DR. SOK-JA JANKET (Orcid ID : 0000-0003-0078-3992)

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Lower risk for cardiovascular mortality for patients with root filled teeth in a Finnish population

J H. Meurman[1], S-J Janket[2], M Surakka[3]; E A. Jackson[4], L K. Ackerson[5], H R Fakhri[2], S Chogle[6], A Walls[7]

[1]Department of Oral and Maxillofacial Diseases, Helsinki University Hospital and University of Helsinki, Helsinki, Finland, [2]Center for Clinical research, General Dentistry, and Department of Periodontology, Boston University H. M. Goldman School of Dental Medicine, Boston, MA, USA, [3]Otorhinolaryngology/Maxillofacial Surgery, Kuopio University Hospital, Kuopio, Finland, [4]Preventive Cardiology, Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA; [5]Public Health, University of Massachusetts, Lowell, MA, USA, [6]Endodontics, Boston University, H. M. Goldman School of Dental Medicine, Boston, MA, USA; [7]Edinburgh Dental Institute, University of Edinburgh, Scotland, United Kingdom.

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Correspondence:

Sok-Ja Janket

Center for Clinical research, General Dentistry, and Department of Periodontology, Boston University H. M. Goldman School of Dental Medicine, Boston, MA, USA;

Email: skjanket@bu.edu

Abstract

Aim To investigate the relationship of radiographic evidence of root filled teeth to cardiovascular outcomes.

Methodology Baseline data for 506 subjects including 256 angiographically verified heart disease patients and 250 matched cardiologically healthy controls participating in the Kuopio Oral Health and Heart study were collected in 1995-1996. Cardiovascular disease (CVD) mortalities were accrued until May 31st 2015 and appended to the baseline data. Mortality status data were obtained from the Finnish National Death Register where all mortality cases and the causes of death are compiled for all Finnish citizens. Of the 506 participants, 473 subjects who had no missing values in the predictor, outcome or confounding factors were included in the analyses to assess the relationship of radiographic evidence of root filled teeth with prevalent coronary artery disease (CAD) cross-sectionally and also with CVD mortality longitudinally. Multivariable logistic regression was used for the cross-sectional part and proportional hazard regression analyses for the longitudinal part of the study adjusting for age, sex, smoking, edentulism, diabetes, hypertension, total/HDL cholesterol ratio, and income. Additionally, whether this association was independent of periodontitis, and a systemic marker of inflammation, serum C-reactive protein (CRP) was examined.

Results: Having ≥ 1 root filled teeth was associated with 84% lower odds of prevalent CAD with Odds Ratio (OR) =0.16, 95% confidence interval (CI) 0.09 - 0.28, $P < 0.0001$. The OR for edentulism was 1.32 (CI: 0.73 - 2.38), $P = 0.36$, suggesting a non-significant increase in risk. Prospectively, having at least one root filled teeth was associated with a 49% lower risk of CVD mortality (hazard ratio [HR] =0.51, CI=0.27 - 0.97, $P = 0.04$) while edentulism was associated with non-significantly increased risk for CVD mortality: HR= 1.25 (CI: 0.65 - 2.42), $P = 0.36$. Adjustment for periodontitis or serum CRP levels changed the OR or HR slightly but the associations remained significant.

Conclusions Having ≥ 1 root filled teeth was associated with significantly lower odds for prevalent CAD cross-sectionally and lower risk of cardiovascular mortality prospectively. These reduced associations with CVD were independent of periodontitis or serum CRP levels.

Introduction

Chronic oral infections including periodontitis (Beck *et al.* 1996) have been associated with increased risk of CVD and a healthy dentition as a marker for reduced past oral infections has been associated with a significantly lower risk of CVD mortality (Janket *et al.* 2014). Acute infections (Corrales-Medina *et al.* 2013) including upper and lower respiratory tract infections are established risk factors for acute coronary syndrome (Hao *et al.* 2013). In acute infections, bacterial toxins may activate the innate immune system (Hotchkiss *et al.* 2003) and initiate intravascular inflammation and thrombosis and consequently may contribute to cardiac events (Cotti *et al.* 2011).

