

## ORIGINAL ARTICLE

## Impact of Periodontal Disease in the Lipid Profile of Patients With Chronic Coronary Artery Disease: a 3-Year, Retrospective Cohort

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### Abstract

**Background:** Inflammation has been recognized as an important risk factor for cardiovascular diseases. Periodontal disease may alter some plasma markers involved in the atherogenic process.

**Objective:** To assess the association between periodontal disease and lipid levels over time in patients with chronic coronary artery disease.

**Methods:** This retrospective cohort study included a sample of patients with chronic heart disease receiving care in an outpatient tertiary care for ischemic heart disease. Of 239 patients eligible for the study, we included 80 patients who had available retrospective data of lipid profile between 2009 and 2011. We performed periodontal examinations of all teeth present in 2011. Multiple models of generalized estimating equations were applied to assess the association between periodontal parameters and changes over time in the following outcomes: triglycerides, total cholesterol, LDL-cholesterol, and HDL-cholesterol levels adjusted for age, body mass index, smoking, use of oral hypoglycemic, and follow-up duration.

**Results:** During a mean follow-up time of 713 days, there were no significant changes in the concentrations of triglycerides, total cholesterol, and LDL-cholesterol. A significant 31.6% increase in HDL-cholesterol levels was observed between 2009 and 2011. We observed a significant negative association between mean individual periodontal attachment loss and HDL-cholesterol levels, indicating that the greater the attachment loss, the lower the HDL-cholesterol level over time.

**Conclusion:** Destructive periodontal disease may be related to a worse lipid control, specifically regarding HDL-cholesterol levels, in chronic cardiac patients. (Int J Cardiovasc Sci. 2016;29(4):270-279)

**Keywords:** Cardiovascular Diseases; Periodontal Diseases / Complications; Coronary Artery Disease; Lipid; Hyperlipidemias.

### Introduction

Cardiovascular diseases (CVDs), including myocardial infarction and angina *pectoris*, are the main public health problems in developed countries.<sup>1</sup> According to data from the World Health Organization, 17.3 million individuals die every year from CVDs worldwide, with 78.5% of these deaths recorded in underdeveloped countries.

The importance of lipids in atherogenesis is well established in the literature.<sup>2</sup> It was believed for many

years that atherosclerosis and CVDs occurred only as a consequence of lifestyle habits. However, the role of inflammation has been recognized in recent years and accepted as a decisive factor in the development of these conditions.<sup>3</sup> Hypercholesterolemia, in particular the increase in plasma levels of LDL-cholesterol and triglycerides (TG), and diabetes mellitus are the main risk factors for CVDs. On the contrary, the increase in HDL-cholesterol levels is associated with a lower risk of cardiovascular events.<sup>4</sup> HDL-cholesterol is recognizably

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antiatherogenic, an effect that can be explained by several mechanisms, including the stimulation of endothelial nitric oxide, inhibition of reactive oxygen, and antithrombotic mechanisms.<sup>5</sup>

Since the publication by Matilla et al.<sup>6</sup> in 1989, many studies have indicated that patients with periodontal disease (PD) may have a greater risk of cardiovascular events when compared with periodontally healthy patients.<sup>7</sup> Associations between PD with endothelial dysfunction<sup>8</sup> and atherosclerosis<sup>9</sup> have also been described in the literature. However, the causality and the possible routes for the association between PD and CVD have not yet been fully elucidated.

Periodontitis is a destructive PD caused by gram-negative bacteria present in a biofilm on the surface of the teeth. These bacteria lead to a destructive inflammatory process in the supporting tissues of the teeth, and this process is one of the main causes of tooth loss.<sup>10</sup> A severe form of this condition can occur in 15% to 40% of the individuals, depending on the study population.<sup>11,12</sup>

Periodontitis has been related to an increase in the cytokines involved in the process of formation of the atheromatous plaque and increased lipid levels.<sup>13</sup> Previous studies showed that PD is associated with increased total cholesterol and LDL-cholesterol levels.<sup>14,15</sup> Severe periodontitis is associated with a modest decrease

