Original paper

Paraoxonase-1, a novel link between periodontitis and ischemic heart disease: A case–control study

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Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl*. 2023;60(1):55–59

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Funding sources
The present study was supported by grants from the Research Institute of Dental Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran (24975).

Conflict of interest
None declared

Acknowledgements
This article has been extracted from the thesis written by Dr. P. Ghorbani. Dr. Ghorbani and Dr. Rezaei Esfahrood equally contributed to this study.

Received on March 23, 2022
Reviewed on June 27, 2022
Accepted on July 18, 2022

Published online on March 28, 2023

Cite as
Ghorbani P, Rezaei Esfahrood Z, Foroughi M. Paraoxonase-1, a novel link between periodontitis and ischemic heart disease: A case–control study. *Dent Med Probl.* 2023;60(1):55–59. doi:10.17219/dmp/152181

DOI
10.17219/dmp/152181

Abstract

Background. Periodontitis is a chronic inflammatory disease and might be a potential risk factor for ischemic heart disease (IHD). However, the link between periodontitis and atherosclerosis is not yet fully understood. Paraoxonase-1 (PON-1) is a new biomarker representing both anti-atherosclerotic and antioxidant activity, which also acts against dental biofilm formation and periodontitis. The possible contributing role of PON-1 in the relationship between periodontitis and atherosclerosis has not been studied to date.

Objectives. The aim of the present study was to investigate the serum level of PON-1 with regard to the periodontal status in IHD patients.

Material and methods. In this case–control study, 67 patients with IHD underwent a periodontal examination and were accordingly allocated to one of the 2 study groups: the case group with chronic periodontitis ($n = 36$); or the control group with a healthy periodontium ($n = 31$). Serum PON-1 activity was measured by means of colorimetric analysis.

Results. There were no significant differences between the groups in terms of demographic data, cardiac risk factors, initial biochemical test results, cardiac pump function, and the number of grafted vessels. The activity of PON-1 in cardiac patients suffering from periodontitis was significantly lower than in cardiac patients with a healthy periodontal status (53.01 ±7.53 U/mL and 59.11 ±9.95 U/mL, respectively; $p = 0.007$).

Conclusions. This finding suggests that the combination of IHD and periodontitis is associated with lower PON-1 activity. Further studies might be required to assess the possible role of periodontal treatment in increasing PON-1 activity and reducing IHD severity.

Keywords: chronic periodontitis, cardiovascular disease, coronary artery bypass, paraoxonase-1

Introduction

Periodontitis is a chronic disease characterized by inflammatory[1,2] and immune reactions.[3] Periodontitis and ischemic heart disease (IHD) have a variety of common risk factors, such as diabetes mellitus, old age, low socioeconomic status, and obesity.[4–6] Both are non-contagious maladies and are expressed by high prevalence on a global scale. Several chronic infectious diseases,[7] as well as inflammatory and immunity disorders, are important risk factors for both. Periodontitis and IHD may represent common pathophysiology.[5,6,8–11] This can be confirmed by identifying the susceptible genes for both diseases.

Epidemiologic evidence shows that periodontitis leads to a higher risk of atherosclerotic cardiovascular disease in the future.[1,12] Untreated periodontal disease can result in a severe systemic inflammatory state.[12] Numerous studies have indicated that increased serum levels of endotoxins (lipopolysaccharides) and inflammatory cytokines, such as C-reactive protein (CRP), thromboxane A2 (TxA2), interleukin-1 beta (IL-1β), prostaglandin E2 (PGE2), and tumor necrosis factor-alpha (TNF-α), are associated with periodontitis.[2,13] These markers are also shown to be capable of initiating and exacerbating atherogenic and thromboembolic events.[2,12–14] The effect of periodontal disease on IHD seems to consist in the change in oral microbiota, and the direct or indirect influence of systemic inflammation. Therefore, periodontitis appears to be a modifiable and nonconventional risk factor for IHD.

Paraoxonase-1 (PON-1) is a 43 kDa polypeptide containing 355 amino acids.[15,16] It is a polymorphic protective enzyme synthesized in the liver. Paraoxonase-1 binds to high-density lipoprotein particles, and it seems to be an important factor in anti-atherosclerotic, anti-inflammatory and antioxidative processes. Moreover, it acts against bacterial biofilm formation. Serum PON-1 activity is significantly lower in patients suffering from cardiovascular, liver, diabetic, and renal diseases, as well as obesity and cancer. This enzyme is suggested to be considered as a new predictive biomarker and a surrogate endpoint. There are limited studies on the importance of PON-1 in periodontal patients.