The microorganisms in advanced dental caries cause pulpitis that can lead to irreversible pulpitis and pulp necrosis with apical periodontitis that elicits systemic inflammatory responses (Gomes *et al.* 2013). Such inflammatory responses are risk factors for the development of atherosclerosis and CVD outcomes (Gomes *et al.* 2016, Pasqualini *et al.* 2012, Petersen *et al.* 2014). Early root canal infection is dominated by Gram-positive microbiota comprising approximately 69% followed by Gram-negative bacteria (27%), and fungi (Kouchi *et al.* 1980, Love *et al.* 2002). In addition to the Gram negative anaerobes native to the infected root canal system (Bae *et al.* 1997), necrotic pulp tissue can become co-infected with periodontal pathogens (Liljestrand *et al.* 2016) through lateral canals and denuded dentine surfaces with non-vital pulp (Jansson 2015). Avoiding discomfort from advanced dental caries is the most important priority for many patients (Stoller *et al.* 2004), and extraction of the offending tooth is often chosen by the patients as a preferred treatment option. But this decision is based on non-dental factors such as patient/family requests or finances (Johnson 1993). However, extraction can affect subsequent nutritional intake (Janket *et al.* 2008, Nowjack-Raymer *et al.* 2003, Savoca *et al.* 2010) and the adverse effects of edentulism on health have been well substantiated (Brown 2009). However, no previous studies have compared adverse outcomes of edentulism to saving teeth by root canal treatment. The adverse effects of edentulism on CVD was estimated by separating the edentulous group. In this cohort 60% of extractions were reported to be due to advanced dental caries and 40% were due to periodontitis, aesthetic reasons, or trauma. Inflamed pulpal tissue or periradicular tissue expresses interleukin-6 (IL-6) (Euler *et al.* 1998). Additionally, interleukin-1α and IL-1 β are expressed by polymorphonuclear leukocytes in the periradicular tissue (Miller *et al.* 1996). Because these cytokines play major roles in the

pathogenesis of CVD (Bujak *et al.* 2009, Gomes *et al.* 2013, 2016, Volpato *et al.* 2001), it was postulated that root fillings will reduce IL-6 or IL-1β leading to decreased risk of future cardiovascular events. Therefore, the aims of this study were to investigate whether:

1. The radiographic evidence of root fillings at baseline would be associated with decreased risk of prevalent coronary artery disease (CAD) cross-sectionally and with reduced CVD mortality longitudinally;
2. Concurrent Periodontitis will affect the association between root fillings and CVD. Periodontitis has been reported as a contributing factor to CVD and some study participants had both periodontitis and root fillings. Thus, periodontitis is another source of inflammation that may contribute to atherosclerosis. Therefore, the inflammatory burden from periodontitis was controlled to establish the independent contribution of inflammation reduction from root fillings on CVD mortality.
3. Systemic inflammation measured by CRP would affect the association of root fillings and CVD outcomes. CRP has been an independent predictor for CVD (Ridker *et al.* 1998) and the contribution of oral infection to CVD was mediated in part via CRP (Janket *et al.* 2014). Therefore, oral inflammation and CRP are in a confounding relationship. Whether the contribution of reduced inflammation from root fillings to CVD outcomes is independent of CRP were examined.

Materials and methods

Ethical consideration and human subjects' protection

This study was approved by the Joint Ethical Committee of the Kuopio University Hospital and the University of Kuopio. Written informed consent was obtained from all participants. The longitudinal portion of the study was approved by the Boston University Institutional Review Board. This project adhered to the guidelines set forth by the Declaration of Helsinki and the Belmont Accord to assure the safety of human research subjects.

Study population

Kuopio Oral Health and Heart (KOHH) study was initiated as a case-control study in 1995-1996, to investigate the association between oral health and CAD in Kuopio, Finland. For the current study, mortality data (median follow-up of 18.8-years) was appended to the baseline data to create a prospective follow-up study assessing CVD mortality. At baseline 256 consecutive patients attending Kuopio University Hospital coronary angiography unit and with a confirmed diagnosis of CAD were invited to participate in the KOHH study. The CAD diagnosis was made by the presence of at least 50% stenosis in one of the epicardial arteries. Also, 250 age- and gender-matched controls were recruited from the general surgery or otorhinolaryngology departments at the same hospital for elective surgery. They were considered as not having heart disease based on their medical history and electrocardiogram taken during the pre-admission tests. The controls were representative of the population of the same catchment area where the cases arose. The same exclusion and inclusion criteria were applied to the control subjects. Potential subjects who had taken antibiotics during the previous 30 days or had chronic infection other than dental disease were excluded. Additional exclusion criteria for the CAD group were: (a) those who needed emergency coronary by-pass surgery or valvular replacement surgery; (b) those whose disease status was so grave that a dental examination or dental x-ray could not be performed safely; and (c) those who were deemed to require antibiotic prophylaxis prior to periodontal probing at the time of baseline data collection. Further details regarding this cohort have been published elsewhere (Janket *et al.* 2010, 2014).