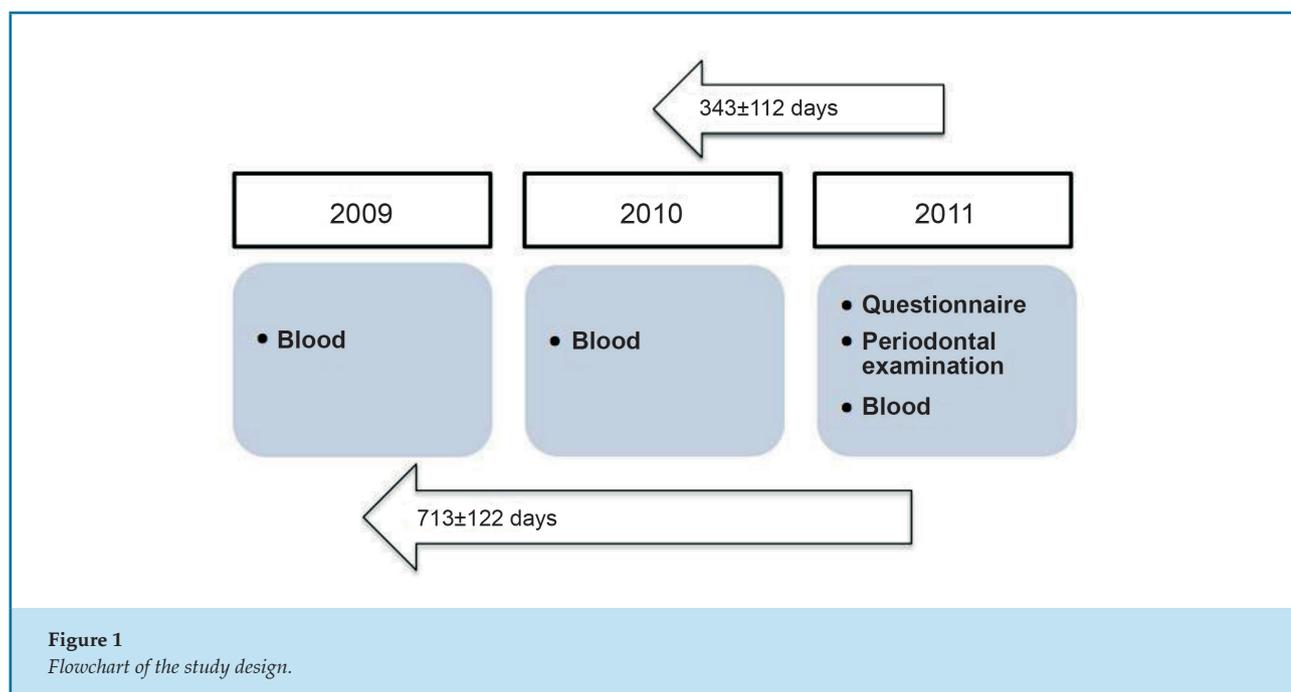
in HDL-cholesterol levels and a robust increase in TG levels.<sup>16</sup> Nevertheless, little is still known regarding the effect of periodontitis on lipid levels in patients with an established diagnosis of heart disease and under cardiac monitoring. In addition, few longitudinal studies are found in the literature, showing that the establishment of temporality in these observed associations is clearly necessary.

This study aimed to assess the association between PD and lipid abnormalities in patients with chronic coronary artery disease under cardiologic care in a tertiary outpatient clinic in southern Brazil.

## Materials and Methods

### Design and Study Sample

This observational, longitudinal, and retrospective study (Figure 1) was conducted and described following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.<sup>17</sup> The study sample consisted of patients with heart disease from a cohort undergoing follow-up in the outpatient clinic for ischemic heart disease of the *Hospital de Clínicas de Porto Alegre (HCPA)*.<sup>18</sup> The patients had a diagnosis of chronic coronary artery disease, defined by the occurrence of at least one of the following events: documented history of myocardial infarction, unstable angina, or ischemia diagnosed by noninvasive tests; percutaneous or surgical

