group B. From Group B, 100 randomly selected individuals (45 men and 55 women), were re-informed and persuaded, and finally agreed to participate in the investigation. They underwent an oral clinical examination in 1985 and were used as a dropout control sample.

In all subjects from Group A (clinically examined group) and the dropout control sample from Group B, the

following parameters were recorded: the number of remaining teeth, excluding third molars; gingival inflammation around every tooth, assessed using the gingival index (25); and oral hygiene status, determined using the plaque index (26) and the calculus index to assess all six surfaces of six representative teeth. Pocket depth was determined with a periodontal probe (27) and recorded to the nearest higher millimeter for six sites of each tooth. Presence or absence of each tooth was recorded. Participants with at least one tooth with a pocket depth of 5 mm or deeper were considered to have periodontitis. All subjects in Group A (clinically examined group) and the dropout sample from Group B answered a questionnaire containing questions on factors such as regular dental visits and the use of tobacco. The subjects were divided into smokers, former smokers, and never smokers. In addition, all age-matched subjects in Stockholm County constituted Group Sc and all age-matched subjects in all of Sweden constituted Group S. In January 1985, Group Sc comprised 105,798 individuals and Group S comprised 1,254,238 individuals.

Socioeconomic and mortality data

The causes of death in Groups A (clinically examined group) and B, as well as in Groups Sc and S, from 1985 to 2001, were obtained from the Center of Epidemiology, Swedish National Board of Health and Welfare, Sweden. The data regarding causes of death have been classified according to the English version of the International Statistical Classification of Diseases and Related Health Problems (ICD), ICD-8, ICD-9 and ICD-10. Socioeconomic data were obtained from the National Statistics Center, Örebro, Sweden.

Statistical analysis

Analysis of variance, chi-square tests, multiple regression analysis, and multiple logistic regression analysis were applied as appropriate. Multiple logistic regression analysis was used to

compare the incidence of total mortality, according to the state of oral health at baseline, while simultaneously controlling for several potential confounding variables. In the multiple logistic regression analysis models, we included the potentially confounding variables of age, gender, education, income, socioeconomic status, smoking habits, dental visits, and hospitalization. Smoking habits was dichotomized into number of smokers (ever smokers) and number of never smokers. The model with these confounders was correlated to premature death. A backwards elimination method was used to control for multicollinearity (correlation between confounders). The statistical model was tested according to Cox & Snell and Nagelkerke.

Differences between data sets with a probability of < 0.05 were regarded as significant. All p -values are two-tailed, and confidence intervals were calculated at the 95% level. All statistical analyses were performed using SPSS, version 14.0 (Chicago, IL, USA).

The Ethics Committee of the Karolinska Institute and Huddinge University Hospital, Sweden, approved the study protocol. The study is in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Results

The demographic data for Groups A (clinically examined group) and B are presented in Table 1. The clinical data of Group A (clinically examined group) and of the dropout sample are displayed in Table 2. In Group A (clinically examined group), 286 subjects had periodontitis, 95 had missing molars, and 191 had no missing molars, and 1390 were periodontally healthy. The number and distribution of missing teeth in subjects with and without periodontitis are shown in Fig. 1A,B. Subjects with periodontitis had significantly more missing molars than subjects without periodontitis ($p < 0.002$; chi-square 10.0).

In Groups A (clinically examined group) and B, a total of 110 subjects (3.4%) had died: 40 subjects (2.3%; mean age 47.3 ± 5.8 years) in Group

Table 1. Demographic data at baseline for Groups A (clinically examined group) and B (n = number of subjects)

	Group A (n = 1676)	Group B (n = 1597)	p-value*
Gender (female/male)	847/829	749/848	Not significant
Age in 1985 (years)	35.7 ± 2.9 ^a	35.4 ± 2.8 ^a	0.01
Education (compulsory/higher)	289/1,385	272/1,325	Not significant
Working in 1985 (yes/no)	1530/145 ^b	1255/341 ^b	< 0.001
Income (Swedish Crowns × 1000)	180.4 ^c	160.0 ^d	< 0.001

*Chi-square or Student's *t*-test for unpaired samples, as appropriate.

^aData are expressed as mean ± SD.

^bTwo missing values.

^cThirty-eight missing values.

^dNinety-six missing values.

