

Prospective, case-controlled study evaluating serum concentration of sirtuin-1 and mannose-binding lectin in patients with and without periodontal and coronary artery disease

Pérola Michelle Vasconcelos Caribé, Cristina Cunha Villar, Guisepppe Alexandre Romito, Júlio Yoshio Takada, Ana Paula Pacanaro, Célia Maria Cassaro Strunz, Luiz Antonio Machado César and Antonio de Padua Mansur 

Ther Adv Chronic Dis

2020, Vol. 11: 1–9

DOI: 10.1177/
2040622320919621

© The Author(s), 2020.
Article reuse guidelines:
sagepub.com/journals-
permissions

Abstract

Background: Atherosclerosis and periodontal disease (PD) are inflammatory diseases that have been shown in studies to have a direct association. Mannose-binding lectin (MBL) is an immune system protein that binds to periodontal pathogens favoring phagocytosis. Conversely, increased serum sirtuin-1 (SIRT1) concentration reduces the inflammatory process.

Methods: This was a prospective, case-controlled study that analyzed serum concentration of biomarkers in patients with or without coronary artery disease (CAD) and PD. A total of 78 patients were evaluated: 20 healthy individuals, 18 patients with CAD, 20 patients with PD, and 20 patients with both PD and CAD. Clinical and laboratory characteristics were analyzed before and after nonsurgical treatment of PD and also at two equivalent times in patients without PD. Serum MBL and SIRT1 concentration were analyzed by enzyme-linked immunosorbent assay.

Results: A negative correlation was observed between changes in serum concentration of MBL and SIRT1 ($r = -0.30$; $p = 0.006$). Comparison between pre- and post-treatment of PD showed a reduction in MBL levels (886.27 ± 906.72 versus 689.94 ± 808.36 ; $p = 0.002$) and an increase in SIRT1 values (0.80 ± 1.01 versus 1.49 ± 1.55 ; $p = 0.005$) in patients with PD and without CAD. The same result was observed in patients with PD and CAD for MBL and SIRT1, respectively, of 1312.43 ± 898.21 versus 1032.90 ± 602.52 ($p = 0.010$) and 1.32 ± 1.0 versus 1.82 ± 1.75 ($p = 0.044$).

Conclusion: PD treatment reduced MBL serum concentration and increased SIRT1 serum concentration in patients with and without CAD.

Keywords: atherosclerosis, inflammation, mannose-binding protein, periodontal disease, periodontitis, sirtuin-1

Received: 2 January 2020; revised manuscript accepted: 25 March 2020.

Introduction

Periodontal disease (PD) is a highly prevalent chronic infectious disease that affects the protective and supporting structures of the teeth. In addition to the negative impact on oral health,

periodontitis also has systemic effects. For example, epidemiological evidence indicates an association between periodontitis and coronary artery disease (CAD).¹ Humphrey *et al.*² showed a direct relationship between increased risk of CAD and

Correspondence to:

Antonio de Padua Mansur
Clinical Department, Heart
Institute (InCor), University
of São Paulo Medical
School, Av. Dr. Enéas
C. Aguiar, 44, CEP, São
Paulo, 05403-000, Brazil
apmansur@yahoo.com

**Pérola Michelle
Vasconcelos Caribé**
Clinical Department, Heart
Institute (InCor), University
of São Paulo Medical
School, São Paulo, Brazil

**Cristina Cunha Villar
Guisepppe Alexandre
Romito**
Division of Periodontology,
Stomatology Department,
Dental School, University
of São Paulo, São Paulo,
Brazil

**Júlio Yoshio Takada
Ana Paula Pacanaro
Célia Maria Cassaro
Strunz
Luiz Antonio
Machado César**
Clinical Department, Heart
Institute (InCor), University
of São Paulo Medical
School, São Paulo, Brazil

the intensity of PD. Bahekar *et al.*³ also showed that both the prevalence and incidence of CAD are significantly increased in PD, concluding that PD may be a risk factor for CAD. Evidence is also available indicating that the infectious nature of PD may start an atherosclerotic lesion, or even intensify a pre-existing atherosclerotic process.⁴ Previous studies have shown that the association between PD and atherosclerotic disease was consistent across different populations.^{5,6} On the other hand, PD treatment reduces inflammatory markers associated with atherosclerosis and improves vascular endothelial function.⁷ PD has been associated with higher levels of different inflammatory biomarkers, such as interleukin-6, prostaglandin and C-reactive protein (CRP).⁸ During the evolution of PD, reactive oxygen species and inflammatory cytokines are released from immune cells to eliminate periodontal pathogens.⁹ Systemic increase in reactive oxygen species favors progression of periodontitis.¹⁰ One of the consequences of increased oxidative stress in periodontitis is the functional inactivation of nitric oxide, resulting in endothelial dysfunction.¹¹ Nitric oxide is the most important mediator that regulates endothelial function. It is a powerful vasodilator, protects the vessels against inflammation and cell proliferation, and modulates the release of different growth factors.¹² Further evidence of the role of endothelial dysfunction was the higher serum and salivary levels of endothelin-1 in patients with CAD and PD.¹³ Endothelin-1 is secreted by endothelial cells after exposure to pathogenic bacteria and represents a potent mediator of endothelial dysfunction.¹⁴ Also, it has been shown that asymmetric dimethylarginine is an endogenous inhibitor of nitric oxide metabolism.¹⁵ A recent study showed higher plasma and salivary levels of asymmetric dimethylarginine in patients with CAD and PD.¹⁶

