Journal of Current Medical Research and Opinion

CMRO 03 (05), 451–458 (2020) ISSN (O) 2589-8779 | (P) 2589-8760

Is There a Relationship between Dental and/or Periodontal Pathology and Values of C - reactive protein, Homocysteine and Lipoprotein (a) in Patients with Cardiovascular Disease? A Case Control Study

Beatriz Gonzalez-Navarro[1], Enric Jané-Salas;[1], Jose Lopez-López[1], Xavier Pintó-Sala[*,†,2]

[1] *Department of Stomatology (Barcelona University) // Master of Medicine, Surgery and Oral Implantology (Faculty of Medicine and Health Sciences, UB - Odontology Hospital University of Barcelona) // Oral Health and Masticatory System Research Group, Intitute of Biomedical Research of Bellvitge (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain.*

[2] *Lipid and Vascular Risk Unit. Internal Medicine Department. Bellvitge University Hospital - Idibell. UB. CiberObn. Hospitalet de Llobregat (Barcelona)*

DOI: https://doi.org/10.15520/jcmro.v3i05.285

Accepted 03-05-2020; Received 01-04-2020; Publish Online 04-05-2020

Reviewed By:
Dr.R. Franco
Department:
Reviewer/CMRO

ABSTRACT

Background:
Dental pathology [dental caries (DC) and apical periodontitis (AP)] and/or periodontal pathology (PD) could influence the onset of cardiovascular disease (CVD). The relationship between conventional CVD risk factors and dento-periodontal pathology has been well demonstrated; however, there is less evidence of the relationship between these pathologies and emerging or unconventional CVD risk factors, including C-reactive protein (CRP), Homocysteine (Hcy) and Lipoprotein a (Lp (a).

Methods:
This case-control study included 99 patients with CVD and 50 healthy controls. All participants underwent a detailed medical history, an intraoral examination, an orthopantomography and a blood test. All the analyses were performed on the data set, using all available information with intention to treat criteria.

Results:
A greater number of patients in the study group presented PD ($p < 0.001$) and AP ($p < 0.001$) compared to the control group. However, we did not find significant differences in the prevalence of caries between both groups ($p < 0.287$). Moreover, none of oral variables was significantly related to concentrations of CRP, Hcy or Lp(a).

Conclusions:
Patients with CVD present more PD and a greater number of AP, suggesting an association between dento-periodontal pathology and cardiovascular pathology. The concentrations of CRP, homocysteine and Lp(a) are not related to the degree of dento-periodontal pathology, so we believe that more studies are necessary to assess this possible association.

Keywords: Periodontitis, Dental Pathology, Lp(a), Homocysteine, CRP

Abbreviations and Acronyms:

PD: periodontal disease
DC: dental caries
AP: apical periodontitis
CVD: cardiovascular disease
c-LDL: low density lipoprotein cholesterol
CRP: C-reactive protein
Lp(a) lipoprotein a
Hcy: homocysteine
SG: study group
Apo A1: apolipoprotein A1
OPG: orthopantomography
CG: control group
CPITN: community periodontal index of treatment needs
DMFT: decay, missing, filling teeth index
Apo B: apolipoprotein B
HbA1c: glycosylated hemoglobinc
-HDL: high density lipoprotein cholesterol

1 INTRODUCTION:

Periodontitis, or periodontal disease (PD), is an oral inflammatory pathology caused by a bacterial infection, which begins with gingival inflammation in areas where there is an apical migration of the epithelium towards the dental roots, accompanied by loss of connective tissue and alveolar bone [1–3]Figure 1. On the other hand, dental caries (DC) is a chronic oral disease where besides bacterial colonization and a low pH of the mouth, there is demineralization that can lead to destruction of dental tissues like enamel, dentin and pulp. If the dental canal is infected, pulp necrosis can occur, triggering an inflammatory response and the appearance of apical periodontitis (AP) [4]Figure 2.