Ascertainment of the endpoints

The outcome, CVD mortality, was assessed using the mortality records obtained from the Finnish Death Registry in 2009, 2010, 2011, 2014, and 2015. The World Health Organization International Classification of Diseases (ICD)-10 codes I00 through I99 were considered deaths due to cardiac causes and the most prevalent one was I25 (chronic ischaemic heart disease). Each resident of Finland has a unique identifier number and the Office of Statistics Finland collects all health data including mortality. The reliability of mortality data was determined to be 99% after comparing 2009 and 2011 records in a random sample of 100 records. The validity of the mortality records was tested by comparing them to the physician's diagnosis of death from the subjects' medical records. Three disagreements in ICD-10 codes were found in 100 randomly examined records, but upon further detailed investigation, all turned out to be in

agreement. For example, one case the Finnish Death Registry listed as “I21.4: Acute subendocardial myocardial infarction” while the physician’s diagnosis of death was “I25.1 Atherosclerotic heart disease”. Although ICD-10 codes were different, they described the similar pathology. Thus, validity was judged to be excellent. These facts were published previously (Janket *et al.* 2014).

Exposure assessment

At the initiation of this study (1995-1996), a single examiner (MS) performed all clinical dental examinations and pantomographic readings according to the World Health Organization format. Pantomographic evidence of root fillings was enumerated by the images of the radiopaque root filling for each patient. The two pantomogram readings by this examiner (MS) exhibited an excellent agreement (kappa=0.9). Edentulous subjects who could not have root fillings were separately categorized from the root filling assessment. There was one person who was edentulous but had root fillings. This was presumed to be a case of an overdenture where root fillings were provided to improve denture retention. The details of clinical oral examination including number of teeth, amount of vertical bone loss (measured from cemento-enamel junction in mm), calculus deposits, and restorations with overhangs as well as salivary immunoglobulins were measured and the results were reported previously (Janket *et al.* 2004, Qvarnstrom *et al.* 2008).

Assessment of covariates

Baseline behavioral and demographic factors were assessed and the results were published elsewhere (Janket *et al.* 2010, Qvarnstrom *et al.* 2010). Briefly, age in years and smoking in three categories (never-smokers, current smokers and past smokers) were assessed. Body mass index (BMI) was calculated by weight in kg divided by squared height in meters. Total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL) were measured by the automated enzymatic technique. Low density lipoprotein (LDL) cholesterol levels were estimated by the Friedewald formula. Hypertension and diabetes were ascertained by medical record review by one of the authors (MS). Subjects were categorized as hypertensive or diabetic if their medical records documented these diagnoses or they received treatments. Periodontitis was categorized using the updated periodontitis definition by which more than one site with probing depth ≥ 5 mm indicates periodontitis(Eke *et al.* 2012). CRP was measured by immuno-turbidimetry utilizing the HITACHI 717 analyzer (Boehringer Mannheim, Mannheim, Germany).

Statistical analyses

Out of the original cohort of 506 subjects, 33 were excluded from the analyses because of missing values in the outcomes, the predictors or the covariates. Thus, using SAS version 9.3, basic characteristics such as age, gender, smoking status, BMI, number of teeth and cholesterol levels were compared in 473 subjects without any missing values stratified by root filling status. There were 117 edentuous subjects, and among the 356 dentate subjects 160 had radiographic evidence of root fillings while 196 did not. In the bivariate analyses, Fisher's exact or non-parametric tests were used. In multivariate analyses, logistic regression was used in the cross-sectional portion of the study to examine the association of prevalent CAD as the outcome with baseline root filling status as the exposure. In the longitudinal portion of the study, Cox proportional hazard modeling was performed after testing the proportional hazard assumption. The outcome in longitudinal analyses was mortality due to cardiovascular causes. The established confounding factors such as age at the entry to the study, gender, smoking (never, past, current), diabetes, hypertension, total cholesterol to HDL ratio (TC/HDL ratio), and personal income were controlled in both cross-sectional and longitudinal portions of the study. Whether concurrent periodontitis or systemic inflammation assessed by serum CRP levels would alter the association of root fillings with CVD mortality was also tested. Additionally, to test whether baseline CAD affects the relationship of root fillings and CVD mortality differentially (effect modification by baseline CAD), the interaction term between baseline CAD and root fillings was analysed. To assess whether affluence alters the relationship of root fillings and CVD mortality, income was controlled. Also the impact of confounding by a generally healthy lifestyle that may be concurrent with root fillings was tested utilizing sensitivity analyses in non-CVD mortality where inflammation may have lesser influence than CVD.

