Oral health status, C-reactive protein and mortality – a 10 year follow-up study

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Abstract

Background: Epidemiological studies have reported a strong association between C-reactive protein (CRP) and cardiovascular diseases (CVD). Elevated CRP levels have been observed both in dentate individuals with chronic dental infections like periodontal disease and in those edentulous. The mechanisms behind these observations, especially the reasons for the elevation of CRP in the edentulous, are poorly understood. The comparative data on the importance of these inflammatory conditions in the oral cavity as causes of elevated CRP levels and CVD risk factors are also limited. **Objective:** To determine if edentulism is associated with increased levels of CRP and investigate the possible mechanism for this association; and to study the influence of periodontal disease and edentulism on 10-year mortality. **Subjects:** Of the 364 subjects aged 76, 81, and 86 years in 1990, 196 were dentate and 168 edentulous. By December 1999, 179 had died, almost half (n=87) of them due to cardiovascular disease. **Results:** Significantly more of the edentulous subjects had elevated (≥3 mg/L) CRP levels as compared to those with at least 20 teeth ($p<0.01$). They also had high salivary microbial counts ($p<0.05$), and more mucosal lesions ($p<0.0001$) than those with at least 20 teeth. In multivariate analysis, high microbial counts (OR 2.3, CI 1.06-5.05) and mucosal lesions (OR 2.18, CI 1.03-4.61) were significantly associated with elevated CRP levels. The risk for all-cause mortality was non-significantly elevated among the edentulous (RR 1.48, CI 0.95 – 2.31) and dentate with periodontal disease (RR 1.58, CI 0.96 – 2.61). CVD mortality was significantly higher among the dentate with periodontal disease (RR 1.97, CI 1.01 – 3.85) when compared with dentate without periodontal disease. **Conclusion:** Among the edentulous, chronic infections like denture-related mucosal lesions are important determinants of elevated CRP, comparable to periodontal disease in the dentate. Elevated CRP per se and edentulism were not significantly associated with increased mortality. Periodontal disease was, however, still associated with a two-fold CVD mortality in this very old population.

Key words: Oral health, elderly, CRP, mortality

Introduction

C-reactive protein (CRP), a sensitive systemic marker of inflammation, has been shown to predict cardiovascular events among middle-aged and elderly subjects[1-6]. Elevated levels of CRP observed in dentate subjects with chronic dental infections, especially periodontitis possibly explain the linkage between dental infections and cardiovascular diseases (CVD)[7-10]. Increased CVD mortality and elevated CRP have also been observed among the dentate elderly with periodontitis[11].

Data on the risk for CVD and mortality in edentulous subjects and CRP levels in these individuals are sparse. Among the participants of The Health Professionals Follow-up Study (HPFS), a weak association was observed between tooth loss and increased CVD[12]. On the other hand, National Health and Nutrition Examination Study I, its epidemiological Follow-up Study (NHEFS)[13] and The First National Health and Nutrition Examination Survey (NHANES I)[14], showed that CVD risk in the edentulous was similar to that in individuals with periodontitis. The NHANES III[15] reported significantly higher levels of CRP among the edentulous, as compared to dentate subjects without periodontal disease; the reason for this is poorly understood. Factors like systemic diseases, ill-fitting dentures, inability to maintain good oral hygiene, and hyposalivation can result in the growth of many oral microorganisms, and change the oral microflora of the elderly[16-18]. In the edentulous, the denture plaque may cause chronic oral diseases like denture-associated stomatitis and other mucosal lesions, with systemic consequences[19].

The aim of this study was to determine if edentulism was associated with increased levels of CRP and to evaluate the relationship between edentulism, denture-related chronic mucosal diseases, salivary microorganisms and CRP levels. Furthermore, the influence of these factors as well as periodontal disease on 10-year all-cause and CVD mortality among the dentate and edentulous elderly was also studied. On the basis of the above observations, we wanted to test the hypothesis that like periodontitis, chronic mucosal diseases in the edentulous elderly can cause inflammatory changes in the oral cavity, reflected in elevated CRP levels. Accordingly, both conditions can increase CVD risk via this common inflammatory pathway.