To our knowledge, the possible contributing role of PON-1 in the relationship between periodontitis and atherosclerosis has not been studied to date. The purpose of the present study was to evaluate serum PON-1 activity with regard to the periodontal status in patients with documented IHD who underwent coronary artery bypass grafting (CABG) surgery.

Material and methods

This case–control study included IHD patients who were scheduled for elective CABG in a tertiary university hospital in Tehran, Iran, from June 2020 to June 2021. The study protocol was approved by the Ethics Committee at the Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.DRC.REC.1398.225). Documented informed consent was obtained from all the involved participants. The study was reported in accordance with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement.

The inclusion criteria were IHD patients undergoing elective isolated CABG surgery with at least 15 teeth per individual. Our exclusion criteria were as follows: 1) having a history of smoking or opioid use; 2) patients with systemic diseases, such as diabetes, obesity, rheumatoid arthritis, and systemic infections; 3) patients who had been taking antibiotics, anti-inflammatory (except aspirin) and steroid medications within the last 6 months; 4) individuals who had undergone periodontal surgery, or scaling and root planing within the last 6 months; 5) candidates for an urgent surgery; 6) patients who had a history of infarction within the last 2 weeks; 7) patients with other pathophysiological conditions of the heart, liver or kidneys; and 8) patients with stage II periodontitis.

For all individuals, a periodontal examination was performed prior to the surgery by one dental student who was trained within a standard educational program. The gingival index (GI), bleeding on probing (BOP), the probing pocket depth (PPD), and the clinical attachment level (CAL) were assessed in 6 areas of the teeth (mesiobuccal, midbuccal, distobuccal, mesiolingual/palatal, midlingual/palatal, and distolingual/palatal). The examined teeth were maxillary central incisors, maxillary first premolars, maxillary first molars, mandibular central incisors, mandibular first premolars, and mandibular first molars. The armamentarium that was used for the periodontal examination were the Williams periodontal probe (Hu-Friedy, Chicago, USA), a dental mirror and dental explorer No. 33 (Hu-Friedy).

According to the Löe and Silness classification, GI is an indicator of gingival tissue condition. This index considers the quality of gingiva (the severity of lesions) and the affected areas. Therefore, it does not refer to the pocket depth, bone loss and other changes in the quantity of periodontal tissues. The PPD is defined as the distance between the gingival margin and the base of the periodontal pocket. The CAL is the distance between the cementoenamel junction and the base of the periodontal pocket.

The patients were subsequently allocated to the case and control groups with regard to their periodontal status. Periodontal disease was defined based on the consensus report of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions.[1] The IHD patients with stage III or IV were included in the case group. The control group consisted of individuals who had been diagnosed with either a healthy periodontium or stage I periodontitis.

Demographic information about this population, the patients' cardiac condition, and their results of routine laboratory tests and the periodontal examination were recorded. The baseline inflammatory status was established by measuring the erythrocyte sedimentation rate (ESR), the white blood cell count (WBC), the red blood cell distribution width (RDW), and the mean platelet volume (MPV).

All patients underwent identical cardiac treatment, regardless of the result of the periodontal examination. The investigators, the patients and the medical team were blind to the periodontal allocation.

Table 1. Demographic and medical data of the study participants ($N = 67$)

Characteristic	IHD patients with periodontitis $n = 36$	IHD patients with a healthy periodontium $n = 31$	*p*-value
Age [years]	55.50 ±10.00	58.32 ±8.47	0.160
Gender (F/M)	22 (61.11)	16 (51.61)	0.460
History of hyperlipidemia (+/–)	17 (47.22)	19 (61.29)	0.250
History of hypertension (+/–)	19 (52.78)	20 (64.52)	0.330
Triglyceride [mg/dL]	150.24 ±68.54	164.18 ±70.32	0.440
Cholesterol [mg/dL]	144.84 ±46.13	158.63 ±38.87	0.240
LDL [mg/dL]	84.26 ±29.72	86.28 ±31.56	0.830
HDL [mg/dL]	39.37 ±13.42	41.33 ±17.89	0.710
Serum vitamin D [ng/dL]	21.67 ±11.34	24.20 ±17.77	0.520
Basic albumin amount [g/dL]	3.79 ±0.41	3.72 ±0.44	0.940
ESR [mm/h]	17.13 ±12.70	18.19 ±14.62	0.750
Basic WBC [$\times 10^3$ µL]	7.17± 1.70	8.23 ±2.76	0.370
PLT [$\times 10^3$ µL]	270.64 ±83.22	231.68 ±60.89	0.030*
RDW [%]	13.30 ±1.31	13.49 ±0.93	0.230
MPV [fL]	9.58 ±1.40	10.11 ±1.42	0.060
Number of grafted vessels	3.33 ±0.74	3.50 ±0.71	0.250
EF [%]	45.30 ±11.80	44.29 ±10.00	0.590
PON-1 activity (U/mL)	53.01 ±7.53	59.11 ±9.95	0.007*

