Pulpal Inflammation and Incidence of Coronary Heart Disease

Kaumudi J. Joshipura, ScD,[*†‡] *Waranuch Pitiphat, ScD,*[*†§] *Hsin-Chia Hung, ScD,*[†‖] *Walter C. Willett, DrPH,*[†¶#] *Graham A. Colditz, ScD,*[†#] *and Chester W. Douglass, PhD*[*†]

Abstract

Pulpal inflammation is primarily caused by coronal caries, and leads to root canal therapy (RCT). Chronic inflammation has been associated with various cardiovascular diseases. This study evaluates the association between pulpal inflammation (using RCT as a surrogate) and incident coronary heart disease (CHD). We report results among males from the Health Professionals Follow-Up Study (HPFS), excluding participants with prior cardiovascular disease or diabetes. We obtained RCT data from the HPFS cohort (n = 34,683). Compared to men without RCT, those with ≥1 RCT had a multivariate RR of 1.21 (95% CI 1.05-1.40) for CHD. The association was limited to dentists (RR = 1.38; 95% CI 1.14-1.67). There was no association among nondentists (RR = 1.03). Dental caries was not associated with CHD. The results suggest a possible modest association between pulpal inflammation and CHD. *(J Endod 2006;32:99–103)*

Key Words

Cardiovascular disease, caries, epidemiology, inflammation, root canals

From the *Department of Oral Health Policy and Epidemiology, Harvard School of Dental Medicine, and the †Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; ‡Division of Dental Public Health, University of Puerto Rico School of Dentistry, San Juan, Puerto Rico; §Department of Community Dentistry, Khon Kaen University, Thailand; ‖Institute of Health Care Management, National Sun Yat-sen University, Taiwan; ¶Department of Nutrition, Harvard School of Public Health; and the #Channing Laboratory and the Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts.

Address requests for reprint to Dr. Kaumudi Joshipura, Department of Oral Health Policy & Epidemiology, Harvard School of Dental Medicine, 188 Longwood Avenue, Boston, MA 02115. E-mail address: kjoshipura@hsdm.harvard.edu

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Dental infections have been associated with cardiovascular disease. Several studies have also shown associations between tooth loss and coronary heart disease (CHD) (1, 2) but we do not know the mechanisms or whether these associations are causal. Although antecedent periodontal disease may be a possible explanation, the data suggest that the association between tooth loss and CHD cannot be completely explained by periodontal disease (3). Antecedent dental caries and endodontic inflammation may also possibly contribute to the associations. Although some studies have found associations between a composite measure of oral health (including dental caries, periapical lesions, missing teeth, and periodontal disease) and cardiovascular disease (4, 5), very few studies have evaluated advanced dental caries or pulpal inflammation /root canal therapy (RCT) separately.

The study by Grau (5), a small case-control study, showed a multivariate odds ratio (OR) of 2.60 (95% CI: 1.2-5.7) between a composite dental disease index and stroke. When the composite index was broken up into individual components, stroke patients were more likely to have peri-apical lesions (p = 0.03 without controlling for confounders). There was no association between carious teeth or nonvital teeth and ischemic stroke. Another study by Jansson (6) suggested that the number of peri-apical lesions and number of carious surfaces were significantly associated with cardiovascular death controlling for age and gender. In a multivariate analysis controlling for confounders that evaluated peri-apical lesions, carious surfaces and a composite measure (combining peri-apical and carious lesions and periodontal disease), only the composite measure was significantly associated with cardiovascular death. A recent cross-sectional study among 1056 women in Sweden (7) showed a significant crude association between number of RCT teeth (2 or more vs 0) and CHD. However, the associations were not significant in a multivariate model that included CHD risk factors as well as number of teeth.