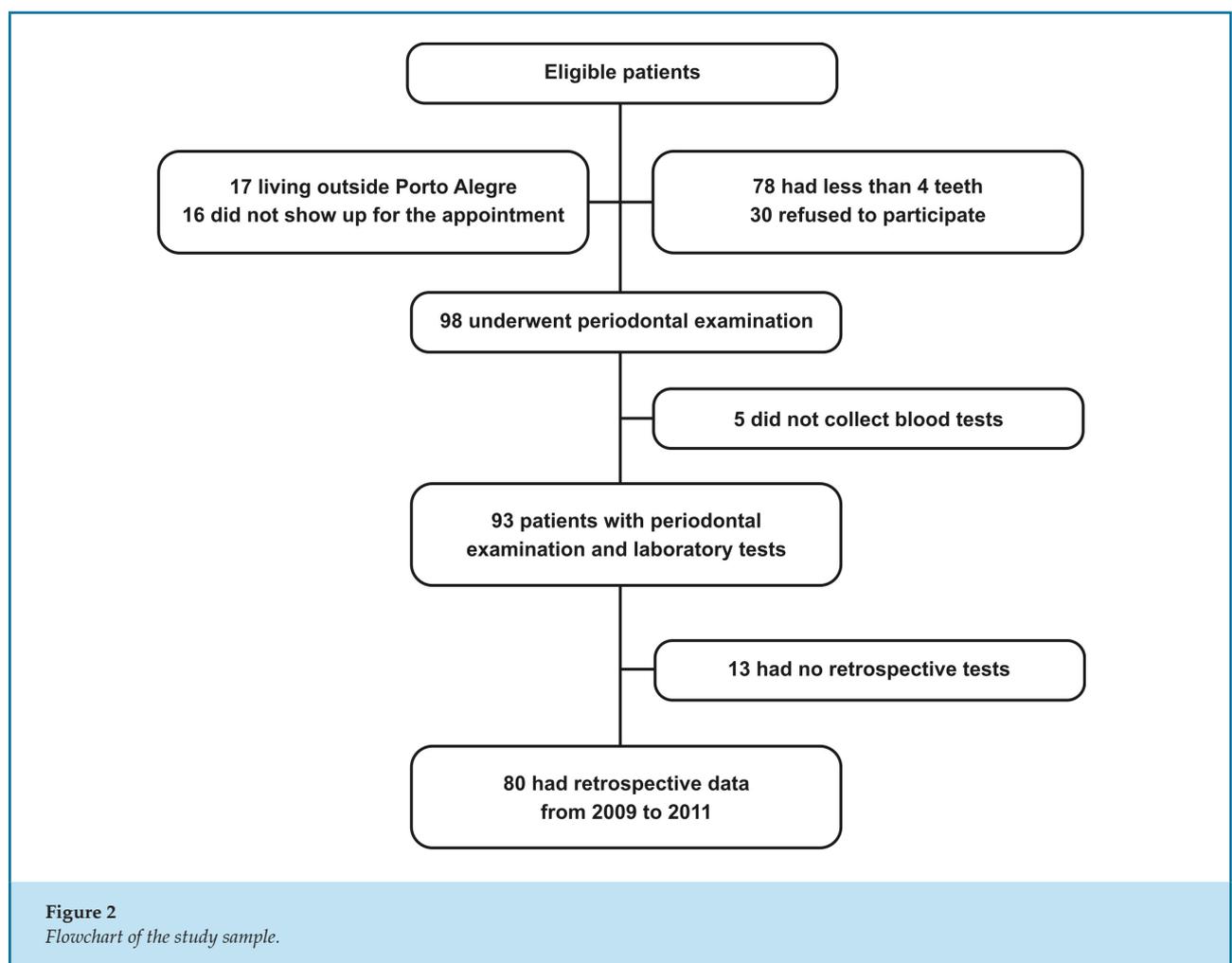


**Figure 1**  
Flowchart of the study design.

myocardial revascularization; and lesion > 50% in at least one of the coronary arteries, measured by angiography. In order to be included in this study, the patients should have at least four teeth and should not have performed periodontal treatment within the last 6 months, or used antibiotics and/or anti-inflammatories within 3 months from the periodontal examination.

Intraoral examinations were carried out in 239 patients between April and December 2011 to access the eligibility for the study (Figure 2). Of these, 78 had less than four teeth, 30 declined participation, 17 did not live in

Porto Alegre, and 16 could not perform the complete clinical periodontal examination. A clinical periodontal examination was performed in 98 patients; of these, five failed to collect blood. Therefore, 93 patients with clinical periodontal examination and blood tests became eligible for this retrospective study. The hospital records of the 93 eligible patients were evaluated in search of results of lipid profile tests conducted between 2009 and 2011. In total, 80 patients presented retrospective data on lipid profile in this follow-up period and were included in this study.