Results

A total of 148 deaths in the cohort were accrued of which 90 were due to CVD. The leading non-CVD causes were cancer, followed by respiratory diseases and neurologic disorders such as Alzheimer's disease. The sample size was too small to analyze the data on non-CVD mortality.

The baseline characteristics stratified by CAD status are presented in Table 1. As expected, most established CVD risk factors were significantly more prevalent in the CAD group. Of the dental variables,

number of remaining teeth and prevalence of periodontitis, were higher and the proportion of edentulism was lower in controls. Moreover, 53.6% of the control group had radiographic evidence of root fillings while only 14.5% had evidence of root fillings in the CAD group. In general, poor oral health was evident in CAD cases.

In multivariate analyses where age, gender, smoking, hypertension, diabetes, income and TC/HDL cholesterol ratio were adjusted, the edentate subjects were at increased odds of prevalent CAD, albeit non-significantly (OR=1.32, 95% CI: [0.73 - 2.38], *p*= 0.36) compared with those who did not have evidence of root fillings. By contrast, those who had evidence of root fillings were at 84% lower odds of having prevalent CAD compared to those with no evidence of root fillings (OR=0.16, 95% CI: 0.09 – 0.28, p < 0.0001). Controlling for periodontitis, which is a different source of oral inflammation, changed the OR slightly to 0.17 but the p-value remained highly significant (p <0.0001). In this cohort, the prevalence of periodontitis was 22.6%. Adjusting for either periodontitis or serum CRP levels did not materially alter the results (OR=0.18, p < 0.0001). The majority of the confounding variables were significantly associated with CAD. Nevertheless, root fillings remained significantly and inversely associated with prevalent CAD even after adjusting for these confounders. These results are presented in Table 2.

In the longitudinal portion of the analyses, having at least one root filled tooth was associated with a 49% reduction in the risk of CVD mortality (HR=0.51, 95% CI: 0.27 - 0.97, *p* = 0.04) in multivariate analyses. The edentulous group was again at a non-significantly elevated risk of CVD mortality (HR=1.27, 95% CI: [0.77 - 2.11], p=0.38). Similar to the results in the cross-sectional analyses, the adjustment of periodontitis or serum CRP levels did not materially alter the inverse association of root fillings and CVD mortality (HR = 0.51, 95% CI: 0.27 - 0.98, *p*= 0.04). Unlike the results from cross-sectional analyses, the only risk factors significantly predictive of CVD mortality in addition to the radiographic evidence of root fillings were age, smoking, and hypertension. These results are presented in Table 3.

In the testing of effect modification by baseline CAD, the interaction was not a significant predictor for CVD mortality (HR=1.15, CI: 0.55 - 2.43, *p*=0.71) adjusting for age, smoking and hypertension. To confirm this, the cohort was stratified by baseline CAD status and separate analyses conducted. The results showed a similar inverse relationship in both cases and controls albeit not significant due to

sample size reduction (HR=0.81 in controls and HR=0.82 in cases) confirming no interaction between baseline CAD and root fillings.

Although root fillings are considered an affluence-dependent intervention, adjusting for income did not materially alter the relationship of root fillings and CVD mortality. In a multivariable adjusted model, being in the top 25% of income was inversely associated with CVD mortality (HR=0.71, 95% CI= 0.39 - 1.30) but this was not statistically significant (p = 0.21).

Discussion

Within the limitations of this study, radiographic evidence of root fillings was associated with a significantly lower risk of cardiovascular mortality after adjusting for established confounding factors. Moreover, this association was independent of baseline periodontitis or systemic inflammation measured by serum CRP levels. Additionally, baseline CAD did not influence the association of root fillings to CVD mortality.