Pulpal inflammation is caused primarily by coronal caries. Pulpitis leads to a periapical inflammatory response, which in turn may lead to a systemic inflammatory response that may increase CHD risk. RCT attempts to eradicate the microorganisms in the root canal biomechanically (8) or with intracanal antimicrobial agents (9). RCT is an elective procedure for teeth with acute nonreversible pulpitis (pulpal inflammation) to prolong the life of the teeth; the alternative treatment is extraction. We are assuming that RCT is for the most part a direct result of and therefore an appropriate surrogate measure of pulpal inflammation.

In this report, we evaluate the association of dental caries and pulpal inflammation, using RCT as a surrogate, with incident CHD within a large cohort study of health professionals. We wanted to test the hypothesis that pulpal inflammation may lead to increased risk of CHD.

Materials and Methods

The population for this report included participants in the Health Professionals' Follow-Up Study (HPFS). HPFS is an ongoing cohort study of male participants in the US that started in 1986, and included 51,529 male health professionals including dentists, veterinarians, pharmacists, optometrists, osteopaths, and podiatrists 40 to 75 yr old (10). Mailed questionnaires to obtain information on medical history, health behaviors, and the occurrence of cardiovascular and other outcomes, were completed every 2 yr by the participants.

RCT and dental caries questions were added in the 1996 questionnaires that were mailed to the whole HPFS cohort. The specific questions asked in 1996 were:

1. How many of your permanent teeth ever had root canal therapy? Responses were: 0, 1, 2-4, 5-9, and 10+
2. Indicate years of all occurrences: Before 1976, 1976-86, 1987-90, 1991 or later. Similar questions were also asked replacing root canal therapy with a cavity.

The RCT exposure variable was time-dependent, and individuals may change their RCT status over time. For example, someone who had no RCT between 1976 and 1986 would have been assigned to the unexposed group to predict the risk of developing CHD in 1987 through 1990. He would have been assigned to the exposed group in 1987 through 1990, to predict the risk of CHD in 1991 through 1996, if he had RCT in 1987 through 1990. Because RCT or caries before 1976 may likely be too distant in the past to be able to impact CHD incidence, and preliminary analyses confirmed this, the remaining analysis focused on occurrences between 1976 and 1996. For the primary analyses, we categorized RCT as none, or one or more root canals between 1976 and 1996. Because the majority of men had had 10 or more carious lesions, we categorized caries as 10+ or <10 teeth with caries history. Only participants who reported at least one carious lesion after 1976 were considered positive for caries.

Of the 43,233 participants who responded to the 1996 questionnaire, we included 43,058 participants who responded to the RCT and caries questions. We excluded 7,294 participants who reported myocardial infarction, stroke, re-vascularization procedures or diabetes before the follow-up and 1,081 participants who did not provide information on time periods for RCT from the analyses. Our final sample consisted of 34,683 participants who were included in the analyses.

Assessment of Endpoints

The primary end point for this study was incident CHD combining documented nonfatal myocardial infarction and fatal coronary disease, which have similar etiologies. We followed 34,683 eligible men and assessed incidence of CHD from 1986 to 2000. We reviewed the medical records for all participants who reported incident CHD. Records were reviewed by physicians who were unaware of the participants' dental status.

Myocardial infarction was confirmed using World Health Organization criteria: symptoms plus either diagnostic electrocardiographic changes or elevated cardiac enzymes (11). Infarctions that required hospital admission and for which confirmatory information was obtained by interview or letter, but for which no medical records were available, were designated as probable. The follow-up rate for nonfatal events was 97%. The fraction of self-reported cardiovascular events ultimately not confirmed by medical records or history was excluded from our case definition.

Deaths were identified from state vital records and the National Death Index or reported by next of kin, co-workers, and the postal system. Follow-up for the deaths was over 98% complete. Death certificates along with medical records were used to ascertain cause of death. Fatal coronary disease was defined as definite: (a) if it was confirmed from a hospital record or autopsy, or (b) if coronary disease was listed as the cause of death on the certificate and this was the underlying and most plausible cause, and evidence of previous coronary disease was available. If no medical records were available, we designated as probable CHD those cases in which CHD was the underlying cause on the death certificate. We also included as cases, sudden death within 1 hour of onset of symptoms with no plausible cause other than coronary disease. Among the total CHD cases, 33% were fatal. However, we only included those fatal cases that occurred after the 1996 questionnaire in our study.

