VOLUME - 11, ISSUE - 02, FEBRUARY - 2022 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper | Anaesthesiology

ENDODONTIC INFLAMMATORY DISEASE: A RISK INDICATOR FOR A FIRST MYOCARDIAL INFARCTION

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ABSTRACT

Aim: To study the association between endodontic inflammatory disease and a first myocardial infarction (MI).

Methodology: The study comprised 500 patients with recent experience of a first MI, each gender, age and geographically matched with a control. Panoramic radiographs were available for 492 patients and 796 controls. Endodontic inflammatory disease was assessed radiographically. The sum of decayed, missing and filled teeth (DMFT) was calculated, and the number of root filled teeth and teeth with periapical lesions were recorded. The associated risk of a first MI was expressed as odds ratios (OR) with 95% confidence intervals (CI), unadjusted and adjusted for confounders (family history of cardiovascular disease, smoking habits, marital status, education and diabetes).

Results: The number of missing teeth was associated with an increased risk of a first MI (adjusted OR 1.04; CI 1.02–1.06). Conversely, decay-free, filled teeth were associated with decreased risk (adjusted OR 0.98; CI 0.96–1.00).

Analysis based on age disclosed the following variables to be associated with an increased risk of a first MI: number of decayed teeth (adjusted OR 1.18; CI 1.02–1.37, in patients <70 years), any primary periapical lesion (adjusted OR 1.57; CI 1.08–2.29, in patients <75 years) and the proportion of root filled teeth (adjusted OR 1.18; CI 1.03–1.36, in patients ≥75 years).

Conclusions: In addition, endodontic inflammatory disease may contribute as an independent risk factor to cardiovascular disease since untreated caries, periapical lesions and root fillings, depending on age, were significantly associated with a first MI.

KEYWORDS :

INTRODUCTION

Periodontitis is defined as "an inflammatory disease of supporting tissues of teeth i.e. the gingiva and the alveolar bone, caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with periodontal pocket formation, gingival recession or both. Events attributed to cardiovascular disease (CVD), such as myocardial infarction (MI) and stroke, remain as leading causes of death worldwide. Current research controversy centers around a hypothesized connection between the presence of chronic oral infections and the development of adverse systemic health conditions. Several epidemiologic investigations have uncovered relationships between chronic periodontal disease and coronary heart disease, premature birth and/or low birthweight, and respiratory disease. However, other studies have not found significant relationships, sparking questions about the proposed association Despite a decrease in cardiovascular and total mortality, there are four million deaths from CVD in Europe each year (Townsend et al., **2016**). Smoking, diabetes, hypertension, hypercholesterolaemia and obesity are well-established risk factors for CVD (www.world-heart-federation.org/resources/risk-factors). Additionally, socio-economic status and psychosocial stress increase the risk for developing CVD (Rosengren et al., **2004**). It is also well known that chronic inflammation accelerates the process of atherosclerosis thereby contributing to CVD (Hansson et al., **2006**).

In recent years, there has been increasing interest in possible connections between CVD and inflammatory conditions originating from the dental pulp. In a case–control population-based study of adolescents, the scores for decayed, missing and filled surfaces (DMFS) were significantly associated with CVD risk factors (Kelishadi et al., **2010**). Several investigations reported an association between periapical lesions and CVD (An et al., **2016**; Costa et al., **2014**; Liljestrand et al., **2016**; Pasqualini et al., **2012**; Petersen et al., **2014**; Virtanen et al., **2017**; Willershausen et al., **2009**, **2014**), as well as root filled teeth *per se* (Costa et al., **2014**; Joshipura et al., **2006**). In contrast, a study on Swedish women reported an association between CVD and tooth loss, but found no association for either periapical lesions or root filled teeth (Frisk et al., **2003**). Some studies reported that root filled teeth were less common amongst patients with CVD than in controls (Cowan et al., **2020**; Willershausen et al., **2009**). However, a higher prevalence of root filled teeth with periapical lesions amongst patients with CVD has also been reported (Pasqualini et al., **2012**), whilst Meurman et al. (**2017**) reported root filled teeth to be inversely associated with CVD: having at least one root filled tooth was associated with a 49% reduction in the risk of CVD mortality.

To date, the association between EID and CVD is somewhat contradictory and not fully understood. The inconsistencies in the results are attributable to many factors such as variations in study design, population differences and ambiguities in assessments of independent and dependent variables. Moreover, established risk factors, if not appropriately accounted for in study design and statistical analyses, affect the results (Jakovljevic et al., **2020**).

MATERIALS AND METHODS

This study was carried out on patients under 80 years of age, who had recently suffered a first MI. Exclusion criteria were prior MI, heart valve replacement or any other condition limiting the ability to comply with the study protocol. The patients were recruited in connection with their hospitalization and scheduled for an outpatient visit at their local Departments of Cardiology and Dental Medicine 6–10 weeks later.