Cardiovascular disease (CVD) is the leading cause of death in industrialized countries [5–8]. It is a pathology of multifactorial origin and an inflammatory basis that occurs with an accumulation of lipids and fibrous tissue in the arterial wall [9]. Different CVD risk factors have been demonstrated [10] and many of them can be quantified by means of a blood test. CVD risk factors have been classified as classic or conventional, among which are excess total cholesterol and low-density lipoprotein (c-LDL), diabetes, high blood pressure and smoking, and unconventional factors, such as C-reactive protein (CRP) [11], homocysteine (Hcy) [12] and lipoprotein a (Lp(a)) [13], among others [14, 15]. Unconventional factors have been identified more recently than conventional factors, and the basis of evidence of their relationship to CVD is less broad than that on conventional factors [16] . CRP is a non-specific systemic inflammation biomarker. Even though the physiological role of CRP in atherosclerosis is not fully defined, the immunoreactivity of CRP has been related to vulnerability and rupture of atheroma plaques [17]. Hcy is an amino acid derived from methionine, which has a proinflammatory and prothrombotic effect and is found to be increased in patients with atherothrombotic diseases. It is also found to be increased in diabetes, renal insufficiency and diseases with high cell turnover, such as cancer and psoriasis, in which a high consumption of folates occurs [14, 18]. Lp(a) is a lipoprotein made up of an LDL particle and a protein with a plasminogen-like structure, apolipoprotein (a) [apo (a)] that binds to the LDL particle via a disulfide bridge. Lp (a) exerts an atherogenic effect due to its cholesterol and oxidized phospholipid content and a probable thrombogenic effect related to fibrinolysis inhibition. Lp(a) concentrations are genetically determined, although they increase in inflammatory diseases because Lp(a) behaves like an acute phase reactant [19].

Thus, since there are numerous studies that link dental and/or periodontal pathology to CVD, our plan was to carry out a case-control study that would allow us to correlate the degree of dental and/or periodontal disease with the concentrations of CRP, Hcy and Lp(a) in a group of patients with and without known cardiovascular disease. Our hypothesis is that CVD patients will present poorer oral health and greater alteration of unconventional risk factors.

⋆ Corresponding author.
† Email: xpinto@bellvitgehospital.cat

2 METHODS:

Study design and participants:

A case-control study was proposed to evaluate oral and systemic variables and analytical parameters in patients with or without cardiovascular disease.

Cases - Study Group (SG): They were recruited from CVD patients who are cared for at the Vascular Risk Unit of the University Hospital of Bellvitge, with a maximum of 3 months from the cardiovascular event. Patients who had suffered an acute myocardial infarction, angina with demonstrated coronary ischemia, arteriopathy of the lower extremities with intermittent claudication or an atherothrombotic stroke were included.

Controls - Control Group (CG): They were recruited from patients who visited the Dental Hospital of the University of Barcelona (Fundación Josep Finestres. Faculty of Medicine and Health Sciences). They had no cardiovascular history and were matched for age and sex.

Each patient underwent a detailed medical history, a thorough oral examination, a blood test with unconventional cardiovascular risk factors, and an orthopantomography (OPG). The blood analysis was carried out at the blood extraction department of the Bellvitge Hospital and the OPG at the Dental Hospital of the University of Barcelona. Radiographic status was diagnosed using digital orthopantomographies taken by 2 proficient technicians with more than a decade of experience (Promax, Planmeca, class 1, type B, 80 KHz, Planmeca, Helsinki, Finland). All the teeth except the third molars were taken into account.

All participants provided written informed consent before entering the study, and the study was approved by the Ethics Committee of the Bellvitge University Hospital Research Institute (IDIBELL - Reference: PR187/15).

Individuals with missing follow-up data were excluded from the study. Additionally, individuals with missing information on any of the covariates included in the multivariable regression models were also excluded Figure 3.

Assessment of PD, DC and AP:

An expert examiner carried out the oral examination.

Oral hygiene was assessed using the Silness and Löe plaque index [20], the absence or presence of plaque on dental surfaces was assessed with an exploration probe. According to the numerical results, we divided oral hygiene as: i) good (0.0– 0.65), ii) regular (0.66–1.85) and iii) poor (1.86–3.0).

Periodontal health was assessed using the community periodontal index of treatment needs (CPITN) [21]. Once the individual results were found, it was correlated with the PD. i) If CPITN <1, no PD; ii) If CPITN 1-1.9, mild PD; iii) If CPITN 2-2.9, moderate PD; iv) If CPITN> 2.9, severe PD was scored.

Caries was analyzed using the decayed, missing and/or filled teeth index (DMFT) [22].

The AP was analyzed using the OPG, evaluating it according to Örstavik [23]. Where we defined 1 as normal periapical structure, 2 as small changes in bone structure, 3 as changes in bone structure with some mineral loss, 4 as periodontitis with well-defined radiolucent area and 5 as severe periodontitis with exacerbated signs. Furthermore, they were finally grouped into AP <3 and AP ≥ 3, depending on the severity of the lesions observed radiographically.

Definition and assessment of other relevant covariates:

Weight, height, body mass index and abdominal perimeter were measured. History of hypertension, diabetes and hypercholesterolemia, use of tobacco and medication were assessed. Systolic and diastolic blood pressures were measured. Levels of high sensitivity CRP, Hcy, fasting blood glucose, triglycerides, total cholesterol, low density lipoprotein cholesterol (c-LDL) levels, high density lipoprotein cholesterol (c-HDL) levels, Apolipoprotein A (apo A1), and apo B were assessed in fasting blood samples at the central laboratory of the Bellvitge Hospital.

