Association between periodontal disease and subclinical atherosclerosis: a systematic review

Associação entre doença periodontal e aterosclerose subclínica: uma revisão sistemática

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Abstract

The association between periodontal disease and the development of atherosclerosis has been studied. The systematic review of literature aims to evaluate the association between periodontal disease and subclinical atherosclerosis. A literature search of the PubMed, Scopus, LILACS, BBO, Cochrane Library and Scielo bibliographic databases was conducted using the following descriptors: "periodontal disease", "periodontitis", "carotid", and "therosclerosis". Articles were excluded if they: presented abstracts written in languages other than Portuguese, English and Spanish; experimental studies; did not contain data testing the degree of association between periodontal disease and subclinical atherosclerosis; did measure the extent of periodontal disease by parameters other than the clinical examination; did not measure the carotid artery intima-media wall thickness by ultrasonography; and covered specific population groups. The studies design, measurement protocols and reported data were compared. A total of 63 papers identified only 10 studies that met the inclusion criteria: 1 longitudinal study, 6 cross-sectional, and 3 case control studies. There was a wide heterogeneity between the studies regarding the methods of measuring periodontal disease and atherosclerosis outcomes. The conclusion is that periodontal infections are strongly associated with the development of subclinical atherosclerosis, however the mechanisms involved on the pathogenic process remain unknown.

Keywords: atherosclerosis; periodontics; carotid artery diseases.

Resumo

A associação entre doença periodontal e o desenvolvimento de aterosclerose tem sido pesquisada. Esta revisão sistemática da literatura se propõe a verificar a associação entre a doença periodontal e a aterosclerose subclínica. A pesquisa utilizou as bases de dados: PubMed, Scopus, LILACS, BBO, Biblioteca Cochrane e Scielo com os termos: "doença periodontal", "periodontite", "carótida" e "aterosclerose". Foram excluídos artigos: que apresentaram resumos escritos em idiomas diferentes do português, inglês e espanhol; com abordagem laboratorial em modelos experimentais; sem descrição ou referência a estimadores de associação entre doença periodontal e aterosclerose subclínica; pesquisas que realizaram a medida da doença periodontal por parâmetros diferentes de exames clínicos; pesquisas que não analisaram a espessura da íntima média da artéria carótida através de exame de ultrassom; e que abordassem grupos específicos. Foram comparados os desenhos de estudo, protocolos de medida e os dados relatados. De um total de 63 referências, apenas 10 artigos contemplavam todos os critérios de inclusão, distribuídos em: 1 estudo longitudinal, 6 transversais e 3 casos controles. Observou-se uma heterogeneidade entre os estudos em relação ao método de mensuração da doença periodontal e os desfechos da aterosclerose. Concluiu-se que infecções periodontais são fortemente associadas ao desenvolvimento da aterosclerose subclínica, entretanto os mecanismos envolvidos no processo patogênico ainda permanecem desconhecidos.

Palavras-chave: aterosclerose; periodontia; doenças das artérias carótidas.

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Introduction

Periodontal disease (PD) is a multifactorial immunologic chronic disease that arises in response to periodontopathogenic antigens[1]. In this disease, inflammation of tooth-supporting tissues occurs, and subsequently, the inflammatory process extends from the gum to the adjacent bone and periodontal ligaments[2]. PD is a common disease, with the mild and moderate forms affecting 30 to 50% of the adult population, and the severe form affecting 5 to 15% of the adults in the United States[3]. These estimates are confirmed by studies conducted with the Brazilian population[4-5]. A study performed in São Paulo showed that 45% of the subjects presented some degree of periodontal impairment and 5% presented severe PD[6].

The association between PD and cardiovascular atherosclerotic disease has received a great deal of attention[7-13]. The findings of the studies on this subject, however, have been controversial[14-17]. Some studies report that periodontal infection, through an inflammatory process[18] , may cause inflammation of the vascular endothelium[19] and contribute to the onset of atherosclerosis, thus increasing the risks of thromboembolic event, such as myocardial ischemia and infarction[20,21]. Besides that hypothesis, there several other suggested mechanisms, in which microbial agents can induce or accelerate atherosclerosis, such as: local aggregation of lymphocytes and macrophages, with production of tissue growth factors[22]; local release of endotoxin (lipopolisacharides); and molecular mimetism of microbial protein 60, inducing an autoimmune response. Besides that, the systemic increase of cytokines, with activation of inflammatory markers and stimulation of pro-coagulants may cause thrombosis and acute ischemia, and may induce changes in lipoproteins, resulting in a pre-atherosclerotic condition[23].