Data Analyses

We documented 1,275 incident cases of CHD among eligible men who were free of CVD at baseline in 1986 when the study started. We evaluated the association between RCT and subsequent incident CHD: RCT from 1976 through 1986 was used to predict cases between 1987 and 1990; RCT from 1987 to 1990 was used to predict cases between 1991 and 1996; RCT from 1991 and 1996 was used to predict cases between 1997 and 2000. We also conducted analyses limited to recent or distant RCT, to assess the induction period. When we evaluated the number of RCT, we used RCT up to 1996 to predict cases in 1997 to 2000, because the number of teeth with RCT was assessed in 1996. We used Cox proportional hazards models to estimate relative risks (RR, incidence rate ratios) and 95% confidence intervals for the analysis. Caries was assessed as a binary measure comparing those with 10 or more teeth with history of caries to fewer than 10 carious teeth. We also evaluated a composite measure combining people with one or more RCT or 10 or more carious teeth compared to those with no RCT and less than 10 carious teeth. Total person-years of follow-up was calculated by summing the follow-up periods contributed by each participant, from the date of returning the 1986 questionnaire up to death, incidence of CHD, or January, 31, 2000.

Analyses limited to confirmed cases yielded similar results to analyses including confirmed and probable cases, although with less precision. Hence, we only present analyses that included both probable and confirmed cases. Each participant contributed only one end-point and the cohort at risk for each follow-up period included only those who remained free from reported incident CHD at the beginning of each follow-up period. Analyses were adjusted for age, smoking, alcohol, family history of myocardial infarction (MI), body mass index, physical activity, multivitamin supplement use, vitamin E use, aspirin use, reported hypertension, and hypercholesterolemia. These factors were updated for each follow-up period. In additional analyses, we controlled for the baseline number of teeth, and incident tooth loss.

We conducted subgroup analyses by age group, smoking status, baseline number of teeth and incident tooth loss during follow-up. We also evaluated the association separately among dentists and nondentists.

Results

Table 1 shows the distribution of age and various age-standardized potential CVD risk factors for participants with and without RCT. Participants with RCT tend to have more carious teeth. A smaller proportion of participants with RCT had fewer than 11 teeth at baseline, but participants with RCT tend to lose more teeth during follow-up than participants without RCT. Men with RCT have slightly less favorable CVD risk profiles; they are older, and slightly more likely to be current smokers.

Table 2 shows the relation between RCT, caries, and CHD. When we evaluated RCT between 1976 to 1996 as a risk factor for subsequent CHD, the association was significant in the analysis adjusting for age, smoking, and family history of MI (RR = 1.25; 95% CI = 1.08-1.44), and remained significant in the multivariate analyses (RR = 1.21; 95% CI = 1.05-1.40). The association became slightly stronger when we excluded men with only one RCT, hence, comparing men with two or more RCT to men with 0 RCT (multivariate RR = 1.24; 95%CI = 1.04-1.47). The associations were weaker and of borderline significance when we limited both these analyses (with and without excluding men with only one RCT) to RCT between 1987 and 1996, and subsequent CHD; multivariate RR = 1.17 and 1.19, respectively. The associ-

TABLE 1. Description of selected age-standardized risk factors in 1986 for CVD by history of RCT in 1976-1996