PD can be prevented or attenuated by the innate immune response, involving a broad spectrum of cells and soluble proteins that recognize and exert effector functions in response to pathogens.¹⁷ Mannose-binding lectin (MBL) is an innate immune protein that binds to mannose-containing carbohydrates present on the surface of bacteria, triggering activation of the complement cascade, and therefore facilitating clearance of bacteria. Thus, MBL promotes defense against invasive pathogens. Experimental studies in rats showed that the MBL pathway is involved in

ischemia-induced inflammation, and administration of anti-MBL antibodies attenuated this inflammatory response of ischemia/reperfusion.^{18,19} A human study also showed that patients with type I diabetes with macro- or microvascular disease had significantly higher levels of MBL compared with patients with uncomplicated type I diabetes.²⁰ MBL serum concentration may also be a possible indicator of atherosclerotic plaque instability. A recent study showed that MBL is present in the atheroma necrotic nucleus and in the middle layer of the vascular wall, contributing to the instability of atheromatous plaques.²¹

SIRT1 regulates a variety of cellular functions, such as genome and metabolic pathway integrity, and is directly associated with greater longevity.²² SIRT1 acts in the regulation of inflammatory responses.^{23,24} A study in rats showed that resveratrol and curcumin promoted a decrease in experimentally induced periodontal lesions by reducing oxidative stress, possibly mediated by sirtuin pathway activation.²⁵ The beneficial effects of SIRT1 on inflammation, lipid metabolism, and atherosclerosis have been well documented in preclinical and animal studies.^{26,27} Stein *et al.* have shown in mice that SIRT1 protects against atherosclerosis by reducing foam cell formation.²⁸ SIRT1 increases nitric oxide production and favors vasodilation.²⁹ Interventions that increase SIRT1 production, such as caloric restriction and resveratrol, have significantly attenuated age-related vascular oxidative stress and inflammation and improved endothelial function.³⁰

Previous studies have shown that SIRT1 plays an important role in protecting against age-related vascular diseases, including inhibiting neointimal formation³¹ and protecting against the atherosclerosis process.³² An *in vitro* study has also shown that SIRT1 delays endothelial cell aging.³³ Zu *et al.* observed in an *in vitro* senescence model of a pig aorta endothelial cell culture that SIRT1 had a beneficial effect in reducing vascular senescence.³⁴ This effect would be, at least partially, a result of lower activation of the AMPK pathway LKB1-dependent. SIRT1 also acts in the periodontal ligaments. *In vitro* studies have shown that SIRT1 is a potent regulator of human periodontal ligament cell differentiation and attenuates the inflammatory response of these cells subjected to mechanical stress.^{35,36}

Periodontal treatment focuses on the elimination of pathological oral microorganisms, avoiding exacerbation of inflammatory processes. Animal studies have shown that periodontitis reduced SIRT1 levels. On the other hand, increased levels of SIRT1 prevented the progression of periodontal disease.³⁶ However, no studies have examined the impact of the association of periodontal and atherosclerotic diseases on serum MBL and SIRT1 levels before and after PD treatment. We hypothesized that periodontal treatment in patients with both CAD and PD with subsequent decrease in inflammatory process and MBL serum concentration will also result in increased SIRT1 levels and, therefore, the possible beneficial effects of higher SIRT1 levels on these diseases. Thus, this study analyzed the impact of PD treatment on serum concentrations and on the interrelationship of SIRT1 and MBL in individuals with and without stable chronic CAD.

Methods

This prospective study analyzed 78 individuals aged 45–79 years, 38 women and 40 men, between October 2016 and September 2018. Patients were divided into four groups according to the absence or presence of PD (PD– or PD+) and of CAD (CAD– or CAD+): (1) control CAD–/PD– group: 20 healthy participants; (2) CAD+/PD– group: 18 patients with CAD without PD; (3) CAD–/PD+ group: 20 patients with PD without CAD; and (4) CAD+/PD+ group: 20 patients with CAD and PD.