Some publications[24-27] have created research protocols aiming at studying the possible association between PD and atherosclerosis using the carotid intima-media complex thickness (IMT) to investigate subclinical atherosclerosis[28]. This method allows the prediction of outcomes of future cardiovascular events with a noninvasive technique. It is performed using Doppler ultrasonography, which has clinical usefulness, because IMT has proven to be a quantifiable risk factor for cardiovascular disease (CVC)[29-31].

The progression of atherosclerotic disease is usually followed by an increase in the thickness of the intima-media layer of the arterial wall[32,33], as well as the appearance of fibrous or calcified plaques[34,35]. Measurement of the carotid artery IMT is a means of evaluating an important marker of the presence of cardiovascular disease[36,37].

The objective of this systematic review is to investigate the association between periodontal disease and subclinical atherosclerosis. From the results of the studies reviewed, even a modest level of association has a large impact in public health policies, for the costs of treating sequelae of atherosclerosis are high and periodontal disease is largely treatable and can be prevented.

Methods

Search strategy

A search for published studies addressing the association between PD and atherosclerosis was carried out in Scopus, PubMed, LILACS, BBO, SciELO and Cochrane Collaboration databases, using the following keywords: "periodontitis", "carotid", "atherosclerosis" e "peridontal disease" and corresponding keywords in Portuguese. The search included all studies published in the above mentioned databases through May 2010. We also performed a manual search of the bibliographic references, editorials and letters to the editor that discussed that possible association. All the papers found in the search were read by a trained author.

In the first stage of the search, the articles found repeated in different databases, and papers written in languages other than Portuguese, English and Spanish were excluded. Articles in which the abstract described that the association of periodontal disease with atherosclerosis was not tested were also excluded from the review.

Most papers selected were available at the CAPES website. Articles not available *on-line* were accessed through the *Rede de Comutação Bibliográfica*, a search service for difficult-to-find articles.

Analysis and selection

Inclusion and Exclusion criteria

Articles included in the analysis should have the association between PD and subclinical atherosclerosis tested with a statistical parameter. Information on the diagnosis of atherosclerosis should have been acquired through the measurement of Carotid Artery IMT by Doppler ultrasonography. Studies conducted in experimental models were not included

Studies that measured the extent of PD by parameters other than other than clinical examination were

excluded. Also excluded were studies on specific populations, such as patients with systemic diseases, diabetes, kidney transplant and chronic renal failure on hemodialysis treatment.

Results

Using the keywords "atherosclerosis", "carotid" and "periodontal disease", 45 papers were found in Scopus database. In the same database, when we used the keywords "atherosclerosis", "carotid" and "periodontitis", 36 papers were found, but only four had not appeared in the previous search. We selected 7 papers in PubMed that were not found in other databases. Two articles were found in LILACS, one in BBO, and four on the Cochrane database. In SciELO, however, we found no relevant studies. The search was performed in all databases using the aforementioned descriptor both in Portuguese and in English. A total of 63 papers were selected for review.

Only three articles were not written in Portuguese, English or Spanish, and six did not address the association between PD and atherosclerosis. Four studies had no abstract, so they had to be read in full. Hence, 54 papers met the search criteria (Figure 1). A study that evaluated the frequency of atheromas by radiography[38] and one that did not evaluated atherosclerosis by ultrasonography[39] were excluded from the analysis. Studies[8-10,16,17,23,32,42-53] in which statistical tests were not used to check the association between PD and atherosclerosis were excluded. One metanalysis[54] was excluded because it addressed all the papers included in our systematic review. Nine experimental studies[55-63] were excluded because the authors did not perform carotid ultrasonography to assess atherosclerosis. Three more studies[25,64,65] were not selected for this review