### Cardiac Care

The outpatient clinic for ischemic heart disease at HCPA has a multidisciplinary team providing for patients the necessary follow-up care. The team includes cardiologists, nurses, nutritionists, and physical educators. All patients receive pharmacological and nonpharmacological cardiac

treatment during follow-up. The drug protocol includes the prescription of statins, oral hypoglycemic agents, insulin, aspirin, and antihypertensive drugs (beta-blockers or angiotensin converting enzyme inhibitors) when indicated. The patients are mainly advised on issues regarding changes in lifestyle habits, such as the

practice of physical activity, smoking cessation, balanced diet, and adherence to pharmacological treatment.

### Interview and Intraoral Clinical Examination

A structured questionnaire was applied in 2011 to obtain demographic, socioeconomic, and behavioral data. Data related to medical history and medication, as well as blood pressure, heart rate, weight, and height were obtained from the electronic medical records of each patient at the hospital.

Two periodontists carried out complete periodontal clinical examinations in six sites per tooth in all present teeth, excluding the third molars. The clinical variables recorded were:

- a) Index of visible plaque:<sup>19</sup> presence (score 1) or absence (score 0) of bacterial plaque without the use of a probe after drying the tooth surface with compressed air.
- b) Index of gingival bleeding:<sup>19</sup> insertion of a periodontal probe 1–2 mm deep into the intrasulcular region, which was passed from the distal to the mesial face. We recorded the absence (score 0) and presence (score 1) of gum bleeding.
- c) Gingival recession (GR): distance from the cemento-enamel junction (CEJ) to the gingival margin, measured in millimeters. When the CEJ was located apically to the margin of the free gum, a negative sign was assigned to the measure.
- d) Depth of scan (DS): distance between the margin of the gum and the most apical portion of the gingival sulcus reachable with a probe, measured in millimeters and rounded off to the nearest millimeter.
- e) Subgingival bleeding (SB): absence (score 0) or presence (score 1) of bleeding 30 seconds after the DS.

The periodontal attachment loss (PAL) value was obtained from the sum of the DS and GR values. The presence of severe periodontitis was defined according to the criteria by Eke et al.<sup>20</sup> in which the patient must present two or more interproximal sites with a PAL  $\geq$  3 mm and two or more interproximal sites with DS  $\geq$  4 mm in different teeth, or a single site with DS  $\geq$  5 mm.

### Reproducibility of the Periodontal Examination

Evaluations of intraexaminer and interexaminer reproducibility were conducted before and during the

study. We performed duplicated periodontal DS and GR examinations in a total of 35 patients, with an interval of 1 hour, in groups of three to five patients. Interexaminer weighted kappa values ( $\pm$  1 mm) ranged from 0.87 to 0.90 for DS and 0.78 to 0.81 for PAL. The interexaminer calibration resulted in values that ranged from 0.70 to 0.80.

### Lipid Profile

Simultaneously to conducting the intraoral clinical examinations, we collected blood samples to determine the lipid profile of the study patients. The patients were scheduled to collect blood during the morning, between 7 a.m. and 12 a.m., to control for possible variations. A trained nurse collected 10 mL of blood from the antecubital fossa from each patient, and stored the samples in ethylenediaminetetraacetic acid (EDTA) tubes for analysis in the Research Center at HCPA.

Levels of total cholesterol, HDL-cholesterol, and TG were measured by automated colorimetric enzymatic methods according to the manufacturer's instructions (GPO). Total cholesterol was measured by the enzymatic colorimetric method (CHOL2) with cholesterol esterase and cholesterol oxidase, followed by a Trinder endpoint. HDL-cholesterol was measured with the HDL-Directo (HDL-D) method using principles of elimination/catalase. The Friedwald formula was used to calculate the levels of LDL-cholesterol (LDL-cholesterol = total cholesterol + TG/5).

Retrospective data of lipid profile were obtained from the hospital records using the same protocol described above, during fasting and in the morning.

### Data Analysis

Data analysis was performed with the software Stata (version 14 for Macintosh, StataCorp, College Station, USA). The individual was considered as the analytical unit and the level of significance was set at 5%.

The outcomes of this study were the concentrations of TG, total cholesterol, LDL-cholesterol, and HDL-cholesterol over time, obtained between 2009 and 2011. These variables showed an asymmetric distribution and were transformed into base 10 logarithms for application of linear models. The independent variables related to the periodontal condition were the presence/absence of severe periodontitis, the individual's mean average clinical attachment loss, the percentage of SB, and the percentage of tooth surfaces with a visible plaque.