The diagnosis of PD was confirmed by clinical evaluation and periodontal examination. The inclusion criteria for the CAD group were patients who had at least six teeth with periodontal probing depth (PPD) and clinical attachment loss (CAL) ≥ 5 mm, with 30% of sites with PPD and CAL ≥ 4 mm and bleeding on probing (BOP). Individuals who had a periodontal with no insertion loss, PPD ≤ 3 mm, BOP in less than 10% of the sites, and no radiographic bone loss were classified as periodontally healthy.

The treatment was performed to eliminate the inflammatory process and to achieve a smooth dental surface without biofilm and stone. Patients in the periodontitis group underwent supra- and subgingival mechanical scaling and root planing using ultrasonic scalers and manual instruments,

after administration of local anesthesia. PD patients were also treated with metronidazole (1.2 g/d for 14 days) and amoxicillin (1.5 g/d for 14 days). Previous studies showed better results with adjunctive use of systemic antibiotic therapy to the treatment of PD.^{37,38} The principal investigator and examiner (PMVC) underwent a calibration to establish consistency and to obtain reliable results in periodontal examinations. Individuals without PD did not receive any treatment.

The inclusion criteria for the CAD group were patients who had a history of CAD, characterized by the presence of a coronary lesion $\geq 70\%$ on past coronary angiography, and also patients that previously underwent to percutaneous or surgical coronary revascularization. Patients were asymptomatic or with stable grade I/II of the Canadian Cardiovascular Society scale.³⁹ Healthy participants were volunteers with a normal clinical history, physical examination, and resting electrocardiogram.

Exclusion criteria were uncontrolled diabetes, chronic kidney disease, smoking, HIV, hepatitis B and C, pregnancy, brachytherapy, orthodontic treatment, anti-inflammatory drugs and corticosteroids, periodontal treatment less than 6 months previously and allergic to the antibiotics prescribed in this protocol. The study was approved by the Ethics Committee (CAPPesq) of the Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, BR (CAAE: 55556116.0.0000.0068). All participants signed a consent form. The study is registered at ClinicalTrials.org (identifier: NCT03753451).

Laboratory tests

A 10-ml sample of peripheral vein blood was collected at baseline and at the end of the study after a 12-h fast. Patients had blood sample reassessed 1 month after periodontal treatment. The biochemical tests analyzed were triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, glucose, CRP, MBL, and SIRT1. Glucose, triglycerides, and HDL cholesterol were obtained using the enzymatic calorimetry method. Low-density lipoprotein (LDL) cholesterol was calculated by Friedwald's equation. Measurements were performed at Dimension RxL (Siemens

Healthcare Diagnostic Inc., Newark, DE, USA). The determination of ultrasensitive CRP was performed by immunonephelometry with dedicated reagents on Siemens Healthcare BN-II equipment (Marburg, Hessen, Germany). Serum MBL levels were determined by enzyme-linked immunosorbent assay (ELISA) using anti-MBL monoclonal antibody HYB 131-01 (BioPorto Diagnostics A/S, Copenhagen, Denmark). SIRT1 concentrations were determined using an ELISA kit (Usin Life Science, Wuhan, Hubei, China). Before and after the interventions, SIRT1 samples were analyzed in duplicate on the same ELISA plate using a Multiscan FC plate reader (Thermo Fisher Scientific Oy, Vantaa, Finland), with a 12% coefficient of variation according to the manufacturer's instructions.

Statistical analysis

The sample size calculation was made by the difference between the serum SIRT1 levels, before and after periodontal treatment. The expected values were based on a previous study conducted in our service in healthy individuals.⁴⁰ The difference between the means for the control group was 1 mg with standard deviation of 1 mg and for intervention groups was 2 mg with standard deviation of 1 mg. The test power was $\beta = 0.90$ and $\alpha = 0.05$. The estimated number of the sample was 20 individuals for each group. Chi-square test was used for analysis of categorical variables. Correlations between variables were performed using Spearman's correlation test. The paired Student's *t* test was used for intragroup analysis between the initial and final protocol values. Unpaired Student's *t* test was used for comparison between groups. Student's *t* test was used for variables with normal distribution, which was verified by the analysis of equality of variances (Folded *F* method). Depending on the result of this analysis, either the Pooled method (variances with $p \geq 0.05$) or the Satterthwaite method (variances with $p < 0.05$) were used. The statistical program used was SAS (version 9.2, Institute, Inc., Cary, NC, USA).