Data presented as mean ± standard deviation ($M \pm SD$) or as number (percentage) (n (%)). IHD – ischemic heart disease; F – female; M – male; LDL – low-density lipoprotein; HDL – high-density lipoprotein; ESR – erythrocyte sedimentation rate; WBC – white blood cell count; PLT – platelet count; RDW – red blood cell distribution width; MPV – mean platelet volume; EF – ejection fraction; PON-1 – paraoxonase-1; * statistically significant.

Measuring PON-1 activity

Fasting blood samples were collected from all patients into simple tubes prior to the operation and given enough time to make a clot. The tubes were subsequently centrifuged at 1,000 rpm for 3–5 min to form a clear serum, which was stored at –70°C. Serum PON-1 activity was measured using a colorimetric assay kit (ZellBio, Lonsee, Germany) according to the manufacturer's instructions.

Statistical analysis

Quantitative and qualitative variables were expressed as mean and standard deviation ($M \pm SD$), and as number and percentage (n (%)), respectively. Continuous and categorical variables were compared between the groups using Student's t test and the χ^2 test, respectively. Statistical analysis was performed using the Stata software, v. 13 (StataCorp, College Station, USA), and $p < 0.05$ was considered statistically significant.

Results

Our study population consisted of 67 patients with indications for CABG surgery, who were enrolled between June 2020 and June 2021 in a tertiary university hospital. Subsequently, the IHD patients were allocated to either the group with a healthy periodontium ($n = 31$) or the group with chronic periodontitis ($n = 36$). Table 1 shows that the patients showed no remarkable variations in the demographic data, cardiac risk factors, the initial biochemical tests, IHD severity, and the number of stenotic coronary arteries. The findings of the periodontal examinations in IHD patients are presented in Table 2.

The baseline inflammatory status in terms of ESR, WBC, RDW, and MPV was comparable between the groups. The platelet count (PLT) was significantly different between the 2 groups ($p = 0.030$). Although it might not have any clinical significance in coagulation activity,

Table 2. Periodontal examination data of the study participants ($N = 67$)

Periodontal index		IHD patients with periodontitis $n = 36$	IHD patients with a healthy periodontium $n = 31$	*p*-value
GI (0–3)	0	0 (0)	31 (100)	<0.001*
	2	36 (100)	0 (0)	
BOP [%]		36 (100)	0 (0)	<0.001*
PPD [mm]		5.8 ±0.9	1.4 ±0.8	<0.001*
CAL [mm]		5.1 ±1.4	2.4 ±1.8	<0.001*

Data presented as $M \pm SD$ or as n (%). GI – gingival index; BOP – bleeding on probing; PPD – probing pocket depth; CAL – clinical attachment level; * statistically significant.

it can represent a higher level of acute-phase proteins in IHD patients with periodontitis.

The activity of PON-1 was significantly lower in patients suffering from both cardiac and periodontal diseases (stage III or IV) in comparison with cardiac patients who had a healthy periodontium or stage I periodontitis ($p = 0.007$) (Table 1).

Discussion

The present study showed that PON-1 activity was significantly lower in IHD patients suffering from stage III and IV periodontitis in comparison with IHD patients with a healthy periodontium or stage I periodontitis.