In the cross-sectional analyses (Table 2), an association between poor oral health and CAD was evident but this association cannot be considered as a causal relationship. Rather, baseline characteristics may describe the state of oral health due to CAD. Age and gender in relation to CAD were the opposite of generally accepted knowledge that those who are younger or female are less prone to CAD in the general population. However, these young and female subjects in the cohort already had CAD at baseline and their increased risks are described in Table 2.

On the contrary, the prospective results in Table 3 showed that individuals who were older or male were at increased risk for CVD mortality in agreement with generally accepted pattern of risk in CVD. This fact suggests that baseline CAD-related factors are not necessarily risk factors for CVD mortality prospectively. For example, the CRP levels which had strong association with prevalent CAD (OR=22) or the Total to HDL cholesterol ratio was not a significant predictor for CVD mortality.

Of the total CVD mortality (N=90), 69 CVD deaths (77%) occurred in the CAD group. Because nearly 80% of CVD mortality occurred in the baseline CAD group, it is reasonable to assume that baseline CAD is on the causal pathway to CVD mortality, and adjusting for an intermediate variable on the causal pathway to the end point of disease is not appropriate in epidemiology (Hennekens *et al.*

1987). Such adjustment would actually bias the results and could even reverse the direction of the association (Cook 2011).

The postulated mechanism is that root fillings may reduce cytokine production such as IL-6 and/or IL-β which increase atherosclerotic inflammation. However, it is possible that confounding by healthy lifestyle could be the reason for the apparent beneficial effects of root fillings. Therefore, a sensitivity analysis was performed to allay this concern for Hawthorn Effects by testing the relationship between root fillings and non-CVD mortality where inflammation may play a lesser role. Indeed, the results were not significant suggesting that a healthy lifestyle may not be the reason for the decreased CVD mortality. If the observed results were due to healthy lifestyle, the same beneficial effects would have been observed in non-CVD mortality.

Although previous studies suggested that a self-reported history of endodontic therapy increased the risk of incident CVD (Caplan *et al.* 2009), the precise estimation of inflammation from endodontic origin was difficult to measure (Caplan *et al.* 2006). To overcome this difficulty, the radiographic evidence of removal of inflammation from endodontic origin was assessed in the current study. While the exact data on the cause for the root fillings is not available, the highly significant correlation between the number of teeth with root fillings and the number of periapical lesions (apical periodontitis) appear to suggest that root fillings were typically rendered to treat apical periodontitis (Spearman correlation coefficient =0.43, $p = 0.0001$).

This assumption appears to contradict the recent report by Huumonen and colleagues that apical periodontitis was more prevalent in root filled than non-root filled teeth (Huumonen *et al.* 2016). However, not all apical radiolucencies (typically assumed apical periodontitis) resolve posttreatment. In fact approximately 36% of post-treatment periapical radiolucencies remained unchanged in size or even increased after 12 months (Zhang *et al.* 2015). The reason for this is because not all periapical radiolucencies are pathologic apical periodontitis: some are scar tissues and others can be cysts or tumours (Garcia *et al.* 2007).Thus the prevalence of apical periodontitis does not translate well to CVD outcomes (Berlin-Broner *et al.* 2016) and some radiolucencies may not need root filling (Nair 2006). Moreover, if there were residual apical radiolucencies after root filling, the total inflammatory burden and subsequent risk of CVD would be much less in root filled teeth than in non-root filled teeth as reported by

Liljestrand *et al.* (2016). These facts are corroborated by a report that apical periodontitis increased oxidative stress (Inchingolo *et al.* 2014) which is a risk factor for atherosclerosis (Kornfeld *et al.* 2015, Sugamura *et al.* 2011) and endodontic treatment reduced reactive oxygen species and increased anti-oxidant potential (Inchingolo *et al.* 2014). These are highly supportive of the hypothesis that root canal treatment will decrease the harmful effects generated by apical periodontitis and will therefore reduce the risk for CVD outcomes. In longitudinal analyses, age, smoking and hypertension were the independent and significant risk factors to CVD mortality. The close relationship of endodontic inflammation and hypertension were reported in a previous longitudinal study where the risk of incident hypertension was significantly increased (RR = 2.0, 95% CI = 1.16-3.46) with the presence of apical periodontitis (Gomes *et al.* 2016).