Results

Clinical features and laboratory data of participants before and at the end of study are shown in Table 1. After PD treatment of the CAD+/PD+

and CAD-/PD+ groups, we observed a reduction in the plaque index from $63.9\% \pm 5.7\%$ to $37.8\% \pm 10.5\%$ ($p < 0.001$), BOP from $34.2\% \pm 6.9\%$ to $16.9\% \pm 5.5\%$ ($p < 0.001$), CAL from 5.3 ± 0.7 to 4.49 ± 0.8 mm ($p < 0.001$), and PPD from 5.3 ± 0.8 to 3.3 ± 0.7 mm ($p < 0.001$). A negative correlation was observed between changes (end of study values minus baseline values) in serum concentration of MBL and SIRT1 ($r = -0.30$; $p = 0.006$). A positive correlation also occurred between changes in MBL serum levels and total cholesterol ($r = 0.30$; $p = 0.006$), non-HDL variations ($r = 0.27$; $p = 0.014$) and LDL variations ($r = 0.25$; $p = 0.024$). On the other hand, there was no correlation between changes in SIRT1 concentrations and total cholesterol, HDL cholesterol, LDL cholesterol, non-HDL cholesterol, triglycerides, glucose, and CRP. For the control group (CAD-/PD-), we observed before and at the end of the study a reduction in serum SIRT1 concentration (0.46 ± 0.47 versus 0.21 ± 0.29 ng/ml; $p = 0.022$) and an increase in serum MBL concentration (509.04 ± 397.13 versus 921.98 ± 923.91 ng/ml; $p = 0.028$). No significant changes were observed in serum concentration of CRP, glucose, and in the lipid profile. For the CAD+/PD- group, we observed before and at the end of the study an increase in serum SIRT1 concentration from 1.12 ± 1.26 to 1.72 ± 1.87 ng/ml ($p = 0.044$). No significant changes were observed in serum concentration of MBL, CRP, glucose, and in the lipid profile. For the CAD-/PD+ group, we observed before and after PD treatment a reduction in CRP serum concentration from 5.69 ± 8.0 to 2.04 ± 2.60 mg/l ($p = 0.043$) and in MBL levels from 886.27 ± 906.72 to 689.94 ± 808.36 ng/ml ($p = 0.002$) and an increase in SIRT1 values from 0.80 ± 1.01 to 1.49 ± 1.55 ng/ml ($p = 0.005$). The other variables analyzed did not show any statistically significant differences before and after PD treatment. For the CAD+/PD+ group, we observed before and after PD treatment a reduction in MBL values from 1312.43 ± 898.21 to 1032.90 ± 602.52 ng/ml ($p = 0.010$), serum total cholesterol from 175.55 ± 63.57 to 150.20 ± 57.60 mg/dl ($p = 0.001$), LDL cholesterol from 99.50 ± 53.67 versus 83.55 ± 48.42 mg/dl ($p = 0.021$) and an increase in SIRT1 concentration from 1.32 ± 1.0 to 1.82 ± 1.75 ng/ml ($p = 0.044$). The other variables analyzed did not show any statistically significant differences before and after PD treatment.

Table 1. Clinical and periodontal features and laboratory data of participants before and at the end of study.