Periodontitis is a chronic disease with a high prevalence of 45–50%.[1,8,9,12] A severe form of the disease affects more than 10% of the worldwide population[17] and is considered to be the 6th most common disease among humans.[18] Periodontitis is initiated with the inflammation of gingiva induced by bacteria present in dental plaque. Randomized control trials report that patients with periodontitis experience higher levels of inflammatory mediators in their serum, which significantly decrease following periodontal treatment.[7,14,18] Frequent bacteremia allows pathogens to enter the systemic blood circulation, activate the inflammatory cascades, and potentially cause endothelial and cardiac dysfunction. Therefore, systemic inflammation might represent a biological link between periodontitis and cardiovascular diseases.[4–7,14,19]

Gram-negative bacteria use homoserine lactones (HSLs) as signals of quorum sensing to enhance their biofilm. Recent evidence indicates that PON-1 might play an essential role in the protection against the formation of bacterial biofilm.[20–22] An experimental study showed that a reduced level of PON-1 led to a decrease in HSL hydrolysis, which induced dental biofilm formation and periodontitis.[21] In addition, an in vitro study suggested that PON-1 played an important role in the osteoblastic differentiation of periodontal ligaments.[23] Several clinical studies showed that the acute-phase response induced by endotoxins and lipopolysaccharides, as well as an increased release of inflammatory cytokines can decrease PON-1 activity in serum.[22,24]

Moreover, PON-1 has a protective function against atherosclerosis.[16] Preclinical studies showed that PON-1 inhibited the oxidation of low-density lipoprotein (LDL).[16,23] Oxidized LDL is plays an essential role in foam cell formation and plaque development.[7] Sufficient levels and activity of PON-1 can decrease oxidative stress, lipid peroxidation and the risk of IHD.[1,16] In the same manner, low PON-1 activity and the insufficiency of the enzyme in plasma have been shown to be related to high susceptibility to IHD.[22,24]

Since 1980, some evidence has been published, explaining that the dental health of patients with myocardial infarction was significantly poorer in comparison with the control group. Until October 2018, there was no published information about the effect of periodontal treatment on the initial intervention for acute myocardial infarction. The Periodontitis and Vascular Events (PAVE) study was the only published pilot study testing the effect of periodontal treatment on the secondary prevention of cardiovascular outcomes, and it concluded that periodontal treatment did not lead to a considerable decrease in cardiovascular events.[7] However, it must be noticed that due to the small number of patients, this pilot study was not strong enough to evaluate the influence of periodontitis on cardiovascular events. Our study showed lower PON-1 activity in IHD patients with periodontitis in comparison with IHD patients who had a normal periodontal status. Nevertheless, the clinical significance of the activity of PON-1 as a protective agent against both IHD and dental biofilm formation requires further studies.

On the other hand, in a cohort study conducted on 8,999 patients with periodontitis who had received periodontal treatment (nonsurgical or surgical, if necessary) and had been followed up according to the treatment protocols from 1979 to 2012, subjects who showed a weak response to periodontal treatment presented with more acute IHD as compared to those who appropriately responded to the treatment.[1] This suggests that successful periodontal treatment may reduce the incidence of acute IHD. Previous evidence showed a higher level of CRP in patients who had both IHD and periodontitis as compared to patients who had either periodontal disease or heart problems.[18] The effect of periodontal treatment is related to a considerable decrease in the CRP level and enhancement in the cardiovascular health criterion.[1] Confirming our findings, PON-1 has a direct effect on the prevention of LDL oxidation and plaque formation, and its association with periodontitis might be meaningful. Noack et al. showed that diabetic patients had an increased risk of periodontitis and lower PON-1 activity as compared to pre-diabetic patients.[24] It may corroborate our finding that the activity of PON-1 as an anti-inflammatory and anti-atherosclerotic marker was reduced in IHD patients with periodontitis. Diminished PON-1 activity may exacerbate the inflammation-induced atherosclerotic process in the heart.

Examining the patients by a dental student is a limitation of the study. Moreover, the sample size under examination was small. Nevertheless, the patients were from a homogenous population with regard to the cardiac risk factors and the severity of coronary artery disease. To the best of our knowledge, there is no similar study assessing the role of PON-1 activity in periodontal and cardiac conditions simultaneously. Hence, the measurement of PON-1 activity might be considered a new biomarker in the evaluation of periodontal and cardiac treatment.

Conclusions

The protective function of PON-1 might be important for the tissues frequently affected by severe oxidative stress and bacterial infections, such as the periodontium. Paraoxonase-1 as a new biomarker may introduce a novel link between periodontitis and atherosclerosis. Patients with IHD are recommended to maintain a routine periodontal check-up as part of their management to detect changes in the inflammatory status of the periodontium. Further studies are suggested to assess an increase in PON-1 activity following periodontal treatment in IHD patients and its effect on clinical practice.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee at the Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.DRC.REC.1398.225). Documented informed consent was obtained from all the involved participants.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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