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Self-reported gingivitis and tooth loss poorly predict C-reactive protein levels: a study among Finnish young adults

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Abstract

Objectives: Our aim in this cross-sectional study was to investigate whether self-reported gingivitis and tooth loss were associated with elevated levels of C-reactive protein (CRP) using the same study population where these dental conditions have earlier been associated with prevalent angina pectoris.

Material and Methods: The study population consisted of those Northern Finland birth cohort 1966 members who lived in Northern Finland or in the Helsinki region ($n = 8463$) at the time of the survey (1996–1997). The participation rate in a health examination was 71% ($n = 6033$). Gingivitis and tooth loss were determined on the basis of self-reported questions. Prevalence proportion ratios (PPR) and 95% confidence intervals (CI) were estimated using multivariate regression models.

Results: The results showed that self-reported gingivitis and tooth loss were weakly associated with elevated levels of CRP (> 3 mg/l): adjusted PPR 1.1, CI 1.0–1.3 and PPR 1.1, CI 0.7–1.7, respectively. The proportion of variation in CRP explained by self-reported gingivitis and tooth loss was small, being $< 1\%$.

Conclusion: The results suggest that self-reported gingivitis and tooth loss have a miniscule effect on CRP levels among a general population of young adults.

Key words: CRP; dental diseases; inflammation

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C-reactive protein (CRP) is a marker of unspecific inflammation, which has been found to predict cardiovascular events (Koenig 2005). To date, it is known that factors such as stress, inflammatory diseases, smoking, diet, lack of physical exercise, obesity and atherosclerotic lesions increase CRP levels (Labarrere & Zaloga 2004). Whether chronic oral infections such as gingivitis or periodontitis increase CRP levels is not clear.

Observational non-experimental studies have shown that subjects who have periodontal infections such as gingivitis (Wu et al. 2000) and periodontitis (Fredriksson et al. 1999, Noack et al. 2001, Loos 2005, Montebugnoli et al. 2005) have higher levels of CRP than subjects without gingivitis and periodontitis, respectively, supporting the hypothesis that these oral infections increase CRP levels. On the other hand, the results of randomized intervention studies, in which the aim has been to reduce CRP levels through periodontal therapy, are less convincing and do not support unequivocally the hypothesis that periodontal infection could have an effect on CRP levels (Ioannidou et al. 2006).

Besides its role as a marker of inflammation, CRP is a causal factor in the pathogenesis of atherosclerosis (Pepys & Hirschfield 2003, Kluft 2004). Should an association between oral infections and CRP exist, it would support the assumption of a causal association of oral infections through systemic inflammation to atherosclerosis and consequently to coronary heart disease.

We have earlier reported in this population that self-reported gingivitis, tooth loss and dental caries and were all associated with diagnosed angina pectoris, which is often a sign of underlying coronary heart disease (Ylöstalo

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et al. 2006). A logical extension to our previous findings was to study the role of CRP in these associations. Our aim in this paper was to study whether self-reported gingivitis and tooth loss were associated with elevated levels of CRP in a general population of young adults aged 31 years.

Material and Methods

The Northern Finland birth cohort covered 96% of all births in 1966 (n = 12,058) in the provinces of Lapland and Oulu (Rantakallio 1988). Data on oral and general health as well as data on health habits were collected through a postal questionnaire, which was sent to all cohort members whose address was known (n = 11,541). The response rate was 75% (n = 8690).

The present study was based on a subpopulation of the cohort consisting of all members of the cohort who lived in Northern Finland and in the Helsinki region (n = 8463) at the time of the survey (1996–1997). These subjects were invited to a health examination, which included CRP and serum lipid determinations. The participation rate in the health examination was 71% (n = 6033). Twenty subjects refused to participate in the study after a health examination.

The subjects participated in a 31-year follow-up of this cohort after providing informed consent. The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine, Oulu University.