Variable	CAD-/PD-			CAD+/PD-			CAD-/PD+			CAD+/PD+		
	Baseline (n=20)	END (n=20)	p-value	Baseline (n=18)	END (n=18)	p-value	Baseline (n=20)	END (n=20)	p-value	Baseline (n=20)	END (n=20)	p-value
Age (years)	56.5 ± 6.7			62.0 ± 11.1			54.2 ± 4.8			62.3 ± 7.3		
BMI (kg/m ²)	27.8 ± 6.7			29.3 ± 6.5			27.3 ± 4.1			27.9 ± 3.9		
Total cholesterol (mg/dl)	204.45 ± 57.39	199.05 ± 70.61	0.453	158.22 ± 41.7	153.50 ± 31.1	0.595	207.00 ± 31.93	201.35 ± 33.31	0.243	175.55 ± 63.57	150.20 ± 57.40	0.001
HDL cholesterol (mg/dl)	60.20 ± 18.21	58.05 ± 14.55	0.222	44.01 ± 13.25	46.78 ± 13.25	0.151	59.15 ± 14.22	57.25 ± 13.27	0.191	45.00 ± 17.01	43.95 ± 14.94	0.420
LDL cholesterol (mg/dl)	118.75 ± 50.89	117.40 ± 58.53	0.847	82.67 ± 38.15	81.11 ± 25.47	0.821	123.05 ± 29.82	122.25 ± 32.54	0.860	99.50 ± 53.67	83.55 ± 48.42	0.021
Non-HDL cholesterol (mg/dl)	222.65 ± 362.49	141.00 ± 69.25	0.302	114.17 ± 40.89	107.83 ± 29.47	0.437	147.85 ± 28.17	144.10 ± 29.73	0.439	130.55 ± 59.90	107.25 ± 57.52	0.002
Triglycerides (mg/dl)	146.20 ± 114.69	119.00 ± 79.90	0.126	165.67 ± 96.98	138.89 ± 82.17	0.054	123.45 ± 58.66	105.85 ± 58.12	0.059	153.05 ± 93.80	128.95 ± 71.53	0.214
Glucose (mg/dl)	104.10 ± 25.28	96.60 ± 14.23	0.134	150.78 ± 70.19	134.72 ± 35.98	0.092	98.25 ± 10.36	100.70 ± 10.47	0.239	150.85 ± 84.04	132.75 ± 53.50	0.096
usCRP (mg/l)	3.95 ± 4.69	3.53 ± 4.40	0.420	3.83 ± 9.45	3.45 ± 4.63	0.857	5.69 ± 8.01	2.04 ± 2.60	0.043	10.08 ± 6.40	2.85 ± 3.17	0.097
SIRT1 (ng/ml)	0.46 ± 0.47 *	0.21 ± 0.29	0.022	1.12 ± 1.26	1.72 ± 1.87	0.044	0.80 ± 1.01	1.49 ± 1.55	0.005	1.32 ± 1.00 *	1.82 ± 1.75	0.044
MBL (ng/ml)	509.04 ± 397.13†	921.98 ± 923.91	0.028	890.69 ± 630.98	985.02 ± 638.74	0.278	886.27 ± 906.72	689.94 ± 808.36	0.003	1312.43 ± 898.21†	1032.90 ± 602.52	0.010
Periodontal Variables												
Plaque index (%)							63.29 ± 6.40	38.79 ± 10.48	<0.001	64.53 ± 5.06	36.79 ± 10.71	<0.001
Bleeding on probing (%)							35.17 ± 8.40	18.21 ± 5.36	<0.001	33.24 ± 5.03	15.67 ± 5.51	<0.001
Clinical attachment level (mm)							5.66 ± 0.62	4.68 ± 0.77	<0.001	4.92 ± 0.65	4.31 ± 0.76	0.001
Probing depth (mm)							5.54 ± 0.67	3.26 ± 0.74	<0.001	4.99 ± 0.77	3.27 ± 0.65	<0.001

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MBL, mannose-binding lectin; SIRT1, sirtuin-1; usCRP, ultrasensitive C-reactive protein. *p < 0.006; SIRT1 (CAD-/PD- versus CAD+/PD+); †p < 0.001; MBL (CAD-/PD- versus CAD+/PD+).

Discussion

Our study shows that PD treatment is associated with reduced serum MBL and CRP concentrations and increased SIRT1 serum levels. Patients in the CAD+/DP+ group had the highest initial MBL concentration, suggesting an additive inflammatory power of the association of CAD and PD in the serum MBL concentration. Our study also showed higher initial mean MBL values in the CAD patient groups compared with the control participants. The relationship between MBL and atherosclerotic disease is controversial and poorly understood. Increased serum concentration of MBL was associated with a higher risk of myocardial infarction, as well as a worse prognosis in the surgical revascularization of CAD.⁴¹ On the other hand, MBL deficiency at serum levels <100 ng/ml was also associated with a higher incidence of myocardial infarction and higher CAD progression.^{42,43} For PD, Maffei *et al.* did not observe elevated serum MBL levels, and MBL deficiency was not related to increased susceptibility to PD.⁴⁴ However, these authors arbitrarily set MBL deficiency to serum concentration values <800 ng/ml, whereas in most studies serum levels <100 ng/ml were used as a criterion for MBL deficiency. Louropoulou *et al.* showed that even in individuals with deficiency in MBL production the presence of PD was associated with increased MBL serum levels.⁴⁵ These results were similar to those observed previously, showing MBL as an acute-phase reagent.⁴⁶ Our results are consistent with most studies, that is, we observed increased MBL in the presence of PD and decreased serum concentration after PD treatment. The finding of MBL as an inflammatory marker was confirmed by the direct correlation observed with CRP values. Our study showed a significant reduction in CRP serum levels in response to treatment of PD. The treatment of PD reduced the MBL and PCR serum levels and it is well known that lower intensity of chronic inflammation also reflects reduced progression of the atherosclerosis process.

Our study also shows that PD treatment is associated with increased SIRT1 serum concentration. The increase in SIRT1 serum concentration was probably a consequence of PD treatment. SIRT1 is a potent regulator of human periodontal ligament cell differentiation and may have clinical implications for periodontal bone regeneration.⁴⁷ Therefore, in our study, there is still the possibility that increased SIRT1 levels could partially

influenced a better clinical response to PD treatment. However, studies analyzing the metabolic pathway of SIRT1 in patients with PD are scarce. Higher SIRT1 serum concentration reduced oxidative stress; this increase may be beneficial in patients with PD. The reduction in CAL achieved through periodontal treatment was associated with a reduction in plasma levels of reactive oxygen metabolites.⁴⁸ The treatment of PD was associated with lower levels of proinflammatory biomarkers. Studies in periodontal ligament cell cultures have also shown a reduction in proinflammatory substances, such as matrix metalloproteinases and interleukins, a process dependent, at least in part, on SIRT1 signaling.^{49,50} Nonetheless, no studies have analyzed the relationship between serum levels of SIRT1 and MBL, alone or combined, in patients with PD and CAD.