For the present analysis, diabetes was defined as any of the following: presence of a positive history of diabetes at baseline, the use of glucose-lowering medications at baseline, baseline glycosylated hemoglobin (HbA1c) levels ≥6%, and/or baseline fasting blood glucose levels ≥126 mg/dL. Hypertension was defined as any of the following: presence of a positive history of hypertension at baseline, the use of hypertension-lowering medication at baseline, and/or baseline systolic and diastolic blood pressures ≥ 140-90 mmHg. Finally, dyslipidaemia was defined as any of the following: presence of a positive history of dyslipidaemia at baseline, the use of cholesterol-lowering medication at baseline, and/or baseline fasting blood total cholesterol levels ≥200 mg / dL, or c-LDL levels> 130mg / dl or c-HDL levels <40mg / dl. Every smoker was defined as either being current smoker or former smoker.

Statistical Analyses:

A descriptive statistical analysis was carried out for all the variables. The number of valid cases, mean, standard deviation, and 25th and 75th percentiles (P25-P75) described continuous variables. On the other hand, the categorical variables were described by absolute and relative frequencies of each category over the total of valid values (N). In case of missing values, their number per group were described.

Comparisons of categorical variables were made using the Student's t-test for independent data or the $\chi 2$ test as applicable. In the case of intra-group comparisons to evaluate the evolution, the Student's t-test was used for paired data.

All analyses were performed on the data set using all available information with intention to treat criteria.

3 RESULTS:

Study population:

Of the 104 cases and 52 controls participants, we excluded 1 duplicated individual and 6 who didn't get the OPG done. This yielded a final study population of 99 cases and 50 controls included in the analyses Figure 3.

Baseline characteristics of the study participants:

The baseline demographic and clinical characteristics of the study participants are summarized in Table 1. Overall, median age was 50.47 years, 30.2% were women and 70.5% were overweight or obese. At baseline, 81.7% were current or ex-smokers, 16.2% had diabetes, 41.7% had hypertension and 53.7% had dyslipidemia. Regarding the drug treatments, 17.4% were treated with oral antidiabetic drugs, 45% were on antihypertensive drugs and 67.1% were on statin therapy (100% of the study group used statins).

Analytical parameters:

The most relevant analytical parameters of the study participants are summarized in Table 2. Most of the analytical parameters studied are significantly higher in the SG than in the CG. It should be noted that although the observed values of CRP are higher in the SG than in the CG, 3.09 mg/L and 2.15 mg/L respectively, these differences were not statistically significant. On the other hand, CG patients presented significantly higher c-LDL values compared to SG patients, 3.32 mmol/L vs. 2.06 mmol/L, respectively. It should also be emphasized that SG patients presented significantly higher plasma values of Hcy and Lp(a), when compared to the healthy patients group [(Hcy: 14.25 vs 10.92; p = 0.0032) (Lp(a): 124.53 vs 52.84; p <0.0001)].

Oral and dental pathology:

In Table 3, oral health data comparing both groups is presented. In this section, some patients were excluded because they did not have teeth needed for indexing or because they were edentulous. In the case of oral hygiene, 7 individuals from SG were discarded; to analyze the CPITN and its relationship with PD, 6 patients from SG and 1 from CG were excluded, and for assessment of the DMFT and AP, 6 SG patients were discarded. 77.2% of the study group presented poor or deficient oral hygiene, which is statistically significant when compared to the control group. Furthermore, the group with CVD presented higher number of cases and worse periodontal status (p <0.001), and a greater number of AP (1.02 vs. 0.32) than the group without CVD. On the other hand, we did not find statistically significant differences regarding the caries index (DMFT), between both groups (1.07 vs. 0.68, respectively).

Multivariable-adjusted associations between oral and dental pathology and CRP, Hcy, Lp(a):

In Table 4, we describe the multivariate regression models of each oral variable in relation to the analytical parameters. We did not find any oral variable that was significantly related to CRP, Hcy or Lp(a) concentrations.

4 DISCUSSION:

CRP is a non-specific inflammation biomarker related to CVD risk [24]. Several studies highlight a relationship between PD and CRP, concluding that patients with higher PD severity had higher plasma CRP levels [25, 26]. However, in other studies [27] such as in this research work, we

did not find significant differences between the CRP concentrations between both groups, although a tendency was observed for the SG to have a higher CRP level than the CG. It should be noted that in a study on the relationship between dental pathology and CRP concentrations [27], CRP was measured in crevicular fluid and not in blood serum as in the vast majority of studies. Likewise, we must consider that SG patients have greater protection against inflammation primarily due to pharmacological treatments, particularly statins, as well as due to the recommendations of secondary prevention specialists regarding exercise and diet, factors that have a clear influence on CRP concentrations [28].