The present cohort has been extended from a case-control study to a longitudinal form. As such, concerns for potential risk amplification due to the high prevalence of baseline CAD were raised (Sommerfelt *et al.* 2012). However, the simulated data have proven that the "time to event analyses" such as Cox proportional hazard regressions which use semi-non parametric method were unaffected by the high CAD proportion at baseline (Janket *et al.* 2014). Therefore, the results from the present study can be generalized to other populations. Nonetheless, future clinical trials in a CAD-free population are needed to confirm the findings.

Serum CRP can originate from two different sources: infection- or obesity-related inflammation. Metabolic inflammation is sterile, low grade inflammation observed in obesity, diabetes or atherosclerosis (Janket *et al.* 2015). Obesity and diabetes can increase intestinal permeability and cause spontaneous endotoxemia (Cani *et al.* 2007) reflected as an increased serum level of lipopolysaccharide (LPS) (Amar *et al.* 2008). LPS is a component of the Gram-negative bacterial cell wall. This is important because Gram-negative bacteria are the predominant pathogens in periodontitis, and periodontitis is associated with obesity and diabetes. Thus, metabolic inflammation and periodontitis are in a confounding relationship, and the impact of obesity-related metabolic inflammation has to be controlled to establish the independent contribution of periodontitis to CVD risk increase. As CRP which is largely a marker for metabolic inflammation (Gupta *et al.* 2012) has been controlled in the present study, the results are independent of metabolic inflammation.

Others reported that CRP levels were inversely associated with socioeconomic status (SES)(Kohler *et al.* 2013). The present data also show significant association between low income and increased CRP levels in a t-test but this did not translate to CVD mortality in the multivariable adjusted models. The current results from a Finnish cohort with uniformly high living standard are in agreement with other studies from Scandinavia reporting non-significant impact of SES on oral health and chronic diseases association(Cabrera *et al.* 2005).

Strengths:

Previous research considered self-reported history of endodontic therapy as a marker for inflammation (Caplan *et al.* 2006, Joshipura *et al.* 2006). However, assessing inflammation from self-report may not be reliable as the authors stated (Caplan *et al.* 2006). This difficulty was avoided by assessing the radiological proof of root fillings which is one of the strengths. A long follow-up (median = 18.8 years) and precise dental examination given at baseline are additional strengths of the present study because precise dental measurements increase the fidelity of the results.

Limitations:

As shown in Table 1, those who did not opt for root fillings have fewer remaining teeth. This indirectly suggests that these individuals might have chosen extraction rather than root canal treatment. Unfortunately, information regarding the cause for the fewer remaining teeth is not available. It has been presumed that edentulism results from severe cases of dental infection/inflammation leading to significant adverse outcomes (Lee *et al.* 2006). In the present study where dentate groups were divided by root filling status as well as edentulism, edentulism was not a significant risk factor for CVD outcomes (p =0.34) due to small sample sizes resulting from stratification. However, when the edentulous group was compared to the dentate group without stratifying by root filling status, a significant association of edentulism to CVD mortality (HR=1.63 [CI: 1.02 - 2.60]; p = 0.04). This is consistent with the previous reports showing detrimental consequences of edentulism (Brown 2009, Osterberg *et al.* 2007).

Conclusion

Within the limitations of this study, radiographic evidence of root fillings was significantly associated with lower odds for prevalent CAD at baseline and reduced risk of CVD mortality longitudinally controlling for

established confounders. These results suggest that root fillings may be associated with reduced CVD risk. However, the residual confounding from the baseline CAD cannot be completely ruled out.

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Conflict of Interest statement

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Figure legend

Figure 1 Age, gender, and smoking adjusted CVD survival estimates stratified by edentulism and endodontic treatment status