	0 RCT	≥1 RCT
Number of participants	22189	12494
Age (yr)	52.1 ± 9.2	54.2 ± 9.1
Current smokers (%)	8.5	9.1
Family history of MI (%)	12.4	12.5
Physical activity (MET-hr**/wk)	22.5 ± 35.1	22.1 ± 33.7
Obesity: Body Mass Index (kg/m2)	24.8 ± 5.5	25.0 ± 5.2
History at baseline (%)		
Hypertension	16.4	17.0
High cholesterol	9.4	10.2
Supplement use (%)		
Multivitamin	40.7	41.3
Vitamin E	17.2	17.6
Aspirin	24.7	25.9
Any tooth loss during follow up (%)		
1986-1996	14.8	31.8
1990-1992	4.9	10.9
1994-1996	5.1	16.0
Number of teeth at baseline (%)		
0-10	2.5	0.6
11-16	1.5	1.8
17-24	8.0	11.6
25-32	88.0	86.0
10 or more carious teeth (%)	40.7	66.6
Sugar intake (teaspoons/d)	1.18 ± 2.43	1.30 ± 2.35
Sugar intake (grams/d)	—	—

Continuous variables presented as mean and standard deviation.

**MET indicates metabolic equivalent hr = sum of the average time per week spent in each activity × MET value of each activity. MET value = (caloric need/kg body weight/hr activity) ≈ (caloric need/kg body weight/hr at rest).

ations between RCT and incident CHD became slightly stronger after adding number of teeth in the model (not shown in Table 2).

When we compared men with 10 or more carious teeth between 1976 and 1996 to men with less than 10 carious teeth, the multivariate RR was 1.17 (0.95-1.43) for developing CHD between 1996 and 2000 (Table 2). The combination of one or more RCT or 10 or more carious teeth compared to 0 RCT and less than 10 carious teeth also did not show any association (RR = 1.16; 95% CI = 0.90-1.51).

Table 3 shows the association among different subgroups for one or more RCT between 1976 and 1996. The association between RCT and incident CHD was limited to dentists. Among dentists there was a significant association between baseline RCT and incidence of CHD in the analysis adjusted for age, smoking, and family history for MI, (RR = 1.41), which remained significant in the multivariate analysis (RR = 1.38; 95% CI = 1.14-1.67), whereas there was no association among nondentists (RR = 1.03). The multivariate RR among dentists changed from 1.38 to 1.39 when we add baseline number of teeth, and remained 1.39 when we add tooth loss during follow-up.

Participants who were ≤55 years old at baseline showed a stronger multivariate association (RR = 1.45) than participants who were older than 55 at baseline (RR = 1.17) (Table 3). Additionally, stronger associations were seen among current smokers (RR = 1.33) than men who were past smokers or who had never smoked (RR = 1.20). The associations were similar across subgroups of number of teeth or cumulative tooth loss. The patterns were similar but stronger in subgroup analyses limited to dentists. The strongest association was seen among current smoker dentists (RR = 1.98; 95% CI = 1.19-3.32). Among the dentists, the associations were also higher among people with fewer teeth, and men who did not lose teeth during follow-up (not shown in Table 3).

All associations were stronger when comparing two or more RCT with 0 RCT between 1976 and 1996, while excluding participants with one RCT (Table 2). The strongest associations were seen for dentists (RR = 1.38 for two or more RCT; 95% CI = 1.10-1.74); men 55 and younger (RR = 1.49; 95% CI = 1.00-2.23); and current smokers (RR = 1.42; 95% CI = 0.90-2.24) (not shown in Table 2).

Discussion

Our measure of pulpal inflammation is based on self-reported RCT obtained from questionnaires. RCT could have been performed in response to a chronic or acute pulpal inflammation (which cannot be differentiated in our RCT measure). In an earlier publication (12), we have shown that first time patients in a dental clinic are well able to report the number of RCT in their mouth (Spearman correlation = 0.83 comparing number of RCT from self report and clinical examination). We expect the validity of RCT to be even higher in our population of health professionals. However, as mentioned earlier, some of the RCT may have been performed for reasons other than pulpal inflammation, such as apical periodontitis and in the case of preventive endodontics to prepare the teeth for crowns. We could not distinguish between acute and chronic inflammation. The proportion of RCT that may be related to apical periodontitis is not known, but is likely to be too small to affect CHD risk. Importantly, periodontitis was not related with CHD in this cohort (1). Although RCT may be validly reported, they may not always be related to pulpal inflammation, hence using RCT as a surrogate for