In our study we also observed a significant reduction in serum concentration of total cholesterol and LDL cholesterol and reduced levels of HDL cholesterol after PD treatment in the CAD+/DP+ group. This result was similar to results observed in previous studies.⁵¹ Possible explanations for these findings are the influence of multiple proinflammatory cytokines in increasing the synthesis of triglyceride rich lipoproteins and in interfering in metabolic enzymatic pathways of lipoproteins, such as the lipoprotein lipase. This prospective, case-controlled study with a well-selected population, has some limitations, which include the relative small number of participants, despite the statistically appropriate sample size, and the short follow-up period.

In conclusion, our study shows a reduction in serum MBL and CRP concentration and an increase in serum SIRT1 levels after PD treatment, providing a better biochemical and metabolic blood profile. It is possible that this improvement in blood rheology with a reduction of the systemic immunoinflammatory process had a positive impact on vascular health, and in the long term could contribute to lower atherosclerosis progression. Similarly, increased serum concentration of SIRT1 could also have a clinical benefit by reducing the severity of PD and even preserving periodontal health. However, prospective and long-term follow-up studies using drugs that increase serum concentration of SIRT1 are mandatory to assess the impact of higher levels of SIRT1 on prognosis in PD and CAD.

Acknowledgements

Part of the work was presented in the following article: Caribé *et al.* Influence of the treatment of periodontal disease in serum concentration of sirtuin 1 and mannose-binding lectin. *J Periodontol.* 2019 Nov 20. doi: 10.1002/JPER.19-0236. [Epub ahead of print].

Author contributions

PMVC, CCV, GAR and APM contributed to the conception or design of the work. PMVC, CCV, GAR, JYT, APP, CMCS, LAMC and APM contributed to the acquisition, analysis, and interpretation of data. PMVC and APM drafted the manuscript. PMVC, CCV, GAR, JYT, APP, CMCS, LAMC and APM critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: this study was partially funded by the Coordination of Improvement of Higher Education Personnel - Brazil (São Paulo) (CAPES) - Finance Code 001 to PMVC.

Conflict of interest statement

The authors declare that there is no conflict of interest.

ORCID iD

Antonio de Padua Mansur  <https://orcid.org/0000-0003-3051-1090>


References

1. Carrizales-Sepúlveda EF, Ordaz-Farías A, Vera-Pineda R, *et al.* Periodontal disease, systemic inflammation and the risk of cardiovascular disease. *Heart Lung Circ* 2018; 27: 1327–1334.
2. Humphrey LL, Fu R, Buckley DI, *et al.* Periodontal disease and coronary heart disease incidence: a systematic review and meta-analysis. *J Gen Intern Med* 2008; 23: 2079–2086.
3. Bahekar AA, Singh S, Saha S, *et al.* The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. *Am Heart J* 2007; 154: 830–837.
4. Paquette DW, Brodala N and Nichols TC. Cardiovascular disease, inflammation, and periodontal infection. *Periodontol* 2007; 44: 113–126.
5. Destefano F, Anda RF, Kahn HS, *et al.* Dental disease and risk of coronary heart and mortality. *BMJ* 1993; 306: 688–691.
6. Beck JD, Elter JR, Heiss G, *et al.* Relationship of periodontal disease to carotid artery intima-media wall thickness: the atherosclerosis risk in communities (ARIC) study. *Arterioscl Thromb Vasc Biol* 2001; 21: 1816–1822.
7. Gurav AN. The implication of periodontitis in vascular endothelial dysfunction. *Eur J Clin Invest* 2014; 44: 1000–1009.
8. Zhang Q, Chen B, Zhu D, *et al.* Biomarker levels in gingival crevicular fluid of subjects with different periodontal conditions: a cross-sectional study. *Arch Oral Biol* 2016; 72: 92–98.
9. Ungvari Z, Buffenstein R, Austad SN, *et al.* Oxidative stress in vascular senescence: lessons from successfully aging species. *Front Biosci* 2008; 13: 5056–5070.
10. Tamaki N, Tomofuji T, Maruyama T, *et al.* Relationship between periodontal condition and plasma reactive oxygen metabolites in patients in the maintenance phase of periodontal treatment. *J Periodontol* 2008; 79: 2136–2142.
11. Higashi Y, Goto C, Jitsuiki D, *et al.* Periodontal infection is associated with endothelial dysfunction in healthy subjects and hypertensive patients. *Hypertension* 2008; 51: 446–453.
12. Hampton TG, Amende I, Fong J, *et al.* Basic FGF reduces stunning via a NOS2-dependent pathway in coronary perfused mouse hearts. *Am J Physiol Heart Circ Physiol* 2000; 279: H260–H268.
13. Isola G, Polizzi A, Alibrandi A, *et al.* Analysis of Endothelin-1 concentrations in individuals with periodontitis. *Sci Rep* 2020; 10: 1652.
14. Amiri F, Viridis A, Neves MF, *et al.* Endothelium-restricted overexpression of human endothelin-1 causes vascular remodeling and endothelial dysfunction. *Circulation* 2004; 110: 2233–2240.
15. Boger RH. Asymmetric dimethylarginine: understanding the physiology, genetics, and clinical relevance of this novel biomarker. Proceedings of the 4th International Symposium on ADMA. *J Pharmacol Res* 2009; 60: 447.
16. Isola G, Alibrandi A, Currò M, *et al.* Evaluation of salivary and serum ADMA levels in patients with periodontal and cardiovascular disease as