Table 1 Baseline characteristics of the cohort

	No CAD (N= 242)	CAD (N=231)	p-value
Age, Mean (SD)	59.3 (9.8)	59.9 (9.1)	0.5
Sex (N, %) Men Women	 155 (64) 87 (36)	 145 (63) 86 (37)	 0.77
Body Mass Index (BMI) Mean (SD)	25.6 (3.7)	23.6 (3.3)	<.0001
Number of teeth Mean (SD)	15.7 (10.5)	7.7 (10.5)	<.0001
Proportion with Edentulism, N (%)	36 (14.9)	81 (35.1)	<.0001
Periodontitis	54 (22.3)	28 (12.1)	<.0001
Proportion with at least 1 endoTx, N (%)	134 (53.6)	37 (14.5)	<.0001
CVD mortality, N (%)	21 (8.7)	69 (29.9)	<.0001
Education (years), Mean (SD)	11.8 (3.5)	10.5 (2.6)	<.0001
Annual Income in Euro (SD)	34058 (11525)	31319 (9723)	0.005
Smoking, N (%) Never Current Past	 197 (81.4) 24 (9.9) 21 (8.7)	 121(52.4) 25 (10.8) 85 (36.8)	 0.001 0.74 0.0001
Hypertension, N (%)	50 (20.7)	115 (49.8)	0.001
Diabetes, N (%)	14 (5.8)	36 (15.6)	0.0004
LDL cholesterol* (mmol/L) Median† (IQR)	3.7 (3.1 - 4.3)	3.4 (2.9 - 4.2)	0.003
Triglyceride (mmol/L) ‡ Median (IQR)	1.5 (1.2 - 2.0)	2.0 (1.4 - 2.6)	<.0001
HDL cholesterol (mmol/L)§ Median (IQR)	1.3 (1.1 - 1.5)	1.1 (0.9 - 1.3)	<.0001
Total/HDL cholesterol ratio, Median (IQR)	4.7 (3.8 - 5.4)	5.2 (4.2 - 6.2)	<.0001
CRP (mg/L) Median (IQR)	4.0 (2 -5)	10 ((8 - 26)	<.0001
Fibrinogen (g/L) Median (IQR)	2.9 (2.6 - 3.2)	3.1 (2.8 - 3.7)	<.0001

*LDL was estimated by Friedewald formula. †IQR: inter-quartile range. ‡To convert mmol/L of triglyceride to mg/dL, multiply by 88.57. § To convert mmol/L of cholesterol to mg/dL, multiply by 38.67.

Table 2 Multivariate-adjusted odds ratios for the prevalent coronary artery disease

	Exposure groups	**Odds ratio** (95% confidence interval)	**p-value**
Model 1	Edentate	1.32 ((0.73 - 2.38)	0.36
	No EndoTx*	1 (reference)	-
	EndoTx	0.16 (0.09 - 0.28)	**0.0001**
Confounding adjusted for Model 1	Sex	2.35 (1.33- 4.14)	**0.003**
	Age	0.98 (0.95 - 1.00)	0.05
	Smoking	3.10 (2.21 - 4.30)	**<.0001**
	Total/HDL cholesterol ratio	1.37 (1.15 - 1.64)	**<.0001**
	Hypertension	3.57 (2.14 - 5.98)	**<.0001**
	Diabetes	1.67 (0.74 - 3.78)	0.22
	Income > 75 percentile	1.18 (0.66 - 2.13)	0.57
Model 2	Edentate	1.21(0.66 - 2.23)	0.54
	No EndoTx	1 (reference)	**-**
	EndoTx	0.17(0.10 - 0.29)	**0.0001**
Confounding adjusted for Model 2	Sex	2.35 (1.33 - 4.15)	**0.003**
	Age	0.98 (0.95 - 1.00)	0.06
	Smoking	3.10 (2.21 - 4.35)	**<.0001**
	Total/HDL cholesterol ratio	1.37 (1.15 - 1.64)	**0.0006**
	Hypertension	3.60 (2.15 - 6.04)	**<.0001**
	Diabetes	1.69 (0.74 - 3.83)	0.21
	Income > 75 percentile	1.18 (0.66 - 2.13)	0.57
	Periodontitis	0.82 (0.42 - 1.61)	0.56
Model 3	Edentate	1.25 (0.65 - 2.42)	0.50
	No EndoTx*	1 (reference)	-
	EndoTx	0.18 (0.10 - 0.32)	**0.0001**
Confounding adjusted for Model 3	Sex	2.63 (1.45 - 4.77)	**0.002**
	Age	0.96 (0.94 - 0.99)	**0.01**
	Smoking	3.03 (2.11 - 4.35)	**0.0001**
	Total/HDL cholesterol ratio	1.28 (1.06 - 1.54)	**0.01**
	Hypertension	3.43 (1.97 - 5.98)	**0.0001**
	Diabetes	1.40 (0.60 - 3.31)	0.44
	Income > 75 percentile	1.46 (0.77 - 2.77)	0.25
	Serm CRP > 3 mg/L	22.1 (7.37 - 66.6)	**0.0001**

* EndoTx: Pantomographic evidence of endodontic treatment among dentate subjects.