Laboratory tests

Blood samples were taken after an overnight fast. High sensitive CRP levels were quantified with a highly sensitive immunoenzymometric assay. Serum total cholesterol, high-density lipoprotein (HDL) and triglycerides were determined using standard enzymatic methods.

Explanatory variables

Gingivitis was determined on the basis of the following question: ''In your opinion, do your gums bleed when you brush your teeth?'' (No/Yes). Tooth loss was determined using a question on how many missing teeth respondents had (0, 1–5, 6–10, more than 10 but not all, all). Answers were classified into two categories according to the number of missing teeth (0–5 teeth missing *versus* 6 or more teeth missing).

Potential confounders

Systemic diseases (diabetes, rheumatoid arthritis, elevated blood pressure, angina pectoris) were determined on the basis of the following questions: ''Have you ever had 'disease in question' diagnosed by a doctor?'' The subjects' body mass index (BMI) was based on self-reported measurements of weight and height.

Data on dental caries were determined using the question: ''In your opinion, do you have caries in your teeth at the moment?''(No/Yes).

The amount of tobacco smoked (pack-years) was calculated for those who smoked regularly almost every day. The smokers were classified into three categories on the basis of pack-years (0–5, 6–10, 11 or more). Non-frequent smokers and non-smokers each formed a category of their own.

Use of alcoholic beverages was classified into three categories based on drinking habits (no use, moderate use and abundant use). Where the amount of alcoholic beverages normally used was more than three portions of wine (16 cl) or beer (33 cl), or three to four portions of spirits (4 cl), this was classified as abundant use. The estimated mean alcohol intake was 5 g a day in the group of moderate users and 17.1 g a day among the abundant users' group.

Physical exercise was determined by the frequency of physical exercise: more than three times a week *versus* less. Consumption of vegetables was determined also by frequency of use: at least three times a week *versus* less.

Statistical methods

We estimated prevalence proportion ratios (PPR) and their 95% confidence intervals (CI) using generalized linear models. We chose a binomial distribution and a log link function (Skov et al. 1998). Adjusted PPR were estimated using a log link function, Poisson distribution and an unstructured correlation matrix (Zou et al. 2004). The selection of potential confounders was based on previous knowledge.

Categorization of CRP (3 mg/l as a cut-off value) as well as categorization of serum total cholesterol, HDL cholesterol and triglycerides was performed on the basis of a statement by the American Heart Association and Centers for Disease Control and Prevention (Pearson et al. 2003). In order to exclude the possibility of residual confounding related to dichotomizing continuous explanatory variables, we performed an additional analysis where originally continuous covariates were not dichotomized.

We calculated the proportion of explained variation using a linear regression model. A logarithmic transformation of CRP was made to normalize the skewed distribution of CRP before fitting a linear regression model.

The data were analysed using SAS statistical package, version 9.1, PROC GENMOD and PROC GLM procedures. The test for homogeneity was performed using Rothman's EPISHEET programme.

Results

In this population, the mean CRP level was 2.0 mg/l whereas the median CRP was 0.8 mg/l. Among those who reported having gingivitis, the mean CRP was 2.2 mg/l, whereas among subjects who did not have gingivitis it was 2.0 mg/l. The mean CRP levels did not differ between subjects who had lost six or more teeth and those who had less than six teeth missing, being 2.0 mg/l in both groups.

The proportions of subjects having elevated levels of CRP in relation to potential determinants of CRP are presented in Table 1. It can be observed that especially diabetes and rheumatoid arthritis patients as well as subjects with classical cardiovascular risk factors such as an unfavourable lipid composition or who were overweight were more likely to have elevated levels of CRP (> 3 mg/l) compared with their healthy counterparts. Subjects who had lost teeth (six or more) or who reported having gingivitis were also more likely, but to a lesser extent, to have elevated levels of CRP (> 3 mg/l) compared with their dentally healthy counterparts (Table 1).