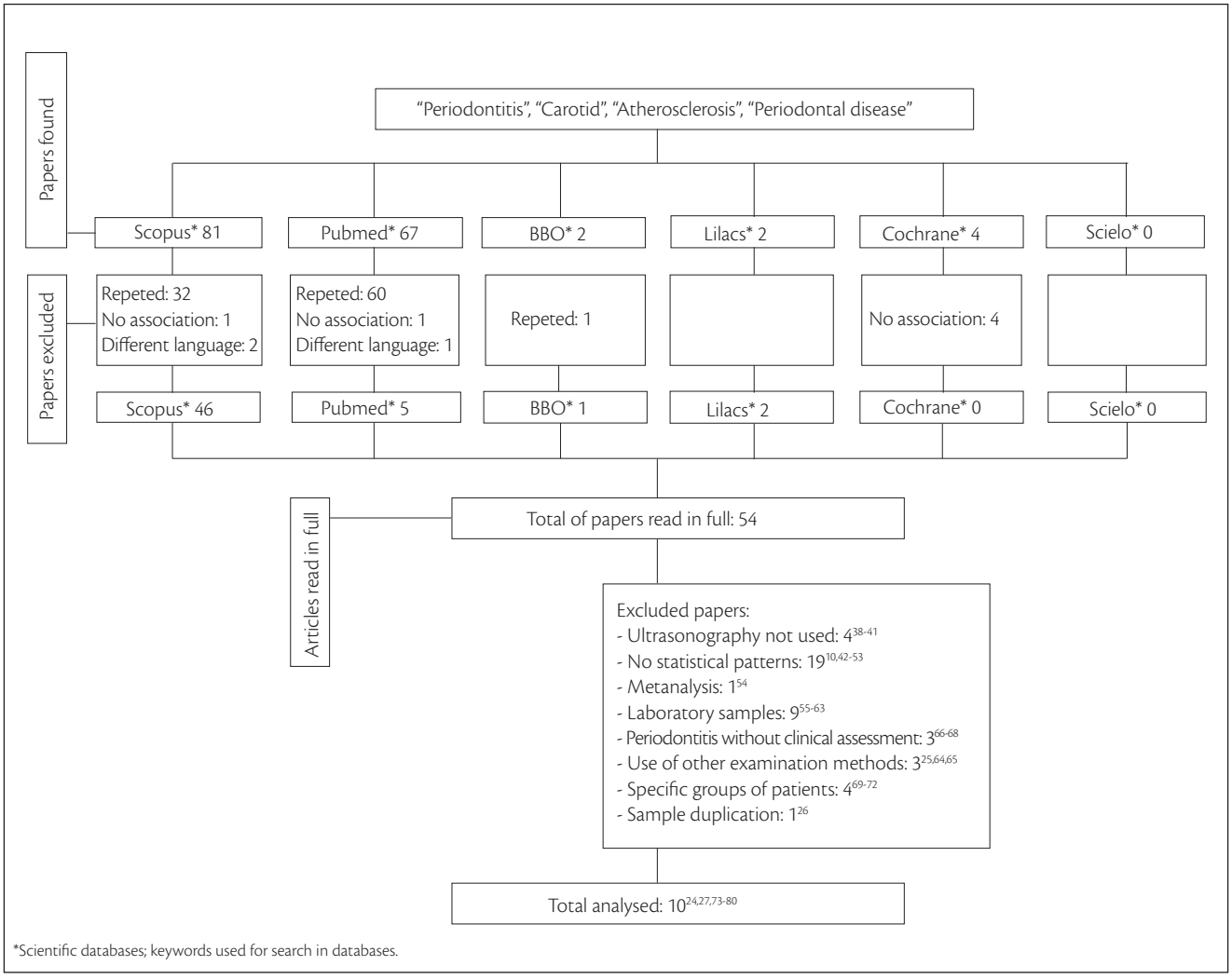

Figure 1. Fluxogram of papers selected for analysis.

because the authors evaluated PD by interproximal or panoramic radiography.

Studies in which PD was assessed by examinations other than physical or radiographic[66-68], as well as those that addressed group of patients with specific conditions such as diabetes[69], hemodialysis[70], renal transplant[71] and hypercholesterolaemia[72] were excluded. One study[26] that mention the same sample of another study was also excluded from the analysis.

After careful selection, our review included ten studies: one longitudinal[27], six cross-sectional[24,74-78] and three case-control studies[73,79,80], as shown in Table 1. Most studies were carried out in industrialized and developed countries such as the United States (USA) Sweden and other European countries.

The only longitudinal study[27] selected had a six to nine-month follow-up. Regarding sample size, the largest study included 6,017 patients[24], and the smallest, 35 patients[77].

Pocket depth probing (PDB) and clinical insertion level (CIL) index were the methods mostly used to classify the patients on the extent of PD. However, other clinical signs were also analyzed, such as bleeding on probing, tooth mobility, and plaque index. Only two studies[73,76] used radiographic analysis as a complementary method of examination.

Most studies classified patients according to the severity of periodontitis based on bone loss occurred throughout life, by measuring six sites per tooth. However, the methods for data collection on periodontitis were not standardized. Only one study[27] classified patients as to their dental condition, including caries, tooth loss and tooth repair, based on the CPO-D index.