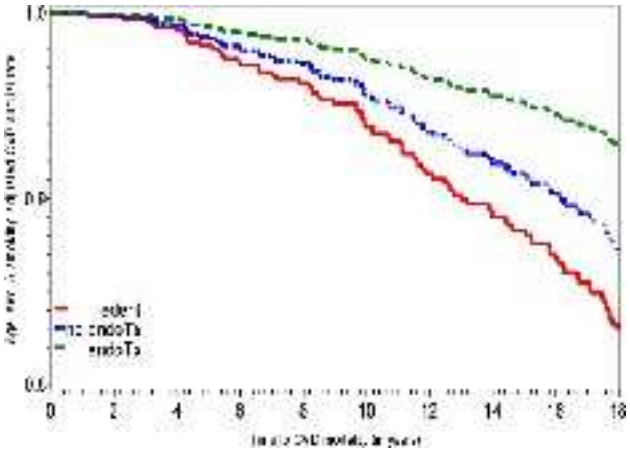
- All models were controlled for age, sex, smoking, hypertension, diabetes, T/H cholesterol ratio, and income.
- Model 2 adjusted for the covariates controlled in the model 1 plus periodontitis.
- Model 3 adjusted for the covariates controlled in the model 1 plus C-reactive protein > 3 mg/L.
- Bold p-values denote significance.

Table 3 Multivariate-adjusted hazard ratios for the cardiovascular mortality

	Exposures	Hazard ratio (95% confidence interval)	p-value
Model 1	Edentate	1.27 (0.77 - 2.11)	0.34
	No EndoTx*	1 (reference)	-
	EndoTx	0.51 (0.27 - 0.97)	**0.041**
Confounding adjusted for Model 1	Sex	0.73 (0.41 - 1.29)	0.28
	Age	1.11 (1.07 - 1.14)	**<.0001**
	Smoking	1.54 (1.18 - 2.02)	**0.001**
	Total/HDL cholesterol ratio	1.05 (0.89 - 1.24)	0.59
	Hypertension	1.64 (1.07 - 2.52)	**0.02**
	Diabetes	1.03 (0.57 - 1.84)	0.93
	Income > 75 percentile	0.71 (0.39 - 1.30)	0.26
Model 2	Edentate	1.27 (0.74 - 2.16)	0.38
	No EndoTx	1 (reference)	**-**
	EndoTx	0.52 (0.27 - 0.97)	**0.042**
Confounding adjusted for Model 2	Sex	0.73 (0.41 - 1.29)	0.33
	Age	1.11 (1.07 - 1.14)	**<.0001**
	Smoking	1.54 (1.18 - 2.02)	**0.002**
	Total/HDL cholesterol ratio	1.05 (0.89 - 1.24)	0.50
	Hypertension	1.64 (1.07 - 2.52)	**0.03**
	Diabetes	1.03 (0.57 - 1.86)	0.91
	Income > 75 percentile	0.71 (0.39 - 1.30)	0.29
	periodontitis	0.99 (0.51 - 1.93)	0.88
Model 3	Edentate	1.19 (0.70 - 2.04)	0.52
	No EndoTx*	1 (reference)	-
	EndoTx	0.51 (0.27 - 0.98)	**0.043**
Confounding adjusted for Model 3	Sex	0.75 (0.42 - 1.34)	0.33
	Age	1.11 (1.08 - 1.15)	**<.0001**
	Smoking	1.55 (1.18 - 2.04)	**0.002**
	Total/HDL cholesterol ratio	1.06 (0.90 - 1.25)	0.50
	Hypertension	1.60 (1.04 - 2.46)	**0.03**
	Diabetes	1.03 (0.58 - 1.86)	0.91
	Income > 75 percentile	0.72 (0.40 - 1.32)	0.29
	Serum CRP > 3mg/L	1.06 (0.49 - 2.29)	0.88

* EndoTx: Pantomographic evidence of endodontic treatment among dentate subjects.

- All models were controlled for age, sex, smoking, hypertension, diabetes, T/H cholesterol ratio, and income.
- Model 2 adjusted for the covariates controlled in the model 1 plus periodontitis.
- Model 3 adjusted for the covariates controlled in the model 1 plus C-reactive protein > 3 mg/L.
- Bold p-values denote significance.



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