Table 2. Clinical oral data at baseline for Group A (clinically examined group) and for the dropout sample (n = number of subjects)

Variable	Group A (n = 1676)	Dropout sample (n = 100)	p-value*
Plaque index	0.71 ± 0.49	0.73 ± 0.37	NS
Gingival inflammation	1.28 ± 0.53	1.39 ± 0.52	< 0.05
Calculus index	0.46 ± 0.58	0.24 ± 0.22	< 0.001
Number of missing teeth	1.24 ± 2.29	1.87 ± 3.47	= 0.01
Periodontitis (yes/no)	286/1390	42/56 ^a	< 0.001

*Chi-square or Student's *t*-test for unpaired samples, as appropriate.

^aValues from two subjects are missing.

Data are expressed as mean ± SD. NS, not significant.

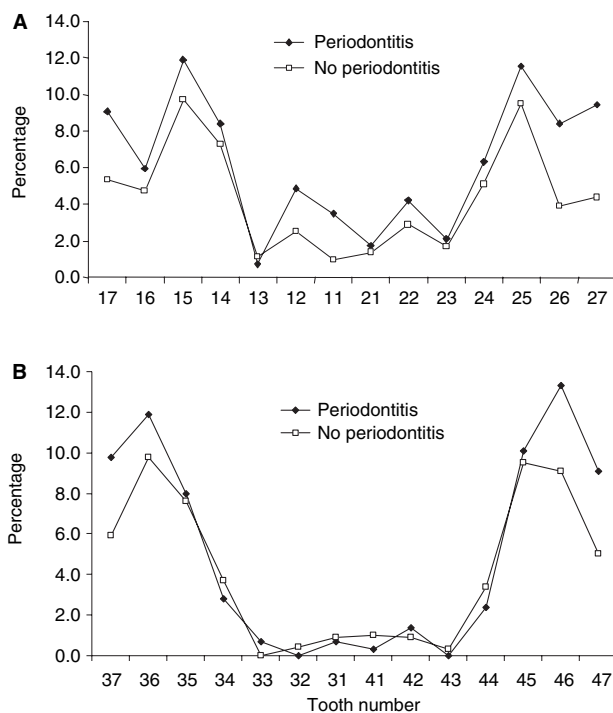


Fig. 1. (A) Proportions (%) of missing maxillary teeth in subjects with and without periodontitis. (B) Proportions (%) of missing mandibular teeth in subjects with and without periodontitis.

A (clinically examined group), and 70 subjects (4.4%; mean age 44.8 ± 4.9 years) in Group B. Significant differences were observed between the groups in age ($p < 0.05$) and in the numbers of deceased individuals ($p = 0.001$, chi-square 10.0). The causes of death and the numbers of deceased individuals in Groups A (clinically examined group) and B are presented in Fig. 2A,B.

The demographic data and risk factors at baseline for the deceased individuals and survivors in Group A (clinically examined group) are shown in Table 3. The clinical oral data at baseline for the same individuals are displayed in Table 4. As seen from the table, all oral hygiene data, as well as the presence of periodontitis and the number of missing molars, were significantly higher in subjects who later died than in survivors. The result of logistic regression analysis of being dead (dependent variable), and several independent variables, is shown in Table 5. The total numbers of individuals who died of neoplasms or diseases of the circulatory or digestive systems were significantly higher in the periodontitis group with missing molars ($n = 95$) than in the periodontally healthy group ($n = 1390$) ($p < 0.01$, chi-square 9.46).

In Group Sc, 4047 individuals (3.8%) with a mean age of 45.8 ± 5.8 years, and in Group S, 41,044 individuals (3.3%), with a mean age of 45.7 ± 5.6 years, had died.

The proportions of the three most frequent causes of death in Sweden (i.e. neoplasms, diseases of the circulatory system, and diseases of the digestive system) from 1985 to 2001, in subjects from Group A (clinically examined group), with and without periodontitis, in subjects from Group B, and in subjects from Groups Sc and S are shown in Table 6.

Discussion

This study addresses the issue of periodontal disease as a risk marker for mortality by evaluating the relationship between periodontitis and premature death 16 years after the diagnosis of periodontitis. Our results confirm the