Descriptive data are presented as frequency distributions, box-plot graphs, means, and standard deviations. Generalized estimating equations (GEE) were applied to assess the association between the base 10 logarithm lipid values and the different periodontal variables. GEE models with a Gaussian family, interchangeable correlation matrix, and robust standard error were used. For each of the four lipid variables, multiple models were applied to each of the periodontal variables, adjusted according to follow-up duration, age, body mass index, smoking habit, use of oral hypoglycemic agents, and year of follow-up. The number of present teeth was explored in the analysis but was not considered in multiple models since we found no association between this variable and the lipid profile,

nor a confounding effect in other associations. Coefficients and standard errors are reported.

## Results

The mean follow-up time was 713 days (Figure 1). Most of the sample was composed of individuals aged  $\geq 60$  years, men, and former smokers (Table 1). Overall, the individuals had poor oral hygiene, demonstrated by high indices of visible plaque ( $68.78 \pm 20.56\%$ ) and mean DS of  $2.97 \pm 0.71$  mm. In addition, we observed high levels of SB ( $74.24 \pm 24.20\%$ ) and PAL (mean  $4.82 \pm 1.49$  mm). The approximate average number of missing teeth was 13 ( $13.06 \pm 6.56$ ). Regarding the use of medications, 73 (91.3%) patients used statins and 72 (90.0%) used aspirin. Twenty-four (30.0%) patients were diabetic and used oral hypoglycemic drugs.

**Table 1**  
Demographic, behavioral, and periodontal characteristics of the sample

Variables	Estimates
<b>Demographic/behavioral</b>	<b>n (%)</b>
Age	
40–49 years	3 (3.75)
50–59 years	24 (30.00)
$\geq 60$ years	53 (66.25)
Sex	
Male	51 (63.75)
Female	29 (36.25)
Smoking	
Non-smokers	29 (36.25)
Prior smokers	40 (50.00)
Smokers	11 (13.75)
Total	80 (100.0)
<b>Periodontal</b>	<b>Mean <math>\pm</math> standard deviation</b>
Visible plaque (%)	$68.78 \pm 20.56$
Depth of scan (mm)	$2.97 \pm 0.71$
Periodontal attachment loss (mm)	$4.82 \pm 1.49$
Subgingival bleeding (%)	$74.24 \pm 24.20$
Teeth loss (number of teeth)	$13.06 \pm 6.56$