We found that subjects with gingivitis or subjects who had lost six or more teeth were about 10% more likely to have elevated levels of CRP (> 3 mg/l) after controlling for potential confounders than did subjects without these conditions (PPR 1.1, CI 1.0–1.3 and PPR 1.1, CI 0.7–1.7, respectively). The effects of cardiovascular risk factors as well as systemic diseases such as diabetes and rheumatoid arthritis were

Table 1. Proportion of subjects having elevated levels (>3 mg/l) of CRP according to selected determinants

	n	%	PPR (95% CI)
Gender			
Female (52.1%)	644/2993	21.5	1.7 (1.5–1.9)
Male (47.9%)	343/2748	12.5	1.0
Gingivitis			
Yes (23.8%)	256/1339	19.1	1.2 (1.0–1.3)
No (76.2%)	707/4276	16.5	1.0
Tooth loss			
6 or more missing teeth (2.3%)	26/131	19.9	1.2 (0.8–1.6)
0–6 missing teeth (97.7%)	934/5485	17.0	1.0
Self-reported caries			
Yes (35.2%)	348/1986	17.5	1.0 (0.9–1.2)
No (64.8%)	620/3650	17.0	1.0
Diagnosed hypertension			
Yes (12.0%)	143/684	20.9	1.3 (1.1–1.5)
No (88.0%)	836/5032	16.6	1.0
Diagnosed angina pectoris			
Yes (1.5%)	25/88	28.4	1.7 (1.2–2.3)
No (98.5%)	954/5625	17.0	1.0
Diabetes			
Yes (1.2%)	24/69	34.8	2.1 (1.4–2.8)
No (98.8%)	956/5652	16.9	1.0
Rheumatoid arthritis			
Yes (1.1%)	25/63	39.7	2.3 (1.7–3.1)
No (98.9%)	956/5658	16.9	1.0
Body mass index			
− 20 (8.7%)	53/483	11.0	1.0
20.01–23.00 (31.1%)	219/1732	12.6	1.2 (0.9–1.5)
23.01–25.00 (22.8%)	152/1271	12.0	1.1 (0.8–1.5)
25.01–27.00 (17.2%)	174/954	18.2	1.7 (1.3–2.2)
27.01–(20.2%)	347/1124	30.7	2.8 (2.2–3.7)
Total cholesterol			
5.2 mmol or more (41.0%)	450/2348	19.2	1.2 (1.1–1.4)
Less than 5.2 mmol (59.0%)	535/3384	15.8	1.0
HDL cholesterol			
1.04 mmol or less (5.8%)	92/335	27.5	1.7 (1.4–2.0)
More than 1.04 (94.2%)	893/5397	16.6	1.0
Triglycerides			
2.26 mmol or more (7.5%)	118/429	27.5	1.7 (1.4–2.0)
Less than 2.26 mmol (92.5)	867/5302	16.4	1.0
Alcohol use			
Non-users (9.1%)	108/516	20.9	1.0
Abundant use (43.4%)	407/2453	16.6	0.8 (0.7–1.0)
Moderate use (47.5%)	457/2688	17.0	0.8 (0.7–1.0)
Smoking			
Never smokers (36.7%)	352/2043	17.2	1.0
Irregular smokers (14.2%)	122/792	15.4	0.9 (0.7–1.1)
0–5 pack-years (26.4%)	237/1466	16.2	0.9 (0.8–1.1)
6–10 pack-years (10.1%)	97/561	17.3	1.0 (0.8–1.2)
11– pack-years (12.6%)	138/698	19.8	1.1 (1.0–1.1)
Physical exercise			
Less than 4 times/week (52.9%)	542/2995	18.1	1.1 (1.0–1.3)
At least 4 times/week (47.1%)	433/2667	16.2	1.0
Use of vegetables			
Less than 3 times/week (42.7%)	410/2427	16.9	1.0 (0.9–1.1)
At least 3 times/week (57.4%)	564/3263	17.3	1.0

CRP, C-reactive protein.

stronger than the effects of self-reported gingivitis or tooth loss (Table 2).