TABLE 2. Association between RCT and dental caries with incidence of CHD

Number of RCT or Carious Teeth	CHD Cases	Person-yr	Relative Risk (95% CI)	
			Adjusted for Age, Smoking, Family History of MI	Multivariate[1]
0 vs ≥1 RCT 1976-1996[2]	1275	468,016	1.25 (1.08-1.44)	1.21 (1.05-1.40)
0 vs ≥2 RCT 1976-1996	991	374,875	1.29 (1.09-1.52)	1.24 (1.04-1.47)
RCT before 1976	1275	468,016	1.03 (0.90-1.19)	1.03 (0.89-1.18)
0 vs ≥1 RCT 1987-1996[3]	994	330,239	1.22 (1.03-1.44)	1.17 (0.99-1.39)
0 vs ≥2 RCT 1987-1996	777	264,611	1.26 (1.03-1.53)	1.19 (0.98-1.45)
≥10 vs <10 caries[4]	411	117,054	1.09 (0.90-1.34)	1.17 (0.95-1.43)
≥1 RCT or ≥10 caries[5] vs 0 RCT and <10 caries	390	112,118	1.15 (0.89-1.49)	1.16 (0.90-1.51)

1Models adjusted for age (5-yr categories); smoking (never, former, current: 1-14, 15-24, >25 cigarettes/d); alcohol (7 categories); family history of myocardial infarction (MI, before age 60); body mass index (quintiles); physical activity (quintiles); multivitamin supplement use; vitamin E use; aspirin use; reported hypertension and hypercholesterolemia.

234,683 men and 1275 cases.

333,983 men and 994 cases (cases in 1990-2000). Recent RCT was classified as 1987-1996.

429,469 men and 411 events (cavity 1976 to 1996 to predict CHD 1996-2000).

5Only positive if responded positively to RCT and caries between 1976 and 1996.

TABLE 3. Sub-group analysis of the association between one or more root canal treated teeth and CHD

	Multivariate Relative Risk[1] (95% CI)		
	All Males	Dentists	Nondentists
Overall	1.21 (1.05-1.40)	1.38 (1.14-1.67)	1.03 (0.83-1.29)
≤24 Teeth	1.19 (0.87-1.61)	1.54 (0.97-2.45)	1.00 (0.66-1.52)
>24 Teeth	1.22 (1.03-1.43)	1.34 (1.09-1.66)	1.05 (0.80-1.36)
Incident tooth loss (−)	1.21 (1.01-1.44)	1.43 (1.15-1.79)	0.94 (0.71-1.26)
Incident tooth loss (+)	1.24 (0.96-1.61)	1.24 (0.86-1.80)	1.24 (0.86-1.79)
Baseline age ≤55	1.45 (1.04-2.02)	1.67 (1.07-2.61)	1.26 (0.76-2.08)
Baseline age >55	1.17 (1.00-1.37)	1.33 (1.08-1.64)	0.99 (0.77-1.27)
Current smokers	1.33 (0.89-1.97)	1.98 (1.19-3.32)	0.89 (0.48-1.68)
Past or never smokers	1.20 (1.02-1.40)	1.33 (1.08-1.63)	1.05 (0.83-1.33)

1Models adjusted for age (5-yr categories); smoking (never, former, current: 1-14, 15-24, ≥25 cigarettes/d); alcohol (7 categories); family history of myocardial infarction (before age 60); body mass index (quintiles); physical activity (quintiles); multivitamin supplement use; vitamin E use; aspirin use; reported hypertension and hypercholesterolemia.

pulpal inflammation may bias the actual association between pulpal inflammation and CHD towards the null.