Controls, matched for gender, age (±3 months) and geographical area (same postal code) and without a prior MI or heart valve replacement, were identified through the Swedish population registry. A total of 805 patients and 805 controls from 37 different regions were included.

Information on medical and family history of CVD, pharmacological treatment, level of education, occupation and marital status as well as risk and health-preserving factors, such as smoking and alcohol use, was collected by means of structured questionnaires. Periodontal status of MI patients and controls was diagnosed from panoramic radiographs.

Statistical Analysis

Statistical analysis was performed using SPSS system 18. Matched pair analysis was performed by individual matching of each case to its respective control. For comparison between the groups, Fisher's nonparametric permutation test for matched pairs was used for continuous variables and the Sign test was used for dichotomous variables and other order categorial. Statistical significance was considered as $p < .05$.

Unadjusted and adjusted conditional logistic regressions were performed for each variable with MI as the dependent variable. The main results are presented as crude unadjusted odds ratios (ORs) with 95% confidence intervals (CI), together with OR (95% CI) adjusted for all variables that differed significantly between MI patients and controls.

Subgroup analysis regarding MI within two different dichotomized age subgroups was performed together with an interaction analysis between age groups and independent variables.

RESULTS

Clinical characteristics

Detailed clinical characteristics of the patients and controls have been presented in Table 1. The majority of the included subjects were men (81%).

The mean age was 58±8 years. A family history of CVD was more common in patients than in controls, and smoking was more frequent amongst patients at admission.

Table 1 Clinical Characteristics

Variables	Patients, n = 500	Controls, n = 500	p-Value
Age, years	58 ± 8	58 ± 8	–
Male sex	300 (60)	300 (60)	–
Known family history of CVD	158 (32)	90 (18)	<.001*
Smoking habits (patients at admission)			
Current	195 (39)	102 (20)	<.001*
Previous	165 (33)	215 (43)	
Never	140 (28)	183 (37)	
Smoking habits (patients at follow-up)			
Current	50 (10)	102 (20)	.22
Previous	310 (62)	215 (43)	
Never	140 (28)	183 (37)	
Diabetes mellitus	50 (10)	45 (8)	.25

Comparison of patients and controls (all subjects)

Panoramic radiographs were available for 492 (98%) patients and 492 (98%) controls. The assessment of endodontic variables in the patients and controls, as well as results from the paired analysis, are presented in Table 2.

The DMFT score, number of missing teeth and proportion of missing teeth were significantly higher amongst patients, whilst the number of filled teeth were higher amongst the controls.

Table 2 Endodontic Variables In Patients And Controls

	Patients			Controls			Paired analysis[b]	
Variable	Mean (SD)	Median (min; max)	N	Mean (SD)	Median (min; max)	N	p-Value	N
DMFT								
Incl. 3rd molars	22.5 (6.0)	23 (3; 32)	797	21.9 (6.2)	22 (0; 32)	796	.013*	788
Excl. 3rd molars	18.7 (5.8)	19 (2; 28)	797	18.2 (5.8)	18 (0; 28)	796	.0025*	788
Decayed								
Teeth (n)	1.04 (1.78)	0 (0; 15)	797	0.982 (1.67)	0 (0; 12)	796	.50	788
Any tooth[a]	315 (39.5)			310 (38.9)			.83	788
% teeth[c]	4.68 (8.86)	0 (0;75)	785	4.21 (8.03)	0 (0; 86)	792	.25	772
Missing								
Teeth (n)	7.49 (6.26)	6 (0; 32)	797	6.32 (5.14)	5 (0; 32)	796	<.0001*	788
% teeth[c]	23.4 (19.6)	18.8 (0; 100)	797	19.8 (16.1)	5.6 (0; 100)	796	<.0001*	788
Filled (no caries)								
Teeth (n)	14.0 (5.6)	14 (0; 28)	797	14.6 (5.2)	15 (0; 29)	796	.015*	788
Any tooth	780 (97.9)			789 (99.1)			.064	788
% teeth[c]	58.2 (20.6)	58.3 (0; 100)	785	58.0 (20.2)	58.0 (20.2)	792	.77	772
Root filled								
Teeth (n)	2.13 (2.29)	1 (0; 14)	797	2.09 (2.21)	2 (0; 12)	796	.68	788
Any tooth	563 (70.6)			566 (71.1)			.91	788
% teeth[c]	9.99 (12.38)	6.45 (0; 87.5)	785	9.22 (11.03)	6.45 (0; 80)	792	.13	772
Periapical lesions								
Teeth (n)	0.93 (1.25)	1 (0; 9)	799	0.85 (1.15)	0 (0; 7)	797	.17	791
Any tooth	404 (50.6)			389 (48.8)			.43	788
% teeth[c]	4.26 (6.33)	3.23 (0; 66.7)	785	3.76 (5.63)	0 (0; 44.4)	792	.11	772
Primary periapical lesions								
Teeth (n)	0.92 (0.66)	0 (0; 5)	797	0.25 (0.60)	0 (0; 6)	796	.18	788
Any tooth	170 (21.3)			153 (19.2)			.31	788
% teeth[d]	1.68 (5.35)	0 (0; 100)	797	1.36 (3.89)	0 (0; 50)	792	.17	772
Secondary periapical lesions								
Teeth (n)	0.65 (0.99)	0 (0; 8)	797	0.61 (0.90)	0 (0; 7)	796	.36	788
Any tooth	318 (39.9)			320 (40.2)			1.00	788
% teeth[e]	32.0 (35.6)	25 (0; 100)	563	19.8 (16.1)	15.6 (0; 100)	566	.39	407