Self-reported gingivitis and tooth loss together accounted for <1% of the overall explained variation. The results showed that gender, BMI and unfavourable lipid composition accounted for about 90% of the explained variation in CRP levels (Fig. 1). The proportion of variation explained by the model was 11.5%.

We did not detect any essential modification in the relations of gingivitis and tooth loss to elevated levels of CRP by BMI (test for homogeneity: 0.26 and 0.78, respectively).

Discussion

We have reported previously that self-reported gingivitis, dental caries and tooth loss were associated with prevalent angina pectoris (Ylöstalo et al. 2006). In this paper, our aim was to investigate, using the same study population, whether self-reported gingivitis and tooth loss were also associated with CRP levels. The existence of such an association would support the hypothesis that these dental diseases are related through systemic inflammation to atherosclerosis and consequently to coronary heart disease.

The results of this study showed that self-reported gingivitis and tooth loss were weakly associated with elevated CRP levels. This suggests that associations in this population between dental conditions and prevalent angina pectoris are not mainly due to mechanisms related to an inflammatory response. An alternative explanation is that the associations are due to confounding. This would also comply with the results of our earlier studies, which have shown that unhealthy dental health habits as well as dental conditions such as self-reported gingivitis, tooth loss and dental caries were, in this same study population, associated with several risk factors for cardiovascular diseases including behavioural risk factors such as unhealthy diet, lack of physical activity, smoking and heavy consumption of alcohol as well as biological risk factors such as obesity, high waist circumference, elevated blood pressure and unfavourable serum lipid levels (Ylöstalo et al. 2003, 2006).

Previous observational non-experimental studies have consistently shown that periodontal infections such as gingivitis (Wu et al. 2000) and periodontitis (Fredriksson et al. 1999, Noack et al. 2001, Loos 2005, Montebugnoli et al. 2005) associate with elevated levels of CRP. Moreover, some intervention studies have shown that periodontal treatment reduces CRP levels (Mattila et al. 2002, Iwamoto et al. 2003, D'Aiuto et al. 2004, 2005, Yamazaki et al. 2005). At present, a few randomized intervention studies on the effect of periodontal treatment on CRP levels also exist. Meta-analysis based on these studies showed no

Table 2. Factors associated with elevated levels (>3 mg/l) of CRP

	PPR	95% CI
Gender (female *versus* male)	2.3	2.0–2.7
Gingivitis (yes *versus* no)	1.1	1.0–1.3
Tooth loss six or more teeth *versus* 0–5 teeth	1.1	0.7–1.7
Elevated blood pressure (yes *versus* no)	1.0	0.8–1.2
Angina pectoris (yes *versus* no)	1.6	1.0–2.4
Diabetes (yes *versus* no)	1.3	0.8–2.0
Rheumatoid arthritis (yes *versus* no)	2.3	1.5–3.4
Body mass index		
20 or less	1.0	
20.01–23.00	1.3	1.0–1.8
23.01–25.00	1.4	1.0–2.0
25.01–27.00	2.3	1.6–3.2
27.01–	3.3	2.4–4.6
Total cholesterol (5.2 mmol or more *versus* less)	1.1	0.9–1.2
HDL cholesterol (1.04 mmol or less *versus* more)	1.3	1.0–1.6
Triglycerides (2.26 mmol or more *versus* less)	1.3	1.1–1.6
Alcohol use		
Non-users	1.0	
Abundant use	0.9	0.7–1.1
Moderate use	0.8	0.7–1.1
Smoking		
Never smokers	1.0	
Irregular smokers	0.9	0.7–1.1
0–5 pack-years	0.9	0.8–1.1
6–10 pack-years	1.0	0.8–1.3
11– pack-years	1.3	1.0–1.6
Physical exercise (<4 times/week *versus* ⩾4 times/week)	1.1	0.9–1.2
Use of vegetables (<3 times/week *versus* ⩾3 times/week)	1.0	0.9–1.2

Adjusted prevalence proportion ratios (PPR) and their 95% confidence intervals (95% CI). Adjusted for other variables presented in the table. ($n = 5121$).
CRP, C-reactive protein.