We found a significant association between history of RCT and incidence of CHD. Furthermore, the association was limited to the dentists. One hypothesis for the stronger association among dentists is that RCT may be a more valid measure of pulpal and periapical inflammation among dentists than among nondentists. That is, some root canals are performed on teeth that do not have pulpitis, for example, preventive endodontics in fixed prosthodontics cases before crown placement. When the RCT is done for crown preparation, the RCT would not be an indication of pulpal or periapical inflammation. Perhaps dentists are less likely to submit themselves to the root canal procedure when there has been no pulpal inflammation. Our a priori assumption that an RCT is directly linked to pulpal inflammation may less often be the case for the nondentist participants in this study. Consequently, the link between RCT and pulpal inflammation, and hence, between RCT and incident CHD is perhaps stronger among dentists than among the nondentists in this study population, accounting for the stronger association with incidence of CHD.

Alternative explanations for finding associations only among dentists could be: (a) compared to dentists, nondentists would be more likely to have affected teeth extracted than saved with RCT, implying more misclassification of RCT/inflammation among nondentists (i.e. true cases of inflammation would not be noted among nondentists because the teeth wouldn't have had RCT); (b) dentists are more aware of the linkages between RCT and crowns or periodontal surgery; and (c) dentists would more likely correctly classify RCT re-treatments as being on the same tooth, whereas nondentists might think that re-treatments were two different root canals on two different teeth. Our study included only males, so we cannot directly generalize to females, but there is no reason to expect that the results would be different for females.

One report from a representative sample in Florida showed that the most common reported reasons for a dental visit in which endodontic treatment was performed were toothache (40%) and infected tooth/abscess (30%); these reasons are usually associated with the clinical diagnosis of pulpitis and acute apical periodontitis (13). Following RCT, 79% of the teeth that did not have advanced procedures such as apicoectomy, root amputation, and re-treatments, had permanent restorations placed, including amalgam, resins, post and cores, and crowns. The manuscript did not specifically report on the proportion of root canals performed in preparation for a crown since the analysis was based on dental participants' self-reported reasons for a dental visit, rather than actual causes for RCT. This question concerning relative frequency of different reasons for RCT needs further research.

Consistent with some previous studies (5, 6), we did not find an association between dental caries and incident CHD in multivariate analyses. Number of carious teeth was not associated with CHD. Possible reasons could include: (a) there is no biologic relationship; (b) our question on caries did not distinguish between active caries and fillings (i.e. caries in the distant past); and (c) only deep caries may have an impact that would not be captured by the number of carious teeth. The association between RCT and incidence of CHD that was found in only one of the two groups assessed may a result of chance. However, the fact that the association was present among the dentists, rather than the nondentists, increases the biological plausibility as discussed above. The dose response for number of RCT, the persistence of the association within all subgroups among the dentists, and the lack of association with caries also makes the association between RCT and incidence of CHD among dentists, less likely to be a result of chance. It is also possible that the association may be because of residual confounding by behavior related factors such as diet and utilization of dental care. However, it is unlikely that the residual confounding would result in an association limited only to dentists.

Earlier studies showed associations between RCT and/or periapical lesions and CVD, but the associations were not significant in multivariate analyses (4, 5). These studies had lower power and only the composite measures were significant in multivariate analyses, hence, it is hard to know whether there was a real association between RCT and CHD. Two recent abstracts by Caplan et al. showed elevated multivariate relative risks relating RCT and CHD in the Atherosclerosis Risk In Communities Study (14) and Veterans' Administration Dental Longitudinal Study (15), although the associations were small.

People with more RCT may have a greater number of teeth, which may be protective against CHD, and could thus dilute the association between RCT and CHD. Although RCT may be an alternative to extractions for individual teeth, our data show increased tooth loss among people with RCT, rather than among people with no RCT. Another prospective study also showed that 19% of the teeth with RCT were extracted within a 48-month follow-up period (16). Also, the associations are not substantially different between people with or without tooth loss, and adjusting for tooth loss did not change the RR. Hence, number of teeth does not seem to impact the associations.

It is possible that CHD could influence whether a person undergoes RCT. However, our study design is prospective and excludes participants with pre-existing CHD. Hence, the association observed is not because of CHD affecting the likelihood of RCT.