Regarding cholesterol concentrations, we observed that SG patients present plasma concentrations of total Cholesterol, c-HDL, c-LDL, apo A1 and apo B lower than those of CG. These differences can be attributed to the fact that 100% of SG patients are treated with hypolipidemic drugs, while only 2% of CG patients were treated with these drugs. Similar differences between CVD patients and controls were observed in two similarly designed case-control studies [29, 30]. It should be noted that statins very markedly decrease c-LDL and apo B, but they hardly modify c-HDL and apo A1. Therefore, although both excess of c-LDL and apo B, as well as deficiency of c-HDL and apo A1 are associated with atherosclerosis; it is expected to find lower values of c-LDL and apo B in SG patients, all treated with statins, and lower concentrations of c-HDL and apo A1 are maintained. The latter related to their disease (also because CVD patients more frequently have obesity, diabetes and metabolic syndrome which are disorders related to a decrease in c-HDL and apoA1) and not corrected by the effect of statins.

Furthermore, we also found that patients who have suffered an atherothrombotic cardiovascular event have higher levels of Lp(a) and homocysteine than CG. This data is in agreement with those observed in other studies on the relationship between Lp(a) [15, 19] and homocysteine with CVD [14, 31]. Performing multivariate regression models for all oral variables, we did not find that these variables are related to the concentrations of Lp(a) and homocysteine; that is, we observed that neither Lp(a) nor homocysteine are found to increase with respect to any of the oral variables, or vice versa. As cited previously, homocysteine is an amino acid derived from methionine that has a proinflammatory and prothrombotic effect and its concentrations are increased in patients with atherothrombotic diseases [18] . It could be increased in those patients who had more oral inflammation, represented by a higher PD, a greater number of caries and/or a greater number of AP, but it is not a good marker of inflammation. As we have mentioned, in our study, patients with greater dental and/or periodontal pathology do not have higher plasma homocysteine levels, therefore, in our study, it could not be considered a marker related to oral pathology. In previous studies, PD patients have higher levels of Hcy and after the periodontal treatment alone [32, 33] or in conjunction with folic acid therapy [27], their plasma levels decrease.

The function of Lp(a) is not well known. Containing a c-LDL molecule, it transports cholesterol in the plasma. A characteristic fact is its affinity for oxidized phospholipids that are highly proinflammatory and proatherogenic, since they attract inflammatory cells to the vessel walls and stimulate the proliferation of smooth muscle cells [34, 35]. Lp(a) is an acute phase reactant in addition to an atherothrombotic risk factor, and is increased in inflammatory diseases. For this reason, it seems that the treatment of PD not just with curettage but also with a subgingival dose of doxycycline could contribute to a decrease in systemic inflammation, which would be associated with a decrease in CRP and Lp(a) concentrations [36].

5 STUDY LIMITATIONS:

Patients with demonstrated CVD from a minimum of 3 months have been included in this study. These patients are treated with statins and other drugs with anti-inflammatory effects that cause a decrease in the concentrations of CRP, Hcy and Lp (a).

6 CONCLUSIONS:

Patients who have suffered an atherothrombotic accident present more dental and periodontal pathology (DC, PD or AP) than those without a history of CVD.

CVD patients have higher levels of C-reactive protein, Homocysteine and Lp(a).

The concentrations of CRP, homocysteine and Lp(a) are not related to the degree of dento-periodontal pathology (such as PD, caries or AP).

REFERENCES

[1] Li Y, Shong X, Cheng G. Hs-CRP and all cause, cardiovascular and cancer mortality risk: a meta-analysis. Atherosclerosis. 2017;259:75–82.

[2] Page RC, Eke PI. Case Definitions for Use in Population-Based Surveillance of Periodontitis. Journal of Periodontology. 2007;78(7s):1387–1399. Available from: https://dx.doi.org/10.1902/jop.2007.060264.

[3] Ryden L, Buhlin K, Ekstrand E. Periodontitis Increases the Risk of a First Myocardial Infarction: A Report From the PAROKRANK Study. Journal of Vascular Surgery. 2016;64(3):827–828. Available from: https://dx.doi.org/10.1016/j.jvs.2016.07.056.

[4] Silness J, Löe H. Periodontal Disease in Pregnancy II. Correlation Between Oral Hygiene and Periodontal Condition. Acta Odontologica Scandinavica. 1964;22(1):121–135. Available from: https://dx.doi.org/10.3109/00016356408993968.

[5] Network EH. European cardiovascular disease statistics. 2017;p. 15–15.

[6] Peters S, Wang X, Lam TH. Clustering of risk factors and the risk of incident cardiovascular disease in Asian and caucasian populations: results from the Asia Pacific cohort studies collaboration. BMJ Open. 2018;8(3):19335–19335.