Subjects and Methods

Subject sample

Details of the design and sampling of the Helsinki Aging Study (HAS) have been published earlier[20]. Briefly, 651 subjects aged 75 (n=239), 80 (n=212), and 85 (n=200) years underwent medical examination in 1989 and 600 elderly who were alive one year later were invited for an oral examination at the University Dental Clinic. Of these, 364 subjects (196 dentate, 168 edentulous) underwent baseline examination, and 121 participated in the follow-up examination, five years later. The subjects were followed until December 1999. Altogether, 179 participants had died during the 10-year period and the primary cause of death for 49% of the decedents (n = 87) was CVD (Figure 1). The information about the death (cause and date) was obtained from the Finnish Death Register.

Data collection

The details of the medical examination have been reported previously[11,21]. At baseline, blood samples were collected, after an overnight fast, from all participants for routine laboratory investigations. In 1998, these frozen (-20°C) serum samples were used to measure the CRP using a sensitive immunoenzymometric assay which made use of two monoclonal antibodies (sensitivity =0.3 mg/l, Medix Diacor)[6]. The range of this assay was 0.3 to 30 mg/l. The median normal circulating concentration of CRP is 0.8 mg/l and in 90% of

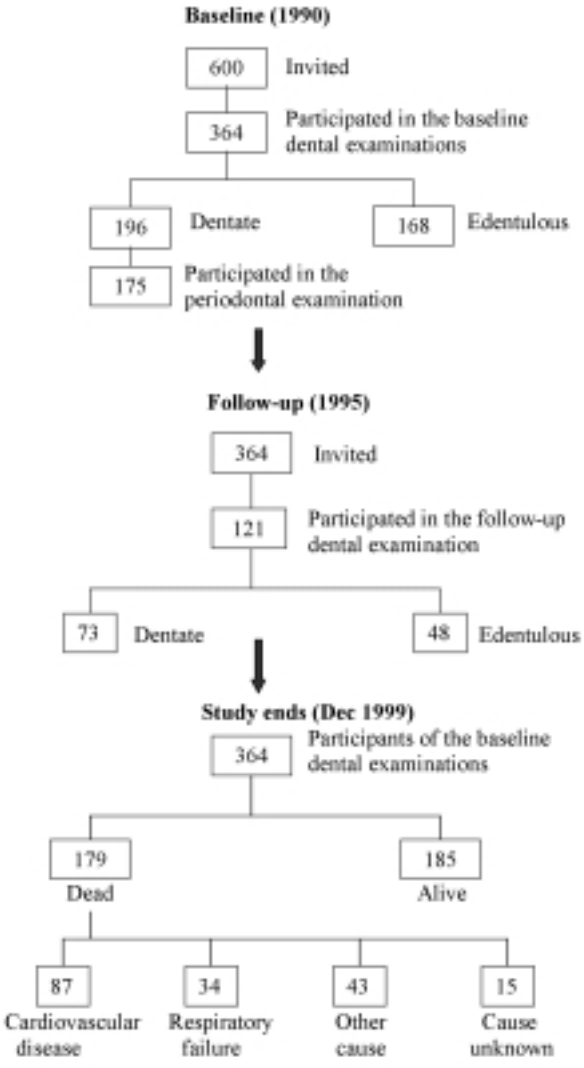

Figure 1. Participants of the denal study

the apparently healthy people the serum concentration is less than 3 mg/l[22]. In our study, as in some of the previous studies[23,24], CRP concentration of 3 mg/l was the cut off level.

Participant's social class was judged on the basis on their occupation and level of education (class I = upper, class IV = lower). The subjects were asked about their smoking history and alcohol consumption during the interview and in the questionnaire. They were accordingly categorized into current smoker, ex-smoker, or non-smoker; and taken once a week or more, less than once a week, or not taken at all respectively. History of CVD was based on a previous history of myocardial infarction or angina or stroke.

Four faculty members carried out the dental and oral examinations using a mouth mirror, a dental explorer, and a periodontal probe. Among the edentulous, tongue, corners of the mouth, and oral mucosa under and around the dentures were examined using a modified scheme recommended by the WHO[25]. The diagnosis was based on clinical examination only[26]. All the signs in the mucosa indicating a disease caused by yeast, such as angular chelitis, plaque-like lesion (hyperplastic or pseudomembranous), and erythematous lesions on tongue, mucosa, or hard palate, were termed as "oral candidosis". "Denture stomatitis", on the other hand, included localized or generalized erythema and/or granular type hyperplasia under a denture. Any and all inflammatory conditions of the mouth, including mucosal lesions and denture stomatitis, were broadly categorized under "Inflammation of the mouth".