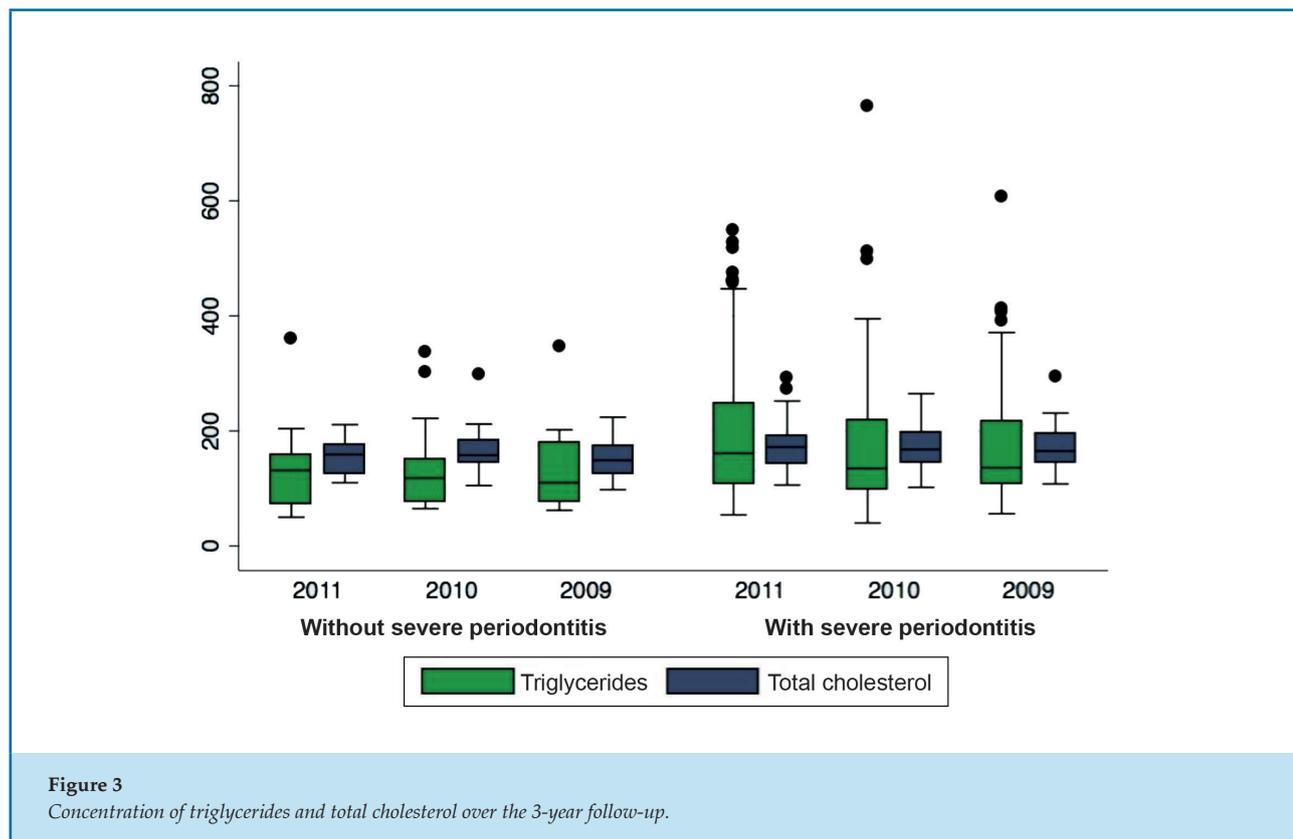
Figure 3 shows the changes in TG and total cholesterol concentrations over the observation period. On average, there was an increase in the levels of these two markers between 2009 and 2011 (10.9% for TG and 5.0% for total cholesterol), but no significant differences in these changes over time. A significant increase of 6.4% in LDL-cholesterol was also observed. Regarding HDL-cholesterol levels, there was a significant 31.6% increase between 2009 and 2011 (Figure 4).

The associations between periodontal variables and lipid profile over the observation period are described in Table 2. No significant association was observed between periodontal variables and levels of TG and LDL-cholesterol. In contrast, we observed a significant association between total cholesterol and visible plaque, indicating that higher levels of visible plaque were associated with higher concentrations of total cholesterol over time. We also observed a significant negative association between (mean) PAL and HDL-cholesterol levels, indicating that the greater the PAL, the lower the levels of HDL-cholesterol. Severe periodontitis and SB showed no associations with the lipid profile.