[7] Meurman JH, Qvarnström M, Janket SJ, Nuutinen P. Oral health and health behavior in patients referred for open-heart surgery. Elsevier BV; 2003. Available from: https://dx.doi.org/10.1067/moe.2003.22.

[8] Boushey CJ. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. JAMA: The Journal of the American Medical Association. 1995;274(13):1049–1057. Available from: https://dx.doi.org/10.1001/jama.274.13.1049.

[9] Tsimikas S, Hall JH. Lipoprotein (a) as a potencial causal genetic risk factor of cardiovascular disease: a rationale for increased efforts to understand its pathophsysiology and develop targeted therapies. J Am Coll Cardiol. 2012;60(8):716–737.

[10] Klein H, Palmer CE, Knutson JW. Studies on Dental Caries: I. Dental Status and Dental Needs of Elementary School Children. Public Health Reports (1896-1970). 1938;53(19):751–751. Available from: https://dx.doi.org/10.2307/4582532.

[11] Braunwald E. Shattuck lecture-cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. N Engl J Med. 1997;337:1360–1369.

[12] Chrysant SG, Chrysant GS. The current status of homocysteine as a risk factor for cardiovascular disease: a mini review. Expert Review of Cardiovascular Therapy. 2018;16(8):559–565. Available from: https://dx.doi.org/10.1080/14779072.2018.1497974.

[13] Hu H, Wang C, Jin Y. Catalpol inhibits homocysteine-induced oxidation and inflammation via inhibiting Nox4/NF-kB and GRP78/PERK pathways in human aorta endothelial cells. Inflammation. 2019;42(1):64–80.

[14] Bhardwaj S, Prabhuji MLV, Karthikeyan BV. Effect of non-surgical periodontal therapy on plasma homocysteine levels in Indian population with chronic periodontitis: a pilot study. Journal of Clinical Periodontology. 2015;42(3):221–227. Available from: https://dx.doi.org/10.1111/jcpe.12374.

[15] O'Donnell CJ, Elosua R. Cardiovascular Risk Factors. Insights From Framingham Heart Study. Revista Española de Cardiología (English Edition). 2008;61(3):299–310. Available from: https://dx.doi.org/10.1016/s1885-5857(08)60118-8.

[16] Örstavik D, Ford P, R T. The periapical index: a scoring system for radiographic assessment of apical periodontitis. Endod Dent Traumatol. 1986;2(1):20–34.

[17] Ridker PM, Hennekens CH, Buring JE, Rifai N. C-Reactive Protein and Other Markers of Inflammation in the Prediction of Cardiovascular Disease in Women. New England Journal of Medicine. 2000;342(12):836–843. Available from: https://dx.doi.org/10.1056/nejm200003233421202.

[18] Kalkan RE, Dede FÖ, Gökmenoğlu C, Kara C. Salivary fetuin-A, S100A12, and high-sensitivity C-reactive protein levels in periodontal diseases. Oral Diseases. 2018;24(8):1554–1561. Available from: https://dx.doi.org/10.1111/odi.12927.

[19] Tsimikas S, Hall JH. A test in context: lipoprotein (a): diagnosis, prognosis, controversies, and emergin therapies. J Am Coll Cardiol. 2017;69(6):692–711.

[20] Lacey B, Herrington WG, Preiss D, Lewington S, Armitage J. The Role of Emerging Risk Factors in Cardiovascular Outcomes. Current Atherosclerosis Reports. 2017;19(6):28–28. Available from: https://dx.doi.org/10.1007/s11883-017-0661-2.

[21] Benjamin EJ, Blaha MK, Chiuve SE. Heart disease and stroke statistics - 2017 update: a report from the American heart association. Circulation. 2017;135(10):146–603.

[22] Tsimikas S, Brilakis ES, Miller ER, McConnell JP, Lennon RJ, Kornman KS, et al. Oxidized Phospholipids, Lp(a) Lipoprotein, and Coronary Artery Disease. New England Journal of Medicine. 2005;353(1):46–57. Available from: https://dx.doi.org/10.1056/nejmoa043175.

[23] Armitage GC. Development of a Classification System for Periodontal Diseases and Conditions. Annals of Periodontology. 1999;4(1):1–6. Available from: https://dx.doi.org/10.1902/annals.1999.4.1.1.

[24] Armitage GC. Clinical evaluation of periodontal diseases. Periodontology 2000. 1995;7(1):39–53. Available from: https://dx.doi.org/10.1111/j.1600-0757.1995.tb00035.x.

[25] Saleheen D, Haycock PC, Zhao W. Apolipoprotein (a) isoform size, lipoprotein (a), concentration, and coronary artery disease: a mendelian randomisation analysis. Lancet Diabetes Endocrinol. 2017;5(7):524–557.