The dentate participants underwent clinical examination that included examination for dental caries, periodontal status and prosthetic evaluation. Community Periodontal Index for Treatment Needs (CPITN) method was used for recording the periodontal status. The details of the examination have been reported earlier[27]. Periodontal status was dichotomized and those with CPITN codes 3 and 4 (periodontal pockets $\geq$4 mm) were categorised as having periodontitis. However, as CPITN does not measure alveolar bone loss or recession, these could not be taken into account.

Salivary microbial (mutans streptococci and yeast) counts were analyzed using commercial kits. The methods of collecting saliva and assessing the microbial counts have been reported elsewhere[28]. Briefly, estimation of salivary mutans streptococci (SM) was done by the Dentocult-SM strip mutans® method and salivary yeast was done by the Oricult-N® method (Orion Diagnostica, Espoo, Finland). The growth densities of SM, and number of colonies of salivary yeast were classified into 4 categories (0 to III) from no growth to $\geq 10^6$ CFUs/mL, and no colonies to >50 colonies/side of the slide, respectively[28,29]. In this study, we took the average of SM and yeast categories for each individual to determine their total microbial count. Those whose average category was less than 2 were said to have 'low' microbial count and the rest as having 'high' microbial count.

Informed consent was obtained form all subjects prior to the study. The Ethics committee of the Helsinki University Central Hospital, and the Institute of Dentistry, University of Helsinki, Finland approved the protocol of the study.

Statistical analysis

Statistical analyses were performed using the SPSS for MS Windows (Version 9.0, SPSS Inc., Chicago, USA). Chi-square test was used to compare proportions and continuous variables were analysed with ANOVA or non-parametric tests (if the distribution was not normal despite logarithmic transformation). No adjustments were made for multiple comparisons. Logistic regression was used to investigate the associations of the number of teeth, mucosal lesions, and microbial count with the risk of elevated CRP level and high microbial count. The known elevators of CRP like history of smoking, alcohol use, blood pressure, and history of chronic inflammatory diseases like chronic bronchitis, emphysema, asthma, and muscle and joint diseases were adjusted for. Cox proportional hazards model was used to study the predictors of mortality. Age and gender were forced in as covariates. The survival data were also controlled for smoking, hypertension, cholesterol, body mass index, history of CVD and social class. p-value < 0.05 was considered statistically significant.

Results

The association of baseline demographic characteristics and CV risk factors with periodontal status of the participants and their status in 1999 is shown in Table 1. Participants who had died within the 10 year period were significantly older, of lower social class, more often diabetic, had a lower BMI, systolic and diastolic blood pressures and serum cholesterol levels (Table 1). After adjusting for age and sex, diabetes and lower serum cholesterol significantly predicted death (data not shown). As compared with dentate subjects, the edentulous were of older age, predominantly females, of lower social class, and were more likely to be current smokers (Table 1). The only statistically significant

difference between dentate subjects with and without periodontal disease was that the latter had significantly higher mean diastolic blood pressure (Table 1).

CRP levels and edentulism

Edentulous subjects had more often elevated CRP levels (≥3 mg/L) than those with 20 or more teeth or dentate without periodontal disease or dentate without dentures (Table 2). Denture stomatitis was associated with elevated CRP but this relationship was affected by denture status. More subjects with complete dentures and denture stomatitis had elevated CRP levels than those without complete dentures and not having stomatitis. Among the edentulous, those with mucosal lesions or any inflammation in the mouth had significantly more often elevated CRP levels (p=0.007 and p=0.04 respectively, data not shown). This relationship was not significant among the dentate. A similar trend was observed for salivary microbial counts, which were significantly higher in the edentulous, and those with denture stomatitis, oral candidosis or inflammation in the mouth.

There was a non-significant trend for those with at least 20 teeth and those dentate without periodontitis to be more often alive at 10 years.

Factors showing independent association with elevated CRP were the presence of mucosal lesion (RR 2.18, CI 1.03-4.61) and high salivary microbial count (RR 2.31, CI 1.06-5.05) (Table 3). Mucosal lesion was also significantly associated with high salivary microbial count (Table 3).