- subclinical marker of cardiovascular risk. *J Periodontol*. Epub ahead of print 7 January 2020. DOI: 10.1002/JPER.19-0446.
17. Turvey SE and Broide DH. Innate immunity. *J Allergy Clin Immunol* 2010; 125: S24–S32.
 18. Vries de B, Walter SJ, Peutz-Kootstra CJ, *et al*. The mannose-binding lectin-pathway is involved in complement activation in the course of renal ischemia-reperfusion injury. *Am J Pathol* 2004; 165: 1677–1688.
 19. Jordan JE, Montalto MC and Stahl GL. Inhibition of mannose-binding lectin reduces posts ischemic myocardial reperfusion injury. *Circulation* 2001; 104: 1413–1418.
 20. Hansen TK, Tarnow L, Thiel S, *et al*. Association between mannose-binding lectin and vascular complications in type 1 diabetes. *Diabetes* 2004; 53: 1570–1576.
 21. Fumagalli S, Perego C, Zangari R, *et al*. Lectin pathway of complement activation is associated with vulnerability of atherosclerotic plaques. *Front Immunol* 2017; 8: 288.
 22. Lee YM, Shin SI, Shin KS, *et al*. The role of sirtuin 1 in osteoblastic differentiation in human periodontal ligament cells. *J Periodontol Res* 2011; 46: 712–721.
 23. Kim YS, Lee YM, Park JS, *et al*. SIRT1 modulates high-mobility group box 1-induced osteoclastogenic cytokines in human periodontal ligament cells. *J Cell Biochem* 2010; 111: 1310–1320.
 24. Casati MZ, Algayer C, Cardoso da Cruz G, *et al*. Resveratrol decreases periodontal breakdown and modulates local levels of cytokines during periodontitis in rats. *J Periodontol* 2013; 84: 58–64.
 25. Corrêa MG, Pires PR, Ribeiro FV, *et al*. Systemic treatment with resveratrol and/or curcumin reduces the progression of experimental periodontitis in rats. *PLoS ONE* 2018; 13: e0204414.
 26. Lam YY, Peterson CM and Ravussin E. Resveratrol vs. calorie restriction: data from rodents to humans. *Exp Gerontol* 2013; 48: 1018–1024.
 27. Yang Z, Meng Q, Zhao Y, *et al*. Resveratrol promoted interferon- α -induced growth inhibition and apoptosis of SMMC7721 cells by activating the SIRT/STAT1. *J Interferon Cytokine Res* 2018; 38: 261–271.
 28. Stein S, Lohmann C, Schafer N, *et al*. SIRT1 decreases Lox-1-mediated foam cell formation in atherogenesis. *Eur Heart J* 2010; 31: 2301–2309.
 29. Mattagajasingh I, Kim CS, Naqvi A, *et al*. SIRT1 promotes endothelium-dependent vascular relaxation by activating endothelial nitric oxide synthase. *Proc Natl Acad Sci USA* 2007; 104: 14855–14860.
 30. Allard JS, Heilbronn LK, Smith C, *et al*. In vitro cellular adaptations of indicators of longevity in response to treatment with serum collected from humans on calorie restricted diets. *PLoS ONE* 2008; 3: e3211.
 31. Li L, Zhang HN, Chen HZ, *et al*. SIRT1 acts as a modulator of neointima formation following vascular injury in mice. *Circ Res* 2011; 108: 1180–1189.
 32. Zhang QJ, Wang Z, Chen HZ, *et al*. Endothelium-specific overexpression of class III deacetylase SIRT1 decreases atherosclerosis in apolipoprotein E-deficient mice. *Cardiovasc Res* 2008; 80: 191–199.
 33. Ota H, Eto M, Ogawa S, *et al*. SIRT1/eNOS axis as a potential target against vascular senescence, dysfunction and atherosclerosis. *J Atheroscler Thromb* 2010; 17: 431–435.
 34. Zu Y, Liu L, Lee MY, *et al*. SIRT1 promotes proliferation and prevents senescence through targeting LKB1 in primary porcine aortic endothelial cells. *Circ Res* 2010; 106: 1384–1393.
 35. Lee SI, Park KH, Kim SJ, *et al*. Mechanical stress-activated immune response genes via sirtuin 1 expression in human periodontal ligament cells. *Clin Exp Immunol* 2012; 168: 113–124.
 36. Tamaki N, Cristina Orihuela-Campos R, Inagaki Y, *et al*. Resveratrol improves oxidative stress and prevents the progression of periodontitis via the activation of the Sirt1/AMPK and the Nrf2/antioxidant defense pathways in a rat periodontitis model. *Free Radic Biol Med* 2014; 75: 222–229.
 37. Feres M, Soares GM, Mendes JA, *et al*. Metronidazole alone or with amoxicillin as adjuncts to non-surgical treatment of chronic periodontitis: a 1-year double-blinded, placebo-controlled, randomized clinical trial. *J Clin Periodontol* 2012; 39: 1149–1158.
 38. Sgolastra F, Gatto R, Petrucci A, *et al*. Effectiveness of systemic amoxicillin/metronidazole as adjunctive therapy to scaling and root planing in the treatment of chronic periodontitis: a systematic review and meta-analysis. *J Periodontol* 2012; 83: 1257–1269.