[26] Wang J, Tan GJ, Ln H. Novel biomarkers for cardiovascular risk prediction. J Geriatr Cardiol. 2017;14(2):135–50.

[27] Segura-Egea JJ, Dominguez BS, Monroy CC. Medicina endodoncica: implicaciones sistémicas de la patologia y terapéutica endodoncicas. Endodoncia. 2010;28:233–273.

[28] Sezgin Y, , Bulut Ş, Bozalıoğlu S, Sezgin A. Levels of High-Sensitivity C-Reactive Protein in Heart Transplant Patients With and Without Periodontitis. Experimental and Clinical Transplantation. 2019;17(Suppl 1):123–125. Available from: https://dx.doi.org/10.6002/ect.mesot2018.o65.

[29] Ross R. Atherosclerosis - An inflammatory disease. N Engl J Med. 1999;340(2):115–141.

[30] Keceli HG, Ercan N, Hendek MK, Kisa U, Mesut B, Olgun E. The effect of the systemic folic acid intake as an adjunct to scaling and root planing on clinical parameters and homocysteine and C-reactive protein levels in gingival crevicular fluid of periodontitis patients: A randomized placebo-controlled clinical trial. Journal of Clinical Periodontology. 2020;Available from: https://dx.doi.org/10.1111/jcpe.13276.

[31] Ainamo J, Barmes D, Beagrie G. Development of the World Health Organization (WHO) community periodontal index of treatment needs (CPITN). Int Dent J. 1982;32(3):281–91.

[32] Tüter G, Kurtiş B, Serdar M, Aykan T, Okyay K, Yücel A, et al. Effects of scaling and root planing and sub-antimicrobial dose doxycycline on oral and systemic biomarkers of disease in patients with both chronic periodontitis and coronary artery disease. Journal of Clinical Periodontology. 2007;34(8):673–681. Available from: https://dx.doi.org/10.1111/j.1600-051x.2007.01104.x.

[33] Bahls M, Lorenz MW, Dör M. Progression of conventional cardiovascular risk factors and vascular disease risk in individuals: insights from the PROG-IMT consortium. Eur J Prev Cardiol. 2020;27(3):234–277.

[34] Banach M. Lipoprotein (a)—We Know So Much Yet Still Have Much to Learn .... Ovid Technologies (Wolters Kluwer Health); 2016. Available from: https://dx.doi.org/10.1161/jaha.116.003597.

[35] Agrawal P, Mallapragada S, Kasana J. Effect of nonsurgical periodontal therapy on serum highly sensitive capsule reactive protein and homocysteine levels in chronic periodontitis: A pilot study. Contemporary Clinical Dentistry. 2017;8(2):279–279. Available from: https://dx.doi.org/10.4103/ccd.ccd_140_17.

[36] Baszczuk A, Kopczyński Z. Hyperhomocysteinemia in patients with cardiovascular disease. Index Copernicus; 2014. Available from: https://dx.doi.org/10.5604/17322693.1102340.

Table 1. Baseline characteristics of the study participants, overall,study and group.

	Overall (N=149)	Study group (N = 99)	Control group (N = 50)	P Value
Age, years	50.47 (6.06)	50.63 (5.75)	50.14 (6.68)	0.645
Men (%)	104 (69.8)	68 (68.7)	36 (72.0)	0.677
Women (%)	45 (30.2)	31 (31.3)	14 (28.0)	
Body Mass Index (%)				
Underweight	2 (1.3)	2 (2.0)		
Healthy weight	42 (28.2)	14 (14.1)	28 (56.0)	<0.001*
Overweight	67 (45.0)	46 (46.5)	21 (42.0)	
Obese	38 (25.5)	37 (37.4)	1 (2.0)	
Abdominal perimeter (%)	98.08 (11.40)	101.08 (11.05)	92.14 (9.71)	<0.001*
Current smoker + Ex-smoker (%)	122 (81.7)	90 (90.9)	32 (64.4)	<0.001*
Diabetes (%)	24 (16.2)	23 (23.2)	1 (2.0)	0.001*
Hypertension (%)	62 (41.7)	52 (52.5)	10 (20.0)	<0.001*
Dyslipidemia (%)	80 (53.7)	75 (75.8)	5 (9.6)	<0.001*
Medication for Diabetes (%)	26 (17.4)	25 (25.3)	1 (2.0)	<0.001*
Medications for hypertension (%)	67 (45.0)	61 (61.6)	6 (12.0)	<0.001*
Statin use (%)	100 (67.1)	99 (100.0)	1 (2.0)	<0.001*

Data presented as mean (SD) or N (%).

Table 2. Most relevant analytical parameters.