Periodontal status, edentulism and mortality

Unadjusted, edentulism was significantly associated with increased total and CVD mortality, as it was with total mortality when adjusted for age and sex. After adjusting for all confounders (age, sex, history of CVD, blood pressure, body mass index, cholesterol, social class and smoking), these associations lost statistical significance.

Table 1. Relationship of baseline characteristics with status in 1999, and baseline periodontal (PD) status (percentage in parentheses)

Baseline characteristics	Status in 1999			Periodontal (PD) status			
	Dead n = 179	Alive n = 185	*p*	PD – n = 95	PD + n = 80	Edentulous† n = 189	*p*
Age:							
76 years	54 (33)	111 (67)		53 (32)	41 (25)	71 (43)	
81 years	57 (54)	49 (46)		23 (22)	25 (24)	58 (54)	
86 years	68 (73)	25 (27)	<0.0001	19 (20)	14 (15)	60 (65)	0.01
Women	125 (48)	137 (52)	0.37	71 (27)	49 (19)	142 (54)	0.05
Social class:							
Class I	15 (39)	24 (61)		12 (31)	12 (31)	15 (38)	
Class II	30 (38)	49 (62)		30 (38)	18 (29)	31 (39)	
Class III	68 (48)	74 (52)		36 (25)	35 (25)	71 (50)	
Class IV	43 (61)	27 (39)	0.02	14 (20)	10 (14)	46 (66)	0.02
Current smoker	17 (53)	15 (47)	0.43	3 (9)	5 (16)	24 (75)	0.01
Alcohol (≥once a week)	23 (51)	22 (49)	0.55	9 (20)	10 (22)	26 (58)	0.39
Diabetics	36 (66)	19 (34)	0.03	15 (27)	11 (20)	29 (53)	0.56
Hypertensives	64 (52)	63 (48)	0.94	36 (28)	24 (19)	67 (53)	0.28
BMI (kg/m_)	25.2±3.6	26.1±3.8	0.03	25.6±3.7	25.5±3.5	25.8±3.8	0.88
Systolic blood pressure (mm Hg)	154±26.0	159±24.9	0.04	160±24.8	155±24.9	155±26.1	0.38
Diastolic blood pressure (mm Hg)	81±11.6	83±11.9	0.05	85±13.9	80±12.1	81±11.6	<0.01
Serum cholesterol (mmol/L)	6.3±1.2	6.7±1.3	0.001	6.6±1.3	6.3±1.2	6.6±1.2	0.28
Serum HDL (mmol/L)	1.5±0.5	1.5±0.5	0.36	1.5±0.5	1.5±0.4	1.5±0.4	0.94
Serum triglyceride (mmol/L)*	1.4±0.8	1.4±0.8	0.62	1.5±0.9	1.2±0.6	1.4±0.7	0.05

† Edentulous also includes few of those who did not meet the CPITN criteria (i.e. had < 2 teeth per sextant)
Values are mean±SD.

Statistical evaluation by Chi square test and ANOVA

* Statistical evaluation by Kruskal-Wallis Test

After adjusting for confounders, periodontitis was associated with almost a two-fold CVD mortality (RR 1.97, CI 1.01-3.85); the association with total mortality fell short from being statistically significant (Table 4).

Table 2. Dental factors associated with elevated CRP levels, high microbial (*Streptococcus mutans* and yeast) count and 10-year survival (Percentage in parentheses)