## Discussion

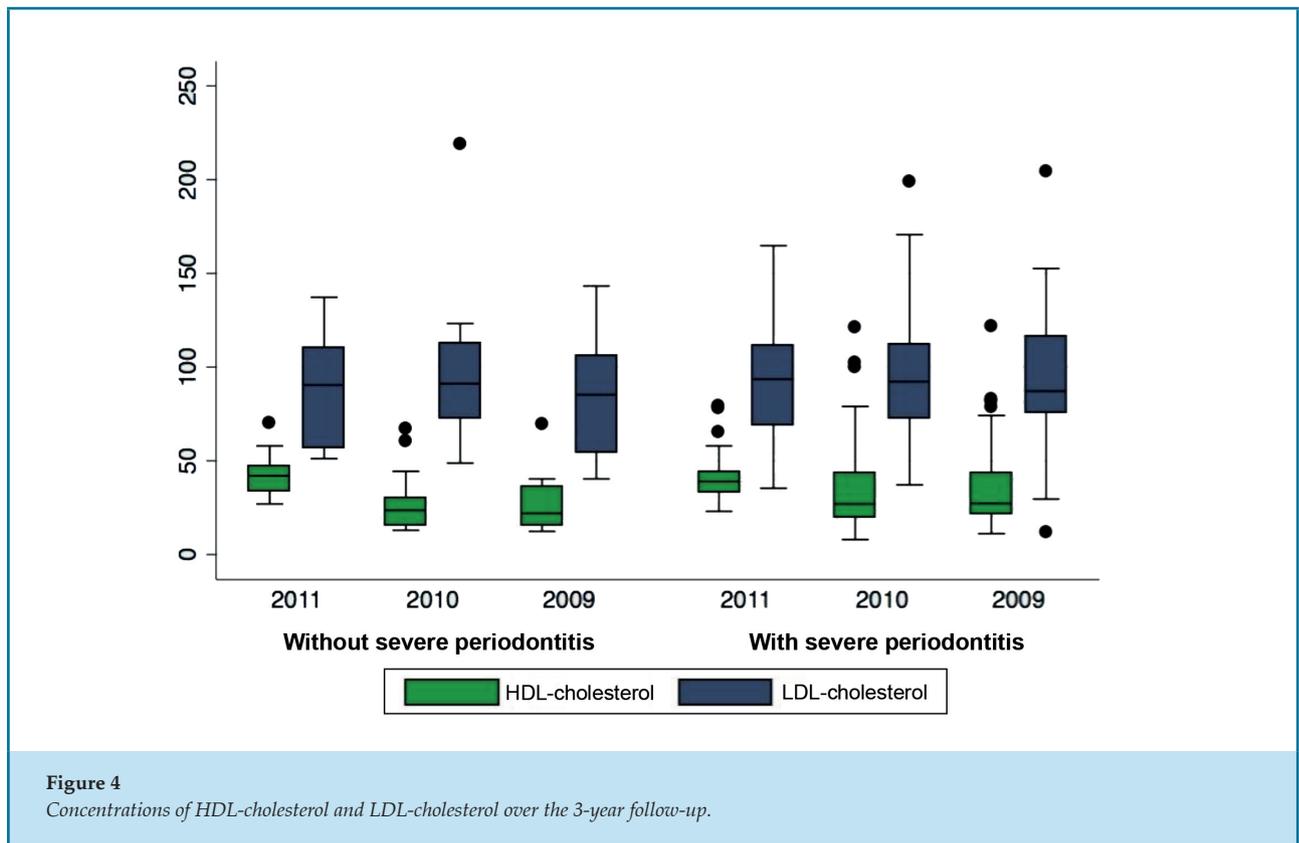
The present study evaluated the association between PD and lipid profile in a cohort of chronic cardiac patients undergoing cardiac follow-up. The main findings indicate that the PD descriptors can negatively affect the lipid control of patients with heart disease, in particular, HDL-cholesterol and total cholesterol. On the other hand, no consistent associations were observed with other lipid markers.

Other studies have also demonstrated a potential effect of oral infections, including periodontal ones, on lipid levels, despite using different methodologies from that of the present study. Severe periodontitis has been associated with higher levels of total cholesterol and TG in a sample of patients with familial hypercholesterolemia.<sup>21</sup> Another observational study showed that apical periodontitis (infectious lesion caused by endodontic problems) associated or not with PD was linked with a higher risk of cardiovascular incidents, despite the loss of significance of this association after important adjustments.<sup>22</sup> In an interventional study, periodontal treatment had a positive effect in reducing lipids in patients with periodontitis but without CVD.<sup>23</sup>



**Figure 3**

Concentration of triglycerides and total cholesterol over the 3-year follow-up.



**Figure 4**  
Concentrations of HDL-cholesterol and LDL-cholesterol over the 3-year follow-up.

**Table 2**  
Multiple GEE models of the association between lipid variables and periodontal injuries, adjusted for age, body mass index, smoking, use of oral hypoglycemic agents, and year of follow-up

	Triglycerides		Total cholesterol		LDL-cholesterol		HDL-cholesterol	
	Coef±SE	p	Coef±SE	p	Coef±SE	p	Coef±SE	p
Severe periodontitis	0.038 ± 0.055	0.42	0.013 ± 0.019	0.49	0.015 ± 0.034	0.64	-0.016 ± 0.031	0.60
PAL mean	-0.018 ± 0.013	0.16	0.005 ± 0.006	0.41	0.015 ± 0.010	0.14	-0.011 ± 0.009	0.03
BP	0.077 ± 0.084	0.35	0.064 ± 0.034	0.06	0.039 ± 0.065	0.54	0.066 ± 0.047	0.16
VPI	0.060 ± 0.095	0.53	0.088 ± 0.043	0.04	0.125 ± 0.076	0.10	0.027 ± 0.056	0.63

Coef: coefficient; SE: standard error; PAL: periodontal attachment loss; BP: Bleeding on probing; VPI: Visible plaque index.