39. Campeau L. Grading of angina pectoris. *Circulation* 1976; 54: 522–523.
40. Mansur AP, Roggerio A, Goes MFS, *et al.* Randomized study of 30 days of resveratrol and caloric restriction on serum levels of sirtuin1 in healthy subjects. *Int J Cardiol* 2017; 227: 788–794.
41. Rugonfalvi-Kiss S, Dósa E, Madsen HO, *et al.* High rate of early restenosis after carotid eversion endarterectomy in homozygous carriers of the normal mannose-binding lectin genotype. *Stroke* 2005; 36: 944–948.
42. Rugonfalvi-Kiss S, Endrész V, Madsen HO, *et al.* Association of Chlamydia pneumoniae with coronary artery disease and its progression is dependent on the modifying effect of mannose-binding lectin. *Circulation* 2002; 106: 1071–1076.
43. Vengen IT, Madsen HO, Garred P, *et al.* Mannose-binding lectin deficiency is associated with myocardial infarction: the HUNT2 study in Norway. *PLoS ONE* 2012; 7: e42113.
44. Maffei G, Brouwer N, Dolman KM, *et al.* Plasma levels of mannan-binding lectin in relation to periodontitis and smoking. *J Periodontol* 2005; 76: 1881–1889.
45. Louropoulou A, van der Velden U, Schoenmaker T, *et al.* Mannose-binding lectin gene polymorphisms in relation to periodontitis. *J Clin Periodontol* 2008; 35: 923–930.
46. Thiel S, Holmskov U, Hviid L, *et al.* The concentration of the C-type lectin, mannan-binding protein, in human plasma increases during an acute phase response. *Clin Exp Immunol* 1992; 90: 31–35.
47. Lee SI, Min KS, Bae WJ, *et al.* Role of SIRT1 in heat stress and lipopolysaccharide induced immune and defense gene expression in human dental pulp cells. *J Endod* 2011; 37: 1525–1530.
48. Machida T, Tomofuji T, Ekuni D, *et al.* Longitudinal relationship between plasma reactive oxygen metabolites and periodontal condition in the maintenance phase of periodontal treatment. *Dis Markers* 2014; 2014: 489292.
49. Park YD, Kim YS, Jung YM, *et al.* Porphyromonas gingivalis lipopolysaccharide regulates interleukin (IL)-17 and IL-23 expression via SIRT1 modulation in human periodontal ligament cells. *Cytokine* 2012; 60: 284–293.
50. Qu L, Yu Y, Qiu L, *et al.* Sirtuin 1 regulates matrix metalloproteinase-13 expression induced by Porphyromonas endodontalis lipopolysaccharide via targeting nuclear factor- κ B in osteoblasts. *J Oral Microbiol* 2017; 9: 1317578.
51. Teeuw WJ, Slot DE, Susanto H, *et al.* Treatment of periodontitis improves the atherosclerotic profile: a systematic review and meta-analysis. *J Clin Periodontol* 2014; 41: 70–79.

Visit SAGE journals online
[journals.sagepub.com/
home/taj](http://journals.sagepub.com/home/taj)

 SAGE journals