Oral status	CRP value*			Microbial count*			Alive at 10 years*	
	Low n = 188	Elevated n = 69	*p*	Low n = 93	High n = 132	*p*	n=185	*p*
No.of teeth:	77 (64)	43 (36)		47 (34)	91 (66)		80 (48)	
1-9 teeth	46 (75)	15 (25)		35 (48)	38 (52) [a]		37 (46)	
10-19 teeth	31 (82)	7 (18)		17 (31)	38 (69)		31 (50)	
20-32 teeth	34 (90)	4 (10) [b]	0.02	25 (53)	22 (47) [a]	0.02	37 (70) [b]	0.08
Periodontal (PD) status:								
PD –ve	53 (81)	13 (19) [c]		40 (46)	46 (54)		61 (64) [d]	
PD +ve	45 (82)	10 (18) [c]		30 (40)	45 (60)		41 (51)	
Edentulous†	88 (66)	46 (34)	0.03	54(35)	98 (65)	ns	83 (44)	0.05
Denture status:								
Dentate without dentures	38 (86)	6 (14) [f]		31 (55)	25 (45) [f]		42 (65) [e]	
Dentate with dentures	66 (77)	20 (23)		44 (39)	69 (61)		62 (50) [e]	
Edentulous with CD	82 (66)	43 (34)	0.03	46 (33)	94 (67)	0.03	80 (46)	0.09
Denture stomatitis:								
No	130 (77)	39 (23)		103 (48)	112 (52)		113 (54)	
Yes	48 (64)	27 (36)	0.04	19 (22)	69 (78)	<0.0001	50 (50)	ns
Dentures and stomatitis:								
No CD without stomatitis	57 (85)	10 (15)		45 (50)	45 (50)		61 (59)	
No CD with stomatitis	8 (80)	2 (20)		1 (8)	11 (92) [g]		9 (64)	
CD without stomatitis	74 (72)	29 (28)		59 (47)	67 (53)		72 (50)	
CD with stomatitis	38 (60)	25 (40) [h]	0.02	17 (23)	57 (77) [i]	<0.0001	40 (48)	ns
Mucosal lesions:								
No	110 (80)	28 (20)		90 (49)	95 (51)		113 (55)	
Yes	68 (64)	38 (36)	0.01	31 (26)	86 (74)	<0.0001	69 (49)	ns
Inflammation of the mouth:								
No	118 (78)	34 (22)		97 (48	104 (52)		123 (55)	
Yes	60 (65)	32 (35)	0.05	25 (24)	77 (76)	<0.0001	60 (49)	ns
CRP value:								
Low (< 3 mg/l)				76 (45)	93 (55)		98 (52)	
High (≥3 mg/l)				17 (30)	39 (70)	0.07	29 (42)	ns

* Adjusted for age and sex

† Edentulous also includes few of those who did not meet the CPITN criteria (i.e. had < 2 teeth per sextant)
Statistical evaluation by Chi square test

[a] Differs significantly from "No teeth group", p<0.05; [b] Differs significantly from "No teeth group", p<0.01.

[c] Differs significantly from "Edentulous group", p<0.05; [d] Differs significantly from "Edentulous group", p<0.01.

[e] Differs significantly from "Edentulous with CD group", p<0.05; [f] Differs significantly from "Edentulous with CD group", p<0.01.

[g] Differs significantly from "No CD without stomatitis group", p<0.05; [h] Differs significantly from "No CD without stomatitis group", p=0.005; [i] Differs significantly from "No CD without stomatitis group", p=0.000

Table 3. Adjusted odds ratios for elevated baseline CRP levels and high salivary microbial counts associated with oral infections

Dependent variables	Independent variables	Odds ratio*	95% CI	Odds ratio**	95% CI
Elevated CRP	Teeth	0.95	(0.91 – 1.00)	0.95	(0.90– 1.00)
	Mucosal lesions (0=No, 1=yes)	2.10	(1.02 – 4.36)	2.18	(1.03 – 4.61)
	Microbial count (0=low, 1=high)	2.13	(1.00 – 4.53)	2.31	(1.06 – 5.05)
Elevated microbial count	Teeth	0.99	(0.96 – 1.03)	0.99	(0.96– 1.04)
	Mucosal lesions (0=No, 1=yes)	2.15	(1.34 – 4.07)	2.13	(1.11 – 4.11)

Logistic regression model used

* Adjusted for age and sex

** Adjusted for age, sex, history of smoking, alcohol consumption, blood pressure, social class [and presence of established risk factors for elevated CRP like emphysema or chronic bronchitis or asthma or muscle and joint disease (only for high CRP)]

(None of these variables were significant in the model)

Table 4. Periodontal status and risk of all-cause and cardiovascular mortality

	Unadjusted		Adjusted for age and sex		Adjusted for other confounder	
	Hazards ratio	95% CI	Hazards ratio	95% CI	Hazards ratio	95% CI
All-cause mortality*						
Periodontal disease						
0=No	1.00		1.00		1.00	
1=Yes	1.58	(0.97 – 2.59)	1.59	(0.97 – 2.61)	1.58	(0.96 – 2.61)
2=Edentulous†	1.85	(1.21 – 2.82)	1.57	(1.03 – 2.41)	1.48	(0.95 – 2.31)
CV mortality**						
Periodontal disease						
0=No	1.00		1.00		1.00	
1=Yes	1.86	(0.96 – 3.58)	1.94	(1.00 – 3.75)	1.97	(1.01 – 3.85)
2=Edentulous†	1.90	(1.06 – 3.39)	1.52	(0.85 – 2.74)	1.40	(0.76 – 2.59)