Infections are known to interfere with lipid metabolism and increase TG, changes that are mediated by cytokines, which are also produced and appear in higher levels in the presence of periodontitis.<sup>14</sup> The periodontal infection that leads to a local inflammatory process is also associated with systemic elevation of inflammatory mediators (cytokines), and several of these mediators are related to a higher risk of CVDs and atherosclerosis.<sup>24</sup> This is the

most widely accepted theory to explain a possible causal association between PD and CVDs and may also explain changes in lipid levels in chronic cardiac patients.

The present study observed a significant negative association between PAL and HDL-cholesterol levels, indicating in this sample of patients with heart disease that the greater the severity of PD, the lower the levels of HDL-cholesterol over time. It is known that serum

levels of HDL-cholesterol represent a protective factor against atherosclerosis, while low levels are known as risk factors for CVDs.<sup>25</sup> In line with our findings, O'Neil et al.<sup>5</sup> showed that the functional capacity of HDL-cholesterol is impaired under periodontal inflammatory conditions, showing that even minor systemic alterations may harm the protective effect of HDL-cholesterol, regardless of the cholesterol efflux. Although studies have linked PD and lipid profile, the results are still inconsistent. There is evidence suggesting positive associations between PD and TG levels,<sup>26</sup> and others showing a negative association between PD and HDL-cholesterol levels or all markers of lipid profile (total cholesterol and TG).<sup>27</sup>

On the other hand, associations between periodontal inflammatory and destructive parameters (definition of severe periodontitis, mean PAL, and SB) with TG, total cholesterol, and LDL-cholesterol were not observed. One aspect that must be put into perspective regarding this issue is the finding that the changes in TG levels, total cholesterol, and LDL-cholesterol in this cohort were minimal during the follow-up period. This may have limited the analyses and possible associations with the PD.

A higher amount of visible plaque was associated with higher levels of total cholesterol. The plaque, *per se*, is not able to alter the concentrations of blood markers, but indicates an oral hygiene standard that is related to an individual's general health.<sup>28</sup> In this sense, the association observed in this study may be explained by behavioral aspects among the patients with major amounts of plaque, such as careless lifestyle, low adherence to the use of medications, and bad dieting habits, among others. However, more studies are needed to better explore this kind of association.

There is no consensus in the literature about the best periodontal variable or periodontitis criterion to be used in studies of association with CVDs. In this sense, we chose to use at least four periodontal variables/criteria: severe periodontitis (based on the DS and PAL, the most used criterion in the literature), mean attachment loss, SB, and the presence of plaque. Therefore, we believe that the present study included both inflammatory and destructive characteristics of periodontitis that may be associated with the lipid profile. Regarding DS, the general average of the present sample was lower because of the regression to the mean. Therefore, we choose not to use this variable in models of association, because it

does not necessarily describe the actual inflammatory condition of the patient. Another important aspect is that this study has a retrospective and longitudinal design; thus, the PAL was included in the analysis because it was the variable that better described the patients' periodontal history over time.

Some of the limitations of this study are related to its experimental design. This is a retrospective study, involving observations across a long period of time and data collected from medical records. Therefore, it becomes unfeasible to collect all variables of interest important to control for potential biases, such as diet, physical activity, and medication. The sample size was limited, which may have decreased the power to find associations. In addition, it is important to emphasize that the patients participated in a cohort of cardiovascular monitoring;<sup>18</sup> thus, there was a positive impact on lipid levels by this cardiac care. In contrast, the methodological qualities of this study should be emphasized, such as the use of controlled GEE models for possible important confounders. Among these confounders, it is important to highlight diabetes, which may be related both to the PD as to the CVD, an aspect included with the adjustment to use of hypoglycemic medication. All periodontal examinations were performed by two calibrated periodontists, following a protocol of evaluation of six sites per tooth, in all teeth, avoiding risk of bias.

## Conclusion

Destructive PD may be related to a worse lipid control, particularly regarding HDL-cholesterol levels, in patients with chronic heart disease. However, no consistent associations were observed with TG, total cholesterol, and LDL-cholesterol. Prospective longitudinal studies are still needed to confirm or refute these associations.

## Author Contributions

Conception and design of the research: Rösing CK, Furtado MV. Acquisition of data: Montenegro MM, Ribeiro IWJ, Saffi MAL. Statistical analysis: Haas AN. Obtaining financing: Polanczyk CA. Writing of the manuscript: Kampits C. Critical revision of the manuscript for intellectual content: Haas AN.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

There were no external funding sources for this study.

### Study Association

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