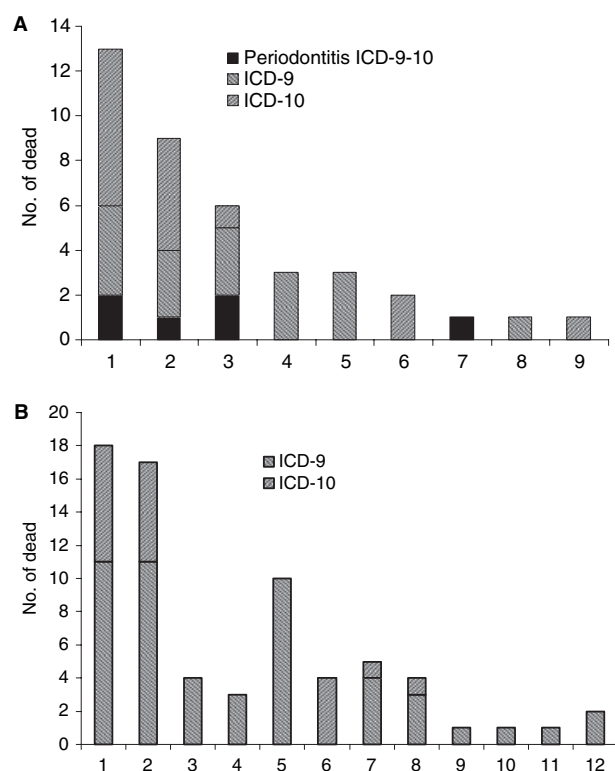


Fig. 2. (A) Number of subjects and causes of dead in Group A: ICD-9 1. Neoplasms (140-239); ICD 10 Malignant neoplasms (C00-C97); 2. ICD-9, Diseases in the circulatory system (390-459); ICD-10 (I00-I99); 3. ICD-9 Diseases in the digestive system (571; 577); ICD-10 (K55, K767, 7299); 4. ICD-9 Endocrine, nutritional and metabolic diseases, and immunity disorders (240-279); 5. ICD-9 Injury and poisoning (800-999); 6. ICD-10 External causes of morbidity and mortality, (V01-Y98); 7. ICD-9 Mental disorders (290-319); 8. ICD-9, Symptoms, signs, and ill-defined conditions (80-799); 9. No diagnosis. (B) Number of subjects and causes of dead in Group B: 1. ICD-9 Neoplasms (140-239); ICD-10 Malignant neoplasms (C00-C97); 2. ICD-9 Diseases in the circulatory system (390-459), ICD-10 (I00-I99); 3. ICD-9 Diseases in the digestive system; 4. Endocrine, nutritional and metabolic diseases, and immunity disorders (240-279); 5. ICD-9 Injury and poisoning (800-999); 6. ICD-10, External causes of morbidity and mortality (V01-Y98); 7. ICD-9 Mental disorders (290-319), ICD 10 Mental behaviour disorders (F00-F99); 8. ICD9 Diseases in the respiratory system (460-519), ICD-10 (J00-J99); 9. ICD-9, Diseases in blood and blood forming organ; 10. ICD-9 Nervous system and sense organs (320-389); 11. ICD-10, Diseases of the musculoskeletal system an connective tissues (M00-M99); 12. ICD-9, Symptoms, signs, and ill defined conditions (780-799).

Table 3. Demographic data and risk factors at baseline for Group A (clinically examined group) (n = number of subjects)

	Dead (n = 40)	Alive (n = 1636)	p-value*
Gender (female/male)	15/25	825/811	NS
Age in 1985 (years)	37.0 ± 3.1 ^a	35.6 ± 2.8 ^a	0.01
Education (compulsory/higher)	12/28	279/1357	NS
Subjects who have never smoked/smokers	9/23 ^b	613/594 ^c	0.01
Dental visits (once a year/more)	29/11	1223/413	NS
Working in 1985 (yes/no)	29/11	1501/134	0.001

*Chi-square or Student's *t*-test for unpaired samples as appropriate.

^aData are expressed as mean ± SD. NS, not significant.

^bn = 32.

^cn = 1207.

hypothesis that periodontitis in young adults with any missing molars is a risk marker for premature death. The prematurely deceased women in the study were expected to live 36.1 years longer and the deceased men 31.6 years longer (28). The individuals who died were probably infected with periodontitis many years before the baseline registrations, as it takes several years of infection before any molar becomes so movable that it is troublesome for its owner and removed (14).

Pussinen *et al.* (29–32) found high serum antibody levels to major periodontal pathogens in subjects with subclinical or clinical coronary heart disease. A recently published prospective study by our group showed that periodontitis subjects with no subclinical or clinical coronary heart disease had significantly higher mean values of carotid intima media thickness than periodontally healthy controls, indicating that periodontitis is associated with the development of early atherosclerotic carotid lesions (7).