The common carotid artery was chosen in most studies for the IMT measurement and ultrasonography examination evaluated atherosclerotic plaques in all studies but one[76]. Besides the common carotid, other measurements were performed in the external carotid, internal carotid and at the carotid bifurcation.

Table 2 shows the results of all studies. It may be observed that there is no categorization pattern established for subclinical atherosclerotic variables, for some were qualitative dichotomic measured in nominal scale, some were quantitative and assessed in an ordinal scale, some had several categories. Besides measurement of the IMT[74,75-77], some authors used the calculated the intima-media area

Table 1. Distribution of studies according to methodology

Study	Study design	Sample (n)	Age group (years)	Location	Time of study	Data collection	Data on IMT
Beck et al.[24]	Cross-sectional	6.017	52–75	USA	1996–1998	PDP, IL, in 6 sites per tooth	CCA, ICA, BCA
Desvarieux et al.[74]	Cross-sectional	711	≥55 (mean: 66±9)	USA	Not specified	PDP, IL, in 6 sites per tooth Plaque, mobility	CCA, ICA
Ravon et al.[76]	Cross-sectional	83	Positive ultrasound: men: mean 69.3±6.7 women: mean 68.3±8.3	USA	Not specified	PDP, IL, in 6 sites per tooth bleeding at probing, bone loss in radiographies	ICA
Desvarieux et al.[75]	Cross-sectional	1.710	45–75	German	1997–2001	PDP, IL, in 4 sites per tooth alternate subjectss	CCA, ICA, BCA, ECA
Schillinger et al.[27]	Longitudinal	411	62–76	Áustria	6 to 9 months	CPO-D index, SLI, PITN, edentulous	CCA, ICA
Soder et al.[79]	Case-control	67;46 cases	30–40	Sweden	Not specified	PDP, IL, in 6 sites per tooth Gingival index, Plaque index	CCA
Back et al.[77]	Cross-sectional	35	52.9±2.7 with DP§ 54.7±3.2 without DP	Sweden	1985–2001/ 2003	PDP, IL, in 6 sites per tooth Bleeding at probing, Plaque index	CCA
Cairo et al.[80]	Case-control	90;45 cases	18–40	Italy	Not specified	PDP, IL, in 6 sites per tooth Plaque, bleeding at probing	CCA
Demmer et al.[78]	Cross-sectional	1.745	≥45	Pomerânia	1997–2001	PDP, IL in 4 sites per tooth R and LS, alternate Bleeding at probing in IC, C, 1st M	CCA
Soder et al.[73]	Case-control	111;80 cases	54.4±3.0 with DP 53.2±.2.8 without DP	Sweden	1985–2003	PDP, IL, Bleeding at probing in 6 sites per tooth, plaque index, 14 rx	CCA

CCA– common carotid artery; ICA– internal carotid artery; ECA– external carotid artery; BCA– carotid artery bifurcation; PITN– periodontal index of treatment needs; PD– periodontal disease; IMT– intima-media thickness; OR– odds ratio; PDP– Pocket depth probing; IL– insertion level; SLI– Silness-Loe index; RS– right side; LS– left side; US– ultrasonography; IC– incisor tooth; C– canine; 1st M– first mola tooth; rx– radiographies

(cIMA)[73,77,79] to evaluate outcomes. The cIMA is used to compensate the narrowing effect of arterial distension (secondary to high blood pressure) on wall thickness[73].

In the majority of studies, both bivariate analysis and multivariate analysis were used, the former to test the association between PD and CVD, and the latter to identify the impact of several confounding factors.

Table 3 presents the statistically significant confounding factors (p values less than 5%) found in multivariate analysis of all studies.

It should be emphasized that only one paper[78] did not make adjustment confounding factors. On the other hand, the association between PD and CVD remained statistically significant after adjustment only for male patients with 16 to 31 missing teeth in the study by Desvarieux et al.[75]. In another study[27], Tooth loss was a predictor factor for progressive carotid stenosis after multivariate logistic regression analysis, suggesting that severe PD is probably the determinant factor of tooth loss in these patients.