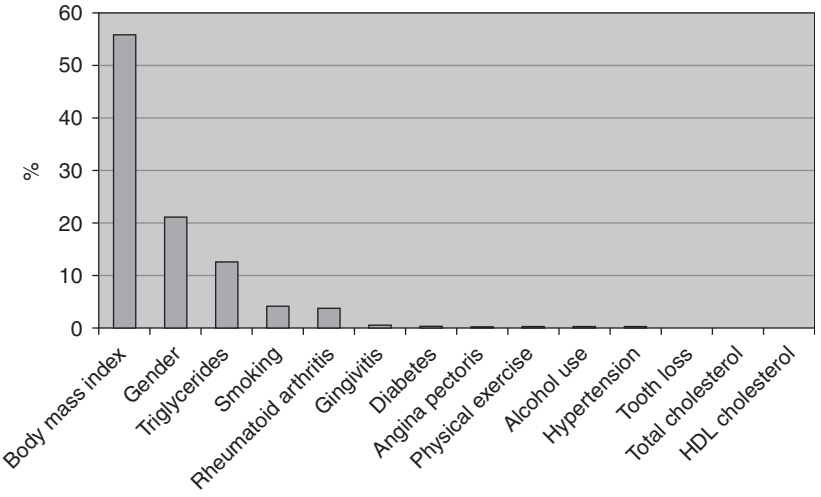

Fig. 1. The proportion of variance explained by the selected determinants of CRP.

statistically significant effect on CRP levels (Ioannidou et al. 2006). Methodological differences, especially those related to confounding, most likely explain the discrepancy in results between observation non-experimental studies, non-randomized intervention studies and randomized intervention studies.

The relative importance of oral infections on CRP is to date largely unknown, because studies on the determinants of CRP in the field of general epidemiology do not normally include oral infections in their analyses. The results of this study, where cardiovascular risk factors and self-reported dental conditions such as gingivitis and tooth loss were simultaneously included in the analysis, showed that cardiovascular risk factors were important determinants of CRP and that self-reported gingivitis and tooth loss were of minor importance. The findings that cardiovascular risk factors were important determinants are in congruence with those studies in the field of general epidemiology that have shown that CRP levels are mostly determined by cardiovascular risk factors, especially obesity (Yamada et al. 2001, Yusuf et al. 2004, Miller et al. 2005). These findings, as well as findings of other studies showing correlations as high as 0.6–0.7 between BMI and CRP (Piche et al. 2005, Guldiken et al. 2007), indicate that cardiovascular risk factors, especially obesity, are important determinants of CRP and thus potential confounders in the association of oral infections with CRP levels.

The importance of oral infections as a source of CRP was also studied by Slade et al. (2003) using the same data as Miller and colleagues. They did not report the relative importance of periodontal infection but showed that the association between periodontal infection and CRP was modified by BMI (Slade et al. 2003); the effect of periodontal infection was pronounced among subjects of normal weight whereas among obese subjects it was marginal. Contrary to this finding, we detected no interaction between BMI and gingivitis or tooth loss in the present study. Whether BMI is also an effect modifier remains to be determined in future studies.

Validity issues

The study population consisted of members of the Northern Finland birth cohort of 1966 who lived in Northern Finland or in the capital city area of Finland at the time of the survey in 1996–1997. This means that the study population is homogenous in relation to age and ethnic origin. In addition, in the multivariate model we controlled for factors such as gender, BMI, serum lipid composition, diet, smoking, alcohol use, systemic diseases and physical exercise, meaning that the possibility of substantial bias due to confounding is not likely.