† Edentulous also includes few of those who did not meet the CPITN criteria (i.e. had <2 teeth per sextant)

* Cox regression model adjusted for confounders like age, sex, social class, body mass index, smoking status, blood pressure and serum cholesterol level

** Cox regression model adjusted for confounders like age, sex, history of cardiovascular disease, social class, body mass index, smoking status, blood pressure and serum cholesterol level

Discussion

Our study identified mucosal lesions in the edentulous as an important factor associated with elevated CRP levels among individuals aged 75 or more. Furthermore, periodontal disease was associated with a two-fold CVD mortality even in this age group.

Participants of this study are representative of the home-dwelling elderly of Helsinki. They underwent a series of in-depth medical and dental examinations during the10-year study period. Such a dental study on subjects aged over 75 years, has not been undertaken before.

The mechanism behind elevated CRP and increased CVD risk is unclear. Recent data suggest that elevated CRP levels may at least partly reflect extravascular infections, including periodontitis, which are among the causes of endothelial dysfunction linked with CVD[30,31]. CRP is elevated in periodontitis and this may be one of the reasons for the association between periodontitis and CVD[7-10]. Corresponding data in edentulous elderly are very few or missing. In the NHANES III[15], the age standardised prevalence of elevated CRP was significantly higher among the edentulous than in those with no pockets, but did not differ

significantly from those with extensive periodontal pockets. In our study, after adjusting for age and sex, a higher percentage of edentulous subjects had elevated CRP level, as compared with the dentate with or without periodontal disease.

The reasons for CRP being elevated in edentulous individuals are not well understood. However, it is well known that with ageing, oral mucosa becomes more vulnerable to mechanical damage[32]. Dentures, inability to maintain optimal oral hygiene, hyposalivation and various medications create an environment that favours microbial growth and make the elderly subjects highly prone to mucosal changes[15,33]. Earlier studies have shown that Gram-positive cocci like mutans streptococci may act as adherence bacteria for yeasts and helping them to attach to the mucosal surface[34], resulting in chronic oral candidiasis. Co-aggregation with mutans streptococci has also been found to increase the adhesion of *C.albicans* on acrylic surfaces[35]. The candida proteinase acts as a keratinase-like enzyme in vitro and may damage the keratinized palatal mucosa[36]. In our study population, mucosal lesions and high salivary microbial counts were significantly associated with elevated CRP levels. Both these conditions were significantly more common among the edentulous with complete dentures. Importantly, those having clinical signs of oral candidosis or denture stomatitis also showed elevated levels of CRP and microbial counts. These inflammatory changes in the oral cavity may thus explain the elevated CRP levels seen in the edentulous.

NHANES I[14], an epidemiologic follow-up study, examined the CHD risk among the edentulous, considered "free of all potential dental infections". The study showed that the risk of CHD among the edentulous was higher than in dentate individuals without periodontitis. In our study, both periodontal disease and edentulism were associated with elevated CVD mortality. However, after adjusting for potential confounders, only periodontitis was associated with significantly increased CVD mortality in these very old individuals.

Among the participants of the HAS medical examination (n=651), significant association was observed between CRP and mortality[6]. However, in the current study (n=364), the association was not statistically significant. This is noteworthy, and probably reflects the fact that participants with high CRP originally included in the HAS had already died before the current study cohort was formed. Most of the effect of CRP on mortality - whatever the mechanisms are - had already taken place and the current results probably represent a "remnant" of the joint effect of chronic infection and elevated CRP.

In conclusion, our study in these very old subjects showed that edentulism is associated with elevated CRP levels, suggesting that loss of teeth does not mean absence of infectious conditions in the oral cavity. Mucosal lesions and high microbial count commonly found among the elderly may be equally important risk factors for elevated CRP levels as periodontal disease. Another important finding of the study was that periodontal disease carried a two-fold CVD mortality during a 10-year follow-up even in this age group.

Increasing attention should be paid to denture hygiene habits of the elderly. Further research is needed to study the denture-related micro flora and its local and systemic effects.

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