The flora of root canals is complex with a multitude of diverse bacteria (17), which are predominantly anaerobic (18). The chronic infection and inflammation could potentially lead to a systemic inflammatory response similar to that postulated for periodontal disease, possibly leading to increased risk of systemic disease. There have been no publications suggesting that RCT has any adverse systemic effects since

the dismissal of the focal infection theory of the early 1900s (19). RCT in our study is a surrogate for pulpal inflammation; we do not expect the RCT itself to lead to adverse systemic outcomes. Further research is needed to corroborate the association between pulpal inflammation and CHD in other populations, to assess whether the association is causal, and to evaluate pathways for this association.

In our study, RCT was associated with a small increased risk of incident CHD among men. The association was limited to dentists where the RCT is more likely to reflect pulpal inflammation as compared to nondental health professionals.

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References

1. Joshipura KJ, Rimm EB, Douglass CW, Trichopoulos D, Ascherio A, Willett WC. Poor oral health and coronary heart disease. J Dent Res 1996;75:1631–6.
2. DeStefano F, Anda RF, Kahn HS, Williamson DF, Russell CM. Dental disease and risk of coronary heart disease and mortality. BMJ 1993;306:688–91.
3. Joshipura KJ, Douglass CW, Willett WC. Possible explanations for the tooth loss and cardiovascular disease relationship. Ann Periodontol 1998;3:175–83.
4. Mattila KJ, Nieminen MS, Valtonen VV, et al. Association between dental health and acute myocardial infarction [see comments]. BMJ 1989;298:779–81.
5. Grau AJ, Buggle F, Ziegler C, et al. Association between acute cerebrovascular ischemia and chronic and recurrent infection. Stroke 1997;28:1724–9.
6. Jansson L, Lavstedt S, Frithiof L, Theobald H. Relationship between oral health and mortality in cardiovascular diseases. J Clin Periodontol 2001;28:762–8.
7. Frisk F, Hakeberg M, Ahlqwist M, Bengtsson C. Endodontic variables and coronary heart disease. Acta Odontol Scand 2003;61:257–62.
8. Grossman L. Evaluation of antibiotic agents for root canal treatment. NY J Dent 1945;15:233–45.
9. Auerbach M. Antibiotics vs. instrumentation in endodontics. N Y State Dental J 1953;19:225–8.
10. Rimm EB, Stampfer MJ, Colditz GA, Giovannucci E, Willett WC. Effectiveness of various mailing strategies among nonrespondents in a prospective cohort study. Am J Epidemiol 1990;131:1068–71.
11. Rose GA, Blackburn H Cardiovascular Survey Methods. WHO Monograph Series, World Health Organization 1982;58.
12. Pitiphat W, Garcia RI, Douglass CW, Joshipura KJ. Validation of self-reported oral health measures. J Public Health Dent 2002;62:122–8.
13. Boykin MJ, Gilbert GH, Tilashalski KR, Shelton BJ. Incidence of endodontic treatment: a 48-month prospective study. J Endod 2003;29:806–9.
14. Caplan DJ, Pankow J, Cai J, Offenbacher S, Beck J. Endodontic infection and coronary heart disease in the ARIC study. IADR 2002.
15. Caplan DJ Lesions of endodontic origin and risk of coronary heart disease. J Dent Res 2004:Abstract No. 1323.
16. Tilashalski KR, Gilbert GH, Boykin MJ, Shelton BJ. Root canal treatment in a population-based adult sample: status of teeth after endodontic treatment. J Endod 2004;30:577–81.
17. Sundqvist G. Taxonomy, ecology, and pathogenicity of the root canal flora. Oral Surg Oral Med Oral Pathol 1994;78:522–30.
18. Bergenholtz G. Micro-organisms from necrotic pulp of traumatized teeth. Odontol Revy 1974;25:347–58.
19. Murray C, Saunders W. Root canal treatment and general health: a review of the literature. Int Endod J 2000;33:1–18.