a. *Categorical variables are presented as number of subjects, n (%).*
b. *Paired analysis was performed with a linear nonparametric permutation test for continuous variables, and Sign test for categorical variables.*
c. *The proportion of teeth of a particular type amongst the total number of remaining teeth.*
d. *The proportion of affected nonroot filled teeth amongst the total number of remaining nonroot filled teeth.*
e. *The proportion of affected root filled teeth amongst the total number of remaining root filled teeth.*

** Significant results (p < .05).*

EID variables and association to the risk of a first MI

Conditional regression analysis was performed to test whether EID variables were associated with increased risk of a first MI. The number of missing teeth (adjusted OR 1.04, 95% CI 1.02–1.06; $p = .0005$) and the proportion of missing teeth (adjusted OR 1.12, 95% CI 1.05–1.20; $p = .0005$) were associated with an increased risk of a first MI.

Higher DMFT was associated with an increased risk of a first MI only in the unadjusted analysis (unadjusted OR 1.03, 95% CI 1.01–1.05; $p = .013$).

In contrast, the number of filled teeth was associated with a decreased risk of a first MI (adjusted OR 0.98, 95% CI 0.96–1.00; $p = .040$), as was the presence of at least one filled tooth in the unadjusted analysis (unadjusted OR 0.41, 95% CI 0.17–0.99; $p = .048$).

DISCUSSION

Mechanisms linking endodontic disease to CHD risk might be similar to those hypothesized for associations between periodontal disease and CHD, in which a localized inflammatory response to bacterial infection leads to release of cytokines into the systemic circulation and subsequent deleterious vascular effects.

By assessing panoramic radiographs from a cohort of MI patients and healthy controls, this study aimed to investigate a possible association between EID and a first MI. The results disclosed that less remaining teeth was significantly associated with the risk of a first MI. Additionally, depending on age, other variables indicating EID were associated with an increased risk of a first MI: the number of decayed teeth in patients aged <70 years, the presence of any primary periapical lesion in individuals aged <75 years and the proportion of root filled teeth in patients aged >65 years. Conversely, the number of filled teeth was associated with a decreased risk of a first MI.

In this case–control study, the finding that patients suffering a first MI had more missing teeth was reported by Rydén et al. (**2016**) and has been a commonly reported finding in several investigations (Pasqualini et al., **2012**; Willershausen et al., **2009**, **2014**).

Teeth may be extracted for a variety of reasons. According to the Swedish registry data, the primary reason is dental caries (SKaPa, **2016**). Root filled teeth are also at increased risk of extraction (Kirkevang et al., **2017**). However, periodontal disease is also a major risk factor for tooth loss (SKaPa, **2016**). Comorbidity of periodontal disease and CVD is fairly well established (Froum et al., **2020**; Rydén et al., **2016**). Because teeth to be extracted are or have been exposed to inflammatory disease, the fact that patients with MI had significantly more missing teeth could reflect their earlier exposure to systemic inflammation from either EID or periodontal disease, or a combination of both.

The biological mechanism explaining the link between oral inflammatory diseases and MI includes release of pro-inflammatory mediators into the circulation which potentially contributes to a systemic inflammatory burden (Jakovljevic et al., **2020**). Independently, EID and periodontal disease may both relate to MI, as has been suggested in previous publications. However, the combined impact of EID and periodontal disease, as well as other oral inflammatory conditions, in this context is still unknown and warrants further investigation. Although missing teeth were hypothesized to indicate a history of EID in the present study, the actual reason for tooth loss in this cohort is unknown. To test if the variable missing teeth as a specific indicator for EID was an independent variable associated with a first MI, an analysis was run adding periodontal disease as a confounder. This revealed a weakened strength of the correlation between missing teeth and the risk of a first MI (Table **4**) suggesting that tooth loss due to periodontal disease may be a more essential risk factor for a first MI than tooth loss due to other reasons including EID. A potential explanation may be a relatively more extensive and prolonged exposure to inflammation associated with a tooth that was extracted due to periodontitis compared to teeth that are extracted for other reasons. Future studies should investigate possible modulatory effects on the risk of MI when several oral inflammatory conditions exist simultaneously. Additionally, exploring ways to summarize the complete oral inflammatory burden, including both endodontic and periodontal variables, could probably reveal a stronger correlation with systemic diseases in some patients.