Some comments should be made concerning the reliability of the results obtained. Subjects were randomly chosen to avoid selection bias and to ensure normal distribution of the sample variables. The large subject pool was representative of the ethnically homogenous Swedish adult population, with an age range of no more than 10 years in order to limit the influence of age differences. The study was a longitudinal prospective design, with respect to premature death, in a cohort of subjects with periodontitis documented in 1985. It can be argued that the periodontitis had healed as a result of frequent visits to dentists, but it should not be forgotten that the patients already suffered from periodontitis in 1985. However, the results of the present study showed periodontitis as a risk marker for premature death. The statistical analysis was performed with adjustments for several demographic variables and established risk markers for mortality, such as age, gender, and smoking, and therefore, none of these confounded the associations observed between periodontitis and premature death.

Table 4. Clinical oral data at baseline for survivors and for individuals deceased at the end of the study (n = number of subjects)

	Dead (n = 40)	Alive (n = 1636)	p-value*
Plaque index	0.95 ± 0.56	0.70 ± 0.49	< 0.01
Gingival inflammation	1.57 ± 0.5	1.27 ± 0.5	< 0.001
Calculus index	0.65 ± 0.73	0.46 ± 0.58	< 0.05
Number of missing teeth	2.33 ± 3.79	1.23 ± 2.33	< 0.01
Number of missing molars	1.33 ± 1.98	0.51 ± 1.20	< 0.001
Periodontitis (yes/no)	23/17	523/1113	< 0.01

*Chi-square or Student's *t*-test for unpaired samples, as appropriate.
Data are expressed as mean ± SD.

Earlier studies have suggested that the reason for mortality could be the combined effect of periodontal diseases, calculus, and dental plaque (2), or the severity of caries, periodontitis, peri-apical lesions, and pericoronitis (33,34). Frisk *et al.* (35) found no significant association between endo-

dontically treated teeth or teeth with peri-apical destruction and coronary heart disease in a cross-sectional study of a representative sample of 1065 women. Desvarieux *et al.* (36) observed, in a cross-sectional study, that both current and cumulative periodontitis become more severe as

tooth loss increases. We have previously shown (14), in a 17-year prospective study, that molars were the teeth most affected in subjects with periodontitis. These results have been confirmed in the present investigation. This study provides further evidence of an association between periodontitis with missing molars and mortality. The missing molars in these young individuals signal a long history of chronic inflammatory and microbial burden of periodontitis but may also reflect an underlying weakness of the host defense system. A very high bacterial load on tooth surfaces and in gingival pockets over a prolonged time period may be responsible for the diseases subsequently causing death. Therefore, reducing the bacterial burden of affected individuals, and identifying the bacteria responsible for the diseases

Table 5. Results of multiple logistic regression analysis of relationship between being dead (dependent variable) and several independent variables (age, gender, education, income, smoking, dental visits, dental plaque, gingival inflammation, missing teeth, and any missing molars in subjects with periodontitis) (n = number of subjects)

Dependent variable	Explanatory variable	Beta	Chi-square	p-value	OR (95% CI)
Dead	Any missing molars in subjects with periodontitis	1.29	5.93	0.015	3.62 (1.28–10.16)

Cox & Snell $R^2 = 0.011$, Nagelkerke $R^2 = 0.062$.
CI, confidence interval; OR, odds ratio.

Table 6. Proportions (%) of the three most frequent causes of death in Sweden from 1985 to 2001 for subjects in Group A (clinically examined group), with and without periodontitis, subjects in Group B, and in group and age-matched controls in the Stockholm County and in all of Sweden^a

Classification	Group A (n = 1676)		No periodontitis (n = 1390)	Group B (n = 1597)	Controls	
	Periodontitis (n = 286) Missing molars (n = 95)	No missing molars (n = 191)			Group Sc (Stockholm County; n = 105,798)	Group S (All Sweden n = 1,254,238)
Neoplasms, ICD-8, -9; (140–239)						
Malignant neoplasms ICD-10; (C00–C97)	2.11	1.57	0.65	1.13	1.00	1.04
Diseases of circulatory system, ICD-8, -9; (390–459)						
Diseases of circulatory system, ICD-10; (I00–I99)	1.05	0	0.58	1.06	0.67	0.67
Diseases of digestive system, ICD-8, -9 (520–579)						
Diseases of digestive system, ICD-10 (K00–K93)	2.11	0	0.28	0.93	0.25	0.17

^aAccording to International Classification of Diseases (ICD), ICD-8, ICD-9 in 1985–96 and ICD-10 in 1997–2000.

causing death in these subjects, are critical.

Our findings have public health consequences and may create a basis for prophylactic measures that, in view of the prevalence and outcome of periodontal diseases, and the costs it incurs to society, are well warranted.

Conclusions

Young individuals with periodontitis and missing molars seem to be at increased risk for premature death by life-threatening diseases, such as neoplasms, and diseases of the circulatory and digestive systems.

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