	Overall (N=149)	Study group (N = 99)	Control group (N = 50)	P Value
CRP (mg/L)	2.78 (3.07)	3.09 (3.41)	2.15 (2.16)	0.077
Total Cholesterol (mmol/L)	4.22 (1.19)	3.75 (0.93)	5.14 (1.10)	<0.001*
HDL (mmol/L)	1.21 (0.39)	1.13 (0.38)	1.37 (0.36)	<0.001*
LDL (mmol/L)	2.49 (1.11)	2.06 (0.79)	3.32 (1.19)	<0.001*
Apo A1 (g/L)	1.38(0.29)	1.33 (0.30)	1.48 (0.23)	0.0024*
Apo B (g/L)	0.92 (0.28)	0.82 (0.22)	1.12 (0.30)	<0.001*
TGC (mmol/L)	1.53 (1.02)	1.54 (0.82)	1.52 (1.34)	<0.001*
Lp(a) (nmol/L)	100.47 (117.60)	124.53 (130.69)	52.84 (64.24)	<0.001*
Homocysteine (μmol/L)	13.14 (6.59)	14.25 (7.42)	10.92 (3.67)	0,0032*
HbA1c (%)	5.79 (0.99)	6.01 (1.11)	5.35 (0.44)	<0.001*

Data presented as mean (SD).

Abbreviations:CRP = high sensitivity C-reactive protein; HDL = high density lipoprotein; LDL= low density lipoprotein; APO A: apolipoprotein A; APO B: apolipoprotein B;TGC: triglycerides; Lp(a): lipoprotein a; HbA1c: glycosylatedhemoglobin .

Table 3. Most relevant data for oral and dentalpathology.

	Overall (N = 142)	Study group (N = 92)	Control group (N = 50)	P Value
Oral hygiene (%)				<0.001*
Good	57 (40.1)	21 (22.8)	36 (72.0)	
Mild	54 (38.0)	41 (44.6)	13 (26.0)	
Deficient	31 (21.8)	30 (32.6)	1 (2.0)	
	N = 142	N= 93	N =49	
CPITN - PD (%)				<0.001*
No PD	58 (40.8)	22 (23.7)	36 (73.5)	
Mild PD	27 (19.0)	22 (23.7)	5 (10.2)	
Moderate PD	26 (18.3)	22 (23.7)	4 (8.2)	
Severe PD	31 (21.8)	27 (28.9)	4 (8.2)	
	N=143	N=93	N=50	
DMFT	0.93 (2.09)	1.07 (2.16)	0.68 (1.94)	0.287
AP	0.78 (1.14)	1.02 (1.29)	0.32 (0.55)	<0.001*
	N = 149	N= 99	N =50	
AP max (%)				0.046*
AP max $<$ 3	95 (63.7)	57 (57.6)	38 (76)	
AP max $\geq$ 3	54 (36.3)	42 (42.5)	12 (24)	

Data presented as mean (SD) or N (%).

Abbreviations:CPITN = community periodontal index for treatment need; PD = periodontaldisease; DMFT= decay, missing or filling teeth; AP: apical periodontitis; APmax: maximum apical periodontitis.

Table 4. Multivariable-adjusted associations between oraland dental pathology and CRP, Hcy and Lp(a).

Variable	Parameter	P Value
Plaque index		
CRP	0.019	0.310
Hcy	0.009	0.320
Lp(a)	-0.000	0.460
CPITN - PD		
CRP	0.002	0.948
Hcy	-0.014	0.368
Lp(a)	-0.000	0.888
DMFT		
CRP	0.066	0.249
Hcy	0.053	0.045
Lp(a)	-0.001	0.230
AP		
CRP	-0.041	0.168
Hcy	-0.006	0.643
Lp(a)	-0.007	0.935

Abbreviations: CRP: C reactive protein; HCY:Homocysteine; Lp(a): lipoprotein a; CPITN = community periodontal index fortreatment need; PD = periodontal disease; DMFT= decay, missing or filling-teeth; AP: apical periodontitis.

Figure 1. Development of periodontal disease. [Drawing of ownelaboration].