It should also be acknowledged that there are a number of other potentially significant factors, not measured and adjusted for, which differ between the MI patients and the controls and which may have contributed both to the difference in the number of remaining teeth and the risk of a first MI. In a study involving 8000 subjects, the number of missing teeth was associated with angina pectoris or acute MI; it was suggested that this reflected a behavioural background of poor self-care and low health prevention awareness (Paunio et al., **1993**). Missing teeth could also lead to unfavourable changes in diet, leading to an increased risk for CVD and mortality (Liljestrand et al., **2021**). It is possible that fewer retained teeth, amongst other factors, reflect a tendency to seek dental care only at a stage of disease when it is too late for root canal treatment and extraction is the only valid option.

In the present study, the patients with MI displayed significantly higher DMFT values than the healthy controls in the unadjusted analysis. This is in accordance with two previous case–control studies (Pasqualini et al., **2012**; Willershausen et al., **2014**) that similarly found DMFT to differ between patients with acute MI or unstable angina and controls. However, in the present study this correlation did not remain significant following adjustment.

The analyses also revealed that the controls had more filled teeth than the patients with MI. In the conditional regression analysis, having more filled teeth was inversely associated with a first MI. An explanation is that individuals with more filled but caries-free teeth have been less exposed to EID and as a consequence a smaller burden of systemic inflammation which in turn reduces the risk of a first MI. It could also suggest that having more filled teeth, free of caries, reflects a generally healthier lifestyle, including the benefits of professional dental care.

A correlation between different variables indicating EID and CVD, including acute MI, has been reported previously (An et al., **2016**; Caplan et al., **2006**; Joshipura et al., **2006**; Liljestrand et al., **2016**; Pasqualini et al., **2012**; Petersen et al., **2014**; Virtanen et al., **2017**). With respect to the variables periapical lesions, root filled teeth or decayed teeth, the full cohort analyses of patients and matched controls in the present study did not identify any significant differences between patients with a first MI and controls.

However, the forest plot (Figure 1) gives an overall indication that higher scores in all the variables selected to represent different types or stages of EID (except filled teeth without caries) tend to increase the risk of a first MI, even if the different variables are not individually statistically significant. This suggests that there is a need for alternative means of identifying and describing an individual's exposure to EID, possibly by means of biological markers in blood (Gomes et al., **2013**) or saliva (Haug & Marthinussen, **2019**). Another option might be to summarize an individual's clinical and radiological variables indicative of EID into a unique and single digit on a predefined ordinal scale.

When matched pairs were divided by gender, only the number of missing teeth and the proportion of missing teeth were significantly associated with a first MI (amongst both men and women). The subgroup division increases the risk for a statistical Type II error, which was especially apparent amongst women contributing only 151 of the 805 matched pairs.

Previous publications have reported that oral inflammatory diseases as a risk factor for coronary artery disease are more significant in younger individuals (Caplan et al., **2006**; Mattila et al., **1989**). In the present study, the categorization of different age intervals revealed some interesting results. Taken together, the results of these subgroup analyses suggest that untreated EID, in various stages, at different periods of life could increase the risk of a first MI. In the age group 28–59 years, the proportion of untreated caries poses an increased risk (OR: 1.43). Untreated caries may progress to pulpal necrosis and apical periodontitis in any tooth affected. This emerged as a risk factor when the age group was extended to 28–64 years (OR: 1.57). Untreated caries and apical periodontitis increase the risk of the need for root canal treatment. As a result, in the oldest age group (65–75 years), the proportion of root filled teeth poses an increased risk of MI (OR: 1.18). Age acting as a possible effect modifier for endodontic variables except missing teeth was partly supported by the interaction analyses, as the p-value for interaction indicated that decayed teeth, as well as one or more primary periapical lesions, increases the risk of a first MI in the younger age groups. However, the number of filled teeth as a protective indicator or proportion of root filled teeth as a risk indicator in the older age groups did not reach statistical significance, $p = .33$ and $p = .090$ respectively. Consequently, the age-depending effect for these variables on the risk of a first MI must be questioned but warrants further investigations.

The major strength of the present study is the large number of patients and that many important variables were included. The comprehensive collection of several possible risk factors for CVD allowed for the statistical analyses to be adjusted for confounding factors. Furthermore, MI was diagnosed in conjunction with an emergency hospital visit, leaving little or no uncertainty about the dependent variable.

In Conclusion results from the present study corroborate with previous findings that tooth loss is independently associated with an increased risk of a first MI.

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