Table 2. Distribution of studies according to results of the association between periodontal disease and subclinical atherosclerosis

Study	Outcome	Interest variable	Statistical analysis	p value	Risk estimation	Adjusted confidence interval (95%)
Beck et al.[24]	IMT≥1 mm	BL: bone loss ≥ 3 mm light<10%, mild 10 – 30%, severe>30%	Multiple logistic regression	p<0.01	OR: 1,31 severe PD OR: 1,10 mild PD	1.03–1.66 0.89–1.35
Desvarieux et al.[74]	Presence of carotid plaque	Tooth loss: 0 to 9 missing teeth 10 to 19: missing teeth 20 to 31: missing teeth edentulous: severe PD for PDP≥ 5mm e IL≥4 mm	Linear logistic regression	p<0.05	OR: 1,95 (10 to 19 missing teeth)	1.25–3.04
Ravon et al.[76]	Carotid stenosis more than 80% in diameter	PD: distance CEJ≥4 mm in≥30% of teeth	Spearman correlation	p<0.05 p<0.001	CAL≥5.0 mm, r=0.23 CEJ ≥4.0 mm, r=0.46	-
Desvarieux et al.[75]	Mean IMT Prevalence of carotid plaque ≥1 mm	Tooth loss: 0 to 8 missing teeth 9 to 15 missing teeth 16 to 31 missing teeth edentulous severe PD for PDP≥5 mm e IL≥4 mm	Linear logistic regression	p<0.05	Men: OR: 1.66 (16 to 31 missing teeth)	1.04–2.65
Schillinger et al.[27]	Carotid stenosis Increase in 1 category: 0 to 29%, 30 to 49%, 50 to 69%, 70 to 89%, 90 to 99%, 100%	light periodontal disease with probing of 4 or 5 mm, severe: IL≥6 mm using PITN SLI: plaque index from 0 to 3 CPO-D	Multiple logistic regression	0.046 loss teeth 0.032 CPO-D 0.021 SLI 0.16 PITN	OR: 2.69 OR: 1.11 OR: 1.77 OR: 1.51	1.62–4.17 1.01–1.22 1.09–2.79 0.89–2.45
Soder et al.[79]	IMT, cIMA	PD, plaque, gingival inflammation, severe in women	Multiple logistic regression	0.019 IMT 0.028 cIMA	OR: 6.05 OR: 5.41	1.34–27.35 1.20–24.43
Back et al.[77]	cIMA, atherosclerotic plaque	PD=I with IL>3 mm, Bleeding at probing>20 e PDP>2.2 (mean)	Student's t test, Fisher's exact test, Mann Whitney test	p<0.05	cIMA (mm^2) 11.4±1.8 without PD 13.8±3.3 with PD	-
Cairo et al.[80]	IMT ≥0.82 mm	Severe PD (at least 30% of sites with insertion loss>3 mm and bone loss +1/3 in the root	Linear logistic regression	p=0.0002	OR: 8.55	2.38–39.81
Demmer et.[78]	Mean IMT of 10 consecutive measurements	PD severity from 3 to 10 – 16 definitions in sites with PDP or IL≥ to the limit of severity. (participants were classified as having or not PDP≥3 mm)	Correlations	p<0.05	r=0.14 men for IL ≥6 mm r=0.13 women for PDP≥5 mm	-
Soder et al.[73]	Increase in IMT, cIMA	Chronic PD=at least one site with PD ≥5 mm	Multiple logistic regression	p<0.05	OR: 3.89 IMT OR: 5.31 cIMA	1.43–10.60 IMT 1.8–15.68 cIMA

PITN– periodontal index of treatment needs; CIL– clinical insertion loss; CEJ– cementum-enamel junction; PD– periodontal disease; IMT– intima-media thickness; cIMA– Calculated intima-media area; OR– odds ratio; PDP– Pocket depth probing; IL– insertion level; SLI– Silness-Loe index; r: ratio.

Table 3. Adjusted confouding factors for atherosclerosis (p<0.05).

Confouding factors	Study									
	Beck et al.[24]	Desvariex[74]	Ravon et al.[76]	Desvarieux et al.[75]	Schillinger et al.[27]	Soder et al.[79]	Back et al.[77]	Cairo et al.[80]	Demmer et al.[78]	Soder et al.[73]
Sex	x	x			x					x
Age	x	x	x	x	x	x		x		x
Education		x		x		x		x		
Ethnicity		x								
Tabagism	x	x		x	x	x	x			
BMI				x	x	x				x
Family history of CVD					x	x				
Hypertension	x	x		x	x	x				
Glucose					x					
Triglycerides	x			x						
LDL	x	x		x						
HDL		x		x						
Cholesterol						x				x
Diabetes	x	x		x	x	x				
Waist-to-hip ratio	x									
Hyperlipidemia					x					

CVD– cardiovascular disease; HDL– high-density lipoprotein; BMI– body mass index; LDL– low-density lipoprotein.