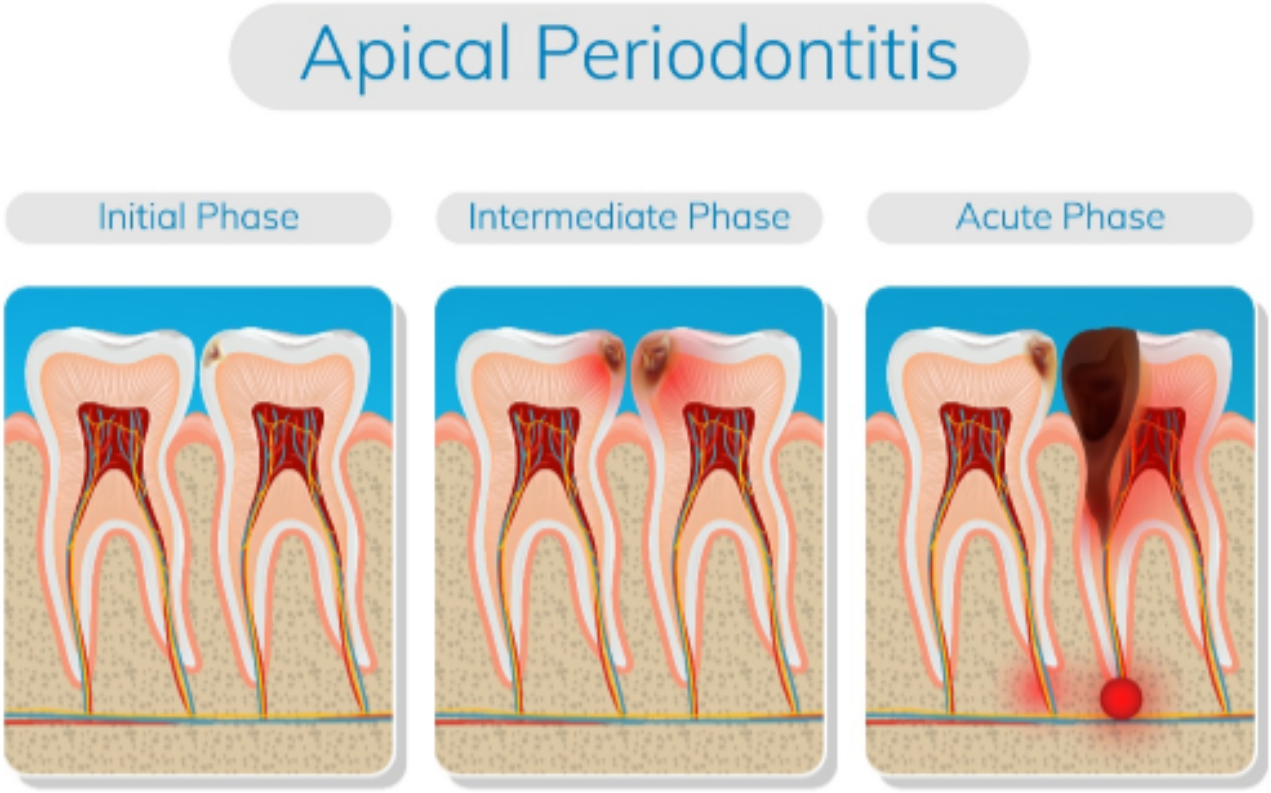

Figure 2. Development of dental caries and apical periodontitis.[Drawing of own elaboration].

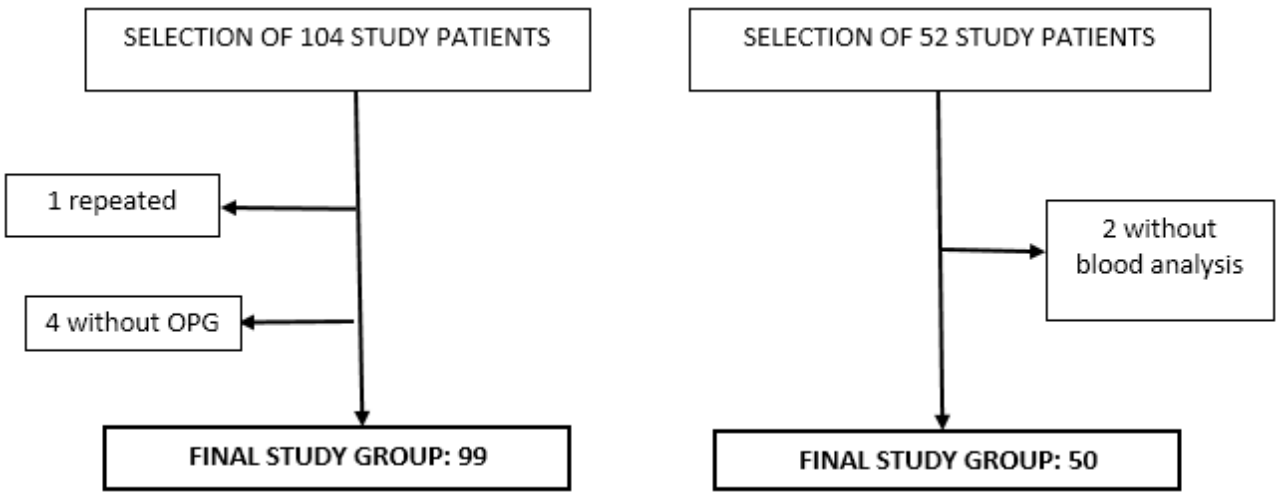

Figure 3. Flow of the study population included in the analysis.