We also performed additional multivariate analyses where covariates, such as BMI and lipid values, were used as continuous variables. These analyses showed that there was no evidence on residual confounding related to the

dichotomizing of these variables. In addition, all potential confounders except gender were associated with CRP levels in an expected manner, which indicates that the determination of diseases based on self-reported questions and measurements of health habits have been quite successful. Contrary to the findings of some studies, in this study women had higher CRP levels than men. This is possibly related to the use of hormonal contraceptives, which are known to increase CRP levels (Williams et al. 2004).

One shortcoming was that we used self-reported diseases as explanatory variables. On the other hand, these are the same dental conditions – self-reported gingivitis, tooth loss and dental caries – which we have earlier found to associate with behavioural risk factors for cardiovascular diseases (Ylöstalo et al. 2003) and prevalent angina pectoris (Ylöstalo et al. 2006).

Previous studies suggest that easily detectable dental conditions correspond quite well with clinical findings (Axelsson & Helgadottir 1995, Unell et al. 1997). One example of this is the number of missing teeth. We chose a cut-off point of six lost teeth to avoid misclassification due to extractions of third molars, minor traumas and extractions related to orthodontic treatment. The validity of tooth loss cannot be assessed in this study, but our previous results support the assumption that there is no substantial misclassification, because tooth loss in this same study population behaved in an expected manner in relation to its determinants such as health habits and socioeconomic factors (Ylöstalo et al. 2004).

Poor agreement between self-reported gingival bleeding and gingivitis has been observed earlier. For example, a study by Buhlin et al. (2002) demonstrated that agreement between self-reported gingival bleeding and the findings of clinical examination is low. Misclassification most likely occurred in this study too, because the prevalence of self-reported gingivitis was lower than that found in the nationally representative study, where gingivitis was clinically determined (Suominen-Taipale et al. 2004). There was no information on periodontitis in this study, which is one of the shortcomings in this study. One additional shortcoming, related to both explanatory variables, was that there are no gradients in these variables, which was due to the small number of lost teeth and the manner in which gingivitis was determined.

When estimating the effect of misclassification, it must be borne in mind that misclassification of exposure, if non-differential, normally attenuates the effect. This means that it is possible that the true effect is more distinct than that observed.

Conclusion

Our motivation for this study was to produce evidence on the nature of the association between self-reported dental conditions and cardiovascular diseases. To this end, we studied the association of gingivitis and tooth loss with CRP levels in a population where self-reported dental diseases have earlier been found to associate with prevalent angina pectoris. This study showed that the association of self-reported gingivitis and tooth loss with elevated levels CRP was weak and that the proportion of explained variation in CRP by self-reported gingivitis and tooth loss was miniscule when compared with the effects of traditional cardiovascular risk factors. Hence, our findings in this study do not support the conception that previously detected associations between self-reported dental diseases and prevalent angina pectoris among the cohort members could be explained by a mechanism related to inflammatory response.

Based on restrictions related to the data, we must present important reservations: it must be underlined that the results of this study cannot be generalized to a general population due to the fact that the data consist of 31-year-old adults and the dental conditions were self-reported, not clinically determined. Therefore, it must be emphasized that the results of this study do not exclude the possibility that a causal association between oral infections and cardiovascular diseases as well as between dental infection and CRP levels exists.

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Clinical Relevance

Scientific rationale for the study: To investigate whether the association of self-reported gingivitis and tooth loss with prevalent angina pectoris is mediated through inflammatory response related to elevated CRP levels in a population where the associations between self-reported dental conditions and angina pectoris have been found earlier.

Principal findings: Self-reported gingivitis and tooth loss were weakly associated with elevated levels of CRP. The effect of gingivitis and tooth loss on CRP levels was small compared with the effect of traditional cardiovascular risk factors.

Practical implications: The results suggest that the role of cardiovascular risk factors as potential confounders should not be underestimated when analysing associations between dental diseases and CRP.