Other study[76] was significant because it showed subjects with mean age of 69 years for males and 68 years for females had positive ultrasonographic exams (meaning presence of atherosclerotic disease), while patients of younger age groups had negative ultrasonographic exams. This variable alone remained significant, even after adjustment for other variables: genre, ethnicity, smoking and past medical history. However, smoking and age were predictors of both PD and CVD (Table 3).

Discussion

Although the majority of studies reviewed[24,73-75] have found a positive association between PD and atherosclerosis, methodological limitations raise doubts on the validity of outcomes and conclusions. The studies presented considerable variation on methodology quality, including small sample size, limited number of statistical analysis, inadequate control of confounding factors, inadequate evaluation of PD and reliance on cross-sectional data. Despite these limitations, the association of PD and atherosclerosis seems plausible.

The studies were mainly conducted in industrialized countries, because the investigation of this disease association requires highly skilled professionals and high-technology instruments, in order to measure the extent of both PD and subclinical atherosclerosis. Those conditions make this kind of research too costly to be performed in developing countries.

Cross-sectional studies are important because they allow the inclusion of large samples of subjects and, therefore, large volumes of data can be collected and analyzed, unlike cohort studies, which are very costly to perform. Thus, cross-sectional design is indicated for the diagnosis of the current situation of the disease under analysis, but not to make estimations of populational risk. In the case of DP, it is possible to measure the extent of past history of DP, based on the CIL index, but it is not possible to predict which phenomenon came first: atherosclerosis or PD.

Longitudinal studies are difficult to be done to analyze the relevant factors, for both DP and atherosclerosis are chronic disease processes that develop slowly over time. It is possible to diagnose atherosclerosis as an intermediate subclinical outcome by measuring the carotid IMT.

The present review shows a clear association between PD and subclinical atherosclerosis because all articles reviewed, regardless of the study design, showed statistically significant association, even after adjusting for confounding factors.

The comparison between results of the studies is limited by the wide range of outcomes found, even using carotid IMT as an inclusion criterion. This finding agrees with that of a systematic review that studied the relationship between PD and coronary heart disease[15]. The difference in patterns of carotid IMT measurement was also a restriction, for authors used IMT values ≥0.82 mm in some studies and ≥1 mm in others[24,75,80].

Other limitations were the variety in PD measurements and lack of consensus as to its definition and classification of PD in epidemiological studies. Reliable measurement methods should include PDB and CIL index in six sites per tooth[24,73,74,76-80].

It is noteworthy the role age and smoking habit play in the development of PD and CVD. Nevertheless, the pathophysiological mechanisms that leads to the progression of atherosclerosis have not been fully understood[18,23].

Some studies[73,76-78,80] presented inadequate control of independent variables and outcomes, so their findings and conclusions were not that reliable. Methodological limitations may not allow consistent conclusions about the possible effects of PD on atherosclerosis development and outcomes. A possible causal relationship between the two associations remains unproved. Analytic studies with more rigorous methodology employing more suitable measurement methods to evaluate exposure and outcome may be useful in future research.

Few studies[10] have evaluated the response endothelial dysfunction or IMT reduction to periodontitis treatment. Perhaps this is the right path to investigate the possible association of PD with CVD. The present systematic review suggests the need for methodological standardization of future studies, to make it possible better data synthesis for metanalysis[80]. Based on data found in this review, further studies on the association of PD and atherosclerosis association should be made by prospective cohort studies with previous sample size calculation and long term follow-up that would allow the observation of PD progression. This way, variables related to atherosclerosis could be tested.

Conclusions

Periodontal infections were found to be strongly associated with the development of subclinical atherosclerosis. However, the mechanisms through which this factor influences the progression and outcomes of clinical atherosclerosis are not yet fully understood. Cardiovascular disease and periodontal infections are complex phenomena. Further studies should shed light on the effects of periodontal therapy in the progression of atherosclerosis.

General risk factors such as age, genre, and tobacco smoking, variables that interfere in the development of cardiovascular diseases and PD should be controlled in those studies.

Due to the methodological characteristics of the studies reviewed, further studies with more rigorous methodology and larger samples should be performed in order to clarify the actual association between PD and atherosclerosis. In addition, research should be performed in countries with specific characteristics, such as the developing countries.

Future studies involving the association of oral conditions and atherosclerosis should be standardized as to their methodology, in order to advance the scientific knowledge of